The Development of Hybrid Process Control Systems For Fluidized Bed Pellet Coating Processes

Hanzhou Feng
THE DEVELOPMENT OF HYBRID PROCESS CONTROL SYSTEMS
FOR FLUIDIZED BED PELLET COATING PROCESSES

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By
Hanzhou Feng

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2019
THE DEVELOPMENT OF HYBRID PROCESS CONTROL SYSTEMS
FOR FLUIDIZED BED PELLET COATING PROCESSES

By

Hanzhou Feng

Approved Nov. 17, 2018

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ABSTRACT

THE DEVELOPMENT OF HYBRID PROCESS CONTROL SYSTEMS FOR FLUIDIZED BED PELLET COATING PROCESSES

By
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May 2019

Dissertation supervised by Carl A. Anderson, Ph.D.

The conventional basic control for pharmaceutical batch processes has several drawbacks. The basic control often uses constant process settings discovered by trial and error. The rigid process operation provides limited process understanding and forgoes the opportunities of process optimization. Product quality attributes are measured by the low efficient off-line tests, therefore these cannot be used to monitor and inform the process to make appropriate adjustments. Frequent reprocessing and batch failures are possible consequences if the process is not under effective control. These issues raise serious concerns of the process capability of a pharmaceutical manufacturing process.

An alternative process control strategy is perceived as a logical way to improve the process capability. To demonstrate the strategy, a hybrid control system is proposed in this work. A challenging aqueous drug layering process, which had a batch failure rate of 30%
when operated using basic control, was investigated as a model system to develop and
demonstrate the hybrid control system.

The hybrid control consisted of process manipulation, monitoring and optimization.
First principle control was developed to manipulate the process. It used a theory of
environmental equivalency to regulate a consistent drying rate for the drug layering process.
The process manipulation method successfully eliminated the batch failures previously
encountered in the basic control approach. Process monitoring was achieved by building
an empirical analytical model using in-line Near-Infrared spectroscopy. The model allowed
real time quantitative analysis of drug layered content and was able to determine the
endpoint of the process. It achieved quality assurance without relying on the end product
tests. Process optimization was accomplished by discovering optimum process settings in
an operation space. The operation space was constructed using edge of failure analysis on
a design space. It provided setpoints with higher confidence to meet the specifications. The
integration of the control elements enabled a complete hybrid control system. The results
showed the process capability of the drug layering process was significantly improved by
using the hybrid control. The effectiveness was substantiated by statistical evidence of the
process capability indices.
DEDICATION

To my family and friends, I could not have done this without you.

Thank you for all your support along the way.
I am grateful to all of those with whom I have had the pleasure to work during this and other related projects. I would especially like to thank my advisor Dr. Carl A. Anderson. Dr. Anderson always worked actively to provide me with guidance and instructions to pursue my academic goals. He created an environment that treated all of us as friends but challenged us in science. His open-minded and unprejudiced attitudes toward scientific questions taught me to think outside the box. As my advisor and mentor, he has shown me, by his example, what a good scientist should be. I am also grateful to my co-advisor, Dr. James K. Drennen, III. Besides his vast research experiences, scientific background, and admirable professionalism, Dr. Drennen always showed his kindness and sincere cares for us. He made the lab like a warm family, for that I truly appreciated. The remainder of my dissertation committee, Dr. Peter L.D. Wildfong, Dr. Ira S. Buckner, and Dr. Christian Airiau, were critical in my graduate training and the progress of my research project. Each of them has provided me valuable inputs, extensive scientific and professional guidance. I would also like to acknowledge Optimal Industrial Automation, Emerson Electric, and Advantest for their critical contributions to the research in this dissertation.

Working in B11 was an unforgettable experience that I will be missing for the rest of my career life. The unique culture was scientifically challenging but supportive. The friendships that I made during my graduate career will be cherished forever. I would like to thank my senior graduate colleagues, Dr. Benoit Igne, Ryan Palermo, Dr. Sameer Talwar, Dr. Bob Bondi, and Dr. Anik Alam, who set high standards for me to become a qualified scientist. I am particularly grateful to Shikhar Mohan, Yi Li, Nayeem Hossain, Dr. Douglas...
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It is impossible for me to put my appreciation for my family into words. It was out of my parents’ love to provide a strict upbringing that made me a self-disciplined person. It was also their love to support my decision of moving to a distant country. My parents’ love is always silently offered and expected nothing in return. Being extremely grateful, I can never repay enough for that.

Finally, to my wife, my best friend, and my soul mate, Luyi. She always provided selfless and endless love to me. If my life was a grayscale image, she coded a function to bring it to colorful. Besides her beautiful mind and kind soul, she is also the strongest person who gave me courage and motivation when I was hesitant and weary. She is always there, walking me through every moment of happiness and hardships. “Companionship is the most everlasting confession of love”. I learned the sentence from books, but grasped the meaning from Luyi.
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<td>AF</td>
<td>Air Flow</td>
</tr>
<tr>
<td>AP</td>
<td>Atomization Pressure</td>
</tr>
<tr>
<td>APAP</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td>CGMPs</td>
<td>Current Good Manufacturing Practices</td>
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<tr>
<td>CQA</td>
<td>Critical Quality Attributes</td>
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<tr>
<td>DB</td>
<td>Bubble Size</td>
</tr>
<tr>
<td>DOE</td>
<td>Design of Experiment</td>
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<tr>
<td>EEF</td>
<td>Environmental Equivalency Factor</td>
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<tr>
<td>ER</td>
<td>Extended Release</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>HPMC</td>
<td>Hydroxylpropyl Methylcellulose</td>
</tr>
<tr>
<td>ID</td>
<td>Information Depth</td>
</tr>
<tr>
<td>IT</td>
<td>Inlet Temperature</td>
</tr>
<tr>
<td>IVIVC</td>
<td><em>in vitro in vivo</em> correlations</td>
</tr>
<tr>
<td>LV</td>
<td>Latent Variable</td>
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<tr>
<td>MD</td>
<td>Mahalanobis Distance</td>
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<tr>
<td>MSC</td>
<td>Multiplicative Scatter Correction</td>
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<td>MSE</td>
<td>Mean Squared Error</td>
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<td>NIR</td>
<td>Near-Infrared</td>
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<td>OPC</td>
<td>Open Platform Communication</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>PAT</td>
<td>Process Analytical Technology</td>
</tr>
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<td>PCA</td>
<td>Principal Component Analysis</td>
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<td>PEG</td>
<td>Polyethylene Glycol</td>
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<td>PLS</td>
<td>Partial-least-squares</td>
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<td>RI</td>
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<td>RMSEC</td>
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<td>RSD</td>
<td>Relative Standard Deviation</td>
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<td>RTD</td>
<td>Resistance Temperature Detector</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SNV</td>
<td>Standard Normal Variate</td>
</tr>
<tr>
<td>SR</td>
<td>Spray Rate</td>
</tr>
<tr>
<td>SSQ</td>
<td>Sum Squared Y</td>
</tr>
<tr>
<td>THI</td>
<td>Terahertz Hyperspectral Imaging</td>
</tr>
<tr>
<td>UB</td>
<td>Bubble Velocity</td>
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<tr>
<td>UV</td>
<td>Ultraviolet-Visible</td>
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Chapter 1: Introduction

1.1 Statement of the Problem

Pharmaceutical manufacturing is a critical part of an effective health care system. Although in the past ten years the industry has witnessed a significant development in continuous processes, to date the manufacturing is still highly dependent on batch processing. Due to its advantages such as better adaptability and cost efficiency, batch process is widely used for production of solid drug products (Wold et al.).

Efficient process control engineering and practice have now matured and are extensively employed in fluid-based petroleum and chemical industries (Benyahia et al., 2012). In these applications, the process dynamics are often driven by chemical reactions, which have response times measured in minutes to hours. In a solid-phase pharmaceutical unit operation, the physical changes usually occur within seconds or minutes (Su et al., 2017). This requires much faster response of the control system. Therefore, the process control experience may not be directly transferable to support the more challenging pharmaceutical processing.

The pharmaceutical industry is under one of the most strict regulations. Pharmaceutical products must be produced to meet the desired specifications by manufacturing procedures strictly controlled at desirable process conditions submitted to the regulatory. Any changes made during this process will lead to re-evaluation by the regulatory agency, therefore the pharmaceutical batches were usually produced at constant settings and operated under the conventional basic control. The process operation relies on tightly constrained material attributes and process parameters, which are discovered mostly by trial and errors (Abe et al., 1998). Because at-/in-line analyzer results are often unavailable, the process endpoint often determined based on operator’s
experience. The processed materials must be tested off-line, and thus the results of the quality test cannot be used in a real time manner to inform the process operation. The variability of quality is trapped in the batch endpoint, potentially producing more substandard products.

Process capability is often used to describe the ability of a process to manufacture quality products that meet the required specifications (Ziemer, 1993) According to the opinions from the pharmaceutical industry (Shanley, 2017), little change has been made to improve the process capability in the past ten years. Using a Six Sigma quality management criterion, the pharmaceutical industry to date still remains at two to three sigma quality levels, whereas five sigma is a general standard practice for industries such as automotive, electronics, etc. The sigma level can be converted to defects rate as shown in Table 1.1. In general, the defect rate of a pharmaceutical process is approximately more than 300 times larger than most other industries.

<table>
<thead>
<tr>
<th>Defects per million opportunities (PPM)</th>
<th>Sigma level</th>
<th>Cpk</th>
<th>Conforming level %</th>
<th>Capability rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>691462</td>
<td>1</td>
<td>0.333</td>
<td>68.27</td>
<td>Terrible</td>
</tr>
<tr>
<td>308538</td>
<td>2</td>
<td>0.667</td>
<td>95.45</td>
<td>Poor</td>
</tr>
<tr>
<td>66807</td>
<td>3</td>
<td>1.000</td>
<td>99.73</td>
<td>Marginally capable</td>
</tr>
<tr>
<td>6210</td>
<td>4</td>
<td>1.333</td>
<td>99.9936</td>
<td>Capable</td>
</tr>
<tr>
<td>233</td>
<td>5</td>
<td>1.667</td>
<td>99.99994</td>
<td>Good</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>2.000</td>
<td>99.9999998</td>
<td>Excellent</td>
</tr>
</tbody>
</table>

The quality deficiency is evidenced by the number of drug recalls. According to FDA’s data (Gaffney, 2014), the two years of 2013-2014 reported 2061 drug recalls. While the sheer numbers are troubling enough, what is more concerning is the reasons of the recalls. The overwhelming majority of the recalls is driven by Class I (21%) and Class II recalls (70 percent). Based on the classifications of drug recalls (FDA, 2010), the data indicates most of the recalls
were issued due to serious adverse health effects. In total, about 30\% of the recalls was caused by failing to meet the prescribed specifications. From the perspectives of consumers and regulators, pharmaceutical companies should provide reliable access to safe, efficacious, stable and affordable high quality pharmaceutical products. Unfortunately, the expectations have not been met.

Although the shortcomings discussed above reflect poor quality practices in the pharmaceutical industry, it also implies there are many opportunities for improvement. Recognizing the need to improve product quality, FDA encouraged the manufacturers to employ the latest scientific advances in pharmaceutical manufacturing and technology. In the guidelines put forth by the International Conference on Harmonization (FDA, 2004a), the desired pharmaceutical manufacturing should include effective and efficient process operations, appropriate product specifications based on process understanding, and continuous real time quality assurance provided by process monitoring. The advancement of new technology and updated regulatory policy has offered opportunities to develop alternative control strategy. The ICH Q8 (R2) guideline introduced the “quality-by-design (QbD)” concept and allow for operation flexibility within a validated design space (FDA, 2009). In the QbD approach, there is no rigid restriction of constant process settings. The use of design of experiments (DOE) with supported prior knowledge is valuable to enhance process understanding. The application of process analytical technology (PAT) allows developing process monitoring system to provide real time quality measurements. These advancements have provided necessary basis and tools to achieve a desired pharmaceutical manufacturing.

The goal of this dissertation was to develop an alternative control strategy for a pharmaceutical manufacturing using batch process. Considering the unique position of the coating process in a series of consecutive unit operations, it is critical to have an effective control to prevent
batch failures and ensure product quality. Therefore, this dissertation considered fluidized bed pellet coating as a suitable model system for demonstrating the development of an alternative control strategy.

Fluidized bed processing is a well-known challenging unit operation. Although the equipment and process parameters influencing the quality of finished products are identified in literature (Banks, 1981), the process itself is known to be multivariate and complex by nature. There are several problems associated with the fluidized bed coating process. The most serious one is the high risk of batch collapse due to agglomeration (Lipsanen et al., 2008). Uneven and lumpy agglomerates are easily produced during the random movement of the coated particles. Depending on the drying capacity and liquid viscosity, the growth of agglomerates may lead to wet-quenching or dry-quenching, causing drastic and instant batch collapse (Dewettinck et al., 1998). The fluidized bed pellet coating process is usually operated using basic control. Fixed process settings discovered in trial and errors are used under the supervision of the operator. Nevertheless, a fixed process condition does not always guarantee successful coating batch production for long-term manufacturing. The dissertation proposes to develop a hybrid control system to improve the process capability of a fluidized bed pellet coating process. The hybrid control system consists of three parts: process manipulation, monitoring, and optimization. The drug product quality is expected to benefit from the successful development of the proposed control strategy.
1.2 Hypothesis and Specific Aims

The dissertation is based on the central hypothesis that a hybrid process control system, developed by integrating first principle control, empirical analytical models, and operation space, can improve the process capability of a fluidized bed pellet coating process.

Given the central hypothesis, the specific aims of this dissertation were to:

(1) Establish a process manipulation method, based on first principle control, to improve the process operation and reduce batch failure.
(2) Build empirical analytical models to allow real time process monitoring of critical quality attributes (CQA).
(3) Construct an operation space, predicated on the concept of design space and edge of failure, to enable process optimization.
(4) Compare the process capability obtained using the hybrid control with the basic control.
(5) Explore the possibility of a broader applications using the hybrid control system.

1.3 Literature Survey

1.3.1 Fluidized Bed Coating

1.3.1.1 Flow Regimes and Solid Particles for Fluidization

Fluidized bed equipment has become an integral part of the pharmaceutical industry for implementing and improving drying, granulating, and many types of coating and layering operations. As the technology of fluidized bed batch processing equipment has evolved, attention has turned to the sophisticated issues of safety, adherence to CGMPs, product-handling systems, quality control and process automation. A sufficient understanding of the interdependence between
the processes and the specific design requirements is essential if high quality and effective products are to be produced in a safe and efficient environment (Olsen, 1989a).

A fluidized bed is a packed bed through which fluid flows at such a high velocity that the particle bed is loosened and the particle-fluid mixture behaves as though it is a fluid. Thus, when a bed of particles is fluidized, the entire bed can be transported like a fluid, if desired. Both gas and liquid flows can be used to fluidize a bed of particles. The most common reason for fluidizing a bed is to obtain vigorous agitation of the solids in contact with the fluid (Yang, 2003). Therefore, this process is commonly used for several purposes, such as fluidized bed reactors, solid separation, fluid catalytic cracking, and coating on solid items (Yang, 2003).

In the pharmaceutical industry, fluidized bed processing is often utilized for coating small particles or pellets. Inside the bed, solid particles are suspended in a fluid-like state using gas introduced from the bottom of the bed. The gas is normally preheated before it is pumped to the bed where it acts as both heat and momentum carrier. In the coating process, a layer is deposited onto the surface of fluidized solid particles by spraying with a solution or suspension of the coating material. The goals are usually to load drug or modify the properties of the particles (Cole, 2002).

Different regimes of fluidizations are displayed in Figure 1.1. The dilute phase flow characterized by the fast fluidization and suspension flow. It is commonly used for pneumatic conveying systems, and might only occur as a by-pass process for emptying the fluidized bed column (Rabinovich and Kalman, 2011). For a wide particle size distribution, the large particles are fluidized at the lower part of the column, while the fine powders might be carried over by a dilute flow regime (Kalman and Rabinovich, 2008). By reducing the gas velocity, the suspension flow is halted and particle clusters might appear. Yerushalmi referred to the flow regime occurring after the appearances of particle clusters as fast fluidization (Yerushalmi and Cankurt, 1979). In
addition, the literature presents the main characteristics of the turbulent fluidization, slugging, bubbling and fluidized flow regimes. The turbulent fluidization regime is characterized by extreme particle turbulence without large discrete bubbles or voids. The slugging flow regime is characterized by a particle dense phase transport that is facilitated by bubbles whose size is comparable to the pipe diameter size. The bubbling flow regime can be similarly characterized, however, the bubbles are much smaller. The fluidized flow regime is characterized by particle dense phase fluidization or transport without bubbles (Rabinovich and Kalman, 2011). The plug flow regimes are not common in fluidized bed system, they may occur in pneumatic conveying system.

Geldart’s classification of particles is a good guidance in deciding the suitability of seed particle for fluidized bed coating (Geldart, 1973). Geldart plotted a powder classification diagram using experimental data, from a wide variety of researchers who have commented on the behavior of the powders with which they worked. The plot of particle density vs. mean size is shown in
Figure 1.2. The fully open symbols represent powders which the authors remarked were extremely difficult to fluidize (group C), the half-closed symbols represent powders where bubble free bed expansion were noted (group A), and the solid symbols where they were specifically mentioned that bed expansion was low and/or bubbling occurred at or very close to minimum fluidization velocity. Geldart commented the justification of group D is not readily apparent as there is relatively little published information is available (Geldart, 1973).

The Geldart C particles have a particle size range below 30 µm. The strong inter-particulate forces greatly affect the fluidization behavior, normal fluidization of such powders is extremely difficult. The powder lifts as a plug or channels as shown in Figure 1.2. The difficulty arises because the inter-particulate forces are greater than those which the fluid can exert on the particle, and these are generally the result of very small particle size, strong electrostatic charges or the presence in the bed of very wet or sticky material. Poor particle mixing and heat transfer would be expected, therefore fluidized bed is inadequate for processing the class C particles.

Other types of particles are easier for fluidized bed processing. Geldart A materials have a small mean size and/or a low particle density (less than about 1.4 g/cm$^3$). Beds of this group expand considerably before bubbling commences. Gross circulation of the particles (akin to convection currents in liquids) easily produce rapid mixing even when few bubbles are present. Bubbles in a two-dimensional bed appear to split and recoalesce very frequently. Group B contains most materials in the mean size and density ranges 40 – 500 µm, and 1.4 – 4 g/cm$^3$. In contrast with group A powders, naturally occurring bubbles start to form at or only slightly above minimum fluidization velocity. There is little or no powder circulation in the absence of bubbles, and bubbles burst at the surface of the bed as discrete entities. When the air velocity increases, bubbles coalescence leads to slugging commences. Group D powders were confined to large and/or very
dense particles. The solids mixing relatively poor, the flow regime around particles in this group may be turbulent, causing some particle attrition with rapid elutriation of the fines produced (Geldart, 1973).

Figure 1.2 Permission granted and reproduced from Geldart. Power classification diagram for fluidization by air.

1.3.1.2 Classifications of Fluidized Bed Systems

The classification of fluidized bed process is easily characterized by the nozzle position. Three configurations are commonly involved in pharmaceutical manufacturing: top-spray, bottom-spray, and tangential-spray with rotating risk (Wen and Park, 2010). The top-spray system has been successfully used to coat materials as small as 100 μm (Dewettinck et al., 1998). A typical top-spray configuration is shown in Figure 1.3 (A). The product container is an unbaflled, inverted and truncated cone. Inlet air stream is drawn through the air distributor, entered the product container from the bottom. The resulting particle motion is unrestricted and presumed random. The nozzle is positioned above the powder bed, from which atomized coating liquid is sprayed.
downward onto the fluidized particles. In this system, controlling the distance that droplets travel before impacting on the particles is very difficult due to the vigorous and random fluidization behavior. Consequently, premature droplet evaporation can be quite severe, and as a result coating imperfections may occur. The higher the degree of drying, the more viscous the droplets get before impinging on the particle substrate, resulting in a degradation of the coating solution’s film-forming properties (Cole, 2002). The spray dried fine coating material is collected by the filter housing at the top of the fluidized bed, and should be considered a loss (Dewettinck et al., 1998). The coating layer produced by a top-spray system always involves imperfections to a certain extent (Ronsse, 2006), this method is less suited for controlled release products, and is nowadays primarily used for barrier (protective) coatings.

The bottom-spray system is also known as the Wurster system. Originally designed to coat pharmaceutical tablets, it is now widely used for processing substrates as small as 50 μm (Turton and Cheng, 2005). The coating chamber contains an unbaffled, open-ended cylinder known as the partition, as shown in Figure 1.3 (B). The size of the gap between the partition and the air distributor is adjustable. The aim of the partition is to create ordered particle movement. Compared to the top-spray configuration, the bottom-spray configuration produces coating films which are more uniform and have a superior quality (less imperfections), and thus bottom-spray is better suited to produce controlled release encapsulated products. In a bottom-spray coating process, the particle motion, the number of passages and the time spent during each passage through the spraying region, is well controlled as opposed to the top-spray configuration, where particles motion is presumably random and uncontrolled. Furthermore, droplets are deposited concurrently, assuring minimum droplet travel distance. Due to the extremely short droplet travel distance,
premature droplet evaporation is almost absent. The film-forming droplets can spread out at the lowest viscosity, producing a very dense film with a superior physical quality (Lan et al., 2011).

The third, and most recently developed fluidized bed system is the tangential-spray (Figure 1.3 (C)) (Bouffard et al., 2007). Instead of using an air distributor, a solid, rotating disc is installed at the base of the reactor. A narrow gap exists between the reactor wall and the rotating disc, through which the process air is drawn. The particle motion resulting from the combination of the lift force created by the upward flowing process air, gravity, and the friction force created by the rotating disc, could best be described as a spiraling helix. Beneath the surface of the rapidly tumbling bed, one or more nozzles are positioned to spray the coating liquid tangentially to and concurrently with the flow of particles. As a result of short droplet travel distances (concurrent spray) and the rapid tumbling of the particle bed, high quality coating films are obtained which are comparable to those produced by the Wurster process.

Figure 1. 3 Permission granted and reproduced from Wen and Park. Schematic drawing of top-spray/bottom-spray/rotary-spray system.
Wurster system is generally acknowledged more suitable for particle coating (Cole, 2002). However, it has several shortcomings (Olsen, 1989a). The poor adaptability of Wurster system requires many design considerations when materials of different particle sizes are processed. For example, for tablet coating the system should be cylindrical. The percentage of open area in the orifice plate should be adjustable because the ratio of airflow through the center partition to the airflow outside the partition will need to be adjusted according to tablet size, shape and density. The partition height above the orifice plate needs to be adjustable for the same reason. When the system is used to coat smaller particles, the expansion space above the partition should be increased to allow greater expansion of the fluidized bed. Furthermore, the shape of the expansion chamber should be changed from cylindrical to conical to provide a deceleration zone for the particles. Also, the height of the partition should be adjustable as it may be necessary to adjust the height during operation considering the large amount of coating is applied. The adjustment of the partition height depends on the particle size, amount of materials, bulk density, and the properties of coating materials. In some cases, a specially designed partition might be required for coating small powders. The scale-up of batch size is particularly difficult for Wurster system, as the number of inner partitions increases as does the diameter of the cylindrical outer wall. The complex design change requires many adjustments of the process parameters and configurations (Olsen, 1989a).

The top-spray fluidized bed has advantages such as high versatility, relative simplicity, and higher batch size. There is much less adjustment required on the equipment design for different materials. It is easy for batch to batch manufacturing. A simple replacement of the nozzles would make the system ready for next batch. Top-spray system also allows larger batch size, especially considering the industrial scale (could be up to 2200 L) compared to Wurster system (approximately 600 L) (Olsen, 1989a). The challenges of using top-spray system are mainly
resulted from the lack of controlled fluidization. It is more difficult to control the travel of coating droplets. However, the risk of wet quenching of the top-spray system is much lower than bottom spray system. The danger posed by wet quenching sometimes will favor the use of top-spraying despite the bottom-spray is ideally more suited for coating.

1.3.1.3 Functions of Coating

A film coating is a thin polymer-based coat applied to a solid dosage form such as a tablet, granule or pellet. The thickness of such a coating is usually between 20 and 100 µm (Cole, 2002). Depending on the purposes, there are two types of coating: conventional and functional. The term conventional film coating has been used to describe coatings applied for reasons of improved product appearance, improved handling, and prevention of dusting, etc (Rowe, 1985; Sakellariou and Rowe, 1995). Although conventional coating offers no particular therapeutic advantages, it has considerable psychological importance in aiding patient compliance in taking the medicine.

Functional coating has been used to achieve several purposes. It can be used for drug loading, where a different drug is applied to a non-functional or drug-loaded substrate such as tablet or particles (Avalle et al., 2014; Chevalier et al., 2010; Ho et al., 2009a; Lilja et al., 2013; Wang et al., 2012), to achieve combined drug administration. Sometimes, the same drug is applied with suitable polymers to add an immediate release layer (Li et al., 2010), in order to achieve a specific drug administration requirement. Many drugs formulated in tablet or particles are light or moisture sensitive (Bley et al., 2009; Tønnesen, 2001). Opacifiers, e.g., titanium dioxide or pigments with high refractive indices, are often included in film coatings to decrease the rate and amount of light degradation. Coating materials with low inherent water vapor permeability is often employed to reduce the ingress of moisture. Film coatings are effective in modifying the drug release regulated by drug diffusion (Ozturk et al., 1990), polymer erosion (Cao et al., 2005), and
osmosis (Herrlich et al., 2012). For diffusion-controlled release, the core is coated with a water insoluble copolymers (e.g., ethyl cellulose or methacrylate ester) alone or in combination with a water soluble ingredient (e.g., Hydroxylpropyl Methylcellulose (HPMC)) such that the film permeability can be modified. For release determined by polymer erosion, the core is coated with either a sparing soluble or pH dependent soluble film (e.g., cellulose acetate phthalate) such that the drug release will be dictated by the dissolution of the polymer. For osmosis-controlled release, a small orifice is drilled through the semipermeable coating film. The drug release is determined by the permeability of the film and the core formulation (Sakellariou and Rowe, 1995).

1.3.1.4 Physical Phenomena in Fluidized Bed Coating

There are numerous possible processes can take place inside the bed, depending on the process conditions, particle characteristics, and coating materials used. Figure 1.4 summarizes the possible physical phenomena during fluidized bed coating, based on possible mechanisms suggested by literature (Maronga, 1998).
Spray dried fine particles result from premature evaporation of the atomized droplets, if they are unable to reach the particle surface and stay attached by adhesion. The fines may be elutriated out or remain in the bed, depending on the weight and density (Saleh et al., 1999). The fine powders that remain in the bed can be joined with other spray-dried fines, resulting in fine-agglomeration, or they can be captured by larger particles causing ‘snow ball’ growth. When an atomized coating liquid successfully impinge on particles, it wets their surfaces. Depending on the conditions inside the bed, wetted particles may collide and form liquid bridges between themselves, or can be dried resulting in a layered growth. If there is excessive wetting, many particles will join together to form large wet clumps, inducing de-fluidization of the bed in a phenomenon known as wet quenching. In the case of moderately wetted particles, a number of solid particles will remain joined together when their liquid bridges are dried. The continuing existence of these solid bridges depends on their strength. If the adhesive force is strong and the solid bridges join together many particles, then these particles will remain joined and the bed will eventually collapse as it can not fluidize these large particles. This phenomenon is also known as dry quenching. At the same time, if the adhesive force is strong but the solid bridges joins together only a few particles, the process will continue and the resulting product will be a few particles joined together to form larger particles, i.e., agglomeration. On the other hand, if the adhesive forces are weak, the dried solid bridges will break, leaving some coating on the surface of the particles. This will eventually lead to coated particles. The challenge in achieving a successful coating process is to ensure that the sprayed coating material reaches the particles, without causing excessive wetting. This has to be done inside the bed in the presence of all three phases as time heat, mass and momentum transfers are taking place at the same time.
1.3.1.5 Effects of Process Parameters

The fluidizing gas velocity is a parameter which influences both the operation stability and coating parameters. The hydrodynamic behavior of the fluidized bed coater is strongly dependent on the fluidizing gas velocity. An adequate choice of this parameter is essential to avoid batch collapse, unplanned agglomeration, and to keep stable operation for long periods.

In general, the lower the gas velocity, the faster the de-fluidization of the bed takes place. The behavior can be qualitatively explained using the Ennis’ model of cohesive forces of mobile liquid bridges (Ennis et al., 1991). According to Ennis, in the case of a fluidized bed the transition to the inertial regime will occur when the particles have reached a sufficient size such that the largest collision velocity will cause particle rebound and prevent agglomeration. Note that this corresponds to the maximum size of agglomerates which can be formed at a given velocity in the bed. The critical size at which the transition takes place depends on the humidity content and relative velocity of particles, which is given by Eq. (1.1),

\[
d_p = \sqrt{\frac{9\mu(1+\frac{1}{2})}{2\rho \frac{h}{U_B/D_B}} \ln\left(\frac{h}{h_0}\right)}
\]  
Eq. (1.1)

In this equation, the humidity content and relative velocity are represented through \( h \) and \( U_B/D_B \) (bubble velocity and bubble size). According to Davidson and Harison’s relationship (Davidson and Harrison, 1963) to estimate the bubble velocity and Mori and Wen’s correlation (Mori and Wen, 1975) for bubble diameter, the term \( U_B/D_B \) increases linearly with fluidizing air velocity. Therefore, by reducing of the fluidizing air velocity, a decrease in relative velocity and increase of humidity content lead to higher values of \( d_p \). Under these conditions \( d_p \) would exceed the initial diameter of the particles, and all collisions between particles are successful. Under this condition, the growth is governed by agglomeration.
The atomization conditions influence the mechanism and quality of deposition by modifying the size of liquid droplets (Dewettinck et al., 1999). The change in droplet size affects the coating growth rate and operation efficiency due to the two competitive phenomena of collision: impingement of liquid on solid particles, and attrition (Guignon et al., 2003). Generally it is accepted that the mean droplet size decreases by increasing atomizing pressure. Saleh et al. studied the influences of atomization air flow rate and liquid flow rate on the droplet size. A sharp decrease in the mean droplet size (from 60 to 20 µm) was observed when the atomizing air flow rate increase four folds from $6.4 \times 10^{-5}$ to $30.6 \times 10^{-5}$ kg/s. The trend was reasonably modeled by Nukiyama-Tanasawa correlation (Nukiyama and Tanasawa, 1938). The impingement efficiency is expected to be increased when a higher atomization pressure is used, because of forming larger number of droplets with greater velocity. However, a possible contradictive effect is that the greater specific surface area of the smaller droplets enhances the chances of premature evaporation and decreasing the impingement efficiency. The mean droplet size formed by the pneumatic spray system did not vary significantly with the liquid flow rate (Saleh et al., 1999). This allowed the droplet size to be controlled independently of the liquid spray rate (Olsen, 1989a, b).

Saleh et al. found the operation efficiency improved with the decrease in solid concentration in the coating liquid (Saleh et al., 1999). Decreasing solid concentration often leads to greater liquid viscosity, inhibiting the tendency of liquid premature evaporation. However, the increased viscosity also strengthens the liquid adhesion to the particle surface, and forms stronger liquid bridges. This, unfortunately, leads to a higher agglomeration rate. The initial particle weight, or batch size, has not been reported having significant influence on coating growth rate, operation efficiency, and agglomerate rate (Saleh et al., 1999). It can be taken as an indication that particle wetting in a fluidized bed coater occurs only in a limited volume of bed called “atomization zone
or spraying zone” (Smith, 1983), which is independent of the total mass of particles. The size of this zone is determined by the penetration depth of the spray, which is a function of the gas velocity, nozzle position, physical properties of the atomizing and fluidizing gas, and particle momentum.

1.3.2 Process Manipulation Approaches

In early fluidized bed coating studies, attempts have been made to monitor and control critical process parameter with manual operation, i.e. basic control (Dewettinck and Huyghebaert, 1998; Lorck et al., 1997a; Maronga, 1998; Wesdyk et al., 1993). In the basic control approach, the process is usually operated using constant process settings. Manual adjustments are often made to compensate the batch to batch variation. A typical example is shown in Table 1.2 (Wesseling and Bodmeier, 1999a), where three coating processes were produced using preset constant setpoints. A well-known challenge associated with the fluidized bed processing is the process is susceptible to the variation of ambient conditions. The inlet air temperature used for fluidized bed processing is usually between 50-70 °C. At this low temperature range, the drying capacity is considerably affected by the saturation humidity of the inlet air. This explains the observed wide range for each parameter in Table 1.2, because the operator has to make adjustment for every batch based on the specific environmental conditions. It is possible to enable automatic control using the basic control, however, only feasible with the availability of an air-preconditioning system. The installment of such system is very expensive, especially for large commercial scale facilities. More importantly, they do not remove all variability. Large gradients with respect to temperature and humidity are common within large manufacturing spaces, especially in the presence of a large work force (Zacour, 2012).
Table 1. Process parameters for the chlorpheniramine maleate layering and the coating of the drug-layered beads.

<table>
<thead>
<tr>
<th>Process parameter</th>
<th>CPM layering</th>
<th>Aqueous ethylcellulose dispersion, Aquacoat®</th>
<th>Organic ethylcellulose solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inlet temperature (°C)</td>
<td>45</td>
<td>45–50</td>
<td>35</td>
</tr>
<tr>
<td>Air volume (m³/h)</td>
<td>70–80</td>
<td>70–80</td>
<td>70–80</td>
</tr>
<tr>
<td>Product temperature (°C)</td>
<td>37–40</td>
<td>41–43</td>
<td>29–31</td>
</tr>
<tr>
<td>Outlet temperature (°C)</td>
<td>35–37</td>
<td>35–39</td>
<td>27–30</td>
</tr>
<tr>
<td>Spray rate (g/min)</td>
<td>3–11</td>
<td>2–10</td>
<td>3–7</td>
</tr>
<tr>
<td>Atomization pressure (bar)</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Nozzle diameter (mm)</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
</tr>
</tbody>
</table>

The first principle approach is established by quantifying the scientific mechanisms. Because first principle control uses experimental data instead of statistical methods to estimate model parameters, they are not as quick and easy to build, but have many advantages. By definition, the calculations are based on material and environmental properties, so the calculations are universal for all systems. Separate calibrations for new or adjusted formulations are unnecessary (Zacour et al., 2012b). The calculations are also independent of equipment scale or type, meaning first principle control is scalable and transferable. Property fluctuations or failure during development can be explained using scientific principles, leading to easier interpretation and greater process understanding. Complex interactions between processing parameters can be accounted for by simply understanding their impact on simpler first principle mechanisms.

First principle control offers substantial economic advantage. The coating process conditions discovered under basic control may not guarantee long-term success. The nature of the coating process is extremely susceptible to many sources of variability, which may directly or obliquely impact final product properties. Strictly controlling all sources of variability requires
extraordinary capital investment. Nevertheless, such expenses could be unnecessary if the investment into a rigorous first principle control system is made.

First principle control has been developed and applied to control fluidized bed drying and tablet coating, with several approaches such as thermodynamic environment controls (Ende and Berchielli, 2005; Reiland et al., 1983; Ronsse, 2006; Strong, 2009), residence time distribution (Plawsky et al., 2010; Rodríguez-Rojo et al., 2008), population balance (Paulo Filho et al., 2006), computational fluid dynamics (Hilton et al., 2013; Nunes et al., 2012; Šibanc et al., 2013), and transport phenomena (Yang, 2003). Among them, Ebey’s work on developing thermodynamics model (Ebey, 1987) is often referred to in the discussion of most relevant first principle approaches for controlling coating process. The control proposes to stabilize the coating environment by regulating the thermodynamic environment at a macroscopic-scale, based on the first principle understanding of the heat-transfer and mass-transfer. An environmental equivalency factor (EEF) is calculated by combining the original process parameters to a single value, which is used to describe an overall drying rate for the process. By such variable reduction, the amount of development and experimentation can be reduced exponentially. (Zacour et al., 2012a)

However, there are several shortcomings of the first principle control (Zacour, 2012). The EEF calculation does not account for the detailed momentum transfer into its calculation. For example, the atomization pressure is treated as a nuisance variable and held constant in the calculation (Lecomte et al., 2003; Lee et al., 2011; Siepmann et al., 2008a). Nevertheless, it may have significant influences on a coating process, because of its important roles affecting the properties of the liquid droplet. Although the use of EEF provides a strategy for managing the thermodynamic environment, additional understanding of its interaction with physical phenomena at the microscopic level is helpful to achieve process optimization and effective control. Another
shortcoming associated with the first principle control is the difficulty in quality assurance. The measurements typically involved in a first principle control are temperature, humidity, etc. The control does not directly measure the in-process materials, therefore provides no feedback to determine the process endpoint. The product quality is still limited in a way similar to the basic control.

1.3.3 Empirical Analytical Models based on Spectroscopic Techniques

Establishing an effective analytical method to determine the CQAs is a pivotal element in the development of a control strategy. Unfortunately, the conventional analytical methods for pharmaceutical products are often off-line and destructive laboratory tests, such as HPLC, *in vitro* drug release, etc. Analytical approaches that are able to provide rapid and non-destructive measurements of the CQAs are desirable to suit the augmented needs of continuous quality assurance for developing effective process control (Yu and Kopcha, 2017).

The Food and Drug Administration (FDA) has encouraged the use of process analytical technology (PAT) to support pharmaceutical development, manufacturing, and quality assurance. (FDA, 2004a) In a PAT framework, process measurements are taken in three ways (Figure 1.5) (FDA, 2004a). At-line: samples are removed from the process and analyzed in close proximity to the process stream; on-line: samples are diverted from manufacturing process and may be returned to the process stream after analyzing; in-line: samples are analyzed, in a real time manner, without leaving a normal process. The distinction of modern PAT-based approach from a conventional off-line is the time required for analysis. The time for manufacturing is insignificant compared with the conventional off-line test, which has a broad range from minutes to several days to obtain the results. Unlike the off-line test, PAT is able to offer real time quality measurement that allows continuous process improvement.
Near-Infrared (NIR) and Raman spectroscopy are two spectroscopic techniques most commonly researched in the field of PAT. NIR spectroscopy is a vibrational spectroscopy, spans the electromagnetic spectrum in the wavelength range of 780 – 2526 nm (Burns and Ciurczak, 2001). It provides information comes from overtones of molecular vibrations. Only vibrations resulting in changes in dipole moment of a molecule can absorb NIR radiation. R-H functional groups have the strongest overtones as the dipole moment is high, O-H, N-H, C-H, S-H bonds are therefore strong absorbers. Because molecules differ in their vibrations, and hence in their vibrational overtone spectra, the NIR region is valuable in characterizing chemical attributes (Andersson et al., 1999). However, the overtones and combination bands often overlap, raising a challenge in data interpretation (Burns and Ciurczak, 2001). A distinct spectra feature characteristic of the analyte of interest is very hard to be obtained in NIR spectrum.

Raman is also a molecular vibrational spectroscopic technique. Unlike NIR, Raman spectroscopy is highly selective. The basic principle in Raman spectroscopy is to irradiate a
substance with monochromatic light and to detect the scattered light with a different frequency to the incident beam. The differences in the frequencies between the incident and scattered radiation result in characteristic Raman shifts (Rantanen, 2007). The Raman scattering refers to the inelastic scattering of electromagnetic radiation as a result of energy exchange between the radiation and molecular vibrations. It must be noted that the irradiation of materials can result in phenomena other than scattering: e.g., absorption, and fluorescence (Wartewig and Neubert, 2005). Because the Raman scattering is inherently weak, the other phenomena strongly interfere the desired signal. The weak Raman signal is prone to various background effects, which complicates its quantitative analysis (Bogomolov et al., 2010).

Although each has some limitations, the advantages offered by NIR and Raman considerably outweigh their drawbacks. They are instantaneous, and non-destructive, requiring minimal or no sample preparation (Muselik et al., 2010). Once calibrated, the methods are simple to operate and suitable for determining the quality attributes of many types of samples. With the availability of fiber probe modules coupled to the spectrometer, both techniques can be implemented to the process streams, allowing continuous real time measurements. Therefore, NIR and Raman have been increasingly used as an alternative analytical method to measure the quality attributes of pharmaceutical products (Roggo et al., 2007; Wartewig and Neubert, 2005).

Several research groups have undertaken the application of NIR and Raman methods for pharmaceutical coating analysis. Andersson was the first to attain the objective of real time analysis of film coating using NIR in a Wurster fluidized bed (Andersson et al., 2000). A subsequent study performed by Hudovornik revealed the comprehensive capability of using NIR to achieve real time analysis of multiple coating characteristics (Hudovornik et al., 2015). After a few attempts of applying Raman spectroscopy to characterize tablet coating properties (Kauffman
et al., 2007; Romero-Torres et al., 2005). Bogomolov employed in-line Raman spectroscopy combined with NIR to enable real time analysis of a fluidized bed pellet coating process (Bogomolov et al., 2010). The literature has demonstrated NIR and Raman can provide means to bypass time-consuming and expensive primary analytical methods. With appropriate modeling method and performance assessment, the NIR and Raman models can provide predictions of the CQAs with much reduced time and efforts. Therefore, the techniques find increasing acceptance in the pharmaceutical industry as promising rapid surrogate tests for the analysis of raw materials and final dosage forms (Kirsch and Drennen, 1995).

The in-line applications of NIR and Raman spectroscopy to monitor a pharmaceutical manufacturing process generate a large amount of spectra data. Chemometric techniques are required to explain the variation in the data and to extract useful process information leading to process understanding and conclusions. Spectral pretreatment before chemometric analysis is often desired to reduce the effect of interfering variance in which one is not interested, thereby increasing the part of the variance due to parameters of interest. Although it is true that the modeling process in multivariate calibration may accommodate for interferences and irrelevant artefacts, careful data pretreatment often turns out to be more effective. General guidelines on how to preprocess data are hard to give since this depends on the very specific application needed, such as the nature of the samples and spectroscopic instrument (Vandeginste et al., 1998). Common interfering factors include light scattering, path length variations, fluorescence, and random noise resulting from variable physical sample properties or instrumental effects. Careful selection of data pretreatments can significantly improve the model performance, the most commonly used methods are standard normal variates (SNV),(Wu et al., 1995), Multiplicative Scatter Correction (MSC)
Both NIR and Raman are secondary methods, meaning calibration is required to relate the spectra signal to the reference method. Although the models can be developed with relatively limited efforts, measurements of the CQAs by reference techniques are still required for calibration model development. Under such circumstances, a technique that can offer efficient and direct measurement of the CQAs, without the need of a calibration step, is extremely favorable. Terahertz spectroscopy is a great candidate to meet the demands. The technique was not originally adopted by pharmaceutical industry, until the development of modern terahertz spectrometers that take advantage of novel semiconductor sources and detectors (Chan et al., 2007; Kindt and Schmuttenmaer, 1996; Lu et al., 1998). Ultrafast femtosecond lasers and semiconductors are employed to generate and detect short pulses of broadband terahertz radiation. The greater radiation powers and higher detection sensitivity of semiconductor-based terahertz spectrometers provide superior spectral results and performance (Schneider et al., 2006). The terahertz region of the electromagnetic spectrum spans the frequency range between the mid-infrared and the microwave. (Maurer and Leuenberger, 2009) The center portion of terahertz region is between 0.1 to 4 THz (wavelength from 0.075 to 3 mm). It primarily has been investigated for its ability to characterize crystalline properties of solid materials (Ikeda et al., 2010; Strachan et al., 2004; Taday, 2004), due to its absorption features dominated by collective phonon modes. Besides this application, the low frequency radiation allows high penetration depth in solid samples, sometimes can penetrate materials that are opaque to other spectral frequencies (Shen, 2011). The unique transmission properties allow for non-invasive analysis and detection in various fields such as
polymer manufacturing, material characterization and quality assurance in pharmaceutical industry.

Terahertz hyperspectral imaging (THI) finds its particular importance in characterizing pharmaceutical coating quality in the recent few years (Brock et al., 2012; Fitzgerald et al., 2005; Haaser et al., 2013a; Haaser et al., 2013b; Ho et al., 2008, 2009b; Ho et al., 2007; Maurer and Leuenberger, 2009; Shen, 2011). Many pharmaceutical coating materials are transparent or semitransparent to the terahertz pulse. Because the macroscopic structure in the coating is much less than the radiation wavelength, the insignificant scattering effect allows the terahertz wave to penetrate deeper in solid samples. At each interface with a change in refractive indices, a portion of the terahertz wave is reflected to the detector, generating a time-domain terahertz spectrum. Compared to a reference signal with specular mirror reflectance, the time delay of the measured signal was due to the traveling of terahertz wave through samples and between instrumental optics and electronics. According to the fundamental mechanism of thickness measurement, Terahertz method has been perceived as a direct method that provides non-destructive and rapid coating thickness measurement (Knop and Kleinebudde, 2013).

1.3.4 Design Space, Edge of Failure, and Process Capability

Quality by Design (QbD) principles have been introduced to the pharmaceutical industry by the FDA, and their implementation has been the object of specific guidelines by the ICH. QbD has been defined as “a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control based on sound science and quality risk management”. Information from pharmaceutical development studies is a basis for quality risk management. It introduces the concept that quality of pharmaceutical products cannot be tested, instead it should be built in by design.
The concept of design space has gained prominence as an effective tool for implementation of QbD. It is defined as a multidimensional combination and interaction of input variables (e.g., material attributes and process parameters) that have been demonstrated to provide assurance of quality (FDA, 2009). A pharmaceutical design space is generally considered to be the area where process parameters can be safely executed to achieve all CQAs and associated product specifications. The establishment of design space is supported by the additional knowledge gained by the changes in formulation and manufacturing processes during development and life-cycle management. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process.

The development of design space for pharmaceutical development has been reported in several works (Fahmy et al., 2012; Kristan and Horvat, 2012; Zacour et al., 2012b). Although the design space was initially conceptualized in context of pharmaceutical product quality, it has expanded the utility to serve understanding the relations of process, product quality, analytical methods, and even clinical properties (Bhatia et al., 2016; Furlanetto et al., 2013; Kristan and Horvat, 2012).

Various analyses, including statistical modeling based on multifactorial design of experiment (DOE), setpoint and optimization studies, are used to establish a design space (Little, 2014). Sometimes, however, design space alone is misleading because it represents an average of the extrapolation of the response surface. The mean response may be safe, but the individual batches may experience high failure rates. Therefore, a reliable design space requires supporting analysis to assure regulatory the setpoints within the design space will have high success rates. Edge of failure and process capability analysis are needed (Little, 2014). Edge of failure is an
important addition to the design space, and defined as the point in the design space where individual batches will fail the specifications. Although the regulatory does not consider the edge of failure as a necessary element of establishing a design space, it is helpful to obtain a certain level of confidence that applied to the entire design space. (FDA, 2009) Edge of failure can be determined experimentally by exploring the design space until failures are found, or by simulating the extrapolated design space even though failures were not experimentally detected. The first way is extraordinarily expensive and time consuming and not required by the health authorities. The second way is much more practical and a simple extension of the design optimization and setpoint selection. The discovered edge of failure is often used to determine the design margin and evaluate process capability.

Process capability is a measure of the ability of the process to produce product that meets all CQAs and acceptance criteria. The concept of process capability can also be defined in statistical terms. Capability indices have been developed to mathematically illustrate the measurement of process capability. Statistical measurements of $C_p$ and $C_{pk}$ are often used to determine whether the process, given its natural variation, is capable of meeting established specifications. They are calculated by,

\[
C_p = \frac{USL-LSL}{6s}\tag{1.2}
\]

\[
C_{pk} = \min\left(\frac{USL-\mu}{3s}, \frac{\mu-LSL}{3s}\right)\tag{1.3}
\]

where $USL$ and $LSL$ are desired upper and lower specification limits of the investigated CQAs, $\mu$ and $s$ are the mean and standard deviation measured in experiments. $C_p$ measures how close a process is running to its specification limits, relative to the natural variability of the process. The larger the index, the less likely it is that any product will be outside the specifications. $C_{pk}$ is an
adjustment of $C_p$ for the effect of non-centered distribution. $C_{pk}$ measures how close the products of a process to its target, and how consistent the products are to their average performance. A high $C_p$ does not necessarily imply a high $C_{pk}$ because the average of the product quality may be towards one of the specification limits. Figure 1.6 graphically portrays the difference. Figure 1.6 (A) shows the effect of process variability on the capability indices. The two processes having their own $C_p$ equals to $C_{pk}$, because the averages of the productions (the distribution of a quality attribute) match the center target of the specifications. However, the $C_{p,A}$ and $C_{pk,A}$ of process A is smaller than process B ($C_{p,B}$ and $C_{pk,B}$) because of its greater variation. The effect of deviation from the center target is shown in Figure 1.6 (B). Process C has the same variation as Process A, but its average is closer to USL, causing a lower $C_{pk,C}$. 
Figure 1.6 Illustration of process capability indices. A: Effect of the variation of the distribution; B: Effect of the deviation from the center limit.

1.4 Summary

Well-developed controls of pharmaceutical manufacturing are necessary to ensure product quality. The dissertation aims to improve the process capability for pharmaceutical batch processing using alternative control strategy. The challenges of controlling the fluidized bed coating process discussed in this chapter made it an appropriate model system to demonstrate the development of the control strategy. This work proposed a hybrid control system for the fluidized bed coating process as a demonstration of developing an alternative control strategy. The hybrid control system consists of three elements, process manipulation, monitoring, and optimization.
Process manipulation method can be established using first principle control approach. The theory of EEF is hypothesized to reduce the susceptibility of a pellet coating process to the variation in ambient humidity by maintaining a consistent drying environment. Empirical analytical models enable real time process monitoring of the CQAs, which allow unbiased and consistent process adjustment and endpoint determination. Process optimization is achievable via the development of operation space, which is expected to increase the confidence of meeting the desired specifications. The completion of the hybrid control system is expected to improve the process capability for the investigated fluidized bed pellet coating process.
Chapter 2: Establish Process Manipulation Method based on First Principle Control

2.1 Introduction

An effective method to manipulate a process is a prerequisite for developing any process control system. Regardless of what type of control is employed, a mechanism to change the process trajectory is required for successful operation. Therefore, establishing a valid process manipulation method is the very first and crucial step for developing a desirable process control strategy.

Control of the coating process requires careful manipulation of the process parameters. Coating, in general, is a challenging process suffering from high risk of batch failures. A failure in coating typically causes the loss of the entire batch. Because coating is often used towards the end of a solid product manufacturing, a batch failure entails the waste of all processed materials and cumulative capital investment. There are many failure modes for the coating process: the most serious problem in pellet coating is agglomeration.

In a coating process, wetting and drying are key physical phenomena (Maronga, 1998). Wetting begins with the droplets of coating liquid impinge on the substrate. Drying evaporates the solvent and leaves the solid content of the droplets on the surface. An excessive drying rate produces fines and leads to elutriation. On the other hand, an insufficient drying rate enhances the chances of forming agglomerates (Maa et al., 1996). The strong liquid and/or solid bridges formed between pellets make it extremely difficult, if not impossible, to break and bring them back to individual pellets. Under certain circumstances, the agglomerates grow rapidly and lead to defluidization and batch collapse.

Manual process operation, referred to as basic control in this work, is the conventional approach to manipulate the pellet coating process. When basic control is used, acceptable process
conditions are usually found through trial and error and are often held constant for future batch production. Desirable coating results can be achieved by operating the process in a suitable drying environment. However, it is not always easy to consistently maintain the process within the range of a desired drying environment, because the drying capacity is often susceptible to the variation in ambient humidity.

A rational way to control the pellet coating is to set conditions that minimize the risk of forming agglomerates. This requires the process to be operated under appropriate conditions. The work in this chapter proposes to develop a process manipulation strategy based on first principle control. The purpose was to provide a steady drying environment that is less susceptible to the variation of ambient humidity, thereby improving the process robustness and reducing pellet coating batch failure.

An environmental equivalency factor (EEF) (Ebey, 1987), premised on simultaneous heat and mass transfers (Crank, 1975), was used to develop the first principle control. During a drying process, the inlet air supplies energy for the solvent vaporization via heat convection. The driving force of the heat transfer is the temperature difference between the inlet air and the pellet. The vaporized solvent is transported to the air stream via mass convection. The difference in vapor partial pressure determines the mass transfer rate. The EEF theory considers the thermodynamic environment of the process is unchanged as long as the same relationship is maintained between the heat and mass transfers.

Based on the first principle understanding of the physical phenomena, an EEF is calculated by consolidating process parameters relevant to the heat and mass transfers to a single value. The EEF is used to indicate and regulate a drying environment. This work is predicated on the
hypothesis that an adequate drying environment deduced from the validated process settings of basic control, consistently controlled by EEF, produces desirable and reproducible coating result.

Near-Infrared (NIR) spectroscopy provides information that comes from overtones of molecular vibrations. Because molecules differ in their vibrations, and hence in their vibrational overtone spectra, the NIR region is valuable in characterizing chemical attributes (Andersson et al., 1999). Historically, the first two quantitative NIR measurements were the determinations of atmospheric moisture and water content in gelatin (Burns and Ciurczak, 2001). Owing to its high sensitivity to water, a diffuse reflectance NIR spectroscopy was utilized to evaluate the effect of the proposed method of controlling the drying environment.

The goals of this study were to (1) determine acceptable pellet coating conditions for calculating a proper EEF target, (2) develop control algorithms to achieve first principle control and manipulate the process, and (3) examine the effectiveness of the process manipulation method on reducing batch failures. A traditionally difficult aqueous drug layering process was studied as a model process. An automation system was deployed to allow feedback process manipulation.

2.2 Materials and methods

2.2.1 Formulation of Drug Layered Pellets

Pellets (SUGLETS, Colorcon, West Point, PA), made of sucrose and starch, were used as cores for fluidized bed coating. The pellets have a diameter range of 1000-1200 μm and were coated with a drug suspension. The formulation of the drug suspension is listed in Table 2.1. Polymer solution was prepared by dissolving the desired amount of hypromellose (HPMC, PharmaCoat 606, Shin-Etsu, Japan) to deionized water added with plasticizer PEG 400. The
estimated viscosity was about 60 mPa·s at room temperature. (ShinEtsu) The model drug acetaminophen (APAP) was mixed with the polymer solution prepared ahead of time for 24 hours before each experiment.

Table 2.1 Formulation of the drug suspension.

<table>
<thead>
<tr>
<th>Components</th>
<th>Concentration (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APAP</td>
<td>10.00%</td>
</tr>
<tr>
<td>HPMC</td>
<td>6.00%</td>
</tr>
<tr>
<td>PEG 400</td>
<td>1.50%</td>
</tr>
<tr>
<td>Deionized water</td>
<td>82.50%</td>
</tr>
</tbody>
</table>

2.2.2. Fluidized Bed System and Spectroscopic Data Collection

Fluidized bed coating was performed using a Diosna Minilab (Dierks & Sohne GmbH, Osnabruck, Germany) fitted with a 7 L insert. A schematic diagram of the fluidized bed system with incorporated process measurements is illustrated in Figure 2.1. The filter house consisted of four filter bags, which were cleared using a back pressure pulse every 60 s at 30 psi for all experiments. The coating liquid was applied to the system by a peristaltic pump, and the atomized droplets were formed by a two-phase pneumatic nozzle. The system contained an internal EGE-Electronik series LN/LG air flow sensor (Spezial-Sensoren GmbH, Gettorf, Germany) to measure volumetric airflow velocity in the inlet air pipe. An electrical heater adjacent to the air pipe was used to heat the inlet air before entering the system. Three internal thermocouples measured temperature of the heated air, product temperature, and outlet air. Two temperature/humidity transmitters (series RHL, Dwyer Instruments, Inc., Michigan City, IN) were added to the system to measure the temperature and humidity of the inlet and exhaust air. The process measurements were made at a frequency of 0.1 Hz.
NIR spectra were collected through the side port of the fluidized bed. A model NIR256L-2.2T2 diffuse reflectance spectrometer (Control Development Inc., South Bend, IN) was used. It was a 256-element photodiode array spectrometer with an extended InGaAs detector. The NIR spectrum had a range of 1085-2229 nm. An external halogen light source (HL-2000, Control Development Inc., South Bend, IN) was used with a reflectance fiber optic probe (Control Development Inc., South Bend, IN). The integration time was experimentally determined before each batch, by calibrating using a Teflon reference sample. The integration time for NIR measurement was usually in a range of 13 – 17 ms, depending on the warm-up time of the light source. NIR data collection frequency was set at 0.2 Hz with an average of 16 co-adds per spectrum.

Figure 2.1 Fluidized bed system with process and spectral measurements.
2.2.3 Automation System

In this study, two control systems were investigated. The control commands were executed using a closed-loop automation. Figure 2.2 displays an overall structure of the system. The analog signal generated by the fluidized bed was collected and sent to an open platform communication system (OPC): DeltaV (V 9.7, Emerson, MO). The DeltaV system had hardware I/O modules (M-series, Emerson, MO) supporting analog, discrete, thermocouple, resistance temperature detector (RTD) inputs. SynTQ (V3.5, Optimal, UK) is a real time data management system where control commands, process and analytical models are implemented (Figure 2.2 blue squares). It communicated with DeltaV to access the data of the fluidized bed. All of the process measurements (process parameters and spectra data) and model predictions are synchronized to a fixed cycle, so that the measurements for a given cycle can be compared. The fluidized bed drug layering process consisted of four phases, including preheating (phase 1), spraying (phase 2), drying (phase 3), and cooling (phase 4). Detailed control commands and process models of each phase were written in orchestration programs stored in SynTQ. The control commands determined the process trajectory, while the process models provided process settings. Constant process settings were used to operate the process when the basic control was used. On the other hand, when the first principle control was in use, a different process model in the spraying phase (red dashed line) was executed. In this case, an EEF value was calculated for each cycle, and used to change the process settings. The details are discussed in section 2.2.5. At the end of each synchronization cycle, SynTQ set the new process settings to the fluidized bed via DeltaV.
2.2.4 Basic Control

The process parameters of the fluidized bed system are listed in Table 2.2. Although all process parameters are measurable, there is a distinction between manipulated parameters and measured parameters. Manipulated parameters are adjustable, whereas measured parameters are only measurable. The air flow velocity (AF), inlet air temperature (IT) and spray rate (SR) were in automatic control, because their setpoints were changed using DeltaV. The atomization pressure (AP) was not included in the automated system, and therefore had to be changed manually.

Appropriate process settings for each coating phase were experimentally determined by accommodating two criteria: (1) successful operations for three consecutive batches, and (2) less than 1% (w/w) agglomeration rate determined by sieve analysis (mesh opening of 2.38 mm). The initial experiments for finding acceptable process condition were conducted at ambient relative humidity (RH) range of 10-20%.
Table 2.2 Process parameters of the fluidized bed system.

<table>
<thead>
<tr>
<th>Types of parameter</th>
<th>Names of parameter</th>
<th>Types of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manipulated parameters</td>
<td>Air flow velocity</td>
<td>Automatic control</td>
</tr>
<tr>
<td></td>
<td>Inlet air temperature</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spray rate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atomization pressure</td>
<td>Manual control</td>
</tr>
<tr>
<td>Measured parameters</td>
<td>Product temperature</td>
<td>No direct control</td>
</tr>
<tr>
<td></td>
<td>Ambient air temperature</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exhaust air temperature</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ambient air relative humidity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exhaust air relative humidity</td>
<td></td>
</tr>
</tbody>
</table>

2.2.5 First Principle Control

An EEF target value was required to establish the first principle control. Acceptable process setpoints discovered in the basic control with associated process parameters were used in the calculation of EEF. The equation used for the calculation is,

\[
EEF = \frac{M \left( \frac{P_w}{RT_w} - \frac{P_\infty}{RT_\infty} \right) h_{fg}}{\rho_{air} C_p (T_\infty - T_b)} \tag{2.1}
\]

Here \(M\) is molar mass of water, \(R\) is gas constant; \(\rho_{air}\) and \(C_p\) are the density and specific heat capacity of the heated inlet air. \(P_\infty\) is the partial vapor pressure of the inlet air, and \(P_w\) represents the partial vapor pressure near the wet surface of the pellets; \(T_w\) and \(T_b\) are wet-bulb temperature and product temperature of the pellets; \(h_{fg}\) is the specific enthalpy change of water evaporation.

The derivations can be found in Ebey’s original work (Ebey, 1987). The EEF target was subsequently used to design a feedback control system, which is displayed in Figure 2.3. Two control algorithms, univariate and Simplex, were designed and used as controllers for implementing the first principle control approaches. The algorithms provided the fluidized bed with control inputs, which were new setpoints for the manipulated parameters. A new EEF value was calculated based on the updated process parameters using Eq. (2.1), and was compared with
the EEF target to estimate the control error. The control error guided the algorithms to calculate new setpoints for operating the fluidized bed. The EEF values were expected to be controlled at the target by using an effective control algorithm.

![Diagram of the feedback loop of the first principle control](image)

**Figure 2.3 Feedback loop of the first principle control**

### 2.2.5.1 Univariate Control Algorithm

Univariate control is a single variable control system with one input and one output (Koivo and Tanttu, 1991). In the investigated system, the control input was one of the manipulated parameters (AF, IT and SR), and the output was the EEF calculated during the process. The manipulated parameters can be adjusted to control the process by comparing the EEF output with the target value. Each manipulated parameter was confined to a predefined range, out of the concern for equipment and operation safety. IT and AF were allowed to change in the ranges of 40-80 °C and 30-75 m³/h, respectively. The range of SR was set 4-15 g/min. The desired setpoint of each manipulated parameter can be calculated by a transformed equation of Eq. (2.1). An example of calculating the IT setpoint is by,
\[ T_\infty = \frac{(T_wT_bR\cdot EEG\cdot \rho_{air}\cdot C_p + M\cdot P_w h_{fg}) + \sqrt{(T_wT_bR\cdot EEG\cdot \rho_{air}\cdot C_p + M\cdot P_w h_{fg})^2 - 4\cdot (T_wR\cdot EEG\cdot \rho_{air}\cdot C_p)(M\cdot T_w\cdot \rho_{air}\cdot h_{fg})}}{2\cdot T_wR\cdot EEG\cdot \rho_{air}\cdot C_p} \] 
Eq. (2.2)

In the equation above, all the terms on the right side are known, whereas the left side \( T_\infty \) is the unknown IT setpoint that needs to be solved. The calculated setpoint was updated at a frequency of 0.1 Hz to manipulate the process.

2.2.5.2 Simplex Control Algorithm

Simplex control was developed by integrating the concept of Multi-Input Multi-Output (MIMO) (Koivo and Tanttu, 1991) and design of experiment (DOE). In this system, all of the three manipulated parameters were control inputs, and also treated as factors in a DOE. The DOE was used to study the relations of the control inputs and identify the optimum setpoints of each manipulated parameter. A Simplex-Lattice design was chosen for its efficiency to study the effects of three factors at multiple levels (Giles et al., 2005). In the DOE, each manipulated parameter had 10 levels spanning their operable ranges. A combination of the setpoints of the manipulated parameters was regarded as an experimental design point, which was illustrated by the blue dots in Figure 2.4.
Figure 2. 4 Simplex-Lattice design of experiments.

The combinations of the setpoints generated by the DOE are listed in Table 2.3. An EEF value was calculated using each combination of the setpoints with other process parameters measured during the process. All of the EEF values at each cycle were compared with the target to calculate the control error. The combination of the setpoints producing the lowest control error was identified as the optimum process settings and used to manipulate the process. The first principle control using the Simplex-Lattice DOE is abbreviated as *Simplex control* in this dissertation.
Table 2. 3 Combinations of the setpoints generated by the Simplex-Lattice DOE

<table>
<thead>
<tr>
<th>Design point</th>
<th>AF (m$^3$/h)</th>
<th>IT (°C)</th>
<th>SR (g/min)</th>
<th>Design point</th>
<th>AF (m$^3$/h)</th>
<th>IT (°C)</th>
<th>SR (g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39.0</td>
<td>72.0</td>
<td>5.1</td>
<td>34</td>
<td>51.0</td>
<td>48.0</td>
<td>8.4</td>
</tr>
<tr>
<td>2</td>
<td>35.0</td>
<td>60.0</td>
<td>9.5</td>
<td>35</td>
<td>39.0</td>
<td>68.0</td>
<td>6.2</td>
</tr>
<tr>
<td>3</td>
<td>51.0</td>
<td>64.0</td>
<td>4.0</td>
<td>36</td>
<td>47.0</td>
<td>56.0</td>
<td>7.3</td>
</tr>
<tr>
<td>4</td>
<td>39.0</td>
<td>48.0</td>
<td>11.7</td>
<td>37</td>
<td>63.0</td>
<td>52.0</td>
<td>4.0</td>
</tr>
<tr>
<td>5</td>
<td>43.0</td>
<td>56.0</td>
<td>8.4</td>
<td>38</td>
<td>39.0</td>
<td>44.0</td>
<td>12.8</td>
</tr>
<tr>
<td>6</td>
<td>43.0</td>
<td>52.0</td>
<td>9.5</td>
<td>39</td>
<td>35.0</td>
<td>52.0</td>
<td>11.7</td>
</tr>
<tr>
<td>7</td>
<td>35.0</td>
<td>64.0</td>
<td>8.4</td>
<td>40</td>
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</tr>
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<td>6.2</td>
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<td>7.3</td>
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</tr>
<tr>
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<td>59.0</td>
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<td>8.4</td>
<td>65</td>
<td>55.0</td>
<td>44.0</td>
<td>8.4</td>
</tr>
<tr>
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<td>71.0</td>
<td>44.0</td>
<td>4.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.2.6 Evaluation of the First Principle Control

The first principle control using EEF was expected to effectively regulate the drying environment. The in-process materials were expected to have similar water content if they were
produced in a similar drying environment. NIR was employed to examine the water content of in-process materials, due to its sensitivity to water and capability of rapid in-line analysis (Burns and Ciurczak, 2001).

Six batches were produced under the ambient conditions displayed in Table 2.4. Batches 1, 4, and 5 were operated using basic control, whereas the rest were by Simplex control. Note, the decrease of RH along with the sequence of batch production resulted from the time of year at which experiments were performed. Batches 1 and 2 were manufactured in summer (July), batch 3 and 4 were in fall (September), and batch 5 and 6 were in winter (January).

The NIR spectra for the spraying phase of each batch were analyzed by principal component analysis (PCA). Batches 1 and 2 were used to build the PCA calibration models for the basic control and Simplex control, respectively. The spectra were preprocessed by Standard Normal Variate (SNV) and followed by mean-centering. The purpose was to remove the baseline variation associated with the fluidization, and emphasize on the absorbance change. If the predictions of the test batches are similar to the calibration, the drying environments of the three batches are considered similar.

Table 2.4 The ambient conditions of batches produced using the basic control and Simplex control

<table>
<thead>
<tr>
<th>Control mode</th>
<th>PCA model</th>
<th>Batch number</th>
<th>Ambient RH (%)</th>
<th>Ambient temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic control</td>
<td>Calibration</td>
<td>1</td>
<td>67.8%</td>
<td>20.4</td>
</tr>
<tr>
<td></td>
<td>Test</td>
<td>4</td>
<td>24.0%</td>
<td>21.1</td>
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<tr>
<td></td>
<td></td>
<td>5</td>
<td>16.6%</td>
<td>21.7</td>
</tr>
<tr>
<td>First principle control</td>
<td>Calibration</td>
<td>2</td>
<td>72.8%</td>
<td>20.2</td>
</tr>
<tr>
<td></td>
<td>Test</td>
<td>3</td>
<td>26.5%</td>
<td>22.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>10.5%</td>
<td>19.8</td>
</tr>
</tbody>
</table>
2.3 Results and discussion

2.3.1 Basic Control and Calculation of EEF

The acceptable process settings were discovered for the basic control. Figure 2.5 (A) shows a typical process trajectory operated using the settings listed in Table 2.5. The greater variation observed in AF (blue) than IT (red) was attributed to the pressure drop of the fluidized bed system for cleaning the filter house. Product temperature (PT) was indicated by green circles and observed in a range of 35-40 °C throughout the process at steady state, indicating the stability of the process (Larsen et al., 2003; Lorck et al., 1997a; Wesdyk et al., 1990). Note that the acceptable batches were all produced in winter under similar ambient conditions: temperature range 19-21 °C and RH of 10-20%. However, the discovered process settings were found non-operational when they were applied to the processes produced in a different season. Four batch failures, resulted from wet quenching, were obtained in a total of 13 batches produced during the fall. The batch failures all occurred at the RH greater than 60%. The result was attributed to the susceptibility of the drying capacity to the variation in ambient humidity. Because the basic control did not have a control mechanism to compensate for the change in ambient humidity, its drying capacity was only determined by the humidity ratio of the inlet air.

Table 2.5 Process setpoints for the drug layering process using basic control.

<table>
<thead>
<tr>
<th>Process setpoints</th>
<th>Preheating</th>
<th>Spraying</th>
<th>Drying</th>
<th>Cooling</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF (m³/h)</td>
<td>40</td>
<td>50</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>IT (°C)</td>
<td>55</td>
<td>60</td>
<td>65</td>
<td>21</td>
</tr>
<tr>
<td>SR (g/min)</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AP (bar)</td>
<td>0</td>
<td>1.6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
The EEF values were calculated using the measured process parameters. Note, the EEF was used to describe the drying environment for the coating process, and therefore it was only calculated for the spraying phase. The calculated EEF values of the process shown in Figure 2.5 (A) were presented in Figure 2.5 (B). The observed fluctuations were due to the common cause process variance. A mean EEF of 0.64 with a standard deviation (SD) of 0.05 were obtained from six batches produced under the basic control. The EEF of 0.64 was used as the target value for developing the first principle control in subsequent studies.

2.3.2 First Principle Control Algorithm

Control algorithms of univariate and Simplex were developed to implement the first principle control approaches. A typical process manipulated by univariate control is shown in Figure 2.6. The example used IT as the control input. The IT setpoints were calculated by Eq. (2.2), and are highlighted in red circles. The measured IT (yellow triangles) display random oscillations around the setpoints. The deviations were attributed to the inherent variability of the heater. A
variation of 6 °C was observed even when the IT setpoint was held constant. The variation resulted from the latency of the heating system. The heater used a binary switch, which was turned either fully on or fully off. It took approximately 30 s to heat or cool the inlet air to the desired temperature. The deviation is expected to be inhibited by using a heating system with reduced latency.

Figure 2. 6 Univariate control using inlet air temperature.

Hypothetically, univariate control can also be achieved by manipulating AF or SR. The effects of each manipulated parameter on the EEF calculation are shown in Figure 2.7. The relationships were obtained by changing one manipulated parameter while maintaining all other process parameters at constant. Increasing IT and/or AF decrease EEF and therefore lead to a greater drying capacity. In contrary, increase of SR causes an increased EEF and lowers the drying
capacity. Nevertheless, the desired AF setpoints often exceeded its operable limit due to its relatively weak influence on the drying environment as evidenced by Figure 2.7. On the other hand, a slight change in SR exerted a tremendous impact on the thermodynamic environment, due to the high latent heat of vaporization of water. Although conceptually possible, it was practically difficult to exclusively use AF or SR to develop a univariate control system.

Figure 2.7 Independent effects of IT, AF, and SR on EEF while all other process parameters are constant.
The fluidized bed system had a faster adjustment for AF and SR. A setpoint of AF and SR can be reached in 5 s or less. The fast adjustment of the AF and SR compensated for the latency associated with the IT. This allowed the development of the Simplex control with the goal of improving the operability for controlling the EEF. The Simplex control simultaneously adjusted all the manipulated parameters to operate the process, which can be seen in Figure 2.8. The results were obtained from three batches differentiated in colors. Despite the significant changes in the setpoints of each manipulated parameter, the EEF outputs of all the three batches are normally distributed (Figure 2.9). The mean of EEF outputs (0.66) is effectively controlled at the EEF target (0.64).
Figure 2. 8 Setpoints of manipulated parameters commanded by Simplex control. From top to bottom: setpoints of air flow; inlet air temperature; spray rate.
It was hypothesized that the Simplex control would improve the operability of controlling the EEF compared to the univariate control. The control errors of the univariate and Simplex control are overlaid in Figure 2.10. The Simplex control (green) had a lower variation (SD = 0.051) than the univariate control (red) (SD = 0.086), indicating a more precise control of the EEF and therefore supported the hypothesis. The errors of the univariate control appear bi-normally distributed. The control accuracy of the EEF was highly dependent on whether the manipulated parameters can be precisely maintained at their setpoints. However, the intrinsic over-shooting and over-cooling problems of the heating system lead to a significant bias in IT, which was propagated to the calculation of the EEF outputs. This may explain the observed bi-normal distribution.
2.3.3 Comparison of the Drying Environment Between Basic Control and Simplex Control

A significant difference in the drying environment was found when the basic control was used. The PCA scores of NIR of batches 4 and 5, though operated under the same process conditions of batch 1, are on the outside of the confidence interval defined by the PCA calibration (Figure 2.11 (A)). The Q residual contribution plot is often used to identify the sources of model uncaptured variance. Extraordinary contributions from the regions of 1400-1500 nm and 1900-1950 nm were observed; the Q residuals of the test batches are approximately 10 times larger than
that of the calibration batch (Figure 2.11 (B)). These wavelength ranges, characteristic of O-H first overtone and combination bands, are typical fingerprint regions indicating water absorption. A new PCA model was calculated by excluding the water-characteristic regions. After the truncation, the scores of the test batches were similar to the calibration (Figure 2.11 (C)). Further examination of the Q contribution plot shows the uncaptured variance is mainly from 1600-1800 nm (Figure 2.11 (D)), characteristic of the first overtone of C-H, C-H\textsubscript{2}, C-H\textsubscript{3}, and Ar-CH. The uncaptured variance was speculated to be due to the between-batch variation of the drug content.

In contrast, the batches produced by the Simplex control did not demonstrate the variability in water content observed in the basic control batches. The PCA calibration model was built with full NIR spectrum. The pattern of the PCA scores of the test batches are very close to the calibration (Figure 2.11 (E)), indicating the NIR spectra of the in-process materials across the three batches were similar. The Q residuals of all three batches are similar (Figure 2.11 (F)). However, it should be noted that the PCA calibration of the Simplex control captured significantly less total variance (X-variance of 84.7%) compared to the basic control (X-variance of 95.4%). This can be explained by the difference in the process manipulation. The basic control used the same process settings, and therefore the variation carried in NIR spectra was primarily associated with the increase of APAP. Unlike the basic control, constantly changed process settings were executed by the Simplex control. The frequent changes in air flow velocity and liquid addition rate may have complex impacts on the NIR spectra. The fluidization bubbles formed at different air flow velocity have varied size and distribution, which may affect the path lengths of NIR reflectance. The change in liquid addition rate lead to significant difference in NIR absorbance because the coating material and water were applied at inconsistent speed. The additional variation resulted from the process manipulation lead to a more challenging interpretation of the PCA result.
More importantly, the Simplex control effectively eliminated the batch failures. Four batch failures were observed in a total of 13 batches produced using the basic control. Even the successful batches gave a broad EEF range of 0.40-0.85, indicating significant variability of the drying environment produced using the basic control. The four batch failures were caused by defluidization associated with wet-quenching and all occurred at RH greater than 65%. In contrary, no batch collapse was observed in the 32 drug layering batches manipulated by the Simplex control. The Simplex control gave an average EEF of 0.66 for batches manufactured at a RH range of 8-75%. The between-batch RSD of the mean EEF was 2.69% The results indicate the Simplex control successfully reduced the batch failures by maintaining a consistent drying environment.
Figure 2. 11 PCA of NIR data collected during spraying phase. A-B: NIR of basic control with full spectrum; C-D: NIR of basic control after variable truncation; E-F: NIR of Simplex control.
2.4 Conclusion

The development of the first principle control (Simplex control) has achieved the goal of reducing batch failure and improving process robustness against the variation of ambient humidity. Acceptable process settings of the investigated process under the basic control were determined. However, the basic control failed to ensure the long-term success of the process. Several batch failures resulted from wet quenching; these were observed when the coating process was manipulated using the same settings but in a different season. The failure of using the basic control was attributed to the susceptibility of the drying capacity to the variation in ambient humidity.

In the first principle control approach, the traditional process settings were replaced by EEF setpoint. An average EEF of 0.64 was acquired from six successful batches operated under the basic control, and used as the process target for process operation. Univariate and Simplex control algorithms were designed to execute process manipulation. The univariate algorithm only used IT to adjust the process to reach the EEF target. The Simplex algorithm was further established by adjusting three manipulated parameters simultaneously to improve control efficiency and accuracy of maintaining an EEF target. Despite the process settings changing continuously, the EEF outputs were normally distributed with the mean effectively controlled at the target value of 0.64. A further comparison between the two control algorithms revealed that Simplex had lower control errors and variance. Therefore, the Simplex algorithm was implemented in the first principle control system.

The effect of the Simplex control on maintaining a constant drying environment was examined by PCA analysis of in-line NIR spectra. The PCA model showed a significant difference between the batches produced using the basic control. The model-unexplained spectral variance was attributed to the variation of the water content of the in-process materials during coating. In
contrast, the three batches of Simplex control had similar spectral properties across all batches as evident from the PCA analysis. No extraordinary source contributing to the Q residual was identified. In subsequent studies, the Simplex control produced 32 successful batches without a single batch failure, as opposed to the basic control which had a failure rate of approximately 30%.
Chapter 3: Develop Empirical Analytical Models for Process Monitoring of Pellet Coating

3.1 Introduction

The work in chapter 2 successfully addressed the issues previously encountered in the operation of drug layering process. The Simplex algorithm controlled the EEF effectively at its target value to provide a consistent drying environment. It succeeded in maintaining the process in a state of control and eliminating batch failure. Nevertheless, the Simplex determined the process endpoint by applying a fixed amount of coating liquid across all the batches. This conventional method for determining the process endpoint ignored the process variation in coating efficiency, therefore may compromise the consistency of product quality.

An in-line process monitoring system is desired to ensure the product quality. By developing real time quantitative analysis, the CQA can be monitored in real time and used to feedback the control system to determine the process endpoint when the desired quality specifications are met. Establishing such process monitoring system requires a potential analytical technique to provide rapid and non-destructive measurement while able to be incorporated in a process stream.

Near-Infrared (NIR) and Raman spectroscopy are increasingly used in the pharmaceutical industry. They have been successfully applied to determine the quality attributes of coating products (Andersson et al., 1999; B.R. Buchana et al., 1996; Kirsch and Drennen, 1995). The most prominent absorption bands in the NIR region are related to the overtones and combinations of fundamental vibrations of C-H, N-H, O-H and S-H functional groups (Burns and Ciurczak, 2001). Raman spectroscopy is sensitive to the conjugated double bonds, aromatic rings and other characteristics of chemical structures present in most active substances (Neuberger and Neususs,
Both techniques offer efficient and non-destructive measurement with minimal sample preparations. Given the advantages provided by the two techniques, NIR and Raman spectroscopy were considered as suitable techniques for developing the process monitoring system.

Both NIR and Raman are indirect methods. Empirical modeling is required to calibrate the NIR and Raman spectra to the reference measurements. The calibration model is subsequently used to predict the CQAs to achieve quantitative analysis. Therefore, the work in this chapter focused on developing empirical analytical models using NIR and Raman spectroscopy to achieve process monitoring of the drug layering process. The goals of this study were to (1) build preliminary empirical analytical models using NIR and Raman spectroscopy, (2) select a more suitable technique based on the performance of the models and develop robust empirical models, and (3) apply the robust model to monitor the drug layering process and examine its capability for ensuring product quality.

3.2 Materials and Methods

3.2.1 Drug layering Process and Sample Collection

The formulation of the drug layering pellets, fluidized bed system, and process measurement were described in chapter 2. A total of 15 batches were produced in the work of this chapter. The process was operated using the Simplex control. The spraying was terminated when the same amount of drug layering suspension (350 g) was applied. Drug layered pellets were withdrawn from the process during fluidization using a built-in sample thieve at predetermined time point. The samples taken during the spraying phase were used for building empirical analytical models. End product samples were also collected after a complete process, which were used for assessing the model performance.
3.2.2 Drug Content Determination

The drug layered content was determined by the ultraviolet-visible (UV) spectroscopy (HP 8453, Agilent Technology, Santa Clara, CA). Acetaminophen (APAP) standard solutions of five concentrations were prepared (Table 3.1) by dissolving the required amount of APAP in deionized water. Three replicates of each standard solution were scanned at 243 nm, and the mean value of the absorbance was used to calculate the calibration curve. The repeatability of the UV method was assessed to ensure the precision, and expressed as relative standard deviation (RSD). The samples for UV analysis were taken from the drug layering process at predetermined time. Three replicates of each sample were analyzed by the UV method to determine the drug content. Each replicate was weighed at about 400 mg.

Table 3.1 UV method development of APAP.

<table>
<thead>
<tr>
<th>Theoretical Concentration (mg/mL)</th>
<th>Mean Absorbance</th>
<th>Repeatability (RSD)</th>
</tr>
</thead>
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<td>0.001</td>
<td>0.053</td>
<td>0.115%</td>
</tr>
<tr>
<td>0.002</td>
<td>0.119</td>
<td>0.005%</td>
</tr>
<tr>
<td>0.003</td>
<td>0.205</td>
<td>0.064%</td>
</tr>
<tr>
<td>0.010</td>
<td>0.626</td>
<td>0.062%</td>
</tr>
<tr>
<td>0.014</td>
<td>0.862</td>
<td>0.065%</td>
</tr>
</tbody>
</table>

3.2.3 In-line Spectroscopic Data Collection

The NIR measurement and data collection were described in chapter 2 (section 2.2.2). The Raman spectra were collected using a RXN2 Hybrid analyzer (Kaiser Optical Systems, Ann Arbor, MI) with a thermoelectrically cooled charge-coupled detector. A schematic diagram of the Raman sensor setup from side view is shown in Figure 3.1 (A). The laser source was operated at 785 nm with a laser power of 600 mW. The spectrometer was equipped with a non-contact optic sampling device (PhAT probe). The excitation light passing through the optical fibers is collimated by a lens
and imaged onto the sample to form a circular illumination area of 6 mm diameter. The PhAT probe was attached to the exterior observation window, where the probe was covered by aluminum foil to prevent laser exposure (Figure 3.1 (B)). The Raman data were collected at a frequency of 0.2 Hz with an exposure time of 3 s. The Raman spectrum had a wavenumber range of 150-1890 cm\(^{-1}\) and spectral resolution of 1 cm\(^{-1}\) increment. Note, both NIR and Raman spectra were collected from the batches produced using the Simplex control.

![Figure 3.1 Setup of Raman data collection. A: Side-view, B: Laser exposure prevention.](image)

3.2.4 Empirical Model Development

Empirical analytical models using spectroscopy were established by relating the spectra to the reference values using partial-least-squares (PLS) regression. The reference values were results obtained using UV analysis. The mathematical computation was performed using MatLab (R2014b, The Mathworks Inc., Natick, MA) and PLS_Toolbox (Eigenvector Research Inc., Manson, WA). The empirical analytical models were developed in two steps. First of all,
preliminary NIR and Raman models were built using a small data set. Two batches were used to build a calibration model for each technique, and one batch was used to test the calibration model. Based on the results of the preliminary models, the technique offering greater model performance (calibration and prediction errors) was selected to develop a robust model.

According to ICH Q2, a desirable analytical model is expected to show the reliability of an analysis, with respect to deliberate or expected variations in the method. If the measurements are susceptible to the variations in analytical conditions, the conditions should be suitably controlled. (FDA, 1996) The processes produced by the Simplex control were expected to have greater process variance, because the algorithm simultaneously adjusted the setpoints of all the manipulated parameters, including air flow (AF), inlet air temperature (IT), and spray rate (SR). To make the model robust against the process variance, the batches used for building the calibration model were required to have a greater range of each manipulated parameter. Table 3.2 shows the ranges of the setpoints of all the manipulated parameters. The ranges of AF, IT and SR of the calibration data set are broader than the test and validation.

Table 3.2 Ranges of the process setpoints of calibration, test, and validation

<table>
<thead>
<tr>
<th>Data set</th>
<th>Number of batches</th>
<th>Ranges of the setpoints</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td>AF</td>
</tr>
<tr>
<td>Calibration</td>
<td>6</td>
<td>35.6-69.3 m³/h</td>
</tr>
<tr>
<td>Test</td>
<td>3</td>
<td>40.0-61.8 m³/h</td>
</tr>
<tr>
<td>Validation</td>
<td>3</td>
<td>40.0-58.2 m³/h</td>
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</tbody>
</table>

A total of 96 samples were collected from the 12 batches. Table 3.3 shows the details of the sampling protocols. Batches 1-6 were used for calibration, batches 7-9 were for test, and batches 10-12 were for validation. The samples were taken from each batch at predetermined time,
in an average of every 10 min. The calibration model was built using 24 samples randomly selected from batches 1-6 (highlighted in yellow). Twelve samples were randomly selected for test and validation, which are highlighted by blue (test) and green (validation) in the table.

Table 3. Samples for calibration, test, and validation.

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Batch #</th>
<th>Sampling time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calibration</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Test</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Validation</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>10</td>
</tr>
</tbody>
</table>

End: spraying endpoint when 350g APAP suspension was applied

Various modeling conditions (data preprocessing, variable selection, number of latent variable (LV), etc.) were attempted. The model performance was assessed with respect to the errors of calibration, cross-validation, and prediction. Note, the model input (X) and response (Y) refer to the spectra and drug content, respectively. The calibration error, expressed as the root-mean-square error (RMSE) of calibration (RMSEC), was calculated by Eq. (3.1),

\[
RMSEC = \sqrt{\frac{\sum_{i=1}^{n} (y_i - \hat{y}_i)^2}{n-A-1}}
\]

where \(y_i\) is the drug layering content determined by UV method, \(\hat{y}_i\) is the model prediction by the NIR or Raman model, \(n\) is the number of samples in the calibration, and \(A\) is the number of included LV. The cross-validation was performed by random subset method, and the error (RMSECV) was calculated as,
\[
RMSECV = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \hat{y}_{CV,i})^2}{n}}
\]  
Eq. 3.2

Here \(\hat{y}_{CV,i}\) is the estimate for \(y_i\) based on the calibration equation with sample \(i\) deleted. The calibration model was optimized by minimizing the RMSEC and RMSECV. The prediction error (RMSEP) of the optimized model was obtained by,

\[
RMSEP = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{n}}
\]  
Eq. 3.3

For the development of a robust model, permutation tests were performed to examine risks of overfitting. Permutation tests provide a probability that the given model is significantly different from one built under the same conditions but on random data. Permutated models are repeatedly obtained by relating the model input (X-block) to the responses (Y-blocks) which were randomly reordered (shuffling). For a regression problem, this means each sample is assigned a nominally "incorrect" Y value (although the distribution of Y values is maintained because every sample's Y value is simply reassigned to a different sample). After each permutation of the Y-block, the predictions for each sample by cross-validation and self-prediction (calibration), and the RMSEC and RMSECV are recorded. The shuffling is repeated multiple times and several statistics are calculated for each permutation. The result is reported in two forms: A table of probability of model insignificance, and a plot of fractional sum squared Y (\(SSQ_Y\)) versus Y-block correlation. The \(SSQ_Y\) can be calculated from RMSEC and RMSECV,

\[
SSQ_{Y,C} = 1 - \frac{SSE_{Y,C}}{SSQ_{Y,Total}}
\]  
Eq. (3.4)

where \(SSE_{Y,C}\) is the sum squared error in Y self-prediction (by calibration), \(SSQ_{Y,Total}\) is the total sum squared Y. For cross-validated predictions,

\[
SSQ_{Y,CV} = 1 - \frac{SSE_{Y,CV}}{SSQ_{Y,Total}}
\]  
Eq. (3.5)
The developed robust model was subsequently used to monitor the drug layering process. The spraying phase automatically ended when the predictions of the drug layered content reached the target limit. The target was set at 0.035 (w/w), or 3.50%, which was a ratio of layered drug content over the pellet weight. The drug layered content of the end products was validated using UV method.

3.3 Results and discussion

3.3.1 Preliminary Model Development

The NIR and Raman spectra of pure components in the drug layered samples were examined to compare the selectivity of the techniques. Figure 3.2 (A) displays the Raman spectra of pure components, APAP, HPMC, and core pellet. Note the spectra were normalized and offset for visualization. APAP and core pellet have multiple distinct features as evidenced by the sharp signals observed in the whole Raman region of 150-1700 cm\(^{-1}\). Although dominated by the broad and overlapping features, distinguishable absorbance of APAP is still visible in the region of 1600-1700 nm (Figure 3.2 (B)).

![Figure 3. 2 Pure spectra of APAP, HPMC, and core pellet. A: Raman spectra; B: NIR spectra.](image_url)
The correlation of spectral change and the increase of drug content was investigated for each technique, by comparing the spectra of coated pellets with the pure spectra of APAP and core pellet. Because the amount of APAP was very small compared to the mass of the core pellets, two drug layering batches coated up to 5 hours (approximately corresponding to a drug content of 0.16 (w/w), or 16%, were produced and used for the comparison study. The Raman and NIR spectra of samples coated at a given time are overlaid with their pure spectra and shown in Figure 3.3. The change in Raman spectra (Figure 3.3 (A)) is dominated by the diminished signal of the core pellet. Decreased Raman signal was observed in most of the spectrum regions that are characteristic of the core pellet, particularly at 400 cm$^{-1}$, 443 cm$^{-1}$, 476 cm$^{-1}$, 524-552 cm$^{-1}$, etc. Limited increase of spectra was observed in regions indicating APAP, such as 610 cm$^{-1}$, 800 cm$^{-1}$ and 969 cm$^{-1}$, etc. Although Raman is often deemed having greater selectivity than the NIR (Févotte, 2007), its weak signal of APAP, which was interfered by the core pellet, compromised its advantage.

Unlike Raman, the NIR spectra had a much stronger correlation with the increase of APAP. Significant increase of NIR absorbance was found in the wavelength range of 1600-1700 nm, which is distinctly associated with APAP. The result suggested NIR spectroscopy has much stronger signal and is more sensitive to APAP. Although NIR spectroscopy is often criticized for having less selectivity, it is noteworthy that the selectivity should be concluded by taking into the consideration of the overall formulation system. In the current drug layering system, the NIR spectrum showed distinct APAP spectral features without noticeable interference from other ingredients. Therefore the NIR spectroscopy was considered selective to APAP.
Preliminary Raman and NIR models were calculated and optimized using the methods described in section 3.2.4. The methods and performance results of the preliminary models are displayed in Table 3.4. The NIR model outperformed the Raman model, which was supported by its lower calibration error (RMSEC) and prediction error (RMSEP). The prediction error of NIR model (RMSEP = 6.76%) was similar to its calibration error (RMSEC = 5.68%) and cross-validation error (RMSECV = 7.57%). Note the errors are expressed in percentages by normalizing to the calibration range, this form applies to the whole dissertation. Unlike the NIR method, the RMSEP of Raman (19.71%) was approximately three times higher than the RMSEC (7.43%), indicating a poor prediction performance. Figure 3.4 shows the prediction of Raman model (Figure 3.4 (A)) has a much larger prediction bias (12.86%), as opposed to the limited bias (1.62%) provided by the NIR model (Figure 3.4 (B)).
Table 3.4 Modeling conditions and model performance of preliminary Raman and NIR models.

<table>
<thead>
<tr>
<th>Model development methods</th>
<th>Preliminary comparison</th>
<th>Raman</th>
<th>NIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable selection</td>
<td>250-1862 cm(^{-1})</td>
<td>1085-2225 nm</td>
<td></td>
</tr>
<tr>
<td>Preprocessing</td>
<td>Normalization MSC</td>
<td>First-derivative Mean-center</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean-center</td>
<td>Mean-center</td>
<td></td>
</tr>
<tr>
<td>Number of latent variables</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>RMSEC (w/w)</td>
<td>7.43%</td>
<td>5.68%</td>
<td></td>
</tr>
<tr>
<td>RMSECV (w/w)</td>
<td>8.86%</td>
<td>7.57%</td>
<td></td>
</tr>
<tr>
<td>RMSEP (w/w)</td>
<td>19.71%</td>
<td>6.76%</td>
<td></td>
</tr>
<tr>
<td>Prediction bias</td>
<td>12.86%</td>
<td>1.62%</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3.4 Predictions versus measurements of preliminary models. A: Raman model; B: NIR model.

The preliminary Raman model failed to provide adequate predictions. The Raman calibration model captured reasonable co-variance: X-variance of 96.81% and Y-variance of 92.55%. Nonetheless, the systematic error indicated the Raman calibration model did not capture sufficient batch to batch variance by using data from only two batches. Besides its inherent drawback of weak signal, the result may also be explained by its susceptibility to the variations in process interface. Unlike the way of immersing the NIR probe into the bulk of pellets, the Raman probe was mounted manually to the exterior observation window. The sensor was removed from
the equipment when the process was completed, and reinstalled ahead of time before a new experiment. The PhAT probe has a spot size similar to the width of the observation window, therefore a slight variation of the sensor position may lead to capturing irrelevant information. Moreover, reinstalling the probe may change the angle of the probe and affect the camera focus. Based on the comparison of the preliminary results, NIR spectroscopy was selected to develop a robust model with the purpose of implementing it to the hybrid control system to allow long-term use. It should be noted that the result in the preliminary study did not rule out the possibility of developing adequate Raman method for other systems.

3.3.2 Robust Model Development

The robust NIR model was developed under the modeling conditions: preprocessing the spectra in the wavelength range of 1146-2076 nm by using SNV and mean-centering. The number of LVs included in the model was preliminarily determined based on the plot in Figure 3.5 (A). The minimized RMSEC and RMSECV were obtained when three LVs were included. To confirm the preliminary conclusion, the results of the permutation tests were examined for testing overfitting. The idea is if the selected model conditions are overfitted, they often provide a fit to random data which is better than would be expected. The permutation examines the extent the modeling conditions might be finding "chance correlation" between the X-block and Y-block.

The SSQ plot (Figure 3.5 (B)) shows the fractional Y-variance captured for calibration and cross-validation versus the correlation of the permuted Y-block to the original Y-block. Note the $SSQ_{Y,c}$ and $SSQ_{Y,cv}$ are expected to increase up to a value of “1” when the model is capturing all the Y-block response. The $SSQ_{Y,c}$ and $SSQ_{Y,cv}$ are shown in centered and standardized form, the
perpendicular axis of any model's result indicates how far away from the data mean that point is in standard deviations. In general, the cross-validation and self-prediction (calibration) values should be relatively close to each other, but should be significantly less than the results for the non-permuted Y-block (on the far right side of the plot). The further away the un-permuted results are from the mean, the more unlikely that the original model is overfitted. The standardized $SSQ_Y$ of the un-permuted model indicates the $n$th standard deviation at which the original model can be considered to fall. For a model using three LVs, a standardized $SSQ_{Y,C}$ of 2.06 and $SSQ_{Y,CV}$ of 1.79 were obtained for the calibration and cross-validation, respectively. The two values dropped to 1.62 and 1.19 when the fourth LV was included. The higher the standardized $SSQ_Y$ values, the more likely that the original model is significant and not overfitted.

Figure 3.5 Selection of LVs. A: RMSEC and RMSECV versus number of LVs; B: Permutation plot of sum squared fractional Y-variance captured by the calibration and cross-validation.

The probability table (Table 3.5) shows the probabilities (calculated using several different methods including Wilcoxon and pairwise signed rank test (Thomas, 2003), and randomization t-test (van der Voet, 1994)) that the predictions for the original, unperturbed model could have come
from random chance. Put another way: the probabilities that the established model is not significantly different from one created from randomly shuffling the Y-block. The result is reported as a probability that the models are not distinguishable at the given probability level. Thus a value of 0.05 indicates that the models are indistinguishable at the 5% limit, which is equivalent to saying they are significantly different at the 95% limit. The results of the permutation test probabilities indicated the most significant model was built using three LVs.

Table 3.5 Probability of model insignificance of permutation test.

<table>
<thead>
<tr>
<th>Number of LV</th>
<th>Methods</th>
<th>Wilcoxon</th>
<th>Sign test</th>
<th>Rand t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Self-prediction</td>
<td>0.014</td>
<td>0.073</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>Cross-validated</td>
<td>0.005</td>
<td>0.044</td>
<td>0.009</td>
</tr>
<tr>
<td>3</td>
<td>Self-prediction</td>
<td>0.002</td>
<td>0.016</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>Cross-validated</td>
<td>0.002</td>
<td>0.017</td>
<td>0.006</td>
</tr>
<tr>
<td>4</td>
<td>Self-prediction</td>
<td>0.002</td>
<td>0.017</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>Cross-validated</td>
<td>0.004</td>
<td>0.014</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Wilcoxon: pairwise Wilcoxon signed rank test
Sign test: pairwise signed rank test
Rand t-test: randomization t-test

The optimized model gave a RMSEC of 7.78%, RMSECV of 11.02%, and RMSEP of 7.08%. The model fittings are shown in Figure 3.6 (A), and the LVs are overlaid in Figure 3.6 (B). The first LV (red) explained 57.72% of X-variance and 65.33% of Y-variance. The more evident weights of LV 1 (red line) are in the regions (1600-1700 nm and 1400-1450 nm) relating to APAP (magenta dashed line) and core pellet (black dashed line), respectively. Extraordinary weights on 1900-2000 nm of LV 2 (blue line) are presumably associated with the core pellet and HPMC. LV3 starts to show noisy features which can be explained by capturing only 3.90% of X-variance.
However, it captured 10.98% of Y-variance. The regions showing noticeable weights were related to the absorbance of core (1400-1450 nm) and possibly variation in the water content (1890 – 1940 nm). Nevertheless, it may also reflect spectra changes associated with the physical effect such as increases of particle size.

The robust NIR model captured less Y-variance (86.96%) than the preliminary model (92.55%). The two batches used for developing the preliminary calibration model were produced at similar ambient RH (52.90% and 55.20%). Therefore, the Simplex control provided nearly identical process settings, leading to similar NIR spectra collected. In these batches, the increase of APAP was the only factor that has significant influence on the NIR spectra. On the other hand, the process settings used for producing the six batches for building robust model had very broad ranges, because the large variation of the ambient RH (10.60%-72.90%). The continuously changed process settings lead to more spectral variance, which did not contribute to the co-variance.

Figure 3. 6 Robust NIR model development. A: Predictions versus measurements; B: LVs overlaid with pure spectra of APAP, HPMC, and core pellet.
3.3.3 Process Monitoring

The robust model obtained was subsequently applied to monitor the drug layering process. Figure 3.7 (A) shows a prediction trajectory monitored by the robust NIR model. The green squares represent the NIR predictions during spraying, while red and blue symbols indicate the predictions during pre-heating, and drying and cooling. The model diagnostic plot in Figure 3.7 (B) indicates the predictions are well confined to the confidence interval of the NIR calibration model, suggesting the batch was in a state of control. The spraying automatically ended when the predictions reached the predefined target of 0.035 (w/w). Because the NIR model was established only using drug layered samples, therefore any predictions outside the spraying phase were model extrapolations, which may explained the bias of 0.005 (w/w) observed at the start of the process shown in Figure 3.7 (A).

The goal of the process monitoring system was to accurately predict the CQAs in real time and allow process endpoint determination. The UV method determined a mean drug content of 0.0333 (w/w) from nine end product samples (three replicates per three batches), while the NIR model gave a mean prediction of 0.0352 (w/w). The bias was mainly due to the drug loss caused by attrition. Subsequent studies showed an average 2.70% drug loss due to the attrition.
The real time process monitoring proved its capability to detect abnormal event during the process. The predictions in Figure 3.8 (A) shows an irregular plateau starting from 36 min, which was caused by nozzle fouling. A continuous prediction trend appears again at 60 min after resolving the nozzle issue. Figure 3.8 (B) shows aberrant changes of the EEF appear at about 45 min. The delay in time was attributed to the mechanism of control algorithm. The Simplex control used all the manipulated parameters to maintain the EEF at its preset target, therefore, it was robust to the changes in the process environment. An abrupt change of the EEF output showed up only when the calculated setpoints of the manipulated parameters exceeded the operable limits. The Simplex control’s capability of maintaining the EEF at the target compromised its detectability of abnormal changes. However, the process monitoring method proved it was able to offset the drawback. NIR spectroscopy is sensitive to the change in chemical attributes of in-process materials. The sensitivity allows it to detect unusual process changes at a much early stage. With this capability, the NIR-based process monitoring offers chances to bring a deviating process back to the state of control, and therefore is useful to reduce batch failure and ensure product quality.
3.4 Conclusion

An empirical NIR model was successfully established using in-line NIR spectroscopy to monitor the drug layering process. A comparison between NIR and Raman spectroscopy was made by building preliminary calibration models using a small data set (two batches per method). The NIR calibration model outperformed the Raman model, as evidenced by its RMSEP (6.76%) three times smaller than Raman (RMSEP of 19.71%). Therefore, NIR spectroscopy was perceived as a more suitable technique for developing the process monitoring method in this work.

A robust NIR calibration model was developed using a larger data set collected from six batches. The optimized model, chosen based on the results of permutation tests, gave a RMSEP of 7.08%, which was similar to the RMSEC (7.78%). The NIR model proved its capability to monitor the drug layering process. For a normal process, the model provided predictions of the drug content to determine the process endpoint. The spraying phase was automatically terminated when the predictions reached the target drug load of 0.035 (w/w). The average of the NIR predictions was greater than the UV measurements with a bias of 0.0019 (w/w), or 5.40% if normalized to the drug.
content. The error was primarily attributed to the drug loss caused by attrition during the drying and cooling phases.

The empirical NIR model achieved the goals of monitoring the drug layering process by providing real time quantitative analysis of drug content. The model also demonstrated its value of early problem detection. An abnormal event resulted from nozzle fouling was successfully detected by NIR at a much earlier stage than using the EEF output from the Simplex control. This was helpful to offset the shortcomings of the Simplex control in detecting anomalous event during the process. However, it should be noted that the effectiveness of the problem detection depends on the sensitivity of the NIR spectrum to the changes in the process. Because NIR has a high sensitivity to material attributes, it can rapidly respond to the changes that directly affect the properties of the coated pellets. Its ability of detecting abnormal event may not be as prominent in cases such as forming many small agglomerates without causing batch failures, as the physical changes often shown up in baseline variation and therefore are more difficult to be detected.
Chapter 4: Develop Hybrid Process Control System by Integrating Process Manipulation, Monitoring and Optimization

4.1 Introduction

Process manipulation and monitoring methods were successfully developed in chapter 2 and 3, respectively. The Simplex control effectively eliminated batch failure by maintaining a consistent drying rate across all the batches. The empirical NIR model provided real time quantitative analysis of drug content to determine process endpoint. Notwithstanding the demonstrated capabilities of improving process operation and quality assurance, the drug layering processes were still not controlled under the optimum conditions. Therefore, the work in this chapter centers on the last step of developing the hybrid control system: process optimization.

The goal of process optimization was to discover the optimum setpoints in a design space. Design space is defined as a multidimensional parametric space within which acceptable quality product is obtained (FDA, 2009). Different approaches can be considered when implementing a design space (e.g., process ranges, mathematical expressions, or feedback controls to adjust parameters during processing). It is typically built by statistical modeling from design of experiment (DOE). The DOE provides knowledge and understanding of the relations between process factors and outputs, which contributes to the design space implementation and continuous process improvement.

In the presence of process variations, the risk of failing to meet specifications is higher when operating the process near the edges of the design space (Little, 2014). It is helpful to determine the edges of failure, beyond which the specifications cannot be met. By taking into account the process variability, operation space can be identified at a specified confidence level.
depending on the needs of the process. It can be graphically illustrated as a smaller region situated in the design space with greater confidence to meet specifications. Therefore, OS was proposed to achieve process optimization.

The goals of the study in this chapter had three folds: (1) understand the relations between process factors and quality attributes of interest by developing a design space, (2) establish OS to achieve process optimization, and (3) compare the process capability of the proposed hybrid control system with the basic control.

4.2 Materials and methods

4.2.1 Drug Layering Process and Sample Collection

The drug suspension formulation, fluidized bed system and associated measurement were described in chapter 2. The process was operated by the Simplex control (chapter 2) and monitored by the robust NIR model built in chapter 3. A total of 21 drug layering batches were produced using the Simplex control. Ten end product samples were withdrawn from each batch and analyzed by UV method. The drug contents were converted to the percentage of label claim.

The procedures of sampling and UV analysis for the process capability measurement is displayed in Figure 4.1. Ten batches produced using the hybrid control system were included for the analysis. Ten replicates were randomly sampled from the end products and analyzed by UV. A mean value (\( \mu \)) and relative standard deviation (RSD) were calculated for each batch. The process capability of batch repeatability was evaluated using the ten mean values, whereas the RSD values were used to assess the batch homogeneity. Similar procedures of process capability measurements were also performed for the basic control.
4.2.2 Automation System

The automation system used in this chapter was similar to the one described in chapter 2 section 2.2.3. Figure 4.1 shows the updated structure of orchestrations in SynTQ. The NIR model built in chapter 3 was implemented in the spraying phase and was highlighted in the orchestration. The process endpoint was determined when the predicted drug contents reached the target.
4.2.3 Design Space and DOE

The design space was developed by conducting experiments using a circumscribed central composite DOE. The investigated factors were environmental equivalency factor (EEF) and atomization pressure (AP). The calculation and interpretation of EEF were described in chapter 2. It was used to describe the drying environment of a coating process (Ebey, 1987). Atomization pressure, a factor involved in momentum transfer during coating, was investigated as the other factor in the DOE. Table 4.1 lists the designed experiments. The center points of the DOE (batches 7, 10, and 11) had the EEF target of 0.64 and AP setpoint of 1.6 bar. The conditions were discovered in chapter 2 from successful batches produced using basic control. The lower (0.55) and upper (0.75) levels of EEF were chosen for two reasons. They were statistically different from the center point (0.64) based on the calculation of confidence interval and were the maximum and
minimum values without causing batch failures. The AP of 1.9 bar was the maximum setpoint allowed by the equipment, and an AP value of 1.3 bar was selected to maintain a same difference (0.3 bar) to the center point. All the 11 experiments were randomized to the ambient RH in a range of 10.3% – 64.0%.

Table 4.1 Circumscribed central composite DOE.

<table>
<thead>
<tr>
<th>Batch #</th>
<th>EEF</th>
<th>AP (bar)</th>
<th>Ambient RH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.55</td>
<td>1.9</td>
<td>23.5%</td>
</tr>
<tr>
<td>2</td>
<td>0.64</td>
<td>1.3</td>
<td>17.7%</td>
</tr>
<tr>
<td>3</td>
<td>0.75</td>
<td>1.6</td>
<td>64.0%</td>
</tr>
<tr>
<td>4</td>
<td>0.75</td>
<td>1.3</td>
<td>40.7%</td>
</tr>
<tr>
<td>5</td>
<td>0.55</td>
<td>1.6</td>
<td>50.0%</td>
</tr>
<tr>
<td>6</td>
<td>0.64</td>
<td>1.9</td>
<td>10.3%</td>
</tr>
<tr>
<td>7</td>
<td>0.64</td>
<td>1.6</td>
<td>62.1%</td>
</tr>
<tr>
<td>8</td>
<td>0.75</td>
<td>1.9</td>
<td>13.6%</td>
</tr>
<tr>
<td>9</td>
<td>0.55</td>
<td>1.3</td>
<td>23.9%</td>
</tr>
<tr>
<td>10</td>
<td>0.64</td>
<td>1.6</td>
<td>15.0%</td>
</tr>
<tr>
<td>11</td>
<td>0.64</td>
<td>1.6</td>
<td>53.3%</td>
</tr>
</tbody>
</table>

The responses of the investigated DOE were coating efficiency, content uniformity, and agglomeration percentage. Coating efficiency describes how much drug is actually layered on the pellets comparing with the theoretically applied drug content. It is a critical attribute for drug layering process because the drug substances are normally very expensive. Reduced costs for product development can benefit from an improvement in coating efficiency. Content uniformity is a widely accepted CQAs for most pharmaceutical solid dosage forms. Agglomeration percentage describes how much agglomerates formed at the end in the whole batch. It was perceived as an important indication of batch yield, because any agglomerates will be removed from the end products before proceeding to the next step.
Coating efficiency and content uniformity were determined by the UV method established in chapter 3 section 3.2.2. Coating efficiency was calculated as the ratio (w/w) of the layered drug content to the theoretically applied (the amount of liquid applied multiplied by the nominal APAP concentration). Content uniformity was expressed in relative standard deviation (RSD) of drug contents by determining 10 replicates of the end products. Agglomeration percentage was determined by a solid sizer (JM Canty Inc., NY). The pellets of the whole batch after coating, i.e. end products, were scanned by a camera, while the pellets were in a consist motion controlled by a shaker. The recorded video was subjected to image analysis, which was able to count the pellets and pinpoint the agglomerates. An agglomerate was identified by meeting the criteria of having a major diameter greater than 1.5 times larger than the average diameter of the whole batch pellets. An example is shown in Figure 4.3, where the identified agglomerates are shown at the left, as opposed to the individual pellets at the right. The agglomeration percentage was calculated by dividing the sum area (black 2-D area in a binary image) of all the identified agglomerates by the sum area of all objects captured in a complete scan. The scan was repeated three times, and the average agglomeration percentage was used for subsequent analysis.

![Figure 4.3 Example of the measurement of agglomerates.](image-url)
An empirical model was calculated for each response using multiple linear regression. The models were used to describe and understand the relations between the DOE factors and their effects on the quality attributes. The relations were graphically portrayed in 3-D knowledge spaces using JMP software (SAS, Cary, NC). A design space was established premising on the knowledge space by setting the specification limits of each quality attribute: coating efficiency $\geq 55\%$, content uniformity (RSD) $\leq 10\%$, and agglomeration percentage $\leq 15\%$. Note there was no standard specification for the quality attributes of interest, therefore the specifications used to develop design space had to be arbitrarily defined for the model system. The knowledge spaces were combined and projected onto a 2-D contour plot. The setpoints of factors that can meet all the defined specification limits constituted the design space. In this work each setpoint in the design space referred to a combination of an EEF target value and an AP setting.

4.2.4 Operation Space

Design space is often an extrapolation of the response surfaces from a DOE. Hypothetically the setpoint within the identified design space indicates a safe and successful operating condition. Nevertheless, it requires supporting analysis to be sure operating in the design space will have high success rates. Therefore, operation space, taking the variations of individual batch into account, was used to discover the process setpoints that offer high probabilities of meeting specifications, i.e. high confidence. It was used in this work to achieve process optimization. Operation space was defined as a region situated in the design space, comprising the setpoints that can meet the specification limits at a greater confidence. Unlike design space, it takes the variations from individual batches into account. The operation space was established by adopting the procedures of edge of failure analysis: (1) calculate response surfaces based on the results obtained from DOE, (2) construct the design space, (3) simulate variations in each factor, (4) predict the responses using
the response surfaces at the simulated variations, (5) calculate the probability of in specifications for each setpoint in the design space, and (6) repeat step (3)-(5) for a large number of times. To acquire reliable results, sufficient repetitions must be made. Monte-Carlo simulation with repetition times of $5.0 \times 10^3$ was used as a default parameter in JMP software, and thus used as a reference value in this work.

4.2.5 Assessment of Process Capability

The goal of the hybrid control system was to improve process capability. The two CQAs for assessing process capability were batch repeatability and batch homogeneity. The sampling and drug content measurement for this study was described in 4.2.1. Process capability indices, $C_p$ and $C_{pk}$, were calculated by,

$$C_p = \frac{USL-LSL}{6s} \quad \text{Eq. (4.1)}$$

$$C_{pk} = \min\left[\frac{USL-\mu}{3s}, \frac{\mu-LSL}{3s}\right] \quad \text{Eq. (4.2)}$$

where $USL$ and $LSL$ are desired upper and lower specification limits of the investigated CQAs, $\mu$ and $s$ are the mean and standard deviation measured in experiments. $C_p$ measures how close a process is running to its specification limits, relative to the natural variability of the process. The USL and LSL of batch repeatability were 115% and 85%, and 15% and 0% for batch homogeneity. The specifications were chosen based on USP defined specifications. (USP, 2011)

4.3 Results and discussion

4.3.1 Design Space

The relations between the investigated factors and their effects on the quality attributes were studied with a DOE. The knowledge spaces were constructed using the DOE results shown
in Table 4.2. Figure 4.4 (A) shows the 3-D knowledge space plot of coating efficiency. The lowest coating efficiency was produced at low level of EEF (0.55) and high level of AP (1.9 bar), whereas the highest coating efficiency was at high level of EEF (0.75) and low level of AP (1.3 bar). In general, higher AP produces smaller droplets with much greater specific surface area, enhancing spray drying effect and decreasing coating efficiency. Its effect on coating efficiency was exemplified by a higher drying rate (low EEF). On the contrary, lower drying rate and larger droplet size maximized the coating efficiency, possibly by inhibiting the effect of spray drying. It is noteworthy that the plot reveals an interaction between EEF and AP. The AP had little impact on coating efficiency when the EEF was held at low level. It was inferred that extremely excessive drying rate was produced at EEF of 0.55. This resulted in significant spray drying, regardless of the level of AP was used. In contrast, AP had significant impact on determining coating efficiency when EEF was at high level (0.75). The coating efficiency was nearly doubled by decreasing AP from 1.9 bar to 1.3 bar. The result of lower coating efficiency at high AP implied that the spraying drying seemingly dictated the coating efficiency, even at lower drying rate. The greatly enlarged specific surface area make the coating droplets extremely susceptible to spray drying. This may be relevant to the high solid concentration (17.5%) of the drug suspension.
Table 4.2 Results of the DOE for establishing design space.

<table>
<thead>
<tr>
<th>Run #</th>
<th>EEF (bar)</th>
<th>AP (bar)</th>
<th>RH%</th>
<th>Coating efficiency (%)</th>
<th>Agglomeration percentage (%)</th>
<th>Content uniformity RSD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.55</td>
<td>1.90</td>
<td>24.00%</td>
<td>46.30%</td>
<td>3.60%</td>
<td>4.20%</td>
</tr>
<tr>
<td>2</td>
<td>0.64</td>
<td>1.30</td>
<td>18.00%</td>
<td>93.70%</td>
<td>17.80%</td>
<td>9.10%</td>
</tr>
<tr>
<td>3</td>
<td>0.75</td>
<td>1.60</td>
<td>64.00%</td>
<td>74.20%</td>
<td>9.50%</td>
<td>15.90%</td>
</tr>
<tr>
<td>4</td>
<td>0.75</td>
<td>1.30</td>
<td>41.00%</td>
<td>94.60%</td>
<td>32.00%</td>
<td>16.30%</td>
</tr>
<tr>
<td>5</td>
<td>0.55</td>
<td>1.60</td>
<td>50.00%</td>
<td>48.10%</td>
<td>6.80%</td>
<td>2.30%</td>
</tr>
<tr>
<td>6</td>
<td>0.64</td>
<td>1.90</td>
<td>10.00%</td>
<td>52.60%</td>
<td>7.20%</td>
<td>7.70%</td>
</tr>
<tr>
<td>7</td>
<td>0.64</td>
<td>1.60</td>
<td>62.00%</td>
<td>57.40%</td>
<td>9.50%</td>
<td>1.80%</td>
</tr>
<tr>
<td>8</td>
<td>0.75</td>
<td>1.90</td>
<td>14.00%</td>
<td>60.80%</td>
<td>7.10%</td>
<td>4.90%</td>
</tr>
<tr>
<td>9</td>
<td>0.55</td>
<td>1.30</td>
<td>24.00%</td>
<td>46.60%</td>
<td>26.80%</td>
<td>7.20%</td>
</tr>
<tr>
<td>10</td>
<td>0.64</td>
<td>1.60</td>
<td>15.00%</td>
<td>49.70%</td>
<td>13.00%</td>
<td>2.80%</td>
</tr>
<tr>
<td>11</td>
<td>0.64</td>
<td>1.60</td>
<td>53.00%</td>
<td>48.90%</td>
<td>11.40%</td>
<td>6.90%</td>
</tr>
</tbody>
</table>

Similar effects of AP and EEF on content uniformity are observed in Figure 4.4 (B). Content uniformity was represented by RSD, and therefore a high RSD value represented a poor content uniformity. A lower RSD was obtained at low EEF, regardless of the level of AP. AP had little impact on RSD when the EEF was kept low, but an extraordinarily increased influence on RSD was found when EEF was held at high level. The similarity of the knowledge spaces of coating efficiency and content uniformity was explained by their relationships. A greater coating efficiency was often accompanied by a higher RSD (poor content uniformity). High coating efficiency is obtained by inhibiting spray drying, which can be achieved by lowering drying rate (higher EEF) and decreasing AP. However, this significantly enhances the risks of forming agglomerates. Liquid bridges are easily formed when the over-wetting pellets collide with each other. Therefore, high coating efficiency and low RSD are considered conflicting results. This was corroborated by the results of batches 2 and 4 in Table 4.2, both had high coating efficiency with high RSD. Although higher coating efficiency is always desired, over pursuing it can compromise content uniformity.
and may even lead to batch failure. Considering the severe consequence of batch failure, a trade-off criterion prone to a lower RSD was used in this work.

Figure 4.4 Knowledge spaces. A: Coating efficiency; B: Content uniformity (expressed in RSD); C: Agglomeration percentage.
It was intuitive to presume a similar relationship should hold between content uniformity and agglomeration percentage, because a lower RSD usually resulted from inhibited formation of agglomerates. However, Figure 4.4 (C) reveals the agglomeration percentage was determined by AP, whereas EEF had insignificant effect. The discrepancy of the results between content uniformity and agglomeration percentage was conceivably related to difference in measurement. The content uniformity was determined by the UV method. A poor content uniformity indicated large chunks of agglomerates were formed during the process, because the large agglomerates (with a minimum size of 2.38 mm) usually contain much more drug than individual pellets. The small agglomerates had little impact on content uniformity, because hundreds of pellets constituted a single sample which was analyzed by UV. In general, the large agglomerates were produced by insufficient drying rate. This explained the significant effect exerted from EEF on content uniformity. On the other hand, agglomeration percentage was determined by image analysis. The image analysis was able to capture all the pellets. Therefore, the small agglomerates had a remarkable influence on the AG. Figure 4.4 (C) shows the lower AP had adverse effects on agglomeration percentage, which was independent of the EEF levels. The properties of larger droplets with lower impingement speed may result in a thick wet surface on the pellet, encouraging the formation of liquid bridges and thereafter creating more agglomerates. Because the high viscosity of the drug suspension, even the highest drying rate used in this work was insufficient to inhibit the wet surface.

The design space was obtained by combining the knowledge spaces and identify the setpoints of in specifications. In Figure 4.5, each colored area represents where the setpoints fail to meet the specification limits. The white area in the middle is the discovered design space. Hypothetically, operating the process using any setpoints in the design space is able to meet the
specifications. However, simply using the design space is misleading because it only represents the average of the quality attributes predicted by the response surface. A regular design space disregard the variations from individual batches. The mean response may be safe, but the individual batch may experience high failure rates. The dashed lines in the plot are boundaries of the design space, which were reckoned as edges of failure. (Little, 2014) If the setpoints are randomly and normally distributed, 50% of the batches produced at the boundaries will fail to meet the specifications.

![Design space of the drug layering process.](image)

**Figure 4.5** Design space of the drug layering process.

### 4.3.2 Operation Space

The effect of repetition times on the operation space was examined. Figure 4.6 from (A) to (C) display the operation space obtained by repeating the Monte-Carlo simulation $1.0 \times 10^4$, $5.0 \times 10^4$, and $1.0 \times 10^5$ times, respectively. The SD of EEF and AP were held constant in the
comparison. No distinguishable difference was found among the three plots, suggesting repetition of $1.0 \times 10^4$ times was sufficient for conducting the EFA. The red region represents where the setpoints have higher probability to meet the specifications. The exact boundaries of an operation space are defined for a specific process, based on the desired confidence level.

The variation of the EEF was revealed having a significant impact on the size of the operation space. Figure 4.7 shows the results of two examples. The SD of AP was held constant in the examples for demonstration. A much larger red region (Figure 4.7 (A)) was obtained by setting the SD of EEF at 0.02, the results indicated many setpoints in the design space can meet the specifications at high confidence level. In contrary, Figure 4.7 (B) exhibits when the SD of EEF is set at 0.08, none of the setpoints can meet the specifications with a confidence higher than 70%. Since AP had very limited range and variation (mainly resulted from the random variance of the air supply), its effect on the operation space was insignificant compared with the effect of the EEF.

Figure 4. 6 Effect of the number of repetitions on the operation space.

![Figure 4.6](image)

The variation of the EEF was revealed having a significant impact on the size of the operation space. Figure 4.7 shows the results of two examples. The SD of AP was held constant in the examples for demonstration. A much larger red region (Figure 4.7 (A)) was obtained by setting the SD of EEF at 0.02, the results indicated many setpoints in the design space can meet the specifications at high confidence level. In contrary, Figure 4.7 (B) exhibits when the SD of EEF is set at 0.08, none of the setpoints can meet the specifications with a confidence higher than 70%. Since AP had very limited range and variation (mainly resulted from the random variance of the air supply), its effect on the operation space was insignificant compared with the effect of the EEF.
Figure 4.7 Effect of the standard deviation of EEF on the operation space.

The optimized process setting was found in the operation space by finding the setpoint having the maximum probability of in specifications. Figure 4.8 shows the operation space established based on the experimentally determined SD of EEF (0.05) and a best estimated SD of AP (0.05). The optimized process setting, symbolized by the white diamond at EEF = 0.72 and AP = 1.80, give the highest confidence at a value of 86.35%. The original setpoints, indicated by the white circle, produced a 68.04% confidence of in specifications. The optimized process setpoints were used in subsequent experiments to test the process capability.
Figure 4.8 Process optimization. White circle: original setpoints; White diamond: optimized setpoints.

Table 4.3 Comparison of the probability of in specifications. Before and after process optimization.

<table>
<thead>
<tr>
<th>Process optimization</th>
<th>EEF mean</th>
<th>EEF SD</th>
<th>AP mean</th>
<th>AP SD</th>
<th>Probability of in specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preliminary process setpoints</td>
<td>0.64</td>
<td>0.05</td>
<td>1.60</td>
<td>0.050</td>
<td>68.04%</td>
</tr>
<tr>
<td>Optimized process setpoints</td>
<td>0.72</td>
<td>0.05</td>
<td>1.80</td>
<td>0.050</td>
<td>86.35%</td>
</tr>
</tbody>
</table>
4.3.3 Assessment of Process Capability

The results of process capability were calculated for both hybrid control and basic control. The results of basic control are discussed at first. Figure 4.9 (A) displays the X-charts of batch repeatability. Each point in the plot is a mean drug content measured by UV for each batch. The horizontal axis shows the sorted ambient RH used for the batch productions. The green solid line is the mean drug label claim of all 10 batches, which is 100.5%. The two red lines, UCL and LCL, are confidence intervals calculated from the mean and SD. The blue dashed lines are USL (115%) and LSL (85%) based on USP specifications. An outlier at RH of 77% was highlighted in the red dashed circle in the figure, which had extraordinarily greater RSD than other batches (discussed in subsequent section), and therefore was not included in the calculation of process capability indices. Figure 4.9 (B) shows the simulated distribution based on the measured mean and SD for the batch repeatability. Only 46.06% of the population falls within the USL and LSL. The value corresponds to a failure rate of $5.39 \times 10^5$ parts per million (PPM). Although the overall mean drug label claim was very close to the center target (100%), the process had extremely poor capability for batch repeatability, as evidenced by the capability indices of $C_p = 0.21$ and $C_{pk} = 0.20$. The low indices were attributed to the poor precision of between-batch drug contents. The basic control determined the process endpoint by applying a fixed amount of coating liquid. This method ignored the variation in coating efficiency, which was proved rather evident in Table 4.2.
The results of batch homogeneity are shown in similar plots (Figure 4.10), where USL of 15% (blue dashed line) was used as specification limits, note the LSL is zero. The outlier, RSD of 74.9% at RH of 77%, is highlighted in red dashed circle in Figure 4.10 (A). Also, a RH-dependent pattern is seen in the plot: higher RH resulted in higher RSD (comparing the range above 50% with that of lower than 22%). The results pointed out a special cause variance existed in the process produced by basic control. Due to its extraordinary leverage on the calculation, the outlier batch was excluded in the calculation of process capability indices. Figure 4.10 (B) shows 93.13% of the population falls in the specifications (failure rate of 686.51 PPM). The batch homogeneity had $C_p = 1.13$ and $C_{pk} = 1.11$. The indices suggested the batch homogeneity of the drug layering process was marginally capable.
Figure 4. 10 Process capability of batch homogeneity under basic control. A: X-charts of batch homogeneity; B: Simulated distribution of the batch homogeneity population.

Substantial improvements offered by hybrid control, particularly for batch repeatability, are demonstrated in Figure 4.11. Figure 4.11 (A) shows a much enhanced precision as all the drug content are well confined to the USL and LSL. The $C_p$ and $C_{pk}$ of batch repeatability were increased up to 1.11 and 1.10, respectively. The failure rate was decreased considerably to a PPM value of 898.6, representing 99.97% of the population was in specifications. The significantly reduced variation in drug label claim was attributed to the endpoint determined by the process monitoring system. The NIR model provided accurate predictions of the drug layered content, effectively inhibiting the batch to batch variation. The batch homogeneity was also improved by the hybrid control. The random patterns in Figure 4.11 (C) indicates the special cause variance associated with RH was successfully removed. The RSD of each batch was effectively controlled at similar level and independent of the change in ambient RH. The $C_p$ and $C_{pk}$ were increased to 2.12 and 1.62. Note, the lower $C_{pk}$ is explained by Figure 4.11 (D), where the average RSD is closer to the lower limit. This, in fact, indicated a higher capability for batch homogeneity. Overall, the hybrid process control system had significantly improved the process capability for the drug
layering process. The process capability of batch repeatability was enhanced from extremely poor to marginally capable, whereas excellent process capability was achieved for the batch homogeneity than the previous marginally capable process. The significance was substantiated by statistical evidence ($\alpha=0.05$) of the capability indices (Table 4.4). A process having $C_{pk} \geq 1.33$ is usually acknowledged as a capable process given the widely accepted industrial standard. Therefore, the hybrid process control has not yet achieved “capable control” for batch repeatability ($C_{pk} = 1.10$). It is noteworthy that the capability indices reported in the industry is usually based on the measurements of numerous subgroups from the production line. The less data included in our calculation may underestimate the process capability. Nevertheless, the hybrid control proved its effectiveness of improving process capability compared to the basic control.
Table 4.4 Comparison of the capability indices between basic and hybrid controls.

<table>
<thead>
<tr>
<th>Control mode</th>
<th>Process capability</th>
<th>Batch repeatability</th>
<th>Batch homogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cp</td>
<td>Cpk</td>
<td>Cp</td>
</tr>
<tr>
<td>Basic control</td>
<td>0.21</td>
<td>0.20</td>
<td>1.13</td>
</tr>
<tr>
<td>Hybrid control</td>
<td>1.11 *</td>
<td>1.10 *</td>
<td>2.12 *</td>
</tr>
</tbody>
</table>

*: significant difference at confidence level α=0.05
4.4 Conclusion

Process optimization was efficiently achieved by employing the operation space in this work. The effects of the process factors on the quality attributes of interest were investigated using DOE. Besides EEF, factor affecting the momentum transfers at microscopic level (AP) also had significant influences on the quality attributes (coating efficiency, content uniformity and agglomeration percentage in this work). The results suggested the factors having complex effects at microscopic level should not be ignored. The subtle interaction phenomena was practically difficult to control, therefore it was regarded as a supplementary factor in this work to achieve process optimization.

The size of the operation space was determined by the specified confidence level. Besides, the variation of EEF also had significant effect on the operation space. A lower variation of EEF produced a larger operation space, endowing more flexibility in choosing process setpoints. AP did not show any noticeable impact on the operation space, which was inferred due to its limited variability.

The operation space discovered the optimum setpoints, which were EEF of 0.72 and AP of 1.8 bar. The expected probability of in specifications was increased, by estimation, from 68.04% to 86.35%. By consolidating nine process parameters into a single value, the use of EEF considerably reduced the number of experiments required for the process optimization. Therefore, the use of operation space with EEF allowed efficient process optimization.

The works in this chapter, combining with chapter 2 and 3, completed the proposed hybrid process control system. The process capability indices were calculated and compared with the basic control. The results indicated the hybrid control system considerably improved the process
capability indices. The $C_p$ and $C_{pk}$ of batch repeatability were raised to 1.06 and 1.04, which were approximately six times larger than the basic control. The indices of batch homogeneity had twofold increase than the basic control, supported by the $C_p$ of 1.50 and $C_{pk}$ of 1.14. The improvement was substantiated by statistical evidence at significant levels $\alpha$ of 0.01 and 0.05, respectively. The results supported the central hypothesis of the dissertation: The hybrid control system improved the process capability for the drug layering process compared to the conventional basic control.

The proposed control strategy was expected to have broader applications. The three elements of the demonstrated hybrid control system: process manipulation, monitoring, and optimization are adjustable and flexible. Pellet coatings are also commonly used to provide other functions, such as core protection and drug release modification. In these applications, the challenges are to ensure the quality to achieve the intended functions. Therefore, the next two chapters of the dissertation focuses on exploring alternative analytical methods to monitor different CQAs. With a successful development of alternative process monitoring method, the hybrid control system can be updated and applied to various processes.
Chapter 5: Develop Process Monitoring Method for Quantitative Analysis of Coating Thickness

5.1 Introduction

A hybrid process control system was successfully developed in Chapter 2-4 for a drug layering process. The system manipulated the coating process using the Simplex control. The process endpoint was automatically determined using a robust NIR model. The optimum process setpoints were discovered by an established operation space. The hybrid control succeeded in improving the process capability for the investigated drug layering process. The proposed control strategy was expected to have a broader applications. The elements of the demonstrated hybrid control system, process manipulation, monitoring, and optimization, are adaptable and flexible. By replacing one or several elements, e.g., process monitoring of a different CQA by alternative analytical methods, the hybrid control system can be updated and applied to various processes.

Besides drug layering, fluidized bed pellet coating process is also commonly used for achieving core protection and drug release modification (Bley et al., 2009; Tønnesen, 2001). In these applications, coating thickness is often considered a CQA, which is strictly controlled to ensure the product quality. A sufficient coating thickness can effectively reduce light penetration (Bechard et al., 1992) and inhibit moisture diffusion (Bley et al., 2009). Coating thickness also plays an important role in determining drug release properties (Siepmann et al., 2007; Wesseling and Bodmeier, 1999b). In general, it is easier to control the coating thickness instead of changing the formulation. In previous studies, NIR and Raman spectroscopy presented significant spectral changes correlating with the coating process. The increase of coating thickness is, fundamentally, a result of the deposition of coating materials. Because the sensitivity to chemical attributes, it was presumed NIR and Raman are able to develop quantitative analysis of coating thickness.
A drawback of using NIR or Raman spectroscopy is the requirement of calibration. As indirect methods, the spectra must be related to the reference values to build empirical models. The most reliable reference methods for determining coating thickness are normally image analyses using optical or electron microscope. However, the methods are destructive and often require significant time for sample preparation and data collection. Although the advantages offered by a successful NIR or Raman method considerably outweigh the efforts for building the empirical models, the endeavor of method development should not be omitted.

An analytical method that can provide direct, non-destructive, and rapid measurement is preferred for determining coating thickness. Terahertz imaging (THI) has demonstrated the potential to determine tablet coating thickness (Cogdill, 2006; Fitzgerald et al., 2005; Ho et al., 2009b; Maurer and Leuenberger, 2009). Terahertz radiation is in the far-infrared region of the electromagnetic spectrum (60 GHz–4 THz). The low frequency radiation allows high penetration depth in solid samples (Haaser et al., 2013a). Unlike NIR and Raman spectroscopy, THI offers direct measurements of coating thickness without the need for developing calibration models. These advantages make THI a valuable tool to determine the coating process.

However, THI was reported to have a high detection limit of 30–40 µm (Brock et al., 2012). This shortcoming substantially limits its application to determine coating thickness. Therefore, the indirect methods using NIR and Raman spectroscopy were included in the work of this chapter for comparison. The goals of this study were to: (1) develop empirical models of coating thickness using NIR and Raman spectroscopy, and (2) inspect the capability of THI to provide direct measurement of pellet coating thickness.
5.2 Materials and methods

5.2.1 Formulation of polymer coated pellets

The formulation of the polymer dispersion is listed in Table 5.1. Pellets (SUGLETS, Colorcon, West Point, PA) were used as cores for the polymer coating process. The pellets have a diameter range of 1000-1200 μm. Talc (Alfa Aesar, Haverhill, MA) and Tween 80 (VWR, Radnor, PA) were added to the HPMC (PharmaCoat 606, Shin-Etsu, Japan) solution prepared beforehand. The dispersion was mixed for 15 minutes. After the addition of Eudragit aqueous dispersion (NE30D, Evonik, Germany) and pigment, the dispersion were further stirred for another 15 minutes. The mixed dispersion was diluted using deionized water to reach the desired polymer solid concentration, and passed through a 0.5 mm sieve before used for coating.

<table>
<thead>
<tr>
<th>Polymer dispersion</th>
<th>Components</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit NE 30D</td>
<td>9.00%</td>
<td></td>
</tr>
<tr>
<td>HPMC</td>
<td>1.00%</td>
<td></td>
</tr>
<tr>
<td>Tween 80</td>
<td>1.00%</td>
<td></td>
</tr>
<tr>
<td>Talc</td>
<td>10.00%</td>
<td></td>
</tr>
<tr>
<td>Pigment</td>
<td>0.50%</td>
<td></td>
</tr>
<tr>
<td>Deionized water</td>
<td>78.50%</td>
<td></td>
</tr>
</tbody>
</table>

5.2.2 Fluidized Bed Process, Sample Information, and Spectroscopic Data Collection

Three batches of Eudragit coating were performed by operating the process at the settings shown in Table 5.2. The basic control was used to manipulate the process because all of the three batches were produced at similar ambient conditions. Samples were taken from the process using a built-in sample thieve, at predetermined coating time during the spraying phase. Two batches
were used for calibration, and one batch for test. The coating process was monitored by the in-line NIR spectroscopy. The details of NIR spectra collection were described in chapter 2 section 2.2.2.

Raman spectra were collected using a RXN2 Hybrid at-line analyzer (Kaiser Optical Systems, Ann Arbor, MI) with a thermoelectrically cooled charge-coupled detector. The laser source was operated at 785 nm with a laser power of 400 mW. The spectrometer was equipped with a non-contact optic sampling device PhAT probe. The focal length was 250 mm and spot size was 6 mm. The coated pellets were held in a sample holder with a depth of 10 mm and a diameter of 8 mm. The sample holder was positioned perpendicular to the PhAT probe. The exposure time was set as 20 s, and each sample was scanned three times over the wavenumber range of 150-1890 cm\(^{-1}\) at a 1 cm\(^{-1}\) increment. The final spectrum was a co-add of the three scans.

Table 5.2 Process settings of polymer coating produced using basic control.

<table>
<thead>
<tr>
<th>Process setpoints</th>
<th>Preheating</th>
<th>Spraying</th>
<th>Drying</th>
<th>Cooling</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF (m(^3)/h)</td>
<td>40</td>
<td>50</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>IT (°C)</td>
<td>55</td>
<td>50</td>
<td>65</td>
<td>21</td>
</tr>
<tr>
<td>SR (g/min)</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AP (bar)</td>
<td>0</td>
<td>1.6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

5.2.3 Reference Method: Image Analysis

Image analysis was used as a reference method to determine the pellet coating thickness. Ten pellets were randomly selected from the samples taken from the process. Each pellet was cross-sectioned using a Microtome (Thermo Scientific, Boston, MA). The image of the cross-sectioned pellet was taken using an optical microscope and saved in RGB format (Olympus, Japan). Each image had 1920×2560 pixels, with pixel size of 0.836×0.836 μm. An in-house function written in MatLab was applied to make numerous thickness measurements on each image. An
image of the cross-sectioned surface is presented in Figure 5.1 (A). The coating surface is highlighted in green circles and the interface of the coating and core is indicated by red circles. A thickness distribution was obtained for each pellet. The standard deviation (SD) was calculated to indicate the intra-pellet thickness variation. An example of the distribution is shown in Figure 5.1 (B). The pooled mean ($\mu$) and SD were calculated from the thickness data of the 10 pellets. The mean thickness of each sample was used as reference value for developing empirical models.

![Figure 5.1](image)

Figure 5. 1 Image analysis of pellet coating thickness using optical microscope. A: Cross-sectioned surface of pellet and coating layer identified; B: Intra-pellet thickness distribution.

5.2.4 Indirect Method: Empirical Models using NIR and Raman Spectroscopy

NIR and Raman models were built by relating the to the reference values. The model development protocols were described in chapter 3 section 3.2.4 and section 3.2.4.3. In this case, the reference values were the mean coating thickness values of the samples determined by optical microscope.

5.2.5 Direct method: Terahertz imaging

A total of six samples with different weight gains were selected for the THI analysis. Eight replicate pellets of each sample were fixed in a holder and subsequently imaged individually using
a THI in reflectance mode (TAS7500IM, Advantest, San Jose, CA). The terahertz incident beam was manually focused on the highest point of the pellet surface by moving the position of the sample holder in a 3-D coordinate system. The spatial resolution of the images was set to 0.1 mm. A single time domain waveform was collected by averaging 128 replicate scans for each pellet. The measurements were repeated six times and thus six terahertz waveforms were obtained for each pellet. The mechanism of THI measurement is graphically illustrated in Figure 5.2. The following equation was used to directly derive the coating thickness from the terahertz waveform,

\[ d = \frac{c \Delta t}{2n_1} \]  

Eq. (5.1)

Here \( d \) is coating thickness measured by THI, \( c \) is the speed of light in air. \( \Delta t \) is the time difference between the reflection of the terahertz pulse off the coating surface (r1) and the reflection from the interface of the coating and core pellet (r2). \( n_1 \) is the RI of the coating material. The refractive index (RI) used to calculate the coating thickness was determined by scanning a coating film patch using the THI transmission mode. The film patch was prepared by casting the same coating dispersion on a Teflon petri dish. The film was dried in an oven at 60°C for 24 hours before scanning. The RI used for thickness calculation was the average of the spectra RI over the bandwidth of the THI system (1-4 THz). A stainless steel sphere with diameter of 1.59 mm was used to acquire a reference surface reflection.
5.3 Results and discussion

5.3.1 Image Analysis using Optical Microscope

The image analysis used in this work allowed numerous measurements of thickness made on each pellet. The number of measurements is of great importance to acquire a statistically representative average thickness. Its effect is illustrated in Figure 5.3. The subplots from (A) to (D) present the histograms of thickness data obtained from 6, 36, 72, and 360 measurements, respectively. Increasing the number of the measurements caused a change in average thickness from 52 to 59 µm. Meanwhile the distributions of the thickness gradually conformed to a normal distribution. In this work, 360 thickness measurements were made on each individual pellet. The mean (µ) and SD were calculated from a total of 3600 thickness measurements. In Figure 5.4, the average thickness values are indicated by the open circles, while the SD values are shown as the spread at each time point. The near linear relation of the thickness versus coating time was due to the limited range of the coating thickness investigated in the work.
Figure 5.3 Effect of the number of thickness measurements on the coating thickness distribution.
Figure 5. 4 Increase of coating thickness versus coating time.

5.3.2 NIR model

The most evident feature of the raw NIR spectra is the baseline variation, as shown in Figure 5.5 (A). The baseline variation was mainly associated with the fluidization. A principle component analysis (PCA) model was built by preprocessing the NIR spectra of a calibration batch using SNV and mean-centering. The distribution of the scores on PC1 and PC2 are displayed in Figure 5.5 (B). A clear pattern of the PC scores is seen in the plot, where the dark blue circles indicate the beginning of the coating, and yellow circles represent the end of the spraying. The PC1 explained 84.45% of the spectra variance, which was attributed to the increase of coating thickness, whereas the PC2 captured 8.04% spectra variance, which was presumably associated with the variation in water content.
Quantitative NIR models were calculated using the spectra of two calibration batches and the reference values provided by the image analysis. The NIR spectra were preprocessed by SNV and followed by mean-centering to emphasize the spectra features of the absorbance. The predictions of the NIR model versus measurements are presented in Figure 5.6 (A). The optimized NIR model gave RMSEC of 3.53% and RMSEP of 3.40% (normalized to the calibration range). Figure 5.6 (B) shows the two latent variables (LV) overlaid with the pure spectra of core pellet and coating film. The two LVs both resemble the spectra features of the coating film, as evident from the weights in the regions of 1390 nm and 1670-1750 nm.
A main advantage offered by the image analysis used in this work was the availability of a large data set of thickness measurements. This allowed one to inspect the uncertainty of the coating thickness and its effect on the model performance. Figure 5.7 elucidates the steps of the analysis using bootstrapping. A thickness probability distribution was created for each sample at a different coating thickness. A normal distribution was simulated using the determined $\mu$ and SD acquired from the image analysis. Thickness values were randomly drawn from the distribution and used as reference values to build new NIR calibration models. The calibration error (RMSEC) of the simulated models were compared with the original model established using the average thickness data. The analysis was repeated $k$ times ($1 \times 10^4$ in this study), and therefore $k$ models and associated RMSEC were calculated.
The variability of the thickness was found independent of the average coating thickness, as evident from the random pattern shown in Figure 5.8 (A). The results of the bootstrapping analysis is shown in Figure 5.8 (B). The RMSEC of the original model (4.37 µm) is represented by the red line, whereas simulated RMSEC were represented by the blue histogram. The RMSEC of the original model was lower than 96.34% of the simulated models. The results indicated using the average thickness data was reasonable to build NIR model.
5.3.3 Raman model

The raw Raman spectra of core and coated pellets are shown in Figure 5.9 (A). The Raman spectra of coated pellets reveal a baseline drift which is proportional to the coating thickness. The drift was associated with the components, talc and HPMC. These two components had much stronger Raman signal than the Eudragit polymer. They were also characterized by the considerable baseline slopes, which dominated the observed Raman spectra of coated pellets. To remove the baseline interference, the Raman spectra were preprocessed using baseline correction. The preprocessed spectra are shown in Figure 5.9 (B). Remarkably decreased intensity is seen in the regions characteristic of the core pellet, especially in 1000-1200 cm\(^{-1}\). However, the spectra changes were hardly distinguishable between the thickness of 72.23 µm and 99.25 µm.
A preliminary Raman model was built in the coating thickness range of 24.82-99.50 µm. Figure 5.10 shows the model predictions versus reference measurements. A slight non-linear trend is found near the higher end of the thickness range. The model gave a RMSEC of 9.77% (relative to the calibration range). The results suggested Raman method may not be suitable for analyzing samples with high coating thickness. It was important to have the knowledge of the maximum coating thickness beforehand. If the coating thickness of interest is above the limit, alternative methods should be explored.
The concept of information depth (ID) was proposed to estimate the maximum thickness range that allows development of a quantitative Raman model. The ID was defined as the maximum depth in a solid sample to which an incident radiation wave can penetrate, meanwhile still allowing sufficient photons backscatter for detection by the spectrometer. ID is graphically illustrated in Figure 5.11. Before coating starts, the spectra only contain chemical information of the core pellet (Figure 5.11 (A)). With the increase of the coating thickness, (Figure 5.11 (B) and (C)), the chemical information of the spectra gradually emphasize on the coating layer. The spectra change eventually becomes imperceptible when the thickness exceeds the maximum limit, as is shown in Figure 5.11 (D). Therefore, ID is conceptually indicated by Figure 5.11 (C). A sufficient spectra change is a precondition for building empirical models using any spectroscopic methods,
therefore ID determines the maximum range of thickness allowed for developing a quantitative model.

The high selectivity of Raman spectroscopy allows one to use the distinct spectral features of each component to quickly estimate the ID. The baseline corrected Raman spectra of pure core pellet (red) and coating (blue) are shown in Figure 5.12. The ideal spectra features for probing the ID should have distinct signal and minimum interference from other components. Given this requirement, the intensity at 1728 cm\(^{-1}\) and 943 cm\(^{-1}\) were used to indicate the spectral changes of the coating and the core, respectively. Figure 5.13 (A) shows the intensity at 1728 cm\(^{-1}\) is proportional to the coating thickness. However, an inflection point indicated by the change from near-linear increase to a plateau was observed at a thickness value of 72.23 µm. A similar result was also found at 943 cm\(^{-1}\) in Figure 5.13 (B). Therefore, the ID was approximately deduced at a thickness of 72 µm. Note, ID is affected by coating formulations and instrumental settings. Light penetration is considerably blocked by the opacifiers in the coating layer. The penetration is also dependent on the wavelength and power of the laser source. Therefore, the ID in this work is an empirical parameter defined for the specific sample.
Figure 5. 12 Pure Raman spectra of core pellet (red) and coating film (blue).

Figure 5. 13 Analysis of information depth. A: Change of Raman intensity at 1728 cm\(^{-1}\); B: Change of Raman intensity at 943 cm\(^{-1}\).
A Raman thickness model was developed within the discovered ID. The optimized Raman model was built by preprocessing the spectra using baseline correction, Savitzky-Golay 1st Derivative and mean-centering. The model gave a RMSEC of 4.91% and RMSEP of 2.98%, considerably outperformed the preliminary model built in a broader thickness range (RMSEC of 9.72%).

The significant difference in the thickness ranges of NIR and Raman models may be explained by their inherent characteristics. NIR spectroscopy is sensitive to both chemical and physical attributes of in-process materials. The increase of coating thickness naturally results in increasing particle size, of which has effects on baseline, absorption and scattering (Ciurczak et al., 1986; Ely et al., 2008). The effects of particle size on spectra, and the correlation of particle size and coating thickness lead to a greater covariance captured by the NIR model. This helps the model to predict the coating thickness at higher levels. On the other hand, Raman spectroscopy is less sensitive to the change in the physical attributes, and thus the prediction range is highly contingent on the information depth.

5.3.4 Terahertz image (THI) analysis

The amplitude of a terahertz waveform is proportional to the RI difference between two adjacent medium. The raw terahertz waveforms of the reference (red) and coated sample (blue) are displayed in Figure 5.14 (A). The amplitude of the surface reflection of the sample is much weaker than the reference. The RI of the reference material, stainless steel, is of 2.76 (Filmetrics). It is much higher than the RIs of commonly used pharmaceutical materials which are usually in the range of 1.3 – 1.7 (May et al., 2011). The slight shift of the peak in the sample spectrum relative to the reference was due to the difference in their diameters. The diameters of the coated samples were usually 0.2 mm less than the reference (1.59 mm). The diameters determined the travel
distance of the terahertz pulse (from pulse generator to sample surface and back to detector). The smaller the sample, the longer distance terahertz pulse needed to travel. Figure 5.14 (B) shows the RI measurement in a frequency domain plot. The measurements were made by scanning both sides of the film patches made of the same coating formulation. The RIs were similar in the frequency range of 1-4 THz, therefore an average value of 1.72 was used to calculate the coating thickness.

![Figure 5.14 Terahertz image analysis. A: Terahertz time domain waveform; B: Refractive index measurement.](image)

The sample waveforms were normalized to the reference in both amplitudes and time scales. Figure 5.15 (A) shows an example, in which the sample waveform (green) is normalized to the reference (red). The second reflection signal, represented as the smaller peak in the sample after the first and strongest surface reflectance peak, is an indication of the interface of coating and core pellet. The time delay was obtained by averaging the estimations from six waveforms collected for each pellet. The coating thickness was subsequently calculated using Eq. 5.1. The results of the THI measurements were compared with the reference provided by optical microscope. Figure 5.15 (B) shows a non-linear pattern near the lower end of the thickness. An average thickness value of 48.85 µm was provided by THI, as opposed to 37.82 µm measured by the optical microscope. The results of samples with larger thickness were similar between two techniques.
It was conjectured that measurement of THI reached the detection limit near 50 µm. Close to this limit, it was difficult to resolve the reflectance of the coating/core interface from the reflectance of the surface. The observed detection limit was higher than the one reported in literature (30-40 µm) for tablet coating (Haaser et al., 2013a). The terahertz pulse propagating in a direction normal to the sample surface produces the highest reflectance intensity, which theoretically provides most accurate measurement. Due to the size and spherical nature of the pellets, and the manual experimental setup, the pellet curvature may lead to considerable terahertz radiation scattered away from the detector, resulting in significant signal loss. A decrease in the amplitude of the reflectance pulse is associated with an increased difficulty in resolving the second reflectance. Unlike the established empirical models, THI provided a direct measurement of the coating thickness. Also, THI performed better for samples with higher coating thickness, whereas the thickness ranges of NIR and Raman models were limited by the ID. Therefore, THI was perceived as a promising analytical method complementary to the empirical modeling approaches.
5.4 Conclusion

Coating thickness is a well acknowledged CQA that should be strictly controlled for a functional pellet coating process. This study investigated two approaches for quantitative analysis of pellet coating thickness. Empirical models of NIR and Raman spectroscopy were developed as indirect methods to determine coating thickness, whereas THI was employed to provide direct coating thickness measurements.

The customized image analysis using optical microscope offered more representative thickness data for empirical model development. The effect of the variation of thickness on the NIR model development was probed using bootstrapping simulation. The calibration error (RMSEC) of the ordinary model was smaller than 96.34% of the simulated models. The results justified the use of average thickness as the model responses. The optimized NIR model gave a RMSEC of 3.53% and RMSEP of 3.40%. All the errors were normalized to the range of the calibration (20.1-123.65 µm).

Non-linearity was found in the Raman model built in the thickness range of 24.82-99.25 µm. The information depth was examined by tracking the spectral changes in the course of increase in thickness. Limited spectral change was observed when the coating thickness exceeded 72.23 µm. Therefore, the information depth was estimated near this thickness value. By limiting the thickness range of 24.82-72.23 µm, a Raman model built had considerably lower calibration error (4.91%) than the original model in the range of 24.82-99.25 µm (9.77%). Although the range of Raman model was narrower than the NIR method, it still covered a sufficient range used in routine pharmaceutical coating process.
Terahertz imaging was investigated as an alternative technique that may offer direct, non-destructive, and efficient estimation of pellet coating thickness. The thickness determinations provided by THI were similar to the optical microscope in the range of reference thickness greater than 50 µm. However, significant discrepancy of the results was found below this thickness level. The estimated detection limit of THI was at about 50 µm, higher than the one reported in literature (30-40 µm). The difference may be explained by the weak terahertz signal associated with the size and spherical shape of the samples.

The empirical model of NIR had a broader range of coating thickness, and lower RMSEC (3.53%) and RMSEP (3.40%). However, the concern was that the broader thickness range was obtained by capturing correlated variance other than coating thickness, complicating the model interpretation. Although the Raman model had a narrower thickness range, its superior selectivity indicates the model is more selective to the coating thickness, and easier for data interpretation. Also, the greater selectivity allows a quick estimation of the information depth, which enables an efficient decision making for technique selection. If the thickness of interest exceeds the information depth, alternative techniques should be explored. Terahertz imaging does not require empirical modeling, it offers direct, rapid, and non-destructive thickness measurement. It provided more accurate measurement at a greater thickness level. But its shortcoming is the higher detection limit, restricting its use to measure samples with smaller coating thickness. Despite each technique has its own drawbacks, with their demonstrated strengths, NIR, Raman, and THI were considered as complementary tools that are valuable for developing quantitative analysis of coating thickness.

6.1 Introduction

The capability of using analytical techniques such as NIR and Raman to determine pellet coating thickness was successfully demonstrated in Chapter 5. By implementing the process monitoring method of coating thickness, the hybrid control strategy was expected to be applicable for pellet coating process with the purposes of core protection and drug release modification.

From the patient’s perspective, the rate at which the drug is released in vivo is clearly the critical performance criterion. The development of in vitro in vivo correlations (IVIVC) involve correlation between in vitro drug release profiles and pharmacokinetic data de-convoluted to show the in vivo release profile (Level A). (FDA, 1997a). Besides its important role in IVIVC study, in vitro drug release testing is a key evaluation in drug development and quality control (Nickerson et al., 2009; Williams and Liu, 2000; Yuksel et al., 2000). It is employed to guide formulation design and process optimization (Lorck et al., 1997b; Siepmann et al., 2008b).

However, the drug release test is time-consuming and requires many samples. (Freitas et al., 2005) The destructive nature limits the product understanding when in need of a reexamination of the sample for trouble-shooting. For a drug product developed using quality by design approaches, the demand of conventional drug release test can be significantly reduced by developing surrogate tests (FDA, 2004a, b). Spectroscopic methods are logical candidates to substitute the in vitro drug release tests. In previous works, NIR and Raman methods demonstrated their capability to allow quantitative analysis of the coating thickness. Because the drug release properties of many coated products are affected by the coating thickness, it was hypothesized a quantitative relationship exists between the drug release rate and the spectra.
Therefore, the study of this chapter focused on developing empirical analytical models to predict the drug release for a pellet coating process. Taking into account the proven advantages of greater thickness range and superior model performance, the study in this chapter was investigated using in-line NIR spectroscopy. The goals of this study were to: (1) establish empirical models using NIR spectroscopy to determine the drug release profiles, and (2) assess the prediction performance of the model. An extended release (ER) pellet dosage form was studied as a model system for this work. Note this approach is specific to the investigated formulation system, including coating and core materials, and therefore the study serves as a demonstration of the modeling strategy.

6.2 Material and methods

6.2.1 Formulation of Extended Release Pellets

Extended release pellets were produced by applying a water-insoluble polymer dispersion to the drug layered pellets prepared in chapter 4. Ethyl cellulose dispersion (Surelease type B NF, Colorcon, PA), was applied to coat the drug layered pellets to achieve the desired ER drug release properties. HPMC (PharmaCoat 606, Shin-Etsu, Japan) was added as a pore former to the polymer dispersion, which was subsequently diluted by deionized water to the target solid concentration shown in Table 6.1. Note, medium chain triglycerides and oleic acid were components contained in the Surelease dispersion.
Table 6.1 Formulation of ethyl cellulose polymer dispersion

<table>
<thead>
<tr>
<th>Components</th>
<th>Concentration (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl cellulose</td>
<td>9.10%</td>
</tr>
<tr>
<td>HPMC (606)</td>
<td>0.60%</td>
</tr>
<tr>
<td>Medium chain triglycerides</td>
<td>1.61%</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>1.05%</td>
</tr>
<tr>
<td>Deionized water</td>
<td>87.64%</td>
</tr>
</tbody>
</table>

6.2.2 Fluidized Bed Process, Sample Information, and Spectroscopic Data Collection

The coating process was operated using the Simplex control developed in chapter 2. The EEF target was set 0.76. The details of the fluidized bed system, process measurements and NIR setup are referred to Chapter 2 section 2.2. Six batches were produced in this work. Samples were withdrawn from the process during the spraying phase, at a time interval corresponding to approximately 4% weight gain change. A total of 28 samples were collected for calibration (batches 1-5), and five samples for test (batch 6). The maximum range of the weight gain was 4.49-26.2%.

6.2.3 Reference Method: In-vitro Drug Release Test

The drug release test was carried out using USP apparatus 1 (basket method). Six replicates of each sample were tested. The rotational speed of the drive shaft was set at 50 rpm in a dissolution apparatus (Dissolution system 2100B, DISTEK Inc., NJ). Deionized water was used as the test medium, and the water bath temperature was controlled at 37 ± 0.5°C. Aliquots of the release medium were scanned every 15 min at 243 nm by a UV-Vis spectrometer (Agilent Technologies, CA). The absorbance values were later converted to cumulative release percentages using a UV-Vis calibration curve. All the measurements were normalized to the sample weights (average of 2400 mg). The drug release profiles used for developing NIR models consisted of six
measurements made at 1, 2, 3, 4, 6, and 8 hours. The desired drug release profiles were defined using the USP monographs of Theophylline extended release capsules as a reference (USP).

6.2.4 NIR Drug Release Model Development

The NIR method development was similar to the protocols of empirical modeling described in Chapter 3 section 3.2.4. A key distinction of this study lies in the reference values. The reference values were drug release data determined by *in-vitro* drug release test. The release data were used in two ways, raw data and release indices obtained by curve fitting. The NIR models were established using two approaches. The model-independent NIR models were calculated by relating spectra to the raw drug release data, whereas the model-dependent NIR models were built using the release indices as reference values.

6.2.4.1 Model-independent Approach

The model-independent approach calculated the NIR models using two partial-least-squares (PLS) regression algorithms: PLS-1 and PLS-2.

6.2.4.1.1 PLS-2 Algorithm

Due to its relative simplicity, PLS-2 algorithm was firstly used to build a NIR model. Figure 6.1 (A) shows how the spectra is mathematically related to the reference values. X is a matrix ([n x w]) containing the NIR spectra of n samples scanned at w wavelengths. Y is the reference of drug release measurements, which consist of samples measured at multiple time points, and therefore is a matrix with a dimension of [n x p]. The column size p is the number of time points of the drug release measurement. In this study, the drug release measurements were made
at six time points and thus \( p = 6 \). By correlating \( X \) and \( Y \), a single PLS-2 model was calculated for the whole group of samples at all the time points.

6.2.4.1.2 PLS-1 Algorithm

The models built using PLS-1 algorithm were more similar to the regular empirical models described in chapter 3 (drug content) and chapter 5 (coating thickness). Figure 6.1 (B) shows the reference data \( Y \) are multiple vectors, each with a dimension of \([n \times 1]\). The number of the vectors is equal to the time points of the drug release measurement. PLS algorithm was applied to each \( Y \) vector separately, therefore a total of six PLS-1 models were calculated for the corresponding time points.

![Figure 6.1 NIR calibration model development using model-independent approach. A: PLS-2; B: PLS-1.](image)

6.2.4.2 Model-dependent approach

The model-dependent approach used the release indices as reference values. The release indices were obtained by curve fitting the raw drug release data using various mathematical equations. Each release index was an approximate indication of a drug release profile. The release profiles were fitted using mathematical equations of first-order, Hixson-Crowell and Weibull as follows,
First-order:

\[ \frac{M_t}{M_\infty} = 1 - e^{-kt} \quad \text{Eq. (6.1)} \]

Hixson-Crowell:

\[ (1 - \frac{M_t}{M_\infty})^{1/3} = k \cdot t \quad \text{Eq. (6.2)} \]

Weibull:

\[ 1 - \frac{M_t}{M_\infty} = 1 - \exp\left[\frac{- (t - T_i)^\beta}{\alpha}\right] \quad \text{Eq. (6.3)} \]

where \( \frac{M_t}{M_\infty} \) is the cumulative release percentage at time \( t \). The drug release indices of first-order and Hixson-Crowell are indicated by \( k \), whereas the Weibull fitting has two indices of \( \alpha \) and \( \beta \). NIR spectra were related to the drug release indices to build PLS calibration models. In Figure 6.2, \( X_1 \) is the NIR spectra of calibration, \( Y_1 \) represents the reference drug release data, and \( k_1 \) is the release indices obtained by fitting \( Y_1 \) using the equations described above. Notice, because two release indices were calculated for Weibull fitting, therefore two Weibull models were generated.
Figure 6.2 NIR calibration model development using model-dependent approach.

Fitting errors were calculated for each mathematical equation used for curve fitting. The steps are illustrated in Figure 6.3. The curve reconstruction was achieved by placing the estimated drug release indices back to the same mathematical equation used for curve fitting, and to calculate the reconstructed drug release profile, $Y_r$. A RMSE was calculated between $Y$ and $Y_r$ to indicate the fitting performance of the equation used. The fitting error $RMSE_{fit}$ was expressed by,

$$RMSE_{fit} = \sqrt{\frac{\sum_{t=1}^{p}(Y_t - Y_r)^2}{p-1}}$$

Eq. (6.4)

where $p$ is the total number of time points, $Y_t$ is the reference measurement at a specific time point $t$, and $Y_r, t$ is the reconstructed release percentages at the same time point.
The procedures of predicting drug release using the developed NIR calibration models are illustrated in Figure 6.4. X2 is the test spectra. The calibration model predicts the release indices kp for the test. Predicted drug release profiles are subsequently calculated by curve reconstruction using kp. The prediction error $RMSE_{pred}$ is calculated by,

$$RMSE_{pred} = \sqrt{\frac{\sum_{t=1}^{p}(Y_{t} - Y_{r,t})^2}{p-1}}$$

Eq. (6.5)

Here $Y_{2,t}$ is the reference measurement of the test at time t.
6.2.5 Model Performance Assessment

Unlike a normal evaluation of the NIR model performance by comparing the prediction error to the reference error, there is no well-accepted standard to guide the assessment of the NIR model prediction of drug release profiles. Therefore, two methods were used in this work from different standpoints. The first approach was similarity factor (f2) used by regulatory agency to examine product’s bioequivalence. The second approach was mahalanobis distance (MD), which is often used to measure the difference between two multivariate data set.

6.2.5.1 Similarity Factor (f2)

Similarity test, f2, is a mathematical index (0 <= f2 <= 100) often used to measure the difference between the drug release of test and reference formulations. The index was constructed by a function of Euclidean distance between two drug release vectors. Notice that f2 of 100 implies
the two release profiles are identical, whereas $f_2$ of 0 indicates the two profiles are completely different: the release of one formulation is completed before the other begins. An average difference of 10% at all time points would give an $f_2$ close to 50. A $f_2 \geq 50$ is considered similar in terms of bioequivalence (FDA, 1997b, 2014). Therefore, $f_2$ was used as a method premised on regulatory perspective to assess the difference between NIR prediction and reference. It is calculated by,

$$f_2 = 50 \cdot \log\left(\frac{1}{\sqrt{\frac{1}{p} \sum_{t=1}^{p} (Y_{2t} - Y_{1t})^2}} \right) \cdot 100 \quad \text{Eq. (6.6)}$$

where $f_2$ is an unweighted RMSE over the whole drug release profile with a total $p$ time points, $Y_{1t}$ and $Y_{2t}$ are the release percentages of reference measurements and predictions at a time point $t$.

6.2.5.2 Mahalanobis Distance (MD)

Drug release profiles measured at multiple time points are essentially a multivariate data set. The data are highly correlated because the release percentage at each time point is related with all other time points. Therefore, classic Euclidean distance may not be the most appropriate method to assess the difference between two release profiles. MD is a statistical distance often used to measure the difference between two multivariate means. The MD is expressed as,

$$MD = \sqrt{(Y_2 - Y_1) \cdot S_{pooled}^{-1} \cdot (Y_2 - Y_1)} \quad \text{Eq. (6.7)}$$

where $Y_1$ and $Y_2$ represent the reference and prediction of the release profiles, respectively. $S_{pooled}^{-1}$ is the inverse of the sample variance-covariance matrix pooled from the prediction and measurement (Tsong et al., 1996).
To acquire MD measurements with statistical evidence and reduce the probability of making type I error, error propagation was used to take into account various types of uncertainty related to the predictions. The sources of the uncertainty were drug release test, sampling, NIR data collection, fitting and modeling errors, etc. The variance of the drug release measurements were used to indicate the uncertainty of the drug release test and sampling, which was calculated from the release data of sample replicates at different coating weight gain. The uncertainty of NIR data was from the sample under interrogation, NIR spectrometer, and common cause process variance. The uncertainties were nested in the individual NIR spectra collected in real time. Therefore, instead of using the average, the individual in-line NIR spectra were used to calculate the prediction of drug release. The uncertainty of the modeling indicated by the drug release fitting error and modeling error. The curve fitting error $RMSE_{fit}$ and overall prediction error $RMSE_{pred}$ were calculated using Eq. (4) and (5), respectively. The variances of the described sources were pooled together, and translated to the predictions via error propagation.

6.3 Results and Discussion

6.3.1 NIR Drug Release Model

6.3.1.1 Model-independent Approach

The first NIR model was developed using PLS-2 algorithm. The predictions of drug release provided by PLS-2 are overlaid with reference measurements and are shown in Figure 6.5 (A). The samples coated at different weight gains are indicated by colors. The solid points are reference measurements, and the open circles are predictions. Each sample had considerably high prediction error. The PLS-1 approach considerably improved the prediction error, as evidenced by the data shown in Figure 6.5 (B). The PLS-1 models were established by preprocessing the spectra using
SNV and mean-centering, and including two latent variables. The difference in the model performance was inferred associated with how the Y was used in the calculation. In PLS-2 algorithm, Y was a multivariate and highly correlated data set. Because the release percentage of each time were strongly related to adjacent time points, an irrelevant variance contained at one time point inherently propagated to the next time point. The more irrelevant Y-variance caused a co-variance captured by the PLS-2 model.

![Graph A](image.png)

![Graph B](image.png)

Figure 6.5 Predictions of drug release profiles provided by NIR models built using model-independent approach. A: PLS-2 predictions (open circles) and reference measurements (solid circles); B: PLS-1 predictions (open circles dashed lines) and reference measurements (solid circles lines).

### 6.3.1.2 Model-dependent approach

The raw drug release data were fitted using different mathematical equations described in 6.2.3.2. The results are listed in Table 6.2. The release indices of first-order and Hixson-Crowell fittings are represented by k and hck, respectively. The two indices of Weibull fitting are indicated by α and β. The fitting errors for each mathematical equations are also shown in the Table. Note, batches 1-5 were calibration batches, and batch 6 was the test batch.
Table 6. 2 Estimated release indices and fitting errors of first-order, Hixson-Crowell, and Weibull equations.

<table>
<thead>
<tr>
<th>Batch #</th>
<th>Sample #</th>
<th>Release indices by curve fitting</th>
<th>Fitting errors (RMSE_{fit})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>First-order</td>
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<tr>
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The NIR models calculated using first-order, Hixson-Crowell, and Weibull fittings were called first-order model, Hixson-Crowell model, and Weibull model for short in the results and

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discussion. The optimized models of first-order and Hixson-Crowell were developed by preprocessing the spectra using SNV followed by mean-centering, and the Weibull model was optimized using preprocessing of first derivative and mean-centering. All the models were calculated using three latent variables. The predictions of release indices versus the reference values obtained by curve fitting are shown in Figure 6.6: first-order (A), Hixon-Crowell (B), and Weibull (C). Note, the β index of Weibull fitting was not used to build the model. The β index obtained by curve fitting had a very limited range of 1.04 – 1.30. Also, the changes in the drug release profiles were dominated by the change in scale (α) instead of shape (β). Therefore the index β was kept at a constant average value of 1.20. The predicted release profiles were reconstructed using the predicted release indices. The comparisons of predicted drug release by the model-dependent approach with the reference measurements are shown in Figure 6.7.

![Figure 6.6 Predicted versus curve fitted release indices. A: First-order, B: Hixon-Crowell, and C: α index of Weibull.](image)
6.3.2 Assessment of Model Performance

6.3.2.1 Similarity Factor ($f_2$)

Similarity factor values were calculated for the test samples with different coating weight gain. Figure 6.8 reveals the $f_2$ values of most of the models are above 50 with the exception of PLS-2 model which has $f_2$ values all below 50. For the other models with $f_2$ greater than 50, they were considered “similar” to the reference measurements at a criteria based on regulatory perspective. The criteria was originally defined to assess the sameness between two products made of different formulation or manufactured at different times (Ma et al., 2000). From a perspective of bioequivalence, $f_2$ is a reasonable method to compare two products. A stricter criterion may jeopardize drug product’s affordability and availability.
Nevertheless, the goal of a NIR model is to provide predictions as close as possible to the reference measurements. Therefore, $f_2$ assessment is not the most appropriate way to assess the prediction performance. A simulation study was performed to illustrate this drawback. In Figure 6.9 (A), the green lines are *in-vitro* drug release measurements, the red area is composed of numerous simulated drug release profiles that have $f_2 \geq 50$ (compared to the average of the measurements), and the blue dashed lines are the boundaries indicating $f_2 = 50$. A PCA calibration model was built using the drug release data of the measurements to test the simulated drug release profiles. The PCA scores are shown in Figure 6.9 (B). Most of the simulations (red diamonds) are
on the outside of the confidence interval defined by the reference measurements (dashed circle). The results indicated the criteria of $f_2 \geq 50$ is not premised on statistical inference.

![Figure 6.9 Illustration of $f_2$ criteria by simulation. A: Simulated drug release profiles with $f_2 \geq 50$; B: PCA calibration model (reference measurements) and test (simulated drug release).]

6.3.2.2 Mahalanobis Distance

The effects of uncertainties, from various sources, on the predictions of drug release were studied by error propagation. Figure 6.10 (A) shows the reference measurements. The observed variation was mainly associated with the uncertainty of drug release test and samples. The error propagated drug release profiles predicted by first-order, Hixson-Crowell, and Weibull models are shown in Figure 6.10 (B) – (D), respectively. Although all the predictions had much greater variances than the reference measurements, the ones of the Hixson-Crowell model were considerably lower than the other models. Since all the models had similar uncertainty of drug release tests, sampling and NIR data collection, the lower variations observed in the Hixson-Crowell model were attributed to its lower overall prediction error. The prediction error consisted of errors from modeling and curve fitting. The two types of errors were convoluted because of the curve reconstruction. By taking into account the fitting error (calculated and shown in Table 6.2),
the de-convoluted errors are shown in Figure 6.11. Note, in the figure, the errors refer to mean squared error (MSE). The red bars indicate the fitting errors of each equation, whereas the green bars represent the modeling error, which was obtained by subtracting the fitting error from the overall prediction error.

The first-order model had reasonable modeling error, indicating there was valid correlation between the coatings of the ER pellets with the NIR spectra. This was supported by the studies in chapter 5, where empirical NIR models were developed and were able to predict the pellet coating thickness. However, the first-order model had very poor fitting to the drug release profiles, indicating the drug release of the ER pellets was not primarily controlled by diffusion mechanism (which is expected to be fitted well by first-order kinetics). The Weibull model gave much better fitting results than first-order and Hixson-Crowell models, however it did not provide the most accurate predictions. Extremely high prediction errors were observed for sample 2 and 4, which were due to their high modeling errors when predicting the $\alpha$ index (the prediction errors of samples 2 and 4 were 8.6 and 10.8 times larger than sample 3). The reasons for the higher prediction errors were unclear due to Weibull’s lack of physical connection with the drug release mechanism, and inferred mainly associated with the mathematical computation of PLS model (possible interactions among the $\alpha$ index and the uncertainty of samples).

In general, the Hixson-Crowell model gave lower prediction errors. It had reasonably low fitting errors as evidenced by the data shown in Figure 6.11. A conjectured drug release mechanism is illustrated in Figure 6.12. The structure of ER pellet before subjecting to the drug release test is shown in Figure 6.12 (A). As the drug release test started, the release medium gradually diffused through the EC film to the drug layer. The drug layer, which had water
soluble drug dispersed in a hydrophilic polymer HPMC matrix, hydrated when it was in contact with water, as depicted in Figure 6.12 (B). At the initial stage, the drug release followed a zero-order model, which was supported by an average R² of 0.999 for release percentage below 30%. Literature reports hydrated HPMC forms a viscous gel layer, acting as a barrier to drug diffusion by opposing penetration of water (Wen and Park, 2010). Therefore, excess of drug may be present to maintain saturation on the surface of the hydrated gel layer, and the drug release rate was mainly controlled by diffusion from non-disintegrating matrix. Although the EC film is water-insoluble, it was presumed had decreasing impact on the overall drug release as the release test continued. Besides the pathways within the EC film created by water-soluble pore former (HPMC), the swelling nature of the drug layer exerted pressure on the EC film and may resulted in film breakage. This was supported by the fact that holes were visualized on the surface of EC film after the drug release test. The breakage of the EC film significantly lessened its importance of regulating the drug diffusion through the membrane. Besides the drug layer’s swellable property, it was also erodible and dissolvable, and therefore the volume and surface area of the drug layered pellet beneath the EC film gradually diminished. This possible process is shown in Figure 6.12 from (C) to (D). Consequently, the drug release of ER pellets was considered regulated by a combination of diffusion, swelling/erosion, and geometry/area changes (Wen and Park, 2010). Owing to its spherical shape, this might explain why the drug release profiles can be fitted better by Hixson-Crowell model. It should be noted that Hixson-Crowell model assumed a constant concentration gradient is maintained during the drug release (Frenning et al., 2003; Hixson and Crowel, 1931), which was not the case in practice. The gradually decreased concentration gradient lead to further reduced rate constant in addition to the effect of the diminished surface area. This might explained its greater fitting errors than the Weibull model.
Because of the lower fitting errors and the correlation between NIR spectra and the pellet coating thickness, the Hixson-Crowell model gave an acceptable overall prediction performance, which was superior to the first-order and Weibull models. Since the objective of this study was to build an empirical drug release model using NIR, the in-depth investigation of the drug release mechanism was considered as a future direction which should be pursued in future studies.

Figure 6. 10 Drug release profiles calculated by error propagation. A: Reference measurements; B: Predictions of the first-order model; C: Predictions of the Hixson-Crowell model; D: Predictions of the Weibull model.

Figure 6. 10 Drug release profiles calculated by error propagation. A: Reference measurements; B: Predictions of the first-order model; C: Predictions of the Hixson-Crowell model; D: Predictions of the Weibull model.
Figure 6.11 Comparison of the overall prediction error, fitting error, and modeling error of the NIR models built using model-dependent approach.

Figure 6.12 Schematic illustration of the possible drug release mechanism of the ER pellets.
The MDs of the predicted drug release profiles were calculated and the average values are listed in Table 6.3. The last column in the table shows the MDs of reference measurements, indicating the multivariate distances of each individual drug release profile to the average release profile. The MD of reference measurements reflected the inherent uncertainty in sampling and drug release test, therefore was perceived as the reference error.

Table 6.3 Mean mahalanobis distances between the predictions and reference measurements.

<table>
<thead>
<tr>
<th>Sample #</th>
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<th>Weibull</th>
<th>Reference Measurement</th>
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</thead>
<tbody>
<tr>
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</tr>
<tr>
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<td>5.77</td>
<td>2.62</td>
<td>1.43</td>
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<tr>
<td>Mean</td>
<td>12.74</td>
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<td>20.99</td>
<td>1.33</td>
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The Hixson-Crowell model outperformed first-order and Weibull models. Tukey all pairwise test was used to make statistical comparisons between the predictions and measurements for all of the three models. The results are shown in Table 6.4. The symbols of “***” and “*” indicate a statistical difference at significant level of 0.001 and 0.05, respectively. The predictions of sample 2, 3, and 4 provided by the Hixson-Crowell model were statistically indistinguishable from the reference measurements. Figure 6.12 shows the desired drug release profile (using USP monographs of Theophylline as a guide) is in the middle of sample 3 and 4. Therefore, the Hixson-Crowell model was considered having a superior prediction performance for the investigated ER pellet sample.
Table 6. 4 Tukey all pairwise comparison of the mahalanobis distances between predictions and reference measurements. **: P < 0.001; *: P < 0.05.

<table>
<thead>
<tr>
<th>Sample #</th>
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<td>5</td>
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Figure 6. 13 Predictions of Hixson-Crowell model versus desired drug release profile.
6.4  Conclusion

An empirical NIR model was successfully developed to determine the drug release profiles of ER pellets. Different approaches were used to build the drug release model. The prediction performances of NIR models were assessed using f2 and MD. The f2 were all greater than 50 except the one calculated by PLS-2 algorithm. F2 provides important criteria from the regulatory perspectives. However, the simulation study proved the criteria of f2 = 50 was not based on statistical inference.

MD was used to establish a stricter criteria based on statistical inference. The variations from several sources associated with the NIR predictions were estimated. The effects of the variations on prediction performance was probed by error propagation. The MDs of reference measurements were calculated and used as the reference error. The MDs between the NIR predictions and reference measurements were compared with the reference error. Tukey all pairwise test was employed to deduce the statistical conclusion. Given the desired drug release profile defined by USP monographs, the NIR model developed using Hixson-Crowell equation was perceived the optimized model.

The drug release profiles of an ER pellet dosage form were adequately predicted in the desired range. The stricter criteria defined by MD were advantageous to ensure the reliability of the predictions, allowing it to be used as a process monitoring method implemented in the proposed hybrid control system. The successful development of the NIR method holds promise to reduce the use of destructive and time-consuming drug release tests, allow real time quality assurance, and support a process to achieve real time release.
Chapter 7 Summary

To date, most pharmaceutical batch processes are still operated under the basic control. The basic control has several drawbacks. To avoid additional regulatory submission, the process settings discovered by trial and errors are often held constant. The rigid process operation limits the opportunities for improved process understanding and optimization. Because in-line analyzers are often unavailable, the product quality is usually tested off-line using end product tests. The quality attributes measured in this way cannot be used in feedback to make efficient process adjustment and allow continuous process improvement. As a result, the product quality is trapped in the batch process endpoint. The uncertainty in end product quality requires frequent reprocessing and may lead to more batch failures. Consequently, the basic control does not effectively ensure the product quality and hence has limited the process capability.

The pharmaceutical industry has been seeking solutions to address the issues mentioned above. Alternative process control strategy is seemingly a logical way to improve the process capability. Unlike another promising solution using continuous process, the development of alternative process control does not require expensive capital investment for building the infrastructures. Given the greater adaptability of batch processes, the alternative control approach is expected to have broader applications. A hybrid process control system was proposed in the dissertation as an example to illustrate the alternative control strategy. The goals of the hybrid control were to ensure product quality and improve process capability. A challenging unit operation, fluidized bed pellet coating process, was investigated as a model system to develop and demonstrate the control system.
The hybrid control system consisted of three elements: process manipulation, monitoring, and optimization. A process manipulation strategy was developed in chapter 2 with the goal of achieving successful process operations. The manipulation was premised on the first principle understanding of the coating process. Environmental equivalency factor (EEF) was used to regulate the drying environment, which was executed using the Simplex control algorithm. The Simplex control was able to maintain the EEF at its target by simultaneously changing three manipulated parameters. The same EEF produced a consistent drying environment during the coating process, which was supported by the NIR PCA results. The batch failures frequently encountered under the basic control was successfully eliminated by using the first principle control.

Several process monitoring systems were developed using various spectroscopic methods. Real time quantitative analyses of CQAs were enabled by building empirical models using in-line NIR and Raman spectroscopy. The process endpoint automatically ended when the desired quality limits were met, which was demonstrated in the drug layering study. In chapter 5, the capabilities of quantitative determination of pellet coating thickness were investigated using NIR, Raman, and Terahertz imaging. Each technique had unique strengths, and were all considered valuable tools due to their complementary characteristics. In chapter 6, an empirical NIR model was built to predict the drug release profiles of an ER pellet dosage form. Given the desired drug release range, the model-dependent approach using Hixson-Crowell was able to provide adequate predictions. The predicted drug release profiles were statistically indistinguishable from the corresponding reference measurements.

An operational space was established for a drug layering process in chapter 4 to achieve process optimization. A design space was developed ahead of time using design of experiments. The investigated process factors were the EEF and atomization pressure. The results indicated both
factors had significant influences on the quality attributes of interest, including coating efficiency, content uniformity, and agglomeration percentage. Edge of failure analysis was performed by taking into account the individual variability of each process factor. This allowed to calculate the probabilities of in specifications for each setpoint in the design space. The operation space was discovered in the design space based on a specified requirement of confidence level. The optimized process was endowed with greater confidence to meet the specifications.

The hybrid control system substantially improved the process capability for the drug layering process compared to the basic control. The results were supported by the statistically increased process capability indices. The works in this dissertation served to illustrate the capability of the alternative process control strategy. The control elements are adaptable and can be altered to suit the specific needs of a process. The successful demonstration of the alternative control strategy offers encouraging opportunities to improve the process capability for pharmaceutical manufacturing using batch processing.
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Filmtricts, Refractive index of stainless steel.


ShinEtsu, Usp hypromellose pharmacoat.


USP, 711 dissolution.

USP, 2011. 905 uniformity of dosage units.
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