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Studies to investigate variables affecting coating uniformity in a pan coating device

Preetanshu Pandey
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Studies to investigate variables affecting coating uniformity in a pan coating device

Preetanshu Pandey

Dissertation submitted to the
College of Engineering and Mineral Resources
at West Virginia University
in partial fulfillment of the requirements
for the degree of

Doctor of Philosophy
in
Chemical Engineering

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Morgantown, West Virginia
2006

Keywords: Pan coating, video-imaging, coating variability, coating model, Monte Carlo,
discrete element modeling, tablet area, baffles

Abstract

Studies to investigate variables affecting coating uniformity in a pan coating device

Preetanshu Pandey

The purpose of this study was to investigate the variables that affect the mass coating variability (CV) in a pan coating process. A novel video-imaging technique was used to record the movement of tablets inside the pan. The effects of pan loading, pan speed and particle shape were studied. The response variables were circulation time, surface time, projected surface area, dynamic angle of repose, cascading velocity (2 directions), and dispersion coefficient. Experiments were conducted at 3 different pan speeds, 6, 9 and 12 rpm, and two pan loadings. The circulation time ranged from 2.8-10.8 s, depending on the operating condition, and increased with increasing pan load and decreasing pan speed. The distributions of circulation time, surface time, and projected surface area were found to be non-normal. The average velocity of tablets in the cascading layer was found to be significantly higher than spheres. A linear model ($R^2 > 0.98$) best described the variation of velocity as a function of pan speed. The video-imaging technique was also successfully used to quantify the effect of baffles on the mixing inside the pan.

The video-imaging data were used as an input to a mechanistic model to predict CV from measurements using Monte Carlo simulations. The effects of pan speed, coating time, tablet size, pan loading, spray flux distribution inside the spray zone, spray shape, and spray area were investigated. Coating experiments were conducted to verify the predictions from the Monte Carlo simulations, and the trends predicted from the model were found to be in good agreement to the experiments when the exact experimental conditions were taken into consideration for the simulations.

Results of DEM (discrete element modeling) simulations were compared with those obtained from video-imaging experiments and the trends obtained from DEM and experiments were found to be in good agreement. Velocity profiles along the entire top cascading layer of particles were also estimated. The particles in the cascading layer were found to reach their maximum velocity at positions close to the mid-point of the cascading surface. Comparison of simulated velocity profiles showed good agreement with published scaling laws for rotating drums, and an improved correlation for scaling with respect to the pan loading was proposed.

This information will be useful to any coating process and will be of importance when devising ways to reduce the CV in coating operations. It can also be used effectively to develop scale-up models, test the effects of parametric changes on CV, and subsequently reduce the time required to get products to market.

Dedicated to my family.....

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1. Introduction

The uniformity of coating applied to large particles and tablets in rotating drum coating devices is of significant interest to the Pharmaceutical Industry. The coating of solid dosage forms, such as capsules, granules, and tablets, provides one of the following attributes:

- Improves the aesthetic appearance of the tablet
- Provides protection from the environment (air, moisture, light etc.)
- Masks unpleasant odors or tastes
- Provides a means of identification
- Facilitates handling (coating eliminates dust)
- Controls site (in the body) of drug release (enteric coating)
- Controls rate of drug release (sustained release coating)
- Provides an active drug coating to the substrate

Coating of small particles is often carried out in fluidized beds but tablets are not generally coated in such equipment due to the mechanical damage that occurs in the device. Rotating drums are used to coat tablets and are widely used in many engineering (chemical and metallurgical) processes, such as mixing, drying of granular materials and powders, milling, and granulation.

The uniformity of coating applied to these particles is very important especially when the coating plays an active role in the drug release process (a functional coat such as enteric, sustained, active drug coated). Tablets should be exposed to the coating spray

or zone at the same rate to ensure uniform coating; however, this is almost impossible to achieve in practice. To improve coating performance, it is imperative to study in detail the motion of tablets in the pan. Understanding the factors that affect the coating uniformity can help resolve performance and manufacturing issues. These factors include the movement of tablets within the rotating pan or drum, the frequency and duration of tablet appearance on the bed surface and the projected surface area of tablet that ‘sees’ the spray, which in turn are dependent on the operating conditions, *e.g.*, pan speed, pan solids loading, and the presence/absence of baffles [1]. The regularity with which particles pass through the spray zone plays an important role in determining the overall uniformity of coating for the batch of material being coated [2].

With the advent of process analytical technology (PAT), a new FDA initiative, the industry is focusing on improving manufacturing efficiency and product quality. The goal of PAT is to adopt innovative technologies to increase product quality without raising concern that a new approach will lead to validation risks and production delays. One of the key components of this knowledge-based approach is to understand better the product manufacturing processes. With this in mind, the current study focuses on understanding a key unit operation in the pharmaceutical industry, namely coating. By incorporating the experimental and modeling approaches introduced in this study, the effects of variables used in the pan coating process can be quantified on a sound scientific basis and a rational method for process improvement can be formulated.

The current work utilizes novel video imaging techniques to study the tablet movement in a rotating pan coater. The effects of pan speed, pan loading, tablet shape, and tablet size on the circulation time, surface time, velocities of particles both parallel

and perpendicular to the flow, and projected surface area of tablet exposed towards the spray nozzle were investigated. The video-imaging system was used to quantify the effects of mixing aids, such as baffles, on the movement of tablets inside the pan. The experimental data were used to develop a model for coating variability (CV) using Monte Carlo techniques. The effects of tablet movement dynamics and spray dynamics on CV were investigated using the mechanistic model developed.

This information will be useful to any coating process and will be of importance when devising ways to reduce the coating variability in coating operations. It can also be used effectively to develop scale-up models, test the effects of parametric changes on CV, and subsequently reduce the time required to get a product to market.

2. Literature Review

Coating is one of the oldest pharmaceutical arts still in existence and is of significant interest to the Pharmaceutical and Agricultural Industries. The various types of coating equipment used can be classified broadly into pan coaters and fluidized bed coaters.

2.1. Overview of pan coaters and fluid bed coaters

The fluidized bed coaters, in general, provide more uniform coating and require shorter processing time but are limited to the use of relatively small particles. The major criterion to decide between the fluidized bed coater and pan coater is the size of the substrate. A rule of thumb is that if the product diameter is less than 6.35 mm (1/4 inch) then the preferred equipment for coating is the fluid bed coater [3]. The main reason behind this is the energetic product movement inside the fluid bed, which may cause attrition of the particles. Pan coaters or rotating drums are widely used in Coating and Pharmaceutical Industries to coat relatively big particles or tablets. The main disadvantages of a pan coater are the long processing time and higher product variability. A comparison between these two techniques is summarized in Table 2.1.

Table 2.1. Comparison of pan and fluid bed coating methods [4]

Coater Type	Advantages	Disadvantages
Pan	<ul style="list-style-type: none">• Low Mechanical Stress• Simple Operation	<ul style="list-style-type: none">• Longer Processing Time• Greater Product Variability
Fluid Bed	<ul style="list-style-type: none">• Short Processing Time• Low Product Variability	<ul style="list-style-type: none">• High Mechanical Stress• High Erosion

2.1.1 Pan coaters

Tablets and large particles can be coated in pan coaters or rotating drums relatively easily. As the drum rotates, the bed becomes high enough for the particles to cascade downwards under gravitational force, thus providing a fresh layer of particles to come in contact with the spray and hence get coated with the spraying solution. The coating solution is fed through a two-fluid air atomizing spray nozzle. In a conventional pan coater the hot air flows onto the surface of the tumbling bed and facilitates the evaporation of the solvent. The air is then removed via an exhaust duct. The repeated coating and drying cycles cause a coherent film of coating to be built up on the surface of the tablets. Improvements in the conventional pan coaters came about due to its limitations in both drying and mixing capabilities. The Pellegrini coating pan was introduced, which was somewhat angular and rotated about a horizontal axis. This pan was more suitable for film coating, including aqueous-based coating solutions, although drying still took place only at the surface of the bed.

A significant improvement to the conventional pan came in the form of a perforated pan coater. Such pans have perforated surfaces through which the hot air is removed through the bottom of tablet bed. A schematic diagram of a perforated pan coater is shown in Figure 2.1. There are various types of perforated pan coaters, as shown in Figure 2.2. They differ in the way the exhaust air is drawn out of the bed. The basic idea is to maximize the drying capability of the coater so as to minimize core penetration by the coating solution at high spray rates. One such commercialized perforated pan coater is the Accela-Cota, an invention of Eli Lilly & Co. The presence of baffles increases the efficiency in air exchange and also promotes mixing. Another pan design,

which is a slightly modified form of the Accela-Cota, is the Hi-Coater. The Hi-Coater, shown in Figure 2.3, contains four perforated panels linked to the air ducts that make continuous contact with the exhaust plenum as the pan rotates. A good overview of the different kinds of pan coaters is provided by Porter [5].

Figure 2.1. Schematic sketch of a perforated pan coater [4]

2.1.2 Fluid bed coaters

The fluid bed coater provides greater coating uniformity compared to a pan coater but is suitable only for smaller particles. The Wurster coater is the earliest and most commonly used form of fluid bed coater. In this equipment, a bed of tablets is fluidized by a stream of air passing through a distributor plate. The bed is divided axially by a vertical draft tube or Wurster insert, as shown in Figure 2.4.

Figure 2.2. Various kinds of perforated pans [6]

Figure 2.3. Schematic diagram of a Hi-Coater [4]

Figure 2.4. Schematic diagram of a Wurster fluidized bed coating equipment [41]

The distributor plate is designed such that the flow of air is much higher in the center draft tube than in the annular region. As the particles pass through the central column they get coated by the coating solution sprayed through a nozzle located in the center as the particles move upwards. As air leaves the draft tube the velocity goes down due to the increase in flow area, and the particles fall down into the annular region. The motion of the particles ensures a uniform circulation pattern. The rapid drying of the particles as they are being coated reduces the tendency of the particles to agglomerate.

2.2. Particle motion in a particulate bed

Various experimental techniques (mostly particle tracking) as well as models have been used in the past to study particle motion inside a multi-particulate system. These will be discussed in more detail in sections 2.2.1 and 2.2.2, respectively. Some of the particle tracking techniques used include video-imaging, PEPT (positron emission particle tracking), PIV (particle imaging velocimetry), NIR (near-infrared), MRI (magnetic resonance imaging) etc. The main modeling approaches include theoretical models such as the continuum model proposed by Khakhar et al. [7], discrete element modeling (DEM), and Monte Carlo techniques. The theoretical models help to describe the movement of particles inside the rotating drum and can be useful for mixing studies. However, they do not address the spray dynamics of a pan coating system. The DEM approach has the same problem. In addition, DEM is time intensive as Newton's equations of motions are solved for each particle at every time step (typically of the order of micro seconds). This becomes extremely time-consuming for a pan coating system where the number of particles in the system is high. The advantages of these techniques are that the input parameters can be found from physical properties and no experimental work is required. However, one might argue that some experimental validation and some parameter adjustments will always be required in order to attain realistic results. On the other hand, Monte Carlo simulations capture experimental information and allow prediction of coating mass variability for the conditions used in the experiments [4].

2.2.1. Experimental approaches

In one of the early experimental studies, Prater et al. [9] studied the tablet appearance times using photographic and manual counting methods using a bed

containing different colored tracer tablets. They reported an average circulation time of 25 s and a spread of 2-243 s for their pan coater. Leaver et al. [10] used light emission from a single luminous tablet, in a 60 cm Accela-Cota (Manesty Machines plc, Liverpool), to quantify surface time (time that the tablet spends on the surface per pass) and circulation time (time that the tablet spends within the bulk of the tablet bed). The results showed that both the surface and circulation times decreased with increasing drum speed and loading. The run time in their experiments was 15-20 min. They reported average circulation times between 2-14 s, and average surface times between 5-300 ms, depending on the tablet size (7.5, 9, 11 mm), drum speed (6, 9, 12 rpm) and drum loading (6, 8, 10 kg). Although signal intensity was recorded, no projected surface area data were published. They also found that the baffles have an effect on the surface times with significantly higher surface times being recorded for an unbaffled system. They concluded that there was irregularity of tablet appearances at low drum speeds and in the absence of baffles.

Nakagawa et al. [11] used MRI to measure velocity and concentration of granular flows in a rotating horizontal cylinder. The particles used in the study were mustard seeds of average diameter 1.5 mm. The rotation of the cylinder (diameters 88 mm and 70 mm) was set at one of three levels, 30, 53, and 78 rpm. The flow velocity profile as a function of cylinder rotation rate was obtained. They also reported that the thickness of the flowing layer increased with increasing cylinder rotation speed. Results from this work were compared to DEM simulations by Yamane et al. [12] and were in good agreement when the coefficient of friction and sphericity factors were adjusted in the simulation to give the best fit. Mann and Crosby [13],[14] showed that movement of particles inside

air-suspension coating units (spouted beds) could be analyzed by studying their cycle time distribution (CTD). They used a single magnetic particle with a detecting coil located around the spout at the top of the bed. The electromotive force (emf) induced in the coil, as the tracer tablet passed through it, was used to measure the CTD [15].

Among more recent studies, Wilson and Crossman [16] analyzed the influence of tablet shape and drum speed on coating uniformity by taking pictures of particles in a Mini-Hi-coaterTM (Vector Corp., Marion, IA). Tablets were fractured using a Teflon-coated razor blade and examined under a Nikon SMZ-U microscope with a CCD (charged coupled device) camera to measure coating thickness. The drum speed was set at one of three different levels; 9, 14, and 21 rpm. They showed that the tablet shape directly influenced the intra-tablet coating uniformity and that it decreased from round, oval, capsule to large oval. Results showed that coating uniformity increased with drum speed. They also found that in all cases the coating was thicker on the face than on the edges or ends of tablets. Kennedy and Niebergall [17] used image analysis to evaluate pharmaceutical coatings. The main idea was to provide data for optimization of coating uniformity and thickness in a fluid bed coater. Nonpareils (Sugar spheres, 10-12 mesh) were used as the bed material, and were coated with polyethylene glycol. The images were captured using a digital camera (Kodak DCS 420) and analyzed using Image Pro Plus (Media Cybernetics, Silver Springs, MD) software. Imaging analysis was also used by Van Puyvelde et al. [18] to determine the mixing dynamics of solid materials in a rotating drum with an internal diameter of 57 cm. The variation in mixing dynamics due to changes in drum speed from 5 to 15 rpm, particle (oil shale) size from 0.89 to 5.08 mm, and the drum loading from 10 to 40 % by volume was studied. A Nikon F3 camera was

used to capture 240 consecutive images of the drum, at a rate of 3.8 frames/s, which were analyzed in a post-processing step. Results showed that mixing dynamics followed a constant rate until a completely mixed state was obtained. Also, mixing was shown to occur in a stepwise manner. The main disadvantage of using a digital camera to capture images of particles is that it leads to very large data files to be post-processed.

Parker et al. [19],[20] used PEPT to track a radioactively labeled tracer particle in a partially filled horizontal rotating drum. PEPT was applied to study powder flow in rotary mixers and fluidized beds, and provided information not only on the residence time of the labeled particle in different regions but also on its velocity. They varied the drum speed from 10-65 rpm and used particles (glass spheres) with diameters of 1.5 mm and 3 mm. An active surface layer approximately two-thirds as thick as the underlying bed layer was observed in all cases. They also report that much of the axial movement occurs in the active layer or close to the top of the cascading layer, but some axial movement also occurs within the bed layer.

Heinamaki et al. [21] studied an aqueous-based hydroxy propyl methyl cellulose (HPMC) film coating of tablets performed by a side-vented pan coating apparatus (Thai Coater, model 15, Pharmaceuticals and Medical Supply Ltd. Partnership, Thailand). The variables studied were flow rate of coating solution, spraying pressure, inlet air temperature, pan speed, position of spray gun and angle of spray gun. The surface quality of the film-coated tablets was confirmed by scanning electron microscope (SEM). Rotating speed of the pan was identified as the major parameter with respect to the film thickness and breaking strength of the HPMC coated tablets. The quality of HPMC film coating was found to improve with a decrease in the flow rate of coating solution or with

an increase in the pan speed. Kirsh and Drennen [22] used NIR spectroscopy to determine the amount of polymer film applied to tablets cores in a 6 in. Wurster column (Glatt Air techniques, Ramsey, NJ). This provided a rapid, non-destructive, and simple means to monitor the film coating process. They also indicate that future work will involve using a fiber-optic probe to conduct on-line monitoring of the process. Buchanan et al. [23] also used NIR to rapidly screen tablets in the development of new coating technology. They show strong agreement between the NIR and HPLC (High Performance Liquid Chromatography) methods.

Saadevandi and Turton [24] used computer based video imaging techniques to measure the axial and radial components of particle velocity and voidage profiles in the draft-tube region of a semi-circular spouted fluid bed coating device. Jain et al. [25] used particle tracking velocimetry to study the velocity field within the fluidized layer of particles in a rotating tumbler. The granular flow was illuminated by a laser flash and recorded by a standard PIV system having a CCD camera. They found that the normalized streamwise velocity profile was linear throughout the fluidized layer and became logarithmic as it enters the ‘fixed’ bed.

2.2.2 Modeling approaches

Although tablet coating is one of the oldest pharmaceutical processes, the process is still often considered more of an art than science. The underlying science of the coating process is complicated and the ability of the pharmaceutical scientist to predict reliably the performance of a coated product *a priori* is often limited. Different modeling approaches have been used to characterize the mass coating variability. The most common approach in the industry is to study the effects of coating formulation and

process parameters on coating mass variation through a series of designed experiments with the appropriate statistical analysis and regression [26]. This type of modeling (or regression) results in information specific to a single formulation/product and is particularly useful for optimization purposes but ignores the science behind the process.

There are various techniques used to model the mass coating variability in a pan coating process [30]. These include:

- Phenomenological modeling
- Compartment and population balance modeling
- Monte Carlo modeling
- DEM (discrete element modeling) and CFD (computational fluid dynamics) modeling

Phenomenological Modeling of the Renewal Process

In this approach, the overall coating process is considered to be made up of several coating events, where the tablet receives coating during each event and the final coating weight gain is the summation of coating received in all of these events. Thus the number of cycles a tablet completes in the spray zone during the entire operation and the amount of coating received per pass through spray zone determine the total amount of coating received by an individual tablet. The distribution of the number of cycles can therefore help to quantify the coating variability. Mann et al. [31] used probability theory to derive an expression for the CV in terms of the number of passes/cycles distribution, and the coating-per-pass distribution. They showed that the overall coefficient of variation for fluid bed systems is given by Eq. (2.1).

$$CV = \frac{\sigma_{total}}{\mu_{total}} = \sqrt{\left(\frac{\sigma_x}{\mu_x}\right)^2 \frac{1}{\mu_n} + \left(\frac{\sigma_n}{\mu_n}\right)^2} \quad (2.1)$$

where μ and σ stand for mean and standard deviation respectively, subscript ‘*total*’ stands for the overall distribution, subscript ‘*x*’ stands for the coating-per-pass distribution, and subscript ‘*n*’ stands for the number of cycles distribution.

Mann [15] also showed that the number-of-passes distribution could be described in terms of the circulation-time distribution. Thus, Eq. (2.1) can be modified to Eq. (2.2). The circulation time is a much easier parameter to measure than the distribution of number of cycles.

$$CV = \frac{\sigma_{total}}{\mu_{total}} = \sqrt{\left(\frac{\sigma_x}{\mu_x}\right)^2 \frac{\mu_{ct}}{t_{coat}} + \left(\frac{\sigma_{ct}}{\mu_{ct}}\right)^2 \frac{\mu_{ct}}{t_{coat}}} \quad (2.2)$$

where subscript ‘*ct*’ stands for the circulation time distribution.

It can be seen from Eq. (2.2) that CV is proportional to $\sqrt{1/t_{coat}}$ for fluid bed systems. Cheng and Turton [32] also derived this result using renewal theory for a Wurster fluid bed. This same effect of coating time on coating uniformity is also reported by Hall [33] for several types of industrial coating equipment. However, to the author’s knowledge, no such relationship has been published for pan coaters.

The cycle-time or circulation-time distribution has been measured experimentally using various techniques for both fluid bed and pan coaters. Mann and Crosby [14], Shelukar et al. [34], Waldie and Wilkinson [35], and Cheng and Turton [36] all used a magnetic tracer particle and a detection coil in a draft tube or spouted fluidized bed. The distribution of cycle times was found by measuring the times at which the tracer particle passes through the detector coil (located around the spouted region of the bed).

Similar studies have been performed on rotating drums or pan coaters [11],[20]. Most of these studies have focused on understanding and quantifying the movement of tablets inside a rotating drum, and have not rigorously addressed the spray dynamics.

Compartment and Population Balance Models

Denis et al. [37] developed a model for surface renewal for the coating of tablets in rotating drums, which is similar to that proposed by Sherony [38] for fluidized bed coaters. In this method, the particle bed is divided into two main regions as shown in Figure 2.5. Region 1 (cascading region) is represented by a single perfectly-stirred tank in which coating material is applied evenly on all particles. Region 2 is a plug flow region, which is represented by $N-1$ perfect mixers arranged in series. The comparison of the coating mass distribution obtained from experiments and population balance model showed good agreement for an industrial-scale batch operation. The results also showed that the coating mass distribution is not affected significantly by the number of mixers when more than 10 mixers are used.

Monte Carlo Techniques

Monte Carlo simulations capture experimental information and allow prediction of coating mass variability at the conditions of the experiments. The Monte Carlo method can be thought to be a quantitative exercise performed by randomly sampling from the parameter probability distributions to predict the outcome expected from theory and/or experiments. These parameters affect the events in the process in such a way that a probability distribution is obtained. This is achieved by sampling the parameters of the governing events many times. It is assumed that the average of all outcomes of the

randomly sampled probability distributions will yield accurate estimates of the outcomes of real processes [39].

Figure 2.5. Compartmental model of Denis et al. [37]

Monte Carlo methods have been used extensively to simulate coating, transport, dispersion or agglomeration/granulation of particles in fluidized beds [40]-[43]. Nakamura et al. [40] studied the effect of operating parameters on the coating mass distributions of seed particles in a tumbling fluidized bed coater using Monte Carlo simulation. The coefficient of variation of coating mass was found to be in the range of 10.2-16.1% depending on the operating parameters. They showed that the CV decreases with longer coating time, smaller hold up of particles and better mixing of the particles. The model showed that addition of a unidirectional flow (achieved by the rotation of the turntable) to a random walk is one effective method to achieve near perfect mixing. This helps to homogenize the coating mass distribution. They were not able to reproduce the

effects of particle diameter nor were they able to predict effects of mixing aids such as baffles on coating mass distribution. Ku-Shaari et al. [41] developed a Monte Carlo technique to model the coating uniformity in a bottom spray fluidized bed, similar to the one used by Cheng and Turton [32]. They modeled the movement of tablets as a random walk. The steps in the vertical and the horizontal directions were estimated from the distributions of particle velocities, which were determined experimentally using image analysis by Subramanian et al. [42]. The amount of spray received by a particle is determined from the local spray flux and the voidage profile between the particle and the spray nozzle.

Hapgood et al. [44] studied the spray flux in wet granulation in an agitated granulator. They performed Monte Carlo simulation on the spray zone. The Monte Carlo predictions were in good agreement with the analytical solutions for parameters such as proportion of nuclei formed from single drops and the fraction of the powder surface covered by drops as a function of dimensionless spray flux. They found that the proportion of nuclei formed from single drops falls exponentially with increasing dimensionless spray flux. Also, it was shown that at low dimensionless spray flux, the fraction of the powder surface covered by drops was equal to the dimensionless spray flux but as the dimensionless spray flux increased, the drop overlap became more dominant and the powder surface coverage leveled off. They observed that in the ranges covered, the results were independent of drop size, number of drops, drop size distribution and the uniformity of the spray.

Monte Carlo has been used infrequently for simulating tablet movement in a pan coating device. Rogers and Gardner [45], Black [46], Kohav et al. [47] used physical

dispersion models with the Monte Carlo method to simulate particulate transport and dispersion for powder flow in a horizontal rotating drum. The models were found to predict much less dispersion than that observed in experiments. The shortcoming was that these models neglected the contribution of particle collisions on the bed surface. Cahn and Fuerstenau [48] used Monte Carlo simulation to model axial dispersion of particles moving in a plane perpendicular to the axis of the drum. They studied the effects of drum speed and fill combinations on the average rotational speed of the bed and determined probability distributions of the number of particles leaving sections of bed surface per bed revolution, particle movement direction, and the extent of axial movement. They concluded that a particle was likely to leave a section and move a greater distance as the speed and fill were increased, but data for the average bed rotation and the distributions were not reported.

Although extensive work has been done on coating, transport, dispersion and agglomeration/granulation of particles using Monte Carlo simulation in fluidized beds, no attempts have been made to relate the probability distributions of the events in a pan coater with parameters such as rotational speed, volumetric fill, drum diameter and particle properties [49]. This will be addressed in the Monte Carlo model developed in the current work (section 4.2.1).

DEM (discrete element modeling) and CFD (computational fluid dynamics) modeling

DEM or discrete element modeling is an excellent tool for predicting trajectories of individual particles using Newton's equations of motion. In these calculations, movement due to all of the contact forces from neighboring particles is accounted for. A major advantage of this method is the ease with which one can study changes in particle

motion due to changes in operating conditions (*viz.* pan speed and pan load) and particle properties such as size, density and shape [57],[59]. Also, DEM simulations can provide dynamic information such as transient forces acting on individual particles, which are very difficult to obtain experimentally [50].

Some of the earlier work to simulate particle motion using DEM was not compared directly to experimental results [51]-[53]. McCarthy and Ottino [54] simulated particle motion in the active region and compared qualitatively the results to experiments. Yamane et al. [12] compared their DEM simulations to experimental results obtained using MRI. They used periodic boundary conditions in the longitudinal direction to reduce the computation time. Each time step used in the simulations was 10^{-4} s while Young's modulus and the Poisson ratio were 1×10^5 N/m² and 0.3, respectively. The DEM simulations were done for a 15 mm long, half-filled 6.9 cm diameter cylinder. Although results from this study show great promise for DEM, the experimental and simulation conditions are far from typical settings used in the industry during pan coating operations. Also, the accuracy of measurement of the dynamic angle of repose was limited by the opening at the end wall that was equal to only about seven particle diameters. They used particle sphericity and coefficient of friction as their 'fitting' parameters. Yang et al. [50] studied the flow of particles in a 100 mm rotating drum filled with 3 mm diameter spheres using DEM. The results were compared with PEPT measurements and a microdynamic analysis of particle flow was made with the aim of obtaining insight into the agglomeration phenomenon. Periodic boundary conditions were used along the axial direction to avoid the end wall effect. Good agreement was obtained for the values of dynamic angle between simulation and experiments. The agreement for

the angular velocity of particles was only fair and the disparity was explained by the fact that the DEM simulation may not perfectly represent the PEPT experimental conditions. Also, for simplicity, the work did not consider the axial motion of particles.

Although considerable work has been done in the past using DEM in horizontal rotating drums, there is still a lack of information on the movement of particles in the spray region of a typical rotating drum or pan coater. Most of the earlier works have concentrated on addressing the mixing, segregation, and agglomeration phenomenon rather than focusing from a coating perspective, which is the aim of the current work. For coating, it is desirable to study the movement of particles as they pass under the spray gun in contrast to observations made from a transparent sidewall of the pan. Another major limitation of some of the previous work is the way in which the interaction between the particles and pan wall was simulated, where the wall is simply considered to be composed of a layer of particles (for e.g.,[55]).

It is clear from the previous work, that there is lack of information in this field of study mainly at two levels:

- 1) Experimental information on particle movement inside a pan coater from a coating perspective. Specifically:
 - Projected surface area or orientation of the particle towards the spray nozzle, which is a key component in determining the amount of spray received by a particle
 - Quantification of the effect of mixing aids or baffles used inside the pan to promote mixing

- 2) A model to predict the effect of process variables such as pan speed, pan loading, particle size, spray shape, spray area, coating time etc. on the coating variability.

These two aspects are the primary focus of this study and are addressed by using a video-imaging technique described in the next section. Experimental results from video-imaging were also compared with those obtained from a DEM model from a coating perspective. Monte Carlo techniques were used to develop a model for predicting the coating variability.

3. Experimental set-up and apparatus

The current work utilizes a near real-time video imaging technique to study the movement of tablets in a rotating pan coater. As a first approximation, the amount of coating received by any tablet is proportional to the product of the time spent in the spray zone and the area exposed to the spray. In a previous study, Turton and Sandadi [56] used a black tracer tablet in a bed of white placebo tablets to verify this imaging technique. A potential disadvantage of that study was that the shadows formed by the white tablets were sometimes recognized as the black tracer tablet. This problem was eliminated in later work [1], by using a white tracer tablet in a bed of black tablets. For this reason, the current work utilizes a white tracer tablet inside a bed of black tablets.

There were two different pans used in the current study, both of which were 58 cm (24 in.) in diameter, but varied in width. The first pan was 10 cm wide and will be referred to as the ‘thin’ pan. The other pan was a model of a Vector Hi-Coater and was 33.66 cm (13.25 inches) wide. The latter pan will be referred as ‘wide’ or ‘industrial-scale’ pan.

The ‘thin’ pan consists of two transparent PlexiglasTM discs (2.5 cm thick), 60 cm OD, which are separated by a 10 cm perforated aluminum strip. The pan set-up, with the camera installed, is shown in Figure 3.1. The perforated strip enables the movement of air through the bed using suction. The pan is rotated about its axis using a stepper motor (Dayton model no. 42537A) controlled by a feedback speed controller (Dart Controls Inc., Zionsville, IN). Pan speed can be adjusted continuously from 1 to 30 rpm. The pan is supported on a metal frame and four rubber rollers support the movement of the pan [1].

Figure 3.1. Set-up of the 'thin' pan coater used in the current work [1]

The dimensions of the industrial-scale pan were provided by Alza Corp. (Mountain View, CA). The pan was built of PlexiglasTM manufactured by P.E.P. Plastics (Branchburg, NJ). The pan set-up, with the camera installed, is shown in Figure 3.2. The pan is driven by a motor (Baldor DC Drive, CN 3000A53, Ford Smith, AR) and four rubber rollers supported the movement. The pan speed can be adjusted from 1 to 20 rpm.

An area scan CCD camera (PulnixTM 1020-25) is used for the recognition of a single white tracer tablet in the cascading layer of a bed of black tablets. The camera is equipped with a wide-angle 4.8 mm lens (Cosmicar/Pentax C30405, 2/3" format) for the 'wide' pan, and a 6.5 mm lens for the 'thin' pan. This camera takes images at a framing rate of 25 Hz and is connected to a digital frame grabber board (Micro Disc, Inc., Yardley, PA). Machine-vision software (SherlockTM 32, Coreco Imaging, Bedford, MA) is used to analyze the images. The camera is mounted on a linear positioner (Figure 3.2) that allows fine-tuning of the working distance of the camera. The positioner is connected to a rod with three-sections. The position of each section can be adjusted so as to locate the camera at the desired position relative to the tablet bed. The pan set-up, with the camera installed, is shown in Figures 3.3 (a) and (b).

Figure 3.2. Set-up of the industrial-scale pan coater used in the current work

(a)

(b)

**Figure 3.3. Images of the Industrial scale pan coater used in this study (a) front view
(b) side view**

3.1. Measurement technique

A CCD camera is mounted inside the rotating pan in approximately the same position as the spray gun would normally be located in a pan coater and adjusted to scan an area covering the normal spray zone during a coating operation. The tracer tablet is identified using Machine Vision Software. The frame grabber board captures a frame from the CCD camera at a given time. Each frame is then reduced to a maximum of 1kb x 1kb array of pixel values which range between 0-black and 255-white. The image is thresholded and the background pixels are set to 0. The Sherlock™ software uses edge-detection algorithms, based on the gradients of pixel values, to identify the location of the ‘blobs’ in the array. The algorithm searches for contiguous areas of high pixel values and identifies them as ‘blobs’. The location of the centroid and its area are estimated once the ‘blob’ has been identified. The software is programmed to identify and record the area, location of the centroid and the number of blobs in the region of interest. The total processing time for the algorithm is in the range of 20-30 ms and the new frame or field is then grabbed 40 ms after the previous frame. The image acquisition and analysis is accomplished in near real-time (at a frequency of 25 Hz) using this set-up. Another advantage of this technique is that the full frames of image data need not be stored for post-processing, and a 30 min experiment generates a small data file (< 1 Mb).

Experiments were conducted without the tracer tablet in the pan to verify that the software did not register any false tracer tablet sightings. This fact confirmed the ability of the software to discriminate between a white tablet and any reflections in the bed of black placebo tablets. Similarly, during the course of an experiment, no more than one ‘blob’ or tracer tablet is ever recorded in a single frame. The time at which the tracer

tablet is in view in the region of interest (ROI) is recorded using the internal clock of the computer. The circulation and surface times are calculated from this sequence of recorded times using codes written in Visual BasicTM.

3.2. Calculations of parameters

The parameters used to characterize the particle movement inside the pan include [2]:

- Circulation time, τ_{circ} , which is the time between successive tablet sightings at the bed surface
- Surface time, τ_{surf} , which is the time that the particle spends within the spray zone
- Projected surface area, A_{exp} , which is the surface area of tablet exposed towards the spray nozzle
- Surface velocity, V_y , which is the velocity parallel to the direction of flow of the cascading layer
- Dynamic angle of repose, θ
- Dispersion coefficient, D_x , which characterizes the movement at the surface in the axial direction.

Circulation time (τ_{circ}): The circulation time is defined as the time between successive initial sightings of the tracer tablet in the region of interest (ROI) that is longer than some cut-off time. For all experiments, the ROI was an area approximately 10 cm square located in the middle of the top half of the cascading layer. The cut-off time was varied over a wide range and the effect on the results was studied. The variable examined was the total number of times the tracer particle circulated (number of passes) on the surface in a 30 min time period as predicted by different cut-off times. A typical graph for the ‘thin’ pan obtained by such an analysis is shown in Figure 3.4. As seen in Figure

3.4, the number of passes initially decreases rapidly with an increase in cut-off time, then it remains almost constant for a wide range of cut-off times, and finally it decreases rapidly again. When the cut-off time is too low, the analysis considers all individual sightings as a new pass, hence the calculated number of passes is high. When cut-off time is too high, two or more separate passes are considered to be part of the same pass, causing a decrease in the calculated number of passes. The number of passes was found to remain steady in the range of 400-1800 ms and any value in this range will effectively separate a 'new' circulation or pass from multiple sightings in the same pass. A cut-off time of 500 ms was chosen for subsequent analysis for the 'thin' pan. It should be noted that this cut-off is a function of the operating conditions, such as pan size, pan loading, pan speed and presence/absence of baffles, and must be examined for each operating condition. Figure 3.5 shows a typical raw data set for 4700 polystyrene spheres (9 mm diameter) at a pan speed of 12 rpm. Figure 3.6 shows the results for the cut-off time determination obtained at 6 rpm and 7500 spheres, with no baffles, for the industrial-scale pan. It was found that the circulation frequency did not change over the cut-off times between 1.5-3.5 s for the operating conditions studied. Thus, the cut-off time for the industrial-scale pan was chosen as 2 s.

Figure 3.4. Estimation of ‘cut-off’ time to determine circulation time. Figure shows typical cases at $\nu = 0.17$ and pan speed of 6 and 9 rpm for ‘thin’ pan

Figure 3.5. Circulation time estimation from raw data for a typical case of with 7500 spheres (9 mm diameter) at 12 rpm for ‘thin’ pan

Figure 3.6. Determination of cut-off time for the industrial-scale pan

Surface time (τ_{surf}): This is defined as the time that the tracer particle spends on the surface in the ROI. The surface time, along with the exposed tablet area, determines the amount of spray a tablet receives when it passes through the spray zone on the surface of the bed. This is estimated by the product of the number of frames for which the tracer is seen in the ROI per pass and the time duration of each frame (40 ms).

Projected surface area: This is defined as the surface area of the tablet projected (A_{exp}) towards the camera. The software calculates the dimensions of the smallest imaginary box (width= a , height= b) that can be drawn around the tracer tablet it identifies, as shown in Figure 3.7. Based on the average pixel values in the imaginary box, an occupation ratio for the tracer tablet in the box is calculated. Therefore, occupation ratio is the percentage of the bounding box that contains the connected pixels. A square ‘blob’ for example, would have an occupation ratio (A_{exp}/ab) of 100, while a thin line ‘blob’

may have an occupation ratio of less than 10. The actual area is obtained from the pixel count by calibration for each experiment. The intersection of the diagonals of the box is used to identify the centroid position of the tablet.

Figure 3.7. Calculation of projected surface area of tracer tablet

Velocity (V_x and V_y): This is defined as the velocity of the tracer particle parallel or normal to the direction of flow of the particles in the cascading layer. The changes in location of the centroid positions, between successive frames, were used to calculate the surface velocity of the tablets both parallel (V_y) and perpendicular (V_x) to the direction of flow as shown in Figure 3.8. Codes written in Microsoft Visual BasicTM were used to sort and analyze the data.

Dynamic angle of repose (θ): This is defined as the angle the surface of the bed forms with the horizontal axis, as the pan rotates. It should be noted that the surface of the bed is not a perfect straight line. Since a spray gun is typically focused on the top portion of the bed surface (where the camera is focused), the angle θ is the one measured

and reported in this work (Figure 3.9). Digital images of the cascading layer were taken from a camera, placed outside the coater, and post-processed to obtain this angle.

Figure 3.8. Estimation of tablet velocity both parallel and perpendicular to the cascading layer of tablets [1]

Figure 3.9. Schematic of cascading surface indicating the point at which the dynamic angle was measured. The figure shows the ‘wavy’ shape of the cascading layer [2]

Dispersion Coefficient (D_x): This parameter was used to describe movement of the particle along the axis of the pan. It was estimated using Einstein’s ‘random walk’ theory [57]. Over a period of time, the variance of the displacement of a particle is directly proportional to time (t). If x is the axial displacement of the tracer particle, then the variance of this distribution ($\langle x^2 \rangle$) can be used to estimate the value of D_x from the relation: $\langle x^2 \rangle = 2D_x t$. Visual BasicTM codes were written to determine all of the above parameters.

It is important to point out that it is possible for the tracer to circulate below the top surface of the cascading layer and not be ‘seen’ by the camera. Since the camera replaces a spray nozzle in a coating operation, the particle will not ‘see’ the spray during such an event and hence will not get coated. Thus, the current experimental technique

captures the dynamic nature of the cascading layer where the particles emerge at the top surface and then may disappear into the lower part of the cascading layer. Any model developed for the coating process, where a particle is assumed to continue to remain at the surface once it emerges will not predict the coating uniformity accurately.

3.3. Materials used

This study was performed on standard round placebo tablets supplied by Mylan Pharmaceuticals (Morgantown, WV). The tablets were coated to a 4% theoretical weight gain using Black OpadryTM (Colorcon, West Point, PA) and then coated to a 0.25% theoretical weight gain using Clear OpadryTM (Colorcon, West Point, PA). In each video-imaging experiment, a single white tracer tablet was introduced into the rotating bed of tablets. The tracer tablets were produced by coating the placebo tablets with Clear OpadryTM to 4.25% theoretical weight gain. The resulting images of the tracer tablet obtained from the CCD camera, using the appropriate lighting level, were easily distinguished from both the black tablets and shadows within the bed. Three different tablet sizes were used (6.3, 7.9, and 10.4 mm), as shown in Table 4.2. In addition, experiments were conducted using 9 mm diameter polystyrene spheres (particle density = 0.99 g/cc). This allowed a comparison between the experimental data and the results from DEM simulation for spherical particles developed by IeTeK, Tacoma, WA [58],[59].

4. Results and Discussion

4.1. Experimental results

An experimental matrix was designed to study the effect of various operating conditions on the movement of the particles (Table 4.1). The three levels of pan speed studied were 6, 9 and 12 rpm. The pan loading was quantified by using fractional fill volume (ν), which was defined as the ratio of volume occupied by the particle bed to the total pan volume. It was varied at two levels, 0.10 and 0.17. The run-time for each of the experiments was 30 minutes and the runs were randomized and replicated. The experiments using standard round tablets (dimensions shown in Table 4.2) in a ‘thin’ pan were conducted by Sandadi et al. [1].

Table 4.1. Experimental matrix

Variable	Level 1	Level 2	Level 3
Fractional fill volume	0.10	0.17	-
Tablet size (mm)	6.3	7.9	10.4
Pan speed (rpm)	6	9	12
Baffles	No	Size/Arrangement 1	Size/Arrangement 2
Tablet shape	Standard round tablets (3 sizes)	Polystyrene spheres	-
Pan size	24 in. ‘thin’	24 in. ‘wide’	

Table 4.2. Dimensions of the tablets used in this study [1]

Nominal Size	Shape	<i>d</i> (mm)		<i>t</i> (mm)		<i>h</i> (mm)		Weight (mg)	
		Uncoated Tablets	Coated Tablets	Uncoated Tablets	Coated Tablets	Uncoated Tablets	Coated Tablets	Uncoated Tablets	Coated Tablets
1/4 inch		6.2	6.3	3.1	3.2	1.8	1.8	100.0	104.3
5/16 inch		7.8	7.9	3.8	3.9	2.5	2.5	200.0	208.5
13/32 inch		10.3	10.4	5.0	5.1	3.1	3.1	500.0	521.3

4.1.1. Circulation time

The first set of experiments performed in this study was on 9 mm polystyrene spheres in the ‘thin’ pan. As expected, the average circulation time was found to decrease with increasing pan speed, since particles move faster and come back to the spray region sooner, as shown in Figure 4.1. The circulation time was found to increase with increasing pan loading. As the pan loading increases, the number of particles in the coater increases, thereby the probability of each particle being in the spray zone decreases, causing an increase in the measured circulation time. The 95% confidence intervals, represented by the error bars in Figure 4.1, were seen to decrease with increasing pan speed. The error bars were observed to be smaller at higher pan speeds, which implied that the tracer presented itself in the spray zone in a more uniform manner suggesting better mixing at higher speeds. This was found to hold true for the other variables, such as surface time and projected surface area per pass. However, the effect was more pronounced at the lower pan loading.

The results obtained for spheres were compared with those obtained for round tablets. This provided information on the effect of shape on particle movement inside the pan. To compare effectively tablets with spheres, the volume equivalent diameter of the tablet (d_{equiv}), defined as the diameter of a sphere with the same volume as that of tablet, was evaluated. The volume equivalent diameter of the 10.4 mm tablets was 8.9 mm. For the tablets used, this was closest to the diameter of the spheres (9 mm). The difference in the circulation times of spheres and 10.4 mm diameter tablets was not found to be significant at a confidence level of 95%, as seen in Figure 4.1. The slightly lower average circulation times for tablets can be attributed to the lower number of tablets (~ 6300) in

comparison to spheres (~ 7500) for the same pan loading ($\nu = 0.17$). The relative standard deviation (RSD_{circ}) is a measure of the spread of the distribution and is calculated as the ratio of standard deviation to average circulation time. Figure 4.2 shows a comparison of RSD_{circ} for circulation times of tablets versus spheres at $\nu = 0.17$. The RSD_{circ} for circulation time of tablets (10.4 mm) appears to be slightly lower than spheres at low pan speeds but in general the RSD_{circ} values for spheres and tablets are not significantly different. The slightly lower RSD_{circ} value for 10.4 mm tablets could be due to the lower number of tablets, which achieve better mixing at lower pan speeds, in comparison to spheres at $\nu = 0.17$.

Figure 4.1. Average circulation time as a function of pan speed and pan loading for 9 mm polystyrene spheres in comparison to 10.4 mm diameter tablets. The error bars show the 95 % confidence intervals of the average values

Figure 4.2. Comparison of relative standard deviation of circulation times for 10.4 mm tablets with spheres at $\nu = 0.17$ [2]

4.1.2. Surface time

The average surface time or the time per pass for which the particle receives coating was found to increase with decreasing pan speed and decreasing pan load, as shown in Figure 4.3. Figure 4.3 also shows a comparison of the surface times between spheres and tablets at two different pan loadings. The surface times for tablets were found to be lower than for spheres at $\nu = 0.10$, indicating tablets spend less time on the surface. The differences were not so pronounced at $\nu = 0.17$.

4.1.3. Total projected surface area

The total projected surface area per pass is the total surface area of the tablet that is exposed to direct coating during each pass. This has not been characterized in any previous published work. This information is critical in determining the amount of spray

that the tablet will receive as it passes through the spray zone, and will be used in the modeling part of this work. Figure 4.4 shows that the average projected surface area per pass of the tracer decreases with increasing pan speed as well as pan loading.

Typical distributions of circulation times, surface times, and projected surface area per pass, are shown in Figures 4.5, 4.6, and 4.7, respectively, for a pan speed of 9 rpm and $\nu = 0.10$ for 9 mm spheres. It is evident from these figures that none of these distributions are normal (Gaussian) in nature. This should be kept in mind during any related modeling studies where normal distributions are generally assumed.

Figure 4.3. Average surface time as a function of pan speed and pan loading for 9 mm polystyrene spheres in comparison to 10.4 mm diameter tablets. The error bars indicate 95 % confidence intervals [2]

Figure 4.4. Average projected surface area per pass as a function of pan speed and pan loading for 9 mm polystyrene spheres. The error bars indicate 95 % confidence intervals [2]

Figure 4.5. Distribution of circulation time at a pan speed of 9 rpm and $\nu = 0.10$ [2]

Figure 4.6. Distribution of surface time at a pan speed of 9 rpm and $\nu = 0.10$ [2]

Figure 4.7. Distribution of total projected surface area per pass, at a pan speed of 9 rpm and $\nu = 0.10$ [2]

4.1.4. Average surface velocity

The average velocity (V_y) in the direction parallel to cascading flow was found to increase with increasing pan speed and pan loading, as shown in Figure 4.8, for the ‘thin’ pan. A linear model fits the data very well with a slope of 3.1 and R^2 value of 1.00 for $\nu = 0.17$ and a slope of 2.00 and R^2 value of 0.98 for at $\nu = 0.10$. Figure 4.8 also compares the linear velocity (V), given by $V = R\omega$ (R is the pan radius and ω is the pan speed), with experimentally measured values. The comparison demonstrates that linear velocity might be a good indicator of the velocity at some intermediate fill level of the pan because of similarity in trends, but fails to give the exact values at $\nu = 0.10$ and 0.17 . This information is valuable when scaling up a pan coating process. A typical velocity distribution, obtained at $\nu = 0.17$ and a pan speed of 9 rpm, is shown in Figure 4.9. Leaver et al. [10] and Sandadi et al. [1] postulated that the cause of the increase in average velocity with pan loading is the increase in dynamic angle of repose. To verify this, the dynamic angles were measured for all conditions and are shown in Figure 4.10. In general, the dynamic angle was found to increase with increasing pan speed and pan loading. There was no significant difference in the dynamic angle between the tablets of the three sizes (6.3, 7.9, and 10.4 mm) and hence the angles reported here are only for 7.9 mm diameter standard round tablets.

The average velocity of the tablets was found to be higher than that of spheres as seen in Figure 4.11. The difference is more prominent at $\nu = 0.10$ compared to $\nu = 0.17$. As can be seen from Figure 4.11, for all cases the variation of average velocity as a function of pan speed appears to be linear. The R^2 value for 10.4 mm tablets was found to be 1.00 at both pan loadings.

Figure 4.8. Average velocity parallel to the direction of flow of cascading layer as function of pan speed and pan loading. The error bars indicate 95% confidence intervals. A linear model provides a good fit to the experimental values [2]

Figure 4.9. Typical velocity distribution shown at a pan speed of 9 rpm and $\nu = 0.17$

Figure 4.10. Dynamic angle of repose as a function of pan speed, pan loading and particle shape [2]

Figure 4.11. Comparison of average velocities of spheres and tablets [2]

The slopes of the linear fit were estimated to be 2.58 and 2.89 at $\nu = 0.10$ and 0.17 respectively, and were not significantly different from those observed for spheres. The dynamic angle was found to be significantly higher for tablets in comparison to spheres (Figure 4.10). A possible reason for this is the higher friction between the tablets and the pan wall. The higher angle also offers one possible explanation for the observed higher velocities of tablets. Another reason for higher tablet velocities is that the flowing layer is thinner for non-spherical particles than the spherical ones [12]. Thus, due to flux conservation, the free surface velocities of the non-spherical particles (tablets in this case), are higher. It was also noted that the shape of the cascading layer was much flatter for lower pan speeds and approached a more ‘wave-like’ form (shown in Figure 3.8) at higher pan speeds. This is consistent with the findings of Yamane et al. [12]. The ‘wavy’ shape of the cascading layer was observed to be much more pronounced for tablets than spheres.

4.1.5. Dispersion coefficient (D_x)

A fundamental ‘diffusion’ process may be used to describe axial mixing in a rotating drum or pan. Lacey [60] described the behavior of particles repeatedly spreading over a freshly exposed surface similar to ordinary molecular or thermal diffusion. Therefore, particles have a random-motion component in the direction normal to and in the plane of the line of maximum steepness, analogous to the motion of molecules of a gas. Since there is no bulk or net motion in the direction parallel to the axis of the pan, dispersion takes place along the axis and can be best quantified in terms of a dispersion coefficient. Some researchers have examined the spread of material in a rotating drum, generally in the low speed region. At low speeds a flat inclined surface is formed, over

which the particles roll down. According to Hogg et al. [61], the process can be considered analogous to diffusion in gases, liquids, or solids. They used two types of beads identical in all respects but with different colors and refractive indices. The values of D_x reported in the paper lie in the range 7.1×10^{-3} - 8.6×10^{-3} cm²/rev. Chaudhuri and Fuerstenau [62] used a simple sampling and assaying technique to determine the composition of the powder along the axis of the mixer. The average dispersion coefficients for the Dolomite particles used in their study were reported to be 3.87×10^{-3} cm²/rev. and 7.74×10^{-3} cm²/rev. for the quartz-calcine system.

Parker et al. [20], who utilized a PEPT technique to track the motion of a radioactively labeled particle, also used a diffusive model to study axial dispersion. Their results showed that the dispersion coefficient is strongly dependent on the particle size but not on the drum diameter. Reported values of D_x lie in the range 1.0×10^{-4} - 10.4×10^{-4} cm²/s for drum speeds in the range 10-65 rpm. Dury and Ristow [63],[64] conducted a numerical study of the interface dynamics of a binary particle mixture in a rotating cylinder. They concluded that the dependence of D_x with rotation speed (ω) is linear only for low speeds and that a quadratic function gives a better fit when a broader range of rotation speeds is considered. Sherritt et al. [49] proposed design equations for the axial dispersion coefficient in terms of rotation speed, degree of fill, drum diameter, and particle diameter. The data from a radioactive particle tracking technique proved the correctness of the proposed correlations. They report diffusion coefficients to lie between 10^{-3} to 1 cm²/s for the operating conditions studied.

In the current work, Einstein's elementary theory of the Brownian motion was used to estimate the dispersion coefficient of the tracer particle. The wandering motion of

the particle, modeled as a one-dimensional random walk, originally has a non-normal distribution of displacements about the axis. Over time, this distribution gradually converges to become normal. The particle has an equal probability of moving to either side of the drum axis, hence the mean displacement is zero. However, the variance of the displacement is directly proportional to time [65]. This principle is used to estimate an effective dispersion coefficient. Eliminating the time period when the tracer was out of the ROI or was not visible to the camera created a sequential series of tablet displacements about the centerline. A typical data set for the ‘random walk’ of the tracer tablet, as it moves down the cascading layer, at a pan speed of 6 rpm and $\nu = 0.10$ is shown in Figure 4.12.

The displacement of the tracer tablet across the centerline of the ROI was studied. The dispersion coefficient at a distance of 1 cm on either side of the centerline (a 2 cm span for the pan of width =10 cm) was also evaluated. Figure 4.13 shows the values of D_x for a 2 cm span across the centerline as well as the full pan, for 10.4 mm size tablets. It can be seen that D_x values were lower for the full pan span. This is attributed to the effect of the wall that restricts the movement of the tablet. Figure 4.14 shows the values of D_x for different tablet sizes at three drum speeds. Although the value of D_x was found to increase with increasing drum speed for all cases, no definite trend was observed for the variation of D_x with tablet size.

Figure 4.12. Schematic of ‘random’ walk of the particle around the centerline of the pan as it moves down the cascading layer [1]

Figure 4.13. Variation of dispersion coefficient, D_x , as a function of pan speed for 10.4 mm tablet for different spans across the centerline at $\nu = 0.10$ (Mean and 95% confidence intervals are shown) [1]

Figure 4.14. Variation of dispersion coefficient, D_x , as a function of pan speed and tablet size at $\nu = 0.10$ (Mean and 95% confidence intervals are shown)

A typical x -direction displacement for 9 mm polystyrene spheres, at $\nu = 0.10$ and a pan speed of 6 rpm is shown in Figure 4.15. As seen in Figure 4.16, D_x was found to increase both with pan speed and pan loading. Also, D_x was found to increase with an increase in the pan loading, consistent with the observations of Hogg et al. [61] and Parker et al. [20]. The pan speed has a more pronounced effect at the higher pan loading, possibly due to the increased cascading layer thickness causing more turbulence and mixing. Figure 4.17 compares dispersion coefficients for a 2 cm span of 9 mm spheres and 10.4 mm tablets at $\nu = 0.10$. The D_x values for spheres were found to be much higher than those of tablets, indicating more axial movement occurring for spheres than tablet-shaped particles.

Figure 4.15. Typical x -direction displacement (2 cm span) shown for 9 mm spheres, at $\nu = 0.10$ and a pan speed of 6 rpm [2]

Figure 4.16. Dispersion coefficient as a function of pan speed and pan loading for full pan width and 1 cm on either side (2 cm span) of the center line, for 9 mm polystyrene spheres [2]

Figure 4.17. Comparison of dispersion coefficient (2 cm span) between 10.4 mm tablets and 9 mm spheres at $\nu = 0.10$ [2]

4.1.6. Effect of the presence of liquid on particle movement inside pan

In order to have a complete understanding of the coating process, it is necessary to study the effect of presence of liquid on the movement of particles in the pan, since all video-imaging experiments discussed upto this point were done in a dry environment. Nase et al. [66], proposed ways to characterize the cohesive force in granular materials in a dry as well as wet environment. They studied systems (static pile, rotated tumbler and a hopper) where the predominant mode of cohesion was due to interstitial liquid (capillary cohesion). The dynamic angle of repose was reported to quantify the difference between the dry and wet environments. Similar concepts are used in the current study, to estimate the amount of capillary cohesion between polystyrene spherical balls using ethanol as the interstitial liquid.

In the current work, the effect of the presence of spray on the movement of particles inside the pan was studied. In addition to the set-up described before in Section 3, an air-atomizing nozzle (Spraying Systems Co., Model 1/8 JAC), was placed close to the bed surface such that it sprayed liquid within the area scanned by the camera. Ethanol, fed to the nozzle at a constant rate by a pump (Pulsafeeder Inc., Series CTP-D), was then sprayed on to the bed surface at two different spray rates, 4.5 and 9 ml/min. Since the current set up does not utilize hot air to dry the liquid, a volatile liquid, ethanol, was chosen as the coating solution. It was visually verified that the bed reached its near-saturation level at a spray rate of 9 ml/min rate, as the sides of the pan were seen to become wet. The fractional fill volume during the experiments was 0.10 and the duration of each run was 30 min. Experiments were also done by spraying only air (no liquid) to study its effect on the measured parameters, if any.

The experiments were conducted at two pan speeds, 6 and 9 rpm. Results for circulation time, surface time, projected surface area, and velocity are shown in Figures 4.18, 4.19, 4.20 and 4.21, respectively. The results showed that spraying just air has no significant effect on the majority of parameters measured in comparison to the dry environment. The velocity was found to increase slightly for the case where only air was blowing, indicating that the air flowing from the spray nozzle assisted the movement of spheres as they rolled down the bed. An increase in the dynamic angle of repose was also verified visually. The results for the 4.5 and 9 ml/min spray rates suggest that there was no significant effect of the presence of liquid ethanol on most of the variables studied. However, as seen in Figure 4.21, there was a significant increase in V_y for the 9 rpm case, even in comparison to the case where only air was flowing. This can be attributed to the

increase in dynamic angle of repose due to wetting. The greater the dynamic angle, the higher is the velocity of particles moving parallel to the bed surface [67].

To verify this, the dynamic angle of repose was measured for both dry and wet cases at 3 different pan speeds. The dynamic angles of repose obtained at $\nu = 0.10$ and at different pan speeds are given in Table 4.3. The angle was found to increase consistently with increasing pan speed.

Figure 4.18. Circulation time comparisons at $\nu = 0.10$ at 6 and 9 rpm under various bed conditions [67]

Figure 4.19. Surface time comparisons at $\nu = 0.10$ and pan speeds of 6 and 9 rpm under various bed conditions [67]

Figure 4.20. Total projected area comparisons at $\nu = 0.10$ and pan speeds of 6 and 9 rpm under various bed conditions

Figure 4.21. Comparison of velocity component parallel (V_y) to the flow direction at $\nu = 0.10$ and pan speeds of 6 and 9 rpm to study the effect of liquid spray

Table 4.3. Comparison of experimentally determined dynamic angles of repose for different pan speeds at $\nu = 0.10$ with and without liquid spray

Pan speed (rpm)	Dynamic Angle of Repose (°)	
	No liquid spray	With liquid spray
6	29	30
9	31	33
12	33	34

The results for the dynamic angle of repose are in good agreement with those reported by Nase et al. [66]. They also defined a dimensionless granular Bond number, Bo_g , as the ratio of the maximum capillary force, F_c , to the weight of the particle, W . It was proposed that this number, given by Eq. (4.1), gives an estimate of the liquid-induced particle-level cohesion.

$$Bo_g = \frac{F_c}{W} = \frac{3\gamma}{2d_p^2 \rho_p g} \quad (4.1)$$

where γ is the surface tension of fluid ($\gamma_{\text{ethanol}} = 22 \times 10^{-3}$ N/m), d_p is the radius of the particles used (4.5×10^{-3} m), and ρ_p is the particle density (990 kg/m^3). The Bo_g number is 0.17 for this study. This is identified in Figure 4.22 in the graph presented by Nase et al. [66]. As suggested by Nase et al. [66], for the values of $Bo_g < 1$ suggests that the degree of cohesion between particles is small, and only small differences in angle between the wet and the dry cases ($\sim 1\text{-}2^\circ$) are to be expected. This was also verified by the results obtained in this study (Table 4.2).

Figure 4.22. The dependence of the dynamic angle of repose with Bond number [66]

4.1.7. Results for the industrial-scale pan (quantification of mixing)

All of the previous discussion was based on experiments conducted in the ‘thin’ pan coater. In the current section, results obtained using the industrial-scale coater are presented. The effect of baffles on the particle movement inside the pan is quantified. A comparison between the results obtained from the ‘thin’ pan and the industrial-scale pan are also be made.

The experimental matrix shown in Table 4.1 was completed using the industrial-scale pan shown in Figure 3.3. The pan contained 8 baffles (made out of plexiglass) to promote mixing. The size and arrangement of baffles is shown in Figure 4.23. Baffles are known to help eliminate the dead zones inside the tablet bed and hence improve the mixing inside the pan. The effect of baffles on particle movement was evaluated by comparing cases where only ‘slip bars’ were present in the pan. The 8 slip bars were arranged in the exact same way as the baffles, but were less than 1 inch in depth. The main purpose of the slip bars was to minimize the slipping near the wall.

Figure 4.23. Size and arrangement of baffles used in the industrial-scale pan

Figure 4.24 shows the results for the average circulation time for 9 mm spheres as a function of pan loading, pan speed, and absence/presence of baffles. It can be seen that the average circulation time decreases with an increase in pan speed and a decrease in pan loading, consistent with the results for the ‘thin’ pan. Also, the average circulation time was found to decrease when the baffles were present in the system. The distribution of the circulation time is shown in Figure 4.25, and the case with and without baffles is compared. It is clear from the figure that the distribution has a ‘long tail’ when no baffles are present in the system. Therefore, the baffles clearly help to improve the mixing inside the pan, and hence promote more uniform circulation of the particles through the spray zone. This also explains the lower average value for the circulation time for the case with baffles, indicating that the tracer particle no longer gets ‘lost’ in the dead zones for a long period of time, and emerges at the surface or in the spray zone in a more uniform manner.

In order to quantify the effect of baffles on particle movement the distribution of circulation time was studied. The spread of the distribution can be quantified by the relative standard deviation of the circulation time distribution (RSD_{circ} , defined in Section 4.1.1). This was used to quantify the mixing inside the pan and quantify the effect of the presence of baffles inside the pan. Figure 4.26 shows the effect of baffles on the mixing inside the pan. The RSD_{circ} was found to be significantly lower when baffles were present in the system for both the pan loadings. The effect was seen to be more prominent for the higher pan loading, where the RSD_{circ} (on an average) was reduced by 40%, compared to the lower pan loading where it was reduced by 24% [68]. This is because there were more potential dead zones for baffles to destroy at the higher pan loading, compared to the lower loading.

Figure 4.24. Effect of baffles on average circulation time of particles

Figure 4.25. Effect of baffles on the distribution of circulation time. The case with no baffles is seen to have a ‘longer tail’

Figure 4.26. Effect of presence of baffles on the circulation time distribution

It is evident that the video-imaging technique is capable of capturing the effect of baffles in the system. Any improvements in the mixing inside the pan will have a direct effect on the mass coating variability of the process during the coating process, since the tablets will appear in the spray zone in a more uniform manner.

In order to establish further the ability of the video-imaging technique to quantify the mixing inside the pan, 2 different baffle arrangements were compared. These two arrangements are shown in Figure 4.27 [69]. The ‘side-baffle’ arrangement is the one that is currently used in a commercial Vector Hi-coater. In this arrangement, each baffle starts from one side of the pan wall, and does not go all the way to the other side of the pan wall, as shown in Figure 4.27. This was compared with a ‘center-baffle’ arrangement, where the baffles extended from one side of the pan wall to the other side.

Figure 4.27. Illustration of the 2 baffle arrangements compared using video-imaging

For each baffle configuration, four baffles were used in the pan. The mixing achieved by each of them was quantified using RSD_{circ} , as discussed earlier. Figure 4.28 shows the comparison between the two baffle configurations and also compares them with the case with no baffles (only slip bars) for 9 mm spheres. It can be seen that the center baffles gave the lowest RSD_{circ} and hence the best mixing. Thus, this baffle configuration may potentially give lower mass coating variability during a coating operation. Similar results were obtained for 10.4 mm tablets as shown in Figure 4.29. Thus the video-imaging technique is capable of distinguishing the mixing achieved with different baffle configurations and can be used to optimize and effectively design better baffles for a given system.

Figure 4.28. Comparison of mixing achieved in different baffle configurations for 9 mm polystyrene spheres

Figure 4.29. Comparison of mixing achieved in different baffle configurations for 10.4 mm round tablets

4.1.8. Comparison between ‘thin’ and industrial-scale pan

There were two pans used in the current work, the ‘thin’ pan and the industrial-scale pan, as described in Section 3. A comparison between the results obtained from both the pans is presented in this section. This will provide insight into any changes in particle movement due to a ‘thin’ pan, which is typically easier to set-up for video-imaging studies. A wide angle lens is not required for the ‘thin’ pan and there are no issues of image distortions near the edges, as can sometimes be the case with a wide-angle lens. A comparison was made between the average cascading velocity obtained for the ‘thin’ pan and the industrial-scale pan, as shown in Figure 4.30. A linear model was found to fit the data very well for both the cases ($R^2 > 0.98$). The slopes of the curves were also found to be in good agreement, with a slope of 3.12 for the ‘thin’ pan, and 3.15 for the industrial-scale pan. This shows that the average velocity of tablets through the spray zone is not affected significantly while using the ‘thin’ pan in comparison to the industrial-scale pan.

A comparison between the average velocities of spheres and tablets was made in the industrial-scale pan. It can be seen from Figure 4.31 that the velocity of tablets is significantly higher for tablets compared to spheres at the same pan loading. This is consistent with the findings in the ‘thin’ pan, as shown in Figure 4.11.

Figure 4.30. Comparison of average cascading velocity between 'thin' pan and industrial-scale pan

Figure 4.31. Comparison of velocity of tablets versus spheres in the industrial-scale at $\nu = 0.18$

4.2. Monte Carlo simulations

The Monte Carlo method was used to simulate the movement of tablets in a pan coating device. Both the tablet movement and spray dynamics of the system were taken into account. In order to model the coating variability, there were two main inputs used in the Monte Carlo simulations, as shown in Figure 4.32. The first input was the information on the movement of tablets inside the coater, which is obtained from video-imaging experiments discussed before. This information includes centroid location distribution, circulation time distribution, the projected surface area distribution of tablets as they pass through the spray zone, and the velocity distribution of tablets in 2 directions. The other input was information on the spray dynamics of the system, which includes spray area, spray shape, and spray flux distribution in the spray zone. It should be pointed out that nozzle type, spray solution properties, atomizing air pressure, inlet air temperature, and tablet bed temperature also affect the spray dynamics of the system, but are outside the scope of the current work.

The spray flux distribution inside the spray zone was obtained using a linear patternator, shown in Figure 4.33. The patternator consists of a series of tubes that collect and record the volume of the spray solution at different locations. The volume of spray solution collected in each tube was used to generate a flux profile within the spray zone.

The algorithm used to simulate tablet movement using Monte Carlo simulation is shown in Figure 4.34. The related code is shown in Appendix I. In short, a random starting location was selected from the centroid location distribution generated from the video-imaging experiments. The next tablet location was calculated by randomly selecting x - and y -velocities from the experimentally obtained velocity distributions.

Figure 4.32. Monte Carlo scheme to determine the coating mass distribution in a coating operation

Figure 4.33. Linear patternator used to determine the spray flux distribution inside a spray region

Figure 4.34. Monte Carlo algorithm used in the current work to determine the coating weight gain by each tablet in the pan

$$y_{j+1} = y_j + v_y \Delta t \quad ; \quad x_{j+1} = x_j + v_x \Delta t \quad (4.2)$$

where y is the centroid y -location (in the direction parallel to the cascading layer flow) of the tablet, x is the centroid x -location (in the direction perpendicular to the cascading layer flow in the plane of the cascading layer) of the tablet, Δt is the time increment, and v_x and v_y are the randomly chosen components of tablet velocities in the x - and y -directions. The tablet-wall collisions were taken into account and considered to be perfectly elastic. The time increment used was 40 ms, which is identical to the time taken by the camera to record successive images.

Spray information including spray flux distribution, spray area and spray shape, was used in conjunction with the experimental data collected from video-imaging to predict the coating variability. The projected surface area values were randomly chosen from the experimentally obtained projected surface area distribution. The movement was simulated for all the tablets in the bed for a coating time of 30 minutes and the weight gain of each tablet was calculated using Eq. (4.3). The coating weight variability between the tablets was calculated using Eq. (4.4).

$$m_i = \sum_{1}^n \sum_{Pass} A_{exp} S_{flux} \Delta t \quad (4.3)$$

$$CV = \frac{\sigma_m}{\mu_m} \times 100 \quad (4.4)$$

where m_i (g) is the coating weight gained by tablet ' i ', A_{exp} (mm²) is the projected surface area at each sighting of the tablet in the spray zone, S_{flux} (g/mm²/s) is the spray flux at the centroid location of the tablet, CV is the weight gain coating variability, σ_m is the standard deviation of the coating weight gain distribution, μ_m is the average of the coating weight gain distribution, and n is the total number of passes taken by each tablet through

the spray zone. Each ‘pass’ is defined by the appearance of the tablet in the spray zone before ‘disappearing’ into the bulk of the tablet bed.

The operating variables studied for the Monte Carlo simulations include pan speed (6, 9 and 12 rpm), tablet size (6.4, 7.9, and 10.4 mm), pan loading (2 levels), spray shape, spray area, and spray flux (uniform, non-uniform) inside the spray zone. The fractional fill volume was varied at two levels ($\nu = 0.10$ and $\nu = 0.17$), which covers the range of typical pan loadings used in the industry.

The video-imaging data was used to generate distributions of circulation time, surface time (time spent in the spray zone/pass), projected surface area/pass and velocities in two directions for these conditions. Typical distributions are shown in Figures 4.35 (A), (B), (C), for 10.4 mm tablets at a pan speed of 9 rpm and a fractional fill volume of 0.10.

The main reason for the observed weight gain variability in the coating process is that all of the tablets in the bed do not behave in an identical manner in a given time period. For example, the number of passes each tablet makes through the spray zone is not the same. This was captured by the Monte Carlo simulation and a typical data set is shown in Figure 4.36 for 10.4 mm placebo standard round tablets in a 30 min coating run at a pan speed of 9 rpm. It is desirable to have a ‘narrow’ distribution of circulation frequency between different tablets. This may be achieved by using mixing aids/baffles in the system.

Figure 4.35. Distributions of (A) circulation time, (B) surface time, and (C) projected surface area per pass, for 10.4 mm tablets at a pan speed of 9 rpm and a fractional fill volume of 0.10

Figure 4.36. Distribution of circulation frequency of 10.4 mm tablets in a 30 min run at a pan speed of 9 rpm

4.2.1 Effect of coating time

The effect of coating time on CV was also studied. It was found that the CV decreases with increasing coating time, as shown in Figure 4.37 (A), for 10.4 mm tablets rotating at a pan speed 12 rpm at a fractional volume fill of 0.10. It was also found that the CV is inversely proportional to the square root of coating time (t_{coat}), as shown in Figure 4.37 (B) (Eq. (4.5)).

$$CV \propto \frac{1}{\sqrt{t_{coat}}} \quad (4.5)$$

This dependence is in agreement with previous works done on similar systems such as fluidized beds [32],[33], but, to author's knowledge, has not been reported for pan coating systems.

Figure 4.37. Effect of coating time on coating variability for 10.4 mm tablets at a pan speed of 12 rpm and $\nu = 0.10$

4.2.2. Effect of spray shape and spray area

The effect of spray shape (ellipsoidal and circular) on CV was investigated. Initially, the spray area was maintained the same for both the cases. This meant that the entire pan width was not covered for the circular spray shape and allowed ‘bypassing’ of tablets around the spray area, as shown in Figure 4.38 (A). This resulted in significantly higher CV values for circular spray shape, which, not surprisingly, shows that it is critical that the spray covers the entire pan width and allows no or minimal bypassing. The repeatability of the results obtained from the Monte Carlo simulations is discussed in Appendix II.

In order to study the effect of spray shape alone, the spray area for the circular and elliptical spray shapes was kept the same, and the entire pan width was covered. This was achieved by comparing two circular shaped spray regions with one elliptical spray region, as shown in Figures 4.38 (B) and (C). The ratio of the minor axis of the ellipse to the major axis was kept as 0.5, to maintain the same total spray area. Figure 4.39 compares the results for the two spray shapes for 10.4 mm tablets at a fractional fill volume of 0.10 at 3 different pan speeds. It is clear that the spray shape does not have a significant influence on the coating variability, so long as the spray area is kept the same. An effect of spray shape (circular versus elliptical) on the coating quality (roughness) has been discussed by Porter [70]. He concluded that circular spray pattern produces smoother and glossier tablets, but there is a greater chance of localized overwetting, in comparison to the elliptical spray pattern.

Figure 4.38. Schematic of the different spray shapes or regions studied using the Monte Carlo simulation. Part (A) shows circular-shaped spray region that does not cover the whole pan width, (B) shows 2 circular-shapes spray regions with the same spray area as that of the elliptical-shaped spray region shown in part (C)

The effect of spray area on CV was studied. The circular-shaped (higher spray area) spray area was compared to the elliptical spray area (area of circle/area of ellipse = 4, for this case) [71]-[73]. Again, the entire pan width was covered by the spray for these cases. The coating variability was found to decrease with an increase in spray area, as shown in Figure 4.40 for 10.4 mm tablets at 3 pan speeds and a fractional fill volume of 0.10. These results were observed for all the three sizes (6.3, 7.9, 10.4 mm) of round placebo tablets [74].

4.2.3. Effect of pan loading, pan speed, and tablet size

The average weight gain (μ_m) by tablets in a coating process is given by:

$$\mu_m(g / tablet) = \frac{Spray\ flux(g / s / mm^2) \times Spray\ area(mm^2) \times t_{coat}(s)}{N} \quad (4.6)$$

where N is the number of tablets in the pan.

There are several factors that are known to affect the CV of the process and these are summarized in Figure 4.41. In the current work, the effects of tablet movement and some aspects of spray dynamics on coating variability were investigated. The variables governing tablet movement can be further reduced to include just the independent variables. For example, the tablet velocity has been shown to be a function of pan radius (R), pan speed (ω), tablet diameter (d_p), and pan loading, given by Eq. (4.7) [59]. Fractional fill volume (ν) is a function of the number of tablets in the pan, N , the pan radius, R , and tablet diameter, d_p .

$$\nu \propto R\omega^{2/3} \left(\frac{g}{d_p} \right)^{1/6} \nu^{1.8} \quad (4.7)$$

Figure 4.39. Effect of spray shape (circular versus elliptical) on coating variability for cases with the same spray area for 10.4 mm tablets at $\nu = 0.10$ (no bypassing)

Figure 4.40. Effect of spray area on coating variability for 10.4 mm tablets at $\nu = 0.10$ at 3 different pan speeds

Therefore, the main independent variables governing tablet movement and thereby CV are d_p , ω , R , and N . All the experiments in the current work were performed on a 58 cm diameter pan and hence the pan radius effect was not studied. Thus CV was a function of d_p , ω , and N for a given pan radius as shown by Eq. (4.8).

$$CV = k_l d_p^a \omega^b N^c \quad (4.8)$$

where a , b and c are real numbers, and k_l is a constant.

Figure 4.41. List of variables affecting the weight gain coating variability in a pan coating device

A MATLABTM-based code was written for the Monte-Carlo algorithm shown in Figure 4.34. This was used to obtain CV values for the entire experimental matrix (3 tablet sizes, 2 pan loadings, and 3 pan speeds), with a total of 18 operating conditions. A statistical analysis of these results was conducted using JMPTM (SAS Institute Inc. Cary, NC) software. It was observed that CV was significantly dependent on d_p ($p<0.0001$), ω ($p=0.0002$), and N ($p<0.0001$). The CV was directly proportional to d_p , N and inversely proportional to ω . An increase in pan speed improves the mixing inside the pan, thereby resulting in lower CV values. The exponents a , b , and c were determined from statistical analysis using JMPTM and are shown in Eq. (4.9).

$$CV = k_2 \frac{d_p^{1.2} N^{0.5}}{\omega^{0.4}} \quad (4.9)$$

where k_2 is a constant.

Good agreement ($R^2=0.90$) was obtained between the CV values predicted from the model proposed in Eq. (4.9), and the CV values obtained from Monte Carlo simulations, as shown in Figure 4.42. Incorporating the effect of coating time into Eq. (4.9) by using Eq. (4.5), Eq. (4.10) is obtained.

$$CV = k_3 \frac{d_p^{1.2} N^{0.5}}{\omega^{0.4} t_{coat}^{0.5}} \quad (4.10)$$

where k_3 is a constant.

Figure 4.42. Comparison of CVs predicted from the proposed model in Eq. (4.9) with those obtained from Monte Carlo simulations [71]

4.2.4. Effect of spray flux variation inside the spray zone

The spray flux variation inside the spray zone was measured using the patternator. The spray gun used was a two-fluid air atomizing nozzle (model 1/8JAC+SU11) from Spraying Systems (Wheaton, IL). The normalized spray flux variation data obtained from the patternator as a function of distance (r_l) from the center of spray zone is shown in Figure 4.43. The atomizing air pressure used for this experiment was 40 psi with a gun-to-bed distance of 10.2 cm (4 inches). Figure 4.44 shows the results for 10.4 mm tablets, at a fractional fill volume of 0.10 and at 3 different pan speeds. The uniform spray flux (no variation within the spray zone) was found to give a lower CV in comparison to the case where spray flux varies with respect to the location (non-uniform flux) inside the spray zone. It should also be noted that the value of CV decreased with an increase in pan speed. Better mixing is obtained at higher pan speeds, which results in lower CV.

Figure 4.43. Normalized spray flux as a function of the location of the tablet inside the spray zone, as measured by the linear patternator, at an atomizing air pressure of 40 psi and a gun-to-bed distance of 10.2 cm (4 inches)

Figure 4.44. Effect of spray flux variation inside the spray zone on CV for 10.4 mm tablets at $\nu = 0.10$, as predicted by Monte Carlo simulations

4.2.5. Model verification by coating experiments

In order to verify the predictions of CV from the Monte Carlo simulations, experimental coating runs were conducted at the same conditions. The pan coater used in this study was the same one ('thin' pan coater) that was used to conduct the video-imaging experiments. The coating experiments were conducted at two pan speeds (6 and 12 rpm), and at two pan loadings ($\nu = 0.10$ and $\nu = 0.17$). Ethyl cellulose (EC) was used as the coating material. The spray gun used was the same one used to generate the spray flux profile using the patternator. Black polystyrene (9 mm diameter) spheres were used for the experiments. In order to estimate coating weight gain CV, approximately 100 white polystyrene spheres were introduced into the system.

A 12% solids coating solution, with ethanol as the solvent, was used as the spaying medium. The coating run was conducted for 30 min. The atomizing air pressure was maintained at 40 psi, and the spray rate was 15 ml/min. The gun-to-bed distance was 10.2 cm (4 in.). Air was circulated in the pan to facilitate drying, by using an external port with a vacuum cleaner attached to it. The entire pan set-up was placed inside a fume hood for safety reasons. EC-coated white spheres were isolated from the system after the coating run. They were then weighed individually to estimate their weight after coating. The coating on each sphere was then removed by using ethanol. They were then dried and weighed again to estimate the weight of the sphere before coating. The weight gained during coating by each sphere was estimated using Eq. (4.11).

$$\text{Coating weight gain} = \text{Weight after coating} - \text{Weight before coating} \quad (4.11)$$

A total of about 90 white spheres were recovered from each coating run. The CV of the coating run was estimated using the coating weight gain of these 90 spheres using Eq.

(4.4). A total of 4 operating conditions were used for the coating runs. One of the coating runs was replicated to check the repeatability of the process. The operating conditions and the corresponding experimentally obtained CVs are shown in Table 4.3.

Table 4.4. Experimental CV results for 4 operating conditions and 1 repeat run

Pan loading (fractional fill)	Pan speed (rpm)	Experimental CV
0.10	6	18.35
0.10	12	12.88
0.17	6	23.95
0.17	6	26.12
0.17	12	21.90

It can be seen from the data shown in Table 4.3 that the CV decreases with an increase in pan speed and a decrease in pan loading. This is consistent with the trends predicted by the Monte Carlo simulations (Eq. (4.10)).

In order to effectively compare the CV predictions from Monte Carlo simulations with the experiments, the exact experimental conditions must be taken into account. To do so, there were two additional considerations:

1) *Spray area dimensions*: To estimate the exact dimensions of the spray area, a target comprising a piece of foam sponge, was kept under the spray gun at the same location as the table bed. The spray was then started and the dimensions of the spray area formed on the sponge were measured. These dimensions were then used in the Monte Carlo simulations to match the experimental spray area. The spray area was found to be elliptical in shape and did not cover the entire width of the pan.

2) *Pulsing of nozzle*: It was observed during experiments that the spray nozzle was not delivering the spraying solution continuously and there was a pulsing effect, where the nozzle stayed on for a few seconds and then went off for few seconds before turning back on again, as shown in Figure 4.45. This can be attributed to a solids-build up during spraying. This was taken into account in the Monte Carlo simulations. A high-speed camera (1000 frames/s) was used to record a video of the nozzle during spraying in order to quantify the pulsing rate of the nozzle. An analysis of the video showed that, on an average, the nozzle sprayed for 75 % of the total time. The corresponding calculations are shown in Appendix III.

Figure 4.45. Snapshots of spray nozzle with time to show a sample of the pulsing of nozzle

The spray area dimensions and the pulsing of the nozzle were taken into account in the Monte Carlo simulations and the values of CV were compared with the experimental values. This is shown in Figure 4.46 for the 4 experimental conditions. The error bars in Figure 4.46 show twice the value of standard deviation. The standard

deviations for the simulations were obtained by randomly sampling 90 points from the weight gain distribution predicted by the Monte Carlo simulations for all of the particles in the system. This procedure was repeated 100 times in order to estimate the error bars shown in Figure 4.46. It can be seen that the Monte Carlo simulations underpredicts the value of CV in comparison to the experimentally obtained CV. It should be noted that the Monte Carlo simulations are based on observations from a single tracer particle that was used in the video-imaging experiments. Hence it was assumed that the movement of the tracer particle is representative of movement of all the particles in the system. Even though this is a good assumption for the current case, as is confirmed by some of the DEM results (discussed in Section 4.3), this will not hold true for all of the particles in the system. The experimental CV, on the other hand, is based on the weight gain of 90 individual spheres. It is very likely that the tracer particle does not perfectly represent the movement of all of these particles. This can explain the disparity between the experiments and the simulations. Also, the video-imaging experiments were conducted in a dry environment (no liquid spray), whereas the coating experiments were conducted in a ‘wet’ environment. Even though it was shown earlier (Section 4.1.6) that the presence of ethanol in the system does not make a significant difference to the particle motion, the coating experiments were done using a more viscous solution (12 % w/w EC/Ethanol). This could have affected the motion of particles and caused a disparity between the simulations and coating experiments. It should also be pointed out that the Monte Carlo simulations do not account for all of the factors that control the spray dynamics (for *e.g.*, droplet size, solution properties etc.), which in turn will result in lower CVs for the simulations.

Figure 4.46. Comparison of CVs obtained from experiments and Monte Carlo simulations

4.3. Comparison of results from video-imaging experiments and DEM simulations

A MATLABTM-based DEM code was developed by IeTEK (Tacoma, WA) to simulate the movement of spherical particles in a pan coater [59],[78]. The results obtained from DEM simulations were compared with those obtained from the previously discussed video-imaging experiments. Figure 4.47 shows a snapshot of the graphical user interface (GUI), which provides a pictorial representation of the DEM simulations. The GUI makes it very straightforward to change the particle size, pan size, operating conditions, and physical properties for the DEM simulation.

Figure 4.47. A snapshot of graphical user interface in the DEM simulation [59]

The effect of these parameters on the dynamic angle of repose and average cascading velocity on the inclined surface were investigated and compared with results from video-imaging experiments. The value of coefficient of friction for the 9 mm polystyrene spheres used in this study was 0.5. The Poisson ratio was set to 0.33. The Young's modulus of the particle was set to 1.28×10^9 Pa, which was obtained from tests conducted on the polystyrene balls used in the current work by Micro Photonics Inc. (Irvine, CA).

The simulation techniques used in the current work are superior to the ones typically used due to the following reasons [59]:

- No 'fitting' parameters are used to match experimental and simulation results
- A 3-D contact model is used

- Time step increment used is 10^{-6} s, which is about 1-2 orders of magnitude smaller than used previously for systems with similar number of particles. Hence, the current work captures the dynamics of the system better
- No periodic boundaries are considered, which are typically used to save computation time at the expense of some information about the system
- Axial motion of particles is taken into consideration and velocity distributions in the axial directions are studied
- Particle-wall interactions are rigorously modeled.

It is important to point out that previous work on DEM addresses some of these issues individually, but not collectively, as is done in the current work.

4.3.1. Dynamic angle of repose

The dynamic angle of repose is the angle formed by the inclined cascading surface and the horizontal and is illustrated in Figure 4.48. A visual comparison of the dynamic angle between the experiments and simulations is shown in Figure 4.48. Figure 4.49 shows the comparison of the dynamic angle obtained from DEM simulation and experiments for two different fractional fill volumes and three pan speeds. Although the trends predicted by DEM were consistent with the experimental observations, the dynamic angle was found to be higher for the experiments. A possible reason for this difference is the ‘wavy’ shape of the cascading bed surface, which was observed to be more pronounced in the experiments compared to the simulations.

Figure 4.48. Comparison of simulation (A) and experiment (B) for 9 mm polystyrene balls in a 29 cm diameter pan. Parallel lines are shown in both figures to compare dynamic angles (slope) in both cases [59]

4.3.2. Average cascading velocity of particles in the spray zone

The average cascading velocity of particles in the spray zone can be determined by using video-imaging methods as discussed in Section 4.1.4. For the DEM simulations, the average cascading velocity of particles for any region on the inclined surface can be obtained. Figures 4.50 (a) and (B) show the average cascading velocity of particles in the spray zone for experiments and DEM simulations.

It can be seen from Figure 4.50 that the average cascading velocity increases linearly with pan speed for both DEM simulation and experiments. For the lower fractional fill volume, the simulation results were in agreement with the experimental results. The slope of the linear fit was found to be 2.00 ($R^2 = 0.98$) from experimental data and 1.97 ($R^2 = 1.00$) from simulation results as shown in Figure 4.50 (A) for $\nu = 0.10$. Good agreement was obtained between the slopes obtained from simulations

Figure 4.49. Comparison of dynamic angle obtained from video-imaging experiments and DEM simulations for (A) $\nu = 0.10$ and (B) $\nu = 0.17$, in a 58 cm pan [59]

and experiments. Figure 4.50 (B) shows results for $\nu = 0.17$, where the slope of the linear fit was found to be 3.1 ($R^2 = 1.00$) from experimental data and 2.25 ($R^2 = 1.00$) from simulation results.

Figure 4.51 (A) shows the cumulative normalized frequency of particle velocity in the y -direction obtained in a 58 cm pan with 4700 spheres rotating at a pan speed of 9 rpm. The velocity distribution obtained is Gaussian-like for both experiments and simulations. A possible cause for the disparity between the two distributions is the fact that the experimental results are based on observations from a single tracer particle, whereas the simulation results are an average of multiple-particle observations. Also, the simulation may not represent the experimental conditions perfectly. No effort was made in the current work to match the simulation and experimental results by adjusting physical constants used in the model [59].

The normalized cumulative velocity profiles obtained during the experiments and DEM simulations for the x -direction velocity in the cascading layer are shown in Figure 4.51 (B), under the same operating conditions as Figure 4.51 (A). A very good agreement is obtained for the x -velocity profile as is evident from the figure.

Figure 4.50. Comparison of average cascading velocity (V_y) obtained from video-imaging experiments and DEM simulations for (A) $\nu = 0.10$ and (B) $\nu = 0.17$, in a 58 cm pan [59]

Figure 4.51. A comparison between cumulative velocity distributions, (A) V_y , (B) V_x , in the cascading layer in a 58 cm pan rotating at 9 rpm at $\nu=0.10$ obtained from video-imaging experiments and DEM simulation [59]

4.4.3. Effect of pan speed and pan loading

Three different pan loadings were used to investigate the effects of pan loading on surface velocity of particles. The values of fractional fill volumes for the three different pan loadings were $\nu = 0.10$, $\nu = 0.14$ and $\nu = 0.17$. Figure 4.52 shows the simulation results for all cases. In Figure 4.52, the x-axis is the ‘normalized distance from top of bed’s surface’; a value of ‘0’ refers to the top of the inclined surface and ‘1’ indicates the bottom of the inclined surface.

Alexander and Muzzio [79] studied similar velocity profiles along the cascading layer using images taken by a digital camera installed on the side of a tumbling blender. The velocity profiles reported by them are highly symmetric for all the cases studied. The effect of pan loading on the velocity was not investigated, as all experiments were conducted at 50% fill level. They performed a dimensional analysis and showed that velocity of particles can be given by Eq. (4.12).

$$V = kR\omega^{2/3} \left(\frac{g}{d_p} \right)^{1/6} \quad (4.12)$$

where V is the velocity of particles, k is a constant, R is the pan radius, ω is the pan speed, g is acceleration due to gravity, and d_p is the particle size.

Figure 4.52. DEM simulated profile of average y -direction velocity for 58 cm diameter pan at a speed of 9 rpm for, and (A) $\nu = 0.10$, (B) $\nu = 0.14$, and (C) $\nu = 0.17$ [59]

Using Eq. (4.12), the surface cascading velocities were first normalized by dividing by $\omega^{2/3}$, as shown in Figure 4.52. From Figure 4.53, it can be seen that the surface velocity scales well with the pan speed ($\omega^{2/3}$), as proposed by Alexander and Muzzio [79]. However, there is a significant difference for the surface cascading velocities at different pan loadings, which means that the surface cascading velocities are significantly dependent on pan loading. Therefore, the fractional fill volume was also included in the dimensional analysis of cascading surface velocity. As shown in Figure 4.54, the simulation data were then normalized by accounting for fractional fill volume and there was a good overlap of these simulation data when normalized by $v^{1.8}$ [59].

Hence a new modified correlation is proposed for velocity scale-up:

$$V = kR\omega^{2/3}\left(\frac{g}{d}\right)^{1/6} v^{1.8} \quad (4.13)$$

This relationship provides important information for the pan coating scale-up process. The use of spherical particles for the simulations helps to reduce the simulation time due to its symmetric nature. However, in actual practice, the pharmaceuticals tablets are typically not spherical. Recently, Song et al. [79] have developed an algorithm to use DEM for standard round tablets. They showed that tablets move faster than spherical particles (Figure 4.55), consistent with the findings from the video-imaging experiments (Figure 4.11).

Figure 4.53. Simulated profile data for all fill levels shown in Figure 4.51 normalized by $\omega^{2/3}$, as proposed in Equation (4.12) [59]

Figure 4.54. Cascading layer surface velocity normalized with fractional fill volume and pan speed [59]

Figure 4.55. Comparison of surface velocity profile along the inclined surface between tablet and spherical particles. The diameter of the drum used is 29 cm and pan speed 6 rpm [4]

5. Conclusions

A novel video-imaging technique was used to investigate the movement of tablets inside a pan coating device. The variables investigated were pan loading, pan speed and particle shape. The response variables were circulation time, surface time, projected surface area under the spray nozzle (not quantified in previous work), dynamic angle of repose, cascading velocity (2 directions), and dispersion coefficient. The distributions of circulation time, surface time, and projected surface area were found to be non-normal. A significant difference in particle motion was observed between the standard round shaped tablets and spherical particles with tablets moving faster than spherical particles. A linear model ($R^2 > 0.98$) best described the variation of velocity as a function of pan speed. The average velocity was found to increase with an increase in pan loading. Both of these findings were in agreement with the results obtained from DEM simulations. The dynamic angle of repose was higher for tablets in comparison to spheres and the bed surface was more 'wave-like' in case of tablets. The axial dispersion coefficient (D_x) was found to increase with increasing pan speed and pan loading. The video-imaging technique was also successfully used to quantify the effect of baffles on the mixing inside the pan. The spread of the circulation time distribution was used to quantify the effect of baffles.

The video-imaging data, along with information on spray shape, spray area, and spray flux distribution inside the spray zone, were used as inputs to a mechanistic model to predict CV using Monte Carlo simulations. The effects of pan speed, coating time, tablet size, pan loading, spray flux distribution inside the spray zone, spray shape, and spray area were investigated. The spray flux distribution inside the spray zone was

measured using a linear patternator. CV was found to be inversely proportional to the square root of coating time. Even though in practice this may not be the most practical way to reduce the CV of the process due to time constraints, this information can still be used effectively for situations where an active drug is coated on the tablets and low CVs are extremely critical. The CV model proposed in this work can provide a basis for adjustments in process parameters required during a scale-up operation or in situations where the tablet size, pan loading, or pan speed is changed, in order to achieve the same CV. The Monte Carlo approach is also able to predict the effect of spray shape and area on CV, which was not quantified in any of the previous approaches. The spray shape was not found to affect the CV of the process significantly, but an increase in the spray area was shown to promote lower CVs. Coating experiments were conducted to verify the predictions from the Monte Carlo simulations. Good agreement in trends was obtained when the exact experimental conditions were used for the simulations, although Monte Carlo was found to underpredict the values of CV in comparison to experiments.

Although Monte Carlo results show great promise and provide valuable insights into the coating process, they require experimental data from the video-imaging system, and hence *a priori* prediction is not possible. The DEM approach, on the other hand, can be used as an independent predictive tool and was shown to predict the movement of tablets inside the coater. Results of DEM simulations were compared with those obtained from video-imaging experiments. Good agreement was obtained between velocity distributions in the spray zone in *x*- and *y*- directions between the simulation and experiments. Velocity profiles along the entire top cascading layer of particles were also estimated. The particles in the cascading layer were found to reach their maximum

velocity close to the mid-point of the chord defining the cascading bed surface. The velocity profiles along the top cascading layer were found to be more symmetric for higher pan loadings. Comparison of simulated velocity profiles showed good agreement with published scaling laws for rotating drums, and a new correlation for scaling with respect to the pan loading was proposed. In the future, a combination of DEM with the spray dynamics of the system may, in principle, allow *a priori* estimates of CV.

Future work should focus on studying tablet movement inside the pan coater at different pan sizes by using video-imaging techniques. This information in conjunction with Monte Carlo simulations will help in establishing CV scale-up rules for the pan coating process. As a part of the future work, different baffle designs from various pan coater vendors should be investigated. The baffle designs should be optimized to achieve the best mixing inside the pan, which will result in lower CVs.

6. Nomenclature

a, b, c	real number exponents	
d_{equiv}	volume equivalent particle diameter	cm
d_p	particle diameter	cm
g	gravitational acceleration	m/s ²
k_1, k_2, k_3	constant	
m	mass of the particle	g
r_l	distance from center of the spray zone	m
Δt	time increment	s
t_{coat}	total coating time	s
x	centroid x -location	m
y	centroid y -location of the tablet	m
A_{exp}	projected surface area of tablet during passage through ROI	mm ²
Bo_g	Bond number	
RSD_{circ}	relative standard deviation of circulation time distribution	
D_x	dispersion coefficient	cm ² /s
F_c	maximum capillary force	N
N	number of perfect mixers or total number of particles in the coating device	
R	pan radius	cm
S_{flux}	spray flux	g/mm ² /s
V	cascading layer velocity	cm/s
V_x	velocity perpendicular to the flow direction	mm/s

V_y	velocity parallel to the flow direction	mm/s
W	weight of the particle	N

Greek symbols

ρ_p	particle density	kg/m ³
θ	dynamic angle of repose	degree
σ	standard deviation	
μ	mean	
γ	surface tension	N/m
τ_{circ}	circulation time	s
τ_{circ}	surface time	s
ν	fractional fill volume	
ω	pan speed	rpm

Subscripts

ct	denotes cycle time distribution
m	denotes coating weight gain
n	denotes number distribution
$total$	total mass of coating material on a particle
x	denotes coating mass distribution or direction perpendicular to the direction of cascading tablets
y	direction parallel to the direction of cascading tablets

Abbreviations

CCD	charged coupled device
CFD	computational fluid dynamics
CTD	cycle time distribution
CV	mass coating variability
DEM	discrete element modeling
FDA	food and drug administration
GUI	graphical user interface
HPLC	high performance liquid chromatography
HPMC	hydroxy propyl methyl cellulose
MRI	magnetic resonance imaging
NIR	near-infrared
PAT	process analytical technology
PEPT	positron emission particle tracking
PIV	particle imaging velocimetry
ROI	region of interest
RPM	revolutions per minute
SEM	scanning electron microscope

7. References

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Appendix I. Monte Carlo Matlab code

The Matlab-based code used for the Monte Carlo simulations is shown below.

The shown code is for an elliptical-shaped spray zone. There are two functions that are used in the main code, cumulative function and the random function. The codes for those two functions are also shown below.

Main code

```
function s = sprayshape()
N=2686; % total number of tablets
runtime=1800; % total coating time in sec
a=50; % length of major axis, should be the width of the drum, units
mm, 105/2
% b=a; % length of minor axis- circular
b=a/2; % for elliptical
deltat=0.04; % time increment in sec
f=0.5; % fraction of time a particle remains at the surface
S = 0.001; %
=====
tcirc=xlsread('tcirc'); % tcirc is the data file for circulation time
tcum=cumulativefn(tcirc(:,1));
data=xlsread('data'); % read data file, make data file again after
calibration and units in mm
Acum=cumulativefn(data(:,1));
xcum=cumulativefn(data(:,2));
ycum=cumulativefn(data(:,3));
xmin=min(data(:,2)); % extreme co-ordinates of spray, mm
xmax=max(data(:,2));
xmax-xmin;
ymin=min(data(:,3));
ymax=max(data(:,3));
centerx=(xmin+xmax)/2; % center x-coordinate of spray, mm
centery=(ymin+ymax)/2; % center y-coordinate of spray, mm
vel=xlsread('vel');
xcumvel=cumulativefn(vel(:,1));
ycumvel=cumulativefn(vel(:,2));
ml=0;
tl=0;
% main loop
=====
for i=1:N % loop for different tablets
    j=1;
    t=0;
    mass(i)=0; % initialization
    Nl=0;
    k=1;
    while (t <= runtime) % loop for same tablet by the end of run
        j=1; % step number
        tl=tl+1;
        x(j)=random(xcum); % starting location of tablet- units mm
```

```

        y(j)=random(ycum);
        A(j)=random(Acum); % units mm^2
        vx(j)=random(xcumvel); % will be in mm/s
        vy(j)=random(ycumvel);
        r(j)= sqrt((x(j)-centerx)^2 + ((y(j)-centery)^2)/((b/a)^2));
% for elliptical
        spray(j)=(-9.73E-07*(r(j)^4) + 1.17E-04*(r(j)^3)- 3.97E-
03*(r(j)^2)- 7.29E-03*r(j)+ 1.86E+00); % using data from patternator
        while (y(j)<ymax) % loop for one pass of one tablet, checking
whether particle is still in ROI
            x(j+1) = x(j) + vx(j)*deltat;
            y(j+1) = y(j) + vy(j)*deltat;
            % y1=y(j+1)
            A(j+1)=random(Acum);
            vx(j+1)=random(xcumvel); % will be in mm/s
            vy(j+1)=random(ycumvel);
            if x(j+1)>=xmax % wall collisions correction
            x(j+1)=x(j+1)-2*(x(j+1)-xmax);
            elseif x(j+1)<=xmin % wall collisions correction
            x(j+1)=x(j+1)+2*(xmin-x(j+1));
            end
            r(j+1)= sqrt((x(j+1)-centerx)^2 + ((y(j+1)-
centery)^2)/((b/a)^2));
            spray(j+1)=(-9.73E-07*(r(j+1)^4) + 1.17E-04*(r(j+1)^3)-
3.97E-03*(r(j+1)^2)- 7.29E-03*r(j+1)+ 1.86E+00); % 50 mm ellip
            if (((x(j)-centerx)^2)/(a^2) + ((y(j)-centery)^2)/(b^2))
<= 1) & (((x(j+1)-centerx)^2)/(a^2) + ((y(j+1)-centery)^2)/(b^2))<= 1)
mass(i)=mass(i)+(A(j)*spray(j)+(A(j+1)*spray(j+1)))*S*deltat/2;
                m1=m1+1;
            elseif (((x(j)-centerx)^2)/(a^2) + ((y(j)-
centery)^2)/(b^2)) <= 1) & (((x(j+1)-centerx)^2)/(a^2) + ((y(j+1)-
centery)^2)/(b^2)) > 1)
                mass(i)=mass(i)+ (A(j)*spray(j))*S*deltat/2; % SF is
spray flux, units mg
                    m1=m1+1;
                elseif (((x(j)-centerx)^2)/(a^2) + ((y(j)-
centery)^2)/(b^2)) > 1) & (((x(j+1)-centerx)^2)/(a^2) + ((y(j+1)-
centery)^2)/(b^2)) <= 1)
                    mass(i)=mass(i)+ (A(j+1)*spray(j+1))*S*deltat/2; % SF
is spray flux, units mg
                        m1=m1+1;
                    else
                    end
                j=j+1;
            end
            b1=random(tcum);
            t=t+b1;
            N1=N1+1; % counting total number of passes
            k=k+1; %increment pass number
        end
    N1;
    m1;
    m(i,1)=f*mass(i); % f is the fraction of time spent on surface when
tablet is in the spray zone
end
m;
xlswrite('results',m);

```

Cumulative function

This is used to generate cumulative distributions.

```
function c = cumulative(F)
G=max(F);
H=min(F);
q=10; % number of bins
I=(G - H)/q;
step(1)=min(F);
for i=1:q
    freq(i)=0;
    for k=1:length(F)
        if F(k)<step(i)
            freq(i)=freq(i)+1;
        end
    end
    normfreq(i)=freq(i)/length(F);
    g1(i,2)=normfreq(i);
    g1(i,1)=step(i);
    step(i+1)=step(i)+I;
end
g1(length(g1),2)=1;
c=g1;
```

Random function

This is used to generate and select random values from the cumulative distributions.

```
function b=random(g)
r2 = rand;
for i=1:length(g)-1
    if (g(i+1,2) > r2) & (g(i,2) < r2)
        b1 = g(i,1) + (r2-g(i,2))*(g(i+1,1)-g(i,1))/(g(i+1,2)-g(i,2));
    elseif g(i,2) == r2
        b1 = g(i,1);
    end
end
b=b1;
```

Appendix II. Repeatability of Monte Carlo simulations

The repeatability of the results from the Monte Carlo simulations was tested. The Monte Carlo simulation was performed 20 times under the same conditions, and the results are shown in Table A.1 below. A statistical analysis of the data shown in Table A.1 is shown in Table A.2. The data shown here is for 9 mm polystyrene spheres, at a pan speed of 9 rpm and a fractional fill volume of 0.10. The spray region used in these simulations was a 42 mm circular-shaped region.

Table A.1. Repeatability of Monte Carlo simulations

Run number	CV (%)
1	6.85
2	6.82
3	6.83
4	6.78
5	6.58
6	6.84
7	6.71
8	6.72
9	6.78
10	6.82
11	6.84
12	6.88
13	6.94
14	6.87
15	6.75
16	6.83
17	6.63
18	6.79
19	6.73
20	6.77

Table A.2. Statistical analysis of the data shown in Table A.1

Statistic	Value
Mean	6.788
Standard Error	0.019
Median	6.805
Mode	6.820
Standard Deviation	0.085
Sample Variance	0.007
Kurtosis	0.980
Skewness	-0.806
Range	0.360
Minimum	6.580
Maximum	6.940
Sum	135.755
Count	20.000
Confidence Level (95.0%)	0.040

It is clear from the data shown in Table A.2 that the results from the Monte Carlo simulations are repeatable with very little variation. This is again demonstrated by the simulation data for 7.9 mm tablets, at three pan speeds, and a fractional fill volume of 0.10 shown in Table A.3. The spray region used for these simulations was a 42 mm circular spray zone. Uniform spray flux inside the spray zone was used for this case.

Table A.3. Repeatability results of Monte Carlo simulations for 7.9 mm tablets

Pan speed	CV
6	7.68
6	7.67
9	6.28
9	6.25
12	5.58
12	5.60

Appendix III. Quantification of spray nozzle pulsing

A high speed camera was used to record a video of the nozzle while it was spraying. The video was then analyzed using Motion ProTM software. The frame numbers were used to quantify the amount of time that the nozzle sprays as a percentage of the total time it was turned on for. The profile of the spray nozzle pulsing is shown in Figure A.1. A spray intensity of '0' represents no spray coming out of the nozzle, while a spray intensity of '1' represents spray with full intensity. Since the intensity of spray at every instant was not quantified in the current work, the actual profile was approximated by a profile shown in Figure A.1. The solid line in Figure A.1 denotes the actual spray intensity profile, and the dotted line shows the approximation used in the current work.

Figure A.1. Quantification of pulsing of spray nozzle using high speed imaging taken at t=15 min for a 30 min coating run

From the approximated profile in Figure A.1, it can be seen that the nozzle sprayed the solution for an average of 360 (680-320) frames, and did not spray for a total of 120 frames out of a total time of 480 (740-260) frames. This means that the nozzle did not spray for $(120/480) = 25\%$ of the total spray time.