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REVIEW ARTICLE

The application of modeling techniques to film-coating processes

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Abstract

Background: The modeling of the processes for film coating of solid dosage forms can aid in the prediction and troubleshooting of coating operations. *Aim*: A review of the existing approaches to modeling the coating phenomena was undertaken with the aim of identifying key assumptions and limitations of each approach. *Method*: Models are categorized into macrolevel and microlevel approaches. Macrolevel models can predict mass coating uniformity for a batch of solids. On the other hand, microlevel models consider phenomena at the scale of the liquid droplets sprayed into the process. Macrolevel models consist either of phenomenological approaches, whereby the inherent variabilities in the coating process are described by probability distributions. Alternatively, first-principle models based on rigorous descriptions of solid and gas-phase motion can be used to describe the multiphase flow behavior in coating equipment. *Result*: The advantages of the rigorous macrolevel approach are that extrapolation of results for different operating conditions is more reliable than the phenomenological approach and much more information is available about the flow of both phases. However, these first-principle models are computationally intensive and cannot be used for real-time predictions. On the other hand, microlevel models describe chemical and physical phenomena occurring when droplets of coating solution impact the surfaces of the solid cores and are useful in determining the cause of morphological variations in coating properties. *Conclusions*: Both micro- and macro-level approaches can be used to predict and troubleshoot problems in coating processes. The use of such models in the control of coating operations is not widespread but offers significant potential to improve quality control.

Key words: *CFD; circulation time; coating variability; DEM*

Introduction

The purpose of this article is to discuss the various approaches to modeling that have been used to further the understanding and prediction of film-coating processes. Furthermore, the limitations of the different models, their predictive capabilities, and their potential to be used in troubleshooting and/or process analytical technology are discussed.

Several recent reviews of the modeling of film-coating processes have been given[1–3]. The approach to modeling these processes can be categorized in several ways. In this article, the modeling is described as being carried out at either the macrolevel or the microlevel (ML). The macrolevel approach involves consideration of the coating phenomena applied to the whole batch of particles being coated. On the other hand, modeling at the microscale looks at the coating phenomena, such as wetting and film formation, at the surface of an individual tablet or core. Clearly, the two approaches are related in that what happens at the ML will ultimately affect the results at the macrolevel. The difference in the two modeling approaches lies in the scale at which the model predictions are used. The information gained from these different models and their predictive capabilities is quite different. For example, if a film coating was found to be too porous and creating unwanted dose dumping of an active pharmaceutical ingredient, then an ML analysis/model might be warranted to determine what phenomena caused this effect. On the other hand, if over a period of time a coating process results in some batches exhibiting a wider variability in a dissolution

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test than required then a macrolevel model describing the fundamental processes occurring in the equipment might be warranted. In troubleshooting processes, often a combination of the ML and macrolevel approaches is needed to identify and subsequently solve the problem(s).

For the macrolevel models, a further categorization of coating is to define models as having either phenomenological or rigorous/first-principle approaches. The term phenomenological, as the name implies, applies to models in which the basic physics or phenomena of the coating process are used to describe the behavior of all the tablets or cores in the equipment. Usually, differences in the phenomena that occur within the equipment and over the batch of solids are described with probability distribution functions. These functions form the basis of the model, and by capturing changes in equipment operation and/or feed quality in the functions, the changes in the product quality can be predicted. Renewal, population balance, and Monte Carlo (MC) models are examples of phenomenological modeling and will be discussed in this article. On the other hand, rigorous or first-principle models use the microscale physics of the motion of the different phases to describe what goes on in the bulk equipment. A good example of this type is a discrete element model (DEM) in which every tablet in a coating pan is modeled using Newton's laws of motion. With such a description, the movement of every tablet in the pan can be computed. Such models are extremely powerful because they can, in principle, predict a priori how changes in operating variables (pan speed, spray rate, tablet loading, etc.) affect product quality. The reason that these models are not used more extensively is because of the extremely long times needed to simulate just a minute or two of actual operation. The trade-off between phenomenological and first-principle models is a balance between ease (time) of computation versus predictive capability.

A summary of the categorization of the modeling approaches is shown in Figure 1. In the future, the role of ML and first-principle models is expected to grow, but currently all approaches are still useful to the pharmaceutical scientist and engineer in diagnosing and understanding the film-coating process.

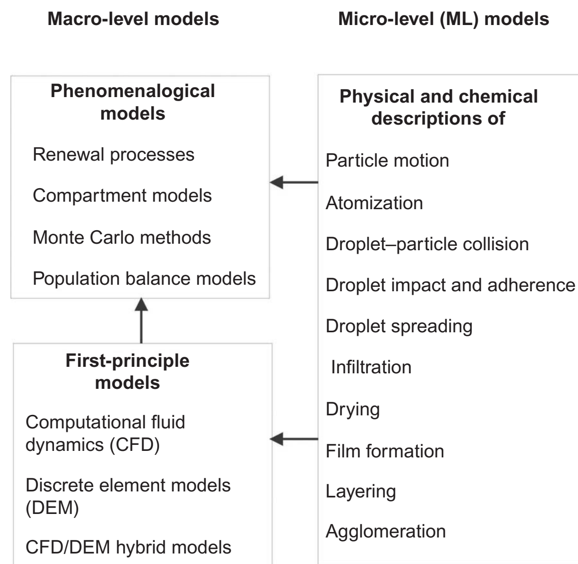

Figure 1. Categorization of models to describe film formation in coating processes (arrows show direction of input to models).

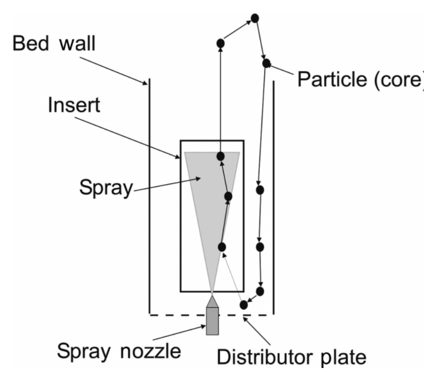

Figure 2. Movement of a single particle or core in a bottom spray-fluidized bed.

Different modeling approaches

Phenomenological modeling

Coating as a renewal process—fluidized beds

Mann et al.[4], Mann[5], and Cheng and Turton[6,7] have all considered the coating of pharmaceutical cores in a fluidized bed to be a renewal process. The underlying physics for this model is shown simply in Figure 2. If one were to track a single core moving through a fluidized bed coater (top, bottom, or tangential spray arrangement) then each time the core passed through the spray zone it would receive an amount of coating. The total coating received by the core would simply be the additions of the coating received from each pass through the spray zone. Therefore, we can write

$$x_{\text{total}} = \sum_{i=1}^{n} x_i , \qquad (1)$$

where x_{total} is the total mass of coating deposited on the tablet or core during the coating process, x_i is the mass of coating the particle receives in the ith pass through the spray zone, and n is the total number of passes through the spray zone that the particle takes during the experiment or coating run (of total length T_{coat}).

Because of the inherent variability in the fluidized bed equipment, particles receive different amounts of coating depending on where they pass through the spray and different particles pass through the spray a different number of times during the coating run. This means that x and n vary and can be considered as random variables with probability density functions associated with them. By making certain assumptions, specifically that the particles behave independently of one another and have identical circulation and coating-per-pass distributions, the following, more useful, expression can be derived:

$$\mathrm{RSD}=\mathrm{CV}=\frac{\sigma_{\mathrm{total}}}{\mu_{\mathrm{total}}}=\sqrt{\left(\frac{\sigma_x}{\mu_x}\right)^2\frac{\mu_{\mathrm{ct}}}{T_{\mathrm{coat}}}+\left(\frac{\sigma_{\mathrm{ct}}}{\mu_{\mathrm{ct}}}\right)^2\frac{\mu_{\mathrm{ct}}}{T_{\mathrm{coat}}}}, \quad (2)$$

where CV is the coefficient of variation or the relative standard deviation (RSD) of the distribution of the total mass of coating on a batch of particles received during a process lasting for T_{coat}, μ and σ represent the mean and SDs of the distributions, and the subscript *ct* and x refer to the cycle time and the coating mass, respectively. Equation (2) shows that the overall coating RSD is because of the variability of two processes. The first is the cycle time distribution, where the cycle time is defined as the time taken for a tablet or core to make successive passes through the spray zone. The second process, the coating-per-pass distribution, takes account of sheltering effects in the spray zone. The term $\mu_{\mathrm{ct}}/T_{\mathrm{coat}}$ is simply the reciprocal of the average number of passes that particles make through the spray zone. One very useful trend shown by Equation (2) is that $\mathrm{RSD} \propto \sqrt{1/T_{\mathrm{coat}}}$. Therefore, all other considerations aside, if we increase the coating time by a factor of 4 (but keeping the amount of coating material the same) the RSD is cut in half. In principle, the CV can be reduced to any desired value simply by increasing the time over which the spraying occurs; however, practical considerations such as excessive erosion, length of batch operation, ability to keep spray nozzles clean, and spray drying of the coated material often prevent using such an operating policy. The other terms in Equation (2) must be estimated or measured. The mean cycle time and mean coating per pass can be estimated if some basic knowledge of the hydrodynamics of the system is known. For example, if a viewing window is available at the side of the bed then an estimate of the downward velocity of the cores can be made. The majority of the time for circulation is made up of the downward movement through the annular bed; if this is taken as ~80% of the total circulation time, Cheng and Turton[6,7], then knowing the height of the solids in the annular bed allows estimates of μ_x and μ_t to be made as follows:

$$\mu_{\mathrm{ct}} \approx 1.25\frac{H}{\nu_{\mathrm{s}}} \quad (3)$$

$$\mu_x=\frac{M_{\mathrm{coat}}}{(T_{\mathrm{coat}}/\mu_{\mathrm{ct}})}\frac{1}{N_{\mathrm{part}}}, \quad (4)$$

where H is the height of cores in the annular section between the bed wall and the Wurster insert or partition, ν_{s} is the velocity of the solids (cores) in the annular region, M_{coat} is the total solids content sprayed into the bed during the time of the coating operation, T_{coat}, and N_{part} is the total number of particles (cores) in the bed. According to Christensen and Bertelsen[8] typical cycle times for particles, even in full-scale equipment, are in the range of 15–60 seconds.

The difficulty with applying this and other phenomenological models is the problem of determining the SDs of the cycle time and coating-per-pass distributions. In general, these parameters must either be measured directly or back-fitted to match a measured coating CV. Studies by Shelukar et al.[9] and Cheng and Turton[6,7] used magnetic tracer methods to follow the circulation of a tagged particle around a bed. Shelukar et al.[9] looked at tablets and Cheng and Turton[6,7] looked at nonpareils, but both groups concluded that the major source of variation was because of the variability in the coating-per-pass distribution and that this was 4–10 times larger than the variability in the cycle time distribution. In general, we may say that

$$\left(\frac{\sigma_x}{\mu_x}\right)^2=4-10\left(\frac{\sigma_{\mathrm{ct}}}{\mu_{\mathrm{ct}}}\right)^2. \quad (5)$$

If Equations (3)–(5) are substituted into Equation (2), then an expression with only one unknown σ_x is obtained. The value of σ_x can be estimated by measuring the CV from a coating run and back-calculating the value of σ_x.

Clearly, although this model provides a clear picture of the physics of the coating process and the sources of the main variabilities, it is limited in its ability to predict, a priori, how much the CV will change when operating variables such as gap height, bed loading, and air flow change. Namely, such changes would have to be determined experimentally for the system of interest and the value of σ_x adjusted to fit the data. However, the more rigorous models may be able to provide this information through simulation and this is discussed further in this article.

Compartment models—fluidized beds

Another way to describe, phenomenologically, the flow of particles in fluidized beds is to model the equipment as several compartments through which tablets move and the time spent in each compartment is used to indicate the amount of coating received. Models of this form have been proposed by Sherony[10], Wnukowski and Setterwall[11], and Maronga and Wnukowski[12]. The model of Sherony consists of dividing the bed into two compartments: a region in which tablets or cores receive spray and a second region in which they do not. This is illustrated in Figure 3. The fraction of tablets in the spray region is identified as α and under the assumption that α is in the range 0.1–0.3, the CV is given by

$$CV = 1.25\sqrt{\frac{(1-\alpha)\mu_{ct}}{T_{coat}}}. \qquad (6)$$

Equation (6) gives rather low values of CV. For example, for $\alpha = 0.2$, $\mu_{ct} = 15$ seconds, and $T_{coat} = 2$ hours, CV = 1.25 $(0.8 \times 15/7200)^{1/2} = 0.05\%$ or 5%. Nevertheless, the dependence of $CV \propto 1/T_{coat}^{1/2}$ is the same as seen for the fluid bed coating model based on the renewal principle. The models of Wnukowski and Setterwall[11] and Maronga and Wnukowski[12] involve using more compartments and predict more reasonable (larger) values of CV at the expense of having more adjustable parameters to fit the experimental data.

As with other models of this type, changes in operating conditions or equipment configuration, for example, different gap heights or spray-to-bed distance for top-spray units, are modeled through changes in the parameters. This normally involves back-fitting parameters to experimental data and this is difficult to achieve a priori. However, results from first-principle models may be used to determine some of these parameters.

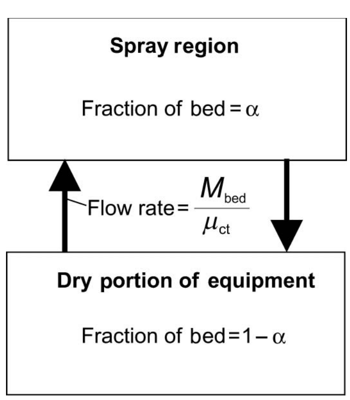

Figure 3. Two-compartment model of Sherony[10] (M_{bed} is the mass of particles in the equipment and μ_{ct} is the mean circulation time).

Compartment models—rotating pans

Similar models for coating in rotating perforated pans or drums can be formulated[13]. The key difference between such models for pan coaters is in the definition of a particle 'pass' through the spray zone. For fluidized beds, bottom spray with Wurster insert, the movement through the insert is relatively regular and if the system is designed to avoid dead spots at the walls then just about every core passes repeatedly through the spray zone and will receive some amount of coating, albeit very small for some passes. The case for rotating pans is fundamentally different in that the center of the particle bed is known to be a dead zone[14], where particles may sit for quite long periods of time before re-entering the circulating part of the bed. Moreover, even when particles make a circulation around the bed, only particles (tablets) at or very close to the top surface (first two or three tablet layers) will receive any coating, whereas others will pass under the spray and be sheltered by the tablets above them and thus receive little or no coating. Nevertheless, by adjusting the parameters describing the time spent in and out of the spray zone, compartmental models can be used to describe the pan-coating process. As with compartment models used to describe fluidized bed equipment, changes in operating conditions or equipment geometry can be accounted for by changes in the model parameters. As with other phenomenological models, such changes would have to be determined experimentally, thus reducing the effectiveness of such models to give a priori predictions of the behavior of a specific pan-coating configuration.

Monte Carlo techniques

As the name suggests, MC models also rely on probability distributions to describe the randomness associated with coating processes. This technique has been used to describe the movement and coating variability in bottom spray fluidized beds[15,16], rotating fluidized beds[17], and rotating pans[18] with good success. Variability in coating coverage because of randomness in particle motion, nonuniformity of spray pattern, and other effects may be simulated in the MC model. However, an accurate description of the randomness of each variable considered must be known and this usually implies a thorough experimental program to obtain such data. Alternatively, rigorous, first-principle models could also be used if the inherent variability in particle movement required by MC modeling is captured in the rigorous approach. As an example, the approach used by Pandey et al.[18] to model variability in pan-coating processes is summarized here. The movement of tablets in the pan and through the spray zone is shown in Figure 4. The movement of tablets at the top of the bed and through the spray zone was recorded using a machine-vision-based video system originally devised by Sandadi et al.[19]

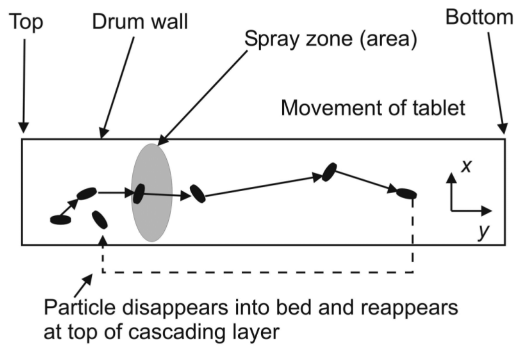

Figure 4. Top view of rotating drum coater, particles move from top (left) to bottom (right). Coating received by a particle depends on the surface area exposed to the spray, the location within the spray zone, and the number of passages through the spray.

The progress of a tagged particle as it moves down the top of the cascading bed of tablets is recorded and from this information, the velocity parallel, V_y, and at right angles, V_x, to the movement of the bed and the times between successive occurrences of the tablet at the surface of the bed, t_{circ}, are recorded. In addition, the surface area, A_p, of the tagged tablet that is exposed to the spray is also recorded. Data are recorded between 30 and 60 minutes during which time the tagged particle passes through the spray zone several hundred times. These data are used to build histograms of V_x, V_y, and A_p. In addition to the data on particle movement, experiments were performed to record the spray flux variation in the pan using a spray patternator.

The MC technique is then applied to a tablet using the following steps:

1. The starting position of a tablet at the surface of the bed (x_i, y_i) is chosen at random.
2. The x- and y-components of velocity for the tablet are chosen at random from the previously recorded histograms (distributions).
3. The distance moved by the tablet in a predetermined time increment, Δt, is calculated as $\Delta x = V_x \Delta t$ and $\Delta y = V_x \Delta t$.
4. The location of the tablet and the time are updated after the step as $x_{i+1} = x_i + \Delta x$, $y_{i+1} = y_i + \Delta y$, and $t = t_i + \Delta t$. If the tablet reaches the bottom of the bed then a new location at the top of the bed is randomly assigned after a period of $t_{circ,i}$ has passed.
5. A check is now made to see whether the tablet lies within the spray zone. If it does not then steps 2–4 are repeated. If it does, then the exposed surface area, A_p, is found by assigning a value from the previously calculated distribution (histogram) and the flux of spray hitting the tablet, based on the location of the tablet in the spray zone, is determined.
6. The cumulative mass of coating received by the tablet is updated as $M_{coat,\,i+1} = M_{coat,\,i} + A_p S_i \Delta t$, where S_i is the local value of the spray flux.
7. The algorithm returns to step 2 and is repeated until the total time equals or exceeds T_{coat}.

From this seven-step algorithm, it is clear that the tablet takes a 'random walk' around the pan and receives coating when it interacts with the spray. If the process above is repeated for every tablet in the pan then the distribution of coating mass on the population of tablets comprising the batch can be found. Although the MC process is computationally quite intensive, the calculations are very simple and the simulation for the whole bed took only 10–20 minutes.

Results for film coating of tablets in a small laboratory drum by Pandey[20] show good agreement with MC simulations. The limitations of this method are the requirements for obtaining detailed information on the statistical distribution of variables needed to perform the MC method. Moreover, how these distributions change with operating conditions would be required to predict the changes in the mass coating distribution for the batch of tablets. Nevertheless, as Pandey[20] has shown, MC simulations are a useful design tool to determine the impact of changing the equipment setup and to evaluate 'what-if' scenarios for changing operating conditions.

Population balance models

Another popular way to model coating processes is the use of population balances that track the change in size of the batch of coated particles through the coating process. The models presented previously by Sherony[10], Wnukowski and Setterwall[11], and Maronga and Wnukowski[12] are all population balance approaches. In addition, Liu and Litster[21] applied a population balance approach using a single-compartment model to a spouted fluidized bed (without insert) and were successful in predicting the changing size distribution of a batch of seeds undergoing a film-coating process. The key assumption for film coating is the form of the growth term in the population balance equations. The usual (and most reasonable) assumption is that particles receive an amount of coating proportional to the surface area of the particle. This means that for a distribution of similarly shaped particles of characteristic dimension d and volume V, the rate of coating addition is $\propto d^2$ or $\propto V^{2/3}$. This description of the rate of coating addition is the same as that assumed in the MC model of Pandey et al.[18] discussed previously. It should be pointed out that for a very wide size distribution, the direct application of such a simple coating model will result in erroneous predictions. This is because this model ignores the hydrodynamics of the particle movement in the equipment. When dealing with wide size distributions, the circulation of different size fractions of particles will take different amounts of time and the combined effect may result in the coating addition not being proportional to the exposed surface area (Sudsakorn and Turton[22]).

First-principle modeling

The characteristics of first-principle models are that the physics associated with the movement of the different phases in the coating equipment are modeled rigorously. This leads to solutions that may be expected to capture the changes associated with modifications to operating conditions and/or equipment geometry. Despite the rigor associated with such models, there are still parameters that need to be 'adjusted' in order for the model solutions to match experimental results. Nevertheless, once these adjustments have been made, the predictions of the models are expected to show the correct trends as input parameters (operating conditions) are changed and the results will show good quantitative agreement. As pointed out previously, the main disadvantage of first-principle or rigorous models is that they are computationally intensive and may require many hours or days of simulation to produce results that model the coating process in industrial-sized equipment over meaningful lengths of time (several minutes to an hour of actual coating time).

Computational fluid dynamic models

Computational fluid dynamic (CFD) approaches to modeling the coating process and the subsequent coating uniformity are quite sparse in the literature. Generally, a CFD approach is not appropriate for systems with a small number of particles as this method considers that particles flow like a fluid phase (continuum) and uses the mass, momentum, and energy conservation equations to describe the flow behavior of each phase. The interactions between the phases (gas and solids) are modeled using closure equations that involve the interphase drag, gas-phase turbulence, and particle–particle and particle–wall collisions. With this approach, different particle sizes can be simulated by the use of different solid phases. Heat and mass transfer can be accommodated relatively easily. Equipment internals such as draft tubes can also be modeled. Work in the coating area has concentrated mainly on calculating the patterns of solids and gas movement in different types of fluidized beds. For example, Duarte et al.[23] used a multiphase flow model to simulate the movement of particles in two-dimensional (2D) and cylindrical spouted beds. Magnusson et al.[24] developed a 3D CFD model that predicted solids movement in a fluidized bed with a Wurster insert. Models have also been developed by Littman et al.[25] and Morgan et al.[26] to describe the movement of particles in conventional spouting fluidized beds.

Recently, Karlsson et al.[27] have modeled the drying and wetting conditions in a laboratory-scale Wurster bed coater using CFD and compared their results with experimental data. Their approach uses multiphase fluid dynamics with heat and mass transfer to model the particle and gas motion within the apparatus and to predict the transport of thermal energy and moisture. Results are in good agreement with experimental data and their approach allows for a mapping of temperature and moisture content within the bed. They also show that, under normal operating conditions, the majority of the drying occurs within the Wurster insert.

Despite the lack of work in applying CFD methods to coating processes, this approach holds promise in its ability to predict the local conditions in the whole of the fluidized bed equipment. Therefore, temperature and humidity profiles along with solids and gas velocities may be predicted within the bed. Circulation time distributions could also be calculated for equipment under a wide variety of operating conditions. The interaction of a spray with the moving gas and solids could also be modeled. As stated previously, CFD models tend to be computationally intensive and are not appropriate for real-time simulations. Nevertheless, they can provide a wealth of information and would allow the pharmaceutical scientist the ability to explore a wide variation in operating conditions and equipment geometry without the need to perform a large number of time-consuming and expensive experiments.

Discrete element models

DEMs solve Newton's laws of motion in three dimensions for all tablets or cores in a device. This modeling approach has gained wide acceptance in situations where the solids move under the influence of gravity and the frictional forces between particles are important. The flow of solids in a typical rotating drum may be modeled using the DEM method. Unlike the CFD approach, each particle or tablet is modeled and its position and velocity is calculated at all times during the simulation. In order for gas flow to be modeled, along with the solids movement, a CFD model must be solved simultaneously with the DEM model. Such an approach was adopted by Terashita et al.[28], who used DEM simulation coupled with CFD to evaluate the effect of new draft-tube designs in a fluidized bed coater. In a study of a rotating fluidized bed coater, Muguruma et al.[29] modeled the particle movement in a rotating fluidized bed using DEM and included modeling the forces associated with 'liquid bridges' for granulation and coating applications. They further assumed that the added liquid is uniformly distributed among all possible particle–particle contact sites and that viscous dissipation effects were negligible. Their model predicted well the effects of the presence of liquid (water) compared with experiments in the rotating fluidized bed.

Yamane et al.[30] used DEM to calculate the following parameters for spheres in a rotating drum:

α the fraction of exposed area of sphere in the cascading layer.
t_i the time spent by a particle on the surface of the bed (in some region representing the spray zone).
T_c the circulation time between successive particle passes through the spray zone.

As discussed in the section on MC simulation, these parameters, along with knowledge of the distribution of spray flux in the spray zone, may be used to estimate the coating distribution and CV for all particles in the drum.

Another advantage of the DEM approach is that equipment design variables such as number, size, and placement of baffles, tablet fill level, nozzle geometry, and coating time can be investigated through modeling. For example, Muguruma et al.[31] investigated the motion of particles in a rotating mixer with two baffles and concluded that an optimal baffle length/height ratio existed that maximized particle mixing. Recently, Kalbag et al.[32] and Kalbag and Wassgren[33] have done extensive simulation of the movement of particles in horizontal pan coaters with baffles. They conclude from their simulations that, among other things, coating variability decreases with the square root of the number of pan revolutions and with the square root of the ratio of spray zone/pan width. On the other hand, coating variability increases with fill level and with decreasing coefficient of friction between the tablet bed and pan wall.

In all the previously cited studies using DEM, the shape of the tablets were assumed to be spherical. However, Song et al.[34] and Song and Turton[35] have shown that standard convex round tablets may be simulated in DEM using a representation of three intersecting spheres. Their results on the movement of individual tablets interacting with flat surfaces showed good agreement with experiments.

The DEM approach to modeling particle movement in pan-coating devices is still in its infancy. Currently, most simulations are performed for spherical particles without modeling the effect of spraying a coating solution and the addition of auxiliary air on the movement of the particles. Although the modeling of these phenomena is technically feasible, the additional computation time is prohibitive. As faster algorithms are developed and computational speed increases, it is expected that these models will become more comprehensive and the modeling of these additional phenomena will be feasible.

Microlevel modeling

Up to this point in the discussion, the physical and chemical processes associated with the deposition, film formation, and drying of the polymer film coating have been given only cursory attention. However, in a successful film-coating operation, these processes all play important roles. The phenomena associated with film coating at the spray droplet–particle interaction level are termed ML processes.

Werner et al.[3] discuss the four steps necessary to implement an ML approach to modeling the behavior of film-coating systems. Namely, (i) identification of ML processes, (ii) establishing relevance of each ML process, (iii) quantification of ML processes through establishing the governing equation for each process, and (iv) validation under conditions similar to those existing in industrial equipment. They go on to describe the life cycles of a single coating droplet and the target substrate particle in terms of the following 11 ML processes:

1. particle motion
2. atomization
3. drying of the droplet during the time of flight between atomization and impact with tablet
4. droplet–particle collision
5. droplet impact and adherence
6. droplet impact and spreading
7. infiltration
8. drying
9. film formation
10. layering
11. interparticle agglomeration.

The quantification of any and all of these processes is complicated and the inclusion of any one of the ML processes into, say, a rigorous model described in the previous section (CFD or DEM) would be difficult (computationally expensive). Inclusion of all ML processes into such a modeling framework would be impossible at present and in the foreseeable future. Nevertheless, problems with coating morphology such as nonconformality, porosity, surface roughness, twinning, and agglomeration are associated with ML processes and an understanding of the physics of the major subprocesses is important.

As Werner et al.[3] describe, the coating of a solid substrate in a fluidized bed device takes place through the interaction of small droplets of coating liquid (diameter ~5–30 μm) issuing from an atomization nozzle with an initial velocity of approximately 100 m/s. These droplets rapidly decelerate as they enter the draft-tube region in which air at velocities between 3 and 5 m/s moves upward entraining the solid substrate. The solvent in liquid droplets evaporates as they are convectively heated and dried by the moving air stream. During this period, in which the droplets undergo spray drying, both the solid concentration in the droplets and the viscosity increase. The viscosity of the coating liquid may undergo changes of up to 10–15 orders of magnitude from initial injection to final film formation. During such massive viscosity changes, the droplet may pass through a rubbery or sticky phase before forming the final glassy coat. The viscosity, surface tension, and impact velocity of the droplets on the solid substrates (cores) determine the relative amounts of liquid spreading, splashing, and rebounding/recoiling that will take place. The surface structure of the substrate will also affect the coating process. For highly porous surfaces, the coating droplets will, at least initially, preferentially absorb into the core rather than spread on its surface, which leads to inefficiencies in coating. In general, the droplets of coating solution reaching the surface of the cores should have a low enough viscosity to promote spreading and the rate of drying of the coating film should be low enough to allow spreading but fast enough to avoid wet and/or sticky particles leaving the freeboard region of the bed and entering the downward flowing annular region, where the agglomeration of cores would be likely to occur.

Quantification, of each of the major ML processes described, is possible albeit by making some simplifying assumptions. However, incorporation of these ML effects into a coating model is far beyond the capability of even the most advanced computer hardware. Nevertheless, simulation of some of these processes such as using CFD to model the effects of changing viscosity and drying on the impact behavior of droplets on solid surfaces would provide valuable insight into the roles played by several of the key process variables.

Conclusions

The film coating of pharmaceutical solid dosage forms can be modeled at different levels of complexity. Phenomenological models provide a good 'picture' of the physics that describe the overall coating process. These models capture the inherent variability in coating processes by assigning probability distributions to key variables. Such models may be used to compare the performance of processes under changing operating conditions but generally do not allow a priori estimates of coating variation (CV or RSD) to be made. Instead, these models always require one or more parameters to be determined experimentally.

First-principle models such as CFD and DEM rigorously model the physics of the movement of gas and solids phases within the coating equipment. These models are computationally intensive and generally not suitable for real-time applications. Nevertheless, they may be used to predict solid (core) velocities, gas velocities, heat transfer within equipment, temperatures of gas and solids phases, and give predictions of the CV of a batch of coated solids. A priori predictions may be possible; although, some experimental verification is usually preferred to 'tune' the key parameters. The extrapolation of these models is likely to be much more reliable than the phenomenological approach.

Although the two previous types of models are useful for describing and predicting the variability in the mass coating uniformity of a batch of solids subject to a coating process, they do not include the physics associated with the ML phenomena that are present when atomized liquid drops impinge with and subsequently coat the solid cores. These phenomena are described by ML processes that depend on the physical and chemical properties of the coating solution and substrate material. These properties may change significantly with time and affect the uniformity of coating on a given solid core's surface. Thus when coating morphology is considered, ML models can give insight into the important processes that occur and can be used to troubleshoot process problems.

Currently, only a few, if any, of the ML processes may be incorporated into the other 'macrolevel' models because of the massive computational burden of modeling ML and macrolevel phenomena simultaneously. Therefore, for the foreseeable future, the pharmaceutical scientist will need to apply both ML and macrolevel models to understand the film-coating process.

The methods described in this article have been used to understand the coating phenomena and, on occasion, to troubleshoot coating operations. Currently, to the author's knowledge, none of the modeling principles outlined in this article have been applied to the development of process control strategies for coating operations. One problem is that any such model must be capable of running in real time, which precludes the direct use of CFD and DEM models. Nevertheless, reduced-order models can be constructed from these rigorous approaches that contain the predictive power of these models but run in real time. The use of such reduced-order models to predict the progress of a coating operation and the use of process measurements to update the model, which can then predict future behavior, such as end of run conditions or a potential problem in a run, could form the basis of a powerful process analytical technology strategy. The use of this type of 'model-predictive' control is common in other industries but has not been implemented in the pharmaceutical industry. It is hoped that this situation will change as the utility of these models is realized.

Declaration of interest

The author reports no conflicts of interest. The author alone is responsible for the content and writing of this paper.

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