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Use of Discrete Element Method to Troubleshoot Aesthetic Defects in Pharmaceutical Tablets

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ABSTRACT

Pharmaceutically elegant tablets are an expectation from pharmacists, health care providers and consumers for solid oral dosage forms. The presence of non-aesthetically pleasing defects in solid oral dosage forms can result in complaints back to the manufacturer and potentially non-compliance with medicines. The purpose of this study was to simulate and analyze the design of a tablet core and the aqueous film-coating process, to gain a better understanding of tablet defect generation, and to help eliminate the defects from the finished product. This evaluation employs Discrete Element Method (DEM) using the software product Altair® EDEM™ to understand the potential mechanisms that are causing the defects, based on the forces tablets experience in the coating operation, along with the number of tablet-to-tablet interactions that occur during the duration of the process. Defects observed during the scale up of the coating process to a commercial production scale confirmed the DEM results where physical damage was observed more on the edges of the tablets than the face of the tablets. Also based on the number of tablet-to-tablet interactions, operating the coating process under thermodynamically wetter processing conditions can result in elevated levels of picking and sticking defects being observed based on the specific tablet design evaluated. The results of these efforts allowed the manufacturing and development team to evaluate improvement opportunities not only in tablet design but also to re-evaluate the thermodynamic design space of the coating operation and the mechanical set up of the coating equipment.

Keywords: Defects, Discrete Element Method, EDEM, Pharmaceutics, Round Concave Tablet, Solid Oral Dosage Forms, Tablet Coating

INTRODUCTION

Pharmaceutically elegant tablets are an expectation from pharmacists, health care providers and consumers. One approach to ensure aesthetically pleasing dosage forms is to apply a film coating [1]. Not only does the coating aid in the appearance and identification of the tablet, but it also helps patients by protecting the product from light, aids in swallowability of the tablets and also protects the caregivers from accidental exposure to the drug substance contained within the film-coated tablet.

Periodically, non-aesthetically pleasing defects can be present in the finished product. These defects have no impact on the safety or efficacy of the tablet but may garner complaints from the marketplace and impact the company's brand and reputation and patient compliance to the medicine. This is of extreme importance for the Japan market. If the defect level present in each batch of drug product does not meet the current standards, the batch can be considered unfit for sale and then must be sorted or in a worse case discarded. Destruction of a batch of product not only interrupts the manufacturer supply chain because the batch will need to be replaced but can also impact the patients depending on the inventory levels. Batches can be sorted by employing an inspection/sorting step. This step can be manual, mechanical, or electronic based on the nature of the defect. The sorting technique could result in a considerable time

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delay in releasing the batch.

Many variables come into effect when applying aqueous film coatings to tablet cores that can impact the elegance of the coated tablet. These include the physical design of the tablet, mechanical strength of the tablet core, mechanical design of the coating equipment, the thermodynamics of the coating operation and handling of coated tablets once the coating process is complete. Each one of these variables will impact the type, severity and number of defects created. In some cases, it takes a combination of the variables to result in the generation of a specific defect.

The purpose of this study was to simulate and analyze the design of a specific tablet core shape with the commercial production coating equipment design i.e., pan size, number of baffles and baffle design and coating pan load. This effort would allow for a better appreciation for the interaction between the tablet shape and the coating equipment and the operation parameters. The defects being observed were a result of a transfer and scale up of a manufacturing process from pilot to commercial scale. The two main defects being observed were edge damage, Figure 1 and picking and sticking, Figure 2. These defects were observed during the end of the batch statistical inspection of the bulk finished product. Understanding of the interactions and the defects being observed can then be applied back to the coating operation, allowing for the appropriate actions to be taken to aid in the reduction or elimination of the defect in future batches of finished product, resulting in increased quality and production yields.

Figure 1. Tablet edge damage defects

Figure 2. Picking and sticking defects on tablet faces

LITERATURE REVIEW

Since the introduction of discrete element method (DEM) simulation techniques [2], there has been an increasing interest in utilizing DEM to improve understanding of the intricate behavior exhibited by particulate systems. Furthermore, there has been a recent expansion in its application across various industries [3], and more recently in the pharmaceutical industry [4]. The coating operation has been one of the very common applications where the coating uniformity and breakage are the main concerns in the process. Although there are many computational studies on the coating of the tablets [5][6][7], there are few computational studies on the breakage of the tablet core itself.

Computational analyses of breakage have been done for general cases wherein the impact of agglomerate particles across various impact velocities [8] and impact angles [9] were examined. However, there has been little work done on pharmaceutical tablets as opposed to general spherical agglomerates. Bharadwaj et al [10] used DEM to compare the characteristic forces exerted on tablets in a friability tester with those experienced during the operation of lab-, pilot-, and commercial-scale film coating pans. But this study also lacks the prediction of the likelihood of tablet breakage during the coating process. Ketterhagen et al [11] overcomes this limitation by providing a probabilistic model to predict tablet fracture in the film coating process. Ketterhagen uses the impact velocity of the tablets during contact to predict probability of breakage of a tablet using a population balance model proposed by Vogel & Peukert [12][13].

All of the above studies mentioned above have been performed for spherical agglomerates using a "glued-sphere" approach. This present study extends from the previous studies and takes into account the physical shape of a pharmaceutical polyhedral tablet and provides a surface distribution of forces on regions of the tablet to predict localized breakage.

METHODOLOGY

Discrete Element Method

Discrete Element Method (DEM) is a numerical method which is used to simulate bulk material. This method was first developed by Cundall and Strack [2] in which all the individual particles in a bulk system are modelled as discrete elements. A Lagrangian-based approach is used in DEM to track these individual particles in the system at every timestep. The contacts between particles are detected at each timestep, and the contact forces are calculated based on this contact. Newton's second law of motion is applied to each particle to calculate the accelerations of each particle. Explicit numerical integration is then done twice to calculate the position of each particle in the subsequent timestep. Contact detection is carried out again for these updated positions, and then this cycle repeats for every timestep. DEM is the highest fidelity numerical modelling approach for particulate solids available because the discrete nature of these particulate solids is not ignored, although it comes with very high computational expense compared to other methods.

DEM was traditionally developed for spherical particles. For non-spherical arbitrarily shaped particles in a bulk, the particles are approximated by idealized numerical elements such as clumped spheres or multi-spheres, and this multi-sphere approach has been widely used and validated for particle distributions which do not have a fixed shape or size [14]. This is due to the simplicity of contact detection algorithms for spheres. However, in this study, a polyhedral particle shape, standard round concave shape [15], was used since tablets in pharmaceutical industries generally include sharp edges that are difficult to capture with spheres. Consequently, the contact detection algorithm needs to be modified to accommodate such polyhedral shapes.

Governing Equations

This study employs DEM using the software product Altair® EDEM™. The default contact model in EDEM is based on the Hertzian theory of contact mechanics [16]. However, for polyhedron-shaped particles, the force equations are modified to account for non-spherical shapes, according to Nassaeur and Kuna [17]. Additionally, a spinning friction model was also introduced to account for the friction that would occur if a particle face were rotating against another particle or geometry.

Contact forces between two particles in the normal direction are given by the following equation:

$$F_n = \left(\frac{0.62}{0.752}\right)\left(\frac{4}{3\sqrt{\pi}}\right)E^*\sqrt{Vd_n}$$

where

$V =$ overlap volume between two particles during contact

$d_n =$ indentation depth which is the extension of the overlapping region in the direction of force

$E^* =$ equivalent Young's modulus, defined as

$$\frac{1}{E^*} = \frac{1-{\nu_1}^2}{E_1} + \frac{1-{\nu_2}^2}{E_2}$$

Dissipative effects were also taken into account by modelling a damping force in the normal direction. The equation for the damping force is given by the following:

$$F_{n,d} = 2\sqrt{\frac{5}{6}}\left(\frac{-\log e}{\log^2 e + \pi^2}\right)\sqrt{2E^*m^*\sqrt{\frac{V}{\pi d_n}}\,{v^{rel}}_n}$$

where

$e =$ coefficient of restitution between two particles

${v^{rel}}_n =$ magnitude of relative velocity between both particles in the direction of normal force

$m^* =$ equivalent mass, defined as

$$\frac{1}{m^*} = \frac{1}{m_1} + \frac{1}{m_2}$$

The tangential force between two particles during contact is given by the following equation which is also limited by the Coulomb friction model μF_n where μ is the coefficient of friction.

$$F_t = -8G^*\sqrt{\frac{V}{\pi d_n}}d_t$$

where

$d_t =$ extension of the overlapping region in the direction normal to the force

$G^* =$ equivalent shear modulus, defined as

$$\frac{1}{G^*} = \frac{2-\nu_1}{G_1} + \frac{2-\nu_2}{G_2}$$

Dissipative effects in the tangential direction were also considered, and are given by the following equation:

$$F_{t,d} = -2\sqrt{\frac{5}{6}}\left(\frac{-\log e}{\log^2 e+\pi^2}\right)\sqrt{8G^*m^*\sqrt{\frac{V}{\pi d_n}}\,{v^{rel}}_t}$$

where

${v^{rel}}_t =$ magnitude of relative velocity in the tangential direction

The terms E, ν, m, and G with subscripts 1 and 2 correspond to the Young' modulus, Poisson's ratio, mass, and Shear modulus of both particles in contact, respectively.

The introduction of spinning friction [18] was essential in this model to account for the friction between two particles whose faces are rotating against each other. This involves calculating the contact area and then applying the torque in the opposite direction to the normal component of the relative angular velocity. The equation for torque on the particle is given as follows:

$$M = \frac{2}{3}\mu F_n\sqrt{\frac{A}{\pi}}$$

where

$\mu =$ coefficient of friction

$A =$ normal area of the overlap region

This torque is limited to avoid numerical instability and any oscillating behavior when the angular velocity is small. This was done by calculating the torque required to damp the angular velocity in one timestep.

$$M = \frac{0.125\omega^{rel}{}_{n}\min(I_1, I_2)}{\Delta t}$$

where

$\omega^{rel}{}_{n}$ = normal component of the relative angular velocity

Δt = timestep used in the model

$\min(I_1, I_2)$ = minimum value of the moment of inertia of the two contacting particles

Material model calibration

Material model calibration is a fundamental component of the Discrete Element Modelling methodology. Material model calibration typically consists of replicating a rheological measurement in the model, so that there is confidence in the model behaving in a physically accurate manner. Bulk density is a rheological measurement that needs to be replicated for any DEM model to capture the inertial effects. The other test done for this study to ensure the tablet-tablet interactions are modelled correctly, is the angle of repose test. Since a coating process is modelled for this study, both the bulk density and the angle of repose measurements were done for both core and coated tablets. The average value for both measurements were computed, and the average value was replicated within the DEM model.

For the bulk density measurement, tablets were filled in a known cylindrical volume, and was weighed. The mass of the bulk of the tablets was then divided by the known volume to calculate the bulk density. This process was done for both core and coated tablets. The average value of 601.9 kg/m^3 was replicated within a similar virtual cylinder within the DEM model. This involved a trial-and-error method with running multiple simulations with different parameters on the same setup, until the target bulk density was achieved.

Similarly, for the angle of repose measurement, the tablets were allowed to form a pile on the horizontal after lifting a hollow cylinder filled with these tablets. The angle that this pile makes with the horizontal was measured, for both core and coated tablets respectively. Again, the average value of 35 degrees was replicated within a similar setup in the DEM model. The angle of repose is sensitive to the coefficient of friction values along with other parameters like the individual particle density and the coefficient of restitution, and therefore, these parameters were changed using a trial-and-error method until the DEM model reproduced the same pile with the same angle in the virtual setup.

Process Modelling

The calibrated interaction parameters are used for the modelling of the industrial scale tablet coater operation. As mentioned earlier, the tablets are polyhedron-shaped with 78 faces and approximately 10 mm in size, which is a very close estimation of the physical particle shape. The particle shape is shown in Figure 3.

A singular batch in the coater consists of approximately 200,000 tablets, therefore, the simulation was also done for the same load of tablet cores. The simulation was split into two stages – the filling stage and the process modelling stage. To introduce realistic settling of the tablets within the coater before the operation, the tablets were introduced into the coating pan from an opening on the side and allowed to settle under gravity. The coating pan was then rotated at 7 rpm, for 30 seconds of operation. The model was run on an NVIDIA Tesla V100 GPU card which took an approximate of 225 hours of clock time for the whole 30 seconds of operation.

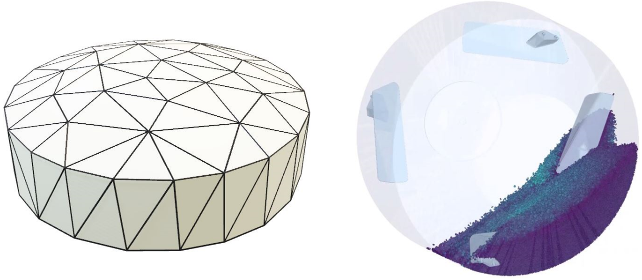

Figure 3: Tablet shape used in DEM (left); EDEM simulation of the industrial tablet coating process (right).

All the forces during each contact of the tablet core, with another tablet core or with the coating pan itself, were calculated using the governing equations. However, data was saved at every 0.1 seconds interval due to practical hardware limitations. This data includes position and orientation of the tablets, their velocities, their contact forces and the location of the contact on both interacting bodies. In total, about 98 million contacts were recorded, for these 200,000 tablets at these 0.1 seconds interval during the whole 30 second operation, and analyzed. The force values on each vertex of the polyhedron during each of these contacts are then compared to determine the region of the polyhedron-shaped tablet with maximum propensity for breakage or defect formation.

RESULTS

In a DEM simulation, for every collision, the impact force increases until it reaches a peak value, and then it decreases with the particles separating from each other. The value of the forces acting on each of the tablets, in this case, and their location of impact for each contact, or collision, was recorded at every 0.1 seconds. Due to this frequency of data recording, it is possible that the peak forces may not be recorded if the peak occurs between data save periods. However, since steady state is achieved relatively early in the process, at about

5 seconds, the simulation consists of random sampling of contacts during twenty-five seconds of steady state operation. This study assumes that the highest recorded forces are indicative of the impact events that lead to tablet defects. Hence, the magnitude of the force itself is insignificant, but the relative distribution of forces is bound to give more insight into the results.

Force Analysis

In this coating pan simulation, there is a huge number of contacts, and forces are evaluated at each of these contacts. However, a large number of these contacts are weak, primarily in the small movements of the tablets in the avalanche region. There are a few contacts which are stronger, and it is assumed that these stronger contacts are the reason for tablet defects. Considering this, the ten contacts with highest force values were analyzed in Figure 4.

On the top, the orange bar represents the total force magnitude, and the blue and yellow bars represent the normal and tangential force components respectively. This shows the strength of the contact relative to the other contacts in the system. In the first column, since the tangential force is very insignificant, it is almost entirely a normal contact, with an impact on the edge of the tablet. The streamline plot at the bottom also shows that this was caused due to the lifting the tablet by the coater baffle and dropping it on the coater itself. Figure 4 reveals that although there are some impacts from tablets colliding with other tablets, it is less significant than the tablets impacting the coater pan itself.

The force values at each vertex were summed for all the contacts in the simulation, and a heat map of the force distribution was plotted in Figure 5. This figure gives a pictorial representation of the locations on the tablet that have the highest propensity for defect formation.

Grouped Statistics

For practical purposes, the defects were classified into two groups – edge defects and face defects. The force distribution on every individual tablet was used to group them. The force value at each vertex were summed up for each of the 200,000 tablets in the system, for every contact that was experienced during the twenty-five seconds of steady-state operation. Out of these summed up force values at every vertex, if the highest force value on an individual tablet was present near the edge of the tablet, that tablet was classified to incur an edge defect, or chipping defect. Consequently, if the highest force value was on the face of the tablet, it was classified as a face defect, or picking defect. Figure 6 shows the regions on the tablet based on which the groups were classified.

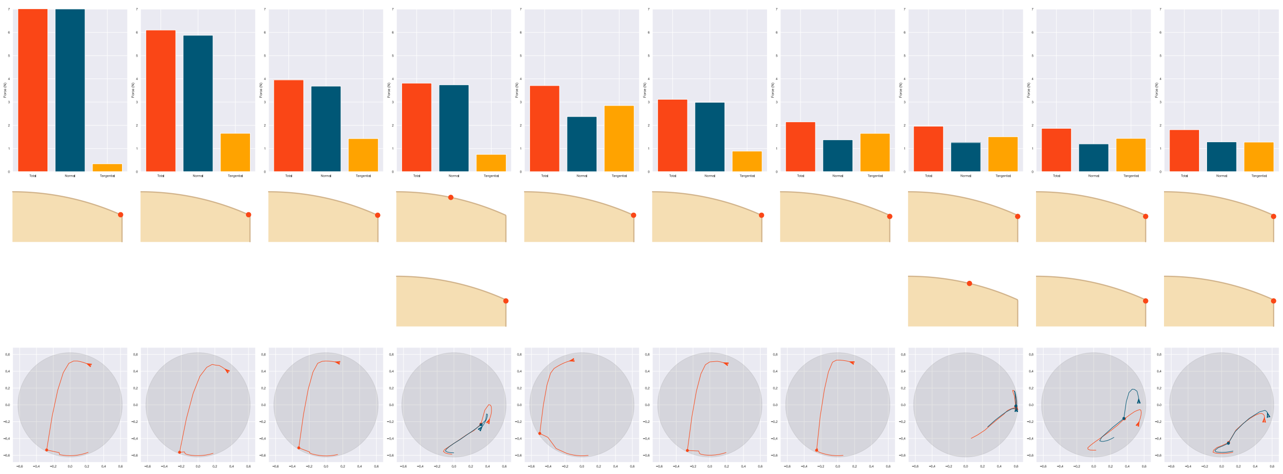

Figure 4: Strength (top) and location of impact on the symmetrical cross-section of the tablets (middle), and the respective tablet trajectories (bottom); for the top ten highest force values (decreasing left-to-right) observed during the coating operation.

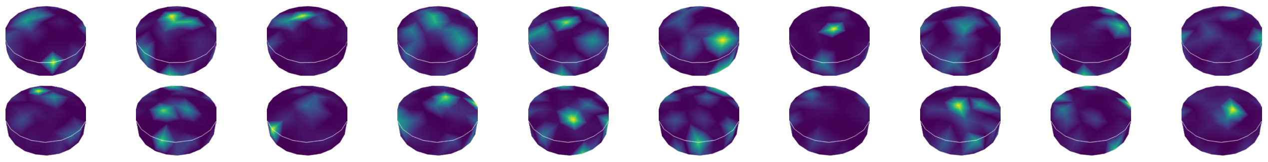

Figure 5: Distribution of the sum of normal force values for the whole simulation on individual tablets with the top ten highest force impacts (decreasing left-to-right)

The simulation found that 72.12% of the particles are prone to have a chipping defect or an edge defect, while only 27.88% of the particles are prone to have a face defect. Although the highest force values on an individual contact was from lifting of the coater baffles, the highest sum of forces across all contacts is caused in the avalanche region of the coater.

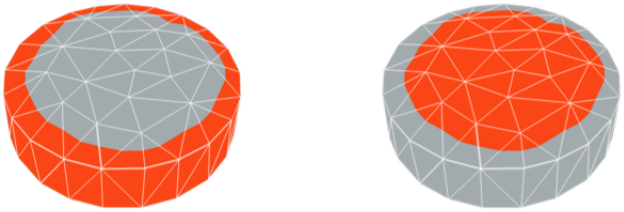

Figure 6. Regions on the tablet classified for edge defects (left) and face defects (right)

CONCLUSIONS

The simulation estimated ~70/30 split between edge defects and face defects. The end-of-batch statistical inspection for visual defects confirmed that physical damage to the tablet edges constituted a far greater percentage of tablet defects than those observed on the face of the tablets. Electronic inspection of the batches also confirmed the simulation results, again showing that the majority of the physically damaged tablets experienced edge damage, with little physical damage being observed on the face of the tablets. During process scale up, when coating conditions fell on the wetter side of the thermodynamic design space, picking defects were observed mainly on the face of the tablets, Figure 2. This would not be unexpected due to the number of tablet-to-tablet interactions that occur during the coating process while the tablets are avalanching in the spray zone of the coating pan. The result of this DEM analysis was used by the manufacturing and development teams to investigate potential modifications. The tablet core robustness was modified to prevent damage to the tablet edges. To prevent picking damage, the coating operation was moved towards the drier thermodynamic space, since reducing the number of tablet-to-tablet interactions would have required altering the production batch size, which was not an option.

The use of the Discrete Element Method to look at the forces that the tablets were experiencing during the coating operation was one part of an investigation that was critically reviewing the drug product formulation and process to establish causal factors associated with tablet edge and face defects. The evaluation looked at the drug production formulation, raw material attribute and variability within a given attribute for the excipients and drug substance. The processing evaluation included the production of the tablet cores, the tablet core robustness to downstream processing conditions and environment, review of the coating process and the thermodynamic space for which processing was being performed. Additionally, the evaluation also included identifying the location within processing time of the coating operation that the tablet damage was occurring, i.e. beginning middle or end of the coating operation. Since the edge and face defects did not result in exposed cores, the investigation concentrated to the loading of core tablet to the coating pan, the start up of the coating process though the middle of the coating operation. No review of the post coating operation was evaluated for the investigation for causal factors again supported by the defects present did not show any signs of exposed cores.

This present study can also inform population balance models to predict breakage of the tablet cores. This DEM model can provide micromechanical data which can be used in conjunction with a breakage criterion resulting in an analytical breakage model. An approach similar to Ketterhagen et al [11] can be taken to utilize the material strength parameter and the impact energy to characterize a stochastic breakage model using the Vogel and Peukert [12][13] model to quantitatively predict breakage.

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