DEM modeling of high shear wet granulation of a simple system

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ABSTRACT

High shear wet granulation (HSWG) is one of the most poorly understood processes with known difficulties in optimization and scale up. The purpose of the current study is to develop a DEM model which can be applied under dynamic process conditions with high predictive capacity to improve process insight. The DEM model is used to predict agglomeration as a function of impeller speed and liquid addition rate in a high shear wet granulator. The DEM model tracks dynamic formation and breakage of liquid bridges between particles as liquid binder in the system is added, and corrects for the change in material properties as a function of the binder content.

1. Introduction

Granulation, a widely used process in pharmaceutical, agriculture, food and paper industries, is the technique of agglomerating particles together into semi-permanent granules (aggregates) made up of easily distinguishable original particles [1]. This size enlargement process is achieved by various means such as (i) compression techniques: bracketing and extrusion (ii) heat bonding: sintering (iii) drop formation: prilling and spray drying and lastly by (iv) process agitation in the presence of a binder during “wet granulation”. In wet granulation, the binder liquid is sprayed onto the surface of a mixed granular bed, resulting in the formation of aggregates as the particles are held together by capillary bridge forces. The granules as formed offer significant improvement over the ungranulated powder in terms of material properties and behavior such as flow, appearance, handling, strength, rate of dissolution while reducing dustiness and segregation. Within the pharmaceutical industry, wet granulation – despite stability concerns with liquid addition, is often resorted to when the formulation displays poor compressibility and flow [2]. However, despite the long history and widespread use of HSWG; the interplay of material, geometric and process variables at different length scales is rather poorly understood which contributes in large parts toward operation on an empirical basis in most manufacturing units [3], especially with regards to end point determination and scale up. Industrial practitioners often use...
prior experience for process optimization in a manner akin to an art form, as opposed to relying on strict scientific principles. While user experience is often critical and cannot be undermined in practical situations, hit and trial optimization incurs huge costs from expensive experimental designs. In a fast paced and dynamically changing industrial landscape, process understanding should be improved to comply with Quality by Design initiatives, and enable streamlined and robust process development.

High shear wet granulation (HSWG) can be broadly considered to be interplay of three rate limiting processes: (a) wetting of particles to create nuclei, (b) consolidation and coalescence of these nuclei to give growth and agglomeration, and (c) Breakage and attrition of these nuclei under high shear [4]. The progress of wet granulation can be tracked by following the load on the impeller and generating a power consumption profile. As highlighted in Fig. 1, the general power consumption profiles obtained have been traditionally subdivided into the following phases: (1) a first slight increase in the profile, usually related to nuclei formation and moisture sorption, (2) a rapid increase in the profile slope, due to the attainment of the pendular state (when particles are held by liquid bridges at their contact points), (3) a plateau phase in the profile which indicates the transition from the pendular to the funicular stage wherein the particle voids begin to fill with the binder [5,6]. These rate processes must be controlled in order to achieve granules with acceptable properties.

Pharmaceutical manufacturers often face a particular problem where there are many and frequently changing formulations with widely varying properties. Typical drugs have flow and compressibility issues, and are frequently hydrophobic particles as reflected by their large contact angles which do not lend to spreading of liquid over the surface. The energetic barrier is overcome by applying mechanical energy through an impeller in a high shear mixer/granulator. Increased energy input has to be carefully evaluated against potential for reduced physiochemical stability. There’s also an issue of scale up, where the stress fields can change and a well performing batch at lab and pilot scale can fail quality testing at commercial scale. This concern is reflected in regulatory guidelines, where a new formulation is expected to demonstrate successful operation at lab, pilot and industrial scales [7].

Efforts to improve process understanding have traditionally been attempted through extensive DOE studies. While these studies have undoubtedly given a lot of insight, there are many mesoscale phenomena which cannot be readily determined. As an example, it is very difficult to attribute local distribution of capillary bridges which determines bulk behavior. It is also difficult to obtain spatially and temporally resolved stress, pressure and velocity distributions especially in a commercial scale granulator which is unique to each case as defined by geometry, process, and formulation. This leads to difficulty in comparing different experiments. It is here that simulations can lend a great advantage. A well calibrated simulation can give fundamental insight not readily obtained by experiments.

Traditionally simulation efforts in the field of HSWG have been dominated by population balance models (PBM) [8–10]. These models have several drawbacks such as development of a coalescence kernel which are often empirical in nature and need multiple fitting parameters. Quite fundamentally, they do not capture the dynamic mesoscale effects which are believed to be transmitted through formation and breakage of discrete capillary liquid between particles. This casts doubts over the ability of PBMs to model dynamic processes [11]. It is often cumbersome to develop governing equations inclusive of process parameters affecting particle size distribution. The discrete nature of capillary bridges and the ability of DEM to model dynamic processing conditions make it an attractive choice to model HSWG. However, a notable disadvantage of this approach is the huge computational cost which is further increased once a first principle capillary bridge model is included. However, it has been well demonstrated that well scaled DEM studies can give good process insight even when using particle sizes higher than those encountered in experimental studies [12]. Some DEM based efforts have thus modeled motion of wet particles, without explicit inclusion of capillary forces [13,14]. Talu et al. [15] included capillary forces to model agglomeration in a 2D system while Lian et al. [16] used a 3D box containing few particles to develop a preliminary understanding of particle agglomeration processes. These studies were done in rather small systems and much process insight cannot be gained. Simulation of larger HSWG systems remains an active area of research within the academia and industry alike. There has been a significant thrust in hybrid modeling approaches, e.g. PBM-DEM approaches are coupled with the idea of developing realistic PBM kernels from DEM simulations. However, capillary bridge forces cannot be modeled in these simulations capillary forces are largely captured by a generic cohesion term. As capillary forces are assumed to be fundamental to HSWG performance, modeling such systems remains an active area of interest and continues to gain momentum, especially with advances in computational hardware.
The current article is based on the premise that HWG process performance is dictated by mesoscale phenomena wherein the capillary bridge forces between particles are of fundamental importance [4]. This is in accordance with the theoretical models described in the preceding paragraphs. However, the mapping of capillary interactions in a dynamic system is complicated given the nature of capillary forces, which invoke the effects of a ‘discrete liquid’ coupled with granular flow dynamics making it a difficult multiphase multicomponent multi-scale problem. Recently, it was pointed out that severe assumptions need to be made about binder distribution and surface wetting of the particles [17]. An additional complexity is that the material properties change with binder content which presents an additional complexity. The current article attempts to address these issues from validated numerical simulations in a high shear granulator in a simple system to map the interactions of different process and material parameters. DEM simulations are performed which explicitly incorporate the capillary bridge forces, and correct for variation of material properties as a function of binder content. It must be recognized that it is currently not possible to model a 1:1 scale simulation relative to the experimental setup, and this causes concerns with validation of the computational model. For the current study, it is assumed that a well scaled DEM simulation captures the dynamic effects of capillary bridges which enable the user to determine the effect of process variables, and hence trend lines from experiments are used to validate the DEM simulations.

2. Materials and methods

2.1. Materials

316 NF grade Fast Flo Lactose (Kerry Inc.) is used as the model compound with water as a binder. In addition to being very frequently used in the pharmaceutical industry, Fast Flo Lactose is chosen to allow quick distribution of water over the particle so that it is easily wetted.

2.2. Procedure

The wet granulation experiments were performed in a 1 l bowl attachment of the KGS granulator (Key International, NJ). The bowls were loaded with fast flow lactose (d50 = 67 μm) at a specified fill level and the impeller and chopper were turned on for a dry run of 2 min. The telescopic spray pump was then turned on to give a specified volumetric flow rate of the binder till a specified end point based on the liquid volume percentage, which corresponded to a plateau region on the impeller power consumption curve. The liquid addition rate from the pump was calibrated prior to every run. 2–3 g of the wet granules were sampled for particle size measurements every 2 min and then dried at 40 °C in a laboratory tray oven. The wet granules were dried till the moisture content of 2.5% or lower was achieved as measured using a SARTORIUS MA 100 moisture analyzer. The operating conditions were optimized with respect to the lactose–water system parametrically analyzed with respect to processing variables of interest. Table 1 lists the process parameters under investigation in the current study. Progress of the HSWG run was monitored from the measurements of temporal evolution of the dynamic strength and particle size of the powder bed. These measurements have been described in detail below.

2.2.1. Dynamic strength

Load on the main impeller, which represents the resistance to impeller motion at a specified speed, can be estimated by measuring the current in DC motor as in our study because the torque generated by the impeller is proportional to the current applied. The dynamic strength of the granules as a function of time was monitored through ammeter readings read manually every 5 s from the display unit of the KGS machine. The ammeter reading was normalized with respect to the average reading during the dry run phase to account for different mass loading rates, impeller speeds and motor heating effects.

2.2.2. Particle size determination

The particle size distributions (PSD) of the dried samples were determined using a Malvern Mastersizer 2000E laser diffraction instrument fitted with a Sirocco dry powder unit. An air pressure of 0.5 bar was used to produce uniform powder dispersion for each sample for homogenous PSD measurement. These conditions were optimized with respect to feed rate and obscuration to achieve a complete dispersion of the primary particles without causing significant particle attrition. A closer look is obtained at the non-granulated and granulated fractions through Scanning Electron Tomography (SEM) images as shown in Fig. 2A and 2B, respectively.

2.3. Discrete element method (DEM)

The current section outlines the DEM based model to simulate the dynamics of the simple lactose–water system in an HSWG. The basic assumption for beginning with a classic DEM based approach is the neglect of continuum fluid forces. This is based on the premise that most important dynamics of the “wet bed” pertinent to process outcomes are at low liquid content, typically 5%–10% liquid volume at end point. For our simulations, droplet penetration times have not been considered based on the fact that lactose is easily wetted and the high shear granulator is operated at sufficiently high speeds (100 rpm or more) so that the powder flux through the spray zone is high relative to the binder delivery. This corresponds to a low spray flux regime wherein nucleation of particles is expected to be droplet controlled as one droplet leads to one nuclei [18] so that binder is well dispersed.

The basic implementation of the DEM model is outlined in Fig. 3. The granular bed is considered as a collection of inelastic frictional spheres, which interact with their neighbors.
through normal and tangential forces. The normal forces \((F_n)\) and tangential forces \((F_t)\), also called collisional forces, are calculated using Walton’s contact mechanics model [19].

2.3.1. Liquid bridge model
In addition to the normal and tangential contact forces, the present study incorporates liquid bridge forces between particles. These are calculated using the liquid bridge model developed by Lian et al. [20] who assumed a toroidal liquid bridge shape (Fig. 4) when the separation distance of two particles is less than the critical value \(S_c\):

\[
0 < S_c \leq (1 + 0.5\theta) V^{1/3}
\]

Here, \(\theta\) is the solid–liquid contact angle and \(V\) is the volume of the liquid bridge. The capillary force \(F_c\) is calculated using the following relation

\[
F_c = 2\pi\gamma \rho (1 + H \rho)
\]

(2a)

where \(\gamma\) is the surface tension of the solvent, \(\rho\) is the radius of the liquid bridge at the neck and \(H\) is the mean curvature of the liquid bridge.

Fig. 2 – SEM images of (A) ungranulated fast flow lactose, and (B) lactose granules with water as binder.

Fig. 3 – Flow chart of the general soft particle DEM algorithm.
of the powder are expected to decrease as water is added.

Thus, the instantaneous liquid bridge volume is used to form one particle. When these particles approach each other to a separation distance less than \( S_c \), a liquid bridge is formed between the particles. The bridges are broken if the particles either move close to each other and are in physical contact, or are separated by a distance greater than \( S_c \). Simultaneous capillary and viscous forces are calculated on the particles forming the liquid bridge as discussed above.

As discussed previously in Section 1, discrete element simulations of granular beds for liquid bridges are faced with a unique challenge with regard to material properties fundamentally describing the soft particle deformation process. These properties are intuitively expected to be a function of the liquid content added. The coefficients of restitution \( e \) [23], coefficient of friction (particle–particle) \( \mu \) [4] and the elastic modulus \( E \) [24] of the powder are expected to decrease as water is added. An exact mathematical form of the functional dependence of these properties on liquid content is unknown and is likely to be very specific to the material system under study. In addition to dynamic tracking of the liquid bridge formation, the current DEM code is equipped to deal with a change in material properties upon water addition. The change in material properties with addition of water is incorporated by assigning a linear dependence of the property upon the moisture content of the particle. For the current simulation, the slopes are calculated by assuming ad-hoc that \( e, \mu, E \) change from 0.6 to 0.1,0.7 to 0.2 and 6000 N/m to 4500 N/m upon addition of water, such that there is 10% water at the end point. These numbers are chosen arbitrarily, within the restriction that the theoretical particle overlap is within limits of the Walton and Braun’s latching spring model [19].

Table 2 lists the DEM parameters under study. Since the DEM computations are very expensive, the cases are run for 10 s till steady state, which is approximately 42 rotations at the default speed for 250 rpm.

### Table 2 – DEM parameters used for the study of high shear wet granulation.

| DEM parameters                        | \( S_c \) | \( R \) | Coefficient of friction (particle–particle) | 0.7 |
|---------------------------------------|-----------|--------|---------------------------------------------|-----|
| Radius of particle (mm)               | 3         |        |                                             |     |
| Number of coarse particles            | 2132      |        |                                             |     |
| Density of particles(kg/m\(^3\))      | 1500      |        |                                             |     |
| Initial coefficient of restitution: interparticle | 0.6       |        |                                             |     |
| Contact angle                         | 0.506     |        |                                             |     |
| Initial coefficient of restitution: particle–wall | 0.6       |        |                                             |     |
| Half filling angle                    | 0.516     |        |                                             |     |
| Normal stiffness: interparticle (N/m) | 6000      |        |                                             |     |
| Normal stiffness: particle–wall (N/m) | 6000      |        |                                             |     |
| Coefficient of Friction (particle–particle) | 0.7       |        |                                             |     |
| Time step (\( \mu s \))              | 0.5       |        |                                             |     |

2.3.2. Post processing and visualization

The results were analyzed by tracking the coordination number (CRN), i.e. number of particles surrounding a given particle, and the liquid bridge (LB) count on every particle as a function of time. Evolution of CRN and LB was taken as a measure of size evolution. LB, in particular is more accurate measure of the particle agglomeration size, because the CRN just represents physical contact and not bonding. Ideally, particles with high CRN and high LB should be considered as “granules”. The DEM
visualizations have been done by using CRN as the scatter variable and LB as the coloring variable. The trend lines obtained for different conditions examined experimentally would be compared with simulations.

3. Results and discussion

3.1. Effect of impeller speed

The mean impeller power consumption and mean particle size of the lactose–water system are shown in Fig. 5A and 5B respectively for a representative single run. The power increased with the impeller speed in both scales. The trend of the variation of the strength with the impeller speed is in agreement with previous studies [25–27]. The higher impeller speeds cause more intensive mixing and compaction of the granules to a higher degree that leads to higher granule strength. Granulation regimes in high shear granulators have been defined by Lister [3] as bumping and roping at low and high shearing rates, where in the former the wet mass is bumped up and down as the impeller passes underneath, while in the latter the wet mass is moved as a ribbon. The powder flow goes through a transition from bumping to roping as the impeller speed is increased. The roping regime gives a better liquid binder distribution because of good bed turnover and stable flow pattern. The decreased particle size with increased impeller speed is attributed to milling action which promotes a crushing and layering mechanism of growth, which is also predicted to produce stronger granules.

Post processing results from the DEM simulations yield the liquid bridge count and the average coordination number for each case. For a given liquid content at an instant, the critical separation distance needed to form a liquid bridge is the same for all cases. Differences in LB count and CRN can be expected to be due to differences in instantaneous interparticle distances reflective of the force balance unique to each case. At 500 rpm, the liquid bridge count from the DEM simulations is the least which is attributed to high shear forces pulling the particles apart. The DEM simulations display the same qualitative trends obtained experimentally, as seen in Fig. 5C. There is also greater impact of particles with the equipment walls which breaks up the granules. In contrast, studies for 100 rpm and 250 rpm display higher liquid bridge count. It is also interesting to note that there is not much of a difference between 100 and 250 rpm suggesting that the kinetics of bridge formation and survival of the bridge under dynamic conditions are similar for these two cases.

Fig. 6 displays the DEM snapshots of agglomeration within the high shear granulator at different impeller speeds. It can be clearly seen that more liquid bridges are formed as function of time. The study at 500 rpm shows a relatively few number of particles with a high LB count highlighting milling action of the impeller.
The lactose–water system is an easily wetted system as characterized by its low wetting angle so that the high affinity of the water and lactose decreases the role of mechanical energy input. The primary particle size growth mechanism is then dictated by the binder supply, corresponding to the drop controlled regime \[28\]. Increasing the rate of binder delivery increases the consolidation rate which is reflected in Fig. 7A, where it can be seen that higher liquid addition rates lead to quicker plateauing corresponding to an end point, but lumps can be easily formed at high liquid addition rates leading to overgranulation and pooling. Increasing the binder decreases the frictional resistance for the low viscosity binder achieving a high consolidation rate \[26\]. The experimental run time was determined from real time visual observations of the bed and the ammeter readings. The 12 and 7 ml/min cases displayed sharp agglomeration in rank order of the liquid addition rates, and were stopped before 10 min. Fig. 7B displays increasing median particle size with increasing liquid addition rate. The DEM visualizations (Fig. 7C) also predict similar trend lines, though there is not a significant difference between 100 and 250 rpm in terms of capillary bridge formation. It must be noted that for the case of 12 ml/min, the simulation had to be aborted before 10 s as increased water content led to numerical instability. The numerical instability could be due to disproportionate increase in capillary and viscous forces as water content is increased leading to unrealistic force values, especially when other forces due to the presence of the fluid are not accounted for.

### 3.3. Effect of material properties

#### 3.3.1. Particle cohesion

Particle cohesion was incorporated in the DEM by specifying a Bond number (K), which represents the ratio of cohesive force to the particle weight. The default lactose simulations are at \(K = 0\), while a cohesive material is modeled by specifying \(K = 50\). As the particles get more cohesive, liquid bridges are not formed readily as the particles are in continuous contact (Fig. 8). This result is intuitive given that increasing the consolidation for cohesive particles, which are already in continuous contact and likely existing as agglomerates, is difficult. This is consistent with the results obtained by Anand et al. [29], who observed little influence of liquid content in dictating discharge of particles from a hopper in dense flow.

#### 3.3.2. Effect of material property correction

Iveson and Litster [26] state that “unless the relative magnitudes of viscous and frictional forces are known, it is impossible to predict beforehand the effect of changing binder content, even qualitatively” due to the dynamic equilibrium between dilation and consolidation, which are in turn dictated by interparticle capillary, viscous and friction forces. Change of particle elastic modulus (E) and coefficient of restitution (e) which changes the deformation behavior and the friction coefficient (\(\mu\)) as increased water is added is likely to have some impact on the process outcome. In the current article, the change of \(e, \mu\) and E is corrected with water content in the simulations described above to account for “softening” and lubricating properties of water as described in Section 3.1. A slope value of 1 implies that all particles are corrected for these material properties as described in Table 2, while a value of 0 implies that no corrections are made to the initial values so that the starting values are kept constant. Correcting the material properties with water suggests that liquid bridge formation is facilitated, as the slope value of 1 displays higher liquid bridge formation (Fig. 9) relative to the unchanged
material properties. From the DEM results, it appears that the rate of consolidation is not significantly changed as both consolidation and dilation are increased proportionally. Greater consolidation is reflected in greater number of liquid bridges due to a greater frequency of particle contacts due to decreased frictional resistance. This suggests that if the change in material properties changes in the manner as executed in the current study, the resulting granules would have a higher rate of consolidation but may have a higher porosity, due to increased dilation when compared with cases where the material properties are assumed not to change with binder content. These results are also highly suggestive that effects arising from change of material properties with increased water content must be accounted for and studied in greater detail to achieve realistic process understanding. Further experimental investigation with respect to quantifying change in material properties and studying the effect of these changes would be needed to lend greater process understanding.

4. Conclusion

An experimentally correlated DEM model was developed which predicted agglomeration performance in a high shear granulator. The effects of liquid addition rate and impeller speed were examined by tracking dynamic formation and breakage of liquid bridges. The trends from the experimental and computational studies compared favorably to lend validity to the model. The DEM model was also used correct for material properties as the binder is added onto the system, and this was shown to have an effect. Reducing the coefficients from friction, restitution and elastic modulus increased the number of liquid bridges formed but the rate of consolidation did not change appreciably. The DEM simulation results also found formation of liquid bridges to be hindered for cohesive particles.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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