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A numerical tool to predict powder behavior for pharmaceutical handling and process

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Abstract

In this article, we discuss about the potential of a numerical model to predict powder flow during pharmaceutical handling and process. The model is based on the Discrete Element Method (DEM). A single experiment measure of angle of repose is required to calibrate the model. This numerical calibration provided the coefficients of static friction and surface energy for the attributes.

This model has been validated with experimental data in different configurations: powder and granules compaction by vibration, powder flow with polydispersity size, mixing in a rotary drum. Each comparison with experimental data leads to a good accuracy of the model.

As perspective, the model was used to predict the formation of granules during wet granulation process. By taking into account the geometry of the reactor, of the impeller and the chopper, it is possible to study the granule growth kinetics depending of process parameters as the shear rate or the filling ratio.

Keywords: Powder handling, Static angle of repose, Coefficient of static friction, DEM simulation, mixing, granulation

1. Introduction

The powder flow phenomenology has been further processed. This parameter intervenes and qualifies the powder behavior in different granular media, used, treated and handled in several fields, such as pharmaceutical, chemical, food processing, mineral, building... Granular media are qualified by several phenomena resulting from different behaviors and properties controlled by their physics, such as their flowability. The flow of the different powders is governed by interparticle forces which have a fatal influence on the fluidity of the powders. The understanding of the granular media handled and in particular their flow becomes a necessity especially in the pharmaceutical field where the treated powder must have the required flow properties in order to guarantee a best handling in the manufacturing chain of different pharmaceutical forms.

It is well known that in pharmaceutical fields, the rarity of free-flowing powders is quite noticeable. The use of non-free-flowing powders leads frequently to many problems during their processing, such as agglomeration of the particles due to high cohesion, which often causes rat-holing, formation of vaults in the machine hoppers for the manufacture of different pharmaceutical forms during discharge, hence the need for pretreatment and transformation of the powders into granules by the granulation process in order to confer them the desired properties.

Several methods for powder flow characterization are widely described in literature. Most of these methods are very easy to use and process. They are classified into direct methods such as shear cells: translation (Jenike and Johanson, 1969), rotation, annular (Schulze, 2008), uniaxial compression and tensile strength, and indirect methods such as angle of repose (Train, 1958), Carr index, flow through an orifice and compressibility. These methods are more adapted to industrial constraints in terms of quality control and have an official status by certification on the European Pharmacopoeia (Saleh and Guigon, 2009).

The rheology and behavioral laws of granular flow have been the subject of many research studies, from both experimental and numerical points of view. Experimental investigations have clearly shown the effect of the particle size distribution of pharmaceutical excipient powders on their flow, with measurements of static angle of repose and compressibility, this was correlated to the coefficients of static friction of the powders (Kudo et al., 2020). Shear cell method was also used experimentally several times for the same purpose (Jager et al., 2015; Salústio et al., 2020) with applications of the Jenike methodology, as well as dynamic analyses of the FT4 Powder Rheometer (Hare et al., 2015).

The main drawback of these experimental methods is the large amount of required powder, which could be expensive and sometimes difficult to produce. Moreover, few studies show the link between flow properties and manufacturing processes such as mixing, granulation, drying. We could cite the work of Yaginuma et al. (2007). The authors have shown relationship between the filling properties of the matrices in the compression cells and the static flow properties such as static angle of repose and compressibility has been shown (Yaginuma et al., 2007).

From a numerical point of view, the Discrete Element Method (DEM), originally proposed by (Cundall and Strack, 1979), is of much interest nowadays for the description, modelling and simulation of different granular media, where the positions, velocities and physical states of the particles are controlled.

DEM has been used to investigate strategies to solve fine powder problems (Baxter et al., 2000; Huang, 2013), to monitor the flow behavior of pharmaceutical powders as a function of several parameters, such as granule surface modification parameters (Persson et al., 2011), these tests were performed using angles of repose and Carr index on modified microcrystalline cellulose particles. Their results showed a heap stability only with non-cohesive granules. A further study of the effect of adhesion on the powder flow behavior was highlighted by the use of a cohesive JKR model (Kendall, 1971) by introducing surface energy values to simulate cohesive systems behavior (Bose et al., 2005). The DEM enabled also to study the effect of particle shape on the general flow of a granular system in a rotary batch seed coater, it allowed to obtain results close to the experimental results, with a calibration of the static friction coefficients (Pasha et al., 2016).

Several comparative studies from an experimental and numerical point of view have been successful for simple systems investigating the effect of different parameters on powder flow behavior. This often concerns monodisperse systems with large particles of rather spherical shape that are easy to simulate in order to reduce calculation times. Reality dictates the opposite, especially in the pharmaceutical field, where very fine powders are used in industrial drug manufacturing chains. The challenge of getting as close as possible numerically to the experimental results is significant, by using the particle size distributions the closest to the experimental attributes, the shape, the number of particles, as well as the different mechanical properties of the sample to ensure an optimum predictive numerical approach.

In this context, the aim of the present article is to show the potential of the DEM method to predict the powder behavior during process used in the pharmaceutical industry. The study consists of three major, but distinct parts, all related to the static angle of repose tests, with both experimental and numerical investigations involving two commonly used pharmaceutical excipients, non-granulated and granulated. The challenge is to numerically reproduce the experimental trials while respecting the polydispersity of the systems and other key parameters. Such an understanding could lead to a mapping of the behavioral trends for different powder samples, but also to assure the process scale-up.

Thus, this paper will focus on the implementation of the angle of repose with the following objectives:

- Model calibration of two coefficients for non-granulated and granulated powders
- Experimental versus numerical results for three powder handling: compaction, flow and mixing
- Numerical prediction for wet granulation process.

2. Materials and Methods

2.1. Experimental study

2.1.1 Powder samples

Experimentally, two types of pharmaceutical powders (generally used as excipients for pharmaceutical preparations) were selected, namely Microcrystalline Cellulose (MCC Spheres 100 μm mean diameter, VIVAPUR) and Lactose Monohydrate (FlowLac 100 μm mean diameter, Meggle) which were used in a fine powder and granular state separately. Their granulations were made according to an experimental protocol of wet granulation in a high shear laboratory wet granulator “GLATT TMG 1/6”. The experimental protocol involved a dry premixing for 2 minutes at 100 rpm with the impeller only, drip spraying of the binder (the binder is a 3% w/v solution of Polyvinylpyrrolidone (PVP K30) dissolved in water), then granulation at 600 rpm with the use of both impeller and cross-blade chopper for 10 minutes.

Afterwards, the granules of the different batches were characterized in terms of particle size distribution using a laser diffraction analyzer (Mastersizer, Malvern3000), shape by scanning electron microscopy (SEM), flowability using a powder tester (HOSOKAWA PT-X) and compaction properties using a Jolting volumeter (JEL STAV II).

2.1.1 Powder characterizations

Flow tests were performed using the static angle of repose with three tests of repeatability, for non-granulated and granulated lactose and MCC powders. The equivalent of 200 gr powder of each sample were poured into the measuring hopper of the HOSOKAWA Powder Tester and the angle of repose was assessed. The Hosokawa powder tester originally developed by Hosokawa Micron corporation is based on Carr's theory by Ralph L. Carr (Hosokawa et al., 1988) to determine the fluidity and flowability of dry powders by measuring their flow characteristics. The Ralph Carr theory is based on the observation of powder behavior by different tests that determine a general index (Carr Index). This index is averaged by testing the angle of repose, angle of fall, spatula angle, compressibility and cohesion or uniformity coefficient. This does not preclude the use of a single test such as the static angle of repose only so that the behavior of the powder can well be described through the value of its angle, by referring to the Carr's Index table.

In our case, the static angle of repose measurements was carried out with hopper vibrations at 50 Hz frequency and a displacement magnitude of 1 mm. The powder heaps are formed on an 80 mm diameter cup by free falling. The angle of repose is measured by image processing technology, by injecting a LED light source through the sample, and the angle formed by the peak lines of the area where the light from the source is blocked by the sample is captured, so the value of the angle is then given by the triangle shaped.

In a second step, compaction tests were carried out with a Jolting volumeter (Jel STAV II). It is used to determine a product's volume before and after compaction and packing density by comparing the

aerated and packed densities. Measurements are made using cylinders of different volumes, ours being 500 ml with rotating vibrations at 1 mm magnitude for one minute.

The compaction was determined by measuring the height of the powder in the cylinder before and after compaction.

2.2. Numerical study

2.2.1 DEM modeling

The numerical method adopted for this study is the Discrete Element Method (DEM). It's theory was originally proposed by (Cundall and Strack, 1979). The granular flux can be predicted by individual particle motion and their mutual interactions. From this concept, the determination of the position and velocity of a given particle i is the time solution of Newton's Second Law for the translational and rotational motions of this single solid particle.

The trajectory of the particle is therefore described by the following dynamic equations:

By translational motion:

$$m_i \frac{d^2 \vec{x}_i}{dt^2} = \sum_j F_{ij} + m_i g \quad (1)$$

And rotational movement:

$$I_i \frac{d\omega_i}{dt} = \sum_j T_{ij} \quad (2)$$

Where: m_i , x_i , ω_i , I_i , t , g , are respectively the mass of a particle i , its position vector, its angular velocity, its moment of inertia, time, gravity. F_{ij} and T_{ij} are respectively the contact and torque forces resulting from all interactions with neighboring particles and the wall. d^2x/dt^2 and $d\omega/dt$ are respectively the translational and angular acceleration of a particle.

Using Newton's second law, which takes into account the external forces acting on the particle, DEM makes it possible to describe the motion of each individual particle, its trajectory, velocity and possibly its physico-chemical state (Suresh et al., 2017). Among these external forces are the particle-particle and particle-wall contact forces. These two forces are the most dominant during granular flows.

The contact force acting on a particle is calculated using a soft sphere model developed by Cundall and Strack (1979). In this model, three types of mechanical contact forces are calculated, namely: the elastic rebound force, the viscous damping force and the frictional force between the particles in contact. During particle-to-particle contact, a deformation resulting from the impact between the two particles is expressed as an overlapping distance δ . Particle-wall contact is treated in the same way as particle-particle contact.

In addition to these different mechanical contact forces, the DEM can take into account other external forces such as cohesive interparticle forces (Van Der Waals, liquid bridge and electrostatic forces).

This method has been consciously chosen in spite of other methods which exists in the literature such as population balance modeling (Ramkrishna, 2000), being a static method which has the power to simulate a very large number of particles but it doesn't take into account the particle dynamics which

is the case of the discrete element method (DEM). And thus the most representative method in the powder flow studies is indeed the DEM with the physical particle-by-particle monitoring that it generates.

2.2.2. Contact models

Modelling by the discrete element method requires a number of contact models for the correct application of the calculation algorithm. A contact model describes the behavior of different elements when they come into contact with each other. The models are generally developed using computer programming languages and then implemented on the various interfaces dedicated to DEM simulations (Narang and Badawy, 2018). The interface used on our study is the EDEM commercial software based on the discrete element method. The basic contact model operated by EDEM is the Hertz-Mindlin contact model described below. We use this model by default for our various simulations without taking into account cohesion forces.

Hertz-Mindlin contact model

The Hertz-Mindlin contact model is the basic one for DEM modeling. In this model, the normal force component is based on the Hertzian contact theory (Hertz, 1882). It describes a relationship between the normal force F_n and the normal overlap δ_n at the contact interface between two particles.

The Hertz's model is based on many assumptions as that, the contact surface between two particles is continuous and conformal, the deformations are small and elastic, the materials of the objects are isotropic and homogeneous, and the dimensions of the particles are much larger than those of the contact surface (Mesnier et al., 2019).

The tangential force model is based on Mindlin-Deresiewicz works (Mindlin, 1949; Mindlin and Deresiewicz, 1953). To better explain the elastic behavior of the grains in contact, Hertz's normal contact model was coupled to Mindlin's model, in order to measure the tangential contact between two spheres under shear stress.

Both normal and tangential forces have damping components whose damping coefficient is related to coefficient of restitution (Tsuji et al., 1992). Finally, the tangential frictional force follows the Coulomb's law model as described by (Cundall and Strack, 1979).

The normal contact force F_n is therefore expressed as a function of the normal overlap δ_n and is given by :

$$F_n = \frac{4}{3} E^* \sqrt{R^*} \delta_n^{\frac{3}{2}} \quad (3)$$

Where the equivalent Young's modulus E^* and the equivalent radius R^* are defined as follows for two particles i and j in contact:

$$\frac{1}{E^*} = \frac{(1-\nu_i^2)}{E_i} + \frac{(1-\nu_j^2)}{E_j} \quad (4)$$

$$\frac{1}{R^*} = \frac{1}{R_i} + \frac{1}{R_j} \quad (5)$$

The tangential contact force F_t is also expressed as a function of the tangential overlap δ_t and is given by :

$$F_t = -S_t \delta_t \quad (6)$$

Where S_t is the tangential stiffness which is expressed in terms of the shear modulus G such as:

$$S_t = 8G \sqrt{R^* \delta_n} \quad (7)$$

Finally, the tangential frictional force follows the Coulomb's law model as described by (Cundall and Strack, 1979) by means of the coefficient of static friction μ_s :

$$F_t = \mu_s F_n \quad (8)$$

Cohesive DEM modeling

The Hertz-Mindlin model with JKR (Johnson-Kendall-Roberts) is a cohesive contact model that takes into account the influence of Van der Waals forces in the contact zone and allows the modelling of strongly adhesive systems, such as cohesive dry powders. In this model, the implementation of the normal elastic contact force is based on the Johnson-Kendall-Roberts theory (Kendall, 1971).

The JKR normal force depends on the overlap δ and the surface energy γ (interaction element) as follows:

$$F_{JKR} = -4\sqrt{\pi\gamma E^*} a^{\frac{3}{2}} + \frac{4E^*}{3R^*} a^3 \quad (9)$$

$$\delta = \frac{a^2}{R^*} - \sqrt{4\pi\gamma a/E^*} \quad (10)$$

Where E^* and R^* are the equivalent Young's modulus and radius, defined in the Hertz-Mindlin contact model. Knowing that if the surface energy is null, the JKR force returns to the normal Hertz-Mindlin force expression such as:

$$F_{Hertz} = \frac{4}{3} E^* \sqrt{R^*} \delta_n^{\frac{3}{2}} \quad (11)$$

2.2.3. DEM Simulations

DEM simulation procedures

The simulations were realized on a DELL workstation (T7910) with two 10 cores processors (Intel Xeon E5-2660v3) with Academic EDEM 2020.1 commercial software. The simulation parameters have been defined for each material, i. e. the mechanical parameters of lactose and MCC summarized in Table 1.

Some other simulation input parameters were generalized for all simulations, such as the Poisson's coefficient fixed at 0.25, the time step was set at 20% of the theoretical Rayleigh time step for particles with a diameter less than 0.7 mm and raised to 40% as the maximum value for those with a diameter of 1 mm. This parameter depends on the size and mechanical properties of the particles as it characterizes the time needed for a shear wave to propagate through a particle. The particle-particle coefficients of static friction will be represented in the results and discussion section as they were the subject of a calibration study. Finally, the cell grid has been set at 3 times the minimum radius ($3R_{min}$), which ensures that the searching distance for neighboring particles is more than 3 times the smallest particle radius. For the contact model, as described before, the “Hertz-Mindlin contact model” and the “JKR Hertz-Mindlin contact model” were selected for both non-granulated and granulated particle simulations.

A DEM simulations setup for both the Hosokawa powder tester and the Jolting volumeter were established using academic EDEM code, by representing numerically the experimental devices with the same geometry and dimension (*Figure 1 and 2*)

The angles of repose for our different powders were measured by the same experimental method (triangular method). While the compaction was measured by capturing the length of the powder into the 500 ml cylinder before and after compaction.

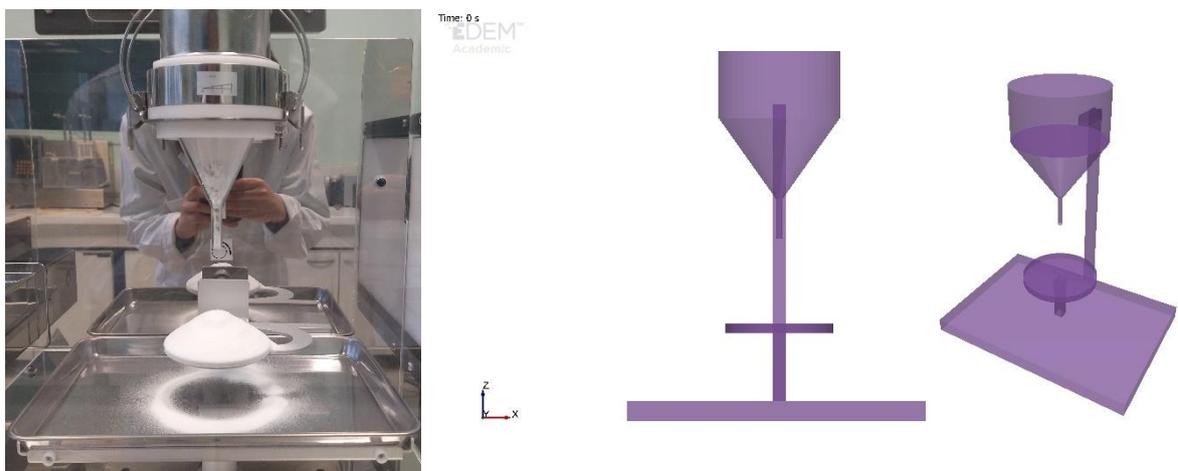


Figure 1. Pictures of the experimental HOSOKAWA powder tester on the left and the simulated by EDEM on the right (front and side views)



Figure 2. Pictures of the experimental Jolting Volumeter on the left (© Engelsmann) and the simulated by EDEM on the right (front and side views)

Table 1. Materials mechanical properties

<i>Material properties</i>	<i>Units</i>	<i>NG - lactose</i>	<i>G - Lactose</i>	<i>NG - MCC</i>	<i>G – MCC</i>
Particle Size Distribution ***	[mm]	0.456 – 0.789	0.546 – 2.541	0.421 – 0.636	0.692 – 1.777
Poisson's Ratio (ν) ***	[-]	0.25			
Density (ρ) **	[kg/m ³]	590	644	460	687
Young's Modulus (E)*	[GPa]	11.4	1.14	8.67	8.67
Shear Modulus (G)*	[GPa]	4.54	4.54	3.47	3.47
Particle – Particle coefficients					
Coefficient of Restitution ***	[-]	0.35	0.15	0.35	0.15
Coefficient of Rolling Friction ***	[-]	0.01	0.05	0.01	0.05
Particle – Geometry coefficients					
Coefficient of Restitution ***	[-]	0.50			
Coefficient of Static Friction ***	[-]	0.45			
Coefficient of Rolling Friction ***	[-]	0.15			

G: Granulated

NG: No-granulated

* Data's from (Bassam et al., 1990; Perkins et al., 2007)

** Experimental data

*** Estimated parameters

3. Results and discussion

3.1. Powder characterization

The pharmaceutical excipients used in our study are basically non-granulated. We have proceeded to a granulation process according to the protocol described in paragraph 2.1.1. both for Lactose and MCC separately in order to test them in both non-granulated and granulated form.

The scanning electron microscope images (*Figure 3*) show clearly their granular appearance and it can be seen that MCC has better sphericity than Lactose.

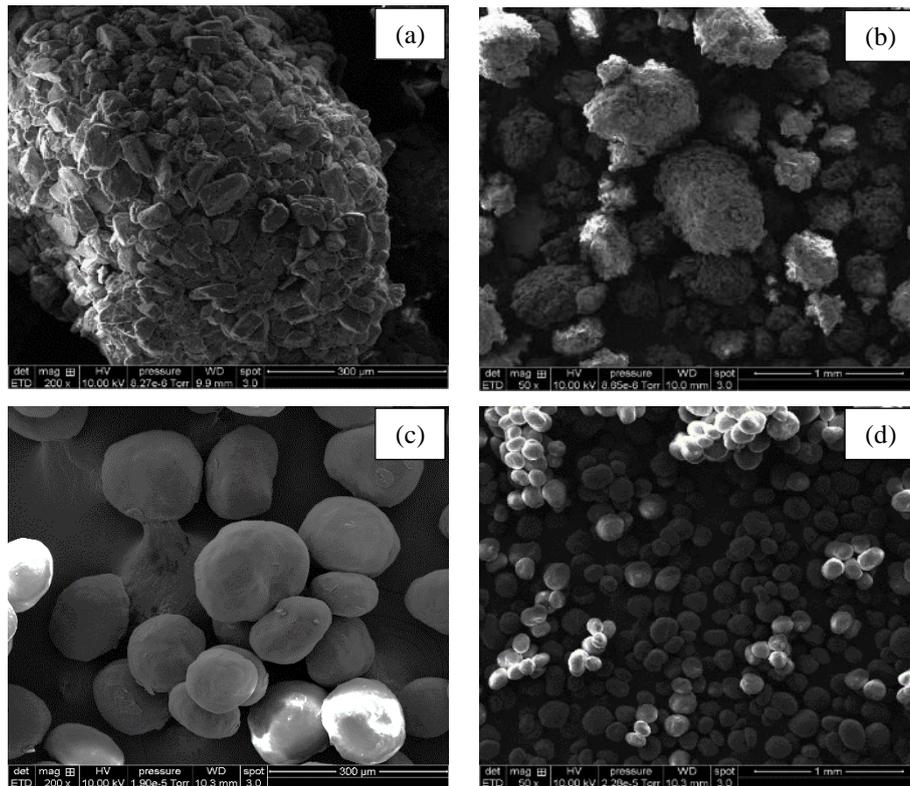


Figure 3. SEM images of Lactose (a at 300 μm , b at 1 mm) and MCC (c at 300 μm , d at 1 mm) granules after 10 minutes of granulation.

As for polydispersity, it was taken into account by following our experimental particle size distribution results (*Figure 4*).

Subsequently the different calibration studies were carried out on our 4 powder types by taking into account the above conditions: Lactose powder, Lactose granules, MCC powder and MCC granules.

3.2. Calibration study

3.2.1. Prediction of the coefficient of static friction

In DEM simulation, different parameters are required. Some of them can easily found in literature,

namely the Young's modulus or shear modulus, others have a low influence on the targeted applications (Coefficient of Rolling Friction, Coefficient of Restitution). But the DEM model requires a precise knowledge of:

- one parameter for simulation of dried powder: friction coefficient μ_s (Eq. 8)
- two parameters for simulations of cohesive powder: friction coefficient and surface energy γ (Eq. 9)

Even if some data can be found in literature, a calibration on experimental is preferred for the estimation of these two parameters. The calibration study consisted on the adjustment of the coefficients of static friction and surface energy by means of angle of repose tests. This study was first carried out from an experimental point of view in order to be positioned on a given range of experimental static angle of repose. From this values, we proceeded to numerical predictive tests in order to approach as close as possible the experimental values and to adjust the parameters which makes us return to the fair value of the experimental angle.

This methodology was adopted for granulated and non-granulated lactose and MCC powders with repeatability. The results of this first study are presented in Figures 5 and 6. Moreover, table 2 shows the results of the adjusted coefficients for each type of powder or granules

Figure 5d illustrates the numerical method of measuring the angle by making a slice in the middle of the heap and tracing a triangle that connects the three extremities. The angle is thus given by the protractor.

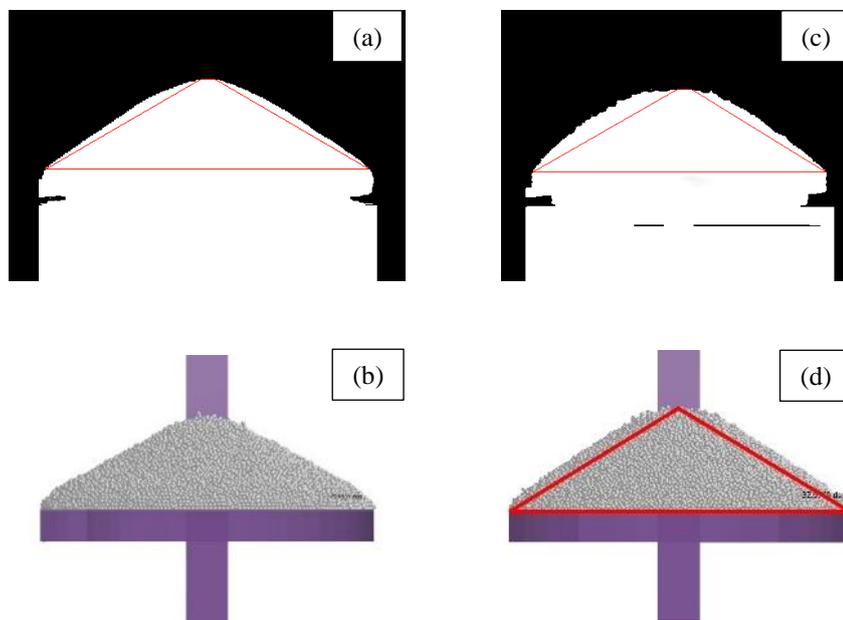


Figure 5. Adjustment of the numerical static friction coefficient of Lactose powder and granules. Experimental angle of repose (a) Lactose powder: 29.70°; (c) Lactose granules: 32.00°. Numerical angle of repose (b) Lactose powder: 29.67°; (d) Lactose granules: 32.07°.

By means of this calibration study we were able to calibrate the coefficients of our attributes for Lactose and MCC powders (granulated and non-granulated) and it has been approved by our experimental and simulation results which are in perfect agreement.

We also observed that the higher the angle of repose, the higher the coefficient of static friction. This is explained by the fact that in order to form a higher and more stable heap, the force that tends to keep a body in a static state must be high.

We also noted that for a same protocol of granulation and for a same binder, the energy surface is the same for the two kinds of granules (lactose or MCC).

It is important to know that these coefficients are specific to each powder type and its calibration is very important for the reliability of the application of these powders in future simulations such as wet granulation. But only one experimental measurement is required to ensure the calibration.

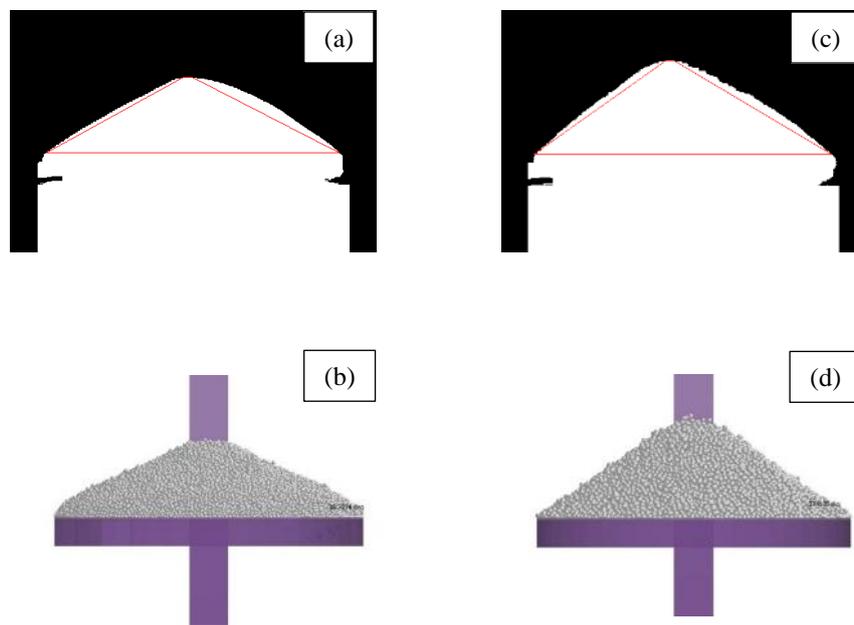


Figure 6. Adjustment of the numerical static friction coefficient of MCC powder and granules.
Experimental angle of repose (a) MCC powder: 28.60°; (c) MCC granules: 33.70°.
Numerical angle of repose (b) MCC powder: 38.70°; (d) MCC granules: 33.80°.

Table 2. Calibrated coefficients of static friction

<i>Material properties</i>	<i>Units</i>	<i>NG - lactose</i>	<i>G - Lactose</i>	<i>NG - MCC</i>	<i>G - MCC</i>
<i>Coefficient of Static Friction</i>	[-]	0.25	0.80	0.35	0.95
<i>Surface Energy</i>	[J/m ²]	0.00	0.09	0.00	0.09
<i>Experimental Angle of Repose</i>	[°]	29.70	32.00	28.60	33.70
<i>Numerical Angle of Repose</i>	[°]	29.60	32.07	28.70	33.80

3.3. DEM simulation to predict powder handling and process

3.3.1 Compaction applications

In this paragraph, we carried out experimental and numerical compaction tests, using the jolting volumeter (described in the material and method section).

During these tests, we used granulated MCC as model powder and we considered the same particle-particle coefficients used in the static angle of repose calibration test (coefficient of static friction:0.95, coefficient of restitution: 0.15, coefficient of rolling friction: 0.05, surface energy: 0.09 J/m²). The tests were carried out with rotating vibrations at 1 mm magnitude for one minute.

The experimental and numerical results before and after compaction are shown in (Figure 10).

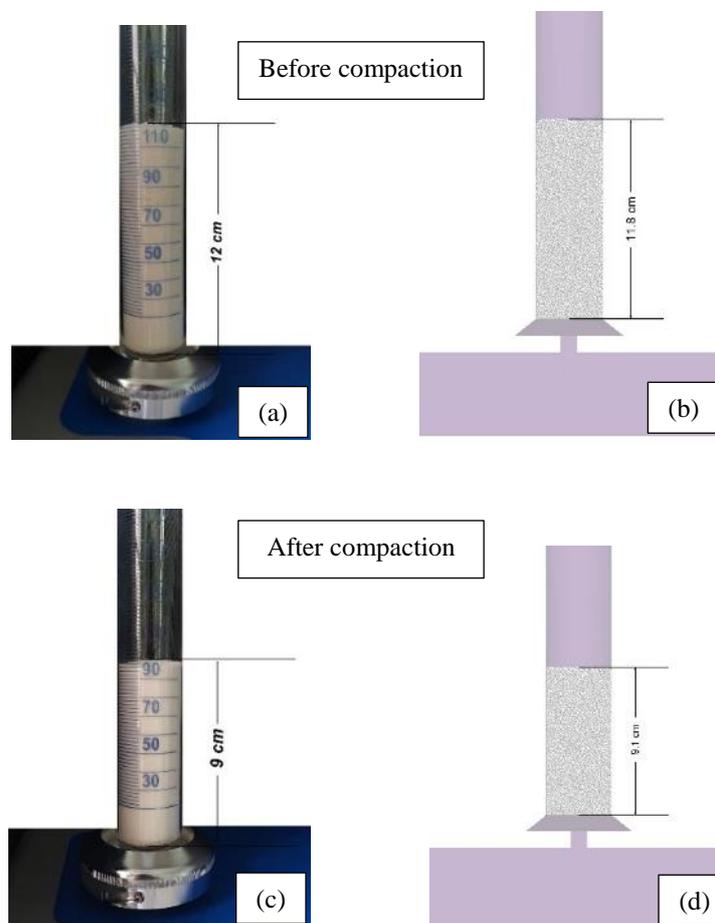


Figure 10. Results before and after compaction of MCC granules.
Before compaction (a) experience = 12.00 cm; (b) simulation = 11.80 cm.
After compaction (a) experience = 9.00 cm; (b) simulation = 9.10 cm.

Following our experimental and numerical compaction tests, we measured the heights of our powders contained in the measuring tubes before and after compaction. This showed that our experimental and numerical results are in perfect accordance with a maximum error of ± 0.2 cm.

This confirms the good accuracy of our prediction results of the coefficients of static friction from the calibration study. This means that the model is able to predict the behavior of monodisperse powder. These results can be used in further simulations; such as studies of the influence of granulometry on powder flow or in advanced wet granulation simulations.

3.3.2. Influence of granulometry on powder flow

Particle size distribution is one of the parameters that governs powders flow behavior. It is known that static angles of repose change according to the particle size. To find out more, we have carried out a series of experimental and numerical tests of static angle of repose.

We used 3 different sizes of MCC powder namely: **powder (A): 0.1 mm; powder (B) 0.5-0.7 mm; powder (C): 1 mm.**

Two different mixes were made with these powders: **mix 1: powder A + powder C; mix 2: powder B + powder C.** For these two mixtures, 4 experimental measurements of static angle of repose were made repeatedly with an increasing percentage of powder A for mix 1 and of powder B for mix 2. To know more about the behavior of these different mixtures, we simulated the same tests numerically using only the Hertz-Mindlin contact model. For reason of calculation time acceleration, we increased the particle size of powder A from 0.1 mm to 0.4 mm so that the number of cell grids would not be too high.

The different percentages by mass as well as the number of particles per test are presented in *table 3*, knowing that the total number of particles per mixture is equivalent to 100 gr of powder.

Table 3. Number of particles per mixture and percentage

Percentage by mass	Mix 1		Mix 2	
	Powder A 0.4 mm	Powder C 1 mm	Powder B 0.5 – 0.7 mm	Powder C 1 mm
0 %	0	161214	0	161214
30 %	34291	97495	38960	89690
70 %	77769	38280	90839	38933
100 %	679000	0	209975	0

As for the first calibration study, the coefficients of static friction were found through the experimental angles of repose by calibration test for each mix but leads to the same results. The friction coefficient is not affect by the granulometry. The different coefficients as well as the experimental and numerical angles for the 4 percentages of each mixture are summarized in Table 4.

The results show once again that the coefficient of static friction is specific to each powder mixture and this calibration was done for mix 1 and 2.

Table 4. Coefficients of static friction, experimental and numerical angles of repose for mix 1 and 2

<i>Mix 1</i>	0%	30%	70%	100%
<i>Coefficient of Static Friction</i>	0.40			
<i>Experimental Angle of repose</i>	32.80	29.00	28.56	27.80
<i>Numerical Angle of repose</i>	32.80	29.07	26.99	27.58

<i>Mix 2</i>	0%	30%	70%	100%
<i>Coefficient of Static Friction</i>	0.40			
<i>Experimental Angle of repose</i>	32.80	31.50	29.84	27.73
<i>Numerical Angle of repose</i>	32.24	31.11	29.84	27.66

The graphics shown in Figures 7 and 8 plot the experimental and numerical angles of repose of the two mixtures made with different sizes of MCC powder as a function of the increasing percentages of the finest particles.

The graph in Figure 7 is for mix 1. In this mixture the 0.4 mm powder particles have been added in increasing percentages, it can be seen that when only 1 mm particles are present the experimental and numerical angles correspond to a value of 33.80°. With the presence of 30% finer powder, the mixture gives a marginally lower angle of repose, and a slight stabilization between 30 and 70% is noticed when the powders are in almost equal quantities. At 100% we continue to have a stability of the angle. It can well be seen that the heaps formed with 1 mm particles are much bigger, due to the fact that spherical monodisperse particles were used, making it easier to pile up on each other, the presence of smaller powder must have destabilized the heap formation in a polydisperse system, since the smaller particles tend to slip between the larger particles and stabilize on the surface of the measuring cup (a concrete case of segregation). In this case of angle of repose measurement, the value of the angle may well imply a good flow of the powder, but this is often misleading during subsequent handling or this segregation phenomenon always tends to limit the processing of the powders. In *figure 9 (a)*, we can clearly see the deposit of powder of size 0.4 mm on the inside of the heap while the outside remains covered with larger particles.

The same tendency was noticed with mix 2 where slightly larger MCC particles than those in mix 1 were used, here their particle size is between 0.5 and 0.7 mm. However, a linear decrease in the angle of repose was observed with the increasing percentage addition of smaller size powder. Local segregation is also present here *figure 9 (b)*.

Moreover, the experimental and numerical tests generally follow each other to within one measurement.

According to this study, granulometry does have an important influence on powder flow, but it is sometimes confusing as we have witnessed with the numerical tests. The presence of too fine particles

often leads to the presence of segregation phenomena and also cohesion. Generally, the more the particles are of medium and spherical size, the better the flow is.

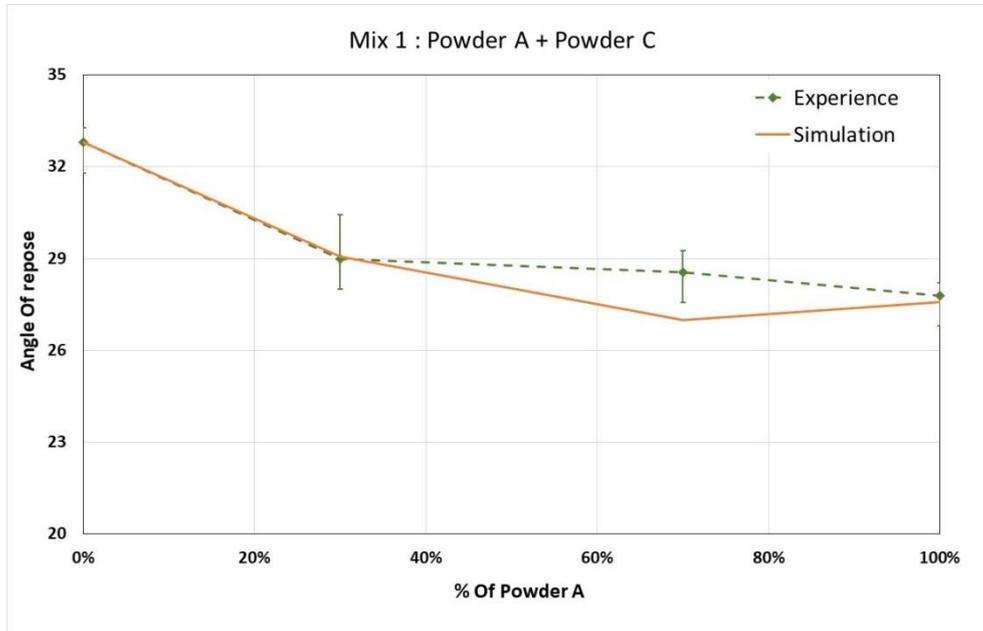


Figure 7. Experimental and numerical angles of repose of mix 1 versus increasing percentage of powder A.

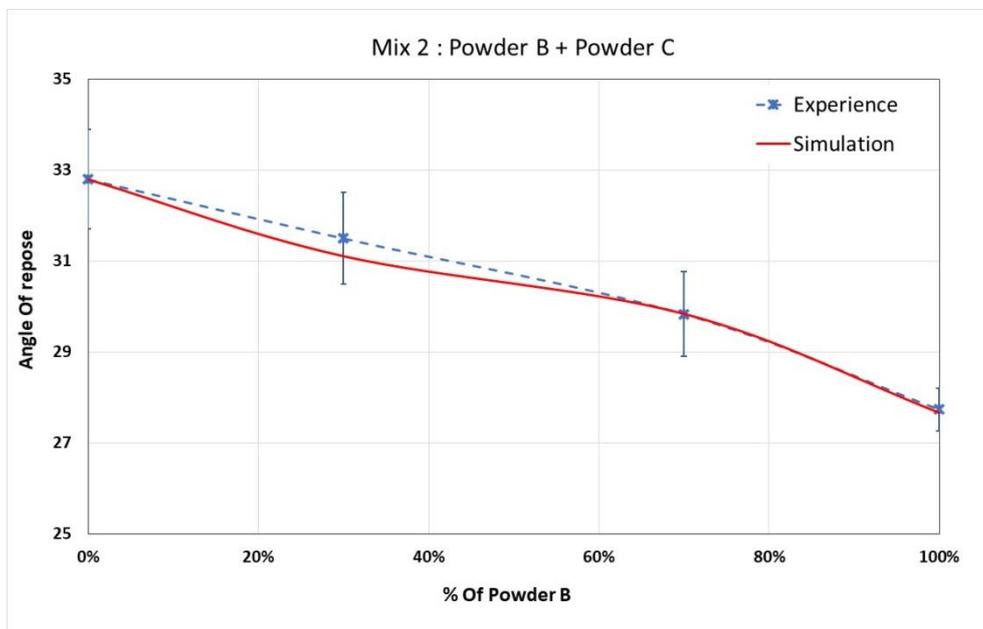


Figure 8. Experimental and numerical angles of repose of mix 2 versus increasing percentage of powder B.

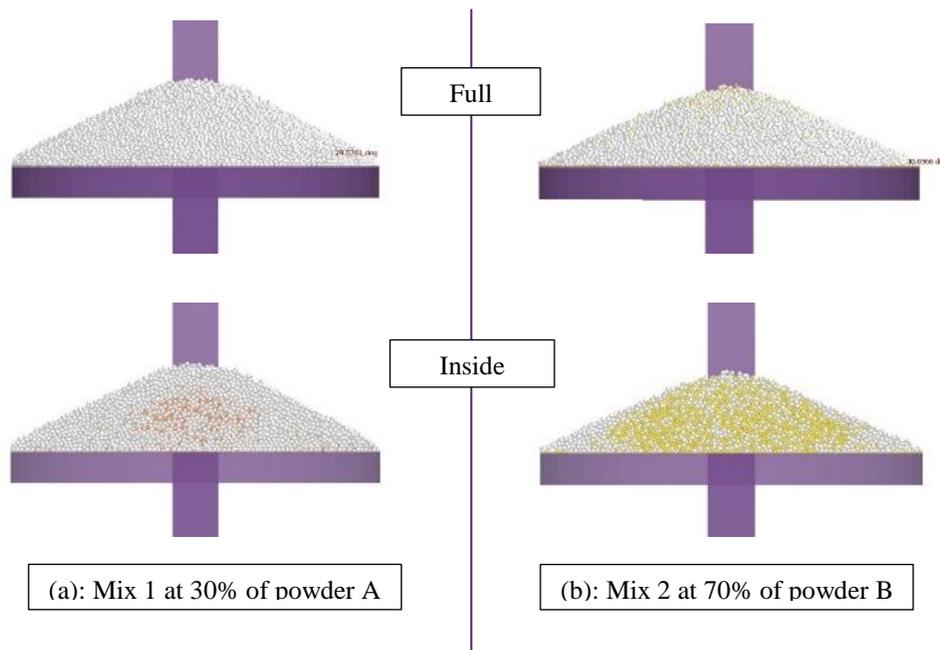


Figure 9. Images of angles of repose of mixes 1 and 2.

3.3.3 **Mixing application = à voir avec Roman si OK?**

This numerical approach was also validated in a previous work carried out in our laboratory to predict particles mixing (Mesnier et al., 2019). In this work, we have investigated the segregation within a granular bed in a rotary drum. The granular bed was composed of calibrated particles of cellulose acetate, 2 mm (orange particles) and 3 mm (black particles). The calibration study allows the estimation of the friction coefficient to 0.3. Images of experimental drum and simulation after six revolutions are shown on figure 10.

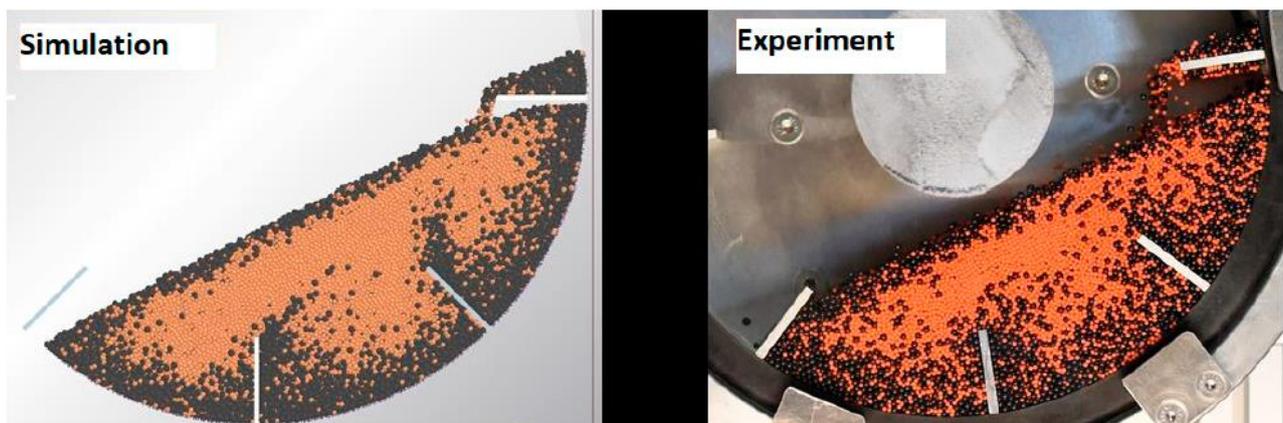


Figure 10. Simulated and experimental images of a rotary drum

We note a good adequation between the two images, and we can conclude that the DEM model lead to a good prediction of the segregation of the small particles (orange) in the core of the drum, compared

to the experimental data. The numerical tool can also be used to predict the influence of baffles or filling ratio to limit the segregation phenomena.

3.3.4. Wet granulation

Numerical prediction and validation studies of coefficients of static friction provide valuable input parameters for the wet granulation process modelling, which is our pharmaceutical application process. This process is studied experimentally and numerically in order to better apprehend it and thus understand the influence of the operating parameters, as well as to monitor granule growth kinetics. For this purpose, based on a preliminary experimental study, the high shear wet granulator "GLATT TMG 1/6" was modelled using EDEM software and granulation simulations were carried out using MCC powder with the input parameters calibrated in this study. The images shown in Figure 11 illustrate some of the numerical steps in the process: (1) filling, (2) granulation with the use of both impeller and cross-blade chopper and (3) formation of granules.

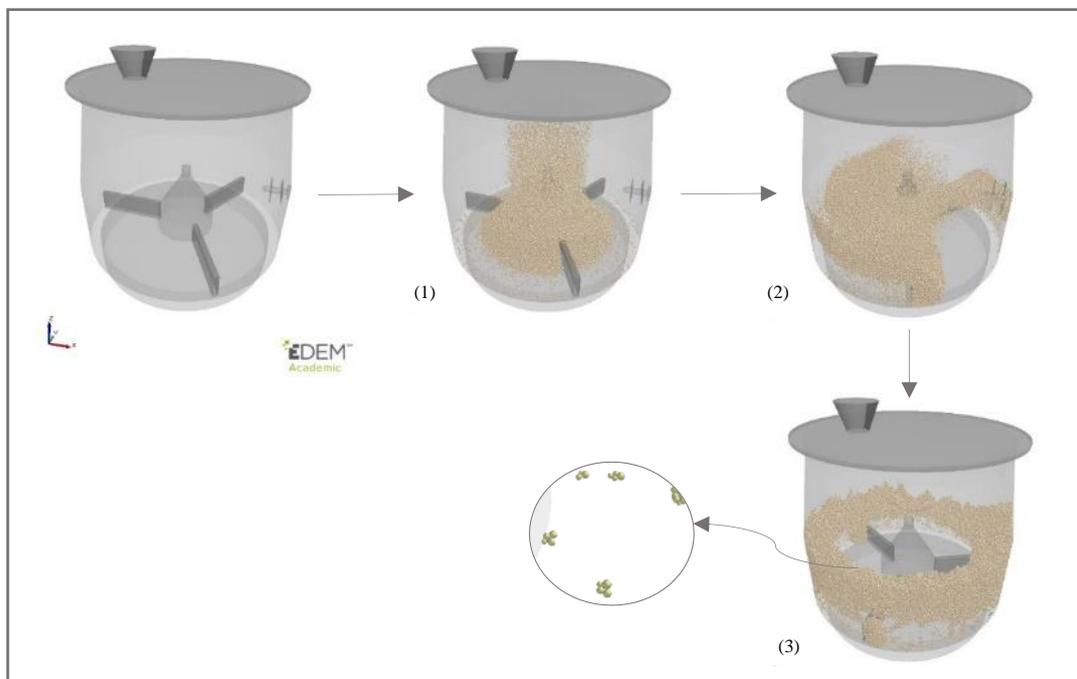


Figure 11. Numerical granulation steps using EDEM - (1): filling of the vessel; (2): granulation; (3): granules formation.

On the step (3), JKR model is active to take into account the formation of granules by cohesion between particles. Indeed, as represented in the zoom on figure 11, it is possible to see cluster growing during time. The influence of process parameters like impeller speed or filled ratio could also be studied numerically, and the scale-up of the reactor could be secure.

Conclusion

In this paper, the flowability of two types of granulated and non-granulated pharmaceutical powders was studied through experimental and numerical trials. The experimental study consisted firstly of preparing granule batches by high shear wet granulation. The granulated and non-granulated powders were characterized by their particle size distribution by laser diffraction and their shape by scanning electron microscopy.

The attributes were then used as powder models for a calibration study by angle of repose trials by means of experimental and numerical tests using the discrete element method (DEM). This allowed us to adjust the coefficients of static friction of our powders by comparing them with the experiment, and also surface energy for granules. The numerical results were in perfect agreement with the experimental ones and thus the coefficients were well calibrated.

The model was then used to predict the behavior of the powder in different handling or processes commonly used in the pharmaceutical field.

In a compaction tester using the same physical powder properties used in the calibration part, including the coefficient of static friction and surface energy, the results validated the calibration study with a good coordination of the experimental and numerical measurements. These two parts showed clearly the effect of the coefficient of static friction on the powder flow.

In addition to this, the influence of particle size distribution was further investigated with a series of experimental and numerical angle of repose tests using three mixtures of MCC powder with 3 different sizes and an increasing mass percentage of the smallest powder size. The results showed the influence and the importance of particle size distribution on powder flow, where a narrower particle size distribution with non-fine powders is recommended to avoid the effect of cohesive forces between the particles. The numerical tool has also predicted the mixing of particles in the drum and highlight the phenomena of segregation.

Finally, the DEM has been used to predict the cohesion of particles during granulation process. The influence of process parameter as the chopper importance, the impeller velocity or the filling ratio can be studied numerically.

Consequently, the method developed in this paper, that requires only one experimental measurement of the angle of repose, makes it possible to very accurately predict the behavior of the powder. The problematics of segregation, mixing or cohesion can be modeled and predicted to limit some manufacturing problems during pharmaceutical industrialization and the tool can be used to secure the scale-up or the scale-down.

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