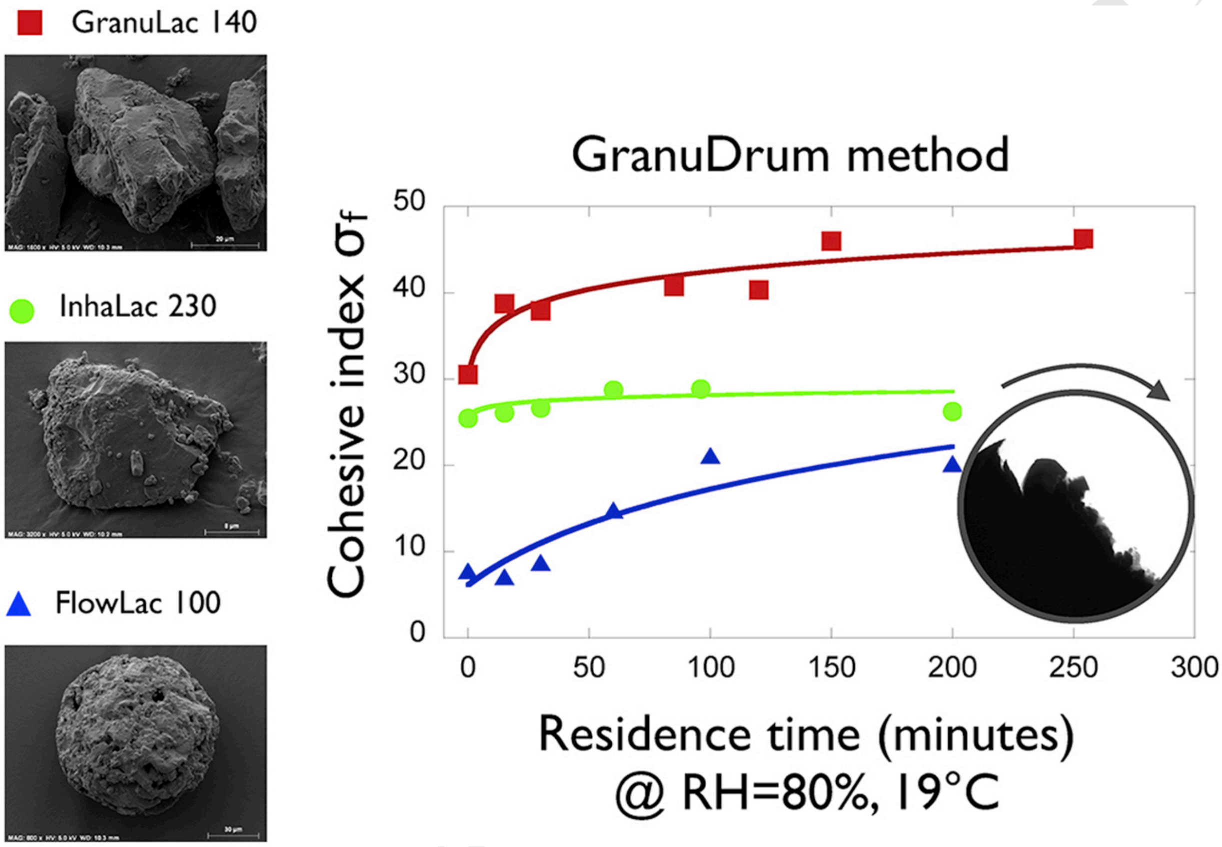
GranuLac 140
InhaLac 230
FlowLac 100
GranuDrum method
Cohesive index σf
0
10
20
30
40
50
0
50
100
150
200
250
300
Residence time (minutes)
@ RH=80%, 19°C

Effect of relative air humidity on the flowability of lactose powders

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Abstract

Moisture is known to affect the flowing properties of powders. However, the quantification and the understanding of the observed effects are far to be obvious. To study air moisture influence on powder flowability in a laboratory, a conditioning system and a precise flowmeter are necessary. Simple flow testers, which are commonly used R&D laboratories, are not able to quantify precisely the effect of moisture on powders. The use of advanced techniques is necessary. In this paper, we present how a precise and user-friendly flowability test associated with a dynamic conditioning system can be used to quantify the influence of moisture on the flowability properties of lactose powders. The effect of residence time T in high humidity conditions is analyzed. Afterward, we show that the relative humidity range that optimizes the flowability of lactose powders is between 30% and 50%. For lower values of the relative humidity, the apparition of electric charges inside the bulk induces cohesive forces. For higher relative humidity, the condensation of the air humidity at the contact between the grains forms capillary bridges

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which favors also the cohesive interactions. A model taking both triboelectric and capillary effects into account is proposed to fit the experimental data.

Keywords: Cohesion, Flowability, Humidity, moisture, Electric charges, Lactose

1. Introduction

Granular materials, fine powders and nanopowders are widely used in industrial applications [1, 2]. In particular, lactose powders are commonly used as an excipient for dry powder pharmaceutical formulations (dry powder inhaler, tabs, capsules). Indeed, lactose is inert, non-toxic and cheap. Therefore, any progress in the understanding of lactose powders behaviors could have huge consequences for pharmaceutical industries for the optimization of industrial processes or to avoid technical issues (caking, clogging, non-compliance or unconformity of the by-product). In order to control and to optimize processing methods, these materials have to be precisely characterized. This characterization methods is related either to the properties of the grains or to the behavior of the assembly of grains. The relation between physico-chemical (size, shape, crystallinity, *etc.*) grain properties and the macroscopic behaviors (flowability, density, cohesiveness, *etc.*) of the powder is far to be obvious. Therefore, both measurement types have to be performed. Many advanced methods are available to measure physico-chemical grain characteristics: laser diffraction to obtain the grain size distribution, morphometer to measure grains shape, X-ray diffractometer to characterize crystallinity, ... However, concerning the physical behaviors of an assembly of grains, most of the techniques used in R&D or control quality laboratories are based on old measurement techniques [3]. During the last decades, some interesting techniques have been developed like shear cells and powder rheometers. However, the evolution of this field is still at his beginning. Indeed, even at the fundamental point of view, the determination of the physical laws that govern the behavior of a granular material is still a matter of intense debates in the physics community [4, 5].

Recently, the rotating drum measurement method has been revisited according to the present fundamental knowledge [6]. The existence of the optimized equipment called GranuDrum opens new perspectives due to both its precision and conceptual simplicity. This equipment measures the flowing angle inside a rotating drum as a function of the rotating speed. The cohesion between the grains is also estimated through the fluctuations of the flow free surface. Figure 1 shows two typical flows in the rotating drum: (left) a non cohesive flow and (right) a cohesive flow. In contrary to the shear tester where the powder is loaded, the rotating drum is a free flow test. The free flowing behavior inside the rotating drum is comparable with powder dynamics inside many industrial processes such as conveyor, mixer, granulator, *etc.*

Granular materials behavior is influenced by (i) steric repulsions, (ii) friction forces (iii) cohesive forces and (iv) interaction with the surrounding fluid (gaz or liquid). The steric repulsion is related to the grains geometry. Friction forces are influenced by both surface state (rough or smooth surface) and chemical nature of the grains. Cohesive forces may be induced by the presence of liquid bridges [7, 8, 9], electric charges [10], van der Waals interactions [11] or magnetic dipole-dipole interactions [12, 13, 14, 15, 16].

The predominance of one of these forces depends on both the environmental conditions and the physicol-chemical properties of the grains.

Moisture is known to affect both static and dynamic behaviors of a granular materials [8, 9, 18, 19]. However, the effect of moisture is far to be obvious. Indeed, moisture influences surface grains conductivity, capillary bridges formation and relative air permittivity [20]. For low relative air humidity, the electrical conductivity necessary for charge dissipation is reduced and the relative permittivity comes close to vacuum permittivity. Therefore, the electric charges created by triboelectric effects lead to uncontrolled electric field, electrostatic forces between the grains and/or between the grains and the container. For high relative air humidity, the electrical conductivity increases, liquid bridges may be formed at the contacts between the grains and the relative air permittivity increases. Therefore, the electrical charges are dissipated more easily. However, the apparition of liquid bridges induces cohesive forces inside the packing. At intermediate relative humidity values the cohesion is expected to decrease. In addition to these effects, the humidity could also modify the chemical characteristics of the grain surface [21], the strength of the Van des Waals interactions [22] and the friction due to lubrication effects [23].

To measure the effect of relative air humidity on the flowability of a powder sample in a laboratory, a conditioning system is necessary before the flowability measurement. Powders are usually conditioned with a static method. The sample is generally poured in a container, which is put in a climate chamber. The exchanges between the air and the powder bulk is limited. Indeed, only the upper part of the powder bed can have exchange with the controlled atmosphere. In the worse case, a crust forming phenomenon prevents access of the humidity to the powder situated in the bottom of the container. Moreover, the static approach may generate physical and/or chemical heterogeneity in the sample, leading to artefacts during the following measurement. In the present study, the powder is conditioned at controlled relative air humidity in a slowly rotating reactor to optimize the exchanges between the surface grain and the moisture.

Watling *et al* [21] have found a significative aging of lactose powders after an exposure at 75% RH, 40°C during six months. The observed effect was mainly related to a dissolution of the smallest particles covering the big ones leading to a modification of the surface state of the coarse lactose. This effect, which needs long time exposure, is not expected in the present study. The influence of shorter residence times of pharmaceutical powders in controlled humidity conditions has been investigated Crouter *et al* [24] (48h) and by Emery *et al* [9] (24h). In particular, Emery *et al* have shown that simple flow testers (tapped density test, angle of repose measurement, flow through an aperture, ...) are not able to quantify the effect of moisture on lactose powders. Only the Jenike shear test was found to give acceptable results. Unfortunately, this test is difficult to operate and time consuming. Therefore, to quantify efficiently the effect of moisture on powders, a reliable and user-friendly flow tester is necessary in addition to the simple tests and to the shear cell measurements.

In the present paper, we show how relative air humidity influences lactose powder flowability after a short residence time (only a few hours). The powder samples are first conditioned at controlled relative air humidity in a rotating reactor to optimize the exchanges between the surface grain and the moisture. Afterward, the flowability is measured with the GranuDrum equipment [6].

2. Materials and methods

2.1. Lactose powders

Three lactose powders produced by the company Meggle and widely used in pharmaceutical industries have been used: GranuLac 140 (G140), InhaLac 230 (I230) and FlowLac 100 (F100). All the samples are α-lactose monohydrate powders. Granulac powders come from milling process. Inhalac powders are milled and sieved lactose powders. Finally, FlowLac powders are obtained from spray-dried lactose suspensions. Powders have been selected in order to have similar grain size distributions but resulting from different process.

2.1.1. Particle sizing

The grain size distributions have been measured with the dry method with a laser diffraction particle size analyzer (Malvern, Mastersizer Sirocco 2000). The measurements have been made with an air injection pressures fixed at 1.2 bar. The refractive index of particles was fixed to 1.5 and the default model was selected.

2.1.2. Scanning electron microscopy

Scanning Electronic Microscopy (Philips ESEM XL30 FEG, Eindhoven, NL) with an acceleration voltage of 5kV was used to analyse qualitatively the grains morphology. Samples were deposited on carbon tapes. Sputtering deposition was done with gold target under argon atmosphere (Balzers, SCD004, Sputter coater).

2.2. Conditioning

Before the flowability measurement, the powder is conditioned during a time T in a slowly rotating reactor. The reactor is a 316L stainless steel tube of internal diameter $D = 48$mm and length $L = 320$mm. The tube axis is placed horizontally. The tube is rotating around its axis at 0.66 RPM. A flux $F = 0.3$ l/min of air with controlled relative humidity flows through the reactor. The humidity of the air passing through the reactor is adjusted by varying the flow ratio of dry air and humidified air. The humidified air is obtain by bubbling through water in a column. The slow motion of the reactor allows the humid air to penetrate inside the bulk. Moreover, the low value of the rotating speed avoid granulation. The accessible values of the relative humidity range from RH=0% to RH=95%. Directly after this preparation, the drum cell is half filled by the powder and is closed hermetically. All the manipulations have been performed at room temperature (19°C ± 1°C).

2.3. Flow measurement method

Experimentally, the most practical geometry to study a free flow of granular materials is the rotating drum. This flow geometry has been extensively studied with non cohesive granular materials [25, 26, 27, 28] (see Figure 1(left)) and with cohesive powders [29, 30, 31] (see Figure 1(right)). In the case of cohesive grains, the flow is intermittent in the whole range of rotating speed.

The experimental setup used to perform the flowability measurement is the GranuDrum from the company GranuTools. This measurement methods has been presented in detail in a previous paper [6]. The measurement cell is a horizontal aluminum cylinder of diameter $D = 84$mm and length $L = 20$ mm with glass side walls. The drum is half-filled with the powder. The cylinder rotates around its axis at an angular velocity Ω producing the flow of the grains. For each angular velocity, 50 images of the rotating powder bed separated by 0.5 s are recorded. The position of the air/powder interface is measured by image processing and analysis. The average interface position and the fluctuations around this average position are computed. From the fluctuations of the interface, the standard deviation σ_f is calculated [6]. This parameter, also called cohesive index, is directly related to the cohesion inside the drum. Other parameters like flowing angle, aeration, thixotropy, first avalanche angle can be measured [6, 34]. In the present paper, we are focused on the analysis of powder cohesiveness through the cohesive index σ_f.

3. Results

Typical scanning electron micrographs of lactose grains are presented in Figure 2 (top). Granulac and Inhalac grains show angular edges due to the milling process. Flowlac grains have roughly spherical shapes related to the spray drying production process from lactose suspension. The grain size distributions obtained by laser diffraction are presented in Figure 2 (bottom) and the main descriptors extracted from these distributions are summarized in Table 1. The presented distributions are corresponding to an air pressure of 1.2 bars. The main parameter selected to characterize the average grain size in the present study is the volume mean diameter (de Brouckere Mean Diameter) $D[4/3]$. Granulac 140 powder has a significative fraction of fine grains and the lowest average size. Inhalac 230 powder size distribution is mainly a sharp peak around 100 μm. Finally, the spherical Flowlac 100 grains have the highest average size.

The cohesive index σ_f measured with GranuDrum instrument for different rotating speeds with the powder extracted directly after the first opening from a new container are presented in Figure 3. These results show that the powders considered in the present study have different flow behaviors and are covering a wide range of cohesiveness. Flowlac 100 is characterized by low cohesive indices σ_f whatever the range of rotating speed. At the opposite, Granulac 140 powder has the higher cohesive indices σ_f at slow rotating speeds but the cohesive index decreases for higher rotating speeds. Results obtained at slow rotating speeds regarding powder cohesiveness can be directly related to grain sizes. Indeed, when the average grain size decreases ($D[4/3]_{F100} > D[4/3]_{I230} > D[4/3]_{G140}$), the influence of the cohesive forces (van der Waals, electrostatic and capillary forces) on the powder bed behavior increases. A deeper analysis of the curves obtained with the GranuDrum instrument allows to obtain additional information about powder rheology. For exemple, a decrease of the cohesive index σ_f with the rotating speed is observed for Granulac 140. In others words, the flowability of the Granulac 140 is improved as the shear rate increases, corresponding to a shear-thinning behavior. We have previously demonstrated that this effect is due to powder aeration during high speed flows [34]. This observation evidences the necessity of deep analysis when powder flowability is considered.

In order to study the temporal evolution of powder cohesiveness when submitted to high humidity conditions, a series of GranuDrum measurement have been performed with different residence times T in the conditioning system. For each measurement, a sample of 80ml coming directly from the box was conditioned in the rotating reactor with a relative humidity fixed at 80%RH and 19°C. After a residence time T, the sample is extracted directly from the reactor and the GranuDrum measurement cell is half filled with 55ml of powder. Afterward, a new sample is taken from the original container to prepare the next measurement. Figure 4 shows the temporal evolution of powder cohesiveness when submitted to high humidity conditions (80% RH). The intermediate drum rotating speed of 8RPM has been selected to plot the results. The relative air humidity does not affect equally the different lactose powders. GranuLac and FlowLac cohesiveness increases significantly with the residence time while InhaLac is less sensitive. After an increase, the cohesive index reaches a plateau. The modification of powders cohesiveness is quite fast. Indeed, the cohesive index is already modified after less than one hour in the reactor.

To measure the influence of the relative humidity RH on powder cohesiveness, a residence time of $T = 150$ minutes has been selected. This residence time corresponds roughly to the beginning of the plateau observed in Figure 4. Figures 5 shows the influence of relative humidity RH on powder cohesiveness for the three selected lactose powders. The cohesion is found to decrease slightly in the range of relative humidity from 0% to 50%. Therefore, the cohesive forces inside the bulk decrease and the flowability is enhanced. Afterward, the cohesion increase importantly from RH=50% to RH=100%.

Then, the relative humidity that optimizes the flowability of lactose grains is situated between 30% and 50%. For low humidity conditions, the cohesion is induced by the apparition of electric charges on the surface of powder grain. For the extremal case RH=0% this effect was particularly important. Indeed, the powder was sticking on all surfaces. During GranuDrum measurement, the analysis of the flow was impossible for rotating speed higher than 8RPM due to this sticking effect. For this reason, the rotating drum speed of 8RPM has been selected to perform the comparisons in the whole present paper. For high humidity conditions, the condensation of water at the surface of the grains leads presumably to the formation of capillary bridges at the contact between the grains, increasing powder cohesiveness. For the short residence times considered in the present study, we do not expect a water absorption inside the grains.

These experimental results show the importance of moisture and its control on powder flowing properties. For example, the cohesive index of FlowLac 100 samples directly from a new container is $\sigma_f^{8RPM} = 7.7$. Therefore, the flowability of this powder can be considered as good (almost excellent) [34]. After a residence time $T = 200$ minutes at high humidity conditions, the cohesive index becomes $\sigma_f^{8RPM} = 20.2$. This cohesive index corresponds to a powder with passable flowing properties. Therefore, moisture modifies drastically the flowing properties of this powder even during a short-term exposition.

3.1. Measurement uncertainties

In order to estimate the uncertainties on the measured cohesive index, the measurements have been repeated six times with a residence time $T = 150$

minutes at a relative humidity of $RH = 95\%$. For each measurement, we started with a new sample coming from the box, conditioned at controlled humidity and analyzed with the rotating drum method. The error bars presented in Figure 5 correspond to the standard deviation calculated from the six measurements. Typically, the uncertainty on the cohesive index corresponds to about 10% of its average value.

4. Discussion

The modification of powder cohesiveness is related to a combined effect of capillary bridges induced by air moisture and triboelectric charges. In the present discussion, a model combining (i) adhesion forces F_{adh} induced by capillary bridges and (ii) electrostatic forces F_e between the grains is proposed to fit the experimental results. We assume that the powder cohesiveness measured by GranuDrum instrument is directly related to the sum of the cohesive forces acting between the grains. This model has been used previously to fit experimental data related to taped density measurement [18].

The effect of moisture on the first avalanche angle in a rotating drum has been investigated by Crassous *et al.* [35]. A model based on capillary condensation of water vapor between the grains is proposed to explain the modification of the avalanche angle due to moisture. By assuming that the kinetics of the process is governed by thermally activated nucleation of capillary bridges, Crassous *et al.* were able to reproduce both time and relative humidity dependence of the process. In this model, the adhesion force F_{adh} between two contacting grains due to capillary bridges formation during a period T at a relative humidity RH can be expressed as

$$F_{adh}(T,RH) \approx \frac{1}{\ln\left(\frac{100}{RH}\right)} \ln\left(1+\frac{T}{\tau}\right), \tag{1}$$

where τ is a characteristic time.

Concerning the electrostatic charges, it has been found empirically that the electrical charge q on beads decreases exponentially as a function of the RH with a characteristic rate 30%, i.e., $q = q_0 \exp(-RH/30)$ [36]. This particular decrease is associated with microscopic capillary condensation on the beads which neutralizes a fraction of the charges. The electric force associated with this charge is proportional to q^2 and therefore decays as

$$F_e(RH) \approx \exp(-RH/15). \tag{2}$$

Associating both triboelectric and capillary effects, we obtain following relation for powder cohesiveness (assuming that the powder cohesiveness σ_f measured with the GranuDrum instrument is directly proportional to cohesive forces):

$$\begin{aligned}\sigma(T,RH) = {} & \sigma_0 + \sigma_e \exp(-RH/15) \\ & + \sigma_c \frac{1}{\ln\left(\frac{100}{RH}\right)} \ln\left(1+\frac{T}{\tau}\right),\end{aligned} \tag{3}$$

where σ_0 is the intrinsic cohesion inside the powder without any charges and capillary bridges, σ_e is the electrostatic contribution to cohesion and σ_c is the capillary contribution to cohesion. This relation gives the temporal evolution of powder cohesiveness and also the effect of relative humidity RH. The powder cohesiveness temporal evolution in high humidity conditions presented in

Figure 4 is well fitted by this model with a logarithmic saturation. Moreover, the decrease of powder cohesiveness followed by an increase as a function of relative humidity (see Figure 5) is also fitted by the model. Despite the simplicity of this model regarding real powder complexity, this model fits quite well the set of measurements.

5. Conclusion

We have shown that the relative air humidity affects strongly the free flow of lactose powders. Moreover, the dynamics is quite fast. Indeed, an increase of cohesiveness is observed after less than one hour in high humidity conditions if powder is conditioned in dynamic approach. However, a precise flowability characterization method is necessary to measure this influence in a laboratory. The GranuDrum instrument is found to be a good method for this kind of study.

Cohesion in powders appears for both dry and wet conditions. When the air relative humidity is low, grain-grain friction inside the flow induces the appearance of electrical charges in the packing. The electrical charges induce cohesive forces between the grains. The condensation in high humidity conditions implies the formation of liquid bridges between contacting grains which induce also cohesive forces. Taking both effects (triboelectricity and capillary) into account, the cohesion is minimized in intermediate values of the relative humidity, i.e. between RH=30% and RH=50%.

Therefore, it is important to take these effects into account in industrial processes and laboratory where surrounding is not always under control (seasonal effect) or for long process where initial powders have not the same time residence, and, so, the same physical and/or chemical properties as the final powders being on the production line.

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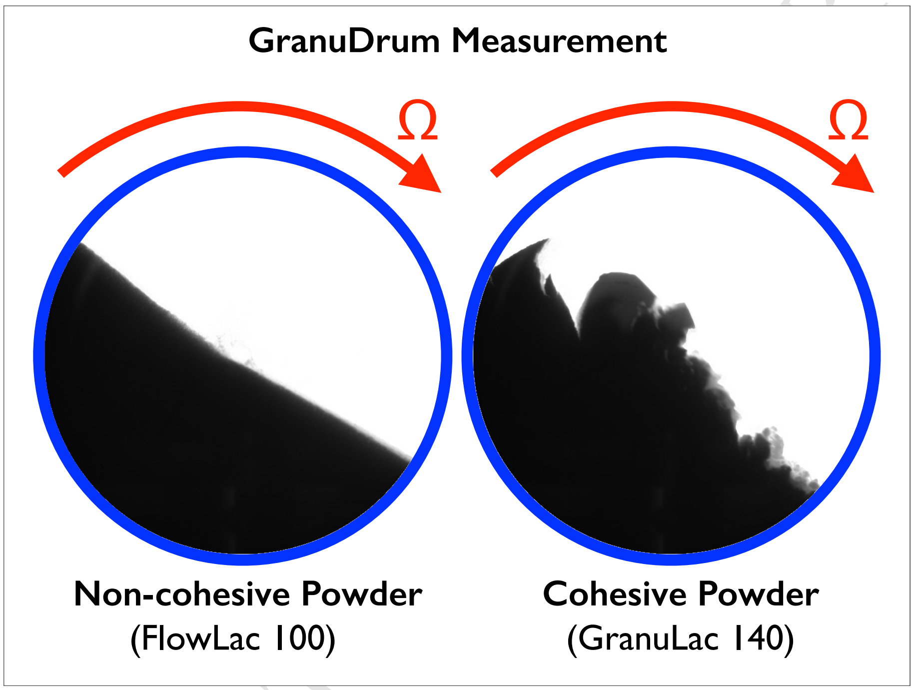
Powder	d(0.1)	d(0.5)	d(0.9)	D[4/3]	Std
G140	10,3	64,8	152,4	74,0	54,5
I230	58,6	97,5	152,2	101,0	38,9
F100	41,6	129,6	247,7	138,8	76,9



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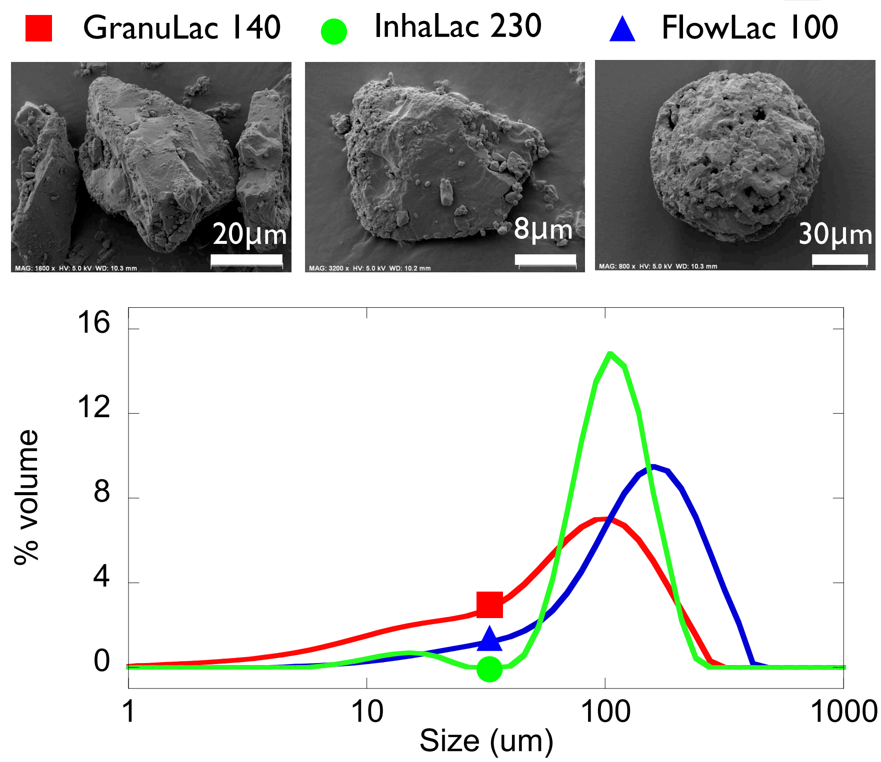

Figure 2: (Top) Typical SEM micrographs of the lactose grains considered in the present study. (Bottom) Size distributions of the three powder samples obtained with a dry laser diffraction method for air dispersive pressure fixed at 1.2 bars.

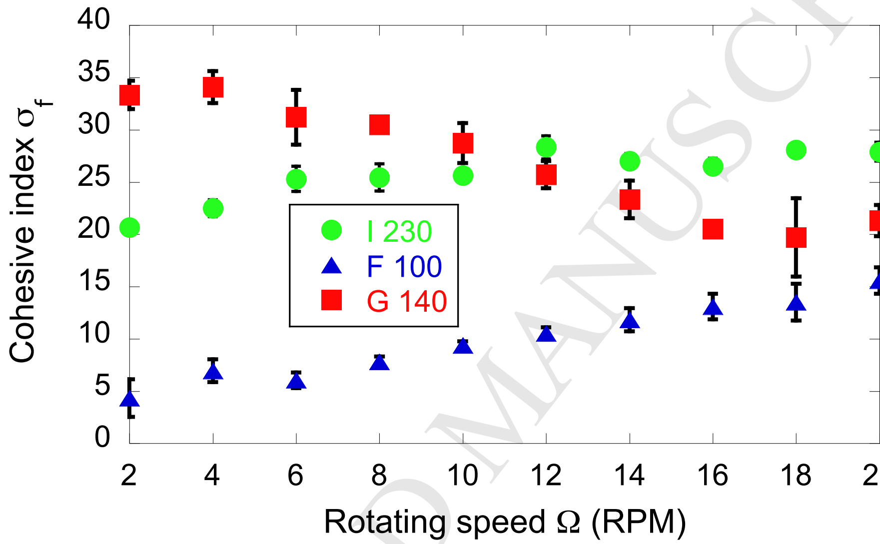

Figure 3: Powder cohesiveness σ_f measured with the GranuDrum instrument as a function of the rotating speed. These measurements have been performed with powder samples taken in the box directly after the first opening. The results corresponding to GranuLac 140 (G140), InhaLac 230 (I230) and FlowLac 100 (F100) lactose powders are presented. Each point correspond to an average over three measurements. Error bars are indicated but are sometimes smaller than the symbol size.

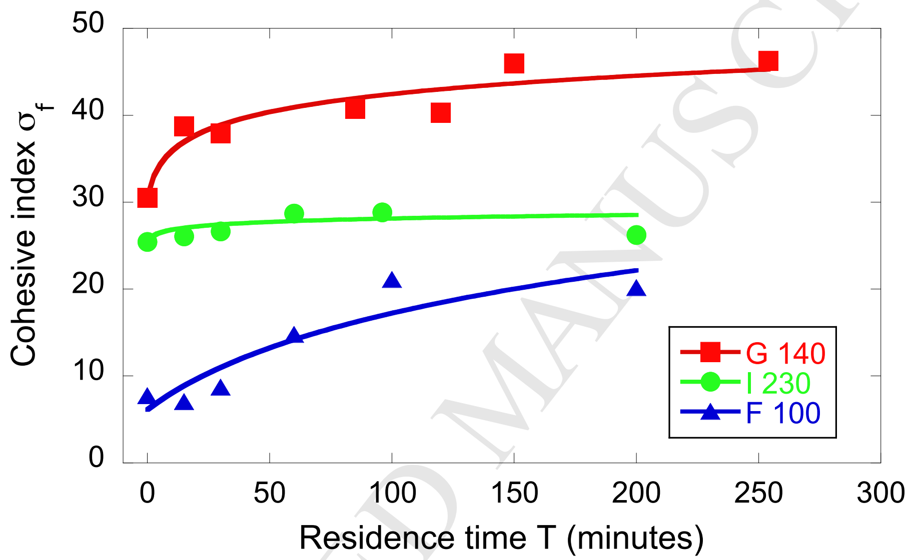

Figure 4: Powder cohesiveness σ_f measured with the GranuDrum instrument at 8 RPM as a function of the residence time T in the reactor at a relative humidity of 80%. The results corresponding to GranuLac 140 (G140), InhaLac 230 (I230) and FlowLac 100 (F100) lactose powders are presented. The solid lines are corresponding to a fit with Eq(3).

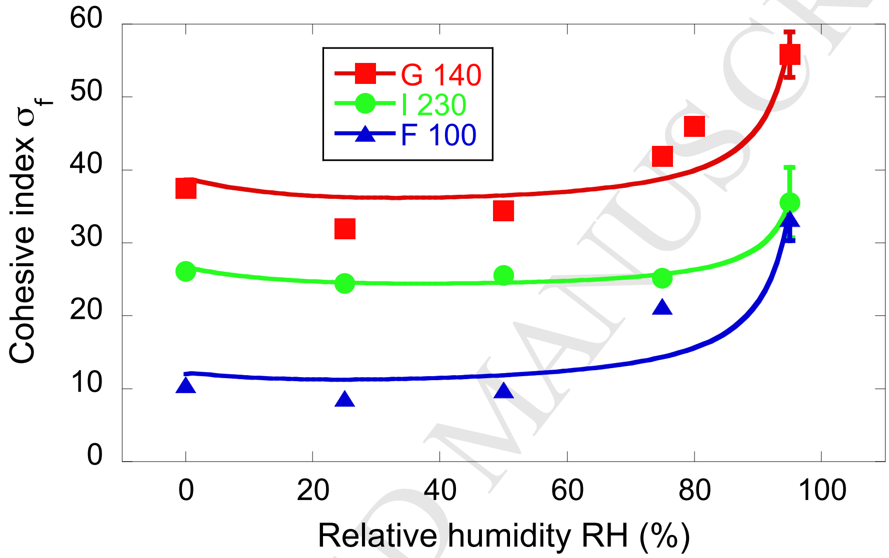

Figure 5: Powder cohesiveness σ_f measured with the GranuDrum instrument at 8 RPM as a function of the relative humidity RH for a residence time in the reactor fixed at $T = 150$ minutes. The results corresponding to GranuLac 140 (G140), InhaLac 230 (I230) and FlowLac 100 (F100) lactose powders are presented. The solid lines are corresponding to a fit with Eq(3). Error bars corresponding to the standard deviation of six measurements are presented for RH=95%.