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Abstract

Granular materials are part of the design, production and final products of different industrial sectors. Powder flowability is a major topic in manufacturing and transport as it is closely related to process feasibility. Nonetheless, the flows of granular materials are not easy to describe or quantify, even in the simple case of dry monodisperse cohesionless particles. Flowability assessment is not a standard or normalized issue; still, no test is able predict powder flow behavior in all the different mechanical situations encountered during processing.

This study aims (1) to evaluate flowability, as device-related, through the force or the energy supplied to the powder bed and (2) to study the effect of glidants and moisture content on flowability. To illustrate these aims, the flowability of two well-known pharmaceutical excipients, Avicel® PH-102 and Retalac® mixed with four different types of precipitated nano-silica (SIPERNAT® D10, D17, 50 S and 500 LS), was assessed using two granular compaction devices: Densitap® and FT4® compaction cell. Our results show that the hydrophilicity of colloidal silica affects surface coverage, ranging from 6% to over 80%. Binary mixtures with hydrophobic additives, D10 and D17, generated smaller silica aggregates with a wider spread on the surface of host particles. For Retalac® conditioned at 20% RH, HR values changed from 1.30 (acceptable flow) to 1.17 (good flow). For Avicel® PH-102, conditioned at 60% RH, HR values changed from 1.22 (fair flow) to less than 1.10 (excellent flow).

1 Introduction

Those who work with granular materials, fine or coarse, such as powders, know that the same powder may flow well in one container but poorly in another. Despite all the available studies describing flow characteristics, it is often difficult to extract common features and general trends for granular materials that are not glass beads. Granular flow complexity is related to its multidimensional character as it links the local particle interactions and their global mechanical behavior, including bulk properties, equipment design, processing conditions, and environmental conditions. The difficulties and limitations of flow behavior assessment have been well-reviewed (Prescott and Barnum, 2000; GDR MiDi, 2004; Schulze, 2008; Saker et al., 2019). To better understand granular-flow behavior, it seems fundamental *to differentiate powder flow, as an observation, from powder flow quantification* related to the assessment method, also known as

flowability. Flowability is device-dependent, and describes the ability to flow in a desired manner in a specific piece of equipment (Prescott and Barnum, 2000; Saker et al., 2019). Different parameters or indexes can be obtained from the multiple flow testers available on the market. Each one of these devices "estimates/quantifies" flowability under specific mechanical conditions. Still, no one test will predict powder flow behavior in all the different mechanical situations encountered during processing and transport. In practice, whether in the laboratory or during the manufacturing process, from know-how or through measurements, the type of test method that describes the best flowability in a given application is chosen.

Densification, or compressibility, or compactness, is a flow property arising from the collective forces acting on the media. When energy is transferred into a granular material, the grains begin to reorganize themselves in a denser structure. This energy can be transmitted to the powder bed using uniaxial compression or vibration. Generally, during uniaxial compression, particles undergo elastic, plastic, or visco-elastic/visco-plastic deformation. Softer solicitations, such as vibrations, give rise to the geometric rearrangement of particles. Compaction by vibration can be divided by subjecting the granular system to harmonically driven motions (Saker et al., 2019) or to free-falls performances, commonly denoted as tapping (Yu and Hall, 1994).

Several studies focus on the densification of granular media because it covers many fields from pharmaceutics to Geotech industries (Rondet et al., 2017). As there is no universal mathematical model to predict flow behavior in every situation, the dynamics of compaction under vibration have been described by several empirical or heuristic models, mostly using glass beads (Knight et al., 1995; Head, 2000; Ribière et al., 2005; Yu and Hall, 1994). In this work, we will simply validate whether two of the most used models fit the dynamic behavior of two excipients, widely used in the pharmaceutical industry.

The first and the most famous model is the one proposed by Knigth et al. (1995) from the James Frank Institute at the University of Chicago (Knight et al., 1995):

$$\rho(N) = \rho_f - \frac{\Delta\rho}{1 + B\ln(1 + \frac{N}{\tau})} \tag{1}$$

where N is the number of taps, ρ_f is the final compactness, $\Delta\rho$ is the difference compared to the initial compactness of the bed, while the B and τ parameters are defined as a function of the acceleration, the control parameter.

The first term shows the rapid arrangement of the particles, while the second expresses that the steady state is reached asymptotically, logarithmic slow (Ribière et al., 2005). This also indicates that grains behave in a manner similar to glass (Head, 2000).

The densification of dry granular materials by tapping is often better fit by an empirical law developed by Kohlrausch-Williams-Watts (KWW model), (Yu and Hall, 1994):

$$\rho(N) = \rho_\infty - \Delta\rho \cdot \exp\left(-\left(\frac{N}{\tau}\right)^\beta\right) \tag{2}$$

where ρ_∞ is the compactness at the steady state, τ is the characteristic relaxation time describing

the arrangement of grains until the steady state is reached and β is the stretching exponent.

From a technological point of view, powder flow is essential to processing efficiency. The aim is to facilitate manufacturing, including flow through hoppers, sieving, pouring, blending, transport, filling, compaction and tableting, even if this rarely brings an added value to the end-use product.

The flowability of cohesive powders can be remarkably improved by the use of flow additives or glidants (Valverde, 2013). For several years, flow regulators have been systematically added to a significant number of formulated products, without any studies validating its function besides process feasibility. In the pharmaceutical industry, the use of glidants is mostly based on historical know-how or trial error methods, without any measurements of the effect on end-use properties (Majerová et al., 2016).

Amorphous silica powders (NP-SC) were introduced quite easily under the hypothesis that only crystalline silica is considered a toxic form at a micrometric scale. Nonetheless, some recent risk assessment studies carried outat the National Institute of Scientific Research in France (INRS) demonstrated the in-vitro cytotoxicity of amorphous silica, which is also highly incremented by reducing the size of the particles (Ricaud, 2007). Therefore, it is crucial to focus on the role of silica nanoparticles on the end-use properties of powders, especially on their flowability, to optimize the choice of additives, minimize their quantity, or to replace them. Nevertheless, to do so, it is essential to better understand how they interact within the formulations/media into which they are added.

Different flow regulator action mechanisms have been proposed in the literature. The first is related to a purely mechanical effect, and the second is related to interparticle forces. A mechanical effect will occur when surface additives allow particles to easily roll over one another, thus reducing friction (Duran Jacques, 1997). The physical mechanism by which interparticle adhesive forces are reduced is less exact, or at least not universal. When referring to interparticle forces, two mechanisms have been proposed. The first is related to surface chemistry changes, and the second concerns spacers among host particles (Quintanilla et al., 2006; Fulchini et al., 2017; Ruzaidi et al., 2017).

The aims of this work are (1) to obtain a deeper understanding of how granular compaction is related to flow behavior by confronting different compaction tests, thus pointing out a standard physical parameter: the specific energy supplied to the powder bed; (2) to study the effect of glidants and environmental moisture conditions on flowability.

To illustrate these aims, granular compaction was performed using two compaction devices: the well-known DensiTap® and the FT4 compression module. Measurements were carried out in the elastic domain, using two pharmaceutical excipients, lactose and microcrystalline cellulose. Several different types of precipitated nano-silica were used as surface additives, differentiated by their hydrophilicity and size distribution. Powder flowability was determined, or classified, according to the Hausner ratio (HR), a widely used index in the industry (Saker et al., 2019).

2 Materials and methods

2.1 Powder Materials

Excipients as host powders

For this study, two well-known pharmaceutical ingredients with excellent compactibility were chosen: Avicel® PH-102 and RetaLac® . Avicel® PH-102 is a high purity microcrystalline cellulose produced by FMC Biopolymer© (United States), generally used in the pharmaceutical industry to tableting by direct compression. The RetaLac® is a co-processed hypromellose/lactose-based excipient produced by MEGGLE (Germany), composed of equal parts of a K-type hypromellose polymer and α-lactose monohydrate. RetaLac® excipient is specifically designed for direct compression and dry granulation of modified release formulations.

Nanoparticles as flow regulators

The SIPERNAT® brand from Evonik (Germany) was chosen for flow regulation in bulk powders. SIPERNATs are highly porous colloidal silicon dioxide powders produced by precipitation from an aqueous solution. From the large panel of SIPERNAT® NPs, two with hydrophobic properties, D10 and D17, and two hydrophilics, 50 S and 500 LS, were chosen. Both D10 and D17 are rendered hydrophobic by a chemical surface treatment. D10 is used in a wide variety of defoamer while D17 primary application is as an anticaking agent in fire extinguishing powders. 50 S and 500 LS products are high absorption capacity carriers, able to absorb liquids up to three times of their own mass. The 50 S is normally used in plant formulations, such as wettable powders and water-dispersible granules. The 500 LS is recommended as a viscosity modifier in liquid systems and flow aid and anti-caking agents for fine powders.

Sample conditioning

All samples were conditioned and maintained at room temperature, inside sealed containers controlled by saturated salt/water solutions to control relative humidity at 20% (Magnesium chloride - $MgCl_2$) and 60% (Sodium Chloride - NaCl). Samples equilibrate until they reached the environment conditions, validated by daily water activity, a_w, measurements using an Aqualab 4TE from METER® .

To study the surface additives' influence on flowability, bulk powders were weighed with 0.5 and 2% w/w for each flow regulator and blended in a 3D shaker mixer Turbula® T2F from the WAB group for 20 minutes. It should be noted that no differences in flowability assessment were obtained when the mixing time increased from 10 to 60 minutes. Once the mixtures were made, samples were conditioned and maintained at room temperature, inside sealed containers controlled by saturated salt/water solutions as described above.

2.2 Physical characterization techniques of powders

Particle size distributions were measured by laser diffraction in liquid media with a Mastersizer 2000 from Malvern Instruments. Ethanol was used in order to improve particle dispersion and to avoid dissolution. All samples were analyzed in triplicate to ensure reproducibility, with an

instrument uncertainty of 1 [μm].
Particle morphology analyses were assessed with a JSM T330A Scanning Electron Microscopy (SEM) from JEOL, and a field emission gun operating at 5 kV. Before analysis, samples were placed onto doubled-sided adhesive and coated with Gold-Palladium mixtures for 6 minutes using an Ion SPUTTER JFC-1100 under an air purge. Particles/glidants mixtures were analyzed with a Field Emission SEM from ZEISS Merlin Compact with the proven GEMINI I electron column. Samples were placed onto carbon conductive tape and coated with about 20 nm of carbon. EDS analyses were performed with a QUANTAX-XFlash6 detector with a peak resolution of 129eV, from Bruker. EDS was performed to confirm the presence of colloidal silicas on the surface of host powders.

Water sorption isotherms were performed at 20°C in 3 Flex from Micromeritics. Before scanning, samples were vacuum dried for ten hours at 15° C. The true density analysisof powder was performed in an AccuPyc 1330 Helium pycnometer from Micromeritics. All data measurements are the average of ten measurements obtained from one powder sample.

2.3 Granular compaction devices

Vibration, free surface conditions

To determine flowability from tapped density measurements, different methods and devices can be used. The most used, described on the United States Pharmacopoeia, suggests freely pouring a test sample weight of 100 g in a 250 mL volumetric cylinder as shown in Fig. 1. The protocol consists of measuring the unsettled apparent volume, V_0, and carrying out 10, 500, and 1250 taps on the same powder sample and reading the corresponding volumes to the nearest graduated unit. If the difference between V_{500} and V_{1250} is less than or equal to 2 mL, V_{1250} is the tapped volume. If the difference between V_{500} and V_{1250} exceeds 2 mL, repeat in increments of V_{1250}, until the difference between succeeding measurements is less than or equal to 2 mL (Pharmacopeia, 2015).

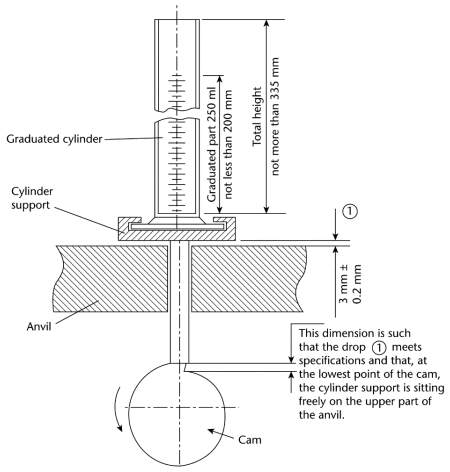


Figure 1: Apparatus description from Pharmacopeia (2015).

In this study, DensiTap® from Granuloshop© was used for measuring bulk density with a graduated

glass cylinder of 250 mL. In this device, the tapping action is provided, under zero shear conditions, by a rotating cam that raises the cylinder platform through a fixed distance of 3 mm at a nominal rate of 250 drops per minute. About 150 mL of powder was freely poured using a funnel into the vessel allowing the aerated density to be determined. It should be noted that it is impossible to fit 100 g of Avicel® PH-102 or RetaLac® in a 250 mL container; this is similar for a wide range of pharmaceutical excipients.

Several authors suggest that flow behavior analysis using tapped density data is strongly affected by the highly irreproducible initial pouring of the powder. As described in previous works, Saker et al. (2019), we found a highly reproducible initial state when controlling powder moisture conditioning. Thus, the data error was determined by considering systematic and random errors, and to do so, each experiment was repeated 3 times.

Uniaxial compaction, packed bed conditions

Compressibility studies in packed bed conditions were performed using an FT4 powder rheometer from Freeman Technology© . The samples were poured into a borosilicate split vessel. The test started with a mechanical conditioning step by establishing uniform stress in the powder bed (Fig. 2, left). When the conditioning cycle is over, the vessel splits allowing a precise volume of 10 mL to be attained. The analysis was achieved by applying increasing levels of force directly onto the granular media with a vented piston, allowing the trapped air within the powder to escape, and by measuring volume changes depending on the applied load (Fig. 2, right).

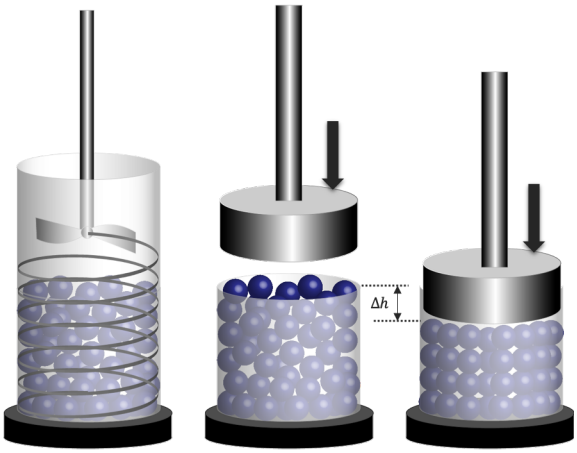
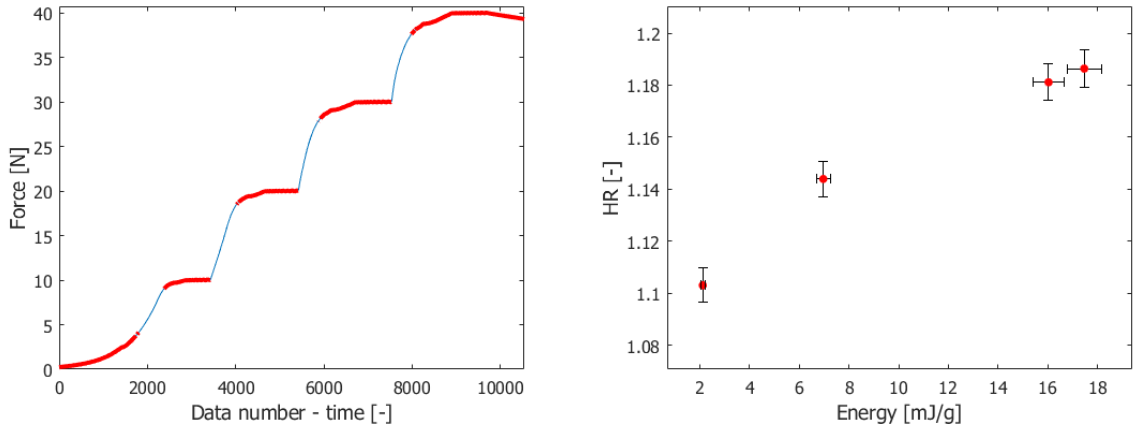


Figure 2: FT4 rheometer compressibility test, from conditioning to compaction.

During the test, the changes in volume for a given applied normal stress were collected. In order to determine the specific energy supplied to the granular media an external data treatment must be carried out. In fact, FT4 software determines the energy supplied to the powder by using a trapezoidal numerical integration. Nevertheless, this data treatment lacks of physical meaning as it integrates all height changes, even the non-drecreasing ones. As the height sensor is extremely sensitive, the energy provided to the system is calculated as time-dependent and so, aberrant values can be obtained. In order to give a mechanical sense to the experimental data, the specific energy supplied to the system was determined with Matlab® by discretizing the normal stress

values as function of the packed bed height evolution. To do so, it is necessary to identify the areas where the normal stress is kept constant by the derivative of force with respect to time (Fig. 3.a in red). Then, to determine an average force, and to be able to relate it to displacement values, we selected around 20 data values in the red zone, where non-evolution was found. Finally, each setpoint gave rise to a specific energy value which is related to HR as shown in Fig. 3b.



(a) Force steps identification

(b) HR in function of the applied energy

Figure 3: Example of FT4 compaction test data treatment. Applied normal stress increments of 10 N until 40 N.

To allow a better comparison between the devices, their characteristics and operating conditions are summarized in Table 1. It should be noted that powder humidity conditioning and control allowed us to obtain a highly reproducible initial state, regardless of the device. This argument allowed us to validate the use of HR as a flow behavior index, others could be used (Carr, Void ratio).

Table 1: Device characteristics

Characteristics/Device	Densitap	FT4
Compaction by	vibration: Free falls	Normal stress
Particles reorganization	Free surface	Packed bed
Scanning	Number of taps	Force [N]
Quantity of powder [mL]	150	10
Vessel material	borosilicate glass	borosilicate glass
Applied Force [N]	215	0 - 40
Vessel dimensions [mm] (diameter/height)	26/300	25/30

3 Results & Discussion

3.1 Physical characterization

The particle size distribution analysis, summarized in Table 2, shows that Avicel PH-102 particles are bigger than Retalac. From the SEM images, scale bar of 100 μm and 500 μm, Avicel® PH-102 particles exhibit an isometric rod shape with a rough surface (Fig. 4), while Retalac® seems to be composed of agglomerates of amorphous-like particles (Fig. 5). Absorption/Desorption isotherms showed that both excipients are hydrophilic and absorb water at low moisture content (Fig. 6). Samples' sorption behavior analyses determined our moisture conditioning choice, 20 and 60% RH.

Table 2: Excipients as host particles

Powder	Particle size distribution ± 1 [μm]					Behavior towards water **
	d_{10}	d_{50}	d_{90}	d_{32}	d_{43}	
Avicel® PH-102	29	104	248	40	126	Hydrophilic
RetaLac®	89	203	408	159	229	Hydrophilic

Some of the physical characteristics of the silica nanoparticles are shown in Table 3. Supplier size specifications describe micro-size particles/aggregates using laser diffraction. The European Commission proposes that materials can be classified as nanomaterials (NM) if their volume-specific surface area, VSSA, is larger than 60 m^2/cm^3 (Rauscher et al., 2019). Thus, according to the VSSA estimations, SIPERNATs D10, D17, 50S and 500LS can be considered as NMs.

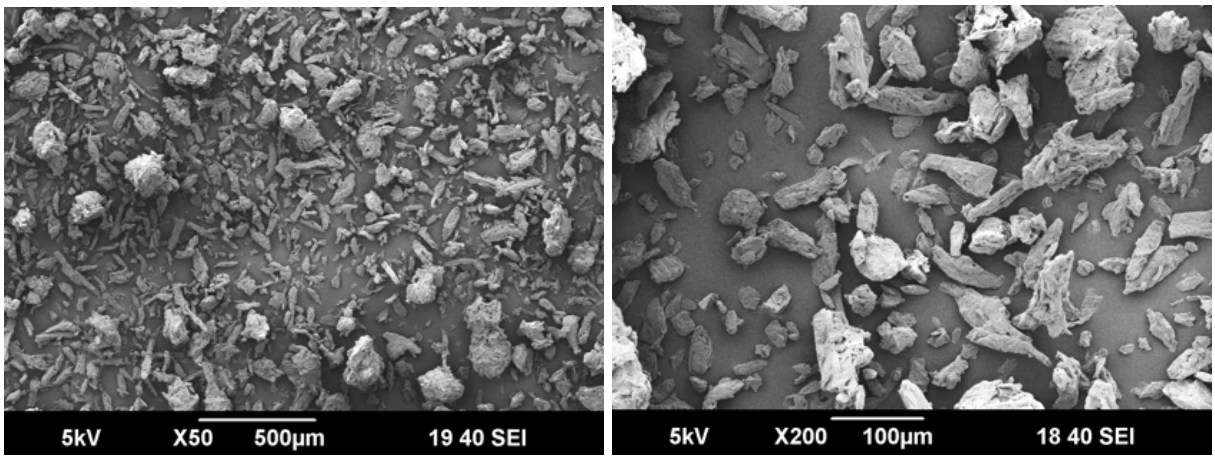


Figure 4: SEM micrographs of Avicel® PH-102, at different magnifications.

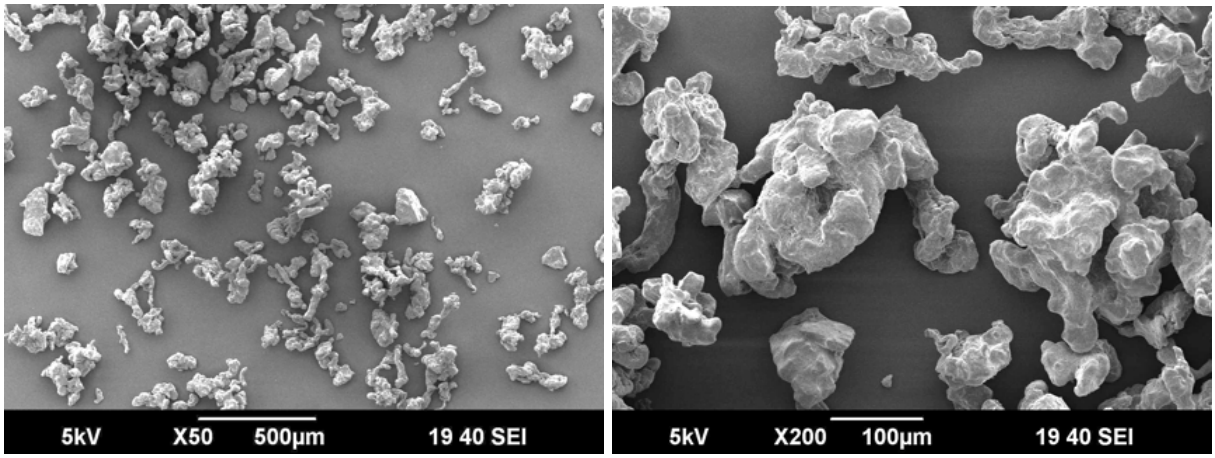


Figure 5: SEM micrographs of RetaLac® , at different magnifications.

Table 3: Physical characteristics of silica nanoparticles

SIPERNAT	Particle size distribution			BET ** $[m^2/g]$	VSSA* $[m^2/cm^3]$	Behavior towards water **
	d_{50}**	d_{50}*	d_{32}*			
D10	6.5	7	7	90	178	Hydrophobic
D17	10	8	6	100	201	Hydrophobic
50 S	18	16	14	500	1060	Hydrophilic
500 LS	10.5	14	12	450	968	Hydrophilic

** Evonik data, * our data, both in [μm]

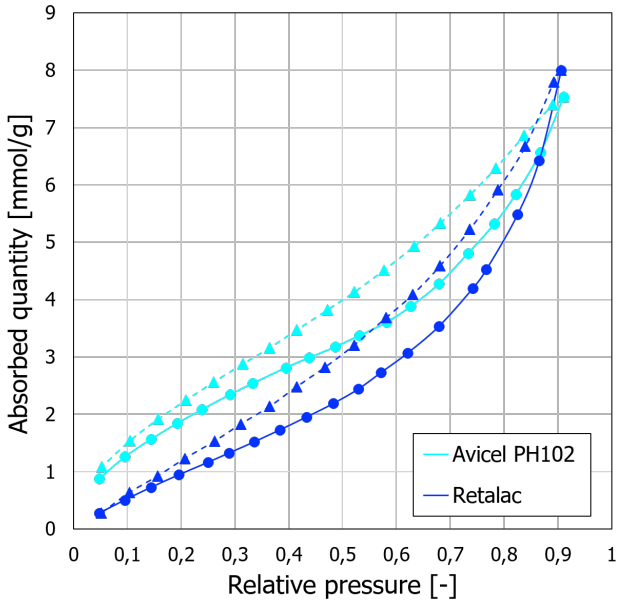


Figure 6: Water sorption isotherms of Avicel® PH 102 (cyan) and Retalac® (blue), at 20°C. Sorption curves are represented with a solid line, and desorption curves with a dashed line.

3.2 Dynamics of compaction under free surface conditions

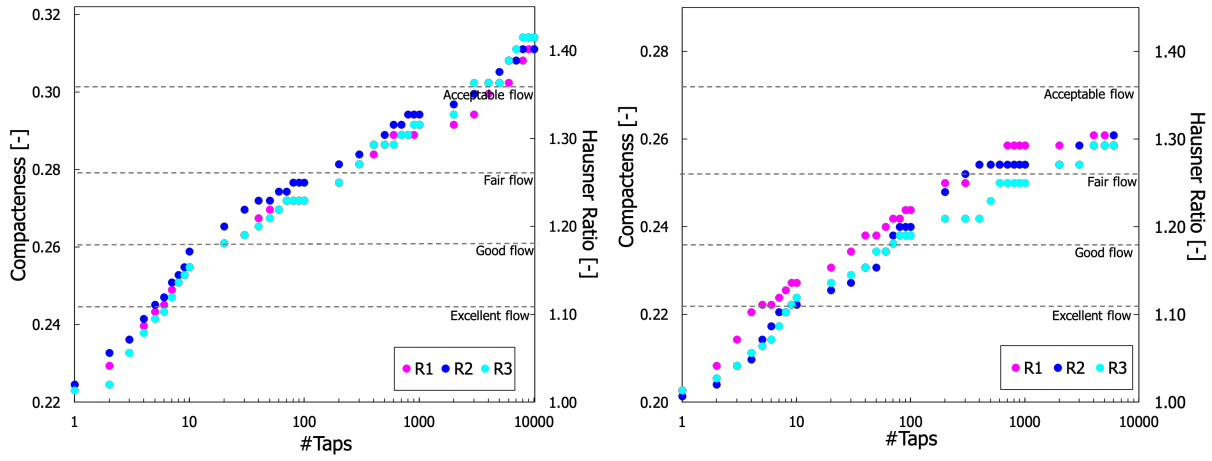
The evolution of powders compactness during vibration according to the number of taps is presented in figure 7. As expected, poorly flowing powders, such as Avicel® PH-102, are more compressible. Also, the repeatability from 3 experiments showed a larger random error using Retalac® , despite the conditioning (Fig. 7).

It is common use in scientific literature to determine tapped density systematically after 500 taps, as the number of taps suitable to reach the steady state (Traina et al., 2013). For Avicel® PH-102 at 500 taps, the powder bed had not reached its maximal compaction state and so, the HR value obtained at this state (or time) is significantly different from the one obtained after 10 000 taps (Fig. 7.a). Using HR_{500} Avicel® PH-102 flowability is classified as "Acceptable", while at 10 000 taps is classified as "Cohesive", which is consistent with its flow behavior observed with the naked eye. In difference, for RetaLac® samples, there is not a significative evolution of the powder compactness after 500 taps (Fig. 7.b).

It should be noted that both samples exhibit an easily reproducible initial state regardless the moisture content. Moreover, the moisture content at 20% or 60% RH has no influence on samples compaction when using Densitap as a flow tester (Fig. 8).

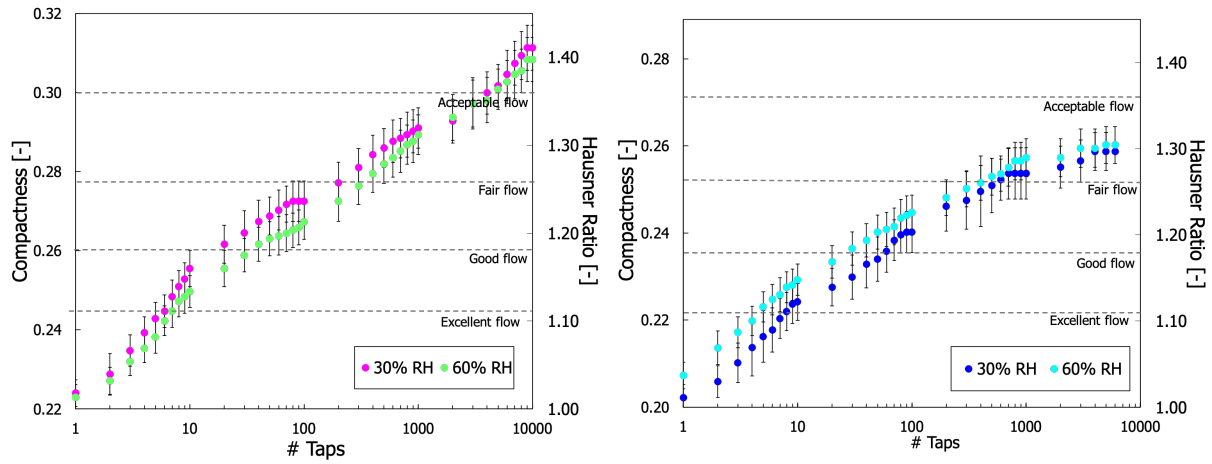
Modeling

The mathematical model describing the dynamic of compaction showed a similar fit for the Chicago and the KWW model with, in both cases, at least a 97% prediction interval (Figs. 9 and 10). The limitation of the Chicago model lies in the fact that it does not fit the experimental data when



(a) Avicel® PH-102 (b) RetaLac®

Figure 7: Study of the dynamic of compaction in DensiTap® samples conditioned at 20% RH.

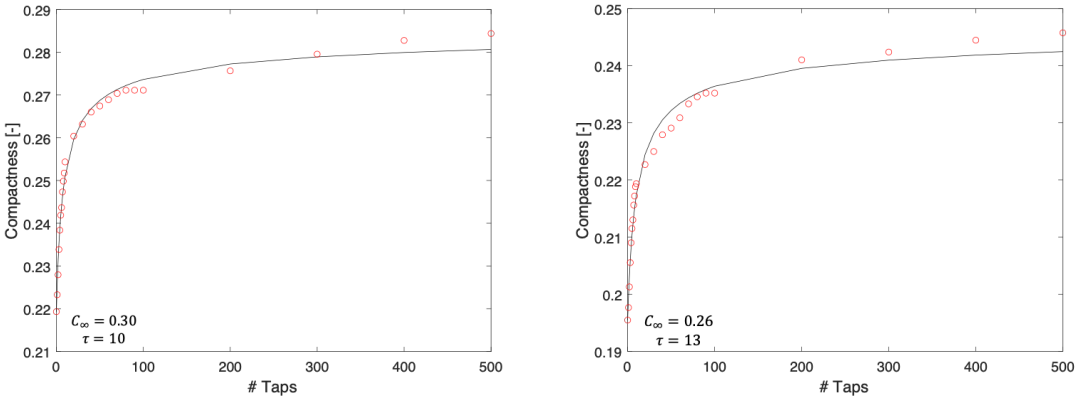


(a) Avicel® PH-102 (b) RetaLac®

Figure 8: Dynamic of compaction as function of the powder moisture content using DensiTap®

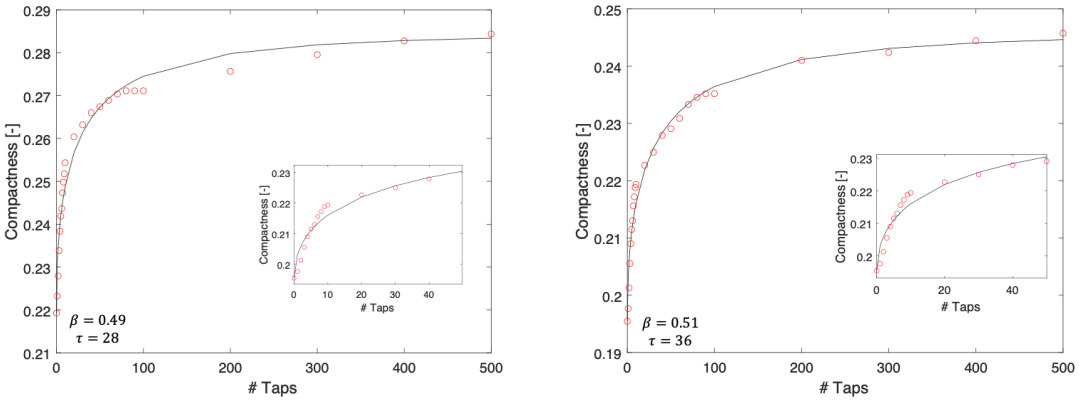
approaching the stationary state (Fig. 9). Thus, it fails to predict the number of taps needed to reach the steady state, τ. For exemple, for Avicel® PH-102 the predicted number of taps needed to reach the steady state was around 100 000 taps while experimentally, only 8 000 taps are required. Nevertheless, the ρ_∞ parameter obtained from the model is predicted fairly accurately. For ex ample for Avicel® PH-102 $\rho_\infty = 0.29 \pm 0.01$, while experimental data showed a $\rho_\infty = 0.31 \pm 0.01$.

In the KWW model, ρ_f is used as a minimization parameter better fitting the experimental data when reaching the steady state. In this case, the value of τ-parameter, seems to be more representative of the progressive arrangement of grains. Nonetheless, a slight deviation from the model is detected for the first 40 taps (Fig. 10). Similar results were obtained for the samples conditioned at 60% RH.



(a) Avicel® PH-102 (b) RetaLac®

Figure 9: Chicago Model obtained from iterative minimization using DensiTap data (500 taps). Samples conditioned at 20% RH.



(a) Avicel® PH-102 - 500 taps (b) RetaLac® - 500 taps

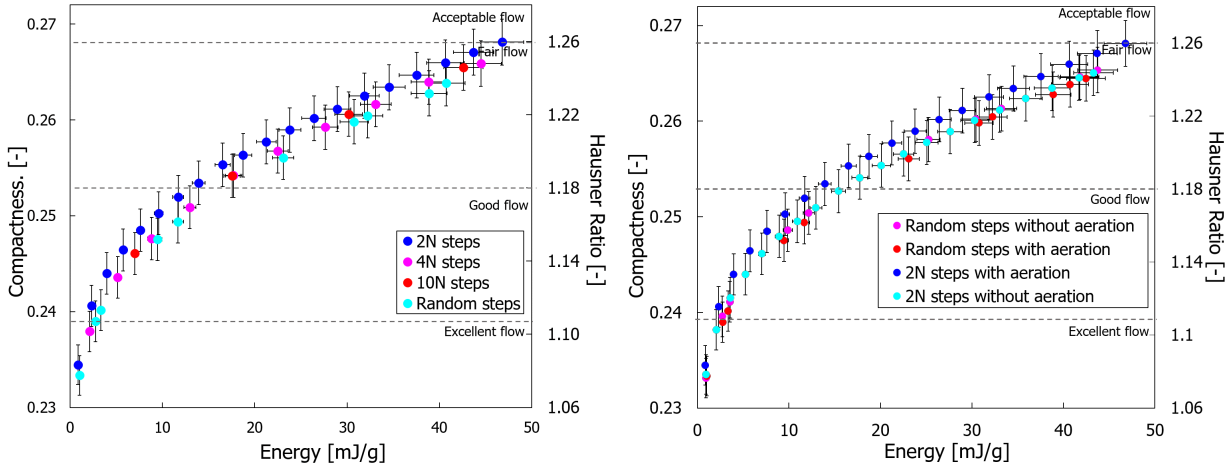
Figure 10: KWW model obtained from iterative minimization using DensiTap data (500 taps). Samples conditioned at 20% RH.

The mathematical model describing the dynamic of compaction showed a similar fit for the Chicago and the KWW model with, in both cases, at least a 97% prediction interval (Figs. 9 and 10). Rondet et al. (2017) compared different densification models highlighting that the KWW equation ensures the best mathematical fitting of the experimental data using R^2 as a fit parameter. This statement is accurate for powders such as Kaolin and Calcium phosphate. Nonetheless, when they analyzed unsaturated microcrystalline cellulose, the authors found a better agreement between the KWW and Chicago model, which agrees with our results. Differences can also arise from the use of R^2, as an inadequate parameter to determine the goodness of fit for nonlinear models.

3.3 From compressibility to flowability, an energetic approach

In this section, we study flowability from compressibility as a function of the consolidation strength. To do so, each applied load gives rise to a steady compaction state that can be related to the HR value. In order to study the energy impact, we tested four different ramps of force from 2 to 40N. Some of the results are shown in figure 11.a using Avicel® PH-102 conditioned at 60% RH. As shown in the figure, powder compactness and flowability evolve exponentially with the specific energy supplied to the powder bed.

Compressibility is surprisingly independent of the force ramp step, meaning that the powder's previous mechanical history does not influence its compaction behavior. We always obtained the same compaction state for a given energy, indifferent to previous loads. To deepen such a statement, we decided to study the influence of the conditioning step, which intends to provide a reproducible initial state by subjecting the samples to the same mechanical treatment, acting as an aeration phase. Two force ramps were tested with and without the conditioning step. Results in figure 11.b showed no significant difference between the samples subjected to mechanical conditioning and the simple act of freely pouring the powder. In this case, compressibility, and so flowability, seemed to only be affected by the maximal load supplied to the granular media.



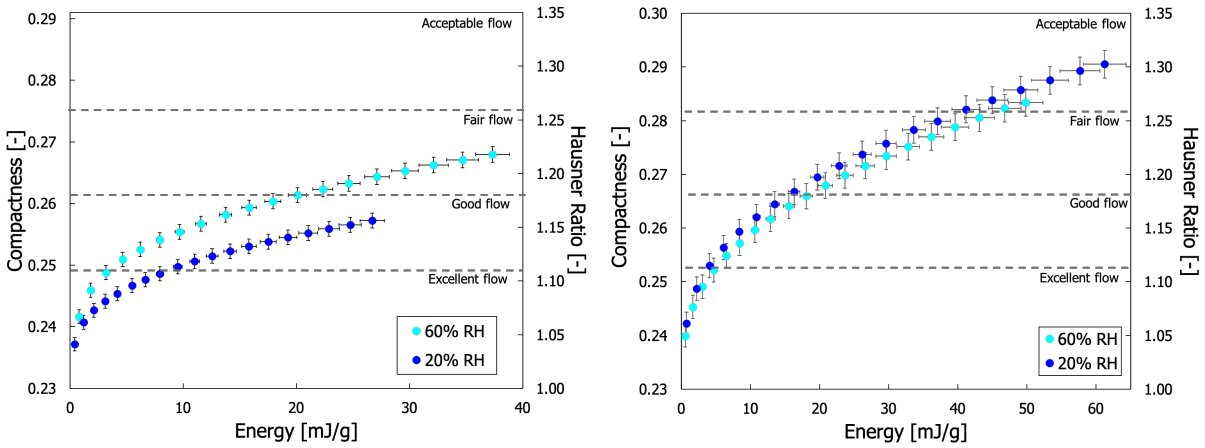
(a) With aeration step

(b) Without aeration step

Figure 11: FT4 compaction test at different force ramps with Avicel® PH-102 at 60% RH.

The effect of moisture content on compactness, and so on flowability, is presented in Figure 12. For Avicel® PH-102, the sample conditioned at 20% RH had a better flowability than the one conditioned at 60% RH, despite the specific energy supplied to the media (12.a). It is well-known that the moisture content in granular media favors the formation of liquid bridges, thus increasing particle cohesion and decreasing flowability. Notwithstanding, for Retalac, moisture content seems to not have any influence on its flowability.

Avicel® PH-102 results are in contradiction with those obtained with DensiTap® (Fig. 8.a). Unlike Densitap, the compression test allows a good differentiation of the two environmental conditionings. The strength of the applied load could explain this. Densitap® transfer a force of about 215 N to the granular media, while in FT4 experiments the maximal load is about 40 N. At low applied forces,



(a) Avicel® PH-102 (b) Retalac®

Figure 12: Compactness and flowability assessment as a function of the specific energy supplied to the system. Samples conditioned at 20% and 60% RH.

like those provided by the FT4 compaction cell, some granular materials, more precisely cohesive powders, such as Avicel® PH-102, will not reach a high compaction state (Fig. 13). For example, in this case, using FT4 and Densitap, the flowability could be described as *Good* to *Fair*, with Fair being more appropriate for the real flow behavior of the powder. On the contrary, Retalac® samples can be classified as having an *Acceptable flow*, regardless of the device. In summary, FT4 results describe flowability during uniaxial compression at low consolidation strength, and so, powder flow properties could differ for higher consolidation stress as shown in figure 13. The energetic approach allows us to understand the differences, or similarities, in flowability assessment when comparing devices.

3.4 Colloidal silicas as glidants

Both host powders were weighed with 0.5 and 2% w/w of SIPERNAT® 50S, 500LS, D10 and D17 (Figs. 14 and 15). For binary Retalac mixtures conditioned at 20% RH, all the configurations studied, in terms of the type of glidant and concentration, significantly improved powder flowability (Fig. 14.a). In contrast, no statistically significant differences were obtained between flow regulators. The increase in moisture content of binary mixtures at 60% RH showed similar results (Fig. 14.b). In the case of Avicel® PH-102, the four NPs used in our study, D10, D17, 50S and 500LS, significantly improved the flowability of the host particles regardless of the moisture content (Figs. 15 and 16). Firstly, no statistically significant differences between NPs with the same behavior towards water were found (Fig. 15.a). Secondly, no differences were obtained when increasing the amount of NPs added to the host particles, independent of its hydrophilic nature (Fig. 15.b).

In summary, the effect of adding 0.5% w/w of SIPERNAT® D10 or 500 LS, on Avicel® PH-102 flowability at different moisture conditions is presented in figure 16. In this case, despite the moisture content, both glidants, D10 and 500LS, improved significantly the flowability of the

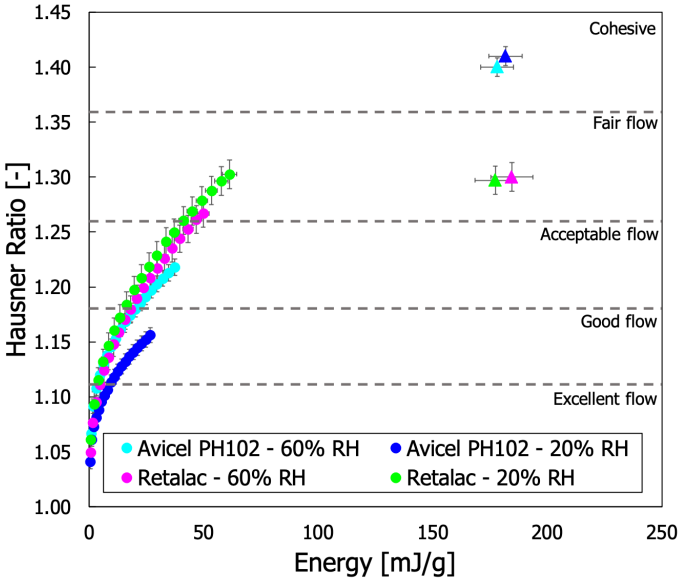
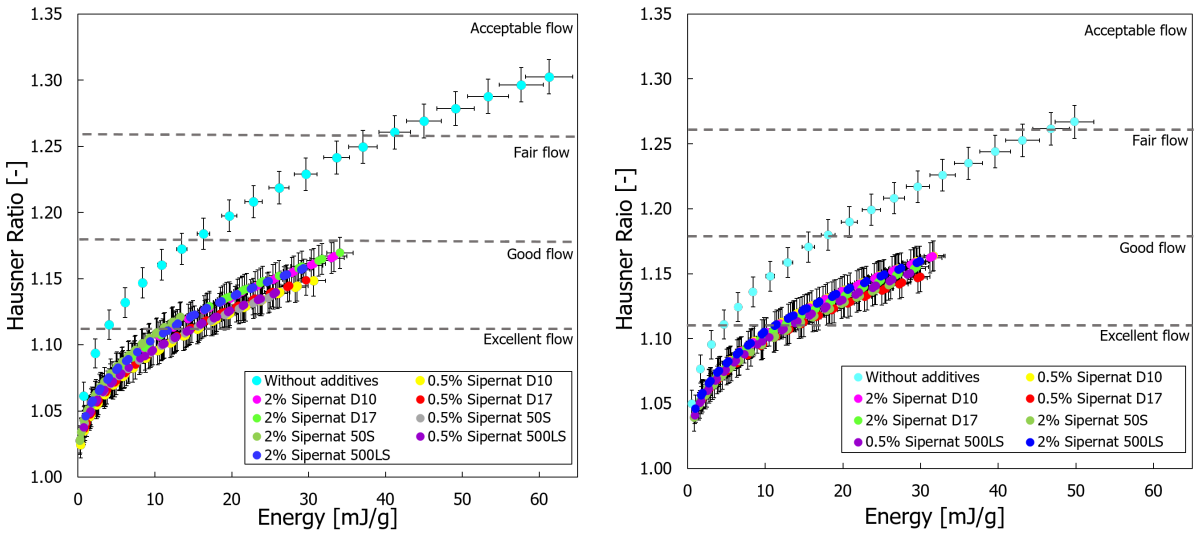


Figure 13: Flowability assessment as function of the specific energy supplied to the granular media using FT4 (circles) and Densitap (triangles) devices.

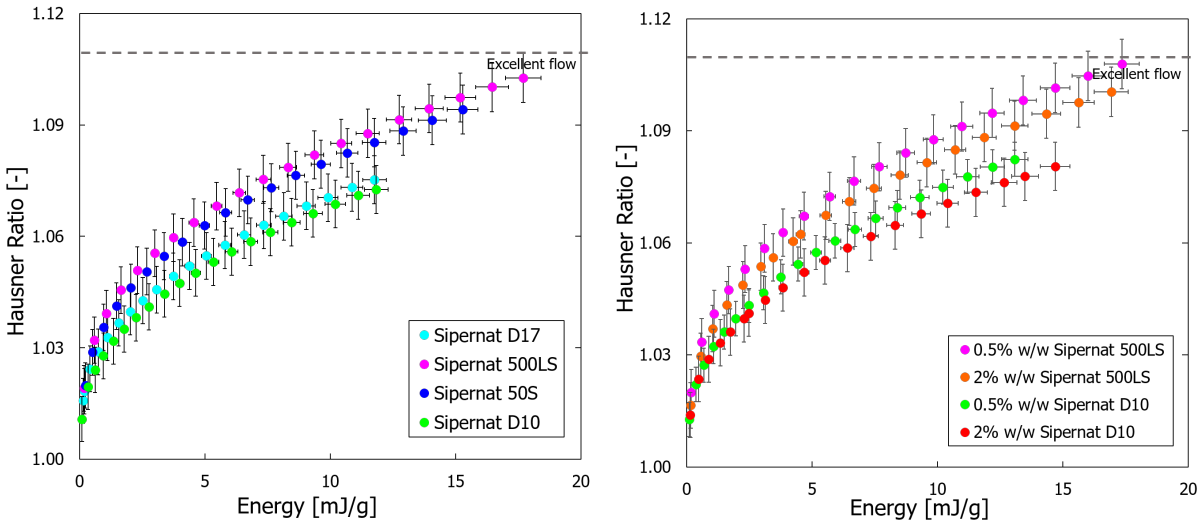


(a) conditioned at 20% RH

(b) conditioned at 60% RH

Figure 14: Flow influence of NPs for RetaLac® using FT4. Force ramp from 0 to 40 N using a 2 N step.

excipient, with a better performance of the hydrophobic one, D10. Similar results were obtain by Müller et al. (2008). In their work, the authors observed, using binary mixtures of corn starch, that hydrophobic flow regulators reduce cohesive forces to a greater extent than hydrophilic ones. Ruzaidi et al. (2017) also showed that hydrophobic nano-silica improved ibuprofen's flowability slightly more than the hydrophilic one. In comparison, Zimmermann et al. (2004) did not find any



(a) conditioned at 20% RH - 0.5% w/w

(b) conditioned at 60% RH

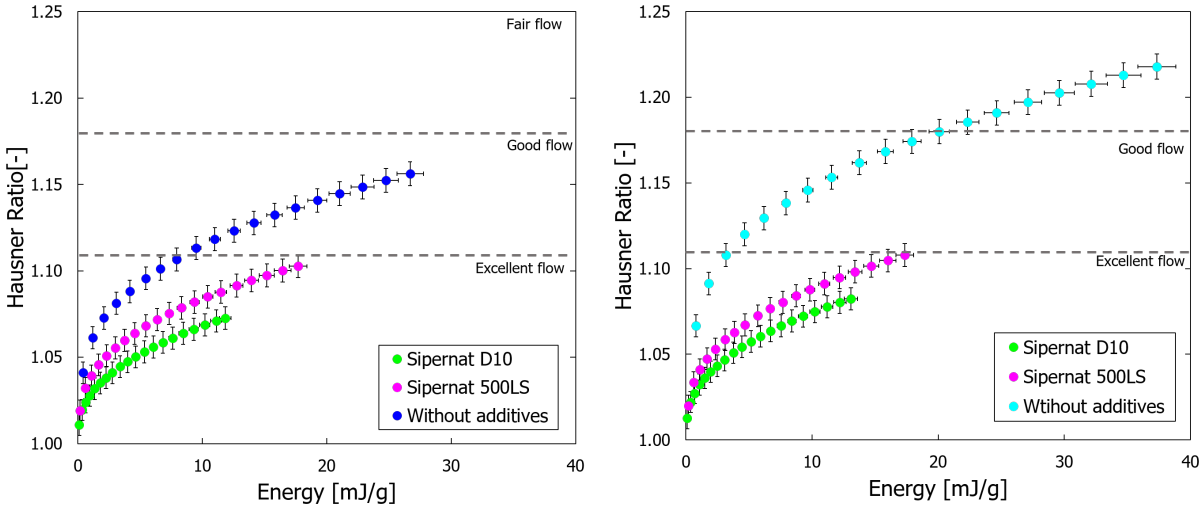
Figure 15: Flowability influence of NPs for Avicel® PH-102 using FT4. Force ramp from 0 to 40N using a 2N step.

direct correlation between the hydrophilicity of the nanomaterials (fumed nano-silica, Aerosils®) and their ability to reduce the tensile strength of powder mixtures with corn starch.

Several hypotheses could explain this behavior. The first one is related to surface chemistry changes. As Avicel® PH-102 is highly hydrophilic, its surface modification may reduce the liquid bridge formation during moisture conditioning. The second one is related to the size of the additives. Kojima and Elliott (2012), using binary mixtures of polymer powder with Aerosils® , showed that the smaller the size of the colloidal silica and their aggregates, the more effectively they worked as lubricants, thus reducing internal friction. Similar results were obtained by Müller et al. (2008), who worked with binary mixtures at 0.2% w/w. Nonetheless, in our case, when comparing SIPERNAT® 50S to 500LS or SIPERNAT® D17 to D10, which are only differentiated by a grinding step, no improvements on flowability were observed.

To get a better look at these results, the SEM analysis of Avicel® PH-102 when adding 0.5% w/w of NPs is shown in figures 17, 18, 19 and 20. From SEM micrographs, it is possible to note that the VSSA values are not representative of the NM's size. Hydrophobic NPs (Figs. 19 and 20), with a smaller VSSA value, gave rise to smaller aggregates than the hydrophilic ones (Figs. 17 and 18). Bulk powder mixture with hydrophilic additives showed large aggregates/agglomerates (200 nm) adsorbed on the surface of the Avicel® PH-102 particles. In difference, Zimmermann et al. (2004) never found large agglomerates of fumed nano-silica adsorbed on the surface of the corn starch particles.

It should be expected that the particle/glidant bond strength influences the flow regulating potency of the NPs. The chemical treatment undergone to produce hydrophobic NPs decreases the number of hydrogen bonds. The lack of additional hydrogen bonds generates aggregates/agglomerates with an inferior bond strength, and so deaglomerate easily, thus giving rise to smaller aggregates.



(a) Moisture conditioning 20% RH

(b) Moisture conditioning 60% RH

Figure 16: Influence of Sipernats D10 and 500 LS in the flowability of Avicel® PH-102. Mixtures prepared with 0.5% w/w of S-NPs and conditioned in different moisture environments.

This statement was validated in our study comparing figures 18 and 19. The smaller the NP aggregates the better the surface coverage.

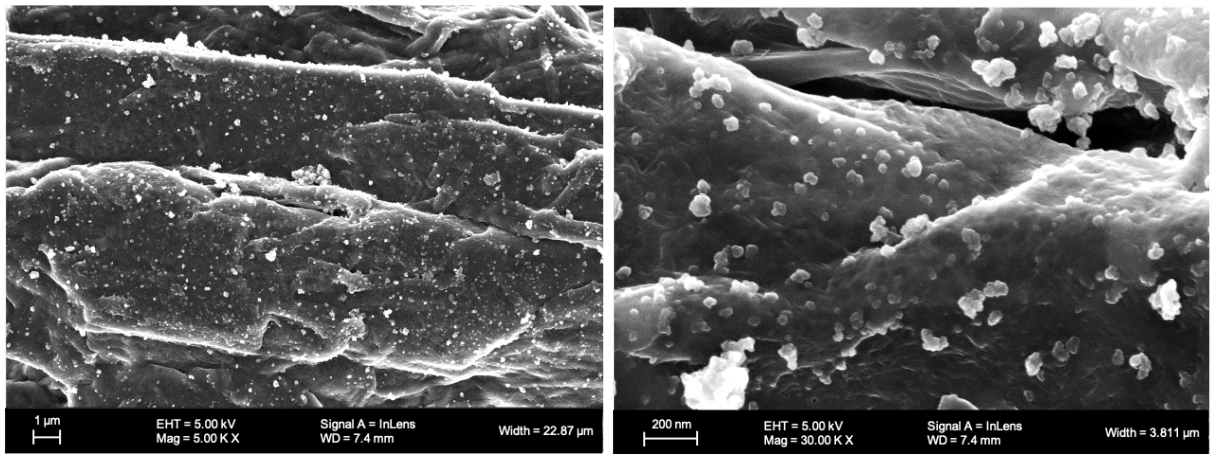


Figure 17: SEM micrographs of Avicel® PH-102 with 0.5% w/w of 50S, conditioned at 20% RH.

The flow regulating potency of the nano-additives also depends on the interparticle contacts: particle-to-particle, particle-to-silica, or silica-to-silica. This statement is related to the amount of NPs added to the mixtures using a relatively simple mathematical analysis (spherical monodisperse nanoparticles with random packing) like the one described by Valverde et al. (1998). In our case, we estimated that when adding 0.5 or 2% w/w of colloidal silica, the interaction between the grains is governed by silica-to-silica interactions. This rather rough estimation supports our results and could explain why no differences were found when increasing the amount of NPs added to the

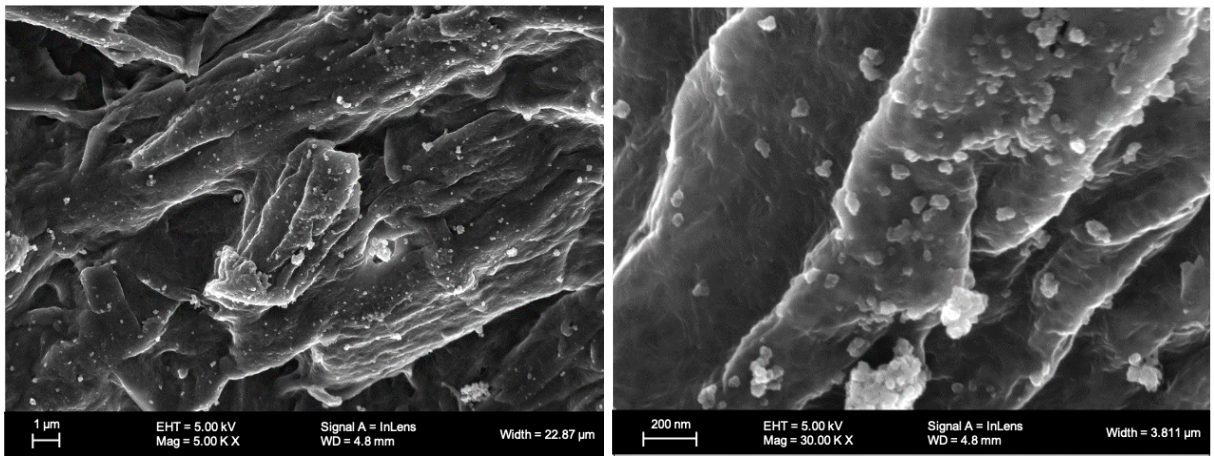


Figure 18: SEM micrographs of Avicel® PH-102 with 0,5% w/w of 500 LS, conditioned at 20% RH.

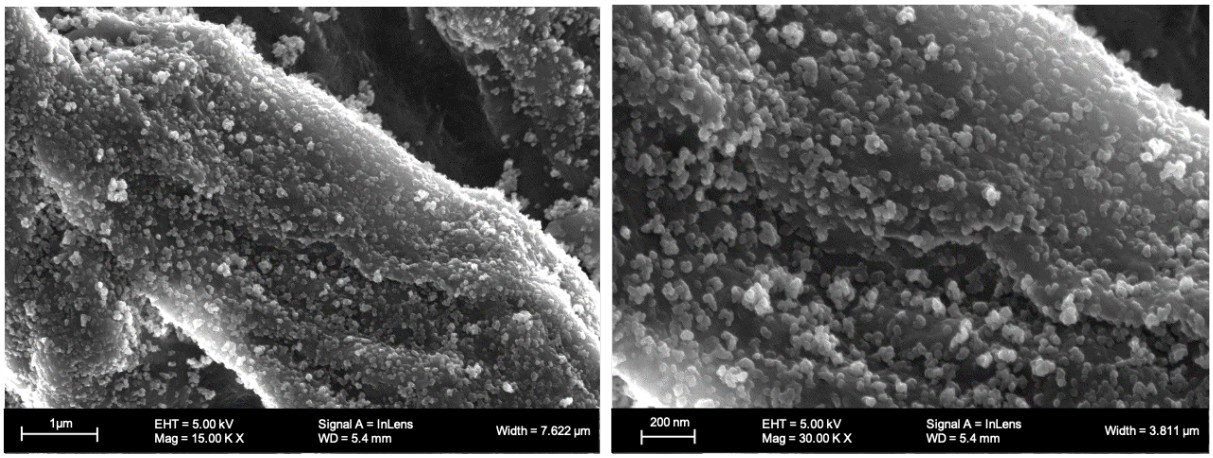


Figure 19: SEM micrographs of Avicel® PH-102 with 0,5% w/w of D10, conditioned at 20% RH.

mixtures, independently of their hydrophilicity (Figs. 15 and 16). All this somewhat rejects the assumption that the silica adsorbates lead to a flatter surface. Moreover, the change in the mixtures' surface chemistry, related to the glidants' hydrophilicity, improved flowability similarly, regardless of the moisture conditioning environment of the samples (Figs. 15 and 16). The mathematical approach also suggests that to cover the surface with 0.5% w/w, the adsorbates should measure 300 nm. Nonetheless, Fig. 19 shows that binary mixtures with SIPERNAT® D10 generated a high coverage of particles with monodisperse fine adsorbates of around 50 nm.

When possible, surface coverage was also estimated using SEM micrographs using ImageJ software (Table 4). The number of adsorbates was determined in different regions of Avicel's surface of binary mixtures. For hydrophobic adsorbates, we obtained about 17% coverage for SIPERNAT® D17 and, at least, 80% for SIPERNAT® D10. For hydrophilic silica additives, a smaller surface area of the host particle was covered, from 6 to 16% for SIPERNAT® 500 LS and 50S, respectively. Even if this image analysis lacks statistical significance, it shows, and corroborates, that smaller

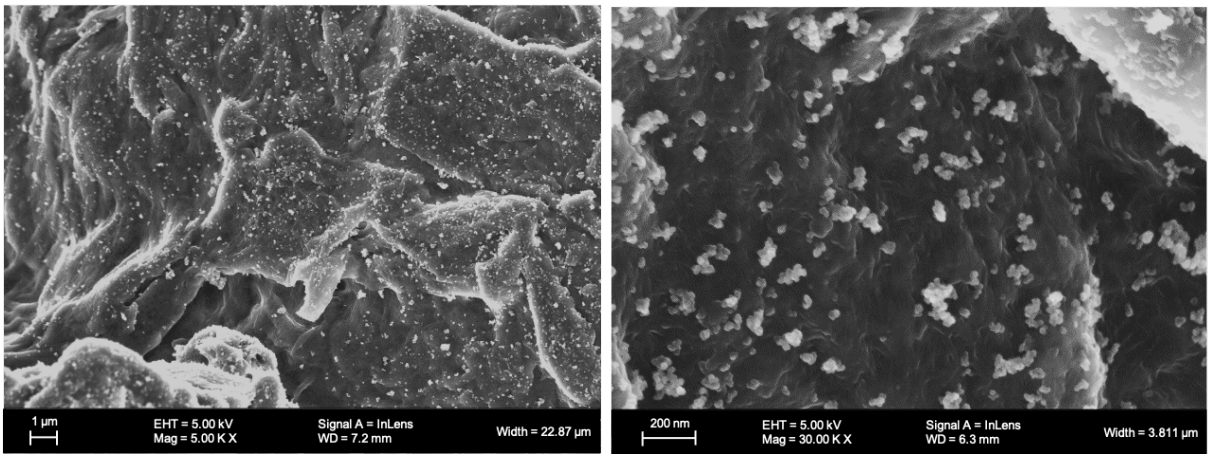


Figure 20: SEM micrographs of Avicel® PH-102 with 0,5% w/w of D17, conditioned at 20% RH.

adsorbates give rise to a better surface coverage, despite its hydrophilicity. It also highlights similar surface coverages with SIPERNAT® 50S and D17 binary mixtures, with a few bigger aggregates for 50S. Interestingly, although SIPERNAT® D10 produced a higher surface coverage, almost total (Fig. 19), flowability enhancement was obtained at lower surface coverages, similarly to when using SIPERNAT® D17.

In the literature, different surface coverage mass ratios, w/w, are proposed to improve flowability.Fulchini et al. (2017) found an optimum surface area coverage of around 20% w/w for mixtures of glass beads made cohesive by silanization. In their case, higher surface area coverages decreased flowability. According to Ruzaidi et al. (2017), for host particles with a mean diameter of 60 μm, the required amount of NPs to improve the powders' flowability is between 0.5 and 1% w/w. From our results, we can conclude that powder flowability improvement by glidants seems to be related to both of the following: nano-silica aggregate size distribution (obtained after mixing) and surface area coverage. We propose to define the amount of NPs to add to powder formulations in terms of surface coverage and not through mass ratios (w/w). A good example is proposed by Zhu et al. (2017). The authors determined by modeling the optimal size of nano additives and the minimal surface area coverage for binary mixtures of zeolite fine powder and nano-silica. It was suggested that, in order to reduce cohesiveness and to improve flowability, zeolite particles (0.5 - 50 μm) should be covered with about 1% of 10 nm-additives.

Table 4: ImageJ software Analysis of SEM micrographs of Avicel® PH-102 surface in binary mixtures of 0.5% (w/w).

SIPERNAT®	Surface [μm^2]	Number of adsorbates [-]	Size of adsorbates [nm]	Coverage [%]
50 S	11	256	18 to 532	16
500 LS*	3.8	57	27 - 236	6
D17	9	214	17 to 316	17
D10 **			≤ 100	≥ 80

* low contrast ** naked eye

4 Conclusions

We have developed an experimental approach based on the energy supplied to powders during compaction under zero shear conditions. In these studies, we measured granular densification (bed height changes) as a function of the force applied to the system. Compaction is achieved during vertical tapping using Densitap and by subjecting the samples to low levels of stress during uniaxial compression using FT4. The compressibility of the powder bed was determined by the amount of energy supplied to the system during the test, but it could also be affected by the sample pre-consolidation state. We obtained a highly reproducible state by only conditioning the powder in a controlled moisture environment, thus validating the index choice.

Measurements were carried out to determine the moisture content's effect and the use of nanoparticles on the bulk flow properties of two well-known pharmaceutical excipients, Avicel® PH-102 and Retalac® . The influence of the moisture content influence was evaluated by conditioning the samples at 20 and 60% RH, while the impact of flow regulators impact was assessed by adding 0.5 and 2% w/w of precipitated silica nano-additives. From these measurements, we found an increase in flowability regardless of the glidant amount. Adding more silica from 0.5 to 2% w/w did not seem to reduce internal friction.

We also noted that all SIPERNAT® grades showed different levels of disaggregation. Surface coverage analysis showed that adding NPs reduced the size of the contact zone, thus decreasing particle-to-particle interactions, and so, cohesion. The hydrophilicity of the colloidal silica affected surface coverage. Binary mixtures with hydrophobic additives generated smaller silica aggregates that were better spread over the surface of the host particles, explaining its better performance. In conclusion, the improvement of powder flowability by flow additives seemed to be strongly related to both the surface area coverage, and the nano-silica aggregate size. We suggest choosing the type and the amount of nanomaterials to add to formulations by considering both the surface area coverage and the size of the flow regulators after mixing. These parameters somehow describe/determine the type of interactions or their transition: particle-to-particle, particle-to-silica, or silica-to-silica.

Finally, the dynamic of compaction of Avicel® PH-102 and Retalac® were fit by the Chicago

and the KWW model. Nonetheless, only the ρ-parameter (final compactness) from the Chicago equation was correctly related to the steady state.

In conclusion, as a general trend, we suggest studying flowability from granular compaction measurements by means of densification strength, related to the force or the energy supplied to the media. An energetic approach shows and explains the differences in flowability assessment between flow-testers. We have observed that device-related flowability agrees with the granular media flow, as an observation, when determined at the densest compaction state.

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