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Validation of a new pertinent packing coefficient to estimate flow properties of pharmaceutical powders at a very early development stage, by comparison with mercury intrusion and classical flowability methods

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The present study compares four characterisation techniques, such as packing and rearrangement under pressure methods or shear cell measurement methods, used to evaluate powder flow properties. The reduction of the powder bed volume under low pressures is analysed using mercury porosimetry and two compressibility methods (uniaxial press and volumenometer). Flow functions, deduced from shear cell measurements, are determined using a Johanson Indicizer^{TM} Tester. The examination of the reduction of the powder bed volume leads to new parameters such as the packing coefficient (C_t) and the volume of mercury intruded (V_{hg}). The packing coefficient appears to be a reliable approximation of powder flow properties, whatever cohesive or free flowing : it is actually well correlated with shear cell measurements and it is more accurate than classical flowability tests recommended by the European Pharmacopoeia. Furthermore, this method is easy to use and consumes a small amount of powders ($<$1 g). All together, this method is able to give—very early in the development—a quite accurate estimation of powder flow properties of new drug substances. This may be very helpful for an early determination of the optimum particle granulometry or for a rapid development of a feasible industrial process.

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1. Introduction and background

Flowability is determinant when processing powders (during storage, conveying, filling, compaction. . .) and is of particular interest in the pharmaceutical industrial field where drug substances are most of the time fine and cohesive powders. The tablet and capsule production machines require materials (i.e. active drugs, excipients, powder mixings or granules) with free flowing properties to allow regular dosage of the active ingredient and good production performances. A good flowing material flows regularly and completely, that means it has a mass-flow behaviour; nevertheless, cohesion forces between particles are necessary to avoid segregation and homogeneity problems when blending. Therefore compromises, concerning particle size for example, are often recommended [1].

Therefore, knowledge of flow properties of materials is of first importance to characterise and compare active drug substances and vehicles, to evaluate prototype formulations and to predict the industrial feasibility of process involving flowability [2]. Elsewhere, it is necessary to completely characterise physico-mechanical properties of powders to control batch to batch variability, to certify reproducibility of materials and to obtain product manufacture and registration [3].

Since the early sixties, several empirical methods have been developed to assess flow properties of powders. Methods such as angle of repose, angle of spatula, angle of fall, angle of difference (difference between the angle of fall and the angle of repose), dispersibility, cohesion, mass flow rate, compressibility have been developed and often used. Carr [4] even proposed a

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methodology to evaluate flow properties of powders using angle of repose, compressibility, angle of spatula and cohesion. The final flow performances of the powder is the summation of all the four measurements and each measurement is an indirect method for assessing diverse particle properties such as particle size and shape, porosity, surface area, cohesion, fluidity, bulk density, moisture content, cohesiveness… [5]. This methodology has been extensively used and recommended [6]. However, today simplified tests are employed : flow rate and compressibility are the two remaining tests, normalised by the European Pharmacopoeia (3rd edition, 1997). Compressibility is obtained by comparing bulk and tapped density of a powder column which is bound to repetitive and regular shocks or vibrations. Guyot [7] and Delacourte [8] showed that if the volume variation of the powder column between 10 and 500 shocks is more than 20 ml, the powder will not flow because of remaining air between particles. The compressibility test is easy and measure indirectly flow properties [5].

Although these measurements are simple to use and allow comparison between products of adequate particle sizes, they present drawbacks. They:

– are unable to represent intrinsic properties of powders [9],
– are often not discriminant to compare flow properties of cohesive powders [10, 11],
– use large amounts of powder (compressibility necessitates at least 100 g for each sample measurement which can be too much for an early characterisation of drug products), and
– the results depend on experimental conditions and on the type of material [12, 13].

Consequently, other methods for assessing powder flow properties have been suggested.

- To assess flow properties of ready to use materials, the measure of tablet weight variation using a compression machine can be used [14]. This is only suitable for free flowing materials from the pharmaceutical field and uses a considerable amount of powder. Actually, this is an indirect method which reveals, with hindsight, that means too late, flow properties of the material.
- The theoretical shear measurement principle developed for soil material has been applied to pharmaceutical powders to get more accurate results [10, 15] especially when studying cohesive powders [16]. It has been validated by comparison with the tablet weight variation method [17]. Despite the accuracy of the results, shear measurements are time and product consuming, which can be a disadvantage when a quick assessment is needed early in the development of a drug product.
- York [18] investigated and quantified the first compression stage of a compression cycle to evaluate particle slippage and rearrangement. It is actually of a common scientific consensus that various stages, defined as followed, occur during the compression of powders: initial rearrangement of individual particles, disintegration of aggregates to primary particles or fragmentation of particles if it occurs, plastic deformation and elastic deformation. Although the strict discontinuity between the different stages is not realistic, rearrangement of initial particles under punch displacement can reasonably occur independently of the other compression stages. York showed the inflection points on the Heckel plots [19] witness a change of compression stage. He considered the degree of slippage and rearrangement under very low pressure can be assessed by measuring the packing fraction before the first inflection point of the Heckel plot. The packing fraction was linked to the particle size but was not related to the flow properties of the tested materials. However, this method presents also some disadvantages, although it consumes few amounts of material. The packing fraction measurement is quite complex and leads to practical difficulties: true density value of the powder and a very accurate measurement of the punch displacement during the compression are necessary to calculate relative density of the compact at a given pressure and draw the Heckel plot [20]. The determination of the first inflection point is indispensable to fix the packing period and the measurement is therefore pressure dependant.

Finally, we can distinguish two kinds of measurement for the assessment of powder flow properties. On the one hand, accurate measurement (shear cell measurements) can be obtained but they necessitate a large amount of product and a great expertise from the operator. On the other hand, very simple tests which are quite inaccurate, empirical, inadequate for cohesive powder assessment and which are also product consuming.

The present study proposes a new parameter to assess flow properties (whatever powders are cohesive or free flowing) avoiding the drawbacks of previous described measurements. It is assumed a strong correlation between the particle rearrangement under low pressure and material flow properties. The methodology exploits the first part of the force-displacement curves, that is the packing phase, obtained in such a way that the determination of the packing fraction is not necessary. For validation, packing characteristics determined during compression are compared to compressibility measurements (volumenometer), to packing properties under isotropic pressure (mercury porosimetry) [21] and to shear cell measurements (flow function).

2. Materials and methods

2.1. Materials

Materials with different flow properties were studied:

– three direct compression excipients—Avicel PH 102, binder supplied by *FMC*, Starch 1500, disintegrant supplied by *Colorcon*, and Pharmatose DCL 21, filler supplied by *DMW*—are analysed such as received for reference, without any sieving. The choice of these materials is based on the fact they have different particle size distributions, different bulk densities and different flow behaviours.

– three drug substances: SRX1, SRX2 CP (CP: Coarse Particles) and SRX2 FP (FP: Fine Particles), SRX1 and SRX2 being two different polymorphs of the same drug substance, supplied by the *Pharmaceutical Sciences Department of Sanofi Recherche* (patented products).

2.2. Methods

2.2.1. Observation

Particle shape was examined with an optical microscope (Leica, DMRM, Die Microscope Reflection Metallurgy), by transmission (*50, *500).

2.2.2. Particle size distribution

The particle size distribution of powders was determined by a dynamic Laser scattering particle size analyser, Mastersizer S, Malvern. The apparatus was equipped with a dry analyser system to suspend particles in the air during measurements and analysed particles from 0.5 μm to 3600 μm. Samples were placed into a vibrant hopper, a depression of 4 bars and steel balls were used to disperse particles. Thereafter, particles passed through the laser light to be analysed. Lactose, cellulose microcrystalline and SRX2 CP were analysed with a long focal length of 1000 mm; Starch 1500 and drug substances (SRX1, SRX2 FP) with a short focal length of 300 mm. The apparatus measured the angular distribution of light diffracted by particle going through the light beam. The diffracted light was analysed according to Mie theory. Therefore, all particles were assimilated to spheres and the equivalent diameter (mean diameter, μm), was given as a result. The results were expressed in terms of a percent volume incremental distribution and in terms of mean diameter in volume (D(4,3)). All products were analysed at least in duplicate with a polydisperse model.

2.2.3. Apparent density

The bulk (d_0) and tapped ($d_{\max}$) densities and the Carr index were measured following the European Pharmacopoeia recommendations (3rd edition, 2.9-15., ≪Volume apparent≫). SRX1 had a very low density which did not allow the compressibility to be measured with 100 g in a 250 ml cylinder. Therefore, the amount of powder used for each measurement and each powder was 50 g for allowing a comparison between products. The cylinder was tapped on a Stampfvolumeter, STAV 2003 and the powder volume was read at: 0–10–20–50–80–100–150–200–300–400–500–1250 taps. The packing kinetics were drawn and the Carr index calculated following: $I_{\text{Carr}} = \frac{d_{\max}-d_0}{d_{\max}}\cdot 100$, where $d_{\max}$ is the maximum tapped density and d_0 the bulk density.

Three measurements were realised for each powder

2.2.4. Mercury porosimetry

The mercury porosimetry measurements were conducted using a porosimeter Micromeritics Autopore 9410, Série III. When mercury is in mechanical equilibrium with a solid, the stress on surfaces at one point follows Laplace law:

$$\Delta P = \gamma \cdot \left(\frac{1}{R1} + \frac{1}{R2}\right) \tag{1}$$

The Equation 1 was applied to cylindrical pores. The Washburn equation [22] was then obtained:

$$P = \frac{1}{d} \cdot 4 \cdot \gamma \cdot (\cos\theta). \tag{2}$$

Therefore, the pressure P required to force the non wetting liquid into circular cross-section capillary (radius $r = d/2$) was given by the Equation 2. According to the equipment supplier, the surface tension γ of mercury was 485 dynes/cm and the global contact angle θ between mercury and the powder was approximated at 130° (Orr, 1970).

Prior to measurements, samples (approximately 1 to 2 g) were placed into penetrometers and a vacuum of 50 μm Hg was kept during 5 minutes at about 25°C. Thereafter, the mercury was filled until the pressure reached 0.5 psia (3.45 kPa) and surrounded the powder sample. The analysis started; the equilibrium time was 10 seconds and, at each equilibrium pressure, the mercury volume introduced was measured. The low and high pressure ranges were able to measure pore size from 360 to 3.6 μm (0.00345 to 0.207 MPa) and from 6 to 0.003 μm (0.207 to 414 MPa) respectively. The accuracy of the low pressure measurements allowed a measurement of the inter-particle pores.

The whole sample porosity was calculated with the total volume of mercury introduced. The volume of mercury intruded (ml/g) was plotted against the pore diameter (μm) and the relative distribution of pore sizes in the powder bed was obtained by calculation of the derivative of this cumulative curve ($D_{\text{V}}/D_{\text{D}}$). Samples were measured at least in duplicate.

2.2.5. Compression

The compression was performed on an uniaxial press Lloyd LR30K, Southampton, UK. A special die was manufactured (EPMO, France) which allowed the compression and ejection of the tablet on the press. The punches used were round flat faced and had a diameter of 11.29 mm (surface: 100 mm^2), the die has a depth of 10 mm and the compression volume was kept constant at 1 cm^3 for each sample. The weight of powder compressed depended on its bulk density, measured in a 250 ml cylinder using 50 g, and calculated to fill this volume of 1000 mm^3. The sample was less than 1 g for each compression measurement. The powder, which amount corresponds to its bulk density, is poured manually into the cell at a 45° angle. Therefore, the assumption was made the powder was in a natural state (including powder history) before compression. The upper punch only was moving at 1.14 mm/min., the lower punch remained fixed. The pressure was measured by an accurate gauge and the upper punch displacement was measured with an external LVDT device which allowed the measurement of the powder only, avoiding the measure of mechanical deformations

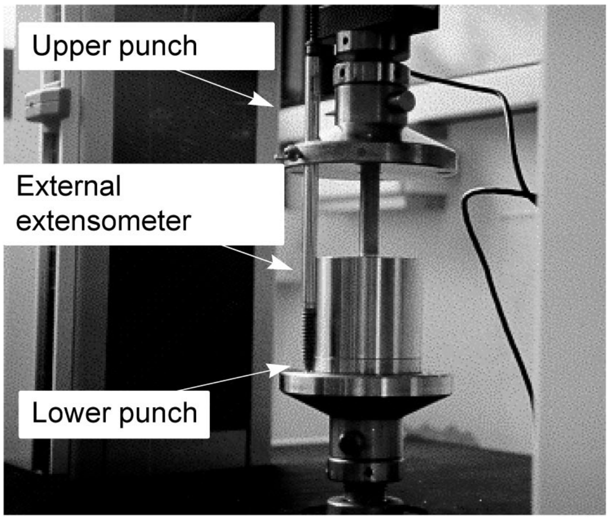


Figure 1 Volume reduction measurements under uniaxial pressure.

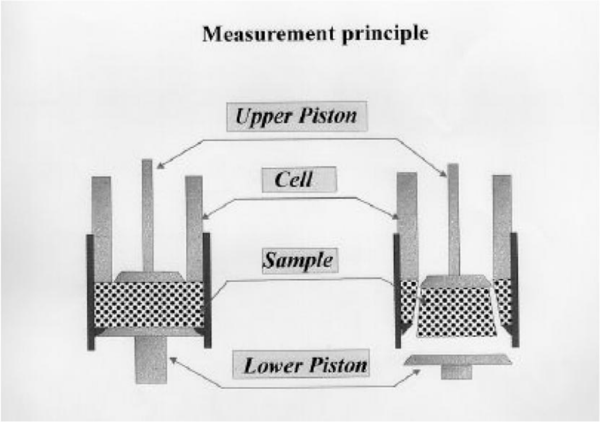


Figure 2 Johanson cell principal.

of the press (Fig. 1). The compression started when the LVDT displacement was zero, that was at 10 mm above the lower punch. Therefore, the powder bed was accurately 10 mm high at the beginning of each compression cycle. The powders were compressed at 200 MPa and the cycles recorded. The cell was lubricated before each compression test with dry magnesium stearate.

Five compression cycles were analysed for each sample.

2.2.6. Shear cell measurement

Shear cell measurements were performed on a Johanson Indicizer$^{\mathrm{TM}}$ System, the Hang-up cell (MTS, Germany). The powder was consolidated in the smallest cell (16–20 cc) at a chosen pressure and then shorn in the axial direction (Fig. 2); the shearing pressure was recorded. The upper punch of the apparatus measured both consolidation and shearing pressures. The shearing pressure was plotted against the consolidation pressure and the linear function fitted to this curve corresponded to the flowability function. The reverse of the slope of the flowability function was called the flowability index or cohesive index $\langle\langle I_c \rangle\rangle$, and is the parameter which represents shear cell results throughout this study. For each consolidation pressure, three shearing measurements were performed and to get a flow function, three to four consolidation pressures were tested.

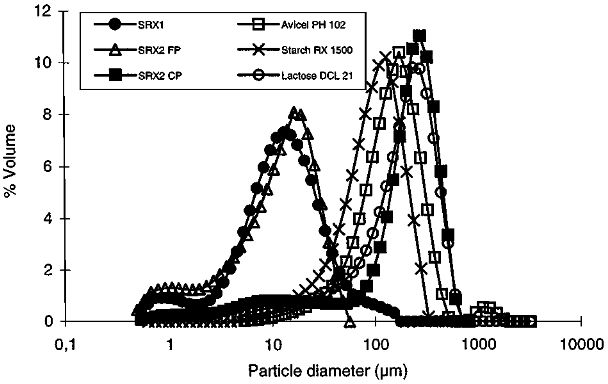


Figure 3 Particle size distributions.

For each measurement, approximately 20 g of powder was necessary. Therefore up to 200 g of powder was required to completely characterise the intrinsic cohesive properties of powders.

At least three measurements were performed.

3. Analysis of the results

3.1. Particle morphology and particle size distribution

Particle sizes and particle size distributions are major powder physical properties, in regard to compactibility, flowability and tablet weight variation [23]. Each sample is analysed (Fig. 3) and mean diameters are indicated in Table I.

SRX1 and SRX2 FP present similar particle size distributions. Although the particle size is equivalent, the particle shape is quite different (Fig. 4a and b), with SRX1 particles having no specific shape while SRX2 FP presents parallelepiped particles, with clear planes. Starch 1500 and Avicel have intermediate particle size distributions. SRX2 CP and Lactose have close particle size distributions. However, these materials have different amounts of fine particles, with SRX2 CP having two particle size populations (one around 10 μm and the other one around 400 μm) and lactose containing no particles smaller than 5 μm.

3.2. Powder column packing under tapping

Each powder sample is poured into the cylinder and tapped under regular shocks. The packing kinetics are shown in Fig. 5 and the calculations are collected into Table I. At 1250 taps, the powder volume remains constant, therefore the maximum packing structure is achieved and the maximum density $d_{\max}$ is obtained at 1250 taps.

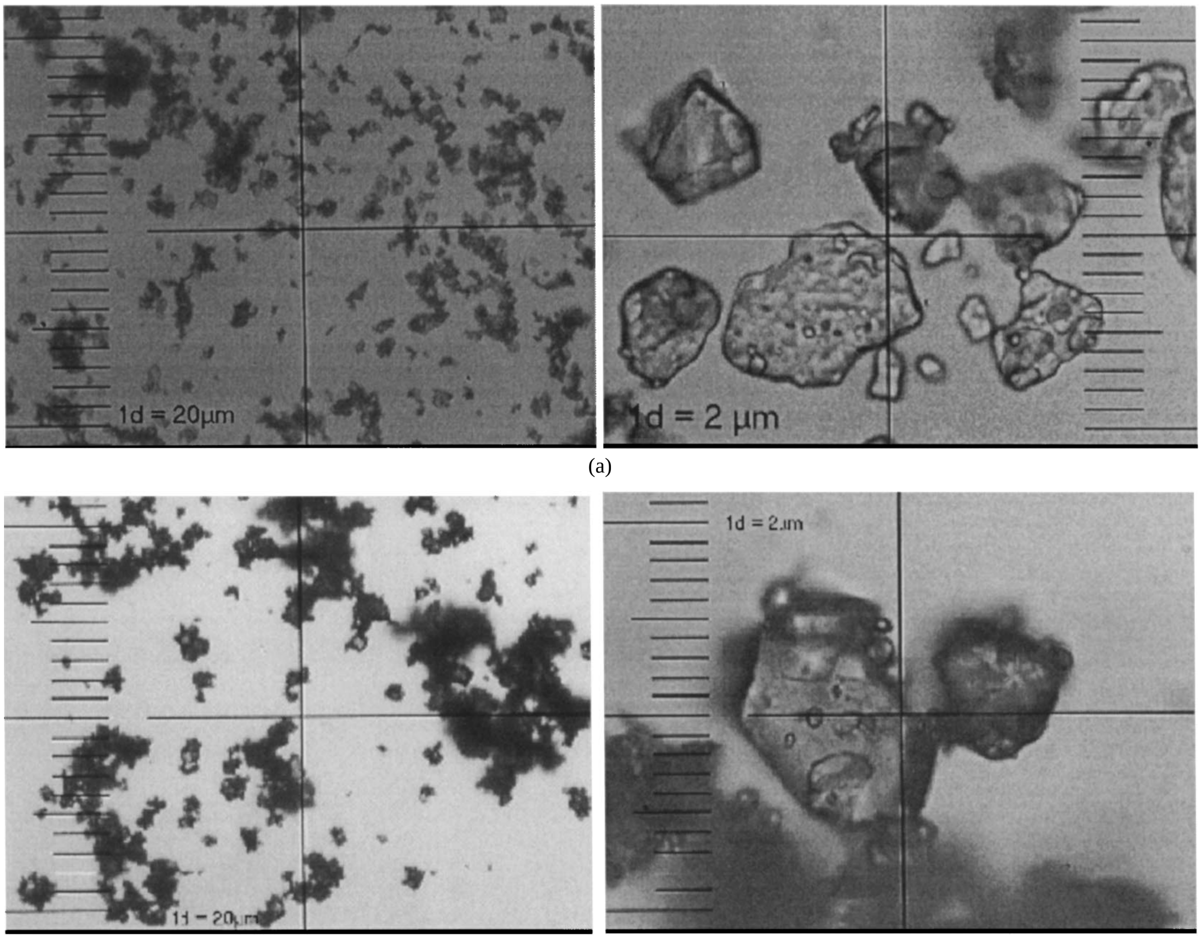
According to tapped density value, materials can be classified into two groups: powders having a tapped density of around 0.870 g/cc and various particle size distributions (Starch 1500, Lactose and SRX2 CP) and powders with a tapped density lower than 0.6 g/cc and having also different mean diameters (Avicel, SRX1 and SRX2 FP). Therefore, regarding particle mean diameters, particle size is not the only powder property which governs bulk, D_0, and tapped, D_{tapped}, densities.

The initial slope of the packing kinetics represents the packing speed under shocks. Lactose, Avicel, Starch 1500, SRX2 CP seem to reach their minimum volume

TABLE I Compilation of the results obtained with packing measurements (compressibility, packing coefficient and mercury measurement) and with the Johanson cell

Products	SRX2 CP	SRX2 FP	Starch 1500	Lactose DCL 21	Avicel PH 102	SRX1
Median diameter (μm)	240	14.5	95	215	155	13
D_0 (g/cc)	0.665	0.388	0.644	0.645	0.341	0.270
(deviation, $n = 3$)	(0.021)	(0.003)	(0.001)	(0.008)	(0.004)	(0.012)
$D_{\mathrm{tapped}=1250}$ (g/cc)	0.882	0.581	0.876	0.863	0.437	0.402
(deviation, $n = 3$)	(0.007)	(0.005)	(0.001)	(0.002)	(0.014)	(0.006)
$V_g = V_0 - V_{1250}$ (ml/g)	0.372	0.860	0.430	0.370	0.645	1.221
(deviation, $n = 3$)	(0.046)	(0.022)	(0.001)	(0.015)	(0.110)	(0.173)
I_{carr}	24.5	33.3	26.6	24.2	23	32.9
(deviation, $n = 3$)	(2.8)	(0.7)	(0.0)	(0.7)	(1.9)	(3.2)
$V_t = V_0 - V_{0.5}$ (ml/g)	0.199	1.186	0.259	0.349	0.740	2.232
(deviation, $n = 5$)	(0.0017)	(0.0033)	(0.0037)	(0.0090)	(0.0289)	(0.0232)
C_t (%)	15.34	49.20	16.57	22.50	24.34	60.25
(deviation, $n = 5$)	(0.13)	(0.14)	(0.24)	(0.58)	(0.95)	(0.63)
V_{hg} (ml/g)	0.090	0.754	0.071	0.092	0.125	1.118
(deviation, $n = 2$)	(0.008)	(0.050)	(0.006)	(0.007)	(0.007)	(-)$^{(1)}$
I_C	31	4.3	7.65	27	7	2.76
(regression coefficient)	(0.9772)	(0.8975)	(0.9791)	(0.943)	(0.9989)	(0.9467)

$^1n = 1$



(a)

(b)

Figure 4 (a) photomicrographs of SRX1 and (b) photomicrographs of SRX2 FP.

quite rapidly (at 200 taps) while SRX2 FP and SRX1 reach a flat line later: at 400–500 taps. Considering the packing speed, materials are classified in a different manner: on one side, cohesive powders which need a large amount of energy to be packed (SRX1 and SRX2 FP) and on the other side, other powders which can be packed more easily (Lactose, Avicel, Starch 1500, SRX2 CP).

The Carr's index is related to powder flow properties as a substantial volume reduction under tapping is correlated with poor flow properties powders [7]. With increasing experience, it has been suggested that a material with a Carr's index below 20% has poor flow properties. According to this parameter, all powders do not flow very well (Table II). SRX2 FP does not flow at all while Starch 1500 and SRX1 have poor flow properties.

TABLE II Carr classification according to the compressibility of powders [5]

I_{Carr} - Compressibility	Classification	Products
5–12%	Excellent flow	—
12–17%	Good flow	—
17–20%	Fair flow	—
20–25%	Passable flow	SRX2 CP Lactose DCL 21 Avicel PH 102
25–33%	Poor flow	Starch 1500 SRX1
33–40%	Very poor flow	SRX2 FP
>40%	Very very poor flow	—

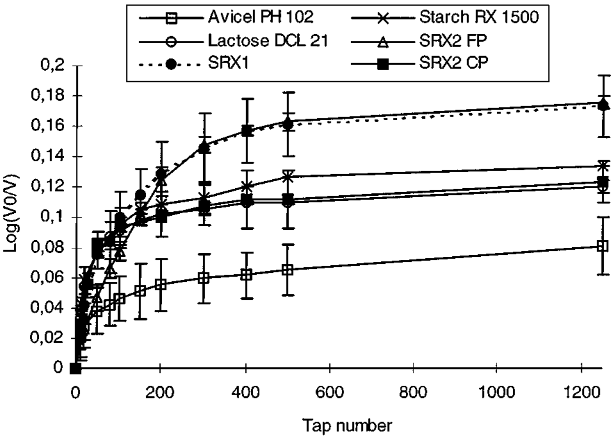


Figure 5 Packing kinetics

This parameter should be completed by a flow rate measurement as recommended by Carr and the European Pharmacopoeia, but this could not be achieved since most of powders studied did not flow at all.

Moreover, results obtained for SRX1 are not reliable because of arches formed when pouring the powder into the cylinder and which do not disappear when tapping. Therefore, volume readings do not represent the real packing volume. Studying this kind of material confirms limitations of this technique when measuring flow properties of cohesive powders.

The analysis of packing kinetics under tapping reinforced the technique is not reliable for a good classification of poor flowing materials and pointed out, if it was necessary, a need for a more pertinent method to simply and quickly characterise powder flow properties, using small, but representative, amounts of powder.

3.3. Porosity measurements by mercury intrusion

Two kinds of porosity are distinguished in a particular system: the inter-particulate and the intra-particulate porosity [21].

At the beginning of the intrusion, mercury surrounds the sample. When pressure increases, it pushes particles as close as possible so that there are no more spaces between particles which can be filled by surrounding smaller particles. At a certain pressure, depending on the material, particles reach their maximum packing rearrangement under isotropic pressure and then only, mercury penetrates the biggest inter-particulate pore volumes of the powder system. This phenomenon is deduced from the porograms (Fig. 6a) as a slope change in the cumulative intrusion of mercury [24]: when particles rearrange under isotropic pressure, mercury intrusion is linearly correlated to the logarithm of the pore diameter (Fig. 6b) and when mercury penetrates a large pore volume, a large mercury intrusion peak is observed. Hence, we suggest the first linear part of the porogram is relevant of the particles packing under isotropic forces and this volume reduction is measured by the volume of mercury introduced during this packing phase (V_{hg}, ml/g) (Table I).

3.4. Volume reduction on uniaxial press

During compression, the upper punch moves down at a very low rate which allows the particles to rearrange themselves under an uniaxial pressure, before any fragmentation or plastic deformation. The upper punch moves down into the powder bed without any significant increase of the pressure: the entrapped air is gradually evacuated and the powder is being packed. The powder bed reaches is maximum packed structure when relative movement of the particles is no more possible without their deformation. According to Gerritsen [25] the powder bed is packed when the upper punch pressure is 0.1 MPa. However, at that pressure, Fig. 7b shows that in the particular case of active materials, powder beds are not completely packed. This pressure appears to be too low to be considered for all materials (Fig. 7b).

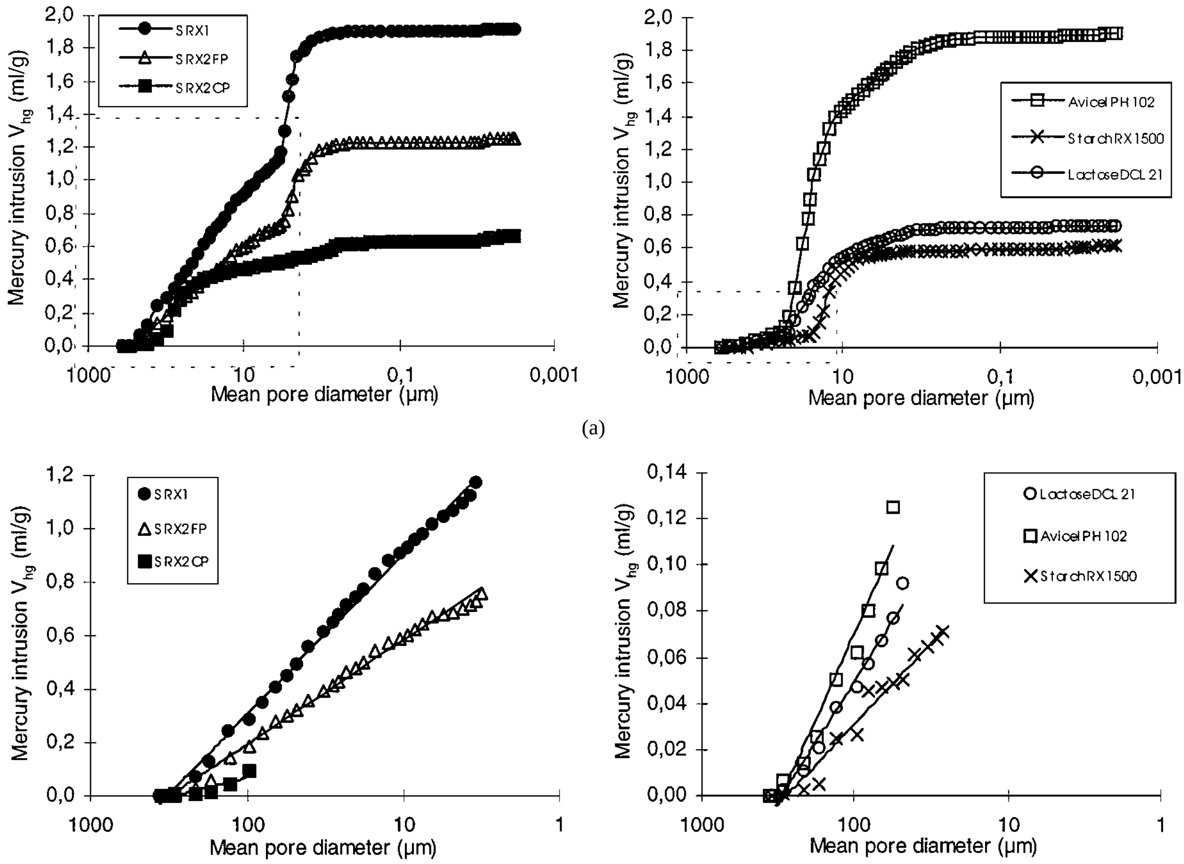
We suggest to define a packing coefficient C_t to quantify this first compression period. It relatively quantifies punch displacement into the powder bed until the pressure reaches a value at which the packing period is achieved:

$$C_t = \left(\frac{H_0 - H_p}{H_0}\right) \cdot 100 (H_P \text{ is the powder bed height under pressure} P).$$

It is necessary to understand that, for having an accurate measurement of the packing period, the upper punch displacement measurement has to start as soon as it is in contact with the powder bed. The exact determination of the zero point is absolutely necessary. One can note this cannot be achieved when using a compaction simulator or any other test machine such as alternative ones. The amount of powder, which is not forced into the cell during filling, is related to bulk density, that means comparison between different material is also possible.

In order to determine the right pressure at which the powder bed is completely rearranged, we calculate the packing coefficient at each pressure from 0.1 MPa to 1 MPa with a 0.05 MPa step. At very low pressure, only packing occurs and the packing coefficient value increases until it leads to a limit suggesting the packing is less important and that other phenomena start to occur (Fig. 8).

In order to visualize the slope change, we calculate the incremental packing coefficient versus the applied pressure (Fig. 9). One can observe the slope change does not occur after 0.5 MPa for any material. We



(a)

(b)

Figure 6 Mercury intrusion into the powder system; over the whole pressure range (a) and zoom on the first intrusion step (b).

suggest 0.5 MPa is then the right limit to consider the packing period is entirely achieved for all the studied materials. Therefore, only packing and slippage are assumed to occur until the upper pressure reaches 0.5 MPa. At this very low pressure we can consider no deformation or breakage of particles can occur.

A high C_t value means the packing period is long while a low value indicates rearrangement is easy. Therefore, this new parameter allows to classify materials according their ability to rearrange under low pressure (Table I) : SRX2 CP < Starch 1500 < Lactose DCL 21 < Avicel PH 102 < SRX2 FP < SRX 1. SRX2 CP, Starch, Lactose and Avicel have a low packing period and C_t is below 25% while the two remaining materials have a much longer packing period—over 50%. These two material are very compressible, which is unfavourable for industrial processes.

During the packing period, the volume reduction of the powder bed is measured. V_t is the volume lost by the powder when the upper punch pressure is lower than 0.5 MPa and is calculated following: $V_t = V_0 - V_{0.5}$.

3.5. Shear measurements

Nowadays, it is widely accepted that shear measurements are the most accurate appreciation of flow properties of cohesive powders and several systems are performed to measure them. The first cell was initiated by Jenike who developed the theoretical and practical parts for the measurement of flow properties of soils [26]. This method is quite complex: it necessitates theoretical knowledge of powder flow properties and great expertise for the experiment. It also consumes a considerable amount of powder. Johanson set up a new system which appears to be less complex and consumes less material although it still need large powder samples (Fig. 10). Nevertheless, results are reliable. A comparison between the Johanson and Jenike cells showed results are quite homogeneous [27] despite the Johanson cell results being more optimistic than the Jenike cell results [28, 29].

Shear cell results are gathered together in Fig. 10. According to these measurements, lactose and SRX2 CP are both free flowing powders while SRX1 and SRX2 FP have no flowing capacities. It is also important to note that SRX1 and SRX2 FP have different flow functions despite the fact they present the same particle size distribution. Therefore, the two polymorphs having the same particle size distribution and quite different particle shape behave differently regarding cohesive properties. This technique can therefore differentiate material which do not flow. On the contrary, it does not distinguish powders having free flowing properties (SRX2 CP and Lactose are superimposed).

4. Discussion: Validation of C_t to assess powder flowability

4.1. Packing, particle size and bulk density

Packing and setting up of particles into the cell is related to particle size and bulk density. Actually, SRX2 CP having the larger particles has the lowest C_t value, at the opposite of SRX1. It is indeed very well known that particle size has a great influence on particle flow

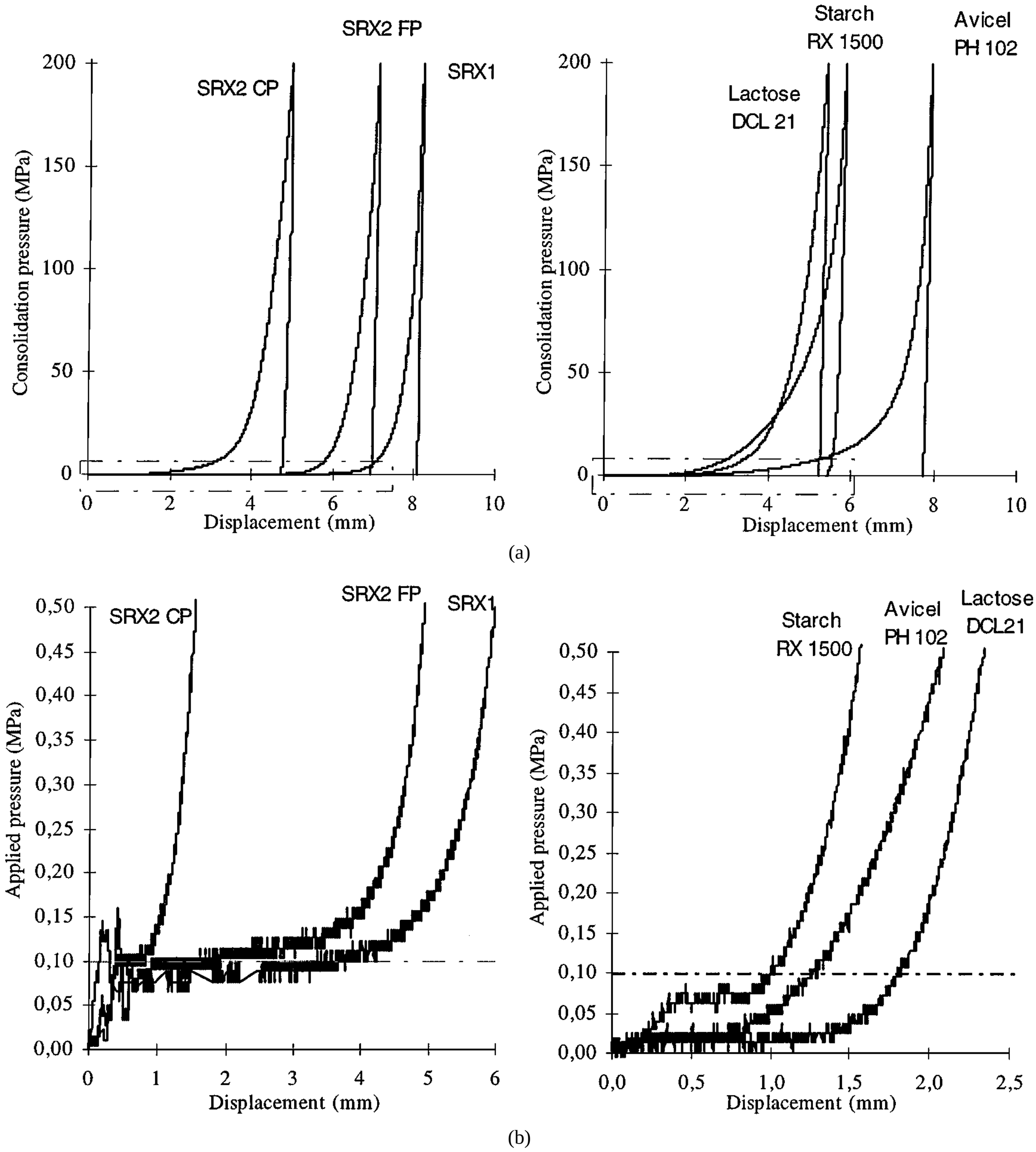


Figure 7 Volume reduction up to 200 MPa (a) and 0.5 MPa (b).

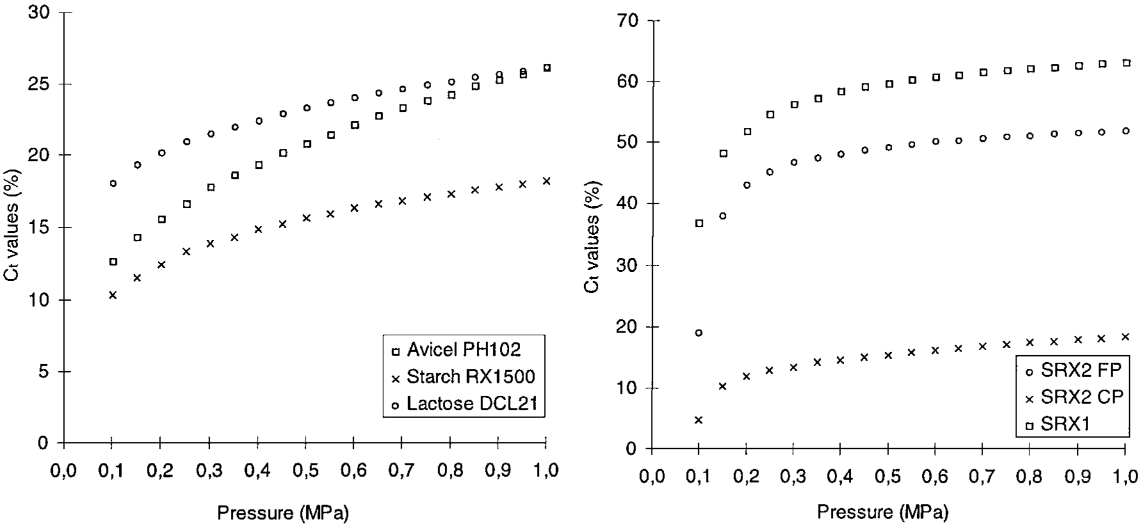


Figure 8 Evolution of the packing coefficient according the applied pressure.

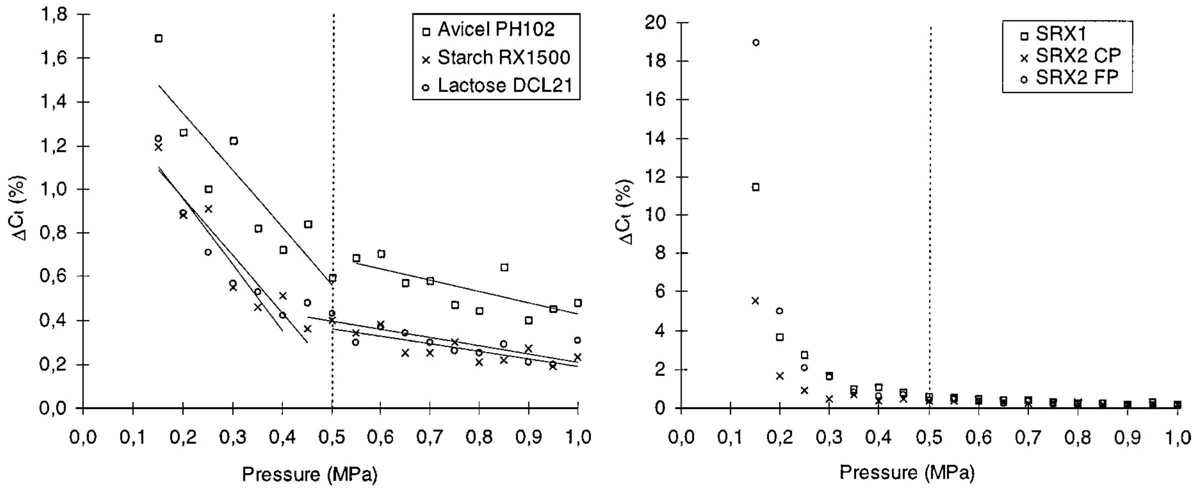


Figure 9 Evolution of the incremental packing coefficient value according the applied pressure.

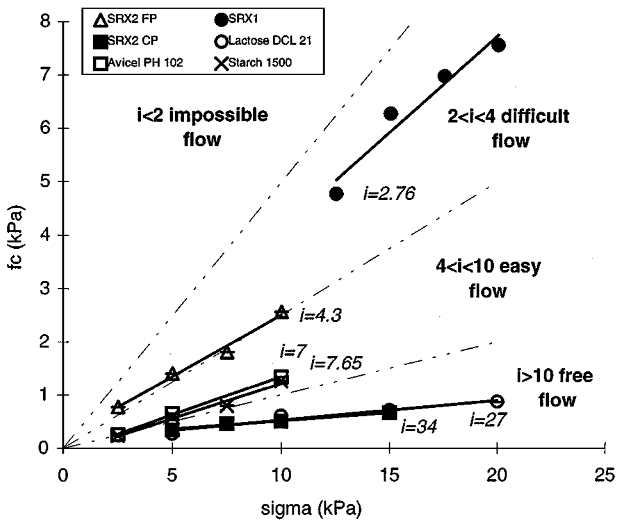


Figure 10 Flow functions of powders.

properties [23]. Fig. 11 shows a relationship between packing coefficient and the mean diameter, although this parameter is restrictive compared to the whole distribution. Even though granulometry is the predominant characteristic, it is not the only one which influences flow properties.

Similarly, packing coefficient is related to bulk density without showing a one-to-one relationship because of counteractions of other powder properties, as Carr demonstrated it [5] (Fig. 12). For example, Avicel, SRX2 FP and SRX1 have close bulk densities and very different C_t. Identical comment may be done considering SRX2 CP, Starch 1500 and Lactose.

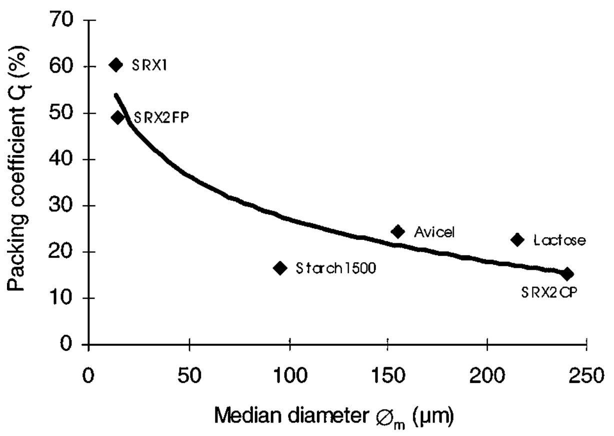


Figure 11 Packing coefficient and powder granulometry.

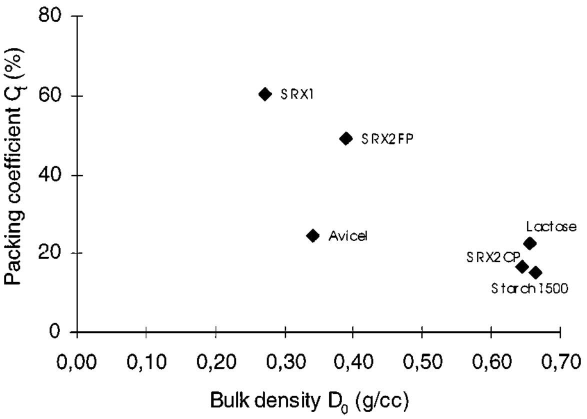


Figure 12 Packing coefficient and bulk density of powders.

Therefore, packing coefficient combines several other material properties, such as particle shape, particle size distribution, interaction between particles, electrostaticity... as well as flow properties to which it can be linked.

4.2. Validation of the packing coefficient

4.2.1. Packing coefficient and mercury porosimetry

The volume of mercury introduced during the first phase corresponds to the volume lost by the powder bed during packing under isotropic pressure and is called V_{Hg} (mL/g). Fig. 13 shows there is a linear relationship between the volume lost by compression under low pressures (V_t, mL/g) and the volume of mercury introduced during the packing period under isotropic pressure (V_{Hg}, mL/g) (Table III). Both techniques evaluate similarly particle rearrangement.

However, the uniaxial compression of a powder bed under low pressures is preferred to quantify packing since mercury porosimetry presents drawbacks such as:

- duration of the experiment,
- use of a toxic material, the mercury,

TABLE III Linear regression coefficients

Products	a, slope	b, intercept	r^2
$V_{hg} = a.V_t + b$ (1)	0.555	−0.0857	0.9234
$V_{hg} = a.V_g + b$ (2)	1.2635	−0.4425	0.9188
$V_g = a.V_t + b$ (3)	0.434	0.2867	0.9812
$V_g = a.V_t + b$ (3') calculated from (1) & (2)	0.439	0.2824	—

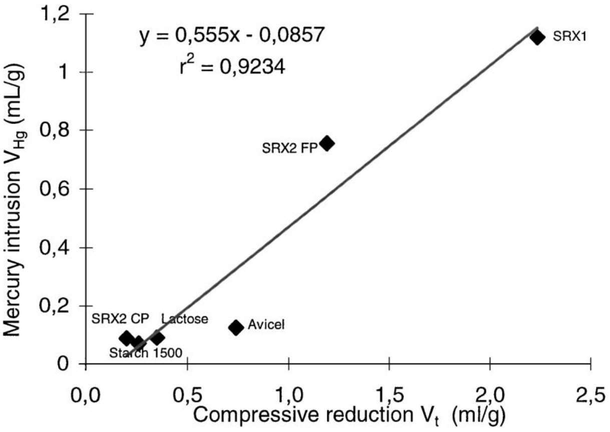


Figure 13 Introduced volume of mercury, V_{Hg} and powder bed volume lost by compression uniaxiale, V_t.

– necessity to have high sensitive sensors for low pressure analysis,

– difficulty to accurately determine the end-point of the packing period.

4.2.2. Packing coefficient and apparent density measurement

The measurement of the tapped density leads to a measure of the particles rearrangement under taps. The volume lost by the powder bed during this test is therefore defined as $V_g = V_0 - V_{1250}$ (mL/g).

Fig. 14 shows the volume lost during tapping, V_g, is linearly correlated to the one lost by the powder under uniaxial compression, V_t ($r^2 = 0.98$) (Table III). The similitude between the two experiments validates again the ability of the uniaxial compression under low pressures to quantify packing and particle rearrangement, whatever the material is. However, as already notified, measurement of tapped densities presents limitations, especially concerning cohesive materials such as SRX1. On the opposite, during the uniaxial compression, an accurate measure of the powder bed volume at 0.5 MPa is a certitude the complete packing period has been taken into account.

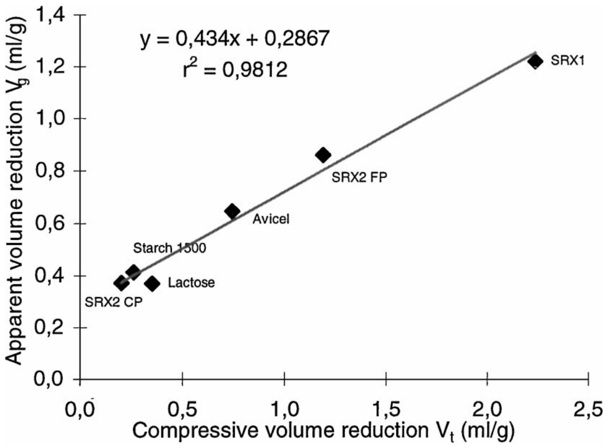


Figure 14 Powder bed volume lost by tapping V_g and compression uniaxiale V_t.

Therefore, the uniaxial compression presents several advantages, compared to the tapped density method:

– rapidity and simplicity,

– small amount of powder for each sample (less than 1 g compared to 100 g necessitated for apparent density measurement),

– application to all materials without any restriction,

– accuracy.

4.2.3. Packing coefficient and flowability

The packing coefficient defined in this study is able to quantify particle rearrangement. We suggest to validate its ability to estimate flow properties by comparison with shear cell measurements. Fig. 15 represents materials on a C_t/Ic diagram and shows a similar relationship than the one obtained between the volume lost during tapping ($V_0 - V_{500}$) and the flowability index obtained with a Jenike cell in 1984 [30]. The packing coefficient allows to distinguish materials with poor flow properties, such as SRX1 and SRX2 FP. On the other hand, it does not allow to differentiate materials having free flowing properties, such as Lactose and Avicel. The correlation obtained in this study confirms the packing properties measured by C_t are representative of flow properties evaluated by I_C. The correlation shows that materials having a packing coefficient lower than 25%, then the Johanson index is greater than 7 which means materials have easy or free flowing properties according to Jenike classification. For such materials, it is then possible to consider a feasible industrial development. When the packing coefficient is above 25%, the Johanson index is below 7, which indicates materials have very poor flow abilities. Consequently, it is possible to exploit in the first place the packing coefficient to quantify flow properties and consider a value lower than 25% is sufficient for an industrial use of the material.

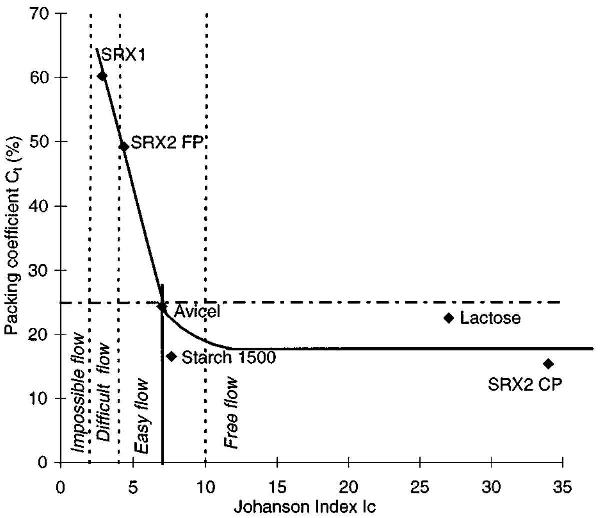


Figure 15 Packing coefficient and Johanson index.

5. Conclusion

The volume reduction of a powder bed is equivalent, whatever the principle utilised to rearrange the particles: the volume lost until upper punch pressure is 0.5 MPa, the volume of mercury introduced during the first step of the measurement and the volume reduction due to repetitive shocks are linearly correlated. The granulometry and the bulk density of a powder are related to the packing coefficient but the study shows that other parameters do influence flow properties, more precisely roughness, electrostaticity, particle-particle friction ... and that they are included in this parameter. Among these three techniques, packing coefficient appears however the most accurate parameter to differentiate cohesive powders and is in good correlation with flow function results.

The "packing coefficient" method presents two main practical advantages:

– the measurement can be carried out when running a compression by plotting force-displacement curves (the parameter corresponds to the early stage of the compression event), meaning it is obtained very quickly and easily,

– the measurement is operated in a 10 cc cell, therefore small amounts of powder are needed (less than 1g).

The presented method is therefore time and product saving. However, although the packing coefficient allows a good knowledge of flow properties of powder, it does not allow any calculations of silo dimensions, such as Jenike or Johanson cells can provide.

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