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Rheological characterization of pharmaceutical powders using tap testing, shear cell and mercury porosimeter

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Abstract

Most of the pharmaceutical processes involved in the manufacturing of solid dosage forms are connected with powder flow properties, at least for some of the intermediate steps. Powder flow characteristics are commonly investigated by various measurements, such as, handling angles, tap testing, shear cell measurements, etc. All these approaches allow the calculation of indices characterising powder flowability. Unfortunately, these methodologies are highly product consuming, which is a limitation in the first steps of a novel drug development, when only a small amount of the product is available. The use of mercury porosimetry to evaluate compressibility and flow properties of powders could be a new and alternative approach to obtain insight in the rheological properties of granular medium by the interpretation of the first part of porograms (low pressures). We have developed such an evaluation and compared the results obtained with those given by tap testing and shear cell measurements, applied to four excipients for direct tabletting and three different drugs. Mercury porosimetry turned out to be a sensitive technique, able to provide quantitative information about powder flow properties, complemented by an evaluation of particles micro porosity and size distribution, in a single step. These characterisations are obtained with only ≈ 250 mg of bulk powder compared to high quantities (> 100 g) needed for other methods.

Keywords: Shear cell; Mercury porosimetry; Tap testing; Powder rheology; Compressibility; Flowability indices

1. Introduction

During a pharmaceutical process, most of the steps such as sieving, pouring, micronizing, mixing, pneumatic conveying, grinding, drying, compaction, are connected with the powders

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flowability (Tan and Newton, 1990). The dosage and therefore the pharmacological effect of drugs are totally dependent on, e.g. the capacity of the powder to be fed into a press die before being compressed.

Flow properties of powder must be studied in terms of quality control of raw materials in order to maintain product uniformity but also to avoid rigid situations in which process breakdown may occur, with respect to imposed conditions. Consequently, powder flow properties should be measured and optimized as part of every development program (Lewis and Simpkin, 1994).

It is obvious that flowing characteristics of powders are highly dependent on their densification (consolidation) states, i.e. powders can be more or less expanded or contracted when stressed, thus leading to a large variety of inter particle forces. Factors associated with the nature of the particles are size (Molerus and Nywlt, 1984), shape, surface morphology, packing ability should be considered when studying powder flowing properties, but particle forces associated with these factors should also be taken into consideration. Then, a powder must be considered as a whole medium that sums up all these interactions at the particle/particle contacts. Powder flowing properties are influenced by any factor that can have an effect on these particle/particle interactions (for a review, see Deleuil et al., 1994).

Powder flow characteristics are commonly investigated under gravity loading conditions. Using measurements such as the angle of repose and other handling angles (Train, 1958), standardised flow rate (Devise et al., 1975), apparent and 'tapped' densities and derived indices such as defined by Carr (1965a) or Hausner (1967). Such measurements have demonstrated the dependence of powders flow on particle's shape and size distribution (Carstensen, 1973), on temperature or relative humidity, but they have been proved difficult to relate to features at particulate level.

Thus, a more fundamental and physical measurement should be easily achievable using shear cells (Jenike, 1964; Schwedes and Schulze, 1990; Kamath et al., 1993). These cells are designed to condition powders under a known load and to measure forces needed to shear powder beds (Chulia, 1984). This measurement is able to provide useful indications of powder flow threshold, while the powder bed is being loaded. Then, if the forces applied on a powder are approximately known during a given process, intrinsic information regarding the frictional and cohesive natures of granular material can be gathered. This information could then be relevant during real process. It is important to note that this methodology is time and product consuming and that correct and reproducible preparation of samples is quite difficult to achieve and results can be very operator and know-how dependent. Once rheological properties of a given powder have been identified by shear testing, tap testing can be profitably used for routine checks or to establish conformity of different batches because empirical connections have been found between tap density values and shear cell determined flow functions (Cohard et al., 1985).

Nevertheless, all these approaches present a major disadvantage being that they are too product consuming, particularly during the first step of a novel drug development when only a very little amount of the product is available.

On the other hand, mercury porosimetry has been largely proposed to routinely measure the pore volume and to calculate pore radii or surface area of porous solids (Kloubek, 1994). Other authors have also suggested that mercury porosimetry can be used to study the compatibility of powders in the same fashion as with an isostatic press (Maijling et al., 1994).

As a matter of fact, when the porous solid is constituted of a bulk powder, totally expanded, the mercury intrusion is preceded by a rearrangement procedure of the powder bed at low mercury pressures. It is then realistic to assume that measurements carried out at this level can be related to rheological properties of powder beds set in shear cell measurement.

The aim of this work is to try to evaluate compressibility and flow properties of pharmaceutical powders by analysing the initial part of the curves obtained from mercury porosimeter measurements. We have also tried to compare results given by different powders through tap testing, and shear cell testing with those derived from

porograms. We will then discuss accuracy of relationships between these different approaches.

2. Materials and methods

2.1. Materials

Seven products of varying flow properties and without critical toxicity were selected.

- Three of them (group 1) are known to display free flowing behaviour and are used as excipients for direct compression: Di Calcium Phosphate, Di Tab® (DT) (Rhône Poulenc Rorer, rue R Aron, Antony, France); Lactose Fast Flo® (FF) (Foremost McKesson Foods Group, San Fransisco, CA 94104, USA); and Lactose Extra Fine Kristal® (EFK) (Hollandsche, B.V. Melksuikerfabriek, Uitgeest, Netherlands).
- One can be considered as an intermediate (group 2): Lactose Fine Kristal® (FK) (Hollandsche, B.V. Melksuikerfabriek, Uitgeest, Netherlands).
- And three others are well-known drugs (group 3) and renowned for their poor flowing properties (all are obtained from Rhône Poulenc Rorer, rue R Aron, Antony, France): Ketoprofen® (KETO); Acebutolol Chlorhydrate® (ACEB); and Celiprolol Chlorhydrate® (CELI).

Table 1
size distributions and apparent particle densities of the powders studied[a]

	Median d_{50} (μm)	Population peak(s) (μm)	ρ_t (g/cm^3)
EFK	98	134	1.563
DT	32	13.5/112	2.355
FF	97	112	1.552
FK	51	66	1.575
ACEB	35	33	1.261
CELI	23	11/79	1.231
KETO	29	33	1.275

[a] Results are given in median d_{50} which represents the diameter at 50% of the population cumulative curves and in diameter(s) at the maximum(s) of the population peaks. The last column gives the apparent particle densities (ρ_t) of the powders studied, obtained by gas pycnometry.

All these powders were tested as received (but stored under controlled room temperature and 50% of relative humidity) for their apparent particle densities with a Quantachrome Multipycnometer (Quantachrome corporation, Boynton Beach, FL 33426, USA) using helium as the inert gas. Apparent particle density is defined here as the true density, with the fraction corresponding to the closed pores added and will be noted ρ_t. Ten replicate measurements were performed, and the variability of the results was on the fourth decimal. Their size distribution was also determined (five replicate measurements) using a Sympatec laser particle size analyser equipped with a liquid (fluid silicone) cell. The use of ultra sounds was optimised to obtain the most reproducible results. All results are reported in Table 1.

2.2. Methods

2.2.1. Tap testing

An Engelsmann powder tester (STAV 2003 Engelsmann AG Apparatebau, Ludwigshafen, Germany) was used to measure tapped densities, three replicate measurements were performed for each powder under normalised conditions as describe in the European Pharmacopeia (1997). For each determination, the test tube was filled with powder sample and the initial volume V_o was measured giving access to bulk powder density ρ_o. Powder volume was measured after 10, 50, 100, 500 and 1250 taps (1250 taps was always sufficient to attain the equilibrium tap volume). When the equilibrium volume was obtained, the final tapped density ρ_{tap} was determined. Results will be expressed latter in terms of compressible volume ($V_o - V_n$) after n taps, and reported in cm^3 per gram of bulk material. Actual compressibility indices I_c of each powder were calculated (variability 0.1%) as defined by Carr (1965b):

$$I_c(\%) = \frac{\rho_{tap} - \rho_o}{\rho_{tap}} \times 100. \quad (1)$$

2.2.2. Shear cell measurements

All measurements were performed with a Jenike shear cell (home made model, diameter of 8 cm and total volume of 125.7 cm^3). Under an uniaxial

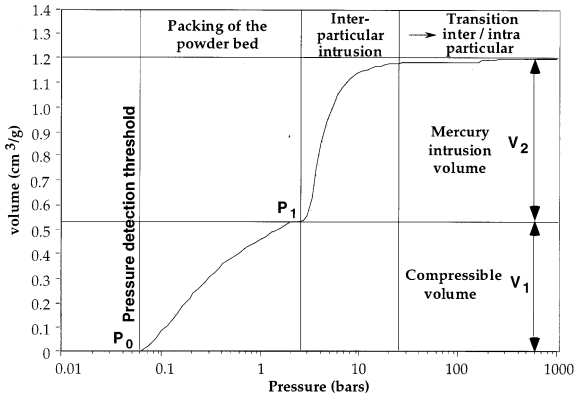

Fig. 1. A classical schematic porogram. We defined different parameters: V_1, compressible measured volume (cm^3/g of powder); V_2, porous interparticular volume (cm^3/g of power); P_0, first recorded pressure at the beginning of the powder packing; and P_1, the locking pressure at the end of the powder packing step, just before the mercury intrusion in the interparticular pores.

normal stress σ, a powder bed may develop irreversible packing, resulting in densification (consolidation) and leading to a tangential force τ needed to shear the bed.

The results of shear cell measurements are classically interpreted as yield loci in the Mohr space $(\tau - \sigma)$. The intercept of the yield loci with τ axis gives the cohesion parameter τ_0 and the slope gives rise to kinematic angles (ϕ) of internal friction (Haaker, 1987; Butters et al., 1991; Podczeck and Miah, 1996). Mohr circles tangent to the yield loci give rise to the major principal normal stress σ_{max} and to the effective consolidation stress (or unconfined yield strength) *fc*.

A plot of fc versus major principal normal stress σ_{max} can be obtained and represents the flow function. In the current case of linear relation, Jenike and Carson (1985) has also proposed to define a flow indice *i* as follows:

$$i = \frac{\sigma_{max}}{fc}. \quad (2)$$

We have adopted a simplified (Deleuil, unpublished data) measurement procedure. Each powder is firstly passed through a sieve to minimize powder history (handling, storage, etc.). In all cases, σ_c (consolidating load) was equal to 13.76 kPa. This value was chosen because it corresponds to a maximal stress that can give an accurate precision (± 0.2) on the flowing indice i (measurements using higher σ_c give less reproducible *i* values for some of the powders studied). Then, only four points (repeated three times) are performed, under axial loads σ in the range of 20–80% of σ_c, to draw yield loci. Such a simplification was used to minimize quantities of raw material needed. As such experiments are highly moisture dependent (Lloyd and Webb, 1987), all the experiments were performed under controlled atmosphere.

2.2.3. Porosimetry measurements

Porosimetry measurements were performed with a Autopore 9220 porosimeter (Micromeretics, ZATE Saint Maximin, Creil, France). This apparatus presents the advantage of continuous data acquisition in a '0' to 4000 bars pressure range. The cell is disposed horizontally during the first step corresponding to the low pressure measurements (from 10^{-2} to 2 bars) and prevents mercury column weight influence.

The first recorded pressure (Fig. 1), at the beginning of powder packing will be noted P_0. Pressure P_1 which corresponds to the end of the powder packing step (before mercury intrusion in the interparticular pores) is determined as the inflection point of the porogram (porogram corresponds to the plot of the mercury intrusion volume as a function of applied pressure). We have taken into account the maximum of the derivative curve to obtain a precise determination of P_1. The compressible volume V_1 that corresponds to the sample volume reduction during the packing step as reported in Fig. 1 is determined for each powder. Interparticular porous volume V_2 (mercury intrusion volume), is also calculated as the difference between total volume of intrusion and evaluated compressible volume V_1.

3. Results and discussion

3.1. Tapped densities

The calculated bulk densities ρ_0, tapped densi-

ties ρ_{tap} and Carr indices I_c are reported in Table 2. It is possible to distinguish two powder groups. The first one is constituted of lactose FF, Di Tab and to a lesser degree lactose EFK. All these materials present I_c values of $\approx 20\%$ or less and thus a good flowability. In the second group, other powders exhibit a calculated I_c higher than 30% characterizing poor flow properties.

Table 2
Tap testing of powders

	ρ_o (g/cm^3)[a]	ρ_{tap} (g/cm^3)[b]	I_c (%)[c]
EFK	0.77	0.98	21.5
DT	0.89	1.04	14.0
FF	0.57	0.65	13.2
FK	0.56	0.89	36.7
ACEB	0.36	0.57	38.6
CELI	0.38	0.57	33.3
KETO	0.31	0.51	38.4

[a] ρ_o: the bulk density.
[b] ρ_{tap}: is the tapped density.
[c] I_c: the Carr indice (%).

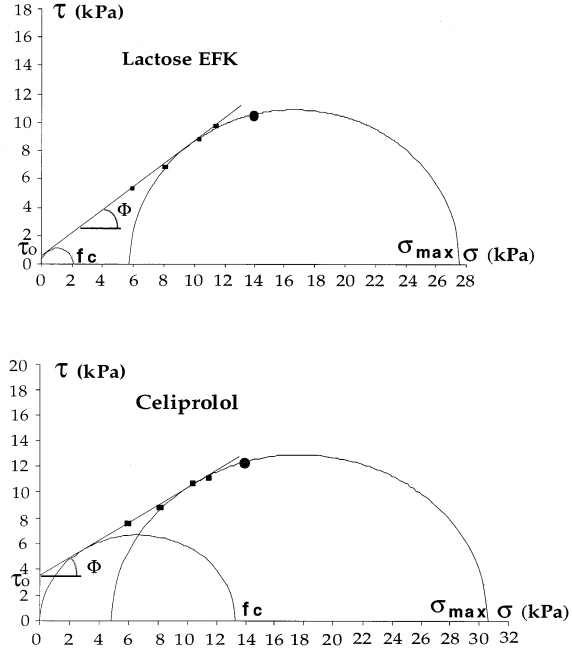

Fig. 2. $\tau = f(\sigma)$ graphs obtained by shear cell measurements for Lactose EFK and Celiprolol.

Table 3
Shear cell testing of powders

	ρ_c (g/cm^3)[a]	τ_0 (kPa)[b]	i[c]
EFK	0.91	0.5	12.9
DT	0.94	0.6	9.8
FF	0.64	0.8	9.3
FK	0.92	2.8	2.8
ACEB	0.66	1.6	4.3
CELI	0.59	3.5	2.3
KETO	0.63	2.1	3.3

[a] ρ_c: the critical density in the steady state.
[b] τ_0: the cohesion parameter.
[c] i: the Jenike indice.

3.2. Shear cell measurements

For shear cell measurements, the powder bed should be conditioned in a steady state situation in which particles move in a plane without any volume variation. This is a limit situation at which shear density equals density before failure. This particular state corresponds to strain under flow conditions and is characterised by critical density ρ_c and critical tangential force τ_c measured under an applied consolidation load σ_c.

The graphs obtained from $\tau = f(\sigma)$ plots are presented in Fig. 2 for the two most divergent powders. Critical density ρ_c corresponding to the shear steady state (ρ_c is obtained by weighing the powder and taking into account the shear cell's volume), cohesion τ_0 and calculated flowability indice i are reported in Table 3 for all powders.

These results simplify the classification of the materials as to their flowability. Three groups can be differentiated.

- Celiprolol, lactose FK and Ketoprofen must be considered as cohesive powders with an i value included between 2 and 4.
- Acebutolol, Di Tab and lactose FF are intermediate flowing powders with $4 < i < 10$; but Di Tab and lactose FF exhibit a comportment close to free flowing.
- Lactose EFK presents a calculated i value of 12.9 and must be considered as a free-flowing powder.

3.3. Comparison between shear cell measurements and tap testing

Compressibility Carr indices Ic are plotted versus Jenike flowability indices *i* in Fig. 3. This representation demonstrates the semi-quantitative features of I_c in regard to *i*, apply to the studied powders. The I_c indice analysis enables the identification of cohesive powders from free-flowing ones, but makes a true classification between materials of comparable packing properties very difficult. On the other hand, *i*, the Jenike indice is more powerful to discriminate powders of low flowability.

3.4. Porosimetry measurements

Fig. 4 shows the obtained porograms for the powders studied. A number of parameters V_1, V_2, P_0 and P_1 were calculated for each powder as reported in Table 4.

Fig. 5 shows the first part of the porograms in detail. The powders clearly present different behaviour for low mercury pressures, in the range $P_0 - P_1$. The curves exhibit linear behaviour in semi-log representation. A first order law can be considered to describe the powder packing zone, such as:

$$V = a + b \log(P) \quad (3)$$

where:

a = compressible volume at $P = 1$ bar;

b = packing slope. b represents the susceptibility to pressure in regard to V.

Calculated values of a and b are summarised in Table 4.

The volume variations in regard to the applied mercury pressure relationship allow the determination of the work, W_p, performed by the mercury and used to reorder the powder bed during all the packing step. W_p can be calculated as follows (Table 4):

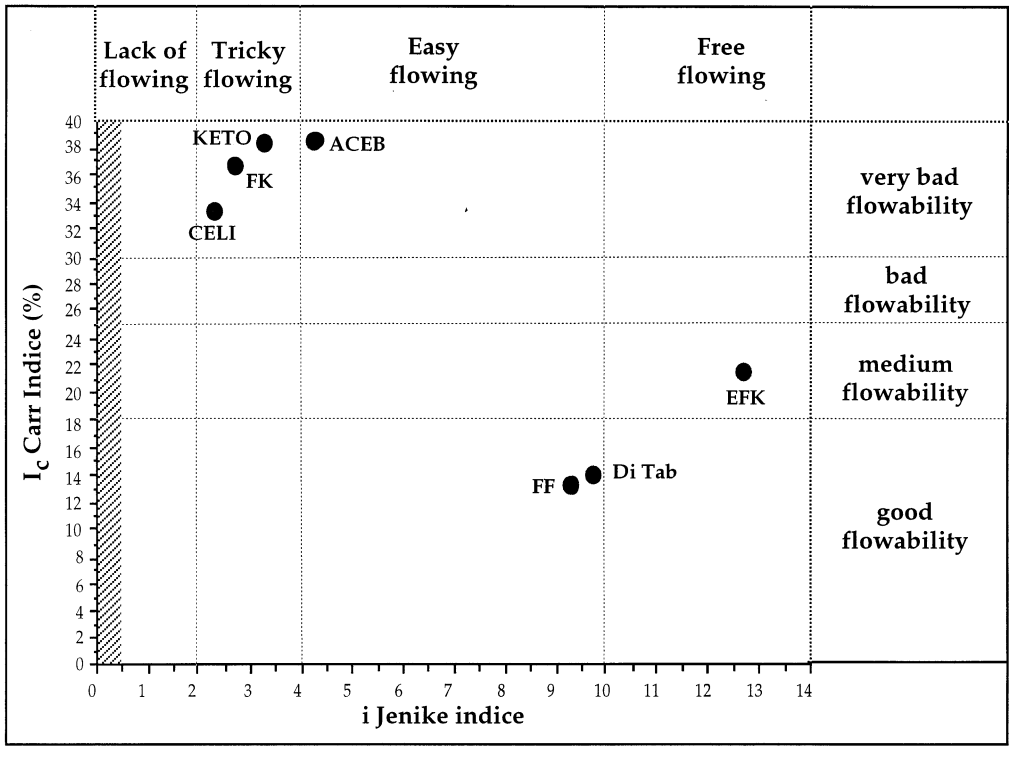

Fig. 3. A comparison between Carr and Jenike indices, respectively I_c and *i*.

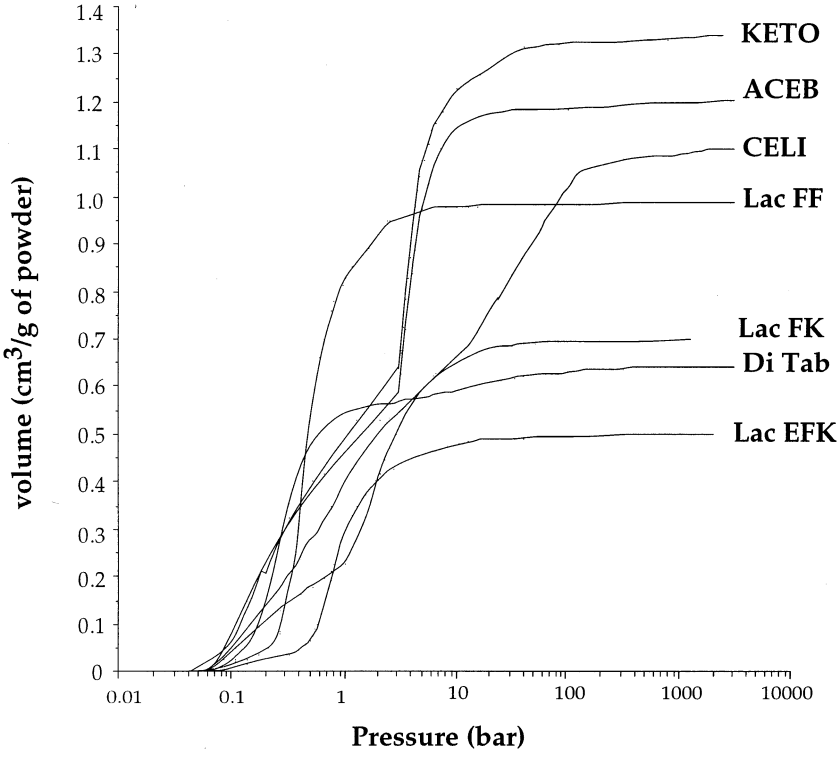

Fig. 4. Porograms of the seven studied powders.

Table 4
Mercury porosimeter measurements of powders

	V_1 (cm^3/g)[a]	V_2 (cm^3/g)[b]	P_0 (bars)[c]	P_1 (bars)[d]	a (cm^3/g)[e]	b (cm^3/g)[f]	W_p (mJ/g)[g]
EFK	0.05	0.45	0.069	0.36	0.067	0.058	0.73
DT	0.06	0.62	0.067	0.17	0.17	0.14	0.63
FF	0.05	0.97	0.061	0.21	0.11	0.089	0.58
FK	0.24	0.45	0.055	1.04	0.23	0.18	7.88
ACEB	0.54	0.67	0.053	1.66	0.47	0.37	25.7
CELI	0.20	0.91	0.062	0.33	0.34	0.28	3.23
KETO	0.63	0.75	0.046	2.63	0.48	0.36	40.5

[a] V_1: compressible volume.
[b] V_2: porous volume.
[c] P_0: first recorded pressure.
[d] P_1: locking pressure.
[e] a: compressible volume at $P = 1$ bar
[f] b: packing slope.
[g] W_p: work transmitted to the powder.

$$W_p = \int P \, dV = \int_{P_0}^{P_1} P\left(\frac{b}{\ln 10}\frac{dP}{P}\right)$$

$$W_p = \frac{b}{2.303}(P_1 - P_0) \qquad (4)$$

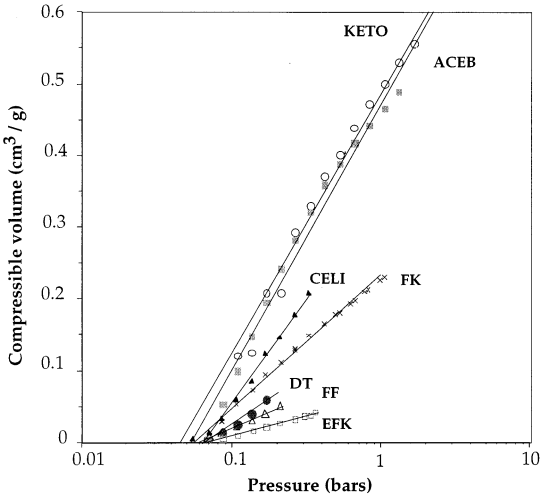

Fig. 5. Compressible volume versus logarithm of pressure, at low pressure values. The linear behavior in this representation made us point out a first order law to describe the powders packing under mercury pressure.

Apparent densities of powders at the end of packing phase ρ_1 (at pressure P_1) and the non-packed densities ρ_{np} (at pressure P_0) were also determined, and values corresponding to the studied materials are reported in Table 5, in comparison with ρ_0, the bulk density determined in tap testing. The specific volume of material under P_0 pressure is calculated from the specific volume of solid $1/\rho_t$ (with ρ_t the apparent particle density) to which is added the compressible measured volume V_1 and the mercury intrusion volume V_2, according to Eq. (5):

$$\frac{1}{\rho_{np}} = \frac{1}{\rho_t} + V_1 + V_2. \quad (5)$$

The density value ρ_1 at the locking pressure P_1 is calculated from the same way according to Eq. (6):

$$\frac{1}{\rho_1} = \frac{1}{\rho_t} + V_2. \quad (6)$$

3.5. Comparison between porosimetry approach and other methods

The density behaviour of the powders studied, as measured by the three different methods, is shown in Table 5. If the critical density as measured in the shear cell is used as a reference value, the powders fall in to three groups. The powders with good flowability: $\rho_{tap} > \rho_c$. The powders with intermediate flow properties: $\rho_{tap} \approx \rho_c$. For powders with bad flowability ρ_{tap} is much smaller than ρ_c.

In the porosimeter, several mechanisms act successively. First, the powder bed is pressed and compacted until the inter-particle contacts become strong enough to resist the pressure of the mercury. With further increasing pressure, the pores are filled and the density of the powder bed

Table 5
A comparison between the different measured or calculated densities

	ρ_0 (g/cm^3)[a]	ρ_{tap} (g/cm^3)[b]	ρ_{np} (g/cm^3)[c]	ρ_1 (g/cm^3)[d]	ρ_c (g/cm^3)[e]
EFK	0.77	0.98	0.88	0.92	0.91
DT	0.89	1.04	0.94	0.96	0.94
FF	0.57	0.65	0.60	0.62	0.64
FK	0.56	0.89	0.75	0.92	0.92
ACEB	0.36	0.57	0.50	0.68	0.66
CELI	0.38	0.57	0.52	0.59[f]	0.59
KETO	0.31	0.51	0.46	0.65	0.63

[a] ρ_o: bulk density (tap testing).
[b] ρ_{tap}: tapped density (tap testing).
[c] ρ_{np}: non packed density, at P_0 (porosimeter).
[d] ρ_l: locked density, at P_1 (porosimeter).
[e] ρ_c: critical density, corresponding to the powder in the steady state (shear cell).
[f] For Celiprolol, the shape of the porogram is such that it is impossible to adjust the end of the packing step under mercury pressure. Then, ρ_1 is considered equivalent to ρ_c, in regard to the values obtained for all the other powders.

Table 6
A comparison between the measured and corrected compressible volumes obtained from porosimetry measurements

	V_1 (cm^3/g)[a]	V_1+V_2 (cm^3/g)[b]	V_0-V_s (cm^3/g)[c]	V_{1c} (cm^3/g)[d]
EFK	0.05	0.50	0.66	0.21
DT	0.06	0.68	0.70	0.08
FF	0.05	1.02	1.11	0.21
FK	0.24	0.69	1.15	0.71
ACEB	0.54	1.21	1.98	1.29
CELI	0.20	1.11	1.82	0.94
KETO	0.63	1.38	2.44	1.64

[a] V_1: measured compressible volume per g of powder.
[b] V_1+V_2: porous volume per gram of powder (detected by mercury porosimeter).
[c] V_0-V_S: porous volume per gram of powder (obtained from tap testing).
[d] V_{1c}: corrected compressible volume per g of powder.

no longer increases (ρ_1). For all powders, the measured density ρ_1 is similar to the critical density ρ_c. This result is interesting because both techniques are completely different in pressure level and method. Apparently, each powder has an intrinsic critical density (ρ_1 or ρ_c), independent of the stress situation, but characteristic of the stochastic optimal arrangement of the particules.

An important point should be discussed here concerning the assessment of the compressible volume from the mercury porosimeter analysis.

The total mercury intrusion volume per gram of powder, detected during the analysis by the porosimeter, is $V_1 + V_2$. On the other hand, at the beginning of tap testing, the porous volume calculated by the difference between bulk volume V_0 and solid volume V_s is systematically greater than $V_1 + V_2$ (Table 6). This observation shows that a fraction of the packing period is not taken into account by the apparatus. The importance of this unmeasured fraction varies with the powder studied. For the most sensitive materials, mercury begins intensive packing of the powder at non-detected pressures, and it should be noted that unfortunately, the slope of $V=f(\log P)$ has highest values at this level.

Therefore, it is better to take into account the real compressible volume V_{1c}, defined as the difference of the void volume of bulk powder and the porous interparticular volume V_2:

$$V_{1c} = (V_0 - V_s) - V_2. \quad (7)$$

Corrected compressible volumes V_{1c} is calculated in these conditions, for all the powders studied are reported in Table 6 with regard to the effective measured volumes V_1.

Fig. 6 shows the compressible volume V_1 versus W_p. The use of V_1 instead of V_{1c} in this representation is justified because the unmeasured powder packing step corresponds to the lowest pressures, and the work transmitted during this step can be considered as negligible when compared to the total work.

Initially, a little work is needed to obtain volume reduction. In this domain, particles are drawn closer whereas friction does not hinder volume reduction. Free flowing powders are characterized only by this first step (Di Tab, Lactose FF and EFK). Powders with poor flowing properties exhibit a decrease in curvature of the slope after this first step. At this pressure level, particles are confined and internal friction becomes important as the number of interparticulate contacts increases.

To achieve these results, we can also plot the compressible corrected volumes V_{1c} versus total work transmitted to the powder at the end of the packing phase. This plot (Fig. 7) shows a linear relationship between V_{1c} and W_p.

A particular case is Celiprolol that must be considered separately. This material differs greatly from others in its compressible volume to packing work relation. The calculated work for this powder is less than expected from the V_{1c} versus W_p

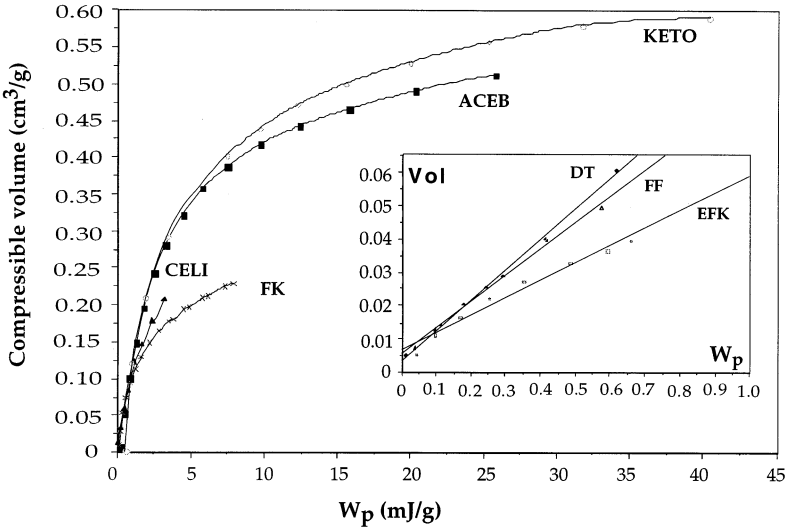

Fig. 6. Compressible measured volume V_1 versus packing work given by mercury for powders during the packing step. Note the scale differences between the free flowing powders and the other group.

plot. This behaviour is explained by the particular porogram of Celiprolol. This porogram shows a linearly shaped curve until the interparticular mercury intrusion plateau is reached. Such a shape makes it impossible to determine graphically its compressible volume. Then, as for the other powders, the packed density under mercury pressure must be close to the critical density determined in the shear cell measurements. The calculated value of the compressible volume for Celiprolol results in a density equivalent to its ρ_c value (0.59). The particular porogram of Celipro-

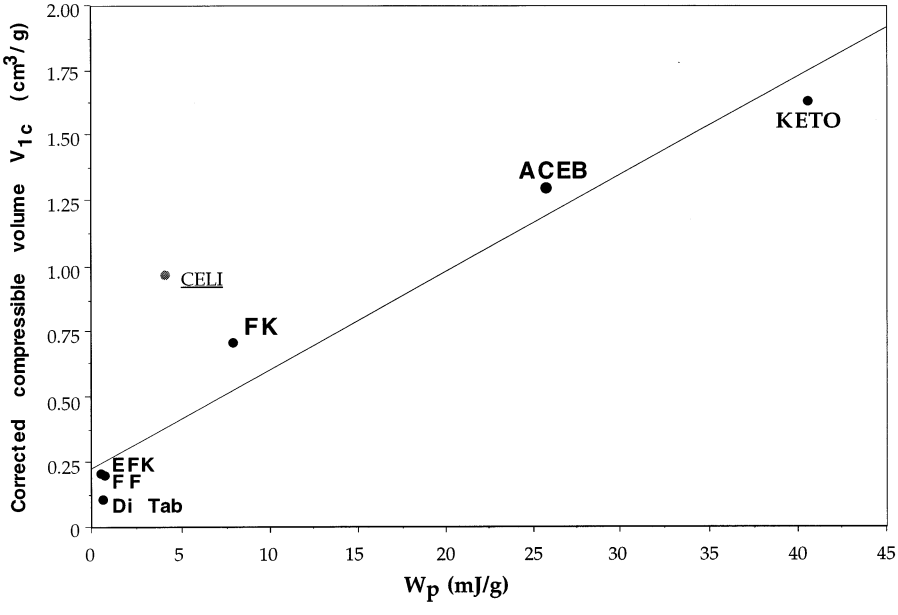

Fig. 7. Linear relationship between the compressible corrected volumes V_{1c} versus the packing work W_p corrected.

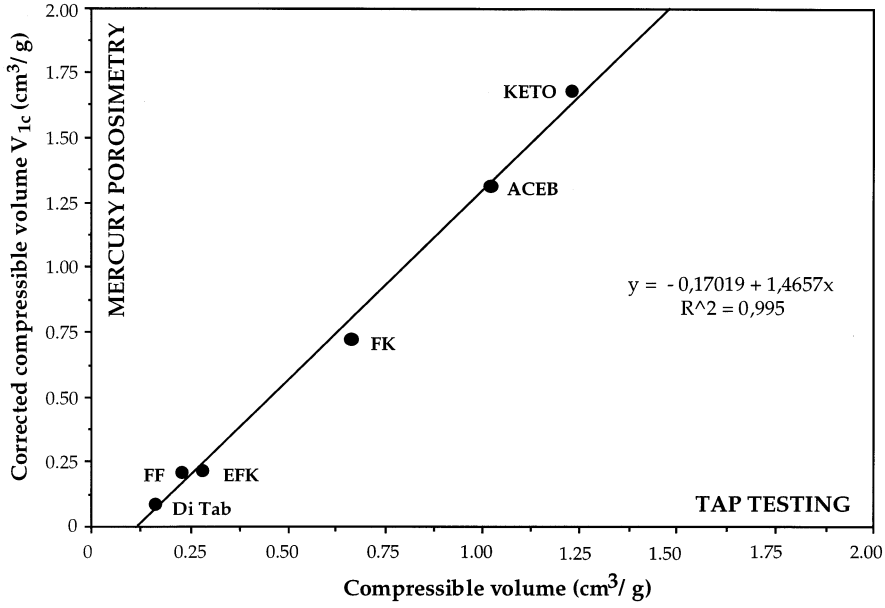

Fig. 8. A comparison between compressible corrected volume (in cm^3 per g of powder) obtained from mercury porosimetry and tap resting.

lol should be associated with its particle size distribution that is rather broad. Then, the most likely hypothesis explaining this particular behavior could be the presence of aggregates (about 100 μm in diameter) constituted of small particles (in a range of size of about 10 μm). Under the mercury pressure, such aggregates must be packed in a first step, but when the pressure increases, aggregates may be broken (they were not however using ultra sounds in the size analysis liquid cell) into a smaller collection, able to rearrange themselves and afterwards to give other smaller aggregates. If this occurs from aggregates to elementary particles, the population at ≈ 10 μm shown by the size distribution analysis, should in fact correspond to elementary particles.

In addition to packing work W_p, evaluated from the porosimeter measurements, three other parameters can be discussed to help distinguish powders in their rheological properties.

First, the pressure P_1, which is different for all powders. P_1 most certainly depends on particle size distribution and surface rugosity of the powder. As the compactability of a powder (DT, FF) is not very dependent on pressure (i.e. the energy received is not transferred to the powder), the locking pressure P_1 and P_0 are rather close. Such powders are 'free-flowing'. Conversely, a great difference between the initial pressure P_0 and locking pressure P_1 may display a conversion of the transferred energy to the powder in cohesion between particles inside the powder bed.

Secondly, the corrected compressible volume V_{1c}, calculated from mercury porosimeter measurements is different for all powders and well-related to the compressible volume $(V_0 - V_n)$, determined by tap testing, as shown in Fig. 8 (slope of the linear plot is 1.47). Thus, mercury porosimetry is more sensitive than tap testing and enables discrimination between powders with very similar compressible volumes.

Thirdly, slope b of the packing curves (Table 4) can be considered to be an intrinsic powder parameter, characterizing flowability.

Finally, differentiation can already be made between Ketoprofen and Acebutolol considering the packing work. The packing work necessary to resist against pressure during the packing stage is 50% greater for Ketoprofen than Acebutolol. This corresponds to the tendency of Ketoprofen to

achieve a more cohesive state than acebutolol, in agreement with shear cell results.

In the same way, Lactose FK is characterized by higher flowability than Ketoprofen and Acebutolol. Lower locking pressure and compressible volume for Lactose FK result in smaller packing work than for Acebutolol and Ketoprofen. We can then classify Lactose FK in an intermediate position between free flowing powders and poor flowing powders. It should be kept in mind that neither Carr nor Jenike indices account for this intermediate classification of Lactose FK.

Likewise, classification of free flowing powders could be corrected depending on the methodology used. With porosimetry, compressible volume V_{1c} is very small with regard to V_2. (i.e. no powder strengthening occurs under mercury pressure). In the same manner, impulses in tap testing have poor effects on particle confinement. The locking pressure, as well as the packing work, registrated values are higher for Lactose EFK than for Di Tab and Lactose FF. This is confirmed by Carr indices but rejected by Jenike indices that set Lactose EFK in a better flowability zone.

4. Conclusion

In this work, we have tried to perform an evaluation of flowability parameters by studying a number of powdered materials with various flow behaviour by three different methods: tap testing, shear cell measurement and porosimetry measurements. Major differences can be pointed out between those three methods.

(a) In porosimetry measurements, the pressure applied on the powder bed during the packing step is exerted through mercury in an isotropic manner. This is a major difference with the other two methodologies, where stresses are applied only in one (tap testing) or two (shear cell) directions.

(b) Tap testing is a quick way to evaluate the flow properties of powders by measuring particle behaviour under gravitational packing. Results are only indicative for densified powders even if a relationship, strictly empirical, exists between the degree of compaction and flow properties.

(c) Jenike approach gives access to powder intrinsic parameters. Flowability index, internal cohesion, friction angle, effective and kinematic yield locii can be obtained. This should have a great relevance to real process but requires the use of considerable quantities of bulk powder and very delicate experiments. These two conditions are very restrictive, particularly in first steps of developments programs where only small quantities of material are available and often highly toxicity properties exist for pharmaceutical drugs.

Since the porosimetry measurements were not used in flow analysis, this work has clearly shown that the first part of porograms can be interpreted in term of compressibility and flowability. This can be appreciated by compressible volume, locking pressure and slope ($\mathrm{d}V/\mathrm{d}(\log P)$) during the packing step. Correlations obtained between porosimetry measurements, tap testing, and particularly shear cell measurements must be confirmed on a larger number of powders, but it seems realistic that mercury porosimetry could possibly provide quantitative and complete information such as flow properties data, size distribution of particles and microporosity, in a single step. Moreover, it should be noted that all data are obtained with 250 mg of bulk powder and that powder sample is confined in a dilatometer, shielding operators from the toxicity drugs. Conversely however, very small quantities of powder may induce some problems of sampling.

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