Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmaceutics and Biopharmaceutics 58 (2004) 427–444
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Review article

Benefits of die-wall instrumentation for research and development in tabletting

Eric Doelker*, Danielle Massuelle

School of Pharmacy, University of Geneva, Geneva, Switzerland

Received 26 January 2004; accepted in revised form 1 March 2004

Available online 18 May 2004

Abstract

Instrumented presses used in tabletting research and development are normally equipped to measure punch force and displacement. Die-wall monitoring is rare, probably because instrumentation and calibration are quite difficult. The authors critically examine the tenets of radial pressure measurement in compression physics. The theoretical background concerning axial to radial stress transmission during the different phases of the compression cycle is presented. The literature reporting on the use of radial stress measurement to assess the self-lubricating properties of materials or the effect of lubricants is reviewed. Examples of interpretation of radial pressure cycles to define the basic material behaviour are given. The influence of particle size and shape as well as that of process and formulation variables on die-wall response are also discussed. Substantial inconsistencies can be seen in the literature with respect to the interpretation of experimental data, often because of the poor reliability of results and mostly because powders are essentially not solid, isotropic bodies. There is also a distinct lack of complementary tabletting parameters that would help understanding their comparative benefits. For this reason, original data on 13 model compounds are presented together with a classification of the materials encountered in pharmaceutical tabletting, based on selected parameters. In conclusion, none of the determined parameters, including those derived from radial pressure measurement, is able, alone, to predict the material behaviour under compression. Although die-wall instrumentation contributes little to the development of improved tablet formulations, it is valuable for characterising the mechanical properties of the materials. This is particularly advantageous given that the mechanical properties account for variations in tabletting performance to a much greater extent than the magnitude of the interparticulate attractions. Nevertheless, because of the peculiar nature of powders compared to solid, isotropic bodies, there is a need to develop new models for analysing their behaviour and to put more emphasis on examination of time-dependent deformation in the later stage of the compression cycle.

Keywords: Die-wall; Instrumentation; Tabletting machine; Radial pressure; Long pressure cycles; Tablets; Compacts; Tablets; R&D

1. Introduction

Nowadays the instrumentation of presses plays an important role in research and development as well as in the production of tablets. Use of instrumented tablet machines is essential for basic research in compression physics, as it facilitates product development, optimisation and scale up, and enables monitoring and control of production.

Tablet machines may be equipped with transducers that can monitor continuously the force acting on the punches (using strain gauges or piezoelectric sensors), the punch displacement (using, e.g. linear variable differential transducers), the ejection force, the force transmitted radially to the die, the so-called 'adhesion' force, and the temperature rise during compaction. Fig. 1 presents a typical set of signals recorded on a single-punch machine which have been digitalised and displayed on a monitor [1].

In tablet production, instrumentation mainly concerns punch force measurement for automatic weight control. In most R&D situations one mainly deals with punch force and displacement determination to derive parameters useful for studying basic material properties (e.g. work of compression, Heckel plot) or tabletting problems (capping or lamination tendency, tooling wear) due to formulation or process variables. Many review articles have been published on the topic in the last decades [2–13].

* Corresponding author. School of Pharmacy, University of Geneva, Quai Ernest-Ansermet 30, CH-1211 Geneva 4, Switzerland. Tel.: +41-22-379-6148; fax: +41-22-379-6567.

E-mail address: eric.doelker@pharm.unige.ch (E. Doelker).

0939-6411/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2004.03.011

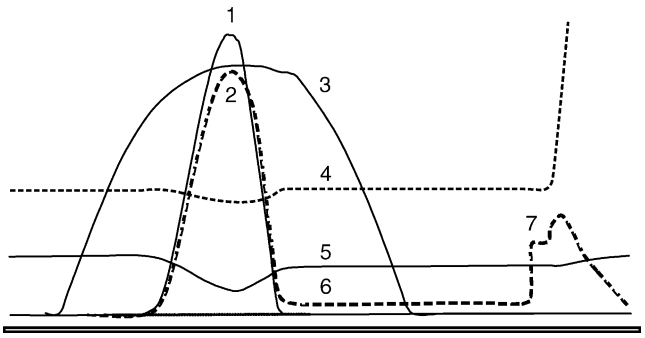

Fig. 1. Typical digitalised signals obtained using a data acquisition system interfacing an instrumented tabletting machine to a computer. The ordinate is the signal intensity and the abscissa is the time (here, about 200 ms for the compression/decompression cycle). Key: (1) upper punch force, (2) lower punch force, (3) upper punch displacement, (4) lower punch displacement, (5) die-wall force (inverted signal), (6) residual lower punch force, and (7) ejection force (the lower punch force is amplified during ejection for better visualisation) [1].

In comparison, much less attention has been paid to the measurement of die-wall response. The reason for that is two-fold: first, die-wall instrumentation is technically difficult and calibration is crucial; secondly, data reported in the literature are often contradictory and thus subject to controversy.

The present article was thus written with the aim of tentatively explaining sources of the contradictory results reported and to draw conclusions about the benefits from die-wall instrumentation. Most of the results shown have been taken from the literature but original data will also be presented.

2. Die-wall instrumentation

Die-wall instrumentation soon followed the installation of transducers for measurement of punch force and displacement, in the mid-1950s. Hydraulic presses, single-punch machines, rotary machines and compaction simulators were successively equipped to determine die-wall pressure.

As for axial force measurement, both strain gauges and piezoelectric transducers were used, but experimental photoelastic techniques were also employed. The different settings for die-wall instrumentation have been reviewed in the literature [1,7,14–20]. Table 1 presents some of the milestones in the field and Fig. 2 shows the most commonly used arrangements for die instrumentation.

Most of these die designs suffer from deficiencies, render calibration difficult and thus data interpretation is not very reliable. The major concern with the most popular cut-away (segmented) die technique (Fig. 2A) is due to non-symmetrical stress/strain distribution within the die. The output signal is thus non-linear and depends on the tablet position in the die and on the tablet height. For these reasons careful calibration as well as complex mathematical corrections have to be carried out [31,33,35]. To overcome these problems, a three-layered die has been described by Rippie and Danielson [30] and further developed by Yeh et al. [32] (Fig. 2B). By restraining the sensing zone to the thin middle layer, this arrangement isolates stresses measured around the tablet and uncouples the stress/strain distribution from those of the rest of the die. The authors are of the opinion that this design is the best reported to date.

Another arrangement is to insert a piston through the die wall and link it to a piezoelectric transducer (Fig. 2C), or to a load cell. However, as the powder to be compressed is directly in contact with the piston acting on the transducer, particles frequently insert at the hole and grip the piston. Moreover, the system may also be dependent on the tablet position and height.

Whatever the method, a careful calibration of the die has to be carried out by applying a set of axial forces on a hydraulic material of different heights and located at different positions of the lower punch. Natural or synthetic rubber, either a plug or as powder, is used owing to its

Table 1
Some important steps in die-wall instrumentation

Authors	Year	Press	Measuring system
Nelson et al. [21]	1955	Hydraulic	Piston inserted through the die and linked to a load cell
Windheuser et al. [22]	1963	Hydraulic	Strain gauges attached onto the outside of a cut die
Ridgway [23]	1966	Hydraulic	Analysis of fringe pattern observed in a Perspex die
Leigh et al. [24]	1967	Single punch	Strain gauges attached onto the outside of a cut die
Marshall [25]	1970	Single punch	Piston touching the outside of a cut die and linked to a piezoelectric transducer
Ridgway and Rosser [26]	1971	Rotary	Analysis of fringe pattern observed in a Perspex die
Edwards [27]	1973	Single punch	Piston inserted through the die and linked to a piezoelectric transducer
Spang [28]	1973	Rotary	Strain gauges attached onto the outside of a cut die
Conte et al. [29]	1977	Single punch	Two piezoelectric load washers mounted in a split die
Rippie and Danielson [30]	1981	Rotary	Three-layered die with integration of a sensing web (strain gauges) into the thick middle layer
Cocolas and Lordi [31]	1993	Compaction simulator	Four piezoelectric transducers located in a spiral arrangement at different heights of the die bore
Yeh et al. [32]	1997	Rotary	Design of split-web die using finite element analysis

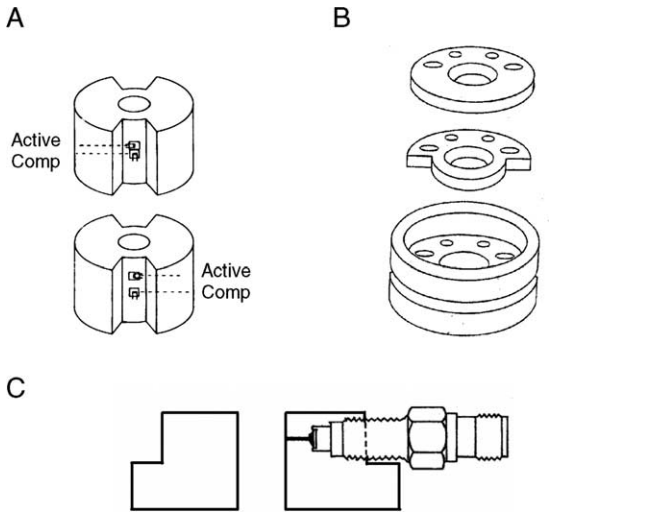

Fig. 2. Some arrangements for die-wall pressure measurement. (A) Cut-away die with active and compensation strain gauges [33], (B) three-layer die with strain gauges [32], and (C) die with a piston inserted through the wall and linked to a piezoelectric transducer [34].

supposedly hydraulic fluid behaviour [22–24,27–30,32,33,35–39], as well as high density polyethylene [31]. However, it has to be emphasised that rubber materials behave like hydraulic fluids when they are solid bodies without any pores. Finally, some hysteresis in the die-wall signal is sometimes observed when the calibration material is positioned at some distance from the strain gauges. This may also depend on the calibration material used [35]. For this purpose, some authors have used pure hydraulic fluids, namely water [24,35] or silicone oil [23].

The complexity of calibrating a segmented die equipped with strain gauges is exemplified by the work of Hölzer and Sjögren [33]. The die-wall signal depends on the position of the lower punch, the rubber height and the applied pressure (Fig. 3).

The variability in the die-wall design and the difficulty of calibrating (including mathematical corrections) may account for part of the discrepancies observed among the data reported in the literature for given materials. Tables 2 and 3 list axial to radial stress transmission ratios, η, reported in the literature for sodium chloride and paracetamol, respectively. Of course, much of the differences are due to the range of maximum applied pressure, the type of tabletting press, the press tooling, as well as the amount of powder compressed and its characteristics (size, shape, crystal defects).

3. Axial to radial stress transmission: theoretical background

A knowledge of some theoretical background is needed to explain experimental radial stress radially transmitted may stress data and thus draw benefits from die-wall instrumentation. The radially transmitted force or pressure (stress) may essentially intervene in two types of analysis:

models related to axial transmission,
models related to radial transmission.

Fig. 4 shows the stresses operating on a powder under compression. The friction force, F_d, is the force lost to the die wall and represents the difference between the two vertical forces:

$$F_d = F_a - F_b \quad (1)$$

where F_a and F_b are the applied force and the force transmitted to the lower punch (in a single-punch press),

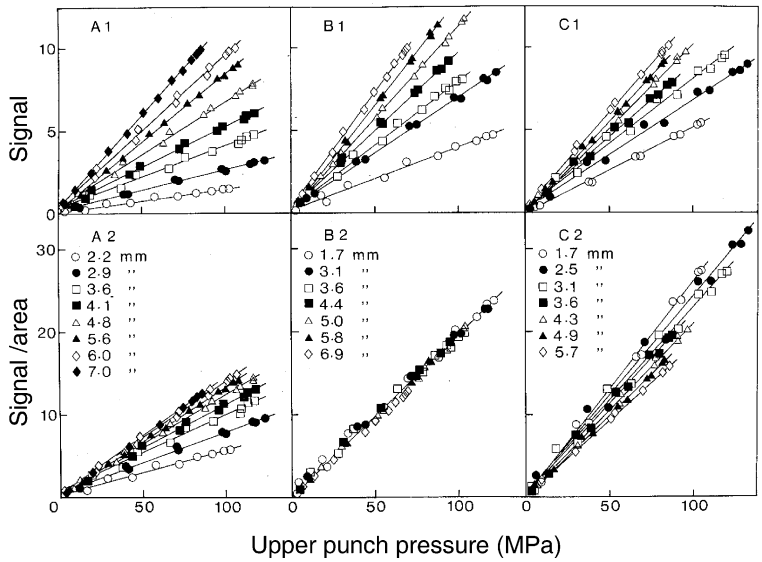

Fig. 3. Influence of compact height on the die-wall signal and on signal per cross-sectional area at various pressures. Lower punch positions: A, 12.2 mm; B, 10.2 mm; C, 8.2 mm [33].

Table 2
Values of stress ratio at maximum applied pressure, η, reported in the literature for sodium chloride

Amount of material or compact height	Particle size (μm) (habit)	Press type	Punch diameter (mm)	Compaction time or speed	Applied pressure (MPa)	Stress ratio (η)	Authors
705 mg	420–840	Hydraulic	9.5	30 s	57	0.59	Higuchi et al. [40]
1000 mg	n.m.	Hydraulic	12.5	n.m.	Up to 150	0.40	Ridgway et al. [41]
4 mm[a]	420–840	Single punch	12.7[b]	11 s	237	0.36	Carless and Leigh [42]
4 mm[a]	420–500	Single punch	12.0[b]	n.m.			Obiorah [43]
	Dendritic				179	0.39	
	Cubic				168	0.35	
2.62 mm	7–20	Rotary	8.0[b]	10 rpm (10 s)	54	0.39	Wiederkehr-von Vincenz [37]
					107	0.60	
					268	0.84	
	130–400				107	0.68	
					268	0.85	
	7–20			31 rpm (0.17 s)	54	0.42	
					107	0.62	
					268	0.82	
3 mm[a]	270	Single punch	11.3	30 rpm	150	0.46	Hölzer and Sjögren [44]
4.6 mm[c]	n.m.	Hydraulic	9.5	5 mm/min	225	0.71	Khossravi et al. [39]

n.m, not mentioned.
[a] At zero theoretical porosity.
[b] Lubricated die.
[c] At maximum applied pressure.

respectively. F_d is sometimes called the frictional force (operating during the compression phase), whereas the ejection force, F_e, is the maximum force recorded on the lower punch during expulsion of the tablet out of the die. The radial force, F_r (radial pressure, P_r) arises as a result of the horizontal expansion of the mass in response to the axial compressive force (pressure).

Here, the term 'pressure', P, will be used interchangeably with that of 'stress', σ. Note also that forces are actually measured and subsequently converted into pressures or stresses using the surface area concerned (punch surface, edge or cross-sectional surface for the die).

3.1. Axial transmission

The radial stress generated by pressing axially a body in a die is present in the numerous equations proposed to describe die-wall friction. In the simple model of pressing from one end in a stationary cylindrical die, these equations relate the pressure applied by the upper punch, P_a, to the pressure transmitted to the lower punch, P_b. A well known derivation is that of Unckel [46]:

$$\frac{P_a}{P_b} = e^{4\mu\eta L/D} \quad (2)$$

Table 3
Values of stress ratio at maximum applied pressure, η, reported in the literature for paracetamol

Compact height[a] (mm)	Particle size (μm)	Press type	Punch diameter[b] (mm)	Compaction time or speed	Applied pressure (MPa)	Stress ratio (η)	Authors
3	14.5	Single punch	12.0	n.m.	112	0.46	Doelker and Shotton [45]
4	420–500	Single punch	12.0	n.m.	160	0.36	Obiorah [43]
	60				180	0.43	
2.62	1–7	Single punch	8.0	10 rpm (10 s)	161	0.57	Wiederkehr-von Vincenz [37]
	170–300				375	0.68	
					161	0.56	
					375	0.67	
3	125–180	Single punch	12.7	Manually	Up to 120	0.35	Krycer et al. [38]

n.m., not mentioned.
[a] At zero theoretical porosity.
[b] Lubricated die.

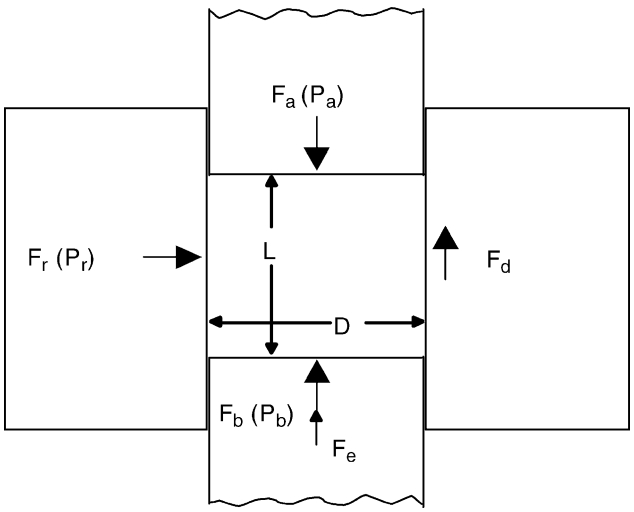

Fig. 4. Forces and pressures operating on a powder under compression in a punch and die assembly. Key: $F_a(P_a)$, force (pressure) applied by the upper punch; $F_b(P_b)$, force (pressure) transmitted to the lower punch; F_d, force lost to the die (axial frictional force); $F_r(P_r)$, force (pressure) radially transmitted to the die wall; F_e, ejection force; D, die diameter; L, height of the compact.

where μ is the coefficient of die-wall friction; η, the stress ratio, defined as the ratio between the radial pressure, P_r, and the applied pressure, P_a; L is the compact length, and D is the diameter of the die.

As μ is the coefficient of friction between the powder mass and the die wall, then:

$$F_d = \mu F_r \tag{3}$$

Unckel, in his equation, used the length initially occupied by the powder fill. Other authors have introduced terms to allow for the effect of changes in the bulk density during compression [47].

All these basic equations describe an exponential decay of the applied pressure down the compact length and postulate constant μ and η values. However, it has been suggested that μ and η may vary along the length of the compact according to the conditions of relative interfacial movement, even though the product $\mu\eta$ could remain constant [48]. This could explain the experimentally observed uneven stress (and density) distribution in compacts. In fact, both axial and radial stress gradients are present although short compacts (like pharmaceutical tablets) are supposed to be reasonably homogenous along the compression axis, especially when the die is lubricated. In contrast, the radial distribution of the axial pressure on the upper and lower punch shows parabolic and symmetric patterns about the central axis of the die [49]. In fact, complex models accounting for both axial and radial stress gradients have been developed, e.g. that of Thompson among them[50]. Note that this author describes the stress ratio η as a measure of powder fluidity. The general conclusion from analysing these models is that monitoring of the radial pressure is needed in order to calculate the coefficient of friction, μ. Finally, mention should be made of the analysis of Mosbab et al. [51], which allows the estimation of intrinsic properties of the material compacted, i.e. Young's modulus and Poisson's ratio.

3.2. Radial transmission

Long [52,53] was the first author to elucidate the theoretical significance of radial vs. axial pressure cycles. Two types of the so-called Long's compression cycles were predicted according to the behaviour of the material compressed, in addition to that of a perfectly elastic body (Fig. 5). Let us examine the compression and decompression profiles obtained with the two types of materials usually encountered. In both cases, line OA (or OA′) is representative of a perfectly elastic behaviour of a solid isotropic plug of material, that is if the axial pressure, P_a, is released, the radial pressure, P_r, would return along this to zero. The radially transmitted pressure is related to the Poisson ratio ν by the relation:

$$P_r = \frac{\nu}{1-\nu} P_a \tag{4}$$

with a slope equal to $\nu/(1-\nu)$ for both types of materials.

When the axial pressure exceeds the elastic limit (yield pressure) A (A′), yield starts and the slope changes differently according to the failure behaviour of the material. For a body with a constant yield stress (strength) in shear, S, the following equation applies:

$$P_r = P_a - 2S \tag{5}$$

so that $P_a - P_r$ remains constant ($= 2S$) and the slope of the line AB will equal unity.

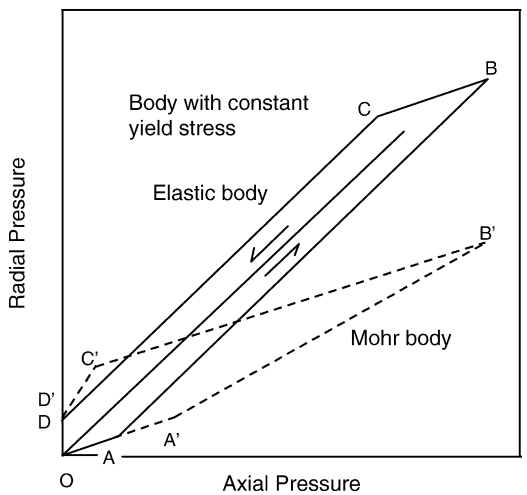

Fig. 5. Theoretical radial pressure cycles for an ideal elastic body, a body with constant yield stress, and a Mohr body. Key: (A, A′), yield points; (B, B′), maximum applied pressures; (C, C′), yield points at decompression; (D, D′), residual die-wall pressures (adapted from Long [52]).

For a Mohr body, i.e. a body with a shear stress depending on the value of the normal stress, Eq. (6) holds:

$$P_r = \frac{(1-\mu)P_a - 2S_0}{1+\mu} \quad (6)$$

where μ is the coefficient of internal friction and S_0 is the yield stress in pure shear.

After the maximum applied pressure is reached (points B and B′), decompression occurs and the plug is no longer forced to yield but recovers elastically. The line BC (B′C′) will be parallel to OA (OA′), with a slope again equal to $\nu/(1-\nu)$.

At point C (C′) the induced radial pressure exceeds the axial pressure and yield again takes place. In the case of a material with a constant yield stress in shear, the line CD will be parallel to line AB and the slope is equal to unity. In the case of a Mohr body, the slope of the line C′D′ is the reciprocal of that of line A′B′ because of stress inversion.

Once the axial pressure has returned to zero but ejection has not yet occurred, the plug will remain under a residual radial pressure, P_{r0}. Its value is:

$$P_{r0} = 2S \quad (7)$$

for a body with constant yield stress in shear and:

$$P_{r0} = \frac{2S_0}{1-\mu} \quad (8)$$

for a Mohr body.

Table 4 summarises the slope values of the various segments. It should be noted that somewhat different notation is used by certain authors [54,55].

In practice, one rarely observes the typical Long's compression cycles. Several reasons have been put forward to explain such deviations [52,53]:

- In case of a perfectly hydrostatic body ($\nu = 0.5$), S is constant and equal to zero, so that A (A′) coincides with O and C (C′) with B (B′). The cycle degenerates into a single straight line defined by $P_r = P_a$ [52].
- A compacted powder is obviously not a solid, isotropic plug and its yield stress cannot be expected to be the same. Thus, segment OA (OA′) is often curved as porosity continuously decreases and point A (A′) is not always visible. It is in fact likely that part of plastic flow is confined to the interparticulate regions [42]. Instead of the slope of the OA (OA′) segment, it is thus better to consider the rest of the cycle where a reasonable degree of densification has occurred.
- The powder yield criterion is not fulfilled when the powder yield locus lies above the wall yield locus [56].
- If the applied pressure has not been large enough to reach the elastic limit, i.e. point A (A′), yield will not take place and the change of slope at point C (C′) will not be observed. This also affects the magnitude of the residual radial pressure.
- Again, if the applied pressure has not been sufficiently high, the part CD (C′D′) may be missing from the cycle, thus affecting the residual radial pressure.
- Die elasticity also affects the shape of the radial compression cycle [53]. This, of course, may be a concern when the die thickness is reduced to position the transducer (cut-die technique). Two different situations have to be considered. First, the cycle is complete and only the slopes of lines OA (OA′) and BC (B′C′) are reduced. The magnitude of the residual radial pressure is unchanged. Second, the cycle is incomplete for one or more of the aforementioned reasons. In this case, line CD (C′D′) is absent and line BC (B′C′) continues to intercept the radial pressure axis, with die elasticity thus causing higher residual radial pressure values.

Table 4
Theoretical slopes and residual die-wall pressure of radial pressure cycles for a body with constant yield stress in shear and a Mohr body

Constant yield stress body		Mohr body	
Segment	Slope	Segment	Slope
OA	$\nu/(1-\nu)$	OA′	$\nu/(1-\nu)$
AB	1	AB′	$(1-\mu)/(1+\mu)$
BC	$\nu/(1-\nu)$	B′C′	$\nu/(1-\nu)$
CD	1	C′D′	$(1+\mu)/(1-\mu)$
P_{r0}	$2S$	P_{r0}	$2S_0/(1-\mu)$
P_a(A)[a]	$2S/(1-\nu)$	P_a(A′)[a]	$S_0 + \mu P_r$

[a] Axial pressure at which yield takes place.

All these justify performing compression studies at sufficiently high applied pressures and comparing different materials at a given relative density (e.g. 0.90).

Finally, in addition to analysing the shape of the compression cycle, it may be informative to calculate the area of the hysteresis loop OABCD (OA′B′C′D′), which indicates the extent of departure from ideal elastic behaviour [7]. Carstensen and Touré [54,57] integrated the various equations related to the compression cycle and reached the conclusion that the hysteresis loop area is linear with the maximum applied pressure in the case of a body with a constant yield stress in shear, whereas it is proportional to the square of the maximum applied pressure for a Mohr body.

4. Use of radial stress measurement to assess the self-lubricating properties of materials or the effect of lubricants during tabletting

Both the friction arising between the material and the die (die-wall friction) and that between particles (interparticulate or internal friction) operate during tabletting. However, internal friction is of significance only at low applied pressures, i.e. during particle slippage and rearrangement, and is definitely not a decisive factor in the tabletting process. In contrast, the friction between the powder mass

and the die wall is a real issue, but only when a sufficient radial pressure has been generated, i.e. beyond a certain consolidation ratio. Only the powder/die friction will thus be considered here.

Friction is present and varies at all tabletting phases: compression, decompression, pre-ejection and ejection. In fact, tabletting problems often originate in the compression and decompression phases but become evident at ejection [58,59].

Friction phenomena occurring during tabletting are usually estimated through various parameters calculated from upper and lower punch force measurements, eventually with punch displacement measurement. These parameters include the ratio of the maximum lower punch force to the maximum upper punch force (referred as to the lubrication ratio, R), or their difference, F_d (Eq. (1)), the ejection force, F_e, the residual lower punch force, the work of friction, and the work of ejection [13]. In fact, factors influencing the friction conditions at the die also affect the radial transmission of the applied pressure. Thus, lubricants (in the broad sense) reduce both the interparticle friction and friction at the die, and hence particles compact more tightly and homogeneously. The result is a decrease in the coefficient of die-wall friction, μ, and an increase in radial stress transmission, η. A consequence may be that the product $\mu\eta$ in Eq. (2) is hardly influenced by the presence of lubricant. The only way to discriminate between the two effects is to monitor the die-wall pressure in order to measure η and then calculate μ. It should be noted that μ can also be experimentally determined using special equipment of a design very different from those of the pharmaceutical tabletting machines [56,60].

Before considering the various coefficients of friction related to the tabletting process, it is convenient to make a clear distinction between static friction—the force to initiate sliding -and dynamic friction—the force to maintain sliding between the two surfaces, that are generally characterised by differing values of friction coefficient.

At least two coefficients of friction can be defined during the tabletting process [59,61]:

$$\mu_1 = \frac{\text{maximum axial frictional force } F_d}{\text{maximum radial force } F_r} \quad (9)$$

and

$$\mu_2 = \frac{\text{ejection force } F_e}{\text{residual die-wall force } F_{r0}} \quad (10)$$

An important limitation has to be noted here. Coefficient μ_2 can be defined as a constant as the compact/die-wall surface does not vary during the sliding process. Coefficient μ_1 is more the result of a formal arithmetic operation. At maximum applied pressure there is no movement and the axial frictional force (force lost to the die) is dependent on the whole compression phase where the applied force has constantly changed as did the surface and its texture.

Note that μ_1 and μ_2 were referred to as the 'static' and 'dynamic' friction coefficient, respectively, and is not consistent with the above definitions. Note also that several authors refer to the product $\mu\eta$ of Eq. (2) as 'apparent coefficient of friction', thus including the stress ratio [48,62,63].

Apart from the tabletting equipment (type of die and its physical state [60,64]) and the product to be compressed, many manufacturing conditions may in practice influence friction coefficient measurements. These include the method of tablet production (unique or continuous) and applied pressure.

The work of Hölzer and Sjögren [61] nicely illustrates the effect of consecutive tablet production and thus die-wall conditioning (Fig. 6). When unlubricated sodium chloride was used (first 20 tablets), μ_1 increased to a constant value of 1.4 (Fig. 6, left). Then, 20 tablets of lubricated sodium chloride were compressed and μ_1 rapidly decreased to a constant value of 0.3. Finally, when returning to unlubricated sodium chloride, more than 30 tablets were needed for μ_1 to reach the starting value of 1.4, indicating that a very

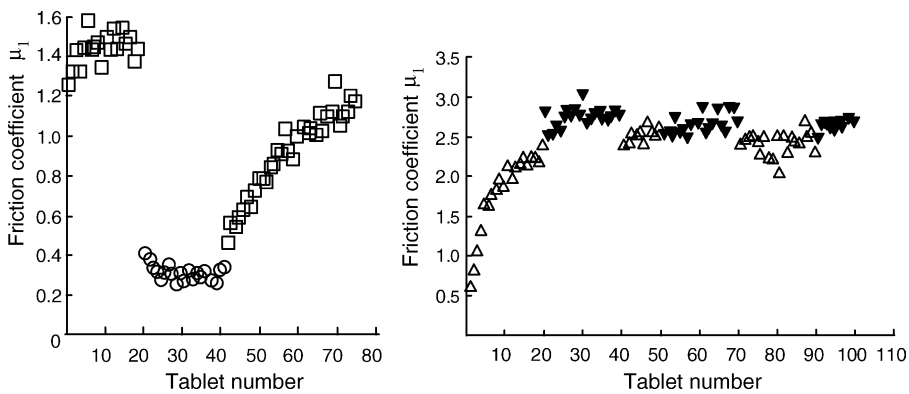

Fig. 6. Effect of die conditioning on coefficient of friction at maximum applied pressure, μ_1, between the die-wall and consecutive tablets of sodium chloride (left) and microcrystalline cellulose (right). Key: □, sodium chloride at 115 MPa; ○, sodium chloride with 1% magnesium stearate; △, microcrystalline cellulose at 60 MPa; ▼, microcrystalline cellulose at 150 MPa [61].

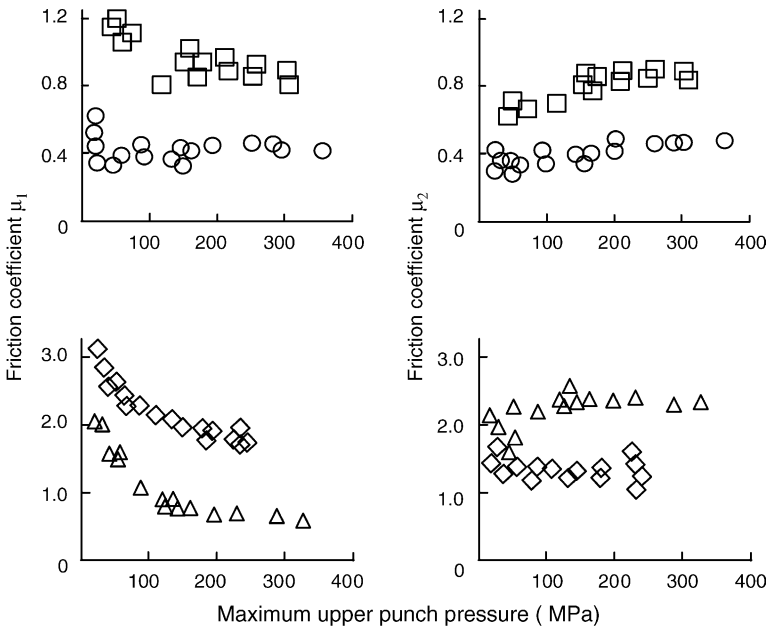

Fig. 7. Variation of the coefficients of friction at maximum applied pressure, μ_1, and at ejection, μ_2, with the maximum applied pressure, P_a, for various model materials. Key: □, sodium chloride; ○, lubricated anhydrous lactose; △, alprenolol hydrochloride; ◇, microcrystalline cellulose (adapted from Hölzer and Sjögren [61]).

resistant film had been formed on the die wall. As for microcrystalline cellulose, only the unlubricated product was tabletted, first at 60 MPa, with a constant μ_1 value reached after 20 tablets (Fig. 6, right). Then, continuing at 60 or 150 MPa did not affect the μ_1 value, nor die cleaning after 50 tablets. Generally, change in μ_1 was due to a change in the axial frictional force F_d and not to the maximum radial force F_r.

The second parameter that can affect the measured μ value is the applied compression pressure. An example is again given by Hölzer and Sjögren [61]. Fig. 7 shows the profiles of μ_1 and μ_2 vs. maximum applied pressure for different materials. For sodium chloride and lubricated lactose μ_1 and μ_2 values were fairly constant. These materials behaved 'normally' as both gave frictional forces, F_d, and ejection forces, F_e, proportional to the applied pressure. In contrast, alprenolol hydrochloride and microcrystalline cellulose exhibited decreasing μ_1 with increasing P_a, but the reasons for that are different for these two materials: for the former a non-linear increase of F_d and for the latter of F_r with applied pressure can be invoked. As for μ_2 it was reasonably constant, but this could be explained by a compensation effect between F_e and F_{r0}. These two materials showed a relaxation of the radial stress above a certain applied pressure, due to capping in the case of alprenolol hydrochloride. It is also worthy of note that for this compound the 'kinetic' coefficient of friction, μ_2, was higher than the 'static' coefficient of friction, μ_1. According to the authors the reason for this discrepancy could be the adhesion of material to the die wall.

In fact, mention should be made of the role of adhesion of the material to the die wall according to Coulomb's equation:

$$F = \mu F_r + C \tag{11}$$

where F_r is the radial force acting normal to the frictional force F, and C the adhesion of the powder to the die wall. Both μ and C can be estimated by measuring of F_d or F_e and F_r by different compressive forces. A good example is given by Kikuta and Kitamori [65] with lactose granules combined with lubricants, even though the coefficient of friction at ejection was determined using special equipment fitted to a hydraulic press (Table 5). Interestingly, a good correlation was observed between the calculated adhesion values C and the binding characteristics of the materials on

Table 5
Relation between coefficient of friction, μ_2, and C values obtained on a specially equipped hydraulic press and the adhesion tendency during experimental testing and tabletting on a rotary machine (adapted from Ref. [65])

Lubricant	Concentration (%)	Mixing time (min)	μ	C (kg/cm^2)	Adhesion[a]	
					Static	Dynamic
Mg stearate	0.1	1	0.20	12	−	++
		10	0.19	8	−	±
		30	0.18	4	−	−
	0.3	1	0.22	5	−	−
		10	0.17	3	−	−
		30	0.12	2	−	−
Talc	1.0	10	0.48	23	+	++
	2.0	10	0.38	14	±	++
	3.0	10	0.35	7	−	±

[a] Qualitative expression: ++, severe; +, moderate; ±, slight; −, none.

Table 6
Frictional parameters of various excipients and drugs compressed at 150 MPa (15 kN), both without and with magnesium stearate (adapted from Ref. [61])

Material	R	F_d (kN)	η	μ_1	F_e (kN)	F_{r0} (kN)	μ_2
Microcrystalline cellulose	0.77	2.03	0.42	1.97	0.25	0.19	1.29
Lactose, anhydrous	0.65	5.29	0.39	2.25	3.18	1.19	2.68
Mg stearate 0.10%	0.64	5.44	0.38	2.44	5.10	1.62	3.15
Mg stearate 0.25%	0.95	0.81	0.42	0.34	0.23	0.61	0.38
Mg stearate 0.50%	0.95	0.68	0.44	0.26	0.26	0.63	0.42
Sodium chloride	0.76	3.63	0.49	1.37	0.86	1.04	0.83
Mg stearate 0.25%	0.93	1.03	0.59	0.33	0.12	0.53	0.23
Mg stearate 0.50%	0.94	0.97	0.59	0.31	0.11	0.47	0.23
Mg stearate 1.00%	0.96	0.56	0.60	0.17	0.09	0.37	0.23
Alprenolol HCl	0.86	2.03	0.56	0.72	0.75	0.51	1.47
Aspirin	0.84	2.46	0.55	0.88	0.16	0.14	1.15
Paracetamol	0.80	3.07	0.38	1.55	1.12	0.65	1.72

both the special testing instrument (static friction) and an actual rotary tabletting machine (dynamic friction). In contrast, no correlation was observed between coefficient of friction and adhesion characteristics of the materials. It is also interesting to point out that different values of μ would have been calculated according to Eq. (10), i.e. by dividing the ejection force by the residual die-wall force.

The benefits of comparing friction coefficients of materials compressed at constant pressure have been shown for both excipients and drugs (Table 6). Note that the authors normalised the frictional force F_d and the ejection force F_e by the contact surface area between tablet and die-wall, as suggested by Rees and Shotton [66]. This was not done for the sake of coherence with the other data reported in the present review. Determination of the coefficients of friction helps to characterise the auto-lubricating properties of the materials tested and to optimise the lubricant concentration (see Section 5.3). In the present case, the much higher sensitivity of the μ_1 parameter relative to the lubrication ratio R (axially transmitted pressure) is also demonstrated.

The last example deals with the effect of internal lubrication (i.e. adding a lubricant to the powder mass) vs. that of external lubrication (i.e. prelubricating solely the die). In the former case, 0.2% magnesium stearate or 0.5% stearic acid was added to a direct tabletting caffeine formulation. In the latter case, the lubricant powder was dusted on the tools. Tabletting was carried out at 9 and 15 kN on a rotary press [59]. Both internal and external lubrication act favourably on the tabletting process and there are only slight differences in μ_2 values between the compression trials with added lubricant and die prelubrication (Table 7). This confirms that the reduction of interparticulate friction is not decisive and that die-wall prelubrication has no deleterious impact on tablet characteristics such as disintegration time and mechanical strength, in contrast to internal lubrication.

5. Die-wall compression cycles

Continuous monitoring of the die-wall pressure as a result of applied pressure has found use in the determination of the material-related compaction characteristics (body with constant yield in shear or Mohr body, polymorphism, pseudopolymorphism, particle size and shape) as well as in the evaluation of formulation (moisture content, binder, lubricant) or process (compaction speed) variables.

The following parameters are employed, either alone or in combination (see Section 3):

- slopes of the various segments of Long's compression cycle,
- axial to radial stress ratio at maximum applied pressure, η,
- residual die-wall pressure after load release or at ejection P_{r0},
- hysteresis loop area of Long's cycle,
- plot of hysteresis area vs. applied pressure.

Table 7
Influence of internal and die-wall lubrication on the tabletting of a caffeine formulation [59][a]

Lubrication	Compression force (kN)	η	F_e (N)	F_{r0} (N)	μ_2	Disintegration time (min)	Crushing force (N)
–	9	0.25	1000	862	1.16	1.1	135
Mg stearate 0.2%	9	0.41	340	718	0.42	1.8	126
Die wall, Mg stearate	9	0.42	60	646	0.09	1.0	149
Stearic acid 0.5%	9	0.36	160	790	0.33	2.3	101
Die wall, stearic acid	9	0.40	240	718	0.33	0.7	137
–	15	0.33	1160	1384	0.85	4.5	>200
Mg stearate 0.2%	15	0.46	340	1005	0.34	10.2	>200
Die wall, Mg stearate	15	0.50	160	933	0.17	5.3	>200
Stearic acid 0.5%	15	0.42	450	1149	0.39	9.2	167
Die wall, stearic acid	15	0.42	300	1292	0.23	4.3	>200

[a] Caffeine formulation: 39% microcrystalline cellulose, 59% anhydrous lactose, 2% caffeine.

Table 8
Parameters from Long's compression cycles of representative materials

Material	P_a (MPa)	Segment slopes				η	P_{r0} (MPa)	Ref.
		OA	AB	BC	CD			
Paracetamol	175	0.17	0.45	0.35	3.00	n.a.	n.a.	[73]
	180	0.14	n.a.	n.a.	n.a.	0.43	8	[43]
Paracetamol DC[a]	175	0.23	n.a.	n.a.	n.a.	0.37	20	[43]
Lactose SD	170	0.22	n.a.	n.a.	n.a.	0.35	25	[43]
	235	0.49	n.a.	n.a.	n.a.	0.71	61	[31]
Dicalcium phosphate	175	0.23	0.45	0.24	1.00	n.a.	n.a.	[73]
	325	0.47	n.a.	n.a.	n.a.	0.68	103	[31]
Sodium chloride, cubic	166	0.26	0.37	0.04	0.71	0.33	45	[74]
Sodium chloride, dendritic	170	0.33	0.47	0.10	0.23	0.42	52	[74]

n.a., not available.
[a] Direct compression paracetamol containing 4% gelatine hydrolysate.

5.1. Material behaviour

A knowledge of the shear failure of a given material is pharmaceutically important in many areas: successful tabletting, sensitivity to lubricant, tablet disintegration or dissolution. Materials with constant shear stress (plastic or ductile materials) are generally presented as forming coherent tablets whereas Mohr bodies (brittle materials) are prone to capping and lamination. This simplistic view has to be modulated by taking into consideration the elastic and viscoelastic properties of the materials Moreover, Hiestand [58,67–69] is of the opinion that possible particle fragmentation during the compression phase is of little importance as the strength of the compact depends on the behaviour of the material on unloading.

Many investigators have attempted to relate the shape of the compression cycles of model materials to their ability to (or not to) form good compacts. For the present discussion we will consider representative materials of the various types reported in the literature [37,71,72].

Regarding paracetamol, known to cap at ejection, Leigh et al. [24] have concluded that its behaviour resembles that of a Mohr body, while that of paracetamol granulated with 3% povidone (which does not cap) is similar to the behaviour of a body with constant yield stress. A classification with respect to constant stress was also proposed for sucrose and sucrose granules. It is noticeable that the authors rid themselves from the requirement for the slope of segments AB and CD to be unity and only rely on the equality of both slopes (see Fig. 5 and Table 4). As for sodium chloride, it was declared as a body with constant yield stress at low applied pressures, with a Mohr behaviour at high pressures [24].

Later, Shotton et al. [43,45,70,73] found that paracetamol, both with and without a binder, exhibited compression cycles resembling a Mohr body. Obiorah and Shotton [43,74] also classified sodium chloride as a Mohr body, in contrast to Long [52].

Table 8 lists some slope values as well as stress ratios and residual die-wall pressures of representative materials. As a matter of fact, values of unity for slopes AB and CD were never observed for sodium chloride, known to deform plastically. Reasons for discrepancies have already been discussed, in particular the fact that these materials are not models of solid, isotropic bodies. The present authors are also convinced that these inconsistencies result in many cases from defect in die calibration. It comes out that classifying materials based on slope calculation is not reliable.

Another way of gaining insight from the radial–axial pressure cycle is to look at the area of the hysteresis loop, which reflects the extent of departure from ideal elastic behaviour. This approach has been followed by Touré [57] when analysing the effect of moisture content on the compactibility of starch granules. A good correlation was observed between hysteresis area and tablet mechanical strength. However, here a single material was investigated.

A recent work by Khossravi and Morehead [39] compared the hysteresis areas of the 1st and 5th compression cycles, representing the quasi-equilibrium state (Table 9). Considering only the hysteresis areas of the 1st cycle, the values are quite similar except for the plastically deforming sodium chloride. In particular the non-tablettable

Table 9
Hysteresis areas for the 1st and 5th compression cycles along with the percent change of representative materials compressed at 225 MPa [39]

Material	Hysteresis area (MPa^2)		
	1st cycle	5th cycle	Percent change
Microcrystalline cellulose	4860	2434	69.9
Sodium chloride	12,725	2795	78.0
Aspirin	4300	3357	21.9
Lactose monohydrate	5707	1490	73.9
Sucrose	6340	1108	82.5
Paracetamol	6290	2720	56.8

paracetamol displays a hysteresis area noticeably higher than that of microcrystalline cellulose, confirming that the value calculated for the first compression–decompression cycle is not an indicator of material compactibility, but of the extent of elastic behaviour. Comparing now the areas for the 1st and 5th cycles, it is not quite clear that they are comparable for plastic materials (sodium chloride and aspirin), in contrast to the case of brittle materials (lactose monohydrate, sucrose, paracetamol), as stated by Khossravi and Morehead [39].

Another type of investigation of the consolidation behaviour of materials is to simply consider the axial to radial stress ratio, η, relying on the observation of Windheuser et al. [22] that materials which permit good conversion of axial pressure to radial pressure tend to form a good compact. Since then, a similar conclusion has been drawn by many authors but seems essentially valid when considering the effect of an additive—most often a binding agent—on the compression cycle of a given material (see Section 5.2). This is not the case when materials of different types are compared [33,37–39,42,43]. Interestingly, it has been observed by Higuchi et al. [40] and by Ridgway et al. [41] that axial to radial transmission increases as the material hardness decreases, probably due to the lower yield strength allowing increased area of contact and thus stress transmission.

Long's compression cycles have been interpreted in terms of hysteresis area as a function of applied pressure in order to distinguish bodies with constant yield stress from Mohr bodies [54,57]. The data of Leigh et al. [24] were re-analysed with the conclusion that sodium chloride behaves like a Mohr body [54,57]. As noted by Krycer and Pope [5], this does not resolve the conflict with independent studies showing that sodium chloride consolidates by plastic deformation rather than by brittle fracture. A Mohr behaviour was also observed for a starch granulation using the aforementioned analysis [54,57]. In addition, a good correlation was found between the hysteresis loop areas of lower punch and of die-wall pressures versus applied pressure [57,75].

Long's compression cycles and axial to radial stress ratios are in fact not much influenced by the type of material considered, because the measured radial pressure contains an elastic component. In contrast, residual die-wall pressure reflects irreversible deformation (except axial expansion). The first investigation into the nature of the residual die-wall pressure was that by Higuchi et al. [40]. First, the authors observed a correlation between the ejection force and the residual die-wall pressure. Second, they could show that this lateral die-wall response actually decays with time, reaching (under the conditions used) equilibrium within roughly 2 min, at a rate dependent on crystal hardness and interparticle friction. Later, Shotton and Obiorah [43,73,74] found that materials forming satisfactory tablets displayed high residual die-wall pressures whereas values were low for materials likely to cap or laminate. This would suggest that the P_{r0} parameter is a measure of the compact capability to withstand the radial force exerted by the die. Unfortunately, viscoelastic materials like microcrystalline cellulose or dextrates were not involved in the above-mentioned studies, and in fact such materials form strong tablets although exhibiting P_{r0} values as low as for instance the poorly compactible paracetamol [37,61]. This indicates that the compact had recovered axially, either elastically or by brittle failure. In fact, conflicting results were reported on elastic recovery of microcrystalline cellulose compacts [37,38], possibly because the mechanism of compaction varies with applied pressure as shown for the elastic recovery as measured after tablet ejection (Fig. 8, left) and for the residual die-wall pressure (Fig. 8, right). Note that Krycer et al. [38] also measured residual die-wall pressure after multiple compression but this apparently did not reveal more information regarding the compaction mechanism. In another report the same investigators warned that

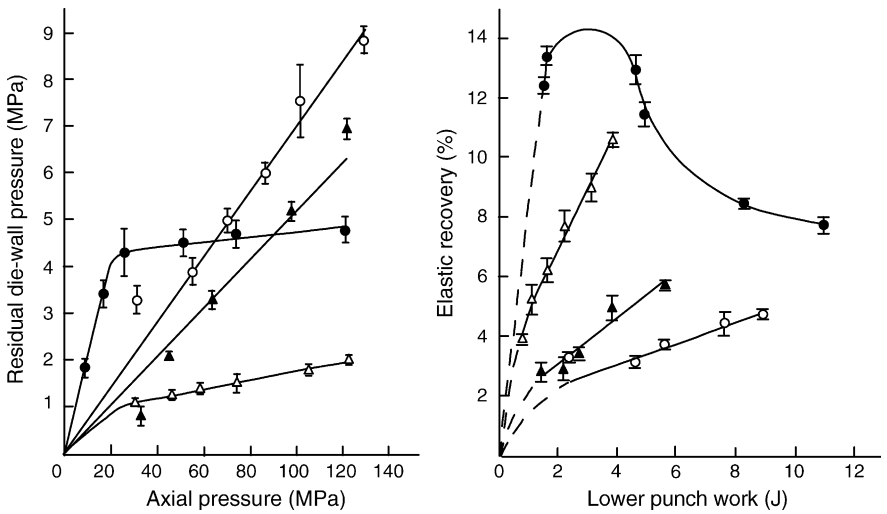

Fig. 8. Residual die-wall pressure, P_{r0}, vs. maximum applied pressure, P_a, plot (left) and elastic recovery, ER, vs. lower punch work plot (right) for various model materials. Key: ●, microcrystalline cellulose; ○, D.T. sucrose; ▲, mannitol; △, paracetamol [38].

the capping tendency cannot always be predicted from residual die-wall pressure and proposed a capping index to be calculated from the gradient of elastic recovery vs. P_{r0} plot [76]. A noteworthy point is that microcrystalline cellulose was not included in the second paper. In fact, elastic recovery was measured after tablet ejection and may not be indicative of the expansion in the die, where failure occurs. At the least, comparative data on more materials are needed to evaluate the benefit of measuring residual die-wall pressure. In contrast, it is a meaningful indicator of possible friction at ejection.

Finally, it is of interest to notice that differences in die-wall response (shape of the pressure cycle, stress ratio and/or residual radial pressure) were observed for different polymorphs of sulfathiazole or barbital [77] and for pseudopolymorphs of lactose [43,70] or magnesium stearate [78].

5.2. Influence of particle size and shape

Very few studies have been published on the effect of particle size or particle shape (crystal habit) on the parameters derived from die-wall pressure measurement [24,37,43,70,74,77]. For the plastically deforming sodium chloride changing particle size did not significantly affect the residual die-wall pressure and ejection force and thus coefficient of friction μ_2. However, coarser particles generated better axial to radial transmission at maximum pressure, and weaker tablets. This contrasts with the similar product potassium chloride (parallel increase in η and tablet mechanical strength) [37]. Regarding the brittle material sucrose, the residual die-wall pressure did not vary with particle size, whereas a decrease in ejection force was observed for coarse particles, and thus a reduced μ_2 value. During compression, the radially transmitted pressure was not influenced by particle size, but weaker tablets were produced with coarser crystals [24,37]. A similar pattern was obtained with the brittle, but poorly compactible paracetamol. The only remarkable difference was that the residual die-wall pressure was much higher for fine particles that resulted in coherent tablets whereas capping was noticed for coarse material [37]. Generally, compression cycle profiles were not very much affected by particle shape, either for the plastically deforming sodium chloride [38,40] or the brittle material lactose [70]. The only significant difference was a reduced axial transmission of the applied pressure and thus an increased coefficient of friction in case of dendritic sodium chloride compared to cubic sodium chloride. This was also evident for more irregular lactose particles that also induced a higher ejection force and thus friction coefficient. As for the crushing strength of lactose tablets, it was superior for regular particles probably because of better densification. In any case, one has to recognise that reports on the effect of particle size and shape are too few to formulate general conclusions. Finally, mention should again be made of the work of Summers et al. [77] who obtained significant differences in the Long's compression cycles for various aspirin crystal habits.

5.3. Formulation and process variables

Investigations dealing with the effect of formulation variables on die-wall response are mainly concerned with two types of additives, namely binders and lubricants, as well as with the moisture content of the mass to compress.

With the exception of dicalcium phosphate [45], all studies involving binders report on the compactibility of paracetamol for obvious reasons [24,38,43,45,70,73,76]. They generally show an improvement of the tablet mechanical strength, but the effect on the radial transmission of the applied pressure is rather controversial. An example is given by the work of Doelker and Shotton [45] for both paracetamol and dicalcium phosphate granulated with 4% povidone, maize starch or methylcellulose. For paracetamol, the radial conversion during compression was lower in presence of a binder, whereas residual die-wall pressure increased (Fig. 9, left). An opposite trend was

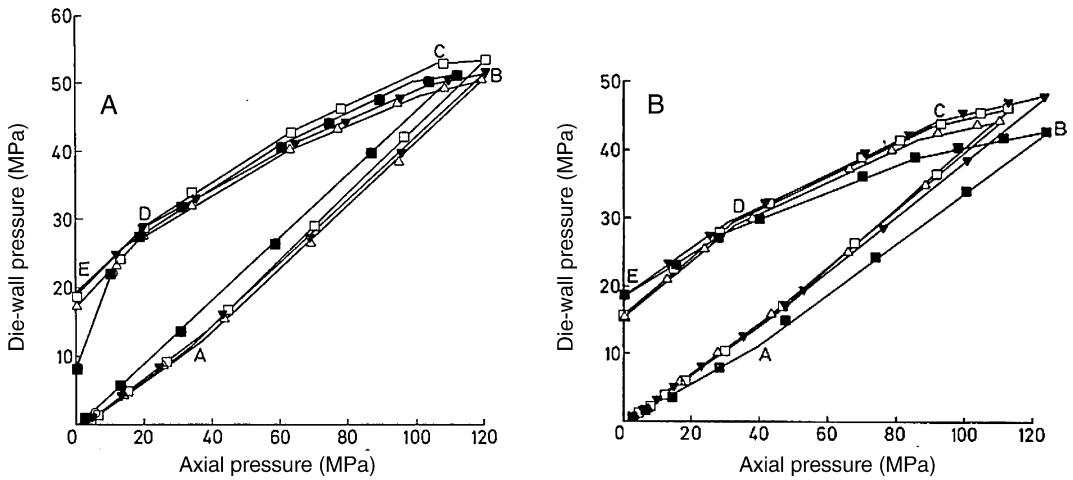

Fig. 9. Pressure cycles for (A) paracetamol powder and granules, and (B) dicalcium phosphate powder and granules. Key: ■, powder; △, povidone granules; ▼, maize starch granules; □, methylcellulose granules [45].

observed for dicalcium phosphate: increased radial transmission and slightly reduced residual die-wall pressure (Fig. 9, right).

Other reports on paracetamol are generally in line with the above-mentioned study [43,70,73], but work by Carless et al. [24,42] displays increased η values for direct compression paracetamol.

It is evident from most studies that a good radial transmission of pressure alone is not sufficient to explain compactibility, as exemplified by paracetamol. On the other hand, for paracetamol again, tablet formation was related to a higher residual die-wall pressure, but the strongest tablets (with povidone as a binder) were not associated with the highest P_{r0} value [45]. Probably, the effect of particle size and that of material hardness play a prominent role besides that of the binder on the axial to radial pressure transmission.

As already mentioned, for measuring the effect of the type and concentration of lubricant during compression most authors rely on the axial frictional force, F_d, the ratio of lower to upper punch force, R (the so-called lubrication ratio), or eventually the work of friction if the press is equipped with displacement transducers, the residual force on lower punch before ejection, F_{b0}, and the ejection force, F_e. Generally, good correlations are obtained with the performance of the lubricant, especially with F_e. To evaluate the possible benefit of monitoring die-wall pressure, a look at the literature led only to the investigations by Hölzer and Sjögren [61] and Schrank-Junghäni et al. [59]. The latter work on the effect of magnesium stearate and stearic acid on the tabletting performance of a caffeine formulation has already been commented upon in terms of coefficient of friction. It can be added that the lubricants (and die-wall prelubrication) drastically increased the axial to radial stress transmission and the residual die-wall pressure. As for Hölzer and Sjögren [59], they have fully reported (except the residual lower punch force) on the various parameters resulting from the tabletting of anhydrous lactose and sodium chloride combined with magnesium stearate (Table 6). Regarding friction at maximum applied pressure, the axial to radial transmission ratio slightly increased in presence of magnesium stearate, in agreement with the known fact that lubricants favour densification. In parallel, the friction force (as assessed through R or F_d) decreased for lubricated materials. It is interesting to note that addition of 0.1% magnesium stearate was not sufficient to prevent adhesion of lactose to the die wall. Friction coefficient also diminished because the effect of lubricant was much more pronounced on the frictional force than on the radial transmission.

The same pattern was true when the friction at ejection was considered, but the effect of the lubricant on the radial transmission was more marked. A point raised by the authors is that the friction coefficient, μ_1, was 0.2–0.4 for well-lubricated materials, 0.7–2 for poorly lubricated materials but non-sticking materials, and above 2 if adhesion to the die wall occurred. However, it is our opinion that similar conclusions could also be drawn if only F_d (or R) and F_e had been considered.

The moisture content of the mass often influences compression characteristics. In fact, a small proportion of moisture is generally present in the formulation and, in some cases, this is necessary to form a tablet. Thus, paracetamol granules are satisfactorily compressed only if the moisture content is above 1% [2,79].

An investigation dealt with the effect of moisture content of sodium chloride [80,81]. At low level (0.02%) die-wall friction was increased probably because of an increase in the radial to axial stress ratio. At moisture contents above 0.55% friction was reduced at all pressures owing to the lubricating effect of water. Studies on the effect of moisture content on tabletting are actually scant and those reporting die-wall monitoring even rarer. We have already commented on the work of Touré [54,57,75]. That of Obiorah [43,73] relates to the influence of moisture content on the behaviour of the two poorly compactible products paracetamol and phenacetin, both as powders and granules. Adding water yielded coherent tablets and led to a slight increase in the OA slope values of Long's cycles, the radially transmitted pressures and the residual die-wall pressures.

A final factor likely to affect radial response is the speed of compression, through its influence on densification and permanent deformation. Actually, when increasing the compression speed of the rotary machine by 60 (contact time of 0.17 instead of 10 s), Wiederkehr-von Vincenz [37] did not observe significant changes in the stress ratio and residual die-wall pressure of sodium chloride, potassium chloride and sucrose.

6. Which parameters are of importance?

When looking into the literature reporting on radial pressure measurement, we are confronted with both inconsistencies and lack of a full complement of parameters that would help to understand their comparative benefits. In particular, we were interested in gaining insight into the effect of the material characteristics on the parameters related to Long's compression cycles and not so much to that of lubrication. We thus decided to carry out a complete investigation of the compression characteristics of 13 materials, representative of the two broad categories as reported in the literature from independent studies:

- 8 materials known to generate high tablet strength: sodium chloride, potassium chloride, paracetemol DC with 5% gelatine (Mallinckrodt), powdered cellulose (Elcema® P 100), microcrystalline cellulose (Avicel® PH 101), pregelatinised starch (Starch® 1500), dicalcium phosphate dihydrate (Emcompress®) and nitrofurantoin,

- 5 materials known to yield low tablet strength: maize starch, hexamine, sodium bicarbonate, phenacetin, and paracetamol.

A 100–200 μm size fraction was generally used, except for the proprietary products. Each material was compressed at 150 MPa on a single punch machine (Korsch EK-0) instrumented as described by Rime et al. [82]. In addition, the radial pressure was measured using a cut-away die instrumented and calibrated in a similar way to that of Hölzer and Sjögren [33]. Polynomials were used to account for the effects of applied pressure, compact height and lower punch position. The weight of each material was calculated from its true density to provide a 2-mm high tablet at zero porosity using a 12-mm flat-faced punch and die set. In order to elucidate the densification characteristics of the materials, the die was prelubricated by dusting with magnesium stearate powder. Thus, friction related parameters will not be reported here ($R > 0.91$, $F_e < 600$ N). For each material, both single and double compression cycles were performed in order to determine the net work of compression. The data are summarised in Table 10, using the symbols defined previously [13]. The assignment of the materials to one class or the other is based on the work of Nyström et al. [71,72].

It is logical to relate the energy brought by the press (as mechanical work done by the upper punch, W_u) and the tablet strength, F_c. However, it has to be recognised that the compaction work is used to (i) cause packing and rearrangement of primary and subsequently of broken particles, (ii) induce elastic deformation, plastic deformation and/or brittle fracture of the material, and (iii) to overcome friction between particles and friction between particles and the die. The most decisive factor (ii) is material-dependent (particle rearrangement is not highly energy demanding and, here, external friction is low because the die was prelubricated). In this respect, materials exhibiting strong attractions and high surface bonding are more difficult to densify. In this respect, powdered and microcrystalline cellulose, where considerable hydrogen bonding is present, show high W_U values compared to the materials yielding unsatisfactory tablets, even though all materials had been compressed at the same pressure. The work of expansion, W_{EXP}, is the recoverable part of the

Table 10
Compression characteristics of representative materials tabletted at 150 MPa (unpublished data)

Material type	W_U (J)	W_{EXP} (J)	PL_1 (%)	PL_2 (%)	P_y (MPa)	Segment slopes				η	P_{r0} (MPa)	A_1 (MPa^2)	A_2 (MPa^2)	ε_c (%)	ε (%)	ER_0 (%)	ER (%)	F_c (N)
						OA	AB	BC	CD									
High tablet strength																		
Plastic materials																		
Sodium chloride	7.4	1.1	84	90	73	0.27	0.47	0.19	0.26	0.37	19.2	2905	2076	5.8	7.0	0	1.1	194
Potassium chloride	6.6	0.7	90	88	44	0.28	0.58	0.26	0.71	0.44	25.5	3696	2149	0.9	4.0	0	3.4	192
Paracetamol DC	7.3	1.0	86	79	76	0.28	0.37	0.22	0.42	0.32	12.3	2036	1505	5.0	9.5	2.4	4.7	111
Viscoelastic materials																		
Powdered cellulose	10.5	1.3	88	79	75	0.29	0.42	0.26	0.37	0.35	5.3	1545	1275	4.1	13.8	4.7	10.3	147
Microcrystalline cellulose	11.3	1.1	90	85	55	0.29	0.47	0.26	0.41	0.35	4.3	1197	1130	1.1	7.9	2.0	7.0	426
Pregelatinised starch	8.2	1.5	82	67	41	0.29	0.54	0.34	0.57	0.40	3.7	2264	1241	2.2	13.5	3.8	11.4	76
Brittle, plastic materials																		
Dicalcium phosphate	7.1	0.6	92	85	215	0.25	0.31	0.19	0.34	0.30	10.3	1528	1571	17.2	19.0	0.8	2.1	75
Nitrofurantoin	7.4	0.8	90	83	124	0.33	0.47	0.23	0.38	0.39	11.2	1994	1668	11.5	15.2	2.2	4.3	108
Low tablet strength																		
Plastic materials																		
Maize stach	9.1	1.1	87	75	58	0.28	0.56	0.31	0.52	0.39	4.5	2357	1302	2.0	13.0	2.4	10.8	16
Hexamine	4.7	0.7	85	83	41	0.31	0.54	0.24	0.89	0.44	9.5	3707	2361	0	3.0	0	4.0	25
Sodium bicarbonate	6.9	0.7	89	86	117	0.26	0.33	0.18	0.44	0.30	11.3	1762	1546	11.0	10.8	0	2.2	34
Brittle, elastic materials																		
Phenacetin	3.3	0.5	86	62	53	0.33	0.50	0.23	0.46	0.40	8.5	2274	1566	1.4	C/L[a]	2.2	C/L[a]	C/L[a]
Paracetamol	3.6	0.8	78	57	69	0.28	0.37	0.22	0.42	0.33	6.6	2095	1947	1.2	C/L[a]	2.4	C/L[a]	C/L[a]

W_U, upper punch work; W_{EXP}, work of expansion (upper punch); PL_1 (plasticity index 1) $= 100(W_U - W_{EXP})/W_U$; PL_2 (plasticity index 2) $= W_N$(net work)/WL (lower punch work, 1st compression cycle), where $W_N = WL - WL$ (lower punch work, 2nd compression cycle, or work of elastic deformation); P_y, yield pressure (stress); η, axial to radial stress ratio; P_{r0}, residual die-wall pressure; ε_c, compact porosity at maximum compression pressure (150 MPa); ε, porosity after compact ejection; ER_0, elastic recovery within the die (compact height when pressure is returned to zero); ER, elastic recovery after compact ejection; A_1, hysteresis area of the Long compression cycle (radial pressure–upper punch pressure cycle); A_2, hysteresis area of lower punch pressure–upper punch pressure cycle; F_c, compact crushing force.

[a] Not measurable because compact capping and/or lamination.

compression work done by the powder compact on the receding upper punch, and thus incompletely represents the elastic deformation. Moreover, elastic recovery also takes place after decompression, both within the die and after tablet ejection. It is, however, a rough indicator used by some authors to estimate the elastic component, alternatively to the plasticity index 1 derived from W_{EXP}. Double compression is frequently performed to quantitate better the work of elastic deformation and calculate the net work of compression and the plasticity index 2 [13]. The higher the PL_2 value, the more work received by the compact. In this sense, low values were recorded for the very poorly compactible phenacetin and paracetamol, but it has to be stressed that for many materials plastic deformation still takes place beyond two compression cycles [38].

Mean yield pressure, as calculated from Heckel plot, is also a measure of the extent of plastic deformation. Thus, the plastic and viscoelastic materials showed relatively low P_y values, in line with published data, with the noticeable exception of sodium bicarbonate for which a high yield value (together with a very low compact strength) was recorded. In fact, it is confirmed that several so-called plastically deforming materials do not possess adequate plasticity to develop large contacting areas [71,72]. Note that the validity of the P_y values listed here is somehow restricted by the fact that the relative density of the compact was determined using an in-die method [83], so that an elastic component was included in the P_y values that may be falsely too low.

With respect to the parameters inferred from die-wall pressure monitoring, it is confirmed that no material displays a radial vs. axial pressure profile similar to the theoretical cycles described by Long [52,53]. Significant differences between materials are not discernible, as already quoted for instance by Krycer et al. [38]. In particular, values of the slopes of the segments OA (OA') and BC ($B'C'$) were too low to calculate relevant Poisson ratios. Thus, values of 0.21, 0.22, 0.22 and 0.24 were obtained for sodium chloride, potassium chloride, microcrystalline cellulose and hexamine, respectively, in disagreement with those reported in the literature (0.25 for sodium chloride [84], 0.27 for potassium chloride [84], 0.30 for microcrystalline cellulose [85] and 0.18 for hexamine [86]). Slopes of segment AB or CD were never equal to unity for materials known to deform by plastic flow (see Table 4), confirming their unsuitability in classifying compaction behaviour. Among the various reasons already discussed for this failure (see Section 3.2), it can be argued that plastic flow beyond pressure A (A') of the cycle could be in fact mainly confined to the interparticular regions and total plastic flow of the material itself has not occurred [42]. This is probably why the same group [24] proposed to consider only the requirement of equality of slopes AB and CD, in contrast to slopes $A'B'$ and $C'D'$ (see Table 4). Values reported in Table 10 do not permit clarification of the inconsistencies reported in the literature for the same compounds and shows that classifying material behaviour on slope calculation is not reliable.

Two other parameters can be derived from Long's pressure cycles. A high axial to radial stress transmission at maximum pressure was originally associated with resistant compacts [22]. Many studies have in fact invalidated this statement on comparing different materials and, here again, this criterion was not fulfilled. However, when examining η values for hexamine, potassium chloride and sodium chloride, the pressure transmitted radially appeared to decrease with increasing hardness as described by Ridgway et al. [41].

Much attention has been given to the residual die-wall pressure as it relates to the irreversible deformation of the material during compaction. High P_{r0} values were recorded by Shotton and Obiorah [43,70,73,74] for materials yielding sound tablets in contrast to materials prone to capping or laminating, supposedly because of pronounced axial recovery by brittle fracture in the decompression phase. Later, this was not observed for viscoelastic materials [37,38,61]. Our findings confirm literature results, particularly in that viscoelastic materials are able to withstand axial elastic recovery.

The significance of the residual die-wall pressure for tablet strength is tentatively evaluated by considering the two models proposed by Hiestand [67] for tablet formation. The 'weak model' (brittle mechanism) assumes only elastic deformation during unloading while the 'strong model' (ductile mechanism) includes plastic deformation during elastic deformation. Both ductile extension and viscoelasticity contribute to the strength of the tablet. This can be correlated with the fact that the residual die-wall pressure will be determined by the shear strength of the compact if remaining intact during decompression. Our results show that the residual radial pressure, alone, does not provide sufficient predictive information for tablet mechanical strength.

A final parameter calculated from the radial vs. axial pressure cycles is their surface area. Areas of the loops were generally larger for plastically deforming materials, indicating the departure from ideal elastic behaviour, compared with viscoelastic and brittle materials. It would be preferable to consider successive compressions in order to discern the elastic component. Following the suggestion of Touré and Carstensen [54,57] these data were also analysed in terms of hysteresis areas of lower punch pressure vs. upper punch pressure cycles. A rather good correlation was observed as can be seen in Fig. 10.

As already mentioned, the degree of success in tablet forming is primarily dictated by the extent of survival during decompression of the bonding area created during the compression phase [58]. Two extreme situations can be envisaged during decompression: elastic and plastic deformations. Elastic deformation can also operate after tablet ejection. It is therefore of utmost interest to quantitate the in-die and out-of-die expansion. This has been done by

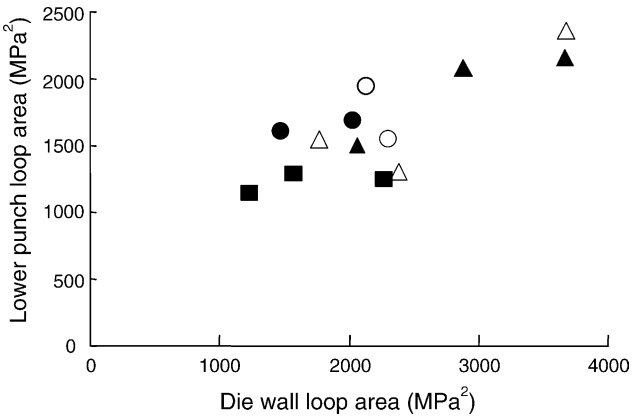

Fig. 10. Plot of the hysteresis areas of the lower punch vs. hysteresis areas die wall for five classes of model materials (see Table 10). Key: High tablet strength: ▲, plastic materials; ■, viscoelastic materials; ●, brittle, plastic materials. Low tablet strength: △, plastic materials; ○, brittle, elastic materials.

Carless and Leigh [42] and by Wiederkehr-von Vincenz [37] for similar model compounds. They observed that elastic recovery occurred mainly after tablet ejection, but these authors were of the opinion that tablet capping and/or lamination, if present, most probably had taken place during decompression or just at ejection. Long [52] actually considers that axial separation is the result of relief of the residual pressure exerted by the die wall. We have reached the same conclusion, noticing that the change in porosity and thus in elastic recovery is generally more pronounced for brittle materials.

Finally, based on our results and those from the literature, in particular those of Wiederkehr-von Vincenz [37] and of Nyström et al. [71,72], we propose a set of parameters that could help classifying the various materials used in pharmaceutical tabletting and to understand their behaviour (Table 11). It is apparent that none of these parameters is able, alone, to predict the strength of the tablets produced (actually, models still remain to be set up), but overall they are able to characterise the mechanical properties of the materials of the various categories defined.

7. Concluding remarks

Interest in die-wall instrumentation is continuing as recognised at the 2003 AAPS Annual Meeting [87]. However, when examining the literature dealing with radial pressure measurement during compression of pharmaceutical materials, one is confronted with a lot of inconsistencies in the authors' conclusions. One reason is the technical difficulties of die instrumentation and calibration that lead to discrepancies in the results reported for similar products. Another reason is that the models used for interpreting data have been proposed mostly for solid, isotropic bodies and not for powders.

Based on literature examination and on some original results presented here, the authors are of the opinion that most parameters derived from die-wall pressure measurement do not bring much to the tablet formulation scene when considering the challenges of low friction during compression and of yielding strong tablets. In fact, it appears that optimisation of many factors, in particular the type and concentration of additives such as binders and lubricants, can be achieved solely through instrumentation of the punches.

Die-wall instrumentation is, in contrast, of help for basic compaction studies aimed at determining the mechanical characteristics of materials, considered as the main factor accounting for the differences in tabletting behaviour. It is also useful for elucidating the friction phenomena during compaction and the related tabletting problems (capping, lamination, tooling wear). In this respect, the axial to radial pressure transmission ratio as well as the slopes and hysteresis surface area of the so-called Long pressure cycles are of limited value compared to the residual die-wall pressure. In particular, slope values do not permit to classify

Table 11
Comparative levels of compression parameters in relation to various classes of materials

Parameter	High tablet strength			Low tablet strength	
	Plastic materials	Viscoelastic materials	Brittle, plastic materials	Plastic materials	Brittle, elastic materials
Work of compression, W_u	Medium	High	Low	Medium	Low
Plasticity index, PL_2	High	Variable	Medium	Medium	Low
Yield pressure, P_y	Low	Low	High	Medium	Medium
Initial curvature of Heckel plot[a]	Absent	Absent	Quite long	Absent	Present
Stress ratio, η	Variable	Variable	Variable	Variable	Variable
Residual die-wall pressure, P_{r0}	High	Low	Medium	Medium	Low
Hysteresis of the Long cycle, A_1	High	Low	Medium	Medium	Medium
Elastic recovery, ER_0	Low	Medium	Low	Low	Low
Elastic recovery, ER	Low	High	Low	High	–[b]

[a] After deduction of the densification due to particle slippage and rearrangement.
[b] Not relevant.

the powdered materials as bodies with constant stress in shear or as Mohr bodies. The residual die-wall pressure is of greater importance because the success of tablet formation is determined by the decompression and ejection phases, but more emphasis should probably be placed on studying the kinetics of time-dependent deformation, again especially in the later period of the compression cycle. Finally, equations taking into account the material compressibility (volume reduction under pressure) have been proposed, but as for the relation between the tablet strength (material compactibility) and the compression parameters inferred from die-wall monitoring, models still need to be developed.

References

[1] J. Barra, E. Doelker, Instrumentation of an eccentric tablet press, in: A. Muños-Ruiz, H. Vromans (Eds.), Data Acquisition and Measurement Techniques, Interpharm Press, Inc, Buffalo Grove, USA, 1998, pp. 189–238.

[2] E. Shotton, J.A. Hersey, P.E. Wray, Compaction and compression, in: L. Lachman, H.A. Lieberman, J.L. Kanig (Eds.), The Theory and Practice of Industrial Pharmacy, 2nd ed., Lea & Febiger, Philadelphia, PA, 1976, pp. 296–320.

[3] E. Doelker, Physique de la compression: Intérêt et limite des machines instrumentées pour l'optimisation de la formulation, Pharm. Acta Helv. 53 (1978) 182–188.

[4] T.M. Jones, Preformulation studies to predict the compaction properties of materials used in tablets and capsules, Acta Pharm. Technol. Suppl. 6 (1978) 141–159.

[5] I. Krycer, D.G. Pope, The interpretation of powder compaction data—a critical review, Drug Dev. Ind. Pharm. 8 (1982) 307–342.

[6] E. Doelker, Developments in compression: compressional tests as an aid in tablet formulation, in: D.D. Breimer, P. Speiser (Eds.), Topics in Pharmaceutical Sciences, 1983, pp. 371–386, Amsterdam, The Netherlands.

[7] K. Marshall, Compression and consolidation of powdered solids, in: L. Lachman, H.A. Lieberman, J.L. Kanig (Eds.), The Theory and Practice of Industrial Pharmacy, 3rd ed., Lea & Febiger, Philadelphia, PA, 1986, pp. 66–99.

[8] E. Doelker, Recent advances in tableting science, Boll. Chim. Farm. 127 (1988) 37–49.

[9] E.G. Rippie, Compression of solids and compressed dosage forms, in: J. Swarbrick, J.C. Boylan (Eds.), Encyclopedia of Pharmaceutical Technology, Marcel Dekker, New York, 1990, pp. 149–165.

[10] P.E. Wray, The physics of compaction revisited, Drug Dev. Ind. Pharm. 18 (1992) 627–658.

[11] M. Celik, Overview of compaction data analysis techniques, Drug Dev. Ind. Pharm. 18 (1992) 767–810.

[12] A.F. Rime, E. Doelker, Caractéristique de compression et comprimabilité des poudres de polymères à usage pharmaceutique, STP Pharma Sci. 3 (1993) 109–129.

[13] E. Doelker, Assessment of powder compaction, in: D. Chulia, M. Deleuil, Y. Pourcelot (Eds.), Powder Technology and Pharmaceutical Processes, Elsevier, Amsterdam, 1994, pp. 403–471.

[14] K. Marshall, Some observations on the elucidation and control of die compaction processes, in: A.S. Goldberg (Ed.), Proceedings of the First International Conference on Compaction and Consolidation of Particulate Matters, The Powder Advisory Centre, London, 1972, pp. 173–181.

[15] D. Sixsmith, Instruments for tablet technology, Manuf. Chem. Aerosol News 48 (1) (1977) 17–21.

[16] G. Schwartz, The instrumented tablet press: uses in research and production, Pharm. Technol. 5 (9) (1981) 102–132.

[17] K. Marshall, Instrumentation of tablet and capsule filling machines, Pharm. Technol. 7 (3) (1983) 68–82.

[18] P. Ridgway Watt, Tablet Machine Instrumentation in Pharmaceutics: Principles and Practice, Ellis Horwood, Chichester, 1988, pp. 288–298.

[19] K. Marshall, Monitoring punch forces and punch movements as an aid to developing robust tablet formulations, Drug Dev. Ind. Pharm. 15 (1989) 2153–2176.

[20] H.S. Thacker, Instrumentation of tablet machines, in: N.G. Stanley-Wood (Ed.), Enlargement and Compaction of Particulate Solids, Butterworths, London, 1983, pp. 227–240.

[21] E. Nelson, L.W. Busse, T. Higuchi, The physics of tablet compression. VII. Determination of energy expenditure in the tablet compression process, J. Am. Pharm. Assoc. Sci. Ed. 44 (1955) 223–225.

[22] J.J. Windheuser, J. Misra, S.P. Eriksen, T. Higuchi, Physics of tablet compression. XIII. Development of die-wall pressure during compression of various materials, J. Pharm. Sci. 52 (1963) 767–772.

[23] K. Ridgway, The use of photoelastic techniques in the measurement of die-wall stress in tabletting, J. Pharm. Pharmacol. 18 (1966) 176S–181S.

[24] S. Leigh, J.E. Carless, B.W. Burt, Compression characteristics of some pharmaceutical materials, J. Pharm. Sci. 56 (1967) 888–892.

[25] K. Marshall, PhD thesis, University of Bradford, 1970.

[26] K. Ridgway, P.H. Rosser, The application of photoelastic techniques to a rotary tabletting machine, J. Pharm. Pharmacol. 23 (1971) 202S–209S.

[27] N.J. Edwards, PhD thesis, University of London, 1973.

[28] R. Spang, PhD thesis, E.T.H., Zürich, 1973.

[29] U. Conte, G. Colombo, A. La Manna, C. Caramella, La mesure de la force radiale à l'aide d'une matrice divisée. Applications aux problèmes pharmaceutiques, Il Farmaco 11 (1977) 551–559.

[30] E.G. Rippie, D.W. Danielson, Viscoelastic stress/strain behavior of pharmaceutical tablets: analysis during unloading and post-compression periods, J. Pharm. Sci. 70 (1981) 476–482.

[31] H.G. Cocolas, N.G. Lordi, Axial to radial pressure transmission of tablet excipients using a novel instrumented die, Drug Dev. Ind. Pharm. 19 (1993) 2473–2497.

[32] C. Yeh, S.A. Altaf, S.W. Hoag, Theory of force transducer design optimization for die wall stress measurement during tablet compaction: optimization and validation of split-web die using finite element analysis, Pharm. Res. 14 (1997) 1161–1170.

[33] A.W. Hölzer, J. Sjögren, Instrumentation and calibration of a single punch press for measuring the radial force during tableting, Int. J. Pharm. 3 (1979) 221–230.

[34] J. Millet, J. Paris, D. Duchêne, F. Puisieux, Etude de comprimés. XII. Mise au point d'un nouvel équipement pour la mesure des forces au niveau des différents organes d'une machine à comprimer alternative, Pharm. Acta Helv. 50 (1975) 109–115.

[35] P.D. Huckle, M.P. Summers, The use of strain gauges for radial stress measurement during tableting, J. Pharm. Pharmacol. 37 (1985) 722–725.

[36] D. Duchêne, A. Djiane, F. Altlas, J. Clerc, F. Puisieux, Etude des comprimés. V. Equipement d'une machine à comprimer alternative pour la détermination des forces intervenant lors de la compression, Ann. Pharm. Fr. 30 (1972) 127–138.

[37] C. Wiederkehr-von Vincenz, PhD thesis, E.T.H. Zürich, 1979.

[38] I. Krycer, D.G. Pope, J.A. Hersey, An evaluation of the techniques employed to investigate powder compaction behaviour, Int. J. Pharm. 12 (1982) 113–134.

[39] D. Khossravi, W.T. Morehead, Consolidation mechanisms of pharmaceutical solids: a multi-compression cycle approach, Pharm. Res. 14 (1997) 1039–1045.

[40] I. Higuchi, T. Shigamoto, S.P. Eriksen, T. Yashiki, Physics of tablet compression. XIV. Lateral die wall pressure during and after compression, J. Pharm. Sci. 54 (1965) 111–118.

[41] K. Ridgway, J. Glasby, P.H. Rosser, Effect of crystal hardness on radial pressure at the wall of a tableting die, J. Pharm. Pharmacol. 21 (1969) 24S–29S.
[42] J.E. Carless, S. Leigh, Compression characteristics of powder: radial die-wall pressure transmission and density changes, J. Pharm. Pharmacol. 26 (1974) 289–329.
[43] B.A. Obiorah, Possible prediction of compression characteristics from pressure cycle plots, Int. J. Pharm. 1 (1978) 249–255.
[44] A.W. Hölzer, J. Sjögren, Evaluation of some lubricant by the comparison of friction coefficients and tablet properties, Acta Pharm. Suec. 18 (1981) 139–148.
[45] E. Doelker, E. Shotton, The effect of some binding agents on the mechanical properties of granules and their compression characteristics, J. Pharm. Pharmacol. 29 (1977) 193–198.
[46] H. Unckel, Vorgänge beim Pressen von Metallpulvern, Arch. Eisenhüttenwesen 18 (1945) 161–167.
[47] D. Train, J.A. Hersey, Some fundamental studies in the cold compaction of plastically deforming solids, Powder Metall. 6 (1960) 20–35.
[48] D. Train, J.N. Carrington, J.A. Hersey, The pressing of polymers in cylindrical dies, Ind. Chem. 38 (1962) 77–80.
[49] R.F. Lammens, T.B. Liem, J. Polderman, C.J. De Blaey, Evaluation of force–displacement measurements during one-sided powder compaction in a die—the influence of friction with the die on upper and lower punch pressure, Powder Technol. 26 (1980) 169–185.
[50] R.A. Thompson, Mechanics of powder pressing: I. Model for powder densification, Am. Ceram. Soc. Bull. 60 (1981) 237–243.
[51] P. Mosbah, D. Bouvard, E. Ouedraogo, P. Stutz, Experimental techniques for analysis of die pressing and ejection of metal powder, Powder Metall. 40 (1997) 269–277.
[52] W.M. Long, Radial pressure in powder compaction, Powder Metall. 6 (1960) 73–86.
[53] W.M. Long, Die design and related questions in powder compaction, Spec. Ceram. 17 (1962) 327–340.
[54] J.T. Carstensen, P. Touré, Compression cycles in tableting, Powder Technol. 26 (1980) 199–204.
[55] E.L. Parrott, Compression, in: H.A. Lieberman, L. Lachman, J.B. Schwartz (Eds.), Pharmaceutical Dosage Forms: Tablets, vol. 2, Marcel Dekker, New York, 1990, pp. 201–243.
[56] S. Strijbos, P. Rankin, R.J. Klein Wassink, J. Bannink, G.J. Oudemans, Stresses occurring during one-sided die compaction of powders, Powder Technol. 18 (1977) 187–200.
[57] P. Touré, PhD thesis, Université Paris-Sud, 1979.
[58] E.N. Hiestand, J.E. Wells, C.B. Peot, J.F. Ochs, Physical process of tableting, J. Pharm. Sci. 66 (1977) 510–519.
[59] H. Schrank-Junghäni, H.P. Bier, H. Sucker, The measurement of die wall forces to determine the minimum concentration of lubricant needed for tablet formulations, Acta Pharm. Technol. 30 (1984) 224–234.
[60] S. Strijbos, Friction between a powder compact and a metal wall, Sci. Ceram. 8 (1976) 415–428.
[61] A.W. Hölzer, J. Sjorgen, Friction coefficient of tablet masses, Int. J. Pharm. 7 (1981) 269–277.
[62] M.-Al. Shammat, D.N. Travers, T.C. Buttery, Die wall reaction and friction during compaction of some direct compression base, J. Pharm. Pharmacol. 31 (1979) 76P.
[63] V.T. Laich, T. Kissel, Axiales Matrizen Wandkraftminimum, Pharm. Ind. 57 (1995) 174–182.
[64] S. Strijbos, Powder-wall friction: the effects of orientation of wall lubricants, Powder Technol. 18 (1977) 209–214.
[65] J. Kikuta, N. Kitamori, Evaluation of the die wall friction tablet ejection, Powder Technol. 35 (1983) 195–200.
[66] J.E. Rees, E. Shotton, The effect of dimensions on the compaction properties of sodium chloride, J. Pharm. Pharmacol. 21 (1969) 731–743.
[67] H.E.N. Hiestand, D.P. Smith, Indices of tableting performance, Powder Technol. 38 (1984) 145–159.
[68] H.E.N. Hiestand, Dispersion forces and plastic deformation in tablet bond, J. Pharm. Sci. 74 (1985) 768–770.
[69] H.E.N. Hiestand, Principles tenets and notions of tablet bonding and measurements of strength, Eur. J. Pharm. Biopharm. 44 (1997) 229–242.
[70] E. Shotton, B.A. Obiorah, Effect of physical properties on compression characteristics, J. Pharm. Sci. 64 (1975) 1213–1215.
[71] C. Nyström, G. Alderborn, M. Duberg, P.-G. Karehill, Bonding surface area and bonding mechanism—two important factors for the understanding of powder compactability, Drug Dev. Ind. Pharm 19 (1993) 2143–2196.
[72] C. Nyström, P.-G. Karehill, The importance of intermolecular bonding forces and the concept of bonding surface area, in: G. Alderborn, C. Nyström (Eds.), Pharmaceutical Powder Compaction Technology, Marcel Dekker, New York, 1996, pp. 17–53.
[73] B.A. Obiorah, E. Shotton, The effect of waxes, hydrolyzed gelatin and moisture on the compression characteristics of paracetamol and phenacetin, J. Pharm. Pharmacol. 28 (1976) 629–632.
[74] E. Shotton, B.A. Obiorah, The effect of particle shape and crystal habit on properties of sodium chloride, J. Pharm. Pharmacol. 25 (1973) 37P–43P.
[75] J.T. Carstensen, P. Touré, D. Duchêne, F. Puisieux, Correlation between hysteresis loop areas of lower punch and of die pressure versus upper punch pressures, Drug Dev. Ind. Pharm. 7 (1981) 645–648.
[76] I. Krycer, The prediction of paracetamol capping tendencies, J. Pharm. Pharmacol. 34 (1982) 802–804.
[77] M.P. Summers, R.P. Enever, J.E. Carless, The influence of crystal form on the radial stress transmission characteristics of pharmaceutical materials, J. Pharm. Pharmacol. 28 (1976) 89–99.
[78] J. Barra, R. Somma, Influence of the physicochemical variability of magnesium stearate on its lubricant properties: possible solutions, Drug Dev. Ind. Pharm. 22 (1996) 1105–1120.
[79] P.I. Seth, Münzel, Der Einfluss des Feuchtigkeitsgehalt eines Granulates auf die Pressbarkeit und die Eigenschaften der Tabletten, Pharm. Ind. 21 (1959) 9–12.
[80] J.E. Rees, E. Shotton, Effect of moisture in compaction of particulate material, J. Pharm. Sci. 60 (1971) 1704–1708.
[81] E. Shotton, E. Ress, The compaction properties of sodium chloride in the presence of moisture, J. Pharm. Pharmacol. 18 (Suppl) (1966) 160S–167S.
[82] A.F. Rime, F. Lescure, D. Mordier, R. Gurny, E. Doelker, A new high performance data acquisition system interfacing an instrumented tablet machine to a microcomputer, Acta Pharm. Technol. 36 (1999) 264–268.
[83] P. Humbert-Droz, D. Mordier, E. Doelker, Méthode rapide de détermination du comportement à la compression pour les études de préformulation, Pharm. Acta Helv. 57 (1982) 136–143.
[84] G. Simmons, H. Wang, Single Crystal Constants and Calculated Aggregate Properties: A Handbook, 2nd ed., MTI Press, Cambridge, 1971.
[85] R.J. Roberts, R.C. Rowe, P. York, The Poison's ratio of microcrystalline cellulose, Int. J. Pharm. 105 (1994) 177–180.
[86] R.J. Roberts, R.C. Rowe, P. York, The relationship between Young's modulus of elasticity of organic solids and their molecular structure, Powder Technol. 65 (1991) 139–146.
[87] S.W. Hoag, Die wall instrumentation: design and application in compaction, AAPS Annual Meeting and Exposition, Salt Lake City, 2003.