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Research paper

Quantification of the compactibility of pharmaceutical powders

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Abstract

The purpose of this study is to investigate and to quantify the compactibility of pharmaceutical powders by a simple linear relationship between the diametral compressive strength of tablets and the applied compaction pressure. The mechanical strength of the tablets is characterized as the crushing force normalized with the dimension of the tablet and termed the specific crushing strength, SCS. The proposed model: $SCS = Cp * P + b$ estimates the slope of the regression line Cp as a dimensionless compactibility parameter and is reported with the corresponding standard deviation S_{Cp}. The linear region of the compactibility profile is selected using the 95% predictability limits bordering the regression line. Eleven different materials were tested and acceptable fits to the linear model were observed in all cases. The ability of the model to discriminate between the investigated materials is excellent, in cases where the difference may be difficult to show a simple *t*-test is used as an inference tool. No difference was found between lactose tablets of different masses (500 and 1000 mg). A relationship between the compactibility parameter and the compressibility characterized by the Walker coefficient is demonstrated.

Keywords: Compactibility; Methodology; Mathematical models; Specific crushing strength; Walker equation; Compressibility

1. Introduction

The compaction properties of pharmaceutical powders are for clarity separated in two distinct terms, i.e. the compressibility as the ability of the powder to deform under pressure and the compactibility as the ability of a powder to form coherent compacts. While the former property has been subject to numerous investigations including development of mathematical descriptive models the latter is seldom in focus although this characteristic should be more relevant and interesting from a practical pharmaceutical point of view. With the growing interest in the functionality of excipients and the related test methods, there is obviously a need for a simple and standardized measure of the compactibilty. A tool is needed where decision-making on differences or similarities between powders in relation to the compactibility is achievable on an objective and statistically established basis.

The mechanical strength of a single compact is easily determined as the force needed to crush the tablet diametrically. As this crushing or breaking force is expected to be dependent on the tablet dimensions it is reasonable to normalize the force to a specific strength by division with the dimensions of the tablet, i.e. the cross-sectional area [1]. To avoid the general disorder in the terminology where force, strength and hardness are mixed up and to emphasize that the strength is normalized the term specific crushing strength (SCS) will be used. The specific crushing strength in units of pressure (Pa) is for flat-faced cylindrical tablets defined as

$$SCS = \frac{F}{Dh}, \tag{1}$$

where F is the crushing force and D and h are the diameter and height of the cylindrical tablet. The tensile strength (TS) is defined as [2]

$$TS = \frac{2F}{\pi Dh}. \tag{2}$$

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The specific crushing strength deviates mathematically from the well-known indirect tensile strength only by the factor $2/\pi$ and has therefore the same power in discriminative analysis. Furthermore, the specific crushing strength is without restrictions regarding the mode of failure as different crack patterns may be observed. The utilization of tensile strength may cause confusion in cases where some tablets fail under tension and some under shear forces [3]. Difficulties may arise in a precise and objective definition of ideal fracture [4] and Eq. (2) is shown to be erroneous since the stress distribution in anisotropic media like tablets is different from isotropic bodies [5]. In a critical review on the subject Darvell [6] concluded that "it is extremely doubtful if the supposed indirect tensile tests actually cause failure in tension and that they therefore measure the tensile strength".

The diametral crushing strength method was criticized by Leuenberger and Jetzer [7] as the authors did not find it to be a scientifically well-based variable for characterizing the compactibility, because complicated fracture patterns may occur instead of ideal failure. However, by analysing the repeatability of the crushing force in 12 samples of 100 tablets the coefficient of variation was within 2–5% for tablets produced on a laboratory scale and 5–12% for industrially produced commercial available tablets [8]. This observed small variability together with the demonstrated normal distribution of the data indicates that the crushing strength is a reliable method in describing the mechanical properties. Recently more than 3000 tablets were tested for an inter-laboratory comparison of 16 commercial crushing force testers [9]. This investigation demonstrated that the diametral crushing test is a stable and uncomplicated method in expressing the mechanical quality of compacts.

Expressing the mechanical strength as the work of failure – the total amount of work needed to break or crush the tablet – is technically more complicated than measurement of the crushing force. The work of failure is calculated by numerical integration of the applied force with respect to the distance travelled by the jaws. Rees and Rue [10] concluded that the work of failure is a better quantitative assessment of the mechanical properties than tensile strength. The three- or four-point bending of a square compact in the flexure test as an alternative to the diametral compression test does not seem to add further important information to this field of study [11]. The mechanical strength determined as indentation hardness might, according to Leuenberger and Jetzer [7], be preferable to the crushing strength method in cases where the material has capping tendencies, which will severely spoil the crushing strength measurement.

The mechanical strength measured by any of the mentioned methods is anticipated to be associated with the number of contact points generated in the compact. It is therefore necessary to illustrate or to compute the relationship between the mechanical strength and the principal generating factor: the compaction pressure. The compactibility of a specific substance is most often expressed graphically in a XY-plot as a relationship between compaction pressure and mechanical strength. If the mechanical strength is reported as the crushing force, it is necessary to attach information on either the dimensions of the compact or the tablet weight [12,13].

There are several examples in the literature indicating that the compactibility profile in its full extension has an essential sigmoid shape [10,14]. At relatively low pressures, it was shown by Kuentz and Leuenberger [4] that the mechanical strength increases by a power function with increasing pressure. At high pressures, it is often observed and expected that the crushing strength levels off and even sometimes decreases to a lower level due to capping or lamination tendencies. It might thus be recognized that the strength/pressure relation is fundamentally s-shaped, but that a linear segment is distinctively apparent and describes the most relevant and informative part of the increase in strength related to the compaction pressure.

A practical approach and the simplest way to quantify the compactibility is the one-point estimate, where for instance the minimum pressure needed to make a compact of a given strength is reported [15]. Alternatively a tensile strength at a given pressure is defined [16] or a strength at a fixed porosity [17]. The advantage of these simple one-point estimates is that they are without any assumptions about the overall mathematical relation between the strength and the pressure. The only calculation required is a point-to-point linear interpolation.

A simple linear relationship between tensile strength and pressure up to 310 MPa was found for lactose monohydrate tablets ranging in mass from 0.4 to 1 g [18]. Earlier Higuchi et al. [19] postulated a logarithmic relationship where the strength measured in Strong Cobb units was linearly dependent on the logarithmic transformed compaction force. Newton and Grant [20] observed a better fit of data derived from lactose and dextrose tablets to a double logarithmic equation than to a straight linear relationship.

A power function Eq. (3) valid only at low pressures was suggested by Kuentz and Leuenberger [4]

$$\mathrm{TS} = k \cdot P^{T/2}, \tag{3}$$

where P is the maximum compaction pressure and k and the exponent T are constants. The Weibull equation which is well known in many other pharmaceutical disciplines was used in an attempt to quantify the tablet strength relationship with compaction pressure [21].

An interesting model-independent method for the determination of the compactibility was proposed by Amidon et al. [22]. A plot with the average breaking force versus three levels of logarithmic transformed compaction pressures is constructed and the area under the curve determined by use of the trapezoid rule. The numerical value of the integral expressing the compactibility is termed $F1x$, where the subscript x represents the midpoint pressure value. As the compaction pressures are increased

exponentially with practically equal logarithmic intervals, the $F1$ value can be expressed mathematically as in Eq. (4).

$$F1 = \log(\sqrt{2}) \cdot (\mathrm{CF}_i + 2\mathrm{CF}_{i+1} + \mathrm{CF}_{i+2})/2, \quad (4)$$

where CF is the mean crushing force at the actual pressure. A problem in the proposed system might be the difficulty in achieving the exact pressure. Furthermore, the calculation based on the logarithmic pressures will give unnecessarily more weight to the values at small pressures in this numerical integration procedure.

In materials sciences like geology and ceramics the history of a material is often unknown in contrast to tabletted materials where the condition of the manufacture, i.e. compaction pressure and speed of compaction is known and documented. The Ryskewitch equation in Eq. (5) [23,24] relates the crushing strength CS of a ceramic material with the porosity:

$$\mathrm{CS} = \mathrm{CS}_0 \cdot \exp(-k\varepsilon), \quad (5)$$

where CS_0 is the estimated tensile strength at zero porosity, ε is the porosity and k is a constant representing the effect of a change in porosity on the crushing strength. In experimental design context the porosity and the strength are both dependent variables and they are responses to variation in the compaction pressure that is the independent or input variable.

A summary of the different methods and mathematical models found in the literature describing the compactibility as the relationship between mechanical strength and the maximum compaction pressure or porosity is presented in Table 1. It is typical and a limitation for all the proposed models that none of the derived parameters or compaction characteristics includes the confidence limits or the standard deviation of the estimate. Several of the models incorporate an estimate of an upper limit of the mechanical strength, i.e. at zero porosity. These values must necessarily be extrapolated from a set of data sometimes far from this end point. The variety of models listed in Table 1 seems to support the statement by Newton and Grant [18] that no single relationship appeared between the applied pressure and compact strength.

Only few investigations are found where a relationship between the two characteristics of powdered material's compressibility and compactibility is studied. A reason for this may be the absence of a simple and recognized expression for the compressibility. Celik and Marshall [25] unsuccessfully examined the relation between the mechanical strength of a number of compacted materials and an index derived from the Walker equation Eq. (6) where the intercept (Vl) was divided with the slope (w).

$$V = -w \cdot \log(P) + \mathrm{Vl}, \quad (6)$$

where V is the relative volume, w is the Walker coefficient and Vl is the relative volume at the pressure 1 MPa.

Recently Alderborn [26] investigated the tensile strength of tablets made of two particle size fractions of sucrose and sodium chloride, in the pressure range 40–700 MPa. From the compactibility curve a compression parameter C_2 was derived as the difference between two threshold pressures, P_{c2} and P_{c1}, indicating the upper and lower limits of a linear relationship between strength and pressure. The same attempt to derive a compressibility parameter from compactibility data based on measurements of indentation hardness was made by Leuenberger and Jetzer [4] in the following equation:

$$H = H_{\max}(1 - \exp(-\gamma\rho P)), \quad (7)$$

where H is the Brinell hardness, $H_{\max}$ is the maximum obtainable hardness value, ρ is the relative density and γ is a parameter expressing the compressibility of the material.

The purpose of this study is to investigate the general applicability of a simple linear relationship between specific crushing strength and compaction pressure and designate the slope of the line Cp including the estimated standard deviation as the quantitative characteristics of the compactibility. The focus will be put on the range of pressure where the mechanical strength is most sensitive to increasing pressure or simply the region where 'things happen'. The aim is furthermore to investigate the relationship between compressibility and compactibility where the compressibility is expressed as the slope of the static (out of die)

Table 1
Summary of methods and models for quantification of compactibility

One-point methods	Pressure at CF = 8 Kp	Fraser [15]
	CS at pressure = 150 MPa	Duberg and Nyström [16]
	CS at porosity = 15%	van Veen et al. [17]
Pressure profile	$\mathrm{CS} = a \cdot P + b$	Newton et al. [18]
	$\mathrm{CS} = a \cdot \log(P) + b$	Higuchi et al. [19]
	$\log(\mathrm{CS}) = a \cdot \log(P) + b$	Newton and Grant [20]
	$\mathrm{CS} = k \cdot P^{T/2}$	Kuentz and Leuenberger [4]
	$\ln(-\ln(1 - \mathrm{CS}/\mathrm{CS}_{\max})) = a \cdot \ln P + b$	Castillo and Villafuerte [21]
	$F1 = \log(\sqrt{2}) \cdot (\mathrm{CF}_i + 2\mathrm{CF}_{i+1} + \mathrm{CF}_{i+2})/2$	Amidon et al. [22]
	$H = H_{\max}(1 - \exp(-\gamma\rho P))$	Leuenberger and Jetzer [7]
Porosity profile	$\mathrm{CS} = \mathrm{CS}_0 \cdot \exp(-k \cdot \varepsilon)$	Ryshkewitch [23]
	$\mathrm{CS} = k(\rho - \rho_c)^{2.7} + \mathrm{CS}_0$	Ramírez et al. [32]

CF, crushing force; CS, crushing strength, including tensile strength; H, indentation hardness (Brinell); P, maximum compaction pressure; ε, porosity of the compact; ρ, density of the compact. All other symbols are constants.

Walker equation and where the compactibility is quantified as Cp. The study will be based on a phenomenological approach where the observed data are analysed without any presumptions about ideal fracture of the tablets. Statistical treatment of data is used in the estimation and evaluation of the parameters and as a tool in the objective exclusion of suspected outliers.

2. Materials and methods

2.1. Materials

The following materials with label coding in bold were used as received: Microcrystalline cellulose (Avicel® PH-101, **Mcc1** and Avicel® PH-102, **Mcc2**, FMC International, Cork, Ireland), calcium hydrogenphosphate dehydrate, **CaPh** (Emcompress®, Penwest, Patterson, NY, USA), sorbitol, **Sor** (Neosorb®P60W, Roquette Freres, Lestrem, France), pregelatinised starch, **Star** (Starch®1500, Colorcon, Indianapolis, IN, USA), lactose, **Lac** (Pharmatose® DCL 40, DMV International, The Netherlands), sodium chloride, **NaCl** (Unichem, Copenhagen, Denmark), sodium carbonate, **NaCa** (Unichem, Copenhagen, Denmark), sodium bicarbonate, **NaBi** (Unichem, Copenhagen, Denmark), β-cyclodextrin, **Cyc**, (American Maize Products Co., Hammond, IN, USA), maize starch, **Mai**, (Eridania-Beghin Say, Vilvoorde, Belgium).

2.2. Methods

The materials were compacted on the compaction simulator described previously [27]. Tablets of approximately 500 mg (495–505 mg) or 1000 mg (990–1010 mg) for sodium carbonate and sodium bicarbonate were compacted using 15.0 mm diameter flat faced punches. When necessary, the die and punches were lubricated with a 5% suspension of magnesium stearate in ethanol. The compression profile was a simulation of an excentric press with a total process time of 2.2 s, corresponding to a contact time from 400 to 540 ms depending on the material. Data were collected every 2.15 ms. The actual weight of the tablets was determined and the height of the tablets was measured (Mitutoyo Indicator, Mitutoyo, Japan). Twenty-four hours after compression the crushing force of the tablets was measured using a hydraulic equipment constructed in our laboratory and based on a 1000 N force transducer (DC K10 C3, Gefran Sensori SRL, Italy) with a piston speed of 75 μm/s [28]. The compaction pressures were chosen between a lower limit giving coherent compacts and an upper limit of 240 MPa. Fifteen to 25 tablets were compacted evenly distributed in the range of compaction pressure.

2.2.1. Data treatment

The specific crushing strength SCS was calculated from the breaking force values measured in N divided by the diameter (15 mm) and the height of the tablet (Eq. (1)). The linear model $\mathrm{SCS} = \mathrm{Cp} \cdot P + b$ was estimated with standard least square methods in a spreadsheet program (Excel, Microsoft). In the result of the regression computation the negative intercept on the ordinate-axis is considered irrelevant while the intercept with the abscissa-axis corresponding to an apparent lower pressure limit might give some interesting information. The standard deviation S_{Cp} of the slope Cp is calculated according to the following equation:

$$S_{\mathrm{Cp}} = \frac{S_{\mathrm{res}}}{\sqrt{\mathrm{SS}_x}}, \tag{8}$$

where S_{res} is the residual standard deviation about the regression line and SS_x is the sum of squares of the x-values (here the compaction pressure). The introducing of the standard deviation of the slope S_{Cp} has of course the benefit that the uncertainty on the estimated parameter is reported. Furthermore, it is easy to assess whether the difference between two slopes (Cp_1 and Cp_2) is incidental or of statistical significance by means of the t-test statistic Z in the following equation [29]:

$$Z = \frac{\mathrm{Cp}_1 - \mathrm{Cp}_2}{S \cdot \sqrt{\frac{1}{\mathrm{SS}_{x1}} + \frac{1}{\mathrm{SS}_{x2}}}}, \tag{9}$$

where S is here the weighted average of the two residual standard deviations and SS_{x1} and SS_{x2} are the sums of squares of the x-values. The Z-value is to be compared with the t-distribution with $(m + n - 4)$ degrees of freedom, where m and n are the respective number of observations.

The objective selection of data points that should be integrated in the regression calculation and the exclusion procedure for outliers are well described and several techniques are available for the solution of this problem. Cooks distance [30] is calculated as the difference between the estimated point and the model after the point has been omitted and is a routine technique available in several software packages (Statistica, StatSoft Inc. and SigmaPlot, SPSS Inc.). A more explicit and practical method is however, to calculate and sketch the 95% predictability limits on both sides of the regression line and from a visual judgment decide whether a given observation falls outside the specifications. The 95% limit of prediction for a future observation is assuming normal distributed residuals easily calculated as shown in the following equation:

$$Y_{\mathrm{pre}} = Y_{\mathrm{est}} \pm t_{(n-2),0.975} \cdot S_{\mathrm{res}} \cdot \sqrt{1 + \frac{1}{n} + \frac{(x - \bar{x})^2}{\mathrm{SS}_x}}. \tag{10}$$

In this equation Y_{pre} is the limits of prediction, Y_{est} is the estimated value at the regression line, t is the corresponding t-value and $\bar{x}$ is the average x-estimate.

The compressibility of the investigated materials is quantified according to a modification of the Walker model in Eq. (11) where the static measurements also known as out-of-die data are used rather than the previously in Eq. (6) used dynamic data from the compaction simulator.

In addition the specific volume replaces the relative volume without the normalization with the pycnometric density.

$$V' = -w' \cdot \log(P) + V_{sp}, \quad (11)$$

where V' is the specific volume in ml/g and w' is the Walker constant here expressing the volume reduction corresponding to one decade in the pressure P. V_{sp} is the specific volume at the pressure 1 MPa.

3. Results and discussion

An example of the sigmoid shape of the compactibility curve (Fig. 1) supports the observations found by several other investigators. A dominating linear segment is however, observable while the pattern is unclear at high pressures where tendencies to laminate are distressing. At small pressures no clear lower threshold is visible, indicating that it is difficult truly to define a 'minimum compressional force for compaction' [13] or 'a critical formation pressure' [26].

The compactibility profile of sorbitol shown in Fig. 2 demonstrates the technique applied in detection of outliers or data points that are excluded from further calculation. Two points at high pressures outside the predictability limits show noticeable deviations and are subsequently rejected from the data set. The exclusion procedure is in any circumstances of less importance since the scatter technically is preserved as the standard deviation of the slope S_{Cp}.

Typical linear compactibility profiles for three inorganic sodium salts are shown in Fig. 3. The linear relationship and the ability of the proposed method to discriminate between these materials are evident. Among the tested materials sodium bicarbonate is obviously producing the least bonding capacity but it is however, still possible to depict a statistical significant regression line with an acceptably small standard deviation.

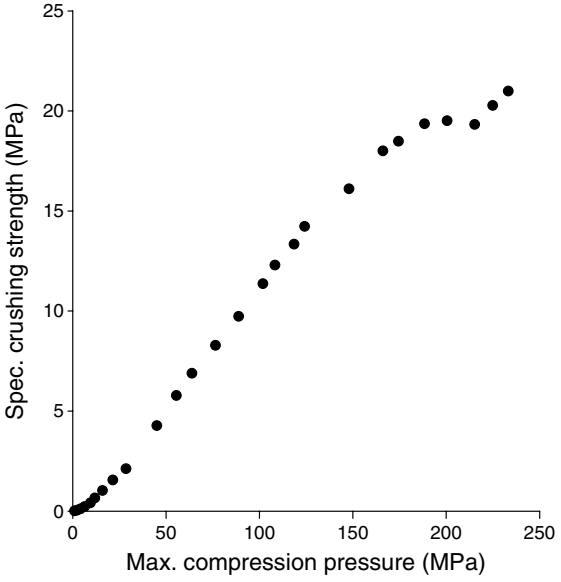

Fig. 1. Example of the sigmoid shape of the compactibility profile for microcrystalline cellulose (Avicel® PH-101).

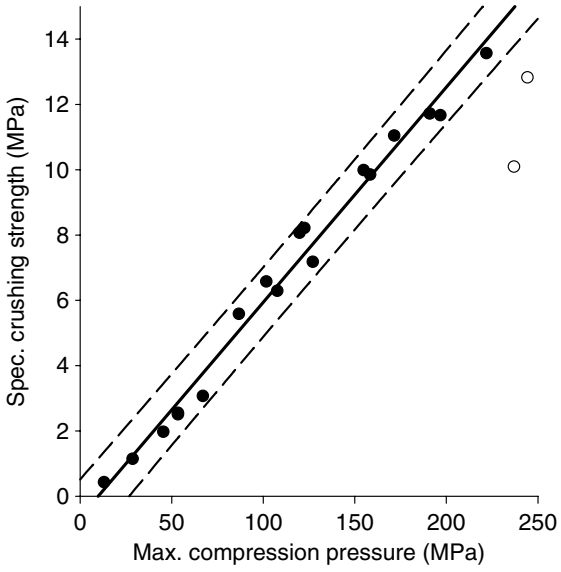

Fig. 2. Compactibility profile (solid line) of sorbitol with the 95% predictability limits Eq. (10) (dashed lines). The regression line is based on the closed symbols while the open symbols are excluded as outliers.

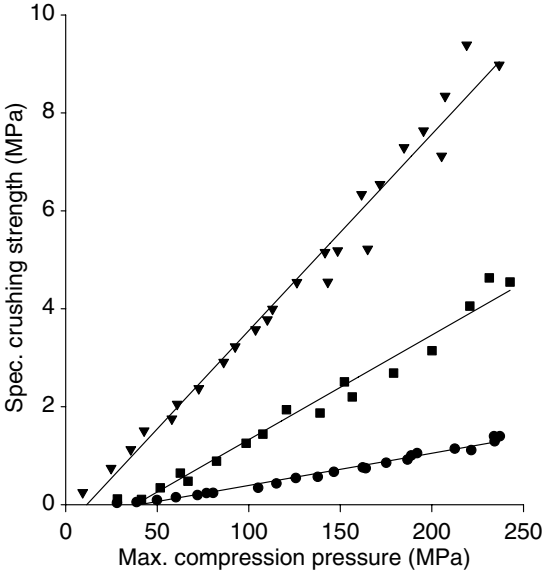

Fig. 3. Compactibility profiles for sodium carbonate ▼, sodium chloride ■ and sodium bicarbonate ●.

The results of the calculated regression lines are summarized in Table 2 where the range in Cp values from 6.5×10^{-3} for sodium bicarbonate to microcrystalline cellulose (Avicel PH 102) 130.2×10^{-3} indicates the ability of the system to discriminate between materials. The relative standard deviation calculated according to Eq. (1) is acceptably small. The apparent lower pressure limit calculated as the intercept with the x-axis is positive in all circumstances but without any general trend related to the compression characteristics of the materials. The upper pressure limit indicates the pressure where the linear trend is leveling off. This is typically seen where the substances are expected to be elastic in their deformation character.

Table 2
List of the compactibility coefficients (Cp) in increasing order with the relative standard deviation Eq. (8) in %, the apparent lower pressure limit estimated as the intercept with the x-axis and the upper pressure limit for deviation from linearity

Code	Slope, Cp ($\times 10^3$)	Relative SD (%)	Lower pressure limit (Mpa)	Upper pressure limit (Mpa)	n
NaBi	6.55	3.0	41	>240	23
CaPh	17.1	7.1	26	>240	19
Star	17.2	6.6	28	145	16
NaCl	21.4	4.1	40	>240	17
Lac	24.5	4.6	22	>240	18
Mai	31.5	4.9	41	140	12
NaCa	39.0	3.2	12	>240	24
Cyc	59.6	3.4	7	145	14
Sor	65.2	2.8	9	220	19
Mcc1	119.0	1.3	7	145	15
Mcc2	130.2	1.1	8	135	25

n is the number of data-points included in the regression.

Newton et al. [18] showed that within certain limits the tensile strength of lactose tablets was independent of the size or the weight of the tablets. This result is confirmed by the observations shown in Fig. 4, where the specific crushing strength of lactose tablets 500 mg (Cp = 0.0245) and 1000 mg (Cp = 0.0278) is related. The small difference in the slopes of the two regression lines is not statistically significant $p = 0.07$ (t-test, Eq. (9)). The t-test used in comparing regression slopes may likewise be used on the two qualities of microcrystalline cellulose (Avicel® PH101 (Cp = 0.119) and PH102 (Cp = 0.1302)). A clear difference is observed as the PH102 quality shows a greater strength compared to the PH101 quality ($p < 0.001$). The application possibility of the proposed statistical technique by introducing the standard deviation of the compactibility parameter is hereby demonstrated.

As discussed earlier the relationship between compactibility and the compressibility of compressed powders has only been subject to few investigations. It was previously shown that the Walker equation (Eq. (6)) gave an acceptable fit to the volume reduction data of a number of substances [27]. However, a more complex model: the log-exp model gave a fully sufficient description of the comprehensive densification of powders where several processes may be active simultaneously [31]. In these previous papers the data were collected dynamically during the compression process. Alternatively the compressibility may be evaluated based on data measured on the finished tablets here termed static data and elsewhere known as 'out-of-die'. Fig. 5 shows the compressibility profiles of the same three inorganic sodium salts previously visualized as the compactibility ability. The fitting of the data of sodium chloride to the Walker equation is clearly less perfect than the other possible more brittle materials.

In Fig. 6 the relationship between compactibility expressed as the Cp coefficient and the compressibility expressed as the w' coefficient from the Walker equation Eq. (11) is shown. The positive relationship between these two compaction properties is clear and the excellent compressive property of microcrystalline cellulose is illustrated by the high levels of both the compressibility and the compactibility. This observation might be interpreted and explained as follows: If a material shows a great tendency to deform under stress and consequently has a large compressibility coefficient numerous new contact points will be created and new strong bonds between particles may be generated. The expected elastic deformation of maize starch and pregelatinised starch (Starch 1500) might be the reason for the deviation of these two substances from the general trend.

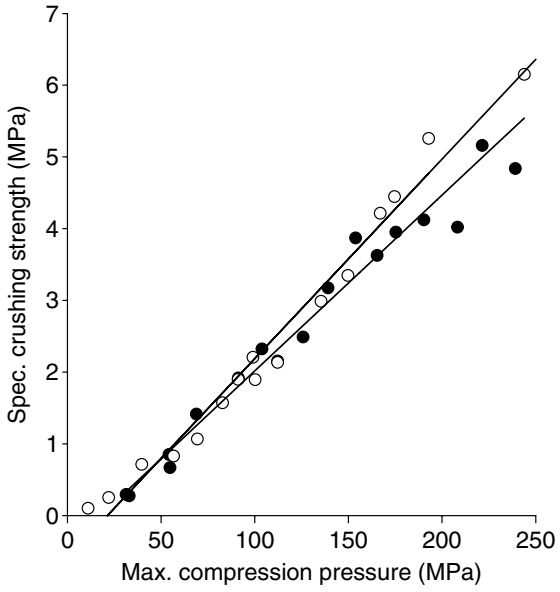

Fig. 4. Compactibility profiles for lactose 500 mg tablets ● and 1000 mg tablets ○.

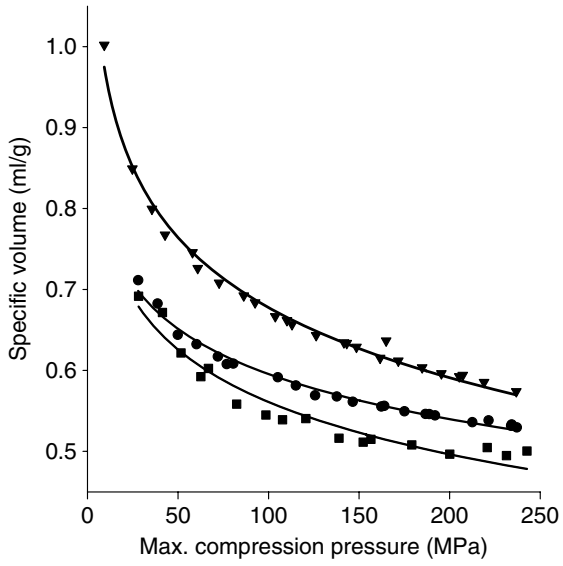

Fig. 5. Compressibility data for sodium carbonate ▼, sodium chloride ■ and sodium bicarbonate ● with the profiles calculated from Eq. (11) included.

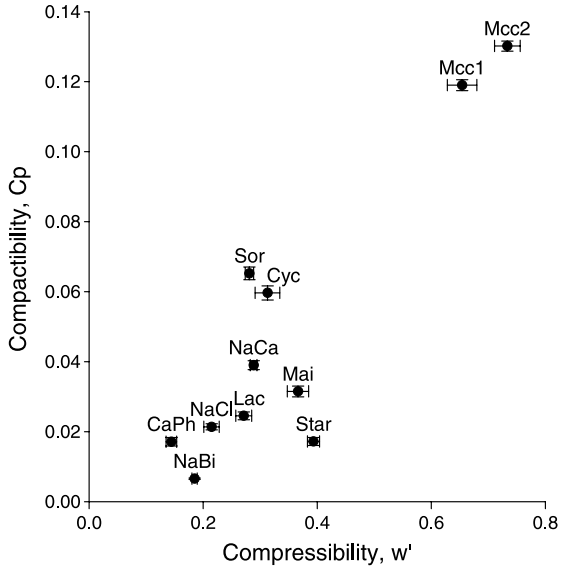

Fig. 6. Relationship between the compactibility parameter Cp and the compressibility parameter w' (Eq. 11) for 11 materials.

4. Conclusions

- It is concluded that the simple linear model for compactibility of pharmaceutical powders is appropriate as an uncomplicated tool for quantification. The compactibility parameter Cp has an excellent discriminative power for the investigated materials and is in general characterized by a small standard deviation. Statistical tests for difference or similarities are easy to perform on the estimated parameter.
- The robustness of the model in relation to deviations in tablet mass is indicated for 500 and 1000 mg lactose tablets.
- A clear relationship between the compressibility and compactibility for the powders in the study was established.

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