Drug Development and Industrial Pharmacy, 2009; 35(10): 1271–1280

informa
healthcare

ORIGINAL ARTICLE

The compressibility and compactibility of different types of lactose

Ilija Ilić[1], Peter Kása Jr.[2], Rok Dreu[1], Klara Pintye-Hódi[2] and Stane Srčič[1]

[1]*Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia and* [2]*Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Szeged, Szeged, Hungary*

Abstract

Objective: The purpose of this study was to investigate and quantify flow properties, compressibility, and compactibility of various pharmaceutical lactose powders found on the market today (DCL-11, DCL-21, M-200, Flowlac-100, and Tablettose 70, 80, and 100). *Methods*: Flow properties were estimated by measuring flow time, angle of repose, and the Hausner ratio. Particle rearrangement was studied using Kawakita's linear model. Compressibility was studied using two 'out-of-die' methods: (i) the Heckel model and (ii) a modified Walker model. Compactibility was quantified using two methods: (i) the tensile strength profile (*Cp*) and (ii) the compactibility factor (*Pr*). Statistical approach was used to analyze the results. *Results*: Flow properties of all materials were passable or better, except for M-200, which has very poor flowability. Compressibility results demonstrated that the most compressible lactose is spray-dried grade of lactose (Flowlac-100) and the least compressible is milled lactose (M-200). Compactibility studies showed that β-lactose (DCL-21) forms tablets with superior tensile strength in comparison with α-lactose. *Conclusion*: Results of the compressibility study showed that the discriminative power of modified Walker model is greater in comparison with Heckel model. Compactibility methods yield similar and comparable results.

Key words: *Compactibility; compressibility; flow properties; Heckel; lactose; Walker*

Introduction

Tablets are by far the most frequently used dosage form; they have advantages for both manufacturer and user. Ease of manufacturing, convenience of administration, and accurate dosing make tablets a versatile and popular dosage form[1,2]. However, the manufacture of tablets can be a complex operation because certain favorable properties of raw materials are required for the production of tablets of satisfactory quality. Two main properties of particulate solid that are necessary for its successful transformation into tablets are good flow properties and compressibility. At present, direct compression is the preferred method for tablet preparation. It has been estimated that less than 20% of pharmaceutical materials can be compressed directly into tablets[3]. The use of directly compressible excipients may yield satisfactory tablets for such materials[1]. It is estimated that currently about 50% of worldwide tablet production is made by direct compression using numerous diluents specifically designed for direct compression[4].

Lactose is the most common filler or diluent in tablets, capsules, and, to a more limited extent, lyophilized products and infant formulas. The general properties of lactose that contribute to its popularity as an excipient are cost effectiveness, availability, bland taste, low hygroscopicity, excellent physical and chemical stability, and water solubility[5]. Lactose may appear in different (pseudo)polymorphs (α-lactose monohydrate, anhydrous α-lactose, and anhydrous β-lactose) with different physical properties. Various lactose grades are available today on the market, such as grade intended for granulation, spray-dried and agglomerated with different properties. This means that there are a variety of different products to choose from with different particle size distribution, flow properties, and compressibility.

Recently, a broad review of coprocessed, directly compressible excipients, including various kinds of lactose,

Address for correspondence: Dr. Rok Dreu, MPharm, Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Ljubljana, Ašekerčeva 7, SI-1000 Ljubljana, Slovenia. Tel: +386 1 476 9622, Fax: +386 1 425 8031. E-mail: rok.dreu@ffa.uni-lj.si

(Received 9 Jan 2009; accepted 29 Mar 2009)

ISSN 0363-9045 print/ISSN 1520-5762 online © Informa UK, Ltd.
DOI: 10.1080/03639040902932945

was published, which offers a detailed review of basic tableting properties between different lactose types[1]. Crystalline α-lactose monohydrate exhibits relatively poor binding properties. It consolidates mainly by fragmentation and is more brittle compared to spray-dried lactose and anhydrous β-lactose, whereas amorphous lactose mainly consolidates by plastic deformation[6,7]. In spray-dried products, the amorphous fraction is responsible for better binding and a higher degree of plastic deformation; therefore, amorphous lactose yields tablets of higher tensile strength than crystalline lactose[8]. Tablettose 70, 80, and 100 are agglomerated types of lactose granulated from α-lactose monohydrate. Their binding properties are reported to be better than α-lactose monohydrate, but not as good as spray-dried lactose[1].

In this study, we quantified and compared flow properties, particle rearrangement, compressibility, and compactibility of seven different types of lactose, six of them intended for direct compression and a single type of lactose intended for granulation.

Materials and methods

Materials

Samples of Pharmatose® DCL-11, DCL-21, and M-200 (DMV International, Veghel, the Netherlands), Flowlac-100 and Tablettose® 70, 80, and 100 (Meggle Pharma, Wasserburg, Germany) were investigated. Microcrystalline cellulose (MCC) (Vivapur® 12; JRS Pharma, Rosenberg, Germany) was used as a dry binder and magnesium stearate as a lubricant. All the materials were used as purchased.

Particle size

Particle size distribution was measured by laser diffraction (Mastersizer S; Malvern Instruments Ltd., Worcestershire, UK) using the following parameters: 300 RF lens, small volume dispersion unit (1000 rpm), true density of 1.550 g/cm^3 (AccuPyc 1330; Micromeritics, Norcross, GA, USA), and refractive index of 1.3566. The dispersion medium used was a saturated aqueous solution of lactose. The particle size of each sample was measured in triplicate.

Differential scanning calorimetry and moisture analysis

Samples were evaluated with a DSC 821e (Mettler Toledo, Greifensee, Switzerland), with temperature range from 25°C to 300°C and heating rate of 10°C/min. Weighed samples were sealed into aluminum pans with holes and measured in a nitrogen atmosphere in triplicate. Differential scanning calorimetry (DSC) was used as method to confirm the presence of α- or β-types of lactose by melting point. It was also used to confirm monohydrate pseudopolymorph because dehydration could be observed in measured DSC curves when the monohydrate form of lactose was present.

An HR73 Halogen Moisture Analyzer (Mettler Toledo) was used to measure moisture content. Approximately 5 g of powder was evenly distributed on an open aluminum pan. Samples were heated to 80°C for 30 minutes to establish weakly bound water, then to 150°C for 30 minutes to establish crystalline bound water. The amount of water was determined by the loss of mass during drying.

Flow properties

The flow properties were estimated by measuring the flow time and angle of repose on a PTG-ER1 (Pharma Test Apparatebau, Hainburg, Germany) apparatus using a stainless-steel cone with a 10-mm outlet nozzle. The cone was filled with 100 mL of bulk powder, and the flow time was measured. The angle of repose was calculated from the height and width of the powder heap.

Particle rearrangement

Bulk density of lactose types was measured by filling a 250-mL cylinder with a known weight of material and reading the volume of the powder. The powder was then tapped by a Stampfvolumeter, Stav 2003 (Stav 2003; J. Engelsmann, Ludwigshafen, Germany) apparatus, and the reduction of volume was measured at predetermined number of taps (interval from 10 to 100 taps in steps of 10 and at 1250 taps). The volume after 1250 taps was used to calculate the tapped density. Kawakita's equation for densification of powder solids was used to interpret the results[9]:

$$\frac{N}{C_N} = \frac{1}{a}N + \frac{1}{ab}, \quad \text{where } C_N = \frac{V_0 - V_t}{V_0}, \tag{1}$$

where V_0 is the initial volume of powder and V_t is the volume of powder after certain number of taps (N). By plotting N/C_N versus N, the constants a and b can be evaluated graphically. Constant a is obtained from slope $1/a$ and represents Carr's index and $1/b$ is obtained from the y-intercept ($1/ab$) and is related to cohesiveness of the powder.

Compressibility and compactibility

Tablets consisted of 84% (w/w) lactose, 15% (w/w) MCC, and 1% (w/w) magnesium stearate. The addition of MCC and lubricant was necessary to eliminate tablet lamination and sticking to the tableting tools. Lactose (126 g) and MCC (22.5 g) were mixed for 8 minutes in a Turbula

(WAB, Basel, Switzerland) mixer at 50 rpm. Then 1.5 g of magnesium stearate was added and the blend was mixed for two more minutes. Tablets were pressed on a single-punch tableting press, Korsch EK0 (Erweka Apparatebau, Frankfurt am Main, Germany), mounted with strain gauges and a displacement transducer using 10.0 mm flat tableting punches and compression pressures ranging from approximately 60–300 MPa at a tableting speed of 36 tablets/min. Around 20 tablets were made at each compression pressure. Five or six compression pressures were used for each material except for M-200, for which around 55 tablets were compressed, equally distributed across the compression pressure range. This was due to the poor or absent flowability of M-200, which made it difficult to compress 20 tablets at the same conditions. The diameter, thickness, mass, and hardness of tablets were measured 24 hours after tableting. Hardness was measured with a Heberlein 2E/205 apparatus (Heberlein, Zürich, Switzerland). True densities of tableting blends were determined with five purges and three runs on a helium gas pycnometer, AccuPyc 1330 (Micromeritics).

Compressibility

The compaction properties of pharmaceutical powders are separated into two distinct terms for clarity: compressibility, the ability of the powder to deform under pressure and compactibility, the ability of a powder to form coherent strong compacts[10]. In our study, compressibility was estimated using an 'out-of-die' Heckel model (Equation 2)[11] and a modified Walker model (Equation 3)[10]:

$$\ln\left(\frac{1}{1-D}\right) = P \times K + A, \tag{2}$$

in which P is the pressure, D the relative density of the compact, and K and A are constants. For the Heckel analysis, only data up to pressures of 200 MPa were used because this range showed the best linearity. The following equation was used as a modified Walker model (Equation 3), based on a model by Walker[12]:

$$V' = -w' \cdot \log(P) + V_{sp}, \tag{3}$$

in which V' is the specific volume of tablet in mL/g and w' is the Walker coefficient, here expressing the volume reduction corresponding to one decade change in the pressure P. V_{sp} is the specific volume at the pressure 1 MPa. Heckel and Walker coefficients (slopes) were estimated using linear regression, in which each point is represented by a tablet. The Standard error (SE) of the slope was calculated using Equation (4):

$$\mathrm{SE} = \frac{S_{res}}{\sqrt{SS_x}}, \tag{4}$$

in which S_{res} is the sum of squares of residual deviation of the regression line and SS_x is the sum of squares of the x values. Introduction of the SE of the slope has the benefit that the uncertainty of the estimated slope can be reported and the confidence interval (CI) of regression can be calculated. The slopes, SEs, and two-sided 95% CIs of the slopes were calculated using SPSS v16. This approach has already been used for quantification of compactibility[10]. Furthermore, statistical significance between slopes was calculated using a t-distribution (t-test) with an OpenEpi statistical calculator[13]. First, Hartley's test for equality of variance was run, then a two-independent-samples t-test with either equal or unequal variance[14] was performed between the samples with a two-tailed 95% CI, depending on whether variance between the samples was equal or not.

Compactibility

Compactibility was estimated using two different approaches. Tensile strength versus the compression pressure relationship was drawn and the slope (Cp) of the linear curve was estimated using linear regression. Tensile strength was calculated using Equation (5) for circular and flat tablets, as proposed by Fell and Newton[15]:

$$\sigma_X = \frac{2H}{\Pi \times d \times h}, \tag{5}$$

in which H is breaking hardness, d is diameter, and h is the height of the flat, circular comprimate. The SE, 95% CI, and statistical testing were performed as described previously.

Compactibility was also estimated using the model proposed by Révész et al.[16], in which tensile strength is normalized with the specific work (W_{spec}) needed to compress the tablet (Equation 6). This is called the compressibility factor (Pr); however, because this parameter is derived from the crushing strength of the tablet, it is more closely associated with compactibility than compressibility.

$$Pr = \frac{\sigma_X}{W_{spec}} = \frac{\sigma_X}{E_2/m}, \tag{6}$$

in which σ_x is the tensile strength of tablet and W_{spec} is the specific or mass-normalized work, which is expressed as the effective work (E_2) invested in the compression of the unit mass of substance (m). E_2 effective work represents the area of hysteresis between the compression and the decompression curves in force–displacement measurement during tablet manufacturing. Pr was calculated from tablets with compression

pressures ranging from 120 to 300 MPa. The *Pr* values of various materials were compared using analysis of variance (ANOVA) for statistically significant (non)equality.

Results and discussion

Overview of studied lactose types

Pharmatose M-200 is a type of lactose intended for wet or dry granulation, whereas all other materials can be used for direct compression. DCL-11 and Flowlac-100 are spray-dried types of α-lactose monohydrate; Tablettose 70, 80, and 100 are agglomerated types of α-lactose monohydrate; and DCL-21 is anhydrous β-lactose. Table 1 represents a summary of specifications of lactose types studied, including particle size results from our study.

Particle size distribution was in a range of approximately 30–200 μm with a median particle size from 78 to 106 μm for most materials, except for Pharmatose M-200 and DCL-21. The lactose M-200 intended for granulation has generally smaller particles with a median particle size of 70 μm, whereas DCL-21 has larger particles with a median particle size of about 270 μm. The particle sizes measured are in agreement with manufacturers' specifications.

DSC and moisture analysis

Melting points for lactose are reported to be between 201°C and 202°C for α-lactose monohydrate, at 223°C for anhydrous α-lactose and at 252.2°C for anhydrous β-lactose[5]. In the case of lactose monohydrate, dehydration will occur around at 140°C[17,18]. At a heating rate of 10°C/min, dehydration will be completed before reaching the melting peak of monohydrate; therefore, melting is expected at temperatures around 220°C, at which anhydrous α-lactose undergoes a phase transition. DSC measurements confirmed that all materials had a dehydration endotherm in the range from 143°C to 147°C and melting points in the range from 215°C to 216°C, except for DCL-21, which is anhydrous β-lactose, in which no dehydration peak was observed and a melting point of 240°C was measured.

Anhydrous lactose may have a maximum of 1% (w/w) of water, whereas lactose monohydrate may have from 4.5% to 5.5% (w/w) of water[19]. All of our samples are in compliance with this specification, with a typical water content of 5.2% to 5.3% (w/w) for monohydrate and 0.25% (w/w) for anhydrous lactose.

Flow properties

The results of flow properties measurements are summarized in Table 2. There is a good correlation between flow time and angle of repose—powders with longer flow times have a higher angle of repose than powders with shorter flow time. Among all types of lactose investigated, only M-200 has very poor flowability, but this is

Table 2. Comparison of flow properties of lactose types.

Type of lactose	Flow time (seconds)	Angle of repose (°)	Hausner ratio (HR)	Flow properties (according to HR[20,21])
DCL-11	8.6 ± 0.2	27.1 ± 1.2	1.18 ± 0.0035	Good
DCL-21	30.5 ± 5.8	36.9 ± 1.0	1.27 ± 0.0020	Passable
M-200	No flow	No flow	1.58 ± 0.0211	Very poor
Flowlac-100	11.4 ± 3.8	28.2 ± 1.3	1.16 ± 0.0030	Good
Tablettose 70	6.9 ± 0.2	28.7 ± 0.2	1.17 ± 0.0059	Good
Tablettose 80	12.7 ± 0.2	30.6 ± 0.3	1.18 ± 0.0060	Good
Tablettose 100	18.0 ± 0.2	31.9 ± 0.3	1.25 ± 0.0189	Fair

Table 1. Lactose types studied: specifications and particle size distribution.

Type of lactose	Crystal form and manufacturing process	Application	Particle size (μm) [D(v, 0.1), D(v, 0.5), D(v, 0.9)]; $n = 3$
Pharmatose M-200	α-Lactose monohydrate, milled	Granulation	34.7, 69.7, 131.1
Pharmatose DCL-11	α-Lactose monohydrate and amorphous lactose, spray-dried	Direct compression	40.7, 105.5, 215.8
Pharmatose DCL-21	β-Lactose and anhydrous α-lactose, physical method of preparation	Not specified	114.0, 268.4, 509.2
Flowlac-100	α-Lactose monohydrate and amorphous lactose, spray-dried	Direct compression	32.8, 95.5, 210.0
Tablettose 70	α-Lactose monohydrate, agglomerated	Direct compression	38.1, 87.8, 171.7
Tablettose 80	α-Lactose monohydrate, agglomerated	Direct compression	33.8, 78.6, 163.3
Tablettose 100	α-Lactose monohydrate, agglomerated	Direct compression	28.5, 86.8, 210.8

Values of D(v, 0.1), D(v, 0.5), and D(v, 0.9) represent particle sizes at which 10%, 50%, and 90% (v/v) of the sample is below this given size, respectively.

expected because it is a type of lactose with the smallest particle size. Other lactose types have good flowability, with DCL-21 having the longest flow time. The lactose with the largest particle size is DCL-21; however, due to the nature of this material (β-lactose), its flow properties remain inferior to spray-dried or agglomerated types.

Particle rearrangement

Particle rearrangement was studied using Kawakita's equation[9]. All powders had linear rearrangement, with R^2 being at least 0.980. Coefficient a represents Carr's index and coefficient $1/b$ correlates with cohesiveness. Rearrangement results are presented in Table 3.

The approximate limit value between good and bad flow properties using Carr's index is 21%[22], which corresponds to an a value of 0.21. Powders with a below this value had good flowability and no problems regarding powder flow were observed during tableting. For DCL-21 with an a of 0.237, there were also no flowability issues observed and the variation of the tablet mass did not appear to increase compared to materials with lower a values. Pharmatose M-200 has very poor flowability and an a of 0.401, so manual forced filling of the die must be applied during tableting. Tablets made with M-200 also show a higher variability in tablet mass and compression force, as expected.

In general, good correlation between flow time, angle of repose, a value, and cohesion coefficient can be expected. Materials with higher angle of repose, a value, and cohesion coefficient have longer flow times and therefore worse flow properties. The cohesion coefficient $1/b$ is highest for M-200 and DCL-21, which is also in accordance with their poor flow properties. Higher cohesion coefficient $1/b$ relates to higher cohesive energy of interaction which consequently hinders particle rearrangement.

Compressibility and compactibility

Compressibility

Compressibility was estimated using two different approaches: a Heckel model (Equation 2) and a modified Walker model (Equation 3). From Heckel and Walker diagrams, the slope, SE, and y-intercept can be graphically estimated using linear regression. From the Heckel plot, the slope (K) was estimated and its inverse value gives yield pressure (P_y). A more plastic material is said to have lower yield pressure. The results are summarized in Table 4.

Heckel plots for all materials yield a straight line with R^2 of at least 0.983. All of the materials have yield pressures between 238.9 and 270.1 MPa. The differences between the powders are not large, and this is expected because the materials are similar. Considering slopes and their SE, it is difficult to conclude whether there are real differences between the plastic properties of different types of lactose. The CI can be a useful tool to determine this, Figure 1 is a graphical representation of Heckel model results using CIs. A good rule of thumb is that, if CIs are not overlapping, then the differences in plasticity are significant, using a two-sided 95% CI. When two CIs are greatly overlapping (e.g., Tablettose 70 and DCL-21), the plasticity of the materials is consid-

Table 3. Rearrangement parameters by Kawakita's densification Equation (1) of lactose types investigated.

Type of lactose	a	$1/b$	R^2
DCL-11	0.123	5.94	0.9994
DCL-21	0.237	23.11	0.9835
M-200	0.401	76.79	0.9800
Flowlac-100	0.113	5.95	0.9995
Tablettose 70	0.094	10.88	0.9959
Tablettose 80	0.119	8.99	0.9989
Tablettose 100	0.167	8.12	0.9994

Table 4. Results of Heckel analysis of the lactose types studied.

Types of lactose	$K \times 10^3$ (MPa^{-1})	P_y (MPa)	RSE (%)	R^2	N
DCL-11	3.92 [3.83–4.02]	255.2	1.22	0.9885	80
DCL-21	4.03 [3.93–4.13]	248.2	1.26	0.9879	80
M-200	3.70 [3.49–3.92]	270.1	2.81	0.9830	24
Flowlac-100	4.19 [4.10–4.27]	238.9	1.05	0.9895	99
Tablettose 70	4.03 [3.93–4.13]	248.2	1.24	0.9881	80
Tablettose 80	3.80 [3.72–3.89]	263.1	1.09	0.9909	80
Tablettose 100	4.12 [4.03–4.21]	243.0	1.10	0.9908	79

The two-sided 95% confidence interval is given in brackets. N is the number of data points included in the regression. RSE is the relative standard error of slope [RSE = (SE/K) × 100].

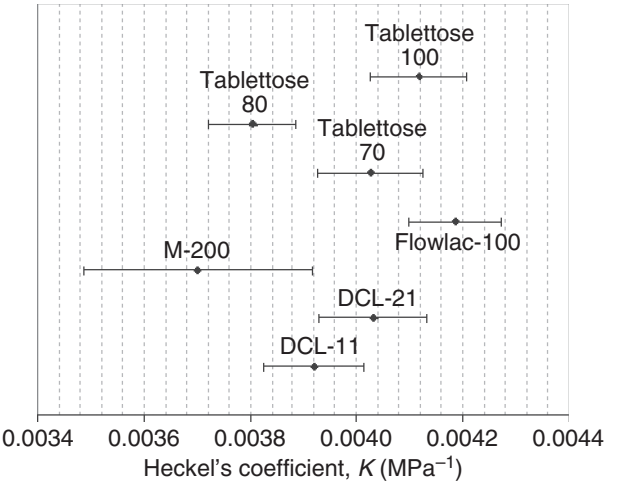

Figure 1. Graphic representation of Heckel analysis results, including 95% confidence intervals.

ered the same. When there is a slight overlap of CIs, statistics (a *t*-test) can be used to check equality or differences in compressibility of the two materials. If the *P* value is greater than 0.05 there is no statistically significant difference between the two lactose types, but there may exist a trend of higher compressibility in one material over the other. Comparing only slopes (K), the plasticity decreases in the following order: Flowlac-100 > Tablettose 100 > Tablettose 70 ≈ DCL-21 > DCL-11 > Tablettose 80 > M-200. The difference between Flowlac-100 and Tablettose 100 is not statistically significant (P = 0.2855), but Flowlac is more plastic than DCL-21 (P = 0.0223) and consequently also Tablettose 70. DCL-21 and Tablettose 70 have equal plasticity, which is not significantly greater compared to DCL-11 (P = 0.1258, compared to Tablettose 70). M-200 is not significantly less plastic than Tablettose 80 (P = 0.3702), but it shows a tendency towards the lowest plasticity among the materials studied. From the three Tablettose types, it is clear that Tablettose 80 is the least compressible agglomerated type of lactose, whereas we cannot discriminate between Tablettose 70 and 100.

It has been suggested[23] that Heckel analysis also has a few drawbacks. It is sensitive to small errors in the experimental conditions and variations in the true density measurements that are needed for calculating Heckel plots. This is more pronounced at high pressures and low tablet porosity, in which a small error in determining the relative density can cause a significant error in the logarithmic transformations[23,24]. More importantly, compared to the Walker model, for instance, the Heckel model lacks discriminative power[23]. So it is possible that the lack of differences between our lactose types studied is due to the method used to quantify their compressibility. This is why we used two different methods to measure compressibility and compactibility. This allows us to compare the methods and determine which is more discriminative, especially when similar materials are studied. The results of the modified Walker model are shown in Table 5.

Table 5. Results of the modified Walker model of the lactose types studied.

Type of lactose	w'	RSE (%)	R^2	N
DCL-11	0.2144 [0.2110–0.2177]	0.78	0.994	100
DCL-21	0.2088 [0.2050–0.2126]	0.92	0.992	100
M-200	0.1786 [0.1742–0.1831]	1.24	0.993	49
Flowlac-100	0.2261 [0.2231–0.2292]	0.69	0.996	99
Tablettose 70	0.2005 [0.1971–0.2039]	0.86	0.993	100
Tablettose 80	0.1921 [0.1886–0.1956]	0.91	0.992	100
Tablettose 100	0.2210 [0.2179–0.2242]	0.72	0.995	99

The two-sided 95% confidence interval is given in brackets. N is the number of data points included in the regression. RSE is the relative standard error of slope [RSE = (SE/w') × 100].

Similar as in case of the Heckel model, compressibility data of our materials fit the modified Walker model very well. The modified Walker model allowed us to use all data points and still achieve a high linearity, with R^2 of over 0.992 for all materials. First, a wider compaction pressure range can be used to calculate Walker's constant (w'), and furthermore the fit of the modified Walker model is more linear with higher R^2 values. The data fit the modified Walker model better than the Heckel model.

Walker's coefficient is considered a measure of the irreversible compressibility of the compact or the system of particles. Higher w' values are associated with better tableting properties, whereas lower w' values are typical for powders with poorer compression properties. According to w', compressibility of tested materials is reducing in the following sequence: Flowlac-100 > Tablettose 100 > DCL-11 > DCL-21 > Tablettose 70 > Tablettose 80 > M-200. Figure 2 is a graphical representation of Walker model results using CIs. No overlapping of CIs is observed between most of the materials, which means that the differences between these materials is statistically significant. Some overlapping can be observed between Tablettose 100 and Flowlac-100 as one pair and DCL-21 and DCL-11 as another pair; these pairs were compared using a *t*-test. Significant differences were found between both pairs; Flowlac-100 is more compressible than Tablettose 100 (P = 0.02183) and DCL-11 is more compressible than DCL-21 (P = 0.02979).

Figure 3 shows the relationship between Heckel's constant (K) and Walker's constant (w'). There is a clear positive relationship between these two parameters. Good compressibility of Flowlac-100 is illustrated by high values of both parameters. On the other hand,

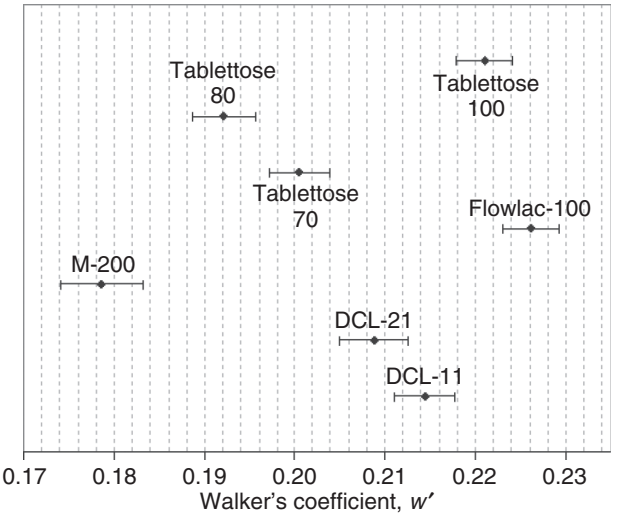

Figure 2. Graphic representation of Walker's coefficients (w') including 95% confidence intervals.

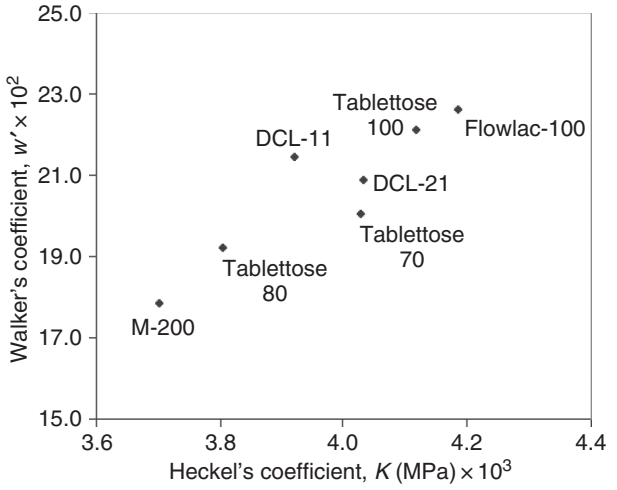

Figure 3. Relationship between Heckel's coefficient (K) and Walker's coefficient (w').

poor compressibility of M-200 is supported by low values of both parameter constants for this particular type of lactose.

It can be concluded that both the Heckel and Walker models describe the compression properties of our materials well, but in our study the Walker model seems to be a better choice for compressibility measurements for a number of reasons. First, our data fit the Walker model slightly better. This is evidenced by the higher R^2 values of the regression slopes using the Walker model. This is especially true when wide pressure ranges are used because the Heckel model is known to deviate from linearity at low or high pressures. In this case, Heckel's constant can be calculated from a narrower compaction pressure range or a lower R^2 can be tolerated. Second, results using the Walker model have smaller SEs. The high sensitivity of the Heckel model to errors is a known issue due to multiplication of the data with the true density and consequent reciprocal and logarithmic transformations. An error in the true density measurement of 1% can change the yield pressure estimate by 10% in certain cases[23]. This means that the Heckel model is extremely sensitive to true density measurements, whereas in the modified Walker model this measurement and its further transformation are not required. Third and most important, the Walker model seems to have more discriminative power compared to Heckel. The relative difference between Flowlac-100 and M-200 as most and least compressible materials [e.g., $(w'_{\text{Flowlac-100}} - w'_{\text{M-200}})/w'_{\text{M-200}}$ versus $(K_{\text{Flowlac-100}} - K_{\text{M-200}})/K_{\text{M-200}}$] is twice as large using the modified Walker model compared to the Heckel model, at 27% and 13%, respectively. The discriminatory power of the modified Walker model is further demonstrated by more narrow 95% CI of the materials. It should be noted, however, that the CI width depends on the SE and its value depends on number of sampling points (N). This means that the Walker model has a narrower CI due to the better fit of the model and also partly due to the slightly higher number of sample points used compared to the Heckel model. Larger differences between the materials with narrower CIs (Figures 1 and 2) allow better statistically significant quantitative determination of compressibility between similar materials.

Compactibility

To estimate compactibility of a specific substance, one needs not only compression data but also the mechanical strength of the comprimate. If mechanical strength is reported as crushing force, it is necessary to attach information on dimensions of the compact. Because crushing force is expected to be dependent on the tablet dimensions, it can be normalized to the geometry of the tablet. This is termed tensile strength (σ_x) and can be calculated using Equation (5) for flat and circular tablets. The mechanical strength of a single compact is easily determined as the force needed to crush the tablet diametrically.

Compactibility can be quantified in several different ways. The simplest is a one-point estimate; for instance, the minimum pressure needed to make a compact of a certain strength[25]. Alternatively, tensile strength can be calculated at a given pressure[26] or at given porosity[27].

It is anticipated that the mechanical strength of the compact will be associated with the nature and number of contact points generated in the compact; the number of contact points in particular is dependent on the compression pressure used. Compactibility is most often expressed graphically in an XY-plot as a relationship between tensile strength and compression pressure (compactibility profile or tensile strength profile). There are several examples showing that compactibility profiles in their full extension have essentially sigmoid shapes[28,29]. At high pressures, it is often observed that the crushing strength levels off and sometimes even decreases to a lower value due to capping or lamination tendencies[30]. Despite this, there is a distinct linear segment present in a compactibility profile. For lactose monohydrate, a wide linear range is reported up to a pressure of 310 MPa for tablets ranging in mass from 400 to 1000 mg[31]. This linear part is most relevant and informative because it describes the increase of tablet strength related to compression pressure. The compactibility of a certain material can be estimated by the slope (Cp) of the linear part in the compactibility profile and the Cp values of different materials can be compared.

Compactibility was measured using two approaches, one of them being a compactibility profile. Although a sigmoid shape is expected, a high degree of linearity is observed for all lactose types because of the dominant linear segment of lactose mentioned above. Negative

Table 6. Summary of compactibility profiles results for the lactose types studied.

Type of lactose	Slope (Cp) $\times 10^3$	RSE (%)	R^2	N
DCL-11	9.61 [9.38–9.84]	1.20	0.9862	100
DCL-21	13.47 [13.27–13.68]	0.76	0.9944	100
M-200	10.43 [10.11–10.75]	1.51	0.9896	48
Flowlac-100	9.56 [9.29–9.83]	1.42	0.9809	99
Tablettose 70	8.83 [8.63–90.30]	1.14	0.9878	98
Tablettose 80	9.32 [9.15–9.50]	0.94	0.9915	100
Tablettose 100	11.67 [11.40–11.93]	1.15	0.9872	100

The two-sided 95% confidence interval is given in brackets. N is the number of data points included in the regression. RSE is the relative standard error of slope [RSE = (SE/Cp) $\times$ 100].

y-intercepts for all materials are consistent with the sigmoid nature of this curve.

Table 6 represents results of compactibility quantification using compactibility profile. A high R^2 combined with a low SE confirms the high degree of linearity of compactibility profiles for all lactose types. Slopes of compactibility curves (Cp) vary from 8.83 for Tablettose 70 to 13.47 for DCL-21. The range of Cp values with their CIs demonstrates the good ability of this parameter to discriminate between different types of the same material. Using only Cp as criteria, the compactibility of the studied materials decreases in the following order: DCL-21 > Tablettose 100 > M-200 > DCL-11 ≈ Flowlac-100 > Tablettose 80 > Tablettose 70. The differences between most materials are significant with no overlapping of CIs present. DCL-11 and Flowlac-100 can be considered to have equal Cp due to major overlapping of their CIs. Tablettose 80 and DCL-11 were compared using the t-test and $P = 0.04716$ was calculated, showing a difference between these two slopes; however, this P-value is borderline with regard to a 95% CI; therefore, these three materials (Tablettose 80, Flowlac-100, and DCL-11) may be considered as having approximately the same Cp. Cp results cannot confirm that spray-dried lactose yields compacts with greater hardness or tensile strength compared to crystalline forms. However, significant differences between the three agglomerated types studied can be observed.

From these results, it can be concluded that β-lactose is more compactible than α-lactose, but superior compactibility of spray-dried grades over agglomerated or milled α-lactose cannot be demonstrated. It should also be noted that, with regard to compactibility, the nature and number of contact points between the particles is very important. Tablets consisting of smaller particles with higher specific surfaces will have higher numbers of contact points, and this may very well lead to higher tensile strengths in such tablets. Milled lactose M-200 has, for instance, superior compactibility compared to Tablettose 70 and 80, as well as also spray-dried Flowlac-100 and DCL-11. This can be explained by the smaller particle size of M-200 compared to other materials, a fact also supported by this materials' high cohesion coefficient measured according to Kawakita and its complete lack of flow properties. The larger particle size of β-lactose (DCL-21) should also be considered when comparing its compactibility to other materials. This particular type of lactose has roughly twice the particle size of other lactose types tested, but despite its larger particles, it shows superior compactibility. This implies stronger interparticulate forces and increased binding between the particles of β-lactose compared to α-lactose.

Compactibility was also measured using the Pr factor. It was noticed that Pr factor is dependent on the compression pressure used. This was characteristic for all materials studied. With higher compression, pressure Pr increases and at a certain point, a plateau is evident. For all types of lactose a plateau was reached at pressures of about 120 MPa. Only compression pressures above this limit were used to calculate a material's Pr.

Compactibility results obtained using Pr are presented in Table 7. The Pr factors of the materials studied decrease in the following order: DCL-21 > M-200 > Tablettose 100 > DCL-11 ≈ Tablettose 80 ≈ Flowlac-100 > Tablettose 70. These results are supported by ANOVA analysis using SPSS. Variance was tested using the Levene test and was determined to be unequal between the samples; therefore, Tamhane post hoc comparison between pairs of materials was used. The ANOVA shows that the differences between DCL-11, Flowlac-100, and Tablettose 80 are nonsignificant and their Pr can be considered equal. All other Prs have $P = 0.000$ between each pair and the differences between them can be considered statistically significant. These results are very similar to the compactibility results using Cp; only M-200 and Tablettose 100 changed places as the second and third most compactible materials. Anhydrous β-lactose in the form of DCL-21 remains the material

Table 7. Summary of Pr factor results for the lactose types studied.

Types of lactose	Pr (Pa/J/Kg)	RSD (%)	N
DCL-11	289.7 [284.6–294.8]	6.83	60
DCL-21	437.2 [432.3–442.2]	4.41	60
M-200	399.5 [390.0–409.1]	7.16	37
Flowlac-100	294.8 [289.4–300.1]	7.05	60
Tablettose 70	266.7 [263.3–270.2]	4.96	59
Tablettose 80	295.9 [290.8–301.1]	6.69	59
Tablettose 100	341.0 [334.4–347.5]	7.37	59

The two-sided 95% confidence interval is given in brackets. N is the number of data points included in the regression. RSD is the relative standard deviation of slope [RSD = (SD/Pr) $\times$ 100].

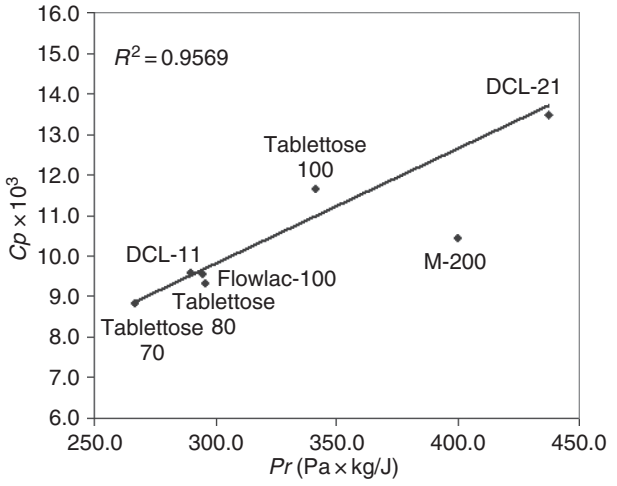

Figure 4. Relationship between *Cp* and *Pr*.

with the best compactibility and Tablettose 70 the worst. The differences between Tablettose 80, Flowlac-100, and DCL-11 remain small and their compactibility is statistically equal.

Considering the similarity of compactibility results between the two methods used, *Cp* was compared to *Pr* in Figure 4. A positive linear relationship was established and only M-200 showed a deviation from linearity with either too low a *Cp* value or too high a *Pr* value. Leaving out the M-200 type of lactose, a linear curve with a reasonably high R^2 of 0.957 could be drawn through the rest of the results. This confirms the suitability of both methods to adequately measure the compactibility of powders.

The relative difference between DCL-21 and Tablettose 70 as most and least compactible materials [i.e., $(Cp_{\text{DCL-21}} - Cp_{\text{T70}})/Cp_{\text{T70}}$ versus $(Pr_{\text{DCL-21}} - Pr_{\text{T70}})/Pr_{\text{T70}}$] is 52.5% and 64% using *Cp* and *Pr*, respectively. This means that the discriminative power of *Pr* is slightly better. Both methods require crushing strength and geometric measurements of the tablet as well as compression force measurements on the tableting press. *Pr* additionally requires displacement measurements, an analysis of the force–displacement curve and tablet mass measurements. Calculation of *Pr* is more demanding and time consuming. For an optimal result, *Pr* should be measured at low tablet porosity, when the value is expected to be constant and at a plateau. Therefore, it seems that *Cp* is a quicker and simpler estimate of compactibility with reasonable discriminative power.

Comparison of compressibility and compactibility results

For comparison reasons, the results of compressibility and compactibility evaluations by both methods are given in Table 8. Tablettose 70 and 80 generally show both poor compactibility and compressibility, whereas Tablettose 100 shows significantly higher compactibility and compressibility. Agglomerated types of lactose exhibit comparable rank in compressibility and compactibility. On the other hand, the most compactible type of lactose DCL-21 shows neither superior nor inferior compressibility. Discrepancy in the compressibility and compactibility rank can also be observed for M-200 and Flowlac-100. Overall comparison demonstrates that compressibility and compactibility can be independent properties of material.

Table 8. Summary of the compressibility and compactibility results.

Type of lactose	Compressibility		Compactibility	
	Walker model, $w' \times 100$	Heckel model, $K \times 10^3$ (MPa^{-1})	$Cp \times 10^3$	*Pr* (Pa/J/kg)
DCL-11	21.44	3.92	9.61	289.7
DCL-21	20.88	4.03	13.47	437.2
Flowlac-100	22.61	4.19	9.56	294.8
M-200	17.86	3.70	10.43	399.5
Tablettose 70	20.05	4.03	8.83	266.7
Tablettose 80	19.21	3.80	9.32	295.9
Tablettose 100	22.10	4.12	11.66	341.0

Conclusion

Flow properties were estimated using flow time, angle of repose, and the Hausner ratio. All of these methods are appropriate for measuring flowability and can be applied equally. All of the lactose powders studied follow a linear rearrangement model. Very good flowability is measured for spray-dried and agglomerated types of α-lactose monohydrate, whereas anhydrous β-lactose has passable flowability. Milled lactose intended for granulation has very poor flowability and cannot be directly compressed.

Regarding compressibility, we can conclude that our data fit the modified Walker model better than the Heckel model. Both models are in correlation, but w' shows a higher degree of discrimination between the materials studied; therefore, it should be used when compressibility of similar materials is studied or where only small differences are expected. We also showed that a statistical approach using CIs and the *t*-test can be successfully applied to Heckel and Walker coefficients when significance testing is required.

A general trend was observed: spray-dried types of lactose with Flowlac-100 and DCL-11 have the best overall compressibility, followed by anhydrous β-lactose with DCL-21, then agglomerated types, and milled α-lactose monohydrate M-200 with the worst compressibility.

Compactibility can be studied equally well using either the *Cp* or the *Pr* parameter, and both methods yield similar and comparable results. Using *Pr*, one must be careful to measure it in a plateau, or else the result will depend on the maximum compression force used. *Pr* requires more data and more calculation, but it yields approximately the same quality of information as *Cp* about compactibility of the powder studied.

A trend appeared with regard to compactibility. Anhydrous β-lactose with DCL-21 clearly has the best compatibility, followed by milled α-lactose monohydrate in the form of M-200 and spray-dried Flowlac-100 and DCL-11. Tablettose 70 and 80, as agglomerated grades of lactose, have the worst compactibility.

Declaration of interest: The authors report no conflicts of interest.

References

1. Gohel MC, Jogani PD. (2005). A review of co-processed directly compressible excipients. J Pharm Sci, 8:76–93.
2. Armstrong NA. (2007). Tablet manufacture. In: Swarbrick J, ed. Encyclopedia of pharmaceutical technology, vol. 4. 3rd ed. New York: Informa Healthcare Inc., 3653.
3. Shangraw RF. (1989). Compressed tablets by direct compression. In: Lieberman HA, Lachman L, Schwartz JB, eds. Pharmaceutical dosage forms: Tablets, vol. 1. 2nd ed. New York: Marcel Dekker Inc., 195–246.
4. Bolhuis GK, Chowhan ZT. (1996). Materials for direct compression. In: Alderborn G, Nyström C, eds. Pharmaceutical powder compaction technology. New York: Marcel Dekker Inc., 419–500.
5. Rowe RC, Sheskey PJ, Weller PJ. (2003). Handbook of pharmaceutical excipients. 4th ed. London: Pharmaceutical Press, 323–32.
6. Roberts RJ, Rower RC. (1985). Effect of punch velocity on the compaction of a variety of materials. J Pharm Pharmacol, 37:377–84.
7. Lerk CF. (1993). Consolidation and compaction of lactose: The application of compaction techniques as prospective functionality tests for tablets excipients. Drug Dev Ind Pharm, 19:2359–98.
8. Sebhatu T, Alderborn G. (1999). Relationships between effective interparticulate contact area and the tensile strength of tablet of amorphous and crystalline lactose of varying particle size. Eur J Pharm Sci, 8:235–42.
9. Ludde KH, Kawakita K. (1966). Die Pulverkompression. Pharmazie, 21:393–403.
10. Sonnergaard JM. (2006). Quantification of the compactibility of pharmaceutical powders. Eur J Pharm Biopharm, 63:270–7.
11. Heckel RW. (1961). Density-pressure relationships in powder compaction. Trans Metall Soc AIME, 221:671–5.
12. Walker EE. (1923). The properties of powders VI: The compressibility of powders. Trans Faraday Soc, 19:73–82.
13. Dean AG, Sullivan KM, Soe MM. (2008). OpenEpi: Open Source Epidemiologic Statistics for Public Health. Version 2.2.1. http://www.OpenEpi.com [updated March 6, 2008, accessed October 16, 2008].
14. Rosner B. (1995). Fundamentals of biostatistics, 4th ed. Pacific Grove (CA): Duxbury Press, 266, 271–2.
15. Fell JT, Newton JM. (1970). Determination of tablet strength by the diametral compression test. J Pharm Sci, 59:688–91.
16. Révész P, Hódi K, Miseta M, Selmeczi B. (1991). Production of tablets by direct compressing, compressibility of active ingredients and auxiliary materials. Gyógyszerészet, 35:215–8.
17. Lehto VP, Tenho M, Vähä-Heikkilä K, Harjunen P, Päällysaho M, Välisaari J, et al. (2006). The comparison of seven different methods to quantify the amorphous content of spray-dried lactose. Powder Technol, 167:85–93.
18. Angberg M. (1995). Lactose and thermal analysis with special emphasis on microcalorimetry. Thermochim Acta, 248:161–76.
19. European Pharmacopoeia 6th ed. (2008). Council of Europe. Strasbourg 01/2008. Lactose monohydrate (01/2008:0187) and lactose, anhydrous (01/2008:1061) monograph.
20. Hausner H. (1967). Friction conditions in a mass of metal powder. Int J Powder Metall, 3:7–13.
21. European Pharmacopoeia 6th ed. (2008). Council of Europe. Strasbourg 01/2008. 2.9.36. Powder flow (01/2008:20936).
22. Carr RL. (1965). Evaluating flow properties of solids. Chem Eng, 72:163–8.
23. Sonnergaard JM. (1999). A critical evaluation of the Heckel equation. Int J Pharm, 193:63–71.
24. Patel S, Kaushal AM, Bansal AK. (2007). Effect of particle size and compression force on compaction behavior and derived mathematical parameters of compressibility. Pharm Res, 24:111–24.
25. Fraser DR. (1973). An investigation of some factors influencing tablet strength. In: Goldberg AS, ed. Proceedings of the 1st international conference on compaction and consolidation of particulate matter. London: Powder Advisory Centre, 149–54.
26. Duberg M, Nyström C. (1985). Studies on direct compression of tablets: XII. The consolidation and bonding properties of some pharmaceutical compounds and their mixtures with Avicel 105. Int J Pharm Tech Prod Mfr, 6:17–25.
27. Van Veen B, van der Voort Maarschalk K, Bolhuis GK, Zuurman K, Frijlink HW. (2000). Tensile strength of tablets containing two materials with a different compaction behaviour. Int J Pharm, 203:71–9.
28. Knoechel EL, Sperry CC, Lintner CJ. (1967). Instrumented rotary tablet machines. II. Evaluation and typical applications in pharmaceutical research, development and production studies. J Pharm Sci, 56:116–30.
29. Rees JE, Rue PJ. (1978). Work required to cause failure of tablets in diametral compression. Drug Dev Ind Pharm, 4:131–56.
30. Zupančič-Božič D, Dreu R, Vrečer F. (2008). Influence of dry granulation on compactibility and capping tendency of macrolide antibiotic formulation. Int J Pharm, 357:44–54.
31. Newton JM, Rowley G, Fell JT, Peacock DG, Ridgway K. (1971). Computer analysis of the relation between tablet strength and compaction pressure. J Pharm Pharmacol, 23:195S–201S.