Modulated Uniaxial Compression Analysis of Respirable Pharmaceutical Powders†

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Abstract

We describe a new instrument and method for measuring compressed bulk density of respirable pharmaceutical powders under low compression pressure: the modulated compression tester. The instrument modulates compression and decompression steps, allowing scrutiny of the overall compression response of samples. Compared to established methods for the determination of density and related parameters for pharmaceutical powders, this instrument has the capability of measuring smaller samples. The relative humidity can also be controlled in the instrument (3 % to 95 % RH), allowing assessment of the effect of moisture on compression response. We have used the instrument to determine the compressed bulk density of Trehalose, Leucine, Trileucine, and Mannitol powders of varying crystalline and amorphous compositions and particle size and size distribution, demonstrating that the new modulated compression tester is suitable for low pressure (< 1200 kPa) density measurement of respirable powders (< 10 μm) and expensive active pharmaceutical ingredients available in limited quantities (typical sample mass requirement of < 100 mg). In addition, the modulation feature of the instrument allows the analysis of the transition from plastic to semi-elastic compression response. The outputs and features of this instrument are useful for formulation development, quality control measurements, discerning between different or similar powders due to differences in the compression response, and optimizing powder compression parameters for pharmaceutical applications.

Keywords: compressed bulk density, respirable powders, powder compression, powder elasticity, dry powder inhalers

1. Introduction

Evaluation of the compression response of fine and respirable pharmaceutical powders is of prime importance because of the implications it has on formulation development, manufacturing and quality of the final product. Adequate characterization of the bulk powder properties is needed through the entire product development lifecycle (de Boer et al., 2017; Sørensen et al., 2005). For solid dosage forms, knowledge of the particle density and powder bulk density are necessary for assessing the aerodynamic properties (Feng et al., 2011), dispersibility (Boraey et al., 2013; Weiler et al., 2010) and parameters that influence powder filling processes, such as flowability (Faulhammer et al., 2014; Osorio and Muzzio, 2013). In order to assess the quality of a final product, the properties of powdered excipients and active ingredients must be precisely and accurately characterized. It is therefore important to characterize the bulk density and compression response of powders for manufacturing and quality control of final pharmaceutical products.

Providing an unambiguous definition of powder density is not straightforward because of the presence of voids within particles and between neighboring particles in a powder. This fact gives rise to a family of density definitions for pharmaceutical powders: true density, particle density, bulk density and tapped density, among others. The true density of a solid object excludes internal and external voids that are not a fundamental part of the molecular packing; thus, true density can be measured reproducibly because it does not include pore volume in its determination (Brockhaus and Carlozzo, 1995). Particle density is the ratio of the particle mass over the volume of the particle with external and internal voids, also known as the hydrodynamic volume (Vehring, 2008). Bulk density is
likewise holds implications for powder handling during for bulk or tapped density measurements. 

Flowability and dispersibility; thus, they are not well suited compared to powders with larger particles, fine powders are typically more cohesive and display relatively poor 

forces (e.g. Van der Waals interactions), electrostatics, material properties and environmental conditions, in addition to particle size and shape (Baldelli and Vehring, 2016; Sarkar et al., 2017; Weiler et al., 2010). As a result, when compared to powders with larger particles, fine powders are typically more cohesive and display relatively poor flowability and dispersibility; thus, they are not well suited for bulk or tapped density measurements.

The cohesive nature of fine and respirable powders likewise holds implications for powder handling during manufacturing as well as for delivery efficiency from inhalation devices (Elia et al., 2016; Rudén et al., 2018; Weiler et al., 2010). Powder products that are meant for inhalation (e.g. dry powder inhalers) are compressed at low pressures and packaged into capsules that require additional energy upon use to disperse them for inhalation (de Boer et al., 2017; Faulhammer et al., 2014; Prime et al., 1997). In such a case, it is important to use low compression pressures when packaging the powder product to achieve particle rearrangement, resulting in a loose powder compact. Utilizing low pressures when plastically compressing respirable powders can also mitigate the deformation or fracturing of the particles (Chen et al., 2017; Raut et al., 2016; Sørensen et al., 2005; Vu et al., 2020), preserving the aerodynamic properties of the particles, while minimizing the volume of powder needed for each capsule. As a result, single-value density measurements, such as bulk and tapped density, are unsuitable for relatively cohesive respiratory powders, so new methods are required for accurate and reproducible Compressed Bulk Density (CBD) measurements.

For the overall compression response of fine powders to be described, they must be actively compressed, taking into consideration the entire compression curves and elasticity of the powders (Vu et al., 2020). Assuming there is no moisture, a powder column is mostly a two-phase system that consists of air and particles. Generally speaking, when a powder is subjected to a compression force, it will go through a series of either reversible or irreversible compression stages. The former occurs as a result of material elasticity and the latter is due to plasticity of the powder (Chen et al., 2017; Vu et al., 2020). The first stage of the compression process is seen as the displacement of the gaseous phase by the solid phase (powder packing and particle rearrangement) within the bulk as a result of the compression force, leading to the reduction of the bed volume (Klevan et al., 2009; York, 1978). After this stage, many air gaps between particles are filled, yet the particles themselves have not fractured or deformed. Once the bed has reached a sufficiently close packing, it starts showing elastic response to the applied force. At higher compression force, non-elastic materials or those elastic materials that have yielded may show permanent, plastic deformation, and particle fracture and further packing become possible. At very high pressures, the powder bed acts like a solid body.

A powder’s compression response strongly depends on the way that particles pack together. When powder is subjected to an axial force, this external force brings the particles closer to one another and causes the volume to reduce. This stage may be referred to as the particle rearrangement stage (Bolhuis et al., 1996; Tousey, 2002; Vu et al., 2020; Yap et al., 2008). It is therefore possible, experimentally, to determine the pressure at which the powder is compressed and starts showing significant reversible response; this is
the transition pressure from plastic to elastic deformation. In general, CBD measurements are based on uniaxially compressing a powder sample and measuring its density under a defined pressure. A number of studies involving low-pressure compression of pharmaceutical powders have been reported (Faulhammer et al., 2014; Heda et al., 1999; Kostelnik et al., 1968; Llusa et al., 2014; Nikolakakis et al., 1998; Podczeck and Lee-Amies, 1996; Sheikh-Salem and Fell, 1981; Sørensen et al., 2005, 2006). A previous report has also used a commercial compression instrument that can accommodate milligram powder quantities for bulk density measurements (Sørensen et al., 2005). While these studies have demonstrated the use of low-pressure compression for bulk density measurements and the use of small sample quantities, none has experimentally differentiated the compression response of respirable powders between densification due primarily to particle rearrangement, i.e. plastic deformation, from densification due to semi-elastic particle or powder deformation. The ability to experimentally identify these compression responses is only achievable at low pressures and is important for establishing suitable compression pressures for packaging or processing respirable powders. The instrument in this paper is similar to the commercially available Geopyc 1360 (Micromeritics, Norcross, GA), which can only handle larger sample masses, as well as the Texture Analyzer (Stable Micro Systems, Surrey, UK), which is designed for a variety of uses, but is not specifically for density measurements of fine respirable powders and does not have RH control capabilities.

We report here the development of a uniaxial low-pressure and modulated compression instrument for CBD measurements of fine and respirable pharmaceutical powders. The focus of this paper is to demonstrate the capabilities of the new instrument and its ability to differentiate between very similar respirable powders at low compression pressures. We also show details of the modulation compression technique and introduce a new parameter for powder elasticity, which can be used to easily distinguish between plastic and semi-elastic compression response.

2. Materials and methods

2.1 Materials

With the exception of crystalline Leucine (raw material), all powder samples used in this study were produced by spray drying and contain particles with mass median aerodynamic diameters (MMAD) in the respirable range (≤ 10 μm). D-(+)-trehalose dihydrate (177,613, Fisher Scientific Co., Ottawa, ON, Canada), Trileucine (BCBP2254V, Sigma-Aldrich Corp., St. Louis, MO, USA), L-Leucine (AC125121000, Acros Organics, New Hampshire, NH), and D-mannitol (SLBH1429V, Sigma-Aldrich Corp., St. Louis, MO, USA) are pharmaceutical excipients and were used to produce the powder samples for this study. These excipients were chosen on the basis of their different effects on particle formation, cohesiveness and mechanical properties (Vehring, 2008).

Most of these excipients were spray-dried by themselves or in mixtures to produce the samples shown in Table 1 and to allow CBD measurements of different formulations, particle sizes and particle size distributions. Monodisperse samples had a particle size distribution with a geometric standard deviation (GSD) of 1.1 while polydisperse samples had a particle size distribution with a geometric standard deviation (GSD) of 1.1 while polydisperse

| # | Trehalose [% w/w] | Leucine [% w/w] | Trileucine [% w/w] | Mannitol [% w/w] | Mass [mg] | GSD | MMAD [μm] | ρ_{t,mix} [g/cm^3] |
|---|---|---|---|---|---|---|---|---|
| 1 | 100 | 78.7–79.5 | (raw material) | 1.29 |
| 2 | 100 | 58.9–59.3 | 1.6 | 2.5 | 1.53 |
| 3 | 99.6 | 0.4 | 86.4–91.7 | 1.1 | 9 | 1.53 |
| 4 | 99 | 1 | 103.9–110.2 | 1.1 | 9 | 1.52 |
| 5 | 95 | 5 | 72.8–77.3 | 1.1 | 9 | 1.50 |
| 6 | 80 | 20 | 63.2–68.5 | 1.6 | 2.5 | 1.48 |
| 7 | 75 | 32.5 | 40.0–42.6 | 1.6 | 2.5 | 1.47 |
| 8 | 75 | 25 | 38.2–40.3 | 1.6 | 4.5 | 1.47 |
| 9 | 55 | 45 | 34.6–37.4 | 1.6 | 3.6 | 1.42 |
| 10 | 100 | 68.3–69.7 | 1.1 | 10 | 1.51 |
| 11 | 100 | 64.4–65.7 | 1.6 | 3.5 | 1.51 |
samples had a particle size distribution with a GSD of 1.6. The median sample mass of the materials and formulations listed in Table 1 was 66 mg. All samples were stored at a relative humidity (RH) below 5% and between 22 and 23 °C in a desiccator for several weeks before being used for measurements.

Field Emission Scanning Electron Microscopy (Zeiss Sigma FE-SEM; Carl Zeiss, Oberkochen, Germany) was used to assess particle size and morphology. Powder samples were mounted directly onto aluminum Scanning Electron Microscope (SEM) stubs (Product 16111; Ted Pella, Inc.; Redding, CA, USA). Subsequently, the samples were sputtered with a gold coating (Denton Vacuum Desk II; Moorestown, NJ, USA) to a thickness of 10 to 15 nm. Images ranging from magnifications of 500× to 20000× were taken at a working distance of 5.3 to 6.3 mm using an accelerating voltage of 3 to 4 kV. Scanning Electron Microscope images of these samples are shown in Fig. 1 to show the differences in particle sizes and morphologies.

The experimental set-up for monodisperse and polydisperse spray drying has been discussed elsewhere (Ivey et al., 2018b; Wang et al., 2019). The aerodynamic particle size distributions were measured in-line with the spray drying process using a time-of-flight aerodynamic particle sizer (3321, TSI, Shoreview, MN, USA) (Ivey et al., 2018a).

The solid phase of the powder samples was assessed using Raman spectroscopy to determine whether they were amorphous, crystalline or a mixture of the two. A custom dispersive Raman spectroscopy system was utilized for this purpose. The system included a 671 nm diode-pumped solid-state laser (Ventus Solo MPC6000; Laser Quantum, Stockport, UK). A detailed description of a similar apparatus has been published elsewhere (Wang et al., 2017).
Samples were placed into a closed sample chamber under nitrogen to prevent moisture exposure. All spectra were measured at a temperature between 22 and 23 °C and at less than 5 % RH.

2.2 Methods

2.2.1 Modulated compressed bulk density instrument

The new powder compression apparatus consisted primarily of a linear actuator, a piston, a sample cavity and a load cell (shown schematically in Fig. 2). These components were housed inside an enclosure that allowed easy access for sample loading and unloading, servicing, alignment of the sample holder and cleaning. The linear actuator and the load cell were connected to a computer for control and data acquisition.

A powder sample was loaded into the sample holder (a stainless-steel die with a cylindrical cavity) which was then placed on top of the load cell and tared. Upon measurement, a piston coupled to a non-rotary, linear actuator (Physik Instrumente, M-229.26S, 25 mm, Karlsruhe, Germany) exerted an axial force on the sample. The diameter of the piston used for measurements was designed such that an engineering fit (sliding fit) was obtained with the sample holder cavity. The resulting clearance of 0.1 mm reduced the friction between the piston and the sample cavity while preventing the powder from flowing out of the sample cavity when compressed. The sample cavity had an internal diameter and height of 5 and 6 mm, respectively, which resulted in powder sample masses of usually less than 100 mg; this small sample mass requirement is useful for testing expensive, limited-quantity, rare or difficult-to-make samples.

A stepper motor controller (Physik Instrumente, C-663 Mercury Step, Karlsruhe, Germany) interfaced with the actuator and was controlled by a computer running custom software. The load cell (FuTeK, LRF400-FSH04041, Irvine, CA, USA), with a maximum load capacity of 44.5 N and a maximum load deflection of 0.117 mm, was used to measure the force being exerted on the powder bed during compression; the measured force was converted to pressure using the known geometry of the sample die. A USB controller (FuTeK, USB220, Irvine, CA, USA) was used to interface with the load cell.

The RH of a small volume of approximately 200 cm³ around the sample can be precisely maintained at 0 % or controlled in 1.0 % increments between 3 % and 95 % RH using a humidity generator (RH-200, VTI, Hialeah, FL). This feature is unique to this instrument and allows measurements under different environmental conditions depending on experimental requirements. Previous similar measurements on fine pharmaceutical powders lack the capability of density measurements under real-time and precise relative humidity conditions (Antikainen and Yliruusi, 2003; Kaerger et al., 2004; Nordström et al., 2009; Sørensen et al., 2005; Thalberg et al., 2004). For the measurements reported in this study, the RH control capabilities of the instrument were used to maintain 0 % RH.

2.2.2 Control and data acquisition

A custom program with a graphical user interface was developed using a system design platform (LabVIEW, National Instruments 2011, Austin, TX, USA) to simultaneously control the instrument and acquire its data. This program was also used to define the measurement criteria and automate each measurement, which simplified instrument operation and reduced operator-induced systematic errors. The program was used to modulate the displacement of the piston, resulting in compression and decompression cycles on the powder. Harmonic, sawtooth, triangular wave and other custom modulation profiles can be used to study powder compression.

2.2.3 Modulated compression profile

For the results discussed here, a triangular modulation mode was used for its simplicity. The triangular wave mode used consisted of a series of linear compression and decompression segments and was defined by specifying the velocity, acceleration and deceleration of the linear actuator, as well as the compression and decompression displacements for each segment of a compression cycle. These compression and decompression segments were repeated until the measurement limits or hardware limits of the instrument were reached. An example of a triangular modulation profile is presented in Fig. 3 along with the pressure exerted on a powder during a measurement.

2.2.4 Modulated compressed bulk density (mCBD) measurement

A cylindrical stainless-steel die, which is the sample holder, was loosely filled with powder sample using a spatula. The spatula was used to level the surface of the powder so that it was flush with the top edge of the cavity.
The previously tared die was then placed on a weighing balance to determine the mass of the powder. The uncompressed sample volume was assumed to equal the volume of the sample holder’s cavity. The die was then placed on the load cell, which was tared before commencement of a measurement. The position of the compressing piston was adjusted for each measurement and zeroed by carefully bringing the ram near the top of the sample cavity until it touched just off on the powder inside the cavity. The piston then advanced into the cavity at a rate defined by the user and compressed the powder. The parameters used for the density measurements discussed in this study were fixed at 0.01 mm/s for the velocity of the piston, 0.2 mm/s² for the acceleration and deceleration rates, a compression displacement of 0.06 mm per cycle and a decompression displacement of 0.02 mm per cycle. Based on these parameters, an individual compression and decompression cycle took approximately 8 seconds.

The position of the piston was logged continuously by the program and was used to determine the instantaneous volume of the sample. The force exerted on the sample was continuously measured with the load cell, and pressure was calculated by taking the ratio of the compression force measured to the cross-sectional area of the piston. For a crystalline Leucine powder (sample #1 from Table 1), Fig. 3 shows a sample modulated displacement profile (solid black trace, left axis) and the changes in compression pressure changes over time (dotted red trace, right axis).

The modulated compression profile allowed for the observation of plastic compression due to particle rearrangement and semi-elastic compression of this sample. It can be seen that the compression pressure remains close to zero kPa upon decompression for the first ~250 seconds in the measurement, while it deviates away from zero kPa after ~250 seconds (corresponding primarily to semi-elastic deformation of the powder).

The compressed bulk density was calculated at each step by dividing the sample mass by the instantaneous sample volume. At the end of a measurement, the data was combined into a graph that shows the compressed bulk density as a function of compression pressure (see Fig. 5).

2.2.5 Powder elasticity ratio

A parameter for powder elasticity was derived from the data to identify regimes of plastic and semi-elastic deformation during the compression process and to establish the transition point between the two. The calculation was based on the assumption that the powder compressed like a spring when behaving elastically. In this case, following Hooke’s law, the force on the powder is linearly proportional to a small compression displacement by a stiffness constant. For a modulated compression displacement, and for perfectly elastic response, the stiffness constant will be the same when calculated for the decompression segment and the compression segment; the ratio of these two stiffness constants will be 1. However, for plastic or semi-elastic response, the two stiffness constants will be different, and the calculated ratio will be zero or less than 1, respectively.

The powder elasticity ratio was calculated from the compression pressures (obtained directly from the measured forces) and the displacements of the compression piston for each compression and decompression segment. The powder elasticity ratio was calculated as the ratio of the change in pressure between the start and end of an individual compression-decompression cycle, over a displacement ratio as follows:

\[
E = \frac{1 - \frac{\Delta P_D}{\Delta P_C}}{1 - \frac{\Delta S_D}{\Delta S_C}}
\]

where \(\Delta P_C\) is the change in pressure between the start and end of a compression segment, \(\Delta P_D\) is the change in pressure between the start and end of a decompression segment, \(\Delta S_D\) is the change in displacement between the start and end of a compression segment, and \(\Delta S_C\) is the change in displacement between the start and end of a compression segment. The value of the powder elasticity ratio ranges from zero for completely plastic response, to one for completely elastic response.

Fig. 4 shows a plot of a subset of the compression displacement and compression pressure data for crystalline Leucine (sample #1 from Table 1) between 2.2 and 2.9 mm and up to 250 kPa, respectively, for the sample measurement shown in Fig. 3.

Fig. 4 shows that up to ~100 kPa and up to a displacement of 2.65 mm, the measured force between the powder and the compression piston returned to zero at the end of
each decompression segment; the calculated powder elasticity ratio was zero and the powder compressed plastically. However, as the pressure on the powder increased beyond ~100 kPa, the measured force between the powder and the compression piston was not zero at the end of each decompression segment. Hence, the calculated powder elasticity ratio was greater than zero and the powder compressed semi-elastically.

The powder elasticity ratio was calculated discretely for each cycle in the modulation profile. Because of this, the transition pressure from plastic to semi-elastic compression response was estimated at the mid-point of the two compression pressures measured at the end of two consecutive compression segments, where the first value corresponds to the maximum compression pressure measured during the last plastic cycle and the second value corresponds to the maximum compression pressure measured during the first semi-elastic cycle. The transition density was estimated by calculating the average value of the densities measured at the maximum compression pressures and the minimum decompression pressures and then finding the average density at the estimated transition pressure (see Fig. 5, top). The accuracy of the transition pressures and densities can be improved by using finer modulation profiles.

As can be seen in the amorphous Trehalose sample measurement shown in Fig. 5 (bottom), the powder elasticity ratio clearly shows the transition from plastic to semi-elastic compression when compared to the smooth profiles of the CBD data (Fig. 5, top).

### 2.2.6 Data processing

The data collected from each measurement was processed to calculate the powder elasticity ratio, the compression pressure at which the powder transitions from the plastic to semi-elastic compression regime, and the corresponding powder density. Graphs were generated for the powder elasticity ratio and mCBD as shown in Fig. 5, where the CBD profile was bound by the densities measured at the maximum and minimum displacements for each cycle in the modulation profile (labeled as Max Compression Pressure and Min Compression Pressure, respectively). An average density for the powder, calculated as the average of the maximum and minimum compression pressures was also included with the CBD data. Pressure data below 10 kPa were not plotted in the results as they were highly variable and had been determined to be strongly linked to previous powder handling (USP, 2015) as well as piston-die friction (measured to be below 0.1 N or 3 kPa when the instrument is aligned properly).

From the measurement of the powder elasticity ratio of 100% amorphous Trehalose (sample #2 from Table 1) shown in Fig. 5 (bottom), it can be concluded that the compression response was entirely plastic up to a pressure of ~80 kPa. In this range the compression overcame...
fractional forces to rearrange the powder into closer packing. At higher pressures the powder showed partially elastic response, but in the entire range of the measurement the response remained partially plastic, indicating that rearrangement or irreversible deformation had still occurred.

3. Results and discussion

It was assessed whether the modulated compression instrument is capable of differentiating between similar respirable powders at low pressures. It was expected that changes in a powder’s composition, particle size or particle size distribution result in different overall compression response, including different plastic or semi-elastic responses to compression, allowing quantified measurements to be used to tell different samples apart. Hence, the following cases were tested: 1) powders with the same chemical composition but consisting of different particle sizes or particle size distributions, and 2) the same particle sizes and particle size distributions but different composition.

3.1 Measurement repeatability

Repeatability of measurements is an important factor for compressed bulk density measurements in the low-pressure region. Powders may compact prior to the measurement during storage or handling. This problem is accentuated if only small sample masses are available such that friction effects during the measurement become more prominent. A successful technique must be able to identify the regions of the compression profile that are repeatable and independent of sample history. To assess this capability, three representative powdered materials were tested in duplicate (i.e. two replicates): 1) 100% spray dried amorphous Trehalose as an example of a cohesive respirable powder, 2) 100% raw crystalline Leucine as an example of a powder with larger particle size and 3) a spray dried mixture of 55% Trehalose with 45% Leucine as an example of a spray dried powder with a dispersibility enhancing excipient. These correspond to samples #2, 1 and 9 from Table 1, respectively and were chosen for their differences in composition, true density, particle size, particle morphology and solid state; they were expected to have different compression responses. The duplicate CBD measurements and powder elasticity ratios are shown in Fig. 6.

The CBD data (Fig. 6, top) show three pairs of distinct CBD profiles, with each duplicate pair closely overlapping in the region above 10 kPa. The profiles based on maximum and on minimum pressure are both reproducible where the replicate measurements are within 1% from the average density of the two samples for each composition at any pressure above 10 kPa. The powder elasticity ratio data (Fig. 6, bottom) also shows three distinct profiles for each duplicate pair, showing transitions to semi-elastic compression response at similar pressures for each pair (vertical lines) and reaching very similar final powder elasticity ratio values at the end of the measurement. CBD values at compression pressures below 10 kPa are also shown. At pressures much below the transition pressure, variability was high and the profiles were not reproducible.

As shown in Table 2, based on the powder densities at the transition between the plastic and semi-elastic regions, all duplicate measurements are within ~2 % of the average. Similarly, the transition pressures are within ~12 % of the average. The main source of error in the estimated transition values is the method by which the powder elasticity ratio is calculated. As discussed in the Methods section, the powder elasticity ratio is only known discretely and calculated once for each modulated compression cycle. Because of this, the spacing with respect to pressure between consecutive powder elasticity ratio values is directly linked to the frequency of the modulation profile. Although the experimental parameters chosen for this study demonstrate excellent measurement reproducibility as shown in Fig. 6 and Table 2, the accuracy of the transition values can be further improved by utilizing a finer modulation profile. Other error sources are small and most prominent at measurement pressures below 10 kPa. These include powder history or handling prior to measurement (random), changes in environmental conditions (random), piston-die friction (systematic), load cell measurement error (systematic), piston position control and knowledge (systematic) and mechanical hardware deflection (systematic). However, under proper sample preparation, instrument alignment, calibration, maintenance and operation, these additional errors do not contribute significantly to the overall measurements.

As seen in these duplicate modulated compression results, the low-pressure measurements made by this instrument show excellent repeatability and the resulting CBD and powder elasticity ratio curves can be used to discriminate between similar respirable powders. For the sake of clarity, the results presented in the following sections contain only a single measurement per sample tested and show only the average CBD.

3.2 Ability to discriminate between powders with the same composition but consisting of different particle sizes

To demonstrate the capability of the mCBD instrument for testing the compression response of small amounts of fine and respirable pharmaceutical powders and discriminating between them, samples with the same composition but different particle sizes were first measured. For instance, changes to the particle size will change the total number of contact points between particles in the powder,
affecting its overall cohesion and its compression response. This is important, for example, in formulation development to achieve certain powder characteristics (de Boer et al., 2017; Prime et al., 1997), as well as for quality control to confirm that powders meet manufacturing specifications, e.g. during scale-up. In either case, the mCBD instrument should be capable of measuring a difference in the compression response of two powders with the same composition but different particle size distributions.

Shown in Fig. 7 are two spray-dried powder samples of 100 % Mannitol. The first sample was polydisperse (sample #11 from Table 1; GSD of 1.6 and a MMAD

Table 2    Average transition pressures and densities from plastic to semi-elastic compression response for the duplicate measurements shown in Fig. 6. Standard deviation is also shown as a percentage of the average values.

| Sample                        | Transition Pressure Meas. 1 [kPa] | Transition Pressure Meas. 2 [kPa] | Transition Density Meas. 1 [kg/m³] | Transition Density Meas. 2 [kg/m³] |
|-------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| 100 % Amorphous Trehalose     | 77.2                              | 81                                | 770                               | 788                               |
| 100 % Crystalline Leucine     | 62.2                              | 52.4                              | 437                               | 433                               |
| 55 % Trehalose and 45 % Leucine | 172                               | 186                               | 331                               | 339                               |

Fig. 6    Duplicate measurements of 100 % amorphous Trehalose, 100 % crystalline Leucine and a mixture of 55 % Trehalose and 45 % Leucine (samples #2, 1 and 9, respectively, from Table 1). The top figure shows the CBD profiles for each sample as a function of the maximum and minimum pressures reached from the modulated compression. The bottom figure shows the calculated powder elasticity ratio for each sample as a function of pressure. Pressure is shown in both figures on a logarithmic scale to clearly show powder response at low pressures. Vertical lines indicate the pressures at which the samples transition from plastic to semi-elastic compression response. Data from compression pressures below 10 kPa are included in the top figure to show the high variability at very low pressures.
while the second sample was monodisperse (sample #10 from Table 1; GSD of 1.1 and an MMAD of 10 μm). Both samples were found to be crystalline using Raman spectroscopy.

The mean mCBD measurements (Fig. 7, top) and the powder elasticity ratio curves (Fig. 7, bottom) show two very distinct compression profiles. Although the chemical composition and solid phases were the same for both samples, the compression responses were different. On the other hand, the transition from plastic to semi-elastic response was very similar at ~99 kPa and ~475 kg/m³ for the polydisperse sample and ~101 kPa and ~468 kg/m³ for the monodisperse sample. The polydisperse sample can achieve higher compressed bulk density with increasing pressure while compressing less elastically than the monodisperse sample. Since the polydisperse sample consists of particles of different sizes, these differences in compression response might be attributed to the smaller particles filling the interstitial spaces, resulting in a reduction in the void space in the powder bed and higher bulk density (York, 1978). This can also be seen in the powder elasticity ratio curves (Fig. 7, bottom), where after the transition point, the elasticity of the polydisperse powder increased less sharply, indicating that some of its particles can continue to rearrange as the pressure increases. Conversely, the sharper increase in the powder elasticity ratio for the monodisperse powder is an indication that most particle rearrangement has already occurred.

In this specific example, there was also a sudden decrease in the elasticity of the polydisperse powder at ~300 kPa of pressure. This decrease corresponds to a release of stress in the powder that could be due to particle deformation or fragmentation (Chen et al., 2017; Vu et al., 2020), or could also be due to breakage of bridges or other structures formed by the particles and which were previously held in place by interparticle forces. This is further indication that the polydisperse powder may be undergoing further rearrangement as the pressure increases, although it is not currently possible to decouple this from particle damage in the semi-elastic response region.

A second example shown in Fig. 8 compares the mean mCBD measurements for a two-component formulation (75 % Trehalose and 25 % Leucine) spray dried into two separate polydisperse powders with GSD of 1.6 and MMAD of 2 μm and 4.5 μm, respectively (samples # 7 and 8 from Table 1). In both samples Trehalose was fully amorphous and Leucine was fully crystalline under Raman spectroscopy.

As can be seen in Fig. 8 (top), the sample with the smaller particle sizes (MMAD of 2 μm) achieved higher densities than the sample with larger particle sizes (MMAD of 4.5 μm; similarly to the previous example shown in Fig. 7, these higher densities could be attributed to the smaller particles being better at filling any interstitial spaces as the powder is compressed. From the particle morphologies shown in Fig. 1, it can be seen that the particles were not spherical and had a significant external void fraction. Even though the compositions were the same and the overall morphologies for particles from both samples were very similar, the surface features of the smaller particles had sharper curvatures, which may lead to smaller contact points between particles, reducing particle cohesion (York, 1978). An alternative explanation to the CBD of these two samples is that particles with a larger MMAD have a lower particle density because Leucine takes a longer time to crystallize (Baldelli et al., 2016), resulting in an overall lower density powder. In either case, whether it is the difference in particle density or the change in the particle cohesion due to the changes in particle size, the CBD profiles are different for both samples, with the larger particle size resulting in an overall lower bulk density at any pressure.

Furthermore, the pressures and densities at which the powder transitions from plastic to semi-elastic response were different, with the sample composed of the smaller
sized particles reaching semi-elastic compression response at higher pressures: ~91 kPa and ~422 kg/m³ for the smaller particle size versus ~48 kPa and ~370 kg/m³ for the larger particle size vs. for the smaller particle size. This is further indication of increased particle cohesion during plastic deformation and particle rearrangement for the larger particles; however, as can be seen in the powder elasticity ratio curves (Fig. 8, bottom), both traces converge quickly in the semi-elastic regime, which is an indication that higher pressure was needed to overcome the increased cohesion between larger particles.

In both examples, it is clear that the instrument can detect differences in the compaction profiles that are directly or indirectly caused by changes in the particle size distributions.

3.3 Ability to discriminate between powders with the same particle sizes but different compositions

It is expected that the compression response of powders is also a function of their composition and not just of the particle sizes and distributions. For instance, the presence of different materials on the surface of a particle can make them more or less cohesive (Vehring, 2008). Again, the degree of cohesiveness plays an important role in formulation development to achieve certain powder characteristics such as dispersibility or flowability (de Boer et al., 2017; Prime et al., 1997), as well as in quality control to assess adherence to manufacturing specifications. In either case, the mCBD instrument should be capable of measuring a difference in the compression response of powders with different compositions but the same particle sizes.

The following measurements compare monodisperse powders containing Trehalose and Trileucine with small increments in the amount of Trileucine. It has been shown that Trileucine, a surface-active amino acid, can be used as a shell former in particle formation to achieve particles with low cohesion and low density (Lechuga-Ballesteros et al., 2008). It is expected that this will affect the compres-
higher densities upon compression more easily.

A further increase in Trileucine to 5% resulted in an even clearer difference between the mean compression response of these powders as shown in Fig. 9 (top), where a difference in the mCBD and powder elasticity ratio curves can be easily observed. However, increasing Trileucine from 1% to 5% resulted in a decrease in powder density upon compression. Comparing these measurements to the SEM images shown in Fig. 1, it can be seen that such an increase in Trileucine caused a strong change to the particle morphology. The particles were much more rugose at 5% Trileucine and the increased number and size of external voids resulted in lower particle density. While the transition pressures and densities calculated for both powders were very similar, the increase in Trileucine (from 1% to 5%), and the corresponding change in the particle morphology, resulted in a lower final powder elasticity ratio (Fig. 9 bottom). This means that the reduction in compressed bulk density of the powder with 5% Trileucine is not entirely due to changes in particle cohesion but to a decrease in particle density caused by the increase of external void space in the more rugose particles.

A similar comparison of two polydisperse powders with the same particle size distributions and particle diameters (GSD of 1.6 and an MMAD of 2.5 μm), 100% Trehalose versus 80% Trehalose and 20% Leucine, is shown in Fig. 10. Similar to Trileucine, Leucine is also a surface-active amino acid used as a shell former in particle formation to achieve particles with low cohesion and low density (Feng et al., 2011). From the comparison of these two powders, it is expected that the sample containing Leucine will have enhanced powder dispersibility and reduced particle cohesion.

From these measurements, the mean compression response of both samples (Fig. 10, top) can be quantitatively distinguished, where the presence of Leucine resulted in an

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**Fig. 9** Comparison of three monodisperse powders (GSD 1.1) with the same particle sizes (MMAD 9 μm) of 99.6% Trehalose with 0.4% Trileucine, 99% Trehalose with 1% Trileucine and 95% Trehalose with 5% Trileucine (samples #3, 4 and 5 from Table 1, respectively). Semi-logarithmic profiles of the average mCBD normalized by true density (top) and powder elasticity ratios (bottom) vs. compression pressure show different compression responses. The pressures at which the powders transition from plastic to semi-elastic compression response are indicated by vertical lines in both plots.

**Fig. 10** Comparison of two polydisperse powders (GSD 1.6) with the same particle sizes (MMAD 2.5 μm) of 100% Trehalose and 80% Trehalose with 20% Leucine (samples #2 and 6 from Table 1, respectively). Semi-logarithmic profiles of the average mCBD normalized by true density (top) and powder elasticity ratios (bottom) vs. compression pressure show different compression responses. The pressures at which the powders transition from plastic to semi-elastic compression response are indicated by vertical lines in both plots.
Despite the powder’s bulk density at a given pressure and also resulted in an increased transition pressure and transition density. The Leucine-containing powder is easier to compress. This is an indication that powder dispersibility is enhanced and particle cohesion is reduced, as expected.

Overall, the measurements show that small amounts of different respirable powders can be differentiated reliably using the modulated compression technique. The compression behavior is determined by a variety of competing factors including size distribution, cohesiveness and rugosity of the particles and their particle density. Being able to assess both bulk density and elasticity of the powder under low pressure aids in the interpretation of the results.

4. Conclusions

Using modulated compression, this new density tester is capable of distinguishing whether a compression step is reversible or irreversible and is therefore useful in revealing the compression response of fine and respirable pharmaceutical powders under low applied pressures. By using modulated compression, bulk density measurements can reveal transitions between plastic and semi-elastic compression responses, something not possible with non-modulated or entirely linear compression methods.

Quantification of this transition can be used to determine a pressure at which it can be assumed that the powder handling history has been erased and reproducible results can be obtained, e.g. for the purposes of selecting a suitable level of compaction for powder filling operations. Additionally, the ability to identify the transition point between these two regimes can aid in making modifications to a powder’s formulation (e.g. adding a dispersibility enhancer to improve flowability) so that the resulting powder can achieve a desired bulk density at a given pressure before the physical integrity of the particles is compromised. This is especially important for fine pharmaceutical powders with a mean particle size smaller than 25 μm and in particular for respirable powders with a mean particle size < 10 μm.

Selected tests presented in this paper demonstrate that the instrument can be used to easily discriminate between similar fine and respirable powders with slight changes in composition, particle size or particle size distribution, based entirely on their compression response. This capability is particularly useful in quality control applications where defined product attributes need to be maintained, or in formulation development where certain properties need to be achieved.

The instrument, the control software and data processing have been designed and implemented such the tester produces repeatable and reproducible measurements at low pressures. The small sample mass requirement of typically less than 100 mg is particularly useful in early product development for performing CBD measurements of expensive, limited-quantity, and rare or difficult-to-make powders.

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