The Compression Behavior of Respirable Powders at Different Relative Humidity Measured by a Compressed Bulk Density Tester for Small Sample Masses

Abouzar Shamsaddini-Shahrbabak and Reinhard Vehring

Department of Mechanical Engineering, University of Alberta, Edmonton, AB, Canada

Particle Engineering

Introduction

Compressed bulk density (CBD) describes the bulk density of a powder under different levels of applied load and is an established method for the analysis of density and compressibility of pharmaceutical powders (1). Among the factors that affect the powder bulk density, the moisture content of a powder is an often overlooked factor, in spite of the fact that it has been shown to play an important role in consolidation and densification behavior of pharmaceutical ingredients (2,3). A new instrument has been developed to measure compressed bulk density of small powder samples and to investigate the effects of relative humidity on the compression behavior.

Method and Materials

In this study six different samples were studied:

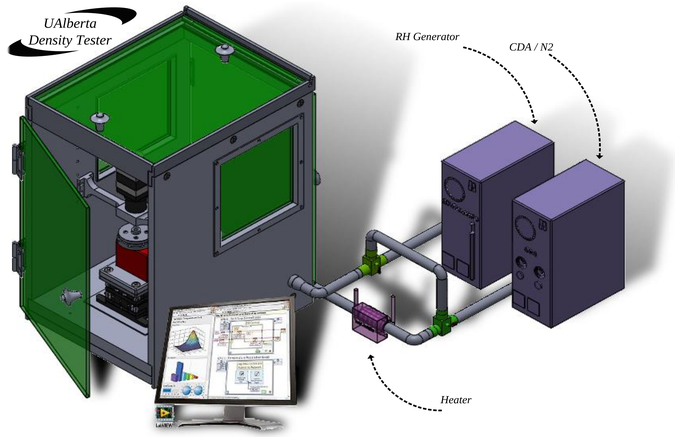
Spray Dried L-Leucine, with an aerodynamic diameter, d_a = 2µm, representing a low particle density, respirable dosage form.
Crystalline L-Leucine, with a Feret diameter, $d_F \approx$ 10µm, representing highly flowable raw material.
Spray Dried Trehalose Dihydrate, d_a = 1.75µm, representing a high particle density, cohesive, respirable powder.
Crystalline Trehalose Dihydrate, $d_F \approx$ 500µm, representing crystalline raw material with large particle size.
Spray Dried Trehalose-Leucine, d_a = 1.55µm, in a 0.8 / 0.2 w/w formulation ratio, representing a powder of engineered microparticles with core-shell structure.
Micronized Paracetamol, $d_F \approx$ 4.5µm, representing an active pharmaceutical ingredient in a traditional respirable dosage form.

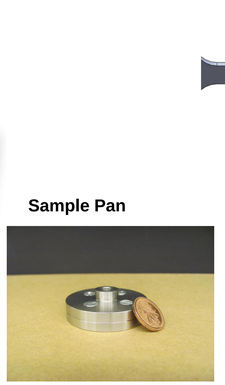
The compressed bulk density measurement was based on uniaxial compression of a known mass of powder confined within a small cylindrical cavity with a volume of about 500 mm^3. A non-rotating spindle (PI Linear Actuator) was used to exert a defined pressure on the powder. The force on the sample pan was measured using a load cell. LabView Software was used for control and processing.

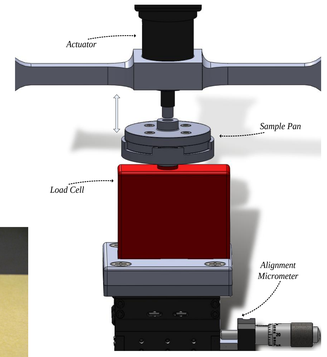
Samples were stored at <5 %RH and 20±2 °C in a desiccator cabinet prior to initiating the experiment. During testing, samples were either exposed to laboratory conditions, typically 30±3 %RH, (blue traces in graphs) or measured in a dry box under nitrogen at <1 %RH (red traces in graphs).

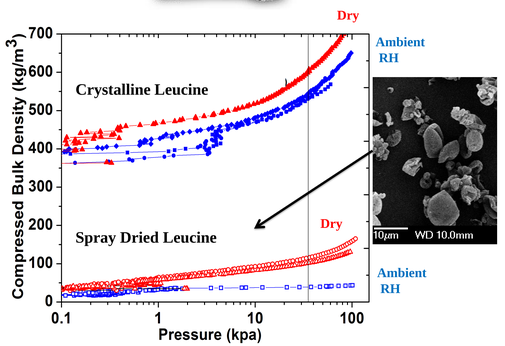
The pressure at 35 kPa was selected as equivalent measure for tap density, ρ_T, based on a previously published correlation (4,5). The initial density at the start of the experiment was used as poured density, ρ_P.

Results

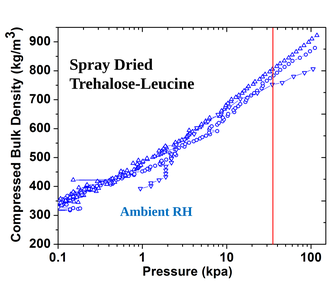




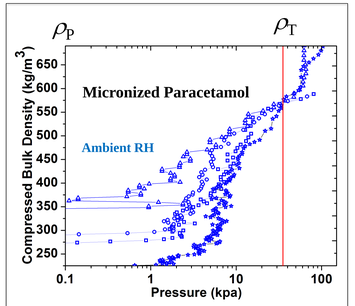




Relative humidity has a strong effect on compressibility of spray dried leucine.

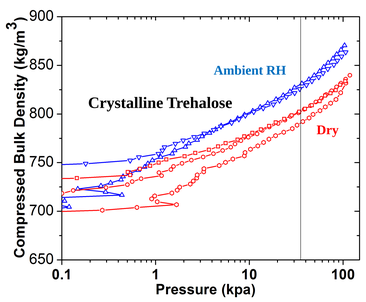


Powder is not fully compacted at 35 kPa. Large change in powder density with increasing load.



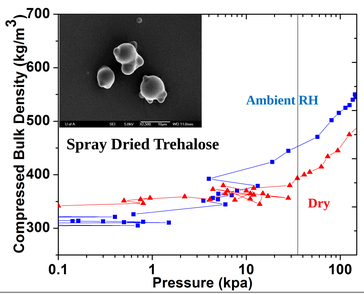
Hausner Ratio: ρ_T/ρ_P	**2.3 – 3.2**
Carr Index: $100\%x(\rho_T-\rho_P)/\rho_T$	**57 - 69 %**

Sample history causes large variability at low pressure and wide range of Hausner ratio and Carr index for the same powder.



Powder with large particle size is close to dense packing even at low load

Dense, cohesive powder with small particle size has a large void fraction even at high load



Instrument Comparison	Micromeritics Geopyc 1360	Freeman FT4	USP Tapped Density	**UAlberta Density Tester**
Sample Volume	> 0.35 cm³	10 cm³	>25 cm³	< 0.15 cm³
Operating Temperature	15 – 35 °C	Ambient	N/A	-24 – 60 °C
Operating RH	20 – 80 %	Ambient	N/A	0 – 90 %
Measurement Time	420 – 780 s	300 – 600 s	> 300 s	40 – 70 s

Conclusion

Classical powder density tests that were developed for powders with large particle size are not well suited for respirable powders. Interparticle forces are large compared to inertial forces for small particles sizes.

Single value density measurements are not sufficient to describe the packing behavior of powders with small particle size. The entire compression curve should be considered.

Relative humidity during the compaction test impacts the results and should be controlled.

The sampling history significantly affects the initial state of compaction, i.e., poured density, of respirable powders which reduces the usefulness of classical parameters of powder behavior such as Hausner ratio or Carr index.

The presented technique is a fast and efficient method to measure compressed bulk density of pharmaceutical, respirable powders. Sample mass requirements are < 40 mg.

References

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