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

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INTRODUCTION

Compressed bulk density provides the bulk density of a powder under different levels of applied load and is an established method of describing density and compressibility of pharmaceutical powders (1). The powder bulk density depends on several factors such as powder handling history, sample preparation conditions, testing environment, and the state of powder compaction (1, 2). An often overlooked factor is the moisture content of the powder, in spite of the fact that it has been shown to play an important role in consolidation and densification behavior of pharmaceutical ingredients (3, 4). In this study, we present a novel technique for measuring compressed bulk density of small powder samples and investigate the effects of relative humidity on the compression behavior.

Traditional density measurement techniques are very material consuming, which is a disadvantage for the characterization of expensive powders in pharmaceutical industry (2, 5-8). In this study, we applied an alternative method (5) that requires only milligram quantities rather than the several grams (2, 8), needed for conventional techniques or tapped density measurements.

METHODS

A variety of respirable powders containing trehalose and L-leucine (Sigma Aldrich, Cat# L8000) were analyzed. The samples shown here represent two very different powders. One sample, spray dried leucine, represents a respirable dosage form with an aerodynamic diameter of 2 μm and a very low particle density (5). As a control for a powder with large particle diameter, trehalose dihydrate crystals (Fisher Bioreagents Cat# BP2687) with a Feret diameter of approximately 0.5 mm were chosen. Samples were stored at < 5 %RH and 20±2°C in a desiccator cabinet prior to initiating the experiment.

The compressed bulk density measurement is based on uniaxial compression of a known mass of powders confined within a small cylindrical cavity with a volume of about 500 mm^3. Powder was manually transferred into the cavity and a micrometer head driven by a non-rotating spindle was used to exert a defined pressure on the powder. The pressure on the powder was measured using a load cell. The poured volume, mass and micrometer's reading were recorded and samples were compressed up to 100 kPa. One batch of each sample was exposed to laboratory conditions, 30±3 %RH, and the other batch was sampled and measured in a dry box under nitrogen at < 1 % RH. The compression tests took between 8 to 20 minutes each.

The measured force versus displacement data was processed into a graph that shows density as a function of pressure on the powder bed. The pressure at 35 kPa was selected as equivalent measure for tap density based on a previously published correlation (5, 9).

RESULTS AND DISCUSSION

The left panel of Figure 1 shows the compression curves for the leucine powder. The compressed bulk density shows a strong dependence on relative humidity: the compressed bulk density of the dry sample increases about fourfold in the pressure test range compared to only a twofold increase for the test at ambient humidity. The equivalent tap densities for the leucine powder were 115 kg/m^3 and 39 kg/m^3 for the dry and ambient humidity cases, respectively. Secondly, the low pressure region below 1 kPa shows large experimental scatter. This was consistently observed for the more than 40 respirable powders tested so far. In all cases, the poured density, i.e., the density for the unloaded powder bed, was found to be highly variable. Thus, parameters like Hausner ratio, i.e., the ratio of tap density to poured density, or the related Carr index, are not useful measures for respirable powders.

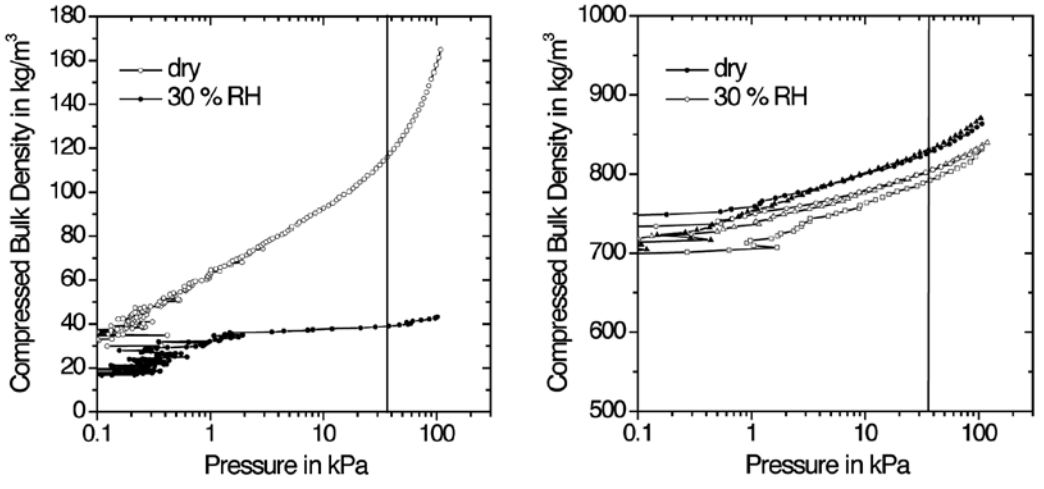

Figure 1. Compressed bulk density of respirable leucine powder, left, and crystalline trehalose, right, tested at different relative humidity (duplicates and triplicates shown). The vertical line indicates the equivalent tap density.

In contrast, the trehalose powder shown on the right panel of Figure 1 was already compacted to a large extent when poured into the cavity and was not influenced strongly by changes in relative humidity. Under both conditions, the compressed bulk density increased by a factor of about 1.2 in the test range. Similar equivalent tap densities of 825 kg/m^3 and 800 kg/m^3 were found for the dry and ambient humidity cases, respectively. The Hausner ratios (11) for this powder were in the range of 1.1 - 1.2 irrespective of measurement condition. The corresponding Carr indices were in a range of 10 - 15, confirming powders of high flowability in all cases, as can be expected for a powder with such large particle size.

CONCLUSIONS

Classical powder density tests that were developed for powders with large particle size are not well suited for respirable powders. The compaction behavior of respirable powders is dominated by interparticle forces and the relative humidity during the compaction test impacts the results. 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.

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