A Material-Sparing Method for Assessment of Powder Deformation Characteristics Using Data Collected During a Single Compression–Decompression Cycle

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ABSTRACT: Compressibility profiles, or functions of solid fraction versus applied pressure, are used to provide insight into the fundamental mechanical behavior of powders during compaction. These functions, collected during compression (in-die) or post ejection (out-of-die), indicate the amount of pressure that a given powder formulation requires to be compressed to a given density or thickness. To take advantage of the benefits offered by both methods, the data collected in-die during a single compression–decompression cycle will be used to generate the equivalent of a complete out-of-die compressibility profile that has been corrected for both elastic and viscoelastic recovery of the powder. This method has been found to be both a precise and accurate means of evaluating out-of-die compressibility for four common tableting excipients. Using this method, a comprehensive characterization of powder compaction behavior, specifically in relation to plastic/brittle, elastic and viscoelastic deformation, can be obtained. Not only is the method computationally simple, but it is also material-sparing. The ability to characterize powder compressibility using this approach can improve productivity and streamline tablet development studies.
Keywords: compression; compaction; materials science; mechanical properties; porosity; solid dosage form; tableting; tablet

INTRODUCTION

Characterizing powder compressibility is an important part of tablet development. Compressibility is typically defined as the decrease in apparent volume due to an increase in the applied pressure.[1] The larger the decrease in apparent volume due to an applied pressure, the larger the material's compressibility is. This property is not unique to powder compaction, but is one of the most fundamental, mechanical properties used in tableting research. The most basic use is the generation of compressibility profiles, or functions of solid fraction (SF) versus applied pressure. Development scientists can use compressibility functions to determine the pressure required to produce a tablet with a given density or thickness. Furthermore, this profile can be very useful in evaluating other relevant tablet properties that are dependent on the level of consolidation. The best example of such a property is tensile strength. Tensile strength typically increases as the applied pressure increases, but comparisons of tensile strength are much more meaningful when made between tablets with similar SFs.

Compressibility profiles have other, more profound uses. The relationship between applied pressure and SF, or some transformation of SF, has long been studied in an effort to provide insight into the fundamental mechanical behavior of powders during compaction. Various consolidation models derive parameters that are related to fundamental behaviors including apparent deformation mechanisms and the ability of the powder particles to rearrange into more dense configurations. When successful, these parameters provide understanding of the material's behavior that can be used to guide development decisions.

One of the most common models used to interpret SF data is the Heckel model.[2,3] The Heckel model assumed compressibility to be a first-order process with respect to porosity of the powder bed. This assumption leads to a linear relationship between −ln(porosity or ε) and the applied pressure or P using Eq. (1):

$$-\ln(\varepsilon) = kP + A \quad (1)$$

One minus the SF of the powder bed is equivalent to ε. The parameter k is related to the irreversible deformation mechanism, and the inverse of this value is known as the yield pressure or P_y. Materials with low P_y are classified as deforming predominantly by a plastic flow mechanism, whereas materials with larger P_y values are thought to be predominantly brittle in nature. It was recognized by Heckel when he proposed the model and has been emphasized by several others since; that the porosity measured when the powder bed is under load can be significantly lower than the porosity that results after the load is removed.[2–6] The difference is attributed to elastic recovery of the powder bed as the pressure is removed.

In addition, certain materials continue to recover after the compact or tablet has been ejected from the die.[7,8] This behavior is attributed to time-dependent reversible deformation or viscoelasticity and is commonly observed in starch-based excipients. Therefore, attempts to characterize the relative plasticity of a powder using data collected while the powder is under pressure can be misleading, especially for relatively elastic and/or viscoelastic materials, whose yield pressures determined in-die will overestimate the relative plasticity. Although out-of-die Heckel analysis is commonly accepted as more reliable than the in-die method, the out-of-die method has disadvantages as well. Out-of-die analysis involves compression of separate tablets at

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every pressure of interest. Therefore, much more material and time are required to perform out-of-die analysis compared with in-die, which can be completed based on a single compression.

The purpose of the work described here is to demonstrate a procedure by which the data collected during a single compression cycle can be used to gain a well-rounded understanding of a material's compression behavior, specifically in relation to plastic/brittle, elastic, and viscoelastic deformation. We will use the data collected from a single compression–decompression cycle to generate a profile equivalent to a complete out-of-die compressibility profile that has been corrected for both elastic and viscoelastic recovery. It will also be demonstrated how these data can be used to generate parameters characteristic of a material's plasticity, elasticity, and viscoelasticity. This procedure should dramatically improve not only the efficiency of tablet development, but also increase the understanding of each formulation's behavior. This work is particularly relevant to the use of modern compaction simulators. These simulators are becoming more integrated into tablet development as they have become able to accurately replicate the compression profiles of production scale presses and require much less material. The efficiency of these devices is a key reason for their popularity. They can generate a large amount of data, indicative of compression behavior under different compression states in a limited amount of time. By applying the approach described here, the usefulness of modern compaction simulators will be significantly enhanced.

The work is based on two simple assumptions. First, the amount of elastic recovery that occurs when a powder bed is decompressed from a specific applied pressure is equivalent to the change in SF that occurs because of elastic deformation during compression up to the same level of applied pressure, even if the pressure of interest is less than the maximum pressure used during the compression cycle. This assumption ignores the fact that the powder bed structure may differ during decompression relative to compression. Nevertheless, we hypothesize that SF changes observed during decompression can be used to correct for elastic deformation that occurs during compression within experimental error. The second assumption in the current work is that the decrease in SF that is due to viscoelastic recovery occuring after ejection is not significantly dependent on the maximum applied pressure. This assumption allows the viscoelastic recovery observed at one level of applied pressure to be used to correct for viscoelastic recovery at other levels of applied pressure. More specifically, we assume that the viscoelastic recovery observed after a compact has been ejected can be used to correct for time-dependent reversible deformation of the in-die SF values at all lower applied pressures. Using these two assumptions, we intend to show that data collected in-die can be used to generate a corrected SF versus applied pressure profile that is indistinguishable from data collected using the out-of-die method. It will also be shown how these corrected data can be used to generate a detailed assessment of a material's behavior during powder compaction.

EXPERIMENTAL

Materials

Four common pharmaceutical excipients were chosen for evaluation in this work because of differences in their predominant deformation behavior. Pregelatinized maize starch (Lycatab® PGS; Roquette, Keokuk, Iowa), microcrystalline cellulose (Avicel® PH200; FMC Corporation, Philadelphia, Pennsylvania), spray-dried lactose (316 Grade; Foremost Farms, Baraboo, Wisconsin), and dibasic calcium phosphate dihydrate (Emcompress DiTab®; JRS Pharma, Rosenberg, Germany) display behaviors ranging from predominantly plastic to predominantly brittle and significantly viscoelastic.[9–14] All experimentation was carried out using powders with equivalent particle size ranges (180–250 μm), which were equilibrated at ambient temperature (~23°C–25°C) in a controlled relative humidity environment (saturated solution of $MgCl_2$, ~32%–33% relative humidity). The general physical properties of each material have been reported in a previously published study.[15]

Data Collection

All samples were compressed using an Instron universal testing system (model 5869; Instron Corporation, Norwood, Massachusetts) equipped with a 50-kN load cell. Each tablet was prepared by weighing 500 mg of powder into a 13-mm stainless steel cylindrical die equipped with flat-faced punches. A 5% suspension of magnesium stearate in methanol was used to apply a lubricating film to the die wall prior to compression. The measurement accuracy of the equipment used was within ±0.5% of the applied load and ± 0.02 mm of the recorded displacement.

Out-of-die compressibility profiles were obtained by compressing tablets to seven different maximum applied pressures ranging from 38–264 MPa. Each material was tested in triplicate at each applied pressure. After ejection, the tablets were allowed to relax under the previously mentioned temperature and humidity conditions, while their thickness and diameter were monitored over time using a digital caliper (model CO 030150; Marathon, Richmond Hill Ontario, Canada). Relaxation was complete within approximately 7–10 days, at which point the final dimensions were measured for determination of out-of-die SF.

In-die compressibility profiles were acquired using data recorded during compression of the powders to the highest applied pressure (264 MPa). Instron Bluehill® 2 software (version 2.17) was used to collect the raw data obtained during compression of each tablet. Displacement was used to calculate powder bed thickness at each applied pressure level. In order to show the versatility of this method, it was applied to data obtained at two different linear compaction speeds (2.4 and 240 mm/min) for all materials. Although it is possible to gain information by comparing compressibility at different speeds, the purpose of this work was to show the applicability of the method despite the effect different loading times have on deformation.

Data Analysis

Correction of Elastic Recovery

In-die compressibility profiles for each material were obtained by calculating the SF under load using Eq. (2):

$$\mathrm{SF} = \frac{4m}{\pi d^2 t \rho} \tag{2}$$

where m is the compact mass (measured post ejection), d is the diameter of the die, t is the thickness of the powder bed under load, and ρ is the true density of the powder obtained using a helium pycnometer (Quantacrhome Instruments

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