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Full Out-of-Die Compressibility and Compactibility Profiles From Two Tablets

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ABSTRACT

In this study, a method is presented that can be used to generate full out-of-die compressibility and compactibility profiles using the data from only 2 tablets. For each material, one tablet was compacted at the maximum pressure of interest and a second tablet at a relatively low pressure. The in-die data collected during compaction to the maximum pressure of interest and the solid fraction change after ejection for both tablets were used to generate a profile equivalent to a complete out-of-die compressibility profile. After measuring the tensile strengths of each tablet, a compactibility profile was produced by fitting the out-of-die porosity and tensile strength data to the Ryshkewitch-Duckworth equation. This method generated accurate out-of-die compressibility and compactibility profiles for each of the materials studied. Not only is this technique computationally simple, but in cases where only small amounts of raw material are available, this method allows a detailed understanding of a material's mechanical behavior to be assessed.

Introduction

Many tools are available to guide the development of pharmaceutical tablet products. These tools range from advanced modeling and simulation of the compaction process[1-3] to using analytical techniques, such as X-ray computed tomography[4] and acoustic techniques.[5] However, the foundation of all tablet development efforts is built on an understanding of the relationships among compaction stress, compact solid fraction, and compact strength for a given material.[6] Accurately determined compressibility profiles (compact solid fraction as a function of compaction pressure) and compactibility profiles (tensile strength as a function of compact porosity) are critical in determining how a given formulation will behave during tablet compression. Furthermore, these data are the basis for a number of other characterization approaches. For example, Heckel analysis,[7,8] which is often used to determine a material's mean yield pressure,[9] is based on transformed compressibility data. Another approach uses the relationship between tensile strength and compaction pressure to determine parameters associated with the relative deformability of a powder.[10]

Different approaches have been used to collect these data. Compressibility data can be collected during the compaction process, so that an entire compressibility profile can be collected from one compression-decompression cycle. It has long been recognized that these data can be misleading because compressibility due to elastic and viscoelastic deformation is not distinguished from plastic flow and brittle fragmentation. Therefore, compressibility profiles are typically determined from out-of-die measurements, where multiple compacts are prepared and the solid fraction at each maximum compaction pressure is measured after the compact has been ejected and allowed to recover for some period of time. This approach, more specifically, reflects compressibility due to irreversible deformation and is usually more meaningful for tablet development.[11-13] The major disadvantage of the out-of-die approach is the amount of material and time required, because separate compacts must be prepared at each pressure of interest and up to several days may be required to allow the compacts to fully relax to their final solid fraction.

Recently, a new approach was presented that allows a full out-of-die compressibility profile to be determined from data collected during formation of a single compact.[14] This method was based on 2 primary assumptions. First, the amount of elastic recovery that occurs upon decompression is equivalent to the change in solid fraction that occurs because of elastic deformation during compression. Application of this correction produced a function of elasticity corrected solid fraction with respect to applied pressure.

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The second assumption was that the extent of viscoelastic recovery occurring post ejection is relatively independent of the maximum applied pressure. This assumption allows for the change in solid fraction due to viscoelastic recovery to the highest applied pressure to be used to correct for the time-dependent reversible deformation occurring at all other levels of applied pressure.

This method was shown to be an accurate way to reproduce an out-of-die compressibility profile using only in-die data and the solid fraction change after ejection for a tablet compressed to a relatively high pressure. It is also valuable due to its computational simplicity and ability to be performed quickly with a limited amount of material. However, it is acknowledged that this data correction procedure does have limitations. The most notable being the inability to capture any potential variations in viscoelastic recovery with respect to pressure. Improvement on the existing method can be accomplished by preparing a second tablet compressed at a relatively low pressure. This will also allow for the generation of a compactibility profile.

Compactibility profiles rely on measuring tensile strengths of tablets compressed to differing levels of porosity. This typically involves preparing a number of tablets at different compression pressures covering the range of porosities of interest. Due to the variability observed in the strength data, replicate compacts are often required. Compactibility profiles can be analyzed using the relationship associated with Ryshkewitch and Duckworth,[15] which assumes an exponential relationship between compact strength and tablet porosity. This relationship has been applied with much success, but should be used with care, especially with inaccurate porosity data.[16]

Collecting these data requires a significant amount of material and a significant amount of time. Modern compaction simulators have greatly facilitated the collection of compressibility and compactibility data, especially using compression speeds and profiles that are more reflective of manufacturing conditions. These simulators allow large numbers of formulations to be evaluated during development. Nevertheless, collecting complete compressibility and compactibility profiles requires enough material that it cannot be done until significant amounts of drug substance are available, later in the development process.

This study aims to demonstrate how out-of-die compressibility and compactibility profiles can be estimated over a broad range of compaction pressures using as few as 2 compacts. This method will not only allow formulators and development scientists to gain an understanding of these basic mechanical behaviors, but will also allow for the characterization of tendencies for elastic recovery,[11-13] viscoelastic recovery,[17-19] and plastic deformation.[20,21] This method can be adapted to any press that is capable of measuring both applied load and punch position during compression, including laboratory-scale presses, compaction simulators, and large-scale instrumented tableting presses. Its applicability to a diverse set of tableting excipients will be demonstrated.

Experimental

Materials

Three commonly used pharmaceutical excipients, pre-gelatinized maize starch (Lycatab® PGS; Roquette, Keokuk, IA), microcrystalline cellulose (Avicel® PH200; FMC Corporation, Philadelphia, PA), and dibasic calcium phosphate dihydrate (Emcompress®; JRS Pharma, Rosenberg, Germany) were chosen for evaluation in this study due to differences in their predominant deformation behavior. Each diluent was incorporated into a base formulation containing an internally blended binder (Copovidone; ISP Technologies, Wayne, NJ), glidant (colloidal silicon dioxide; Evonik Industries, Parsippany, NJ), and lubricant (magnesium stearate; Spectrum, Gardena, CA). The % wt/wt composition of each material in the formulation is provided in Table 1.

In order to limit the variability resulting from disparities in physical properties on the compaction behavior of each material, 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[22]). The general physical properties of each diluent have been reported in a previously published study.[23]

Data Collection

A Huxley-Bertram servo-hydraulic compaction simulator (Model HB1088) was used to compact Lycatab PGS, Avicel PH200, and Emcompress formulations. One tablet was compacted at the maximum pressure of interest and a second tablet at a relatively low pressure. Each compact was prepared by weighing 500 mg of powder into a 13-mm stainless steel, cylindrical die with standard flat-faced B punch tooling. Compaction pressure, P, was determined by dividing the applied load, or force, by the projected area over which that force was distributed using Equation 1:

$$P = \frac{Force}{\pi r^2} \tag{1}$$

where the radius, r, was 6.5 mm for all tablets. Each material was compacted at speeds ranging from 4 to 400 mm/s using constant loading/unloading rates (no dwell time), and using compression profiles simulating a HATA 38 station press at speeds ranging from 25 to 75 rpm using a 50 kN load cell. Experimental data used to confirm the accuracy of the presented method was collected using both profiles and all compaction speeds. A variety of minimum punch separation distances were used to compact tablets across a range of out-of-die solid fraction.

In-die compressibility profiles were acquired using data recorded during compression and decompression of each formulation to the highest applied pressure (HB Powder Compaction Software version 1.2014.10.29). Solid fraction under load was calculated using Equation 2:

$$SF = \frac{4m}{\pi d^2 t^* \rho_{true}} \tag{2}$$

where m is the compact weight measured post ejection, t the thickness of the powder bed, d the diameter of the die, and ρ_{true} the formulation's true density measured using helium pycnometry (Quantachrome Instruments stereopycnometer, Boynton Beach, FL). Although pycnometry can be inaccurate in determining the true density of some moisture-containing materials,[24] the method presented herein does not depend on the method used to determine true density. The distance between the upper and lower punch was used to calculate powder bed thickness (t) at each

Table 1
Base Formulation Components, Functionality, and % wt/wt Composition

Material (Trade Name)	Functionality	% wt/wt
Pre-gelatinized maize starch (Lycatab PGS) or microcrystalline cellulose (Avicel PH200) or dibasic calcium phosphate dihydrate (Emcompress)	Diluent	96.0
Copovidone	Binder	3.0
Colloidal silicon dioxide	Glidant	0.5
Magnesium stearate	Lubricant	0.5