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Characterization of strain rate sensitivity in pharmaceutical materials using indentation creep analysis

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ABSTRACT

Understanding how a material's response to stress changes as the stress is applied at different rates is important in predicting performance of pharmaceutical powders during tablet compression. Widely used methods for determining strain rate sensitivity (SRS) are empirically based and can often provide inconsistent or misleading results. Indentation creep data, collected during hardness tests on compacts formed from several common tableting excipients, were used to predict each material's relative sensitivity to changes in strain rate. Linear relationships between Ln(indentation hardness) and Ln(strain rate) were observed for all materials tested. The slope values taken from these relationships were compared to traditional strain rate sensitivity estimates based on in-die Heckel analysis. Overall, the results from the two methods were quite similar, but several advantages were evident in the creep data. The most notable advantage was the ability to characterize strain rate sensitivity derived from plastic behavior with little influence of elastic deformation. For example, two grades of corn starch had very similar creep behavior, but their yield pressures were affected very differently when the compaction rate was increased. This inconsistency was related to the difference in the viscoelastic recovery exhibited by these two materials. This new method promises to allow a better understanding of strain rate effects observed during tablet manufacturing.

1. Introduction

Pharmaceutical tablets are one of the most widely used and accepted forms of drug delivery. As a result, tablet production must be performed at increased tablet press rates in order to produce enough dosage forms to supply market demand. Unfortunately, the majority of compaction research is done on bench-top presses or small scale machines that operate at much slower rotational speeds, making scale-up challenging. A well-defined tableting process may produce acceptable product both in the laboratory and the pilot plant, but may fail quality control testing during manufacturing. Issues can arise related to die-filling, compression, and other aspects of tablet manufacturing. For example, as rotary tablet presses operate at increased speeds, the time allowed for powder to reproducibly flow into the die is decreased, which may increase variability in tablet weight and strength. In addition, the faster press speed used during large scale production reduces consolidation time. As a result, the formulation particles may deform less, and the finished tablets may not meet strength specifications. A material, whose deformation behavior is highly dependent upon consolidation time and press speed, is said to exhibit strain rate sensitivity (SRS).

Strain rate sensitivity is a significant issue that has several practical implications. Particularly sensitive materials may not have the tablet strength necessary for coating and packaging operations. They may also have increased capping and lamination propensities upon ejection. Post-manufacturing, finished products must be able to withstand the rigors of shipping, handling and dispensing. A mechanically compromised tablet is unsuitable for use by patients for many reasons including the loss of potency associated with a split or fragmented product. Accurately predicting to what extent a material or formulation is sensitive to changes in strain rate is vital in the development of a quality drug product.

Initially, the amount of drug substance available for testing is minimal, and using a trial-and-error approach may be too costly. A variety of lab-scale methods have been proposed for predicting SRS of new materials. Characterization of strain rate sensitivity in pharmaceutical materials (Roberts and Rowe, 1985) has widely relied on mean yield pressure determinations derived from Heckel analysis (Heckel, 1961a, 1961b). This approach, although extensively used and recognized in compaction research, has its limitations (Sonnergaard, 1999). Heckel analysis is itself an empirical model, whose application can frequently provide inconsistent or misleading results. For example, the method using Heckel

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analysis does not differentiate the effect of strain rate on elastic deformation from the effects on plastic deformation. Utilizing only in-die measurements to calculate mean yield pressure can lead to over prediction of strain rate sensitivity for materials that deform extensively during the unloading phase. Additionally, using a single parameter to evaluate plasticity overlooks inherent differences in material properties; such as, particle size and particle morphology. An underlying assumption of the Heckel model is that compaction is performed on materials with monodisperse, spherical particles. However, as-received pharmaceutical powders often contain varying particle size distributions and a range of morphologies which increases yield pressure variability (Fell and Newton, 1971).

Other methods for predicting strain rate sensitivity include stress-relaxation measurements (David and Augsburger, 1977) and deformation testing using diametral compression of cylindrical compacts (Rees and Rue, 1978a). However, the pharmaceutical literature is dominated by the work published by Roberts and Rowe, which continues to be the most widely used method for determining whether a pharmaceutical material is strain rate sensitive.

To provide insight into the intricacies of strain rate effects observed during tablet manufacturing, a method utilizing indentation creep data has been proposed to rank order materials. Indentation creep, using hardness measurements, has been used to predict time-dependent flow of materials (Perales et al., 1996; Lu et al., 2009). The experiment involves applying a constant load to an indenter while measuring its displacement over time as it penetrates into the test specimen. The extent of displacement observed during the creep test depends on a material's ability to plastically deform. Although the indenter is only in contact with the surface of the test specimen, indentation hardness measurements have been used effectively to measure bulk deformation behavior (Roberts et al., 1995; Taylor et al., 2004; Liao and Wiedmann, 2005), and more recently have been used to investigate powder flowability (Hassanpour and Ghadiri, 2007).

One of the biggest advantages of this method is that the data is specifically related to plastic deformation with little or no influence from elastic deformation. The analysis is based on displacement data collected during the hold region after displacement due to elastic deformation has occurred. SRS exponent quantification signifies only plastic deformation allowing viscoelasticity to be assessed independently. This technique provides a more mechanistic understanding of viscoplastic behavior as compared to mean yield pressure, since the linear region of a Heckel plot represents several overlaid deformation mechanisms. Methods for predicting strain rate sensitivity of each deformation behavior, separately, should provide better understanding of the influence of press speed on the tableting behaviors of different materials. More reliable predictions would be valuable in limiting variability encountered with current methods of strain rate sensitivity assessment.

2. Materials and methods

2.1. Materials

Pharmaceutical excipients used in this study display varying sensitivities to changes in strain rate. Pre-gelatinized maize starch (Lycatab® PGS, Roquette, Keokuk, IA), modified corn starch (Powdered NF 400 L, Roquette, Keokuk, IA), partially pre-gelatinized corn starch (Starch 1500®, Colorcon, West Point, PA), microcrystalline cellulose (Avicel® PH105 and Avicel® PH200, FMC Corporation, Philadelphia, PA), spray-dried lactose (316 Grade, Foremost Farms, Baraboo, WI), anhydrous lactose (120 MS, Kerry Bio-Sciences, Norwich, NY), and dibasic calcium phosphate dihydrate (Emcompress DiTab®, JRS Pharma, Germany) were used as received from the listed suppliers.

2.2. Methods

2.2.1. Raw material characterization

Each material was initially characterized for its true density, moisture content, and particle size distribution. True densities were determined by helium pycnometry (Model: SPY-6DC, Quantachrome Instruments, Boynton Beach, FL) and performed in triplicate for each excipient. Inherent moisture content was quantified using loss on drying measurements (Computrac Max 2000 Moisture Analyzer, Arizona Instruments, Phoenix, AZ) of accurately weighed powders. Samples (1.5–2.0 g) were heated to 105 °C and held isothermally until the rate of moisture loss was less than 0.1%/min. Sieve analysis (Performer III Model: SS-3, Gilson Company, Lewis Center, OH) was used to determine the particle size distributions of 50 g powder samples. Collected fractions (>1000, 1000–500, 500–250, 250–180, 180–125, 125–75, 75–53, and <53 μm) were weighed at intervals ranging from 5 to 15 min until the measured weight change was less than 0.1 g. The fine (<53 μm) sieve cut of Avicel® PH200 was retained and stored for use in subsequent experimentation (Section 3.3.1).

2.2.2. Heckel analysis (SRS index)

The density–pressure relationship developed by Heckel (1961a, 1961b) is widely used to model the deformation of powders during compaction. The negative natural logarithm of porosity is equal to a straight line equation (Eq. (1)) where the slope, k, is related to the predominating deformation mechanism, and its inverse is known to as the mean yield pressure (P_y).

$$-\ln(\varepsilon) = kP + A \tag{1}$$

The model parameters P and A are, respectively, compaction pressure and a constant representing particle rearrangement at low pressures. Significant attention in the literature has been paid to the proper analysis of Heckel data, especially related to identifying the linear range (Rees and Rue, 1978b; York, 1979; Celik and Marshall, 1989). The data are never truly linear although the slope changes little within certain pressure intervals. In this study, the Heckel data were considered linear when the first derivative showed less than 15% variation at the slow compression speed. Linear regression was used to determine the average slope values for each material over the selected pressure range.

Mean yield pressure is often used to assess the relative plasticity of a material. As plastic deformation becomes the dominant mechanism of densification, the slope of the linear region increases, and the corresponding mean yield pressure value decreases. To compare materials, a strain rate sensitivity index (Eq. (2)) was developed based on the percentage increase in mean yield pressure between punch velocities of 0.033 mm/s (P_{y1}) and 300 mm/s (P_{y2}) (Roberts and Rowe, 1985).

$$\mathrm{SRS} = \frac{P_{y2} - P_{y1}}{P_{y2}} \times 100 \tag{2}$$

This index was developed using a high speed compression simulator able to operate over a wide range of punch velocities. The relationships between mean yield pressure and punch velocity presented in the original study did not indicate that the mean yield pressure at 300 mm/s was of intrinsic value, but was simply the fastest speed studied. This high rate of compression is not always achievable on standard testing equipment, which can make the consistent application of this method difficult.

An Instron universal testing system (Model 5869, Instron Corporation, Norwood, MA) was used to compact excipient powders