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Multi-Component Characterization of Strain Rate Sensitivity in Pharmaceutical Materials

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MULTI-COMPONENT CHARACTERIZATION OF STRAIN RATE
SENSITIVITY IN PHARMACEUTICAL MATERIALS

A Dissertation
Submitted to the Graduate School of Pharmaceutical Sciences
Duquesne University
In partial fulfillment of the requirements for
the degree of Doctor of Philosophy
By
Jeffrey M. Katz
December 2015
MULTI-COMPONENT CHARACTERIZATION OF STRAIN RATE SENSITIVITY IN PHARMACEUTICAL MATERIALS

By

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ABSTRACT

MULTI-COMPONENT CHARACTERIZATION OF STRAIN RATE SENSITIVITY IN PHARMACEUTICAL MATERIALS

By

Jeffrey M. Katz

December 2015

Dissertation supervised by Ira S. Buckner, Ph.D.

Powder particles are brought into very close proximity by any number of sequential or concurrent consolidation mechanisms during tableting. It is commonly accepted that plastically deforming materials tend to be more strain rate sensitive than brittle materials, but this sensitivity depends on how fast the material can respond to applied stresses. In addition, since many pharmaceutical materials also demonstrate relatively large amounts of elastic deformation, it can be difficult to identify whether a material’s strain rate sensitivity is due to changes in elasticity or due to changes in plasticity at different speeds.

Compaction research is often performed on bench-top or small-scale presses that operate at press speeds orders of magnitude slower than production-scale machines. As a result, a variety of lab-scale methods have been developed to account for this difference.
The most commonly utilized method is based on in-die Heckel analysis of compressibility data, but this approach does have limitations. Most notable is its inability to differentiate between the effects of changes to tablet press speed on elastic deformation from the effect on plastic deformation. A method that could identify the specific mechanical behavior, or behaviors, responsible for a material’s strain rate sensitivity would be significant.

In this dissertation, commonly used pharmaceutical excipients and simple mixtures were evaluated. Strain rate sensitivity was assessed using a multi-component approach. The scaled values of three lab-scale parameters: 1) Indentation Creep SRS Exponent, 2) ΔSF_final, and 3) Heckel-Based SRS Index were used to describe material behavior. Using this combination of parameters, the sensitivity of the materials and mixtures can be quantified in terms of plasticity and elasticity, considered separately.

The combination of factors used in this study allows for a more detailed characterization of strain rate sensitivity. Factors that assess the time-dependency of both plasticity and elasticity offer the potential to understand what role each deformation behavior plays in the overall strain rate sensitivity of a material. This approach can facilitate rational product development and allow unexpected scale-up changes to be avoided.
DEDICATION

This dissertation is dedicated to my parents, Judy Michael and Mark Katz, my step-mother, Lynn Katz, my sister, Jennifer, and my wife, Whitney. All of my family members have been fully supportive of my efforts and for that I am sincerely grateful.
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Graduate school is a process. It requires guidance, support, encouragement and organization from many people at many different times. I would like to take this opportunity to recognize and acknowledge the people who have been instrumental in making my graduate career a success.

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My sister, Jennifer, has always been someone that I have looked up to. Her ability to accomplish anything she puts her mind to is something that I try my hardest to emulate. She is a great friend, an unbelievable supporter of my endeavors, and most of all, a great role model.

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Chapter 1: Introduction

1.1 Statement of Problem

Pharmaceutical tablets are one of the most widely used and accepted forms of drug delivery [1]. A tablet has a number of advantages over other dosage forms including ease of handling, convenient administration and improved patient compliance [2]. Under optimum operating conditions some high-speed rotary tablet presses can produce over 500,000 tablets per hour, making tablets one of the most cost effective dosage forms [3]. However, in early development studies the amount of drug substance that is available for testing is often limited to gram scale quantities. This eliminates the ability to utilize trial-and-error methods for determining the behavior of materials and formulations between scales. As a result, the majority of tablet compaction research is performed on bench-top presses or small scale machines that operate at much slower compaction speeds.

Many problems that arise during the transfer of a tablet product from research to production scale are due to changing compression speeds. Tablet properties may change with respect to weight [4], tensile strength [5], friability [6], and disintegration time [7]. In addition, the consolidation properties (i.e. deformation behavior) of a material can be affected by the rate at which tablet compaction occurs. A material, whose deformation behavior is highly dependent on consolidation time and tablet press speed, is said to exhibit strain rate sensitivity (SRS).

Strain rate sensitivity is a significant problem facing formulation scientists and process engineers responsible for the successful development of drug products. Particularly sensitive materials may not possess the tablet strength necessary to withstand the rigors of downstream unit processes. They may also have an increased propensity for
capping and lamination upon ejection from the tablet die [8]. Post-manufacturing, finished products must be strong enough to remain intact following shipping, handling, and dispensing. A mechanically compromised tablet is unsuitable for use by a patient for many reasons including the loss of potency associated with a split or fragmented product. Strain rate sensitivity can also significantly impact the financial resources allotted to the development team working on a pipeline compound. A tableted product that is mechanically weak or structurally damaged may incur considerable monetary costs related to re-formulation and/or significant process changes. Accurate characterization of the extent to which a material or formulation’s consolidation behavior will change, as a result of changes to tablet press speed, is necessary for the development of a quality drug product.

Characterization of strain rate sensitivity in pharmaceutical materials has widely relied on mean yield pressure determinations [9] derived from Heckel analysis [10,11]. This approach, although extensively used and recognized in compaction research, does have its limitations [12]. For example, the method using Heckel analysis does not differentiate between the effects of tablet press speed 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.

Other methods for predicting strain rate sensitivity have been reported and used to classify materials. Some examples include: deformation testing using diametral compression of cylindrical compacts [13], a novel non-destructive technique [14], numerical analysis of contact time and pressure data [15], and 3-D modeling [16].
Despite well-established considerations for the importance of characterizing strain rate sensitivity, the pharmaceutical literature is dominated by the work published by Roberts and Rowe.

In order to accurately evaluate changes to compaction behavior resulting from changes to tablet press speed, a more detailed characterization approach is required. A method that offers the potential to understand what contribution individual time-dependent deformation behaviors play in the overall strain rate sensitivity of a material could be used to help avoid scale up issues like reduced consolidation leading to poor strength. *A priori* characterization of strain rate sensitivity is valuable for assessing the propensity of a material or formulation to behave differently at high speeds.

1.2 Hypothesis and Objectives

This dissertation is based on the hypothesis that a multi-component, lab-scale assessment of strain rate sensitivity enables overall sensitivity to be quantified, and identification of the specific mechanical behaviors contributing to the observed sensitivity.

Given the central hypothesis, the objectives of this dissertation were to:

1. Establish the effect of compression speed on the tableting profiles (compressibility and tabletability) of three common pharmaceutical excipients with varied deformation behavior.

2. Introduce three lab-scale measurements that comprehensively describe the various aspects of strain rate sensitivity during powder compaction.
3. Quantify strain rate sensitivity using a multi-component parameter and identify the specific mechanical behaviors (i.e., viscoplasticity and viscoelasticity) that contribute to observed sensitivity.

The results of these objectives provide a blueprint for strain rate sensitivity characterization that offers the potential to understand what role individual deformation behaviors play in the overall sensitivity of materials and simple formulations. This dissertation provides a clear demonstration to the pharmaceutical industry that accurate characterization of strain rate sensitivity is possible using material-sparing, lab-scale techniques.

1.3 Literature Survey

1.3.1 Tablet Compaction and Deformation Behaviors

Despite its apparent simplicity, the conversion of a loose powder into a cohesive tablet is a complex process [17]. Initially, *i.e.* at low pressures, powder particles undergo sliding/rearrangement resulting in a closer packing structure and reduced powder bed porosity. At a certain pressure, the reduced pore space and increased inter-particulate friction will prevent any further inter-particle movement [18]. Subsequent volume reduction is, therefore, associated with changes in the dimensions of the particles.

The production of a tablet that is strong enough to withstand subsequent handling while allowing the active ingredient to be properly released upon administration is considered to be a function of the simultaneous processes occurring during its formation. In an effort to develop more robust products, a complete understanding of the fundamental behavior of new materials during tablet formation is required.
From a material point of view, the description of compaction as a process that occurs in a sequence of consecutive, overlapping stages is considered the most common [19-21]. During compression, powder particles can deform either reversibly (elastic deformation) or irreversibly (plastic deformation and brittle fracture/fragmentation). If the applied pressure is less than the yield pressure, powder particles will deform elastically and regain their original shape upon decompression. In this range, stress is linearly proportional to strain and is characterized by Young’s (elastic) modulus [22]. Stored elastic strain is released as the powder particles within the compact expand eliminating bonding area developed during compression.

If the local pressure exceeds the yield pressure, powder particles begin to yield and deform plastically. A permanent change to the shape of the particle facilitates the formation of particle-particle contact regions during compression [23]. As the area at each contact point increases, local stress is relieved resulting in the increased formation of inter-particulate bonds. For brittle particles, fragmentation into smaller, discrete parts is generally preceded by little or no plastic deformation. Fracture stresses are most often controlled by the inherent flaws in the crystalline lattice that initiate failure [22]. As particles fragment, new surfaces are exposed leading to an increased number of inter-particulate points of contact. Unlike plastic materials which improve tablet strength by increasing the contact area between particles, brittle materials exhibit less effective inter-particulate bonding [24].

Although typical stress-strain behavior can provide information about the deformation characteristics of a material and the stresses required to induce such deformation, these data often represent ideal behavior which is rarely observed in
practice. In actuality, pharmaceutical powders almost always exhibit deformation by several different mechanisms with the relative contribution of each varying between materials. The deformation mode that will dominate depends on a number of factors including the pressure range of interest [25], intrinsic material properties [26], and the rate at which pressure is being applied [27]. As a result, characterization of specific deformation behaviors proves to be very challenging.

1.3.1.1 Characterizing Deformation Behavior

Many methods exist to identify the predominant deformation mechanism of a material. The most common characterization approach is compressibility modeling. Compressibility is typically defined as the decrease in apparent volume due to an increase in the applied pressure [7]. 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 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.

Compressibility profiles have other, more profound uses. The relationship between applied pressure and solid fraction, or some transformation of solid fraction, has long been studied in an effort to provide insight into the fundamental mechanical behavior of powders during compaction. Various consolidation models have derived
parameters related to fundamental behaviors including apparent deformation mechanisms and the ability of the powder particles to rearrange into more dense configurations [28-31]. When successful, these parameters provide an understanding of a material’s behavior that can be used to guide development decisions.

The most common model used to interpret solid fraction data is the Heckel model [10,11]. This model assumes compressibility to be a first-order process with respect to porosity of the powder bed. The Heckel equation is derived by solving the linear separable differential equation relating relative density ($D$) and applied pressure ($P$) according to Eq. (1). The step-by-step derivation is provided below:

\[
\frac{dD}{dP} = k(1 - D) \tag{1}
\]

Variables in Eq. (1) are separated to obtain Eq. (2):

\[
\frac{dD}{(1-D)} = kdP \tag{2}
\]

Eq. (2) is integrated across all applied pressures according to Eq. (3):

\[
\int_{D_0}^{D} \frac{dD}{(1-D)} = k \int_{0}^{P} dP \tag{3}
\]

The solved integral in Eq. (4) is rearranged to obtain Eq. (5):

\[
\ln(1 - D_0) - \ln(1 - D) = kP \tag{4}
\]
\[ \ln \left( \frac{1}{1-D} \right) = kP + \ln \left( \frac{1}{1-D_0} \right) \] (5)

The relative density associated with rearrangement, \( \ln \left( \frac{1}{1-D_0} \right) \), is substituted for the variable, A, to obtain the Heckel equation provided in Eq. (6):

\[ \ln \left( \frac{1}{1-D} \right) = kP + A \] (6)

Solid fraction, or relative density, represents the fraction of the total volume that is made up by the solid particles. The remaining fraction, termed porosity (\( \varepsilon \)), is attributed to the pore space between particles and is calculated according to Eq. (7):

\[ \varepsilon = 1 - D \] (7)

Therefore, Eq. (6) can be rewritten with respect to porosity to match Eq. (8):

\[ -\ln(\varepsilon) = kP + A \] (8)

The empirical parameter, A, reflects low pressure densification resulting from particle rearrangement. The slope, k, is related to the irreversible deformation mechanism and its inverse is known as the mean yield pressure (stress) or \( P_y \) [32]. \( P_y \) is widely accepted as an indicator of the relative plasticity of a material.
Heckel analysis is most often implemented using one of two different approaches. The first measures powder bed dimensions during compression while the material is under load. This approach is referred to as the ‘at-pressure’ or ‘in-die’ method. Alternatively, tablet density can be assessed using the measurements of ejected tablet dimensions, and is often referred to as the ‘zero-pressure’ or ‘out-of-die’ approach. While both methods have advantages, both also suffer from weaknesses that limit their use. It was recognized by Heckel, 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 [10,11,33-35]. The difference is attributed to the elastic recovery of the powder bed as the pressure is removed. Although out-of-die Heckel analysis is commonly accepted as more reliable than the in-die method, the out-of-die approach involves compressing separate tablets at every pressure of interest. Considerably more material and time are required to perform out-of-die analysis compared to in-die, which can be completed during a single compression cycle.

Heckel’s original work was performed on metal and ceramic powders sieved to a particular particle size mesh with modified shape and surface texture [10,11]. He concluded that a materials behavior was plastic if a linear relationship between the negative natural logarithm of porosity and pressure existed, even if it occurred over a very limited pressure range. Conversely, Heckel identified a material as being predominantly brittle if no linear relationship could be identified. Applicability of this model to the compression of pharmaceutical materials requires careful attention, in part due to the original model being built on an entirely different class of materials.
A Heckel profile is normally divided into three different regions. First, is a non-linear section (Region I) occurring at low pressure. This is followed by a linear region (Region II) where the data obey Eq. (8). Finally, a second non-linear region (Region III) is observed at high pressure. A typical plot of $-\ln(\varepsilon)$ versus compaction pressure, $P$, is provided in Figure 1.

![Figure 1. Typical in-die Heckel Plot. Regions I and III represent behavior at low and high pressure, respectively. Region II is the linear region described by Heckel](image)

For region I, Heckel attributed non-linearity to particle rearrangement processes in the absence of interparticulate bonding [10,11]. However, it should be noted that more recent investigations have also ascribed non-linear behavior at low pressure to rapid fragmentation of the powder particles [19].
It is widely accepted that within region II particle deformation is the controlling mechanism. Although linearity in the Heckel plot is attributed to irreversible (plastic) deformation, it is also recognized that elastic deformation occurs at all pressures [34,35]. For region III it is recognized that elastic deformation of the compact controls the process, while non-linearity is a result of the mathematical treatment of the data. As the density of the powder bed under load approaches the true density, the negative natural logarithm of porosity approaches infinity.

1.3.1.2 Tablet Compaction Equipment

Pharmaceutical tablets are usually produced by two types of tablet presses: single-punch eccentric presses and rotary presses. A single-punch machine produces tablets by single-sided compaction. In this type of machine, the upper punch moves up and down above the stationary die. The die, and the lower punch remain in fixed positions during compression. After the tablet has been compressed, the lower punch is raised to eject the tablet through the upper opening of the die [36].

Rotary presses produce tablets using double-sided compaction. The complete tablet manufacturing cycle occurs in four steps: (i) die fill, (ii) mass adjustment, (iii) compression/decompression, and (iv) ejection (Figure 2, on the following page).
Figure 2. Compaction cycle of a rotary tablet press. The stages of compaction (represented linearly) are labeled in order from left to right (Re-printed with permission from the publisher [3]).

For this type of machine, many punch and die sets are fitted around the periphery of a turret. The lower punch tip remains in the die at all times while the upper punch tip is removed from the die during tablet ejection and die fill. As the turret rotates, the punch heads are brought in turn between a pair of stationary rollers. Passing between the rollers, the upper and lower punch tips are moving toward each other and exert a compressive force on the powder bed between them [36].

Compared to single-punch presses, rotary presses are capable of being operated at very high speeds. Almost all commercial tablet production is carried out on rotary machines. Single-punch presses are mostly used for development and formulation studies where only a small amount of active ingredient is available for use. Due to the intrinsic
differences between the two types of machines, they have drastically different punch speeds, force versus time profiles, and displacement versus time characteristics [37]. For these reasons, materials do not necessarily perform equally well on the two types of machines. Improved understanding of the changes in material behavior that can occur as a result of a change to tablet press speed is crucial for minimizing development costs.

In recent years, compaction simulators have become very popular due to their efficiency and ability to collect a large amount of data. Compaction simulators are assembled using three main units: a load frame, a hydraulic unit, and a data acquisition system [3]. Simulators are becoming more integrated into tablet development as they have become able to more accurately replicate the compression profiles of specific production-scale rotary tablet presses using small amounts of raw material. These machines are ideally suited to study the basic compaction behavior of materials, evaluate and optimize excipients such as lubricants and binders with respect to the desired tablet properties of the finished product, and provide information related to process and scale-up variables like pre-compression and tablet press speed.

New machines are able to simulate production scale presses by implementing punch displacement profiles that account for the upper and lower pre and main compression rolls, applied force, dwell/contact times, and punch velocity. Unfortunately, factors like die fill, turret movement, and build-up of turret temperature due to long compaction runs at high speed remain hard to replicate using this type of equipment. Compaction simulators are highly valuable tools that should be used to streamline and improve tablet development studies. However, the mindset that these machines can be
used to practically eliminate the need for a thorough understanding of material behavior should be avoided.

1.3.2 Strain Rate Sensitivity

Some pharmaceutical solids respond to stress differently when the stress is applied at different rates. Strain rate sensitivity arises as a result of a mismatch between the applied rate of stress and the rate at which the material being compacted can relieve those applied stresses. Problems can occur during scale-up operations when a formulation developed on a single-punch press is transferred to a high speed rotary tablet press.

From a material point of view, plastically deforming solids are often regarded as more sensitive to changes in the amount of time available for consolidation and bonding to occur due to the time-dependent nature of how those materials deform. Conversely, brittle materials are considered less sensitive to these changes since fragmentation of powder particles occurs rapidly. In addition to plastic deformation, the elastic response of materials to stress can also play a role in the material’s time-dependent behavior. Elastic recovery can occur immediately upon decompression or post-ejection over an extended period of time. This later behavior is attributed to time-dependent reversible deformation or viscoelasticity [38-40]. Since many pharmaceutical materials also demonstrate relatively large amounts of elastic deformation, it can be difficult to identify whether a material’s strain rate sensitivity is due to changes in elasticity or due to changes in plasticity at different speeds.

Time-dependent deformation behavior can manifest itself beyond simply identifying whether that behavior is sensitive to changes in tablet press speeds. As the
time scale for consolidation and bonding is shortened, quality problems such as reduced tablet strength as well as capping and lamination are encountered more frequently. Compromising the mechanical integrity of formed compacts can result in issues with downstream processing, or more importantly affect the dose required by a patient. Knowledge of the extent to which these changes can occur allows for improved formulation development in an effort to mitigate scale-up issues related to properties of the final product.

1.3.2.1 Effect of Strain Rate on Consolidation and Recovery

Tablet dimensions are a combined result of the extent of consolidation and the amount of relaxation that occurs post ejection. It is often observed that powders compacted on a research scale tablet press form tablets of adequate strength and quality. However, as the time allowed for consolidation is decreased, material behavior can change significantly. For example, the apparent density of two tablets compressed to the same pressure can be significantly different depending on the speed at which they were compressed. The amount by which apparent density changes will depend on the primary consolidation mechanism that material displays [13].

Tye et al. [41] examined the tableting behavior of four commonly used excipients having varied deformation behaviors. The out-of-die compressibility profiles of two sets of tablets were compared. The first was compressed on a hydraulic press used to emulate slow speed compaction conditions. The second was generated using a compaction simulator which represented high speed, or manufacturing scale press settings. Of the
four materials, pre-gelatinized starch showed the greatest decrease in solid fraction with speed (Figure 3).

![Compressibility profiles of pre-gelatinized starch compacted using four different dwell times: (x) 8 ms, (■) 27 ms, (♦) 20 s, and (▲) 90 s](Re-printed with permission from the publisher [41])

Longer dwell times (i.e. slower press speeds) resulted in tablets with a higher measured solid fraction, or lower porosity, across all applied pressures. It is commonly accepted that plastically deforming materials tend to be more sensitive to press speed than brittle materials, but this sensitivity depends on how fast the material can respond to applied stress. Under prolonged compression time, pre-gelatinized starch particles can more effectively flow into inherent void spaces increasing inter-particulate contact area and lowering measured porosity.
The effect of tablet press speed on the extent of consolidation has also been assessed by comparing the maximum applied force needed to produce tablets of equivalent solid fraction [42,43]. Armstrong and Palfrey [44] examined the effect of tablet press speed on the compressibility or four commonly used tableting diluents. A modified hand-operated eccentric press was operated at speeds ranging from 0.33 to 2.67 rev/s corresponding to production rates of 20 and 160 tablets/min, respectively. An inorganic brittle material (dicalcium phosphate) showed little change in the force required to produce tablets of equal solid fraction. Deformation of this material occurs by fragmentation of the original particles into smaller, distinct units that subsequently pack together. Fragmenting materials can more efficiently react to changes in the rate of force application since consolidation proceeds quickly.

Conversely, for the plastic materials, an increase in the rotational speed of the press accompanied an increase in the maximum detected force. If the rate at which a load is applied exceeds the rate at which a material can react to that load, an increased resistance to further densification will occur. As a result, the force required to produce a tablet of equivalent solid fraction increases with speed. Due to the nature by which they deform, plastic solids are considered to exhibit greater strain rate sensitivity as compared to solids that primarily fragment during the formation of a tablet. However, strain rate sensitivity is not only a function of the mode by which a material permanently deforms. The relaxation behavior of materials has also been shown to be sensitive to the speed at which a material is compressed [38-40, 45-47].
Tablet relaxation is often quantified as an increase in volume, or tablet thickness and diameter, after ejection from the die [48-51]. Volume change is regularly calculated according to Eq. (9):

\[ \Delta V = \frac{V_\infty - V_{\text{min}}}{V_{\text{min}}} \]  

(9)

where \( V_\infty \) is the tablet volume at various time points after ejection and \( V_{\text{min}} \) is the minimal tablet volume during compression. By using minimum tablet volume for the calculation of changes to the total volume, relaxation measurements can be used to evaluate both the elastic and viscoelastic recovery of the tested material. The extent to which a tablet expands over time can have significant implications on finished product quality. Not only must a tablet be able to survive the mechanical stresses encountered during downstream unit operations, but damaged products will fail to provide the efficacy expected by the patient.

Maarschalk et al. [52,53] examined the effect of tableting speed on the relaxation behavior of pre-gelatinized starch whose behavior is predominantly plastic and/or viscoelastic. Tablets were prepared on a compaction simulator under speeds ranging from 3 to 300 mm/s. Tablet dimensions were accurately measured with a micrometer after ejection from the die and over time until the dimensions were no longer changing. Proper corrections for punch elasticity were made, which is important for the precise calculation of in-die thickness used to determine \( V_{\text{min}} \).

It was evident that the elastic and viscoelastic behavior of starch depended on the speed used to compress each tablet. Higher porosities were measured for tablets that were
compressed at faster speeds. The authors observed that an increase in tablet volume with speed was a result of the competition occurring between permanent deformation and elastic recovery of the tablet. At slow speeds, permanent deformation controlled consolidation while the elastic component was relatively insignificant. The amount of reversible stored energy was low, which coincided with the smallest observed volume changes during relaxation. Conversely, at high speed, the elastic component controlled consolidation as less time was available for permanent deformation to occur. After compression, residual elastic strain was recovered causing a larger increase in tablet volume relative to the same tablet compacted at slower speed.

1.3.2.2 Effect of Strain Rate on Tablet Properties

Powder particles are brought into sufficiently close proximity by any number of sequential or concurring consolidation mechanisms. Some of which have been shown to contribute to a materials strain rate sensitivity. To form a coherent compact, bonding must occur between those particles. During research and development where limitations on testing are controlled by the amount of raw material available, tablets prepared at slow speeds exhibit adequate strength. The tablet presses used to form these tablets are operated at orders of magnitude slower speeds than the machines that would be used to produce similar tablets at the manufacturing scale. Early investigators [54,55] found that the crushing strength of tablets was reduced when the rate of tablet production was increased. Several other important studies have been performed over the years related to the issues of strain rate and tensile strength [5, 56-58].
In a diametral compression test, stress is applied to tablets across their diameter between two flat platens [59-61]. Tablet failure along the diameter, across which the load is applied, allows tensile stress (σ) causing failure to be calculated using Eq. (10):

\[ \sigma = \frac{2P}{\pi Dt} \]  

(10)

where \( P \) is the breaking load, and \( D \) and \( t \) are the diameter and thickness of the tablet specimen. Tensile strength is widely used as an indicator of mechanical strength since its value reflects the amount of bonding that has occurred during compression [62-64].

Cook and Summers [65] studied the speed sensitivity of binary mixtures containing aspirin. Although the primary goal was to assess mixture behavior, the data collected on each individual component illustrated the effect of speed on resultant tablet strength. Tablets compacted on a slow speed mechanical press were compared to tablets compacted at higher speed on a Manesty E2 machine. The punch velocity on the rotary machine (5500 – 7500 mm/min) was significantly greater than the crosshead speed used to control punch velocity on the mechanical press (1 mm/min).

Tensile strength was plotted as a function of mixture composition for each of the materials tested. Individual component data was analyzed by comparing the data point values plotted on the x-axis at 0 and 100 % composition. Those x-axis compositions corresponded to aspirin and all of the other individual components that were tested, respectively. Emcompress®, a calcium phosphate inorganic binder, formed tablets that showed a minimal difference in measured tensile strength between speeds. By contrast, Starch 1500® exhibited a significant reduction in tensile strength as the press speed used
to compact each tablet increased. An increase in porosity was experienced as a result of decreased inter-particulate contact area formed during compression at high speeds. It was hypothesized that less particle-particle contact reduced the effective area over which bonds between particles were formed. The tablet strength of a brittle material was minimally affected by changes to press speed, whereas the plastic material being tested was affected to a much greater extent.

In another study, Marshall et al. [5] studied the effect of punch velocity on the compaction properties of ibuprofen, a material often characterized as consolidating via a balance between elastic and plastic deformation [66,67]. The authors compressed tablets from a recrystallized 1-90 μm size fraction of ibuprofen using a compaction simulator. A series of applied loads were used to compress the material and minimally three replicate compacts were produced at each load. Tensile strength was determined 2 hours after ejection using diametral compression testing. It was concluded that ibuprofen exhibited strength behavior characteristic of a strain rate sensitive material, that is, a reduction in strength was observed with an increase in compression speed. More importantly, this study highlights an important caveat to tensile strength testing methods that has significant implications on the accurate measurement of those values.

The rate at which load is applied to tablet specimens during diametral compression testing can affect measured values. Rees et al. [68] compared tablet strength values of compacts prepared with microcrystalline cellulose and lactose. Two different loading rates, corresponding to platen speeds of 0.05 and 5 cm/min, were tested. An increase in the loading rate produced a significant increase in the breaking strength of both materials. A change to the loading rate during testing has also been shown to cause a
decrease in measured tensile strength [69]. For that reason, efforts have been made to establish methods ensuring similar strain rate conditions during testing [70].

It was proposed by Hiestand et al. [70] to control cross head (platen) speed such that the time between failure load and the failure load divided by e (the base of natural logarithms) should be approximately 5 s. By using a time constant, instead of a pre-determined rate of testing, tensile strength values are considered to more correctly reflect the relative bond strengths of materials. As a result, more meaningful comparisons of changes to tensile strength with speed can be made between materials with different strain rate sensitivities. Although the lack of sufficient tablet mechanical strength is the most common problem encountered during tablet manufacturing, poor mechanical performance in the form of tablet defects can make tablets produced at high speed unsuitable for use.

Capping and lamination are problems which frequently occur during tablet production. Capping is defined as the separation of the top curvature of a tablet from the tablet body either partially or completely during ejection, subsequent handling or physical testing [8]. Lamination, on the other hand, involves the failure of a tablet along planes perpendicular to the applied compression stress causing the splitting apart of a tablet [71]. While the therapeutic efficacy of drug products is crucial for proper treatment, tablets of sufficient mechanical strength must also be able to survive handling, packaging, shipping, and storage prior to reaching the patient. Although capping and lamination aren’t the only mechanical defects affecting finished product integrity (i.e. picking, sticking, etc.), they remain the most commonly observed during manufacturing.
Reported root causes of tablet capping and lamination in the literature include:
non-uniform tablet density distributions [72], anisotropic mechanical properties [73], air
entrapment [74], and die wall pressure leading to internal shear stresses in the tablet [75].
The predominant deformation mode of a material can also have a direct effect on the
physical and mechanical properties of the final product. Malamataris et al. [76] suggested
that capping and lamination frequency depended on the elastic and plastic behavior of the
material being studied. The authors observed that strain rate sensitive materials
experience increased capping and lamination propensity upon ejection, which they
attributed to the relative contribution of both permanent and reversible deformation
changing with speed [76].

In another study, Garr and Rubenstein [77] examined the effect of compression
speed in the range of 24 – 850 mm/s on the capping tendency of paracetamol. Capping or
lamination tendency was determined by close visual examination of tablets upon ejection,
with visual horizontal striations representing lamination. The intensity of capping
increased with an increase in compression speed. This behavior was attributed to changes
in the extent of plastic and elastic deformation with speed. A 65 % increase in elastic
energy was observed between compression speeds of 24 and 850 mm/s when compacted
to a consistent maximum load of 20 kN. By comparison, only a 33 % increase in plastic
energy was observed over the same speed range. Based on this study, along with others
[78,79], it can be concluded that at increased speeds, the powder bed responds by
preferentially deforming elastically over permanent plastic deformation. Consequently,
esthetic strain recovered during ejection causes the formulation particles to separate,
leading to a greater tendency for either capping or lamination. In other words, faster
compression speeds lead to weaker inter-particulate bonding and more elastic recovery, which both favor capping and lamination.

1.3.2.3 Characterization of Strain Rate Sensitivity

Strain rate sensitivity is most frequently characterized using the difference in mean yield pressure values obtained by compacting a material at two different speeds [9]. More specifically, a strain rate sensitivity index (Eq. (11)) was developed based on the percentage increase in mean yield pressure determined from in-die Heckel plots between punch velocities of 0.033 mm/s ($P_{y1}$) and 300 mm/s ($P_{y2}$):

$$ SRS = \frac{P_{y2} - P_{y1}}{P_{y2}} \times 100 $$ (11)

A high speed compaction simulator, able to operate over a wide range of punch velocities, was used to simulate both research and production scale tablet press speeds. A summary of the materials tested by Roberts and Rowe is provided in Table 1 on the following page.
Table 1. Heckel-Based SRS Index values for a wide range of materials (Re-printed with permission from the publisher [9])

<table>
<thead>
<tr>
<th>Material</th>
<th>SRS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium phosphate</td>
<td>--</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>--</td>
</tr>
<tr>
<td>Heavy magnesium carbonate</td>
<td>--</td>
</tr>
<tr>
<td>Paracetamol D.C.</td>
<td>1.8</td>
</tr>
<tr>
<td>Paracetamol drug</td>
<td>10.6</td>
</tr>
<tr>
<td>Lactose</td>
<td>16.2</td>
</tr>
<tr>
<td>Tablettose</td>
<td>19.2</td>
</tr>
<tr>
<td>Anhydrous lactose</td>
<td>20.3</td>
</tr>
<tr>
<td>Avicel PH 101</td>
<td>38.9</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>38.9</td>
</tr>
<tr>
<td>Mannitol</td>
<td>46.4</td>
</tr>
<tr>
<td>Maize starch</td>
<td>49.3</td>
</tr>
<tr>
<td>Corvic</td>
<td>54.1</td>
</tr>
</tbody>
</table>

Materials were ranked in terms of their brittle and ductile behaviors. For materials known to deform plastically (e.g. maize starch) there was an increase in the yield pressure with punch velocity. The authors attributed this increase to be a result of a reduction in the amount of plastic deformation or a transition from ductile to brittle behavior [9]. For materials known to consolidate by brittle fragmentation (e.g. calcium carbonate) there was a minimal change in mean yield pressure with increasing punch velocity.

This index was developed for material comparison and as a tool to improve understanding of the effects of strain rate on deformation. This approach, although extensively used and recognized in compaction research, has its limitations. First of all, Heckel analysis itself is an empirical model whose application can frequently provide inconsistent or misleading results. For example, the method using in-die Heckel analysis does not differentiate the effect of strain rate on elastic deformation from the effects on plastic deformation. Fundamentally, mean yield pressure determinations are derived from
in-die compaction which allows elastic deformation to confound the results. Under load, the measured porosity decreases as the particles elastically deform. As the load is removed and the tablet is ejected from the die, the porosity increases as the elastic deformation is reversed. This recovery causes in-die analysis to under predict mean yield pressure. Consequently, the strain rate sensitivity determined from in-die data will reflect changes in elasticity as well as changes in plasticity.

Secondly, in order to effectively assess strain rate effects using this method, a fairly dramatic compaction speed difference is needed due to the uncertainty of mean yield pressure values. 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. These punch velocities are not always achievable on standard testing equipment making consistent application of this method difficult. Although the strain rate sensitivity derived from in-die Heckel data remains the most wildly used approach for characterizing materials, other methods for evaluating strain rate sensitivity have been reported. Of particular interest to this work are methods that can characterize the strain rate sensitivity of individual deformation modes. Understanding strain rate sensitivity specifically related to plastic flow should provide an opportunity to develop a more complete understanding of the influence of tablet speed on different materials while complementing standard characterization methods.

Stress relaxation measurements have been used to characterize plastic flow of pharmaceutical materials during compaction. Typically, a material is compressed to a pre-defined peak force at which point the position of the upper and lower punches are held fixed. This fixed position estimates virtually constant strain; a requirement for stress
relaxation testing. As the compressed material relaxes, force-decay is monitored and recorded as a function of time. Several examples of stress relaxation experiments exist in the literature [13, 80-83], a few of which report the dependence of force-decay on the deformation behavior of the material being studied.

David and Augsburger [84] investigated the behavior of various materials using an instrumented rotary tablet press. The effects of the duration of the compression cycle and the duration of maximum compressive force (dwell time) were studied. The authors found that increasing the duration of maximum compressive force resulted in an increase in measured tensile strength for all materials tested. For known plastic materials (i.e., microcrystalline cellulose and starch) a much greater increase was observed. The authors hypothesized that the observed tensile strength increase was due to an increase in the extent of plastic flow with time.

To test this hypothesis, force-decay profiles collected at constant strain were modeled using a simplified Maxwell model used to describe viscoelastic behavior [7, 85]. A logarithmic relationship was derived using constitutive equations representing a Hookean elastic spring and a Newtonian viscous dashpot in series. The simplified relationship is provided in Eq. (12):

\[
\ln \Delta F = \ln \Delta F_0 - kt
\]

where \( \Delta F \) is compression force remaining in the viscoelastic region at time \( t \) and \( \Delta F_0 \) is the total magnitude of the compression force at time \( t = 0 \). Compression force decay
was modeled as a first order rate process where its rate constant, \( k \), represents the viscoelastic slope (Table 2).

Table 2. Viscoelastic slope (\( k \)) and total compression force lost
(Re-printed with permission from the publisher [84])

<table>
<thead>
<tr>
<th>Material</th>
<th>Viscoelastic Slope (( k ))</th>
<th>Total Compression Force Lost in Viscoelastic Region (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compressible starch</td>
<td>0.336</td>
<td>63</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>0.332</td>
<td>53</td>
</tr>
<tr>
<td>Compressible sugar</td>
<td>0.281</td>
<td>37</td>
</tr>
<tr>
<td>Dicalcium phosphate</td>
<td>0.182</td>
<td>7</td>
</tr>
</tbody>
</table>

Larger \( k \) values are attributed to increased plastic deformation during dwell time hold periods. Plastic material particles are able to flow into void spaces; increasing particle-particle contact and relieving local stress. For brittle materials, the total compression force lost was minimal, and much less than the force lost for starch and microcrystalline cellulose. Newly developed points of contact, created from particle fracture and associated rearrangement, allows for quick equilibration of the applied stress throughout the powder bed.

Despite its use for assessing time-dependent plasticity, stress relaxation tests can be hard to perform. In particular, properly maintaining constant strain conditions has been identified as being problematic. Slight changes to punch position can cause measureable force changes that can be misinterpreted as being caused by changes in tablet dimensions [13,86]. In order to take advantage of the value of testing materials whose properties depend on the rate and duration of loading, a complimentary technique that utilizes constant stress experimental conditions can be used. Indentation creep experiments
typically involve pushing an indenter into a formed tablet at a pre-determined loading rate and then holding the load on the indenter constant while the displacement of the indenter is monitored as a function of time. Strain rate sensitivity measurements using indentation hardness are routine for metallic and ceramic materials [87-91]. Indentation hardness \( H \) is calculated at each time point during the hold region according to previously established methods [92, 93] using Eq. (13):

\[
H(t) = \frac{F}{A}
\]

(13)

where \( F \) is the applied force and \( A \) is the contact area between the indenter and the compact at a specific time \( t \). Indentation strain rate \( \dot{\varepsilon}_H \) [94-98] is defined as the ratio between the depth of penetration \( h \) at a specific time \( t \) and the corresponding instantaneous rate of penetration \( \frac{dh}{dt} \) using Eq. (14):

\[
\dot{\varepsilon}_H(t) = \frac{1}{h} \times \frac{dh}{dt}
\]

(14)

A plot of ln hardness vs. ln strain rate yields a linear relationship, whose slope \( m \), indicates the change in hardness with respect to changes in strain rate as shown in Eq. (15):

\[
m = \frac{\partial \ln H(t)}{\partial \ln \dot{\varepsilon}_H(t)}
\]

(15)
Materials are compared and assessed for their sensitivity to strain rate by comparing how the penetration of the indenter changes as a function of the displacement rate. It has been shown that indentation creep data can be used to compare the viscoplasticity of particulate materials [99,100]. Since the creep method is based on data collected after elastic deformation is finished, its results should be directly related to time-dependent plasticity.

Using a trial-and-error approach to tablet development is frequently identified as being too time consuming and too costly. As a result, lab-scale strain rate sensitivity characterization methods that are capable of predicting the extent to which an actual formulation’s behavior will change upon scale-up are important for the successful development of tableted drug products. Traditional techniques, although still used in practice, have limitations that complicate interpretation of the data. Other approaches provide information that is not influenced by competing deformation processes. In cases where a detailed understanding of a material’s strain rate sensitivity is called for, alternative evaluation approaches, in combination with traditional methods, should provide more specific results that allow the identification of the specific mechanical behaviors that are responsible for observed strain rate sensitivity.

1.4 Summary

Changes to tablet compression speed can cause considerable changes to material behavior. During development, often relatively small tablet presses are used which operate at slow speeds. Although restrictions on raw material usually exist, simulation of large scale production conditions is difficult using machines that operate at speeds orders
of magnitude slower than those utilized during manufacturing. Understanding to what extent changes in deformation behavior can occur, as the rates of compression and the time over which force is applied to the powder changes, is crucial for the reliable development of tableted products. In efforts to improve development efficiency, powder materials are frequently characterized at lab-scale where much less material is needed for testing. Assessment of time-dependent deformation behavior should facilitate identification of active pharmaceutical ingredients, excipients, and formulations which may be difficult to tablet on high speed rotary tablet machines.
Chapter 2: Effect of Compression Speed on the Tableting Profiles of Three Common Pharmaceutical Excipients

It is important to establish the effects of compression speed on product quality attributes such as tablet solid fraction and tablet tensile strength. In this chapter, compressibility and tabletablility profiles were generated and used to assess the effects of strain rate during tableting. Compressibility (solid fraction vs. compaction pressure) and tabletablility (tablet tensile strength vs. compaction pressure) relationships provide valuable information about a material’s tendency to behave differently at different compression speeds.

A Huxley-Bertram compaction simulator was used to study the compaction properties of three commonly used pharmaceutical excipients at high speed. (Note: due to time constraints on the compaction simulator, only a subset of the materials studied in this dissertation was compacted using this equipment). Tablets for each of the three materials were prepared in the materials science laboratory at the Pfizer research facility in Groton, CT. Subsequent analysis was performed in-house at Duquesne University.

2.1 Experimental

2.1.1 Materials

The pharmaceutical diluents used in this chapter were chosen based on their varied deformation behavior. A base formulation containing an internally blended binder (Copovidone, 3 %), glidant (Colloidal silicon dioxide, 0.5 %), and lubricant (Magnesium stearate, 0.5 %) was used for all experiments. Raw material supplier information,
functionality, and % w/w composition for the three diluents and the base formulation components are provided in Table 3.

<table>
<thead>
<tr>
<th>Material (Trade name)</th>
<th>Supplier (Location)</th>
<th>Functionality</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-gelatinized maize starch (Lycatab® PGS)</td>
<td>Roquette (Keokuk, IA)</td>
<td>Diluent</td>
<td>96.0</td>
</tr>
<tr>
<td>Microcrystalline cellulose (Avicel® PH 200)</td>
<td>FMC Corporation (Philadelphia, PA)</td>
<td>Diluent</td>
<td>96.0</td>
</tr>
<tr>
<td>Dibasic calcium phosphate dihydrate (Emcompress®)</td>
<td>JRS Pharma (Germany)</td>
<td>Diluent</td>
<td>96.0</td>
</tr>
<tr>
<td>Copovidone</td>
<td>ISP Technologies (Wayne, NJ)</td>
<td>Binder</td>
<td>3.0</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>Evonik Industries (Parsippany, NJ)</td>
<td>Glidant</td>
<td>0.5</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>Spectrum (Gardena, CA)</td>
<td>Lubricant</td>
<td>0.5</td>
</tr>
</tbody>
</table>

The diluents listed in Table 3 (Lycatab® PGS, Avicel® PH200 and Emcompress®) comprised the remaining 96 % w/w in each formulation. Throughout this dissertation, for simplicity, formulations will be referred to as either ‘individual components’ or ‘mixtures’. If the formulation contained only one diluent, then it will be referred to as an ‘individual component’ by the name of that material. If the formulation contained two diluents in combination, those will be listed as ‘mixtures’ and will be referred to by providing the % w/w of each diluent in the formulation.
In an attempt to limit the variability resulting from disparities in physical properties on the compaction behavior of these materials, all experimentation was carried out using powders with equivalent particle size ranges (180 - 250 µm), which were equilibrated at ambient temperature (~ 23 – 25 °C) in a controlled relative humidity environment (saturated MgCl₂, ~ 32 – 33 % relative humidity [101]).

2.1.2 Data Collection

2.1.2.1 Raw Material Characterization

Each material was 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 of powder. 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.

2.1.2.2 Tablet Compaction

A Huxley-Bertram servohydraulic compaction simulator (Model HB1088) was used to compact Lycatab® PGS, Avicel® PH 200, and Emcompress® formulations. The
simulator used in this work is a sophisticated tool that enables compaction at very high speeds. Automated operation allows for a large amount of tablets to be compacted in a short period of time. The die-table contains multiple hoppers that can be used to deliver powder to the die, and a take-off arm that mechanically slides an ejected tablet towards the carousel. A 3D rendering of the working area of the Huxley-Bertram simulator is provided in Figure 4. Significant machine parts are labeled.

Figure 4. Huxley-Bertram compaction simulator. 3D view of working area with significant machine parts labeled (Re-printed from equipment documentation provided by manufacturer)

In this work, powder was gravity fed during die-filling, and the carousel was used to separately collect replicate tablets. Machine instrumentation specifications were extracted from the maintenance manual. For the upper and lower load cells the maximum
error in the transducer was reported to be ± 0.5 %. The encoder responsible for recording punch position values also has a reported maximum error of ± 0.5 %.

Each compact was prepared by weighing 500 mg of powder into a 13-mm stainless steel, cylindrical die with standard B punch tooling. Each material was compacted at three different compaction speeds (4, 40, and 400 mm/s) using a 50 kN load cell. The same speed was used for both compression and decompression, and no dwell time was included at the minimum punch separation distance. Compaction pressure, $P$, was determined by dividing the applied load (recorded at each minimum punch separation distance), or force, by the projected area over which that force was distributed. Eq. (16) was used to determine the applied pressure, in MPa, for all tablets:

$$P = \frac{\text{Force}}{\pi r^2}$$  \hspace{1cm} (16)

where the radius, $r$, was 6.5 mm for all tablets. Varied minimum punch separation distances were used to compact tablets across a range of out-of-die solid fraction.

### 2.1.2.3 Out-of-Die Solid Fraction

After ejection, tablets were stored for 7 – 10 days depending on how long it took for measured dimensions to no longer change. The dimensions of each tablet were measured using a digital caliper (Mitutoyo, Japan). The weight ($m$), out-of-die thickness ($t$), out-of-die diameter ($d$), and powder true density ($\rho_{\text{true}}$) of each tablet were used to obtain the out-of-die solid fraction according to Eq. (17):
\[ SF = \frac{4m}{\pi d^2 \rho_{true}} \]  

Reported out-of-die solid fraction values represent the average and standard deviation of 3 replicate compacts at each minimum punch separation distance.

\subsection*{2.1.2.4 Radial Tensile Strength}

The radial tensile strength of each tablet compressed on the Huxley-Bertram simulator was measured using an Instron universal material testing system (Model 5869, Instron Corporation, Norwood, MA) outfitted with a 1 kN load cell. Tablets were compressed across their diameter between two rectangular metal gauges, the width of which was less than one-sixth of the tablet diameter (2.0 mm). The metal gauges were covered with two strips of blotting paper to minimize the effect of shear and compressive stresses at the points of contact with the tablets. Specific cross-head speeds were also utilized in order to ensure similar strain rate conditions during testing (Section 1.3.2.2). The rate of testing used for each material is provided in Table 4.

<table>
<thead>
<tr>
<th>Individual Component</th>
<th>Rate of Testing (mm/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lycatab® PGS</td>
<td>5.0</td>
</tr>
<tr>
<td>Avicel® PH 200</td>
<td>4.2</td>
</tr>
<tr>
<td>Emcompress®</td>
<td>1.1</td>
</tr>
</tbody>
</table>
Tablet failure along the diameter in which the load was applied allows the tensile stress causing failure to be calculated according to Eq. (10). Reported radial tensile strength values represent the average and standard deviation of 3 replicate compacts at each minimum punch separation distance.

2.1.2.5 Tablet Relaxation

Punch separation distance at the maximum applied compressive load was used to obtain minimum in-die tablet thickness. The punch displacement data was corrected for deformation of the machine parts. An example of how this correction was performed is provided. The difference between the corrected and recorded punch separation distance for Emcompress® compressed at 4 mm/s is shown in Figure 5.

Figure 5. Recorded (—) and corrected (—) punch separation profiles for Emcompress® compacted at 4 mm/s
At low pressure, or force, the difference between the recorded and corrected data is minimal. However, as the applied pressure increases a progressively larger difference was observed. The difference in the recorded and corrected punch separation distance at max pressure was equal to 0.42 mm for this example. Failure to correct for the deformation of the machine parts can lead to a significant differences in in-die tablet thickness, and as a result, the minimum tablet volume ($V_{min}$).

To correct the in-die punch separation distance, the displacement measured during compression of the punches in an empty die was added to the punch separation measured during the formation of each compact. Both the loading and unloading force-displacement data for compression of the punches in an empty die were fit to a 6th order polynomial to account for any hysteresis in the complete loading/unloading profile. Punch deformation corrections were performed using empty die data collected at the same speed used to compact each tablet. For example, profiles for the loading and unloading segments of an empty die compressed at 4 mm/s are shown in Figures 6 and 7, respectively.
Figure 6. Empty-die loading profile collected at 4 mm/s

\[ y = -4.8E-10x^6 + 5.9E-08x^5 - 2.9E-06x^4 + 7.3E-05x^3 - 9.5E-04x^2 + 1.7E-02x + 3.4E-03 \]

Figure 7. Empty-die unloading profile collected at 4 mm/s

\[ y = -5.3E-10x^6 + 6.4E-08x^5 - 3.2E-06x^4 + 8.0E-05x^3 - 1.1E-03x^2 + 1.9E-02x + 4.4E-03 \]
Corrected punch separation distance was used to determine the in-die thickness \( h_{in} \) of the powder bed. In-die tablet dimensions were used to calculate the in-die tablet volume \( \text{Volume (In} - \text{Die)} \) according to Eq. (18):

\[
\text{Volume (In} - \text{Die)} = \pi (6.5\text{mm})^2 h_{in}
\]

where the radius of the tablet die was 6.5 mm. Following ejection from the die and viscoelastic relaxation of each tablet, the out-of-die tablet thickness \( h_{out} \) and tablet diameter were also measured. Out-of-die tablet dimensions were used to calculate the out-of-die tablet volume \( \text{Volume (Out} - \text{of} - \text{Die)} \) according to Eq. (19):

\[
\text{Volume (Out} - \text{of} - \text{Die)} = \pi r_{out}^2 h_{out}
\]

where the radius of the ejected tablets \( r_{out} \) was half of the measured diameter. Volume change was calculated according to Eq. (9), presented in Chapter 1 Section 1.3.2.1. Large volume change values indicate larger changes in tablet dimensions in both the axial and radial directions relative to the dimensions of the tablet confined to the die. Reported tablet relaxation values represent the average and standard deviation of 3 replicate compacts at each minimum punch separation distance.
2.2 Results and Discussion

2.2.1 Raw Material Characterization

Summarized data for powder true density and moisture content of Lycatab® PGS, Avicel® PH 200, and Emcompress® formulations is provided in Table 5 below.

Table 5. True density and moisture content values of formulations

<table>
<thead>
<tr>
<th>Formulation’s Primary Ingredient</th>
<th>True density</th>
<th>% Moisture(^a) (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-gelatinized maize starch (Lycatab® PGS)</td>
<td>1.458 (0.004)</td>
<td>8.408 (0.066)</td>
</tr>
<tr>
<td>Microcrystalline cellulose (Avicel® PH 200)</td>
<td>1.550 (0.004)</td>
<td>5.672 (0.040)</td>
</tr>
<tr>
<td>Dibasic calcium phosphate dihydrate (Emcompress®)</td>
<td>2.301 (0.002)</td>
<td>3.130 (0.058)</td>
</tr>
</tbody>
</table>

\(^a\) Loss on drying

The reported true density values were calculated from the true density of the individual materials according to the true density and weight fraction of each component in the formulation.

Particle size distributions, reported as percent undersize, for the same three materials are provided in Table 6, on the following page.
Table 6. Particle size distribution of each diluent determined by sieve analysis

<table>
<thead>
<tr>
<th>Material</th>
<th>Percentage undersize (&lt;53 μm, &lt;75 μm, &lt;125 μm, &lt;180 μm, &lt;250 μm, &lt;500 μm, &lt;1000 μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-gelatinized maize starch (Lycatab® PGS)</td>
<td>22.8, 22.8, 27.7, 49.8, 77.8, 95.0, 99.9</td>
</tr>
<tr>
<td>Microcrystalline cellulose (Avicel® PH 200)</td>
<td>7.2, 7.2, 8.9, 18.5, 32.7, 60.3, 100.0</td>
</tr>
<tr>
<td>Dibasic calcium phosphate dihydrate (Emcompress®)</td>
<td>1.0, 1.0, 2.4, 14.3, 29.8, 84.9, 98.1</td>
</tr>
</tbody>
</table>

The 180 – 250 μm sieve fraction was selected for use based on the particle size distribution of Lycatab® PGS, alone. Selection of this size fraction was warranted given the presence of Lycatab® PGS in each mixture for the studies presented in Chapter 4. The mass percentage in this range was 28.0 % and was the most abundant sieve fraction for this material. Since this material was used most frequently, collecting the 180 – 250 μm sieve fraction would maximize powder usage in both the lab-scale and compaction simulator experiments.

2.2.2 Compaction Properties

The compressibility profiles for each of the three materials studied are shown in Figure 8, on the following page. The figure legend identifies the data point marker type used for each corresponding material.
Figure 8. Huxley-Bertram simulator compressibility profiles for Avicel® PH200 (Δ), Lycatab® PGS (◊), and Emcompress® (□) compacted at 4 mm/s. Data points represent average values (n = 3) and associated error bars represent standard deviation.

The rate of change in solid fraction as a function of applied compaction pressure gives an indication of powder compressibility. For the data presented in Figure 8, it was evident that Avicel® PH200 and Lycatab® PGS were more compressible than Emcompress®. That is, the change in solid fraction over a similar pressure range was greater for those two materials than it was for Emcompress®. Quantitatively, the change in solid fraction across the entire pressure range for Emcompress® was ~ 0.16, whereas for Lycatab® PGS and Avicel® PH200 the change in solid fraction was approximately 0.28 and 0.24, respectively. The larger changes in solid fraction for Lycatab® PGS and Avicel® PH200 were expected based on previously reported data for these materials [102, 103]. Similarly, the poor compressibility of Emcompress® has also been reported.
previously, and was considered to be a function of the deformation tendency of that material during the formation of a tablet [104].

The tabletability of each material was also assessed. Tabletability is the ability of a powder bed to transform into a coherent compact as a result of an applied compaction pressure [7]. Tabletability is represented by a profile of radial tensile strength plotted against compaction pressure. The tabletability profiles for each of the three materials are shown in Figure 9.

![Tabletability Profiles](image)

Figure 9. Huxley-Bertram simulator tabletability profiles for Avicel® PH200 (Δ), Lycatab® PGS (◊), and Emcompress® (□) compacted at 4 mm/s. Data points represent average values (n = 3) and associated error bars represent standard deviation.

The tabletability data for Avicel® PH200 demonstrates high values of tablet tensile strength at all compaction pressures. This can be attributed to the high
compressibility of this material, as discussed previously. Plastic deformation in this material results in the formation of extensive inter-particle contact area, which results in high tablet tensile strength [105]. The material with the lowest tabletability was Emcompress®. Since this material was poorly compressible (Figure 8) relative to the two other materials studied, it was not unexpected to observe such results. Reduced compressibility leads to fewer points of inter-particle contact formed during compaction.

For Lycatab® PGS, the tabletability data shows consistently low tablet tensile strength values when compared to Avice1® PH200. This is in contrast to the high compressibility shown by this material. For starch based products, it is often reported that, although they compress efficiently, they show extensive elastic recovery during decompression and large amounts of viscoelastic recovery post-ejection [41]. In this work, similar behavior was observed. Tablet relaxation data for each material is plotted as a function of compaction pressure in Figure 10, on the following page.
Figure 10. Huxley-Bertram simulator tablet relaxation profiles for Lycatab® PGS (◊), Avicel® PH200 (Δ), and Emcompress® (□) compacted at 4 mm/s. Data points represent average values (n = 3) and associated error bars represent standard deviation.

Clearly, Lycatab® PGS exhibited the greatest amount of tablet relaxation across all pressures. Much smaller changes in tablet dimensions were observed for Avicel® PH200 and Emcompress®. Deformation plays a very important role in the formation of inter-particle contact area. Irreversible deformation mechanisms such as brittle fracture and plastic deformation help in the formation of contact area between particles. On the other hand, excessive elastic relaxation of tablets during decompression and/or large amounts of viscoelastic recovery, can lead to destruction of the inter-particle contact area formed during compression resulting in a lower measured tensile strength (Figure 9).

Meaningful comparisons can be made between materials using the tableting-related profiles presented in Figures 8-10. Information related to consolidation and tablet
relaxation behavior is easily ascertained. However, these data were collected at a compaction speed (4 mm/s) that is much slower than the speeds that would be used to prepare tablets at the manufacturing scale. Depending on the material, powder particles may deform differently at different speeds. This can cause variations in the extent of consolidation, the amount of tablet relaxation behavior, and as a result the measured tablet tensile strength. The following section will be used to identify strain rate sensitivity in the common tableting-related profiles presented in this section. For clarity, strain rate sensitivity data has been grouped by material.

**2.2.3 Effect of Tablet Press Speed on Compaction Properties**

**2.2.3.1 Emcompress®**

The effect of compression speed on the compressibility profile of Emcompress® is shown in Figure 11, on the following page. The figure legend indicates the linear compaction speed used to form each tablet.
Figure 11. Huxley-Bertram simulator compressibility profiles for Emcompress® compacted at three different compaction speeds: 4 mm/s (◊), 40 mm/s (□), and 400 mm/s (△). Data points represent average values (n = 3) and associated error bars represent standard deviation.

For Emcompress® there was no effect of compression speed on the compressibility of this material. Equivalent functions of out-of-die solid fraction versus pressure were achieved regardless of the speed used to form each tablet. All curves were overlaid and indistinguishable from one another. The tabletability profiles, tablet tensile strength versus compaction pressure, compacted at the same three speeds were also collected and are plotted in Figure 12.
Figure 12. Huxley-Bertram simulator tabletability profiles for Emcompress<sup>®</sup> compacted at three different compaction speeds: 4 mm/s (◊), 40 mm/s (□), and 400 mm/s (Δ). Data points represent average values (n = 3) and associated error bars represent standard deviation.

A higher compaction pressure resulted in a stronger tablet at all speeds. It was also evident that the linear compaction speed did not have a significant effect on tensile strength when compared at equivalent compaction pressure values. For example, tablets compacted to a maximum pressure of 150 MPa showed tensile strength values of ~ 1.5 MPa, regardless of speed. For the tablets compressed at 400 mm/s there is a slight reduction in the radial tensile strength above 150 MPa relative to the strength of the tablets compacted at 4 and 40 mm/s. An increase in tablet relaxation behavior appears to be responsible for this change. The volume change versus pressure profile for Emcompress<sup>®</sup> is provided in Figure 13.
Figure 13. Huxley-Bertram simulator tablet relaxation versus pressure profiles for Emcompress® compacted at three different compaction speeds: 4 mm/s (◊), 40 mm/s (□), and 400 mm/s (Δ). Data points represent average values (n = 3) and associated error bars represent standard deviation.

Above 150 MPa, a larger volume change was observed for tablets compacted at 400 mm/s compared to the recovery of the tablets compacted at 4 and 40 mm/s. Higher elastic relaxation during decompression and higher viscoelastic relaxation over time leads to reversing inter-particulate bonding area developed during compression and reduced tablet tensile strength. Although the reduction in tensile strength in this situation is negligible, it remains important to identify the source of these changes.
2.2.3.2 Avicel® PH 200

The effect of compression speed on the compressibility profile of Avicel PH 200® is shown in Figure 14. As before, the figure legend represents the linear compaction speed used to form each tablet.

![Graph showing the effect of compression speed on the compressibility profile of Avicel PH 200](image)

Figure 14. Huxley-Bertram simulator compressibility profiles for Avicel® PH 200 compacted at three different compaction speeds: 4 mm/s (◊), 40 mm/s (□), and 400 mm/s (△). Data points represent average values (n = 3) and associated error bars represent standard deviation.

Avicel® PH 200 showed sensitivity to compression speed in its compressibility profile. At all levels of applied pressure, lower values of solid fraction were obtained for tablets that were compacted at higher speed. In other words, as the amount of time available for consolidation to occur decreased (i.e., an increase in compaction speed), the...
extent of consolidation decreased. The tabletability behavior of Avicel® PH200 was also investigated at the same three compaction speeds. Those profiles are plotted in Figure 15.

Figure 15. Huxley-Bertram simulator tabletability profiles for Avicel® PH 200 compacted at three different compaction speeds: 4 mm/s (◊), 40 mm/s (□), and 400 mm/s (Δ). Data points represent average values (n = 3) and associated error bars represent standard deviation.

A reduction in tablet tensile strength corresponding to a progressive increase in the rate of compaction was observed. Weaker tablets were produced at faster speed. Previously, it was shown for Emcompress®, that similar behavior was attributed to an increase in the tablet relaxation behavior, albeit to a much lesser extent. So, in an attempt to identify the source of the observed reduction in tablet tensile strength with speed for Avicel® PH200, the volume change versus pressure profiles were plotted in Figure 16.
Figure 16. Huxley-Bertram simulator tablet relaxation versus pressure profiles for
Avicel® PH 200 compacted at three different compaction speeds: 4 mm/s (◊), 40 mm/s (□), and 400 mm/s (Δ). Data points represent average values (n = 3) and associated error bars represent standard deviation

The amount of elastic and viscoelastic recovery that occurs is not significantly dependent on the speed used to prepare each tablet. The curves are indistinguishable from one another confirming that the amount of recovery observed is practically equivalent. Since the tablet recovery data was not affected by the same speed changes, the reduction in strength in the tabletability profile can be attributed to the lower out-of-die solid fraction (i.e., compressibility) of those tablets when compared at the same maximum pressure. Tablets with a lower solid fraction have reduced areas of inter-particulate contact area resulting in a reduction in the overall network of bonded interactions.
2.2.3.3 Lycatab® PGS

The effect of compression speed on the compressibility profile of Lycatab® PGS is shown in Figure 17. The figure legend represents the linear compaction speed used to prepare each tablet.

Figure 17. Huxley-Bertram simulator compressibility profiles for Lycatab® PGS compacted at three different compaction speeds: 4 mm/s (◊), 40 mm/s (□), and 400 mm/s (Δ). Data points represent average values (n = 3) and associated error bars represent standard deviation.

The compressibility of Lycatab® PGS is susceptible to changes in the rate of compaction. Large reductions in solid fraction were observed as the tablet press speed was incrementally increased from 4 to 400 mm/s. For example, at a compaction pressure of ~ 85 MPa, the measured solid fraction at 4 mm/s was 0.68 whereas at 400 mm/s the solid fraction was reduced to a value of 0.60. Tablet tensile strength versus pressure data
was also compared as a function of speed. The tabletability profiles for Lycatab® PGS are provided in Figure 18.

Figure 18. Huxley-Bertram simulator tabletability profiles for Lycatab® PGS compacted at three different compaction speeds: 4 mm/s (◊), 40 mm/s (□), and 400 mm/s (Δ). Data points represent average values (n = 3) and associated error bars represent standard deviation.

The tensile strength of Lycatab® PGS compacts is significantly affected by compaction speed. At the same compaction pressure, the tablet strength decreases as the speed used to prepare each compact increases. These results are not unexpected and compare favorably to similar results presented for starch based excipients in the literature [9,44,84,106]. The source of the sensitivity in the tabletability profile appears to be due to a reduction in solid fraction with speed (Figure 17). However, it could also be due to
changes in the tablet relaxation behavior. The reversible response of Lycatab® PGS to speed is presented in Figure 19.

![Figure 19. Huxley-Bertram simulator tablet relaxation versus pressure profiles for Lycatab® PGS compacted at three different compaction speeds: 4 mm/s (◊), 40 mm/s (□), and 400 mm/s (Δ). Data points represent average values (n = 3) and associated error bars represent standard deviation.](image)

Unlike Emcompress® and Avicel® PH 200, the reversible behavior of Lycatab® PGS depends on the speed used to compact each tablet. For the tablets compressed at 400 mm/s, a larger tablet volume change was observed when compared to the tablets compacted at both 4 and 40 mm/s. At higher speed, larger amounts of elastic strain are recovered. This causes a larger increase in tablet volume at higher speed relative to the volume change at slower speed. Since both the tablet recovery data and the
compressibility data were affected by the same speed changes, the reduction in strength in the tabletability profile appears to be due to a combination of both properties. As a result, the extent of bond formation that remains in the ejected tablets is reduced, as are measured tensile strengths.

2.3 Summary

The effect of tablet press speed changes on the compressibility, tabletability, and tablet relaxation properties of three common excipients were studied using a compaction simulator. The sensitivity of each profile is categorized and listed in Table 7.

Table 7. Summary of effect of compression speed on compaction properties

<table>
<thead>
<tr>
<th>Individual Component</th>
<th>Compressibility</th>
<th>Tabletability</th>
<th>Tablet Relaxation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-gelatinized maize starch (Lycatab® PGS)</td>
<td>Sensitive</td>
<td>Sensitive</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Microcrystalline cellulose (Avicel® PH 200)</td>
<td>Sensitive</td>
<td>Sensitive</td>
<td>Insensitive</td>
</tr>
<tr>
<td>Dibasic calcium phosphate dihydrate (Emcompress®)</td>
<td>Insensitive</td>
<td>Insensitive</td>
<td>Insensitive</td>
</tr>
</tbody>
</table>

Practically speaking, insensitivity in these compaction profiles suggests that the compaction behavior of this material is not significantly affected by changes in tablet press speed. For example, in the tablet relaxation profile for Emcompress®, the measured volume change at slow speed (i.e., lab-scale conditions) should be nearly equivalent to the measured volume change at high speed (i.e., manufacturing scale conditions). Where it becomes significantly more complicated is when one of these profiles exhibits
sensitivity. Sensitivity, by itself, would indicate that nearly equivalent compaction properties would not be expected as tablet press speed changes. In the case of Avicel® PH200, sensitivity in the tabletability profile was attributed to sensitivity in the compressibility data. In other words, a reduction in tablet tensile strength with speed was due to a reduction in solid fraction at those same speeds. For Lycatab® PGS, sensitivity in the tabletability profile was due to a combined effect of sensitivity in the compressibility and tablet relaxation data.

Sensitivity, or lack thereof, in these profiles is often explained for these materials in terms of their deformation behavior because they are materials that are well-known and have been studied frequently. However, these profiles cannot always be used to provide a direct connection to the deformation behavior that is responsible for observed strain rate sensitivity. Certainly it can be argued that sensitivity in the tablet relaxation profiles is due to viscoelasticity, but changes in solid fraction at different rates (i.e., compressibility) can be due to viscoelastic behavior as well as due to time-dependent plastic flow. Accordingly, a strain rate sensitivity characterization method that could differentiate between the sensitivity of viscoplasticity and viscoelasticity would be of significance.
Chapter 3: Lab-Scale Measurements that Comprehensively Describe the Various Aspects of Strain Rate Sensitivity During Powder Compaction

There exists a need to characterize a material’s time-dependent deformation behavior in addition to evaluating strain rate sensitivity in compressibility and tabletability profiles. Identifying the specific mechanical behavior, or behaviors, that are responsible for observed strain rate sensitivity would be of great significance during formulation development studies. Time-dependent processes are involved throughout the entire cycle of tablet compaction including the loading, dwell time, and unloading phases [86,107, 108]. When stress is applied to a powder to form a tablet, the mechanical properties of the resulting tablet are a function of the deformation tendencies of that material. The extent of irreversible particle deformation depends on the amount of time stress is applied during loading. Conversely, during decompression and post-ejection from the die, the release of residual elastic strain disrupts the initially formed inter-particle contact area. The relative amounts of reversible and irreversible deformations are time-dependent.

Table 8, on the following page, summarizes each of the three parameters used to evaluate the various aspects of strain rate sensitivity in this work. Selection of the parameters listed in Table 8 was based on the theoretical connection between each one, and the mechanical behaviors related to strain rate sensitivity. The equations used to determine each measurement are provided.
Table 8. Lab-scale parameters used to characterize strain rate sensitivity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Characterized Behavior/Properties</th>
<th>Interpretation</th>
</tr>
</thead>
</table>
| Indentation Creep SRS Exponent    | Viscoplasticity                   | Equation: \( m = \frac{\partial \ln H(t)}{\partial \ln \dot{\varepsilon}(t)} \)  
Exponent describes time-dependent plasticity under constant stress. |
| \( \Delta S F_{\text{final}} \)   | Viscoelasticity                   | Equation: \( \Delta S F_{\text{final}} = S F_{c/d} - S F_{\text{out-of-die}} \)  
Value characterizes time-dependent elasticity occurring post-decompression. |
| Heckel-Based SRS Index            | Non-specific assessment of strain rate sensitivity | Equation: \( S R S (%) = \frac{P_{y2} - P_{y1}}{P_{y2}} \times 100 \)  
Index reflects the percent change in permanent/reversible deformation occurring between two compression speeds. |

Each strain rate sensitivity characterization approach presented in Section 1.3.2 relied on single parameter values in an attempt to describe the complexity of time-dependent deformation. This approach lacks the necessary detail to differentiate the effect of strain rate on elastic deformation from the effects on plastic deformation. As a result, it is hypothesized that a multi-component assessment of strain rate sensitivity enables identification of the specific mechanical behaviors responsible for observed sensitivity.
3.1 Experimental

3.1.1 Materials

The excipients studied in the remainder of this dissertation were chosen based on their varied deformation behavior. Included in this list are the three materials (highlighted red) that were studied on the compaction simulator in Chapter 2. To reiterate, due to time constraints on the compaction simulator, only those three materials were studied at high-speed. Lab-scale data was collected on a wider range of excipient powders. Raw material supplier information for each of the six excipients is provided in Table 9.

Table 9. Raw material supplier information

<table>
<thead>
<tr>
<th>Material (Trade name)</th>
<th>Supplier (Location)</th>
<th>Lot #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-gelatinized maize starch (Lycatab® PGS)</td>
<td>Roquette (Keokuk, IA)</td>
<td>E2517</td>
</tr>
<tr>
<td>Partially pre-gelatinized corn starch (Starch 1500®)</td>
<td>Colorcon (West Point, PA)</td>
<td>IN514248</td>
</tr>
<tr>
<td>Microcrystalline cellulose (Avicel® PH 200)</td>
<td>FMC Corporation (Philadelphia, PA)</td>
<td>PN12824026</td>
</tr>
<tr>
<td>Spray-dried lactose 316 Grade</td>
<td>Foremost Farms (Baraboo, WI)</td>
<td>8512021961</td>
</tr>
<tr>
<td>anhydrous lactose 120 MS</td>
<td>Kerry Bio-Sciences (Norwich, NY)</td>
<td>1320000873</td>
</tr>
<tr>
<td>Dibasic calcium phosphate dihydrate (Emcompress®)</td>
<td>JRS Pharma (Germany)</td>
<td>7089X</td>
</tr>
</tbody>
</table>

Each of the excipients in the preceding table were incorporated into separate base formulations along with an internally blended binder, glidant, and lubricant as presented
in Chapter 2. The composition of the base formulation remained the same and can be referenced in Table 3. In an attempt to limit the variability resulting from disparities in physical properties on the compaction behavior of these materials, all experimentation was carried out using powders with equivalent particle size ranges (180 - 250 μm) which were equilibrated at ambient temperature (~ 23 – 25 °C) in a controlled relative humidity environment (saturated MgCl$_2$, ~ 32 – 33 % relative humidity [101]).

3.1.2 Data Collection

3.1.2.1 Raw Material Characterization

The excipients that weren’t compacted on the simulator were characterized for their 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 after equilibration 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 of powder. 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.
3.1.2.2 Tablet Compaction

Formulations were prepared by blending powders in 5 g batches using a small-scale rotary mixer (Appropriate Technical Resources (ATR), Model # 10101). The blending protocol consisted of an initial 15 min blend period, followed by blending for an additional 2 min after addition of magnesium stearate. An Instron universal testing system (Model 5869, Instron Corporation, Norwood, MA) equipped with a 50 kN load cell was used to compact each formulation into tablets. Each tablet was prepared by weighing 500 mg of powder into a 13-mm stainless steel, cylindrical die. The measurement accuracy of the Instron was within ± 0.5% of the maximum applied load and ± 0.02 mm of the maximum recorded displacement.

A total of 10 tablets were prepared with each material. First, a single tablet was compacted to a maximum pressure of 264 MPa at 0.04 mm/s for all materials. The in-die data from these tablets were used to determine the pressures needed to compact each material to an out-of-die porosity of 20 ± 2%, after relaxation. Then, six tablets were tableted using the maximum pressure identified from the data correction procedure for that material. All tablets were prepared at a compaction speed of 0.04 mm/s. With the remaining material from each blend, 3 additional tablets were compacted to the same maximum applied pressure using a linear compaction speed of 4 mm/s. It was observed that complete relaxation of formed tablets occurred within 7 to 10 days. The final dimensions of each tablet were measured using a digital caliper (Model CO 030150, Marathon).
3.1.2.3 Tablet Indentation

A Vickers diamond-pyramid tip indenter was used to apply a constant load of 10 ± 0.1 N for 60 s. An Instron universal material testing system was operated using a highly sensitive load cell (50 N) with a loading and unloading rate of 10 N/min. Extension values were measured using a deflectometer (Model I3540-015T-ST) positioned as near to the indenter tip as possible. This transducer has a fixed body with a moving core. The moving core is spring loaded and features a ball-tip. Any movement of the area of interest is transferred to the moving tip and hence to the transducer resulting in a signal that is proportional to the deflection.

3 of the 6 tablets compacted at 0.04 mm/s, whose out-of-die porosity deviated the least from 20 %, were chosen for the indentation experiments. Replicate indentations (n = 5) were performed on the upper surface of each tablet. A total of 15 indentations were analyzed for determining the Indentation Creep SRS Exponent. The position of the indentations was consistent but the sequence in which the indentations were formed was random. Instron Bluehill® 2 software (Version 2.17) was used to collect raw data during the indentation creep experiments.

3.1.3 Data Analysis

3.1.3.1 Indentation Creep SRS Exponent

Raw data outputs for the indentation creep studies included: time (s), load (N), and extension (mm) measured using a deflectometer. A typical plot of extension versus time for Lycatab® PGS is provided in Figure 20.
For each indentation measurement the tablet surface was manually detected in order to reset to the ‘zero’ extension position. As a result, all extension values measured by the deflectometer and recorded by the software had a negative sign designation. Accordingly, an extension value of -0.2 mm indicates that the position of the indenter tip is 0.2 mm below the tablet surface. It was noticed for materials that showed relatively small amounts of creep, extension values changed by discrete steps as the time under load increased. An extension versus time profile for Emcompress® is provided in Figure 21 to illustrate this phenomenon.

Figure 20. Extension versus time profile for Lycatab® PGS collected during the 60 second hold region.
This behavior was not unexpected given how little those materials deform under constant stress conditions and the sensitivity of the deflectometer to displacement. However, non-continuous data becomes quantitatively problematic for calculating indentation strain rate (Eq. (14)). Determining $\frac{dh}{dt}$ using the raw data (Figure 21) is complicated by the fact that extension appears to remain constant for periods of time between step changes in position. As a result, extension-time data recorded during the hold region of the creep test were fit to a fractional order polynomial (Eq.(21), following page) using non-linear least squares regression. Use of this equation to fit indentation extension-time data has been published previously [91]:
where $h_i$ is the initial extension at the start of the hold region, $t_i$. Fitting constants [$a - d$] were solved for by minimizing the sum of squares between the recorded and curve fit extension values. Quality of fit is depicted graphically in Figures 22 and 23.

\[
h = h_i + a(t - t_i)^{1/2} + b(t - t_i)^{1/4} + c(t - t_i)^{1/8} + d(t - t_i)^{1/16}
\]  

(21)
Figure 23. Curve fit versus recorded extension values for Emcompress® collected during the 60 second hold region. The data collected at the start of the hold region is plotted in the upper right corner and proceeds diagonally with time.

This curve fitting procedure produces a continuous function that is consistent with the measured compressive extension values without the original granularity (Figure 22). There is also a good agreement between the actual and predicted extension values (Figure 23). These data suggest that the continuous function accurately describes the recorded data. It should be made clear that this function (Eq. (21)) was used strictly for its ability to fit the data for all materials and not because it has any physical significance.

The next step for determining the Indentation Creep SRS Exponent was to calculate hardness using the relationship presented in Eq. (13). Hardness, $H(t)$, is determined by dividing the applied load, or force, by the area over which that force is...
being distributed. Under the experimental conditions used in this dissertation, the
definition of hardness is based on the contact area under load. This deviates slightly from
the traditional hardness measurement that uses residual contact area, but by using this
approach the time-dependency of hardness could be assessed. As mentioned previously, a
Vickers diamond-pyramid tip indenter (Figure 24) [109] was used for all indentation
creep experiments.

![Diagram of Vickers diamond-pyramid tip indenter geometry and area of indentation](image)

Figure 24. Vickers diamond-pyramid tip indenter geometry and area of indentation
(Re-printed with permission from the publisher [109])

Area of contact was determined from the inherent geometry of the indenter tip
and the indenter depth, \( h_p \), as the indenter penetrated the surface. For the Vickers
diamond-pyramid geometry, area of contact ($A$) was calculated according to Eq. (22) [109]:

$$A = 4h_p^2 \tan^2 68^\circ$$  \hspace{1cm} (22)

which reduces to Eq. (23):

$$A = 24.504h_p^2$$  \hspace{1cm} (23)

An example indentation hardness versus time profile for Lycatab\textsuperscript{®} PGS is provided in Figure 25 to illustrate the relationship between these variables.

Figure 25. Indentation hardness versus time profile for Lycatab\textsuperscript{®} PGS collected during the 60 second hold region.
Indentation hardness decreases as a function of hold time because the projected area of the indentation is increasing as the indenter tip further penetrates the sample. Inherently, the test method is designed to test under constant stress conditions. As the projected area of the indentation increases, calculated hardness values decrease due to progressively dividing by a larger area (Eq. (13)).

Indentation strain rate was calculated by solving Eq. (14) at each time point. The \( \frac{dh}{dt} \) values were determined by computing the instantaneous rate of change of the polynomial function (Eq. (21)) fit to the extension versus time data. A typical plot of indentation strain rate versus time for Lycatab\textsuperscript{®} PGS is provided in Figure 26.

![Figure 26. Indentation strain rate versus time profile for Lycatab\textsuperscript{®} PGS collected during the 60 second hold region](image)
It was observed, for all materials, that there was an initial transient region where the calculated indentation strain rate increased. This was followed by the anticipated decrease as the indenter further penetrated the sample. Upon further investigation of the data, it was determined that this occurrence was an artifact in the data analysis routine rather than a physical phenomenon. During the curve fitting procedure, it was noticed that the curve fit function (Eq. (21)) did not describe the data properly in the beginning part of the hold region. Figure 27, below, provides an expanded view of the recorded and curve fit data plotted previously in Figure 22.

Figure 27. Curve fit function (---) overlaid with recorded data (◊) for Emcompress® collected during the 60 second hold region. Zoomed in to capture behavior during the start of the hold region.
It was apparent that the curve fit extension values initially increased \( (i.e., \text{became less negative}), \) rather than decreasing according to the recorded data. This behavior can be used to explain the initial increase in indentation strain rate observed in Figure 26. Subsequently, the natural logarithm of hardness versus natural logarithm of strain rate profile also exhibited uncharacteristic behavior in the data recorded at the start of the hold region. For example, the plot for Lycatab\textsuperscript{®} PGS is shown in Figure 28. The entirety of the hold region data has been plotted.

![Graph showing ln(H) vs ln(\dot{\epsilon}_H) for Lycatab\textsuperscript{®} PGS. Entire hold region data has been plotted.](image)

Figure 28. \( \ln(H) \) vs. \( \ln(\dot{\epsilon}_H) \) profile for Lycatab\textsuperscript{®} PGS. Entire hold region data has been plotted.

Beyond the transient region, linear relationships between the transformed values of hardness and strain rate were observed. For each indentation, the data points
corresponding to positive changes in indentation strain rate were not included in the analysis. A representative set of the final data used to determine the Indentation Creep SRS Exponent for Lycatab® PGS are plotted in Figure 29. The hold region data, excluding the transient region, have been plotted.

![Graph](image)

Figure 29. In ($H$) vs. In ($\dot{\varepsilon}_H$) profile for Lycatab® PGS exclusive of the transient region data

Linear regression was utilized to find the rate of change in hardness with respect to unit changes in strain rate. Higher indentation creep slope values were interpreted to represent materials whose plastic deformation was more sensitive to the rate of deformation. Conversely, smaller slope values indicated that a material’s irreversible deformation was not significantly affected by strain rate changes. Standard deviation of
the slope is reported throughout this dissertation representing variation between replicate indentations on the surface of the same tablet.

### 3.1.3.2 $\Delta SF_{\text{final}}$

$\Delta SF_{\text{final}}$ values were determined from the solid fraction data correction methods presented in detail in Appendix A. In the data presented in Appendix A, the maximum applied pressure used to determine $\Delta SF_{\text{final}}$ was 264 MPa. However, it is important to note that the $\Delta SF_{\text{final}}$ designation does not necessarily always correspond to tablets compressed to a maximum pressure of 264 MPa. When the correction method was applied moving forward, $\Delta SF_{\text{final}}$ simply applies to the maximum pressure used to form any tablet, even if that pressure changes between materials. Viscoelastic recovery can be assessed from any level of applied pressure. For consistency, the change in solid fraction due to viscoelastic recovery from the maximum applied pressure will still be termed $\Delta SF_{\text{final}}$ even though a maximum applied pressure of 264 MPa was not always used. $\Delta SF_{\text{final}}$ values ($n = 6$) in this chapter correspond to the maximum applied pressure used to compact each material at 0.04 mm/s to a consistent porosity of $20 \pm 2\%$. Those applied pressures are reported in Table 13.

The difference between $SF_{c/d}$, or the elasticity corrected solid fraction, and the measured out-of-die solid fraction can be attributed to recovery that occurs after decompression. These differences are presented in Figure 30 for all materials studied in the original work describing this method.
Figure 30. Viscoelastic recovery versus pressure profiles for Lycatab® PGS (□), Avicel® PH200 (◊), Lactose 316 (○), and Emcompress® (✖). $\Delta S_F^{\text{final}}$ values are labeled.

It is evident that the amount of viscoelastic recovery observed in these data is not significantly dependent on applied pressure. Using the difference in solid fraction observed at the highest pressure ($\Delta S_F^{\text{final}}$), the $S_F^{c/d}$ data can be corrected for changes associated with time-dependent reversible deformation. Average $\Delta S_F^{\text{final}}$ values for each material can be found in Table 10, on the following page. The $S_F^{c/d}$ and out-of-die solid fraction values, from which $\Delta S_F^{\text{final}}$ is calculated, have also been provided.
### Table 10. Summary of reversible and time-dependent deformation data

<table>
<thead>
<tr>
<th>Material</th>
<th>$SF_{c/d}^a$</th>
<th>Out-of-die SF</th>
<th>$\Delta SF_{final}^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-gelatinized maize starch (Lycatab® PGS)</td>
<td>0.939 (0.002)</td>
<td>0.824 (0.006)</td>
<td>0.1163 (3E-04)</td>
</tr>
<tr>
<td>Microcrystalline cellulose (Avicel® PH 200)</td>
<td>0.938 (0.002)</td>
<td>0.899 (0.005)</td>
<td>0.0410 (3E-05)</td>
</tr>
<tr>
<td>Spray-dried lactose 316 Grade</td>
<td>0.890 (0.002)</td>
<td>0.887 (0.007)</td>
<td>0.0028 (1E-05)</td>
</tr>
<tr>
<td>Dibasic calcium phosphate dihydrate (Emcompress®)</td>
<td>0.813 (0.001)</td>
<td>0.824 (0.001)</td>
<td>-0.0136 (2E-06)</td>
</tr>
</tbody>
</table>

$^a$Average and standard deviation of three replicate tablets compressed to 264 MPa

Positive values of $\Delta SF_{final}$ indicate that the solid fraction decreased after being ejected from the die. As expected, the $\Delta SF_{final}$ value for Lycatab® PGS is the largest because of its viscoelastic nature. Those materials that experience a large reduction in solid fraction due to radial and axial expansion of the tablet dimensions will characteristically have large $\Delta SF_{final}$ values. Conversely, Emcompress® and lactose 316 show virtually no viscoelastic recovery, post-ejection, so it is expected to see $\Delta SF_{final}$ values close to zero. The solid fraction curves for lactose 316 are plotted in Figure 31, on the following page.
As expected, the $SF_{c/d}$, $SF_{corrected}$, and out-of-die solid fraction curves for this material are virtually superimposable. Since the ejected tablets do not show extensive recovery, the measured out-of-die solid fraction was nearly identical to the elasticity corrected data. The reported error associated with average $\Delta SF_{final}$ values reported throughout this chapter represents the variation in viscoelastic recovery between replicate tablets.

### 3.1.3.3 Heckel-Based SRS Index

Raw data outputs for the slow (0.04 mm/s) and fast (4 mm/s) compaction studies included: time (s), load (N), and extension (mm). Since the yield pressures in Eq. (11) are
in-die values, proper corrections for machine part deformation were required for accurate measurement of powder bed height. This correction was performed according to the methods presented previously in Chapter 2 Section 2.1.2.5. Using the corrected punch separation data, in-die solid fraction was calculated according to Eq. (17), where $t$ is the thickness of the powder bed rather than the thickness of an ejected tablet.

An example in-die solid fraction versus compaction pressure profile for Emcompress® compacted at 4 mm/s is provided in Figure 32 to illustrate the relationship between these variables.

![Figure 32. In-die solid fraction versus pressure profile for Emcompress® compacted at 4 mm/s](image-url)
Solid fraction was converted to porosity using Eq. (7) provided in Chapter 1 and was plotted as a function of compaction pressure in Figure 33. Provided the relationship between porosity and solid fraction, it makes sense that porosity, or pore space, decreases as pressure increases. Powder particles are brought into increasingly closer contact decreasing the space between them.

Figure 33. In-die porosity versus pressure profile for Emcompress® compacted at 4 mm/s

In order to calculate mean yield pressure, porosity-pressure data were transformed by taking the negative natural logarithm of porosity (Eq.(8)). An in-die Heckel profile for Emcompress® is provided in Figure 34, on the following page.
The next step was to determine the appropriate linear range in Figure 34 for calculating mean yield pressure. Several methods for determining the linear range exist in the literature and are used often \([12,110]\). While no single method is universally utilized, the reproducibility of the result is certainly a function of the consistency of the analysis. For that reason, Heckel data in this work were considered linear when the first derivative showed less than 15 \% variation. In order to compare yield pressure values, the same pressure range that was determined for the tablets compacted at 0.04 mm/s was used for the tablets prepared at 4 mm/s. Values of mean yield pressure were obtained for each replicate tablet compressed at the speed of interest. To calculate the Heckel-Based SRS...
Index, mean yield pressure values for both speeds were used with Eq. (11), and the percentage change was computed.

The error associated with this measurement was determined by propagating the uncertainties of the slow and fast mean yield pressures. Each numerical operation in Eq. (11) has an uncertainty associated with its value. The equation used to calculate each uncertainty is presented in Eq. (18) for the subtraction of $P_{y1}$ from $P_{y2}$, and in Eq. (19) for the division of this difference by $P_{y2}$:

$$\sigma_{(\bar{P}_{y2}-\bar{P}_{y1})} = \sqrt{(\sigma_{P_{y2}})^2 + (\sigma_{P_{y1}})^2}$$ \hspace{1cm} (18)$$

$$\sigma_{\frac{P_{y2}-P_{y1}}{P_{y2}}} = \sqrt{\left(\frac{\sigma_{P_{y2}-P_{y1}}}{P_{y2}-P_{y1}}\right)^2 + \left(\frac{\sigma_{P_{y2}}}{P_{y2}}\right)^2}$$ \hspace{1cm} (19)$$

where, for example, $\bar{P}_{y2}$ corresponds to the average mean yield pressure for tablets compressed at 4 mm/s, and $\sigma_{P_{y2}}$ indicates the standard deviation of mean yield pressure at the same speed.

3.2 Results and Discussion

3.2.1 Raw Material Characterization

Summarized data for powder true density and moisture content for all six excipients is provided in Table 11, on the following page.
Table 11. Individual component true density and moisture content values

<table>
<thead>
<tr>
<th>Formulation’s Primary Ingredient</th>
<th>True density</th>
<th>% Moisture&lt;sup&gt;a&lt;/sup&gt; (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-gelatinized maize starch (Lycatab&lt;sup&gt;®&lt;/sup&gt; PGS)</td>
<td>1.458 (0.004)</td>
<td>8.408 (0.066)</td>
</tr>
<tr>
<td>Partially pre-gelatinized corn starch (Starch 1500&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>1.493 (0.003)</td>
<td>8.486 (0.077)</td>
</tr>
<tr>
<td>Microcrystalline cellulose (Avicel&lt;sup&gt;®&lt;/sup&gt; PH 200)</td>
<td>1.550 (0.004)</td>
<td>5.672 (0.040)</td>
</tr>
<tr>
<td>Spray-dried lactose 316 Grade</td>
<td>1.531 (0.005)</td>
<td>0.360 (0.066)</td>
</tr>
<tr>
<td>Anhydrous lactose 120 MS</td>
<td>1.549 (0.005)</td>
<td>0.090 (0.031)</td>
</tr>
<tr>
<td>Dibasic calcium phosphate dihydrate (Emcompress&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>2.301 (0.002)</td>
<td>3.130 (0.058)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Loss on drying

As before, true density values for each formulation were determined from the true density of the individual materials according to the weight fraction of each component. Particle size distribution, given as percent undersize for each of the six materials is listed in Table 12, on the following page.
Table 12. Individual component particle size distribution determined by sieve analysis

<table>
<thead>
<tr>
<th>Material</th>
<th>&lt;53 μm</th>
<th>&lt;75 μm</th>
<th>&lt;125 μm</th>
<th>&lt;180 μm</th>
<th>&lt;250 μm</th>
<th>&lt;500 μm</th>
<th>&lt;1000 μm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-gelatinized maize starch (Lycatab® PGS)</td>
<td>22.8</td>
<td>22.8</td>
<td>27.7</td>
<td>49.8</td>
<td>77.8</td>
<td>95.0</td>
<td>99.9</td>
</tr>
<tr>
<td>Partially pre-gelatinized corn starch (Starch 1500®)</td>
<td>43.8</td>
<td>43.8</td>
<td>48.5</td>
<td>87.9</td>
<td>98.5</td>
<td>99.8</td>
<td>99.8</td>
</tr>
<tr>
<td>Microcrystalline cellulose (Avicel® PH 200)</td>
<td>7.2</td>
<td>7.2</td>
<td>8.9</td>
<td>18.5</td>
<td>32.7</td>
<td>60.3</td>
<td>100.0</td>
</tr>
<tr>
<td>Spray-dried lactose 316 Grade</td>
<td>8.8</td>
<td>8.9</td>
<td>13.9</td>
<td>47.6</td>
<td>90.0</td>
<td>99.9</td>
<td>99.9</td>
</tr>
<tr>
<td>anhydrous lactose 120 MS</td>
<td>4.7</td>
<td>4.7</td>
<td>7.6</td>
<td>66.6</td>
<td>89.5</td>
<td>98.7</td>
<td>99.9</td>
</tr>
<tr>
<td>Dibasic calcium phosphate dihydrate (Emcompress®)</td>
<td>1.0</td>
<td>1.0</td>
<td>2.4</td>
<td>14.3</td>
<td>29.8</td>
<td>84.9</td>
<td>98.1</td>
</tr>
</tbody>
</table>

Reported values for the Indentation Creep SRS Exponent and $\Delta S_F^{final}$ represent data collected on tablets ($n = 6$) compressed at 0.04 mm/s. Additional tablets ($n = 3$) were compressed at 4 mm/s in order to derive the mean yield pressure at fast speed for computing the Heckel-Based SRS Index. Maximum compaction pressures and average out-of-die porosities for each individual component are reported in Table 13.
Table 13. Individual component out-of-die porosity values (0.04 mm/s)

<table>
<thead>
<tr>
<th>Individual Component</th>
<th>Maximum Compaction Pressure (MPa)</th>
<th>Out-of-die Porosity (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-gelatinized maize starch (Lycatab® PGS)</td>
<td>226.0</td>
<td>0.188 (0.002)</td>
</tr>
<tr>
<td>Partially pre-gelatinized corn starch (Starch 1500®)</td>
<td>105.5</td>
<td>0.196 (0.001)</td>
</tr>
<tr>
<td>Microcrystalline cellulose (Avicel® PH 200)</td>
<td>97.9</td>
<td>0.188 (0.006)</td>
</tr>
<tr>
<td>Spray-dried lactose 316 Grade</td>
<td>105.5</td>
<td>0.195 (0.002)</td>
</tr>
<tr>
<td>Anhydrous lactose 120 MS</td>
<td>75.3</td>
<td>0.197 (0.006)</td>
</tr>
<tr>
<td>Dibasic calcium phosphate dihydrate (Emcompress®)</td>
<td>226.0</td>
<td>0.186 (0.002)</td>
</tr>
</tbody>
</table>

3.2.2 Indentation Creep SRS Exponent

Creep behavior describes the tendency of materials to exhibit continuing deformation under constant stress conditions [111]. Displacement values recorded at each time increment are due to the creep properties of the material. This behavior was confirmed by examining the extent of creep displacement for Lycatab® PGS, Avicel® PH 200, and Emcompress® under constant load. These data are plotted in Figure 35, provided on the following page.
Figure 35. Displacement versus time profiles for Lycatab® PGS (◊), Avicel® PH200 (Δ) and Emcompress® (□) collected during the 60 second hold region

During the 60 s hold time, the indenter tip penetrates the compact’s surface as particles creep into empty pores beneath the indenter. Materials that deform via a plastic deformation mechanism, Lycatab® PGS and Avicel® PH200 for example, showed greater creep compared to a brittle material, such as Emcompress®. During the hold period, Lycatab® PGS showed the largest average displacement of the materials studied, creeping 0.014 mm. In comparison, Emcompress® showed an order of magnitude less average creep during indentation. The indentation creep data were used in this work to evaluate time-dependent plasticity, or viscoplasticity. Materials will exhibit a time-dependent mechanical response depending on the predominant mode by which it deforms. These data not only offer the ability to differentiate brittle materials from plastic materials, but
also offer the ability to see differences between materials with the same predominating deformation mechanism.

Figures 36-38 provide example plots of the natural logarithm of hardness \((H)\) as a function of the natural logarithm of strain rate \((\dot{\varepsilon}_H)\) for three of the six materials studied. The material showing the most creep (Lycatab® PGS), a material showing intermediate creep behavior (Avicel® PH200), and the material which showed minimal creep (Emcompress®), have been selected. These materials also correspond to the same three materials studied on the compaction simulator in Chapter 2. Linear regression lines were fit to the data, and the Indentation Creep SRS Exponent is emphasized in bold.

![Figure 36. ln (H) vs. ln (\dot{\varepsilon}_H) profile for Lycatab® PGS](image-url)

\[ y = 0.0548x + 2.6148 \]
\[ R^2 = 0.9999 \]
Figure 37. $\ln (H)$ vs. $\ln (\dot{\varepsilon}_H)$ profile for Avicel® PH200

Figure 38. $\ln (H)$ vs. $\ln (\dot{\varepsilon}_H)$ profile for Emcompress®

y = 0.0288x + 3.5375
$R^2 = 0.9994$

y = 0.0167x + 4.2361
$R^2 = 0.9959$
After transitioning from loading the indenter to holding the constant load, the relationship between hardness and strain rate became consistent. Beyond the transient region, linear relationships between the transformed values of hardness and strain rate were generally observed. The strain rates observed during the indentation creep studies are controlled by the materials themselves, depending directly on the material’s ability to deform. In this work, the ranges of strain rates were consistent, allowing for comparison of time-dependent plasticity between materials.

Table 14 provides a summary of the indentation creep results for all materials studied. The table contains the Indentation Creep SRS Exponent used to evaluate time-dependent plasticity and the average hardness values at the start of the hold region.

<table>
<thead>
<tr>
<th>Material</th>
<th>Indentation Creep SRS Exponent (S.D.)</th>
<th>Hardness at Start of Hold Region (MPa) (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-gelatinized maize starch (Lycatab® PGS)</td>
<td>0.052 (0.006)</td>
<td>12.3 (1.1)</td>
</tr>
<tr>
<td>Partially pre-gelatinized corn starch (Starch 1500®)</td>
<td>0.039 (0.003)</td>
<td>22.4 (2.4)</td>
</tr>
<tr>
<td>Microcrystalline cellulose (Avicel® PH 200)</td>
<td>0.028 (0.002)</td>
<td>24.2 (3.1)</td>
</tr>
<tr>
<td>Anhydrous lactose 120 MS</td>
<td>0.026 (0.003)</td>
<td>36.0 (6.4)</td>
</tr>
<tr>
<td>Spray-dried lactose 316 Grade</td>
<td>0.019 (0.002)</td>
<td>35.8 (5.3)</td>
</tr>
<tr>
<td>Dibasic calcium phosphate dihydrate (Emcompress®)</td>
<td>0.016 (0.002)</td>
<td>53.7 (8.3)</td>
</tr>
</tbody>
</table>
Reported error reflects the standard deviation of 15 indentations made on 3 different tablets (n = 5 per tablet). Prior to comparing the average Indentation Creep SRS Exponent values, an $F$-test [112] was applied to assess the equality of variance between materials. For the $F$-test, the null hypothesis was that the variances (standard deviation squared) were equal; the alternative being that they were unequal. All $F$-test’s were performed at a significance level of $\alpha = 0.05$. The outcome of the $F$-test dictated the test statistic equation that would be used in the subsequent $t$-test comparing means.

Figure 39 provides a summary of the statistical comparisons. The data is presented in matrix form and materials are listed in order of decreasing exponent value. Bolded cells in the matrix represent the $F$-test comparisons that rejected the null hypothesis of equal variance.

<table>
<thead>
<tr>
<th></th>
<th>Lycatab® PGS</th>
<th>Starch 1500®</th>
<th>Avicel® PH 200</th>
<th>anhydrous lactose</th>
<th>lactose 316</th>
<th>Emcompress®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lycatab® PGS</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starch 1500®</td>
<td>YES</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avicel® PH 200</td>
<td>YES</td>
<td>YES</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>anhydrous lactose</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>lactose 316</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Emcompress®</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>x</td>
</tr>
</tbody>
</table>

Figure 39. Statistical summary matrix: Indentation Creep SRS Exponent. Green ‘YES’ boxes indicate statistically significant differences, and Red ‘NO’ boxes indicate statistical equivalence. Bolded cells indicate the comparisons that had unequal variance.
Statistically significant differences for the $t$-test [112] are represented by the green colored boxes in the matrix. Since multiple comparisons were made, a Bonferroni correction [113] was applied to adjust the critical $P$ value ($\alpha$). The original significance level, $\alpha = 0.05$, was divided by the number of comparisons ($n = 15$) to obtain the new critical $P$ value. The rank order of the materials from highest to lowest viscoplasticity was: Lycatab® PGS, Starch® 1500, Avicel® PH 200, Anydrous lactose, lactose 316, and Emcompress®. The values for the Indentation Creep SRS Exponent ranged from 0.016 for Emcompress® to 0.052 for Lycatab® PGS (Table 14). Larger SRS Exponent values indicate larger amounts of time-dependent plastic deformation, or viscoplasticity.

It is commonly accepted that plastically deforming materials tend to be more sensitive to strain rate than brittle materials. Plastic particles are able to flow into void spaces; increasing particle-particle contact and relieving local stress. The strain associated with plastic deformation is time-dependent based on how fast the particles can flow. On the other hand, predominantly brittle particles fragment into smaller pieces that then repack themselves into a more dense arrangement. As fragmentation is typically very rapid, brittle materials will register very little change in strain after the beginning of the hold period.

In addition to differentiating between brittle and plastic materials, the indentation creep method can also differentiate between materials having the same predominating deformation behavior. Take, for example, the comparison of Lycatab® PGS with Avicel® PH200. Out-of-Die Heckel Slope values, determined according to the methods presented in Appendix A, were used to identify a materials predominant deformation behavior. The
average Out-of-Die Heckel Slopes for Lycatab® PGS and Avicel® PH200 are provided in Table 15.

Table 15. Average Out-of-Die Heckel Slope Values derived from in-die data

<table>
<thead>
<tr>
<th>Material</th>
<th>Out-of-Die Heckel Slope (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-gelatinized maize starch (Lycatab® PGS)</td>
<td>0.0111 (0.0004)</td>
</tr>
<tr>
<td>Microcrystalline cellulose (Avicel® PH 200)</td>
<td>0.0111 (0.0006)</td>
</tr>
</tbody>
</table>

Of the materials tested, these two had the highest measured Out-of-Die Heckel Slopes derived from in-die data. Larger slopes signify a greater reduction in porosity with pressure and are observed for materials whose deformation is dominated by plastic flow. The irreversible deformation behavior of these two materials is the same, both being highly plastic. However, when comparing the indentation creep data (Table 14), the plastic behavior of Lycatab® PGS was much more strain rate sensitive. Lycatab® PGS had an average Indentation Creep SRS Exponent of 0.052, nearly double the average slope of Avicel® PH 200 which was measured at 0.028. This difference suggests that although Avicel® PH200 is characterized as being highly plastic, that behavior is not nearly as affected by strain rate changes as is the plasticity of Lycatab® PGS. Subtle differences between materials can be identified using the indentation creep method.

In the practical sense, the ability to pinpoint differences in time-dependent plasticity between materials with the same predominating deformation mechanism is of significant value. While the common perception is that a highly plastic material will
require additional time for its particles to flow under higher speed compaction conditions, the degree to which that behavior is sensitive can vary. If it is observed that a plastic material is not highly strain rate sensitive, it is less likely for that material to behave differently upon scale-up.

3.2.3 $\Delta SF_{\text{final}}$

In addition to assessing the time-dependent permanent deformation tendencies of a material, it is equally important to understand how the compacted particles behave post-compaction. Elastic deformation is characterized by the storage and release of applied stresses upon decompression. For some materials the extent of elastic strain is recovered immediately, but for others this process is time-dependent. All pharmaceutical materials are considered to be viscoelastic, but to varying degrees [41]. A highly viscoelastic material will deform extensively over time as the dimensions of the tablet increase in both the axial and radial directions.

Viscoelastic tendency of each material was assessed by computing the change in solid fraction of a tablet over time. Briefly, $\Delta SF_{\text{final}}$ values represent the difference between the maximum elasticity corrected solid fraction, $SF_{c/d}$, and the out-of-die solid fraction measured from the same tablet [114,115]. $\Delta SF_{\text{final}}$ is an empirical parameter that captures the extent to which a material displays time-dependent reversible deformation during storage, post-ejection. A large positive value indicates that a larger reduction in solid fraction is experienced over time as the tablet recovers. Values close to zero are interpreted as the dimensions of the tablet in the die after decompression being nearly
equivalent to the dimensions of the tablet once it has been ejected and allowed to recover over time. The summary results for $\Delta S_F_{final}$ are presented in Figure 40.

![Bar chart showing $\Delta S_F_{final}$ values for different materials]

Figure 40. Individual component $\Delta S_F_{final}$ values. Data bars represent average values (n = 6) and associated error bars represent standard deviation.

$\Delta S_F_{final}$ values ranged from 0.120 for Lycatab® PGS to 0.001 for anhydrous lactose and Emcompress®. The error reported for average $\Delta S_F_{final}$ values reflect the standard deviation of six replicate tablets. As before, equality of variance was assessed using an $F$-Test prior to a $t$-Test comparing the average $\Delta S_F_{final}$ values. The same statistical testing procedures, presented in detail in Section 3.2.2, were used to compare $\Delta S_F_{final}$ data. Figure 41 provides a summary of the statistical comparisons. Materials are
listed in descending order of average $\Delta S_{F_{\text{final}}}$ value. Bolded cells in the matrix represent the $F$-test comparisons that rejected the null hypothesis of equal variance.

<table>
<thead>
<tr>
<th></th>
<th>Lycatab® PGS</th>
<th>Starch 1500®</th>
<th>Avicel® PH 200</th>
<th>lactose 316</th>
<th>anhydrous lactose</th>
<th>Emcompress®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lycatab® PGS</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starch 1500®</td>
<td>YES</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avicel® PH 200</td>
<td>YES</td>
<td>YES</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lactose 316</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>anhydrous lactose</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Emcompress®</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>x</td>
</tr>
</tbody>
</table>

Figure 41. Statistical summary matrix: $\Delta S_{F_{\text{final}}}$. Green ‘YES’ boxes indicate statistically significant differences, and Red ‘NO’ boxes indicate statistical equivalence. Bolded cells indicate the comparisons that had unequal variance.

Significant differences (green boxes) in $\Delta S_{F_{\text{final}}}$ were observed for all comparisons except Avicel® PH 200 compared to lactose 316 and anhydrous lactose compared to Emcompress® (red boxes). Since both anhydrous lactose and Emcompress® show virtually no viscoelastic recovery it was not unexpected to see their values be statistically similar. Both starches, Lycatab® PGS and Starch 1500®, where the most viscoelastic which corresponds to previously published reports on these materials [9,44,84,106]. Therefore, the rank order of viscoelastic-tendency is: Lycatab® PGS, Starch® 1500, Avicel® PH 200/lactose 316, and anhydrous lactose/Emcompress®.
A material’s strain rate sensitivity can be due to changes in viscoelasticity or due to changes in viscoplasticity at different speeds. Therefore, there exists a need to characterize the sensitivity of both irreversible and reversible deformation. \( \Delta S_{F_{final}} \) values offer the potential to assess changes in viscoelastic behavior that correspond to changes in tablet press speed. In other words, the larger \( \Delta S_{F_{final}} \), the more strain rate sensitive a material’s reversible deformation is.

From a characterization prospective, utilizing methods that can differentiate between the specific mechanical behaviors that contribute to a material’s strain rate sensitivity is imperative. A more comprehensive understanding of time-dependent deformation can be obtained using methods that are more specific. Due to the complexity of strain rate sensitivity, it is not enough to simply classify a material or formulation as being strain rate sensitive, or not. Identifying the mechanical behaviors that contribute to observed sensitivity will lead to more informed decisions during formulation development.

### 3.2.4 Heckel-Based SRS Index

A material’s strain rate sensitivity can be due to changes in viscoplasticity, viscoelasticity, or both as the tablet press speed used to prepare that material changes. The individual parameters presented in Sections 3.2.2 and 3.2.3 can be used to identify the contributing behavior, or behaviors. What these parameters don’t account for is how those behaviors manifest during preparation of a tablet at a slow speed compared to preparation of the same material at high speed. As a result, additional strain rate sensitivity characterization included evaluating material densification behavior during
compaction at two different tablet press speeds. Roberts and Rowe developed the Heckel-Based SRS Index as a method for material comparison and as a tool to improve understanding of the effects of strain rate on deformation.

The densification behavior of two materials, one that is strain rate sensitive and one that is insensitive are shown in Figures 42 and 43, respectively. The figure legend represents the linear compaction speed used to form those tablets.

Figure 42. In-die Heckel plots for Starch 1500\textsuperscript{®} compacted at 0.04 mm/s (—) and 4 mm/s (—)
Both materials exhibit a reduction in porosity as compaction pressure is increased. The deformation behavior of Starch 1500®, whose irreversible deformation is predominantly plastic, was affected by press speed changes. At slower speed (0.04 mm/s) Starch 1500® consolidated to a greater extent as more time was allowed for deformation to occur. Conversely, Emcompress® is a brittle material whose extent of deformation was not affected by compaction speed. Deformation occurs by fragmentation of the original particles into smaller, discrete units that pack together more densely. Fragmentation occurs rapidly and is not significantly affected by the amount of time over which pressure is applied. Therefore, density-pressure behavior of a brittle material will remain consistent as the compression speed changes.

Figure 43. In-die Heckel plots for Emcompress® compacted at 0.04 mm/s (—) and 4 mm/s (—)
Table 16 provides a summary of the Heckel analysis results for each material tested. The table contains the upper and lower pressure values corresponding to the linear range, the mean yield pressure determined at both slow and fast speeds and the Heckel-Based SRS Index derived from the mean yield pressure values.

Table 16. Individual component summary of Heckel analysis results

<table>
<thead>
<tr>
<th>Material</th>
<th>(Lower – Upper) Pressure (MPa)</th>
<th>0.04 mm/s</th>
<th>4 mm/s</th>
<th>Heckel-Based SRS Index (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-gelatinized maize starch (Lycatab® PGS)</td>
<td>75-125</td>
<td>43.0 (1.7)</td>
<td>49.7 (1.3)</td>
<td>13.5 (3.4)</td>
</tr>
<tr>
<td>Partially pre-gelatinized corn starch (Starch 1500®)</td>
<td>15-60</td>
<td>51.9 (1.7)</td>
<td>68.0 (1.0)</td>
<td>23.6 (2.5)</td>
</tr>
<tr>
<td>Microcrystalline cellulose (Avicel® PH 200)</td>
<td>35-80</td>
<td>51.6 (1.2)</td>
<td>57.1 (1.5)</td>
<td>9.6 (4.0)</td>
</tr>
<tr>
<td>Spray-dried lactose 316 Grade</td>
<td>40-100</td>
<td>75.7 (1.8)</td>
<td>81.5 (1.5)</td>
<td>7.1 (3.5)</td>
</tr>
<tr>
<td>anhydrous lactose 120 MS</td>
<td>30-75</td>
<td>86.3 (2.0)</td>
<td>88.2 (2.2)</td>
<td>3.4 (2.2)</td>
</tr>
<tr>
<td>Dibasic calcium phosphate dihydrate (Emcompress®)</td>
<td>125-200</td>
<td>349.9 (5.4)</td>
<td>345.0 (6.6)</td>
<td>--</td>
</tr>
</tbody>
</table>

The materials ranged in strain rate sensitivity from ~0 % for Emcompress® to 23.6 % for Starch 1500®. Standard deviation reported for the mean yield pressures reflects the variation between three tablets compacted at each speed. Error reported for the Heckel-Based SRS Index reflects the propagated uncertainty of the slow and fast mean yield pressures.
Equality of variance was assessed using an \(F\)-Test prior to a \(t\)-Test comparing the average Heckel-Based SRS Index values between materials. Statistical significance testing was performed using the same methods presented for similar tests in Section 3.2.2. Figure 44 provides a summary of the statistical comparisons. The data is presented in matrix form and materials are listed in order from largest to smallest Heckel-Based SRS Index. Bolded cells in the matrix represent the \(F\)-test comparisons that rejected the null hypothesis of equal variance.

<table>
<thead>
<tr>
<th></th>
<th>Starch 1500\textsuperscript{®}</th>
<th>Lycatab\textsuperscript{®} PGS</th>
<th>Avicel\textsuperscript{®} PH 200</th>
<th>lactose 316</th>
<th>anhydrous lactose</th>
<th>Emcompress\textsuperscript{®}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starch 1500\textsuperscript{®}</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lycatab\textsuperscript{®} PGS</td>
<td>LEGEND</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avicel\textsuperscript{®} PH 200</td>
<td>YES</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lactose 316</td>
<td>YES</td>
<td>NO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anhydrous lactose</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Emcompress\textsuperscript{®}</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>

Figure 44. Statistical summary matrix: Heckel-Based SRS Index. Green ‘YES’ boxes indicate statistically significant differences, and Red ‘NO’ boxes indicate statistical equivalence. Bolded cells indicate the comparisons that had unequal variance.

The Heckel-Based SRS Index value for Starch 1500\textsuperscript{®} was statistically different (green boxes) than all other materials tested. Several non-significant differences were observed (red boxes). Experimental error reported for this index seems to be responsible for the statistically insignificant differences between materials. Large errors result from the propagated uncertainty of mean yield pressure values (Eq. (18 and 19)). As a result, a
fairly large compression speed difference is required to differentiate between materials. A 100-fold increase in speed was used in this work (0.04 mm/s – 4 mm/s), which is significantly less than the nearly 10,000-fold increase used in the original studies describing this index [9]. Therefore, a more dramatic compression speed difference would be needed to separate Heckel-Based SRS Index statistically, but the trend in the data still allows for analysis of material behavior.

The rank order of the materials from most sensitive to least sensitive was: Starch® 1500, Lycatab® PGS, Avicel® PH 200, lactose 316, Anydrous lactose, and Emcompress®. For the plastically deforming materials, Starch® 1500 and Lycatab® PGS, higher mean yield pressures were observed when the compaction speed was increased from 0.04 mm/s to 4 mm/s. Increased mean yield pressure values indicate an increased resistance to deformation at higher speed. As a result, the consolidation extent of these materials decreases. The yield pressures of the more brittle materials, anhydrous lactose and Emcompress® lead to insignificant Heckel-Based SRS Index values.

It is recognized that the in-die Heckel data used to compute the Heckel-Based SRS Index reflects particle deformation by both plastic and elastic mechanisms. Therefore, strain rate sensitivity values produced by this method do not distinguish between materials whose plastic deformation is strain rate sensitive and those whose elasticity is strain rate sensitive (i.e., non-specific). However, utilizing this method to measure strain rate sensitivity is still of value. This measurement can be used to identify how a material’s deformation behavior will change as a result of changes to tablet press speed. For a strain rate sensitive material, the parameter value provides a quantitative
measure of the reduction in consolidation exhibited by a material under high-speed conditions.

3.3 Summary

There exists a need to expand upon traditional characterization techniques. As such, the selection of parameters in this chapter was based on their ability to comprehensively describe the various aspects of strain rate sensitivity during powder compaction. In the simplest terms, the Heckel-Based SRS Index describes how a material or formulation behaves at different speeds, while the Indentation Creep SRS Exponent and $\Delta S_{f_{final}}$ describe why the material or formulation is behaving that way. In an effort to provide more specific data for evaluating strain rate sensitivity, parameters that describe viscoplasticity (Indentation Creep SRS Exponent) and viscoelasticity ($\Delta S_{f_{final}}$) have been introduced.

Materials used in this work were carefully selected since materials with a range of deformation behaviors were desired. It was thought that by having materials that ranged from highly brittle to highly plastic and/or viscoelastic (*i.e.*, Emcompress® to Lycatab® PGS), the range of observed strain rate sensitivities would capture the expected range for a much larger set of pharmaceutical powders. Table 17, on the following page, provides a summary of the rank ordered behavior for each of the three specific lab-scale measurements. Designations of ‘high’, ‘intermediate’, and ‘low’ in this summary table are subjective, but are based on the statistical significance between experimental values for that parameter.
Table 17. Individual component strain rate sensitive deformation behavior summary

<table>
<thead>
<tr>
<th>Individual Component</th>
<th>Indentation Creep SRS Exponent</th>
<th>$\Delta S_{final}$</th>
<th>Heckel-Based SRS Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-gelatinized maize starch (Lycatab® PGS)</td>
<td>High</td>
<td>High (0.120)</td>
<td>Intermediate (13.5)</td>
</tr>
<tr>
<td>Partially pre-gelatinized corn starch (Starch 1500®)</td>
<td>High</td>
<td>Intermediate (0.073)</td>
<td>High (23.6)</td>
</tr>
<tr>
<td>Microcrystalline cellulose (Avicel® PH 200)</td>
<td>Intermediate</td>
<td>Low (0.017)</td>
<td>Intermediate (9.6)</td>
</tr>
<tr>
<td>Spray-dried lactose 316 Grade</td>
<td>Low</td>
<td>Low (0.013)</td>
<td>Intermediate (7.1)</td>
</tr>
<tr>
<td>anhydrous lactose 120 MS</td>
<td>Intermediate</td>
<td>Low (0.001)</td>
<td>Intermediate (3.4)</td>
</tr>
<tr>
<td>Dibasic calcium phosphate dihydrate (Emcompress®)</td>
<td>Low</td>
<td>Low (0.001)</td>
<td>Low (--)</td>
</tr>
</tbody>
</table>

By convention, the materials that were more plastic and/or viscoelastic (i.e. Lycatab® PGS and Starch 1500®) were characterized as having sensitivity across all parameters. The behavior of Avicel® PH 200 was unique, particularly related to the strain rate sensitivity of its predominant deformation mechanism. Although this material was characterized as being highly plastic, its plasticity was only moderately sensitive according to the Indentation Creep SRS Exponent. In terms of the predominantly brittle materials that were tested, it was confirmed that their behavior was generally insensitive to speed. The lowest experimental values for each of the three parameters were measured for the lactose grades and Emcompress®.
Chapter 4: Multi-Component Strain Rate Sensitivity Evaluation of Individual Components and Simple Mixtures

The challenges faced during formulation development have been traditionally resolved by including a number of excipients which allow for large-scale manufacturing and provide proper functionality of the dosage form after production. Characterization data for single materials can be used to guide development studies towards an optimum formulation, but the process frequently relies on trial and error approaches. One reason for this is that knowledge of how individual material properties contribute to the behavior of a mixture is limited. Studying the compaction properties of a mixture is vital for improving the efficiency of formulation development.

With respect to strain rate sensitivity, the question that is most often asked during formulation studies is how to mitigate or diminish the sensitivity of the active ingredient? In cases where that component is present in a large percentage, it is reasonable to suspect that components behavior will significantly influence the behavior of the formulation. In these instances it is imperative to formulate such that the sensitivity of this material will not lead to tablet defects like capping and lamination during production.

In this chapter, the strain rate sensitivity of the excipients tested in Chapter 3 will be quantified. A composite evaluation of time-dependent deformation will be used to describe the mechanical behaviors that are contributing to the observed sensitivity. Additionally, a placebo excipient (Lycatab® PGS) was used to simulate the presence of a sensitive active ingredient in mixtures with excipients of varied deformation tendency. Mixture modeling will be used to predict how much strain rate sensitivity could be affected by adding a secondary component with specific sensitivity behaviors.
4.1 Experimental

4.1.1 Materials

The same individual components studied in Chapter 3 (Table 9) were further evaluated and analyzed in this chapter. Additionally, a set of 15 mixtures containing those excipients were tested. For each mixture the same base formulation containing an internally blended binder, glidant, and lubricant as presented in Chapter 2 was used (Table 3). In an attempt to limit the variability resulting from disparities in physical properties on the compaction behavior of these mixtures, all experimentation was carried out using powders with equivalent particle size ranges (180 - 250 μm) which were equilibrated at ambient temperature (~ 23 – 25 ºC) in a controlled relative humidity environment (saturated MgCl₂, ~ 32 – 33 % relative humidity [101]).

4.1.2 Data Collection

4.1.2.1 Raw Material Characterization

Each mixture was characterized for its true density and moisture content. True densities were determined by helium pycnometry (Model: SPY-6DC, Quantachrome Instruments, Boynton Beach, FL) and performed in triplicate for each mixture. 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 ºC and held isothermally until the rate of moisture loss was less than 0.1 %/min.
4.1.2.2 Tablet Compaction

Mixtures were prepared by blending powders in 5 g batches using a small-scale rotary mixer (Appropriate Technical Resources (ATR), Model # 10101). The blending protocol consisted of an initial 15 min blend period, followed by blending for an additional 2 min after addition of magnesium stearate. An Instron universal testing system (Model 5869, Instron Corporation, Norwood, MA) equipped with a 50 kN load cell was used to compact each mixture into tablets. Each tablet was prepared by weighing 500 mg of powder into a 13-mm stainless steel, cylindrical die. The measurement accuracy of the equipment used was within ± 0.5 % of the applied load and ± 0.02 mm of the recorded displacement.

A total of 10 tablets were prepared for each mixture. First, 1 single tablet for each mixture was compacted at 0.04 mm/s to a maximum pressure of 264 MPa. The in-die data from this compaction cycle was used to determine the approximate pressure needed to compact each mixture at 0.04 mm/s to an out-of-die porosity of 20 ± 2 %, post-relaxation. 6 additional tablets were then prepared by compacting each mixture to the identified pressure using a linear compaction speed of 0.04 mm/s (Table 19). With the remaining material, 3 additional tablets were compacted to the same maximum applied pressure used to prepare the tablets at 0.04 mm/s, instead using a linear compaction speed of 4 mm/s. It was observed that complete relaxation occurred within 7 to 10 days at which point the final dimensions of the tablet were measured with a digital caliper (Model CO 030150, Marathon).
4.1.3 Data Analysis

4.1.3.1 SRS<sub>factor</sub>

Multi-component characterization was performed using the replicate measurements for each of the three parameters presented in Chapter 3:

1. Indentation Creep SRS Exponent (n = 15)
2. ∆SF<sub>final</sub> (n = 6)
3. Heckel Based SRS Index (n = 3)

The numerical determination of SRS<sub>factor</sub> was performed using a two-step calculation. First, raw data for each parameter were min-max normalized according to Eq. (29):

\[ z_i = \frac{x_i - \min(x)}{\max(x) - \min(x)} \quad (29) \]

where \( x = (x_1, ..., x_n) \) and \( z_i \) was now the \( i^{th} \) normalized value. Second, the normalized values for each material were averaged using Eq. (30):

\[ SRS_{factor} = \frac{(z_1 + ... + z_n)}{3} \quad (30) \]

By convention larger values of SRS<sub>factor</sub> will be observed for individual components and mixtures whose behavior is predominantly viscoplastic and/or viscoelastic. The error reported for SRS<sub>factor</sub> was determined by propagating the percent uncertainty for each parameter.
4.2 Results and Discussion

4.2.1 Raw Material Characterization

Summarized data for powder true density and moisture content for all fifteen mixtures is provided in Table 18.

Table 18. Mixture true density and moisture content values

<table>
<thead>
<tr>
<th>Formulation’s Primary Ingredients (% w/w)</th>
<th>True density</th>
<th>% Moisture&lt;sup&gt;a&lt;/sup&gt; (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lycatab&lt;sup&gt;®&lt;/sup&gt; PGS (75 %) : Starch 1500&lt;sup&gt;®&lt;/sup&gt; (25 %)</td>
<td>1.467 (0.003)</td>
<td>8.412 (0.080)</td>
</tr>
<tr>
<td>Lycatab&lt;sup&gt;®&lt;/sup&gt; PGS (75 %) : Avicel&lt;sup&gt;®&lt;/sup&gt; PH 200&lt;sup&gt;®&lt;/sup&gt; (25 %)</td>
<td>1.481 (0.004)</td>
<td>7.713 (0.066)</td>
</tr>
<tr>
<td>Lycatab&lt;sup&gt;®&lt;/sup&gt; PGS (75 %) : lactose 316 (25 %)</td>
<td>1.477 (0.004)</td>
<td>6.216 (0.059)</td>
</tr>
<tr>
<td>Lycatab&lt;sup&gt;®&lt;/sup&gt; PGS (75 %) : anhydrous lactose (25 %)</td>
<td>1.481 (0.002)</td>
<td>6.137 (0.103)</td>
</tr>
<tr>
<td>Lycatab&lt;sup&gt;®&lt;/sup&gt; PGS (75 %) : Emcompress&lt;sup&gt;®&lt;/sup&gt; (25 %)</td>
<td>1.669 (0.005)</td>
<td>7.089 (0.114)</td>
</tr>
<tr>
<td>Lycatab&lt;sup&gt;®&lt;/sup&gt; PGS (50 %) : Starch 1500&lt;sup&gt;®&lt;/sup&gt; (50 %)</td>
<td>1.476 (0.002)</td>
<td>8.447 (0.238)</td>
</tr>
<tr>
<td>Lycatab&lt;sup&gt;®&lt;/sup&gt; PGS (50 %) : Avicel&lt;sup&gt;®&lt;/sup&gt; PH 200&lt;sup&gt;®&lt;/sup&gt; (50 %)</td>
<td>1.504 (0.003)</td>
<td>7.040 (0.061)</td>
</tr>
<tr>
<td>Lycatab&lt;sup&gt;®&lt;/sup&gt; PGS (50 %) : lactose 316 (50 %)</td>
<td>1.495 (0.004)</td>
<td>4.384 (0.091)</td>
</tr>
<tr>
<td>Lycatab&lt;sup&gt;®&lt;/sup&gt; PGS (50 %) : anhydrous lactose (50 %)</td>
<td>1.503 (0.003)</td>
<td>4.249 (0.101)</td>
</tr>
<tr>
<td>Lycatab&lt;sup&gt;®&lt;/sup&gt; PGS (50 %) : Emcompress&lt;sup&gt;®&lt;/sup&gt; (50 %)</td>
<td>1.880 (0.002)</td>
<td>5.769 (0.048)</td>
</tr>
<tr>
<td>Lycatab&lt;sup&gt;®&lt;/sup&gt; PGS (25 %) : Starch 1500&lt;sup&gt;®&lt;/sup&gt; (75 %)</td>
<td>1.484 (0.002)</td>
<td>8.469 (0.076)</td>
</tr>
<tr>
<td>Lycatab&lt;sup&gt;®&lt;/sup&gt; PGS (25 %) : Avicel&lt;sup&gt;®&lt;/sup&gt; PH 200&lt;sup&gt;®&lt;/sup&gt; (75 %)</td>
<td>1.527 (0.005)</td>
<td>6.349 (0.153)</td>
</tr>
<tr>
<td>Lycatab&lt;sup&gt;®&lt;/sup&gt; PGS (25 %) : lactose 316 (75 %)</td>
<td>1.513 (0.004)</td>
<td>2.087 (0.059)</td>
</tr>
<tr>
<td>Lycatab&lt;sup&gt;®&lt;/sup&gt; PGS (25 %) : anhydrous lactose (75 %)</td>
<td>1.526 (0.003)</td>
<td>1.876 (0.147)</td>
</tr>
<tr>
<td>Lycatab&lt;sup&gt;®&lt;/sup&gt; PGS (25 %) : Emcompress&lt;sup&gt;®&lt;/sup&gt; (75 %)</td>
<td>2.090 (0.006)</td>
<td>4.381 (0.181)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Loss on drying
True density values were determined from the true density of the individual powder materials. The percentages provided for each component in Table 18 represent the weight fraction of each component, which together comprise 96% of the formulation. The remaining 4% contains a binder, glidant, and lubricant (Table 3). Compaction pressures and average out-of-die porosity for each mixture are reported in Table 19.

Table 19. Mixture out-of-die porosity values (0.04 mm/s)

<table>
<thead>
<tr>
<th>Mixture</th>
<th>Compaction Pressure (MPa)</th>
<th>Out-of-die Porosity (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lycatab® PGS (75 %) : Starch 1500® (25 %)</td>
<td>165.0</td>
<td>0.820 (0.001)</td>
</tr>
<tr>
<td>Lycatab® PGS (75 %) : Avicel® PH 200® (25 %)</td>
<td>136.4</td>
<td>0.819 (0.004)</td>
</tr>
<tr>
<td>Lycatab® PGS (75 %) : lactose 316 (25 %)</td>
<td>166.5</td>
<td>0.814 (0.002)</td>
</tr>
<tr>
<td>Lycatab® PGS (75 %) : anhydrous lactose (25 %)</td>
<td>160.5</td>
<td>0.820 (0.004)</td>
</tr>
<tr>
<td>Lycatab® PGS (75 %) : Emcompress® (25 %)</td>
<td>263.7</td>
<td>0.786 (0.001)</td>
</tr>
<tr>
<td>Lycatab® PGS (50 %) : Starch 1500® (50 %)</td>
<td>190.6</td>
<td>0.814 (0.001)</td>
</tr>
<tr>
<td>Lycatab® PGS (50 %) : Avicel® PH 200® (50 %)</td>
<td>127.3</td>
<td>0.817 (0.001)</td>
</tr>
<tr>
<td>Lycatab® PGS (50 %) : lactose 316 (50 %)</td>
<td>188.3</td>
<td>0.815 (0.001)</td>
</tr>
<tr>
<td>Lycatab® PGS (50 %) : anhydrous lactose (50 %)</td>
<td>142.4</td>
<td>0.819 (0.003)</td>
</tr>
<tr>
<td>Lycatab® PGS (50 %) : Emcompress® (50 %)</td>
<td>263.7</td>
<td>0.783 (0.004)</td>
</tr>
<tr>
<td>Lycatab® PGS (25 %) : Starch 1500® (75 %)</td>
<td>162.0</td>
<td>0.813 (0.001)</td>
</tr>
<tr>
<td>Lycatab® PGS (25 %) : Avicel® PH 200® (75 %)</td>
<td>100.2</td>
<td>0.818 (0.002)</td>
</tr>
<tr>
<td>Lycatab® PGS (25 %) : lactose 316 (75 %)</td>
<td>130.3</td>
<td>0.813 (0.005)</td>
</tr>
<tr>
<td>Lycatab® PGS (25 %) : anhydrous lactose (75 %)</td>
<td>104.0</td>
<td>0.808 (0.002)</td>
</tr>
<tr>
<td>Lycatab® PGS (25 %) : Emcompress® (75 %)</td>
<td>263.7</td>
<td>0.787 (0.002)</td>
</tr>
</tbody>
</table>
4.2.2 SRS<sub>factor</sub> : Individual Components

The unscaled values for each of the three parameters used to determine the composite factor, \( SRS_{factor} \), were collected according to the methods presented in detail in Chapter 3. Table 20, below, provides a summary of the average and standard deviation of each parameter based on the replicates listed in Section 4.1.3.1.

Table 20. Individual component raw data average and standard deviation values

<table>
<thead>
<tr>
<th>Material</th>
<th>Indentation Creep SRS Exponent</th>
<th>( \Delta SF_{final} )</th>
<th>Heckel-Based SRS Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-gelatinized maize starch (Lycatab® PGS)</td>
<td>0.052 (0.006)</td>
<td>0.120 (0.004)</td>
<td>13.5 (3.4)</td>
</tr>
<tr>
<td>Partially pre-gelatinized corn starch (Starch 1500®)</td>
<td>0.039 (0.003)</td>
<td>0.073 (0.005)</td>
<td>23.6 (2.5)</td>
</tr>
<tr>
<td>Microcrystalline cellulose (Avicel® PH 200)</td>
<td>0.028 (0.002)</td>
<td>0.017 (0.005)</td>
<td>9.6 (4.0)</td>
</tr>
<tr>
<td>anhydrous lactose 120 MS</td>
<td>0.026 (0.003)</td>
<td>0.001 (0.002)</td>
<td>3.4 (2.2)</td>
</tr>
<tr>
<td>Spray-dried lactose 316 Grade</td>
<td>0.019 (0.002)</td>
<td>0.013 (0.005)</td>
<td>7.1 (3.5)</td>
</tr>
<tr>
<td>Dibasic calcium phosphate dihydrate (Emcompress®)</td>
<td>0.016 (0.002)</td>
<td>0.001 (0.002)</td>
<td>0.0 (0.0)</td>
</tr>
</tbody>
</table>

Unscaled values were min/max scaled according to Eq. (29). This transforms the data such that the material with the largest experimental value for that parameter assumes a scaled value of 1. Conversely, the scaling will also transform the unscaled value of the material with the lowest experimental value for that parameter to a scaled value of 0. The mix/max scaled values for the data presented in Table 20 is provided in Table 21.
Table 21. Individual component min/max scaled values used to compute $SRS_{factor}$

<table>
<thead>
<tr>
<th>Material</th>
<th>Indentation Creep SRS Exponent</th>
<th>$\Delta SF_{final}$</th>
<th>Heckel-Based SRS Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-gelatinized maize starch (Lycatab® PGS)</td>
<td>1.00</td>
<td>1.00</td>
<td>0.57</td>
</tr>
<tr>
<td>Partially pre-gelatinized corn starch (Starch 1500®)</td>
<td>0.64</td>
<td>0.61</td>
<td>1.00</td>
</tr>
<tr>
<td>Microcrystalline cellulose (Avicel® PH 200)</td>
<td>0.33</td>
<td>0.14</td>
<td>0.41</td>
</tr>
<tr>
<td>Anhydrous lactose 120 MS</td>
<td>0.28</td>
<td>0.00</td>
<td>0.15</td>
</tr>
<tr>
<td>Spray-dried lactose 316 Grade</td>
<td>0.08</td>
<td>0.11</td>
<td>0.30</td>
</tr>
<tr>
<td>Dibasic calcium phosphate dihydrate (Emcompress®)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

The scaled value range will be 0 – 1 regardless of how wide or narrow the range is for the unscaled data. For example, if the unscaled data values have a very narrow range, the smallest and largest values will appear to be much different numerically after being scaled to 0 and 1, respectively. For this reason, it was crucially important to select materials that appropriately spanned the range of expected unscaled data values for each parameter. With respect to strain rate sensitivity, it was important to use materials whose deformation behavior ranged from purely brittle, to highly plastic and/or viscoelastic. As a result, differences in each parameter (i.e. speed sensitivity) are related to the mechanical properties of each material. Given the selected materials, it is thought that the unscaled data value ranges represent the entirety of the range that would be expected for pharmaceutical materials with minimum and maximum observed strain rate sensitivity.
The following figure (Figure 45) presents the compiled data for each of the six individual components tested. A stacked column plot is used to represent the contribution of each parameter to the overall strain rate sensitivity factor, $SRS_{factor}$. The figure legend identifies the color designation that corresponds to each measured parameter. Stacked column data for parameters that are not visible indicate the lowest unscaled value for the corresponding parameter.

![Figure 45](image)

**Figure 45.** Contribution of scaled parameters: Indentation Creep SRS Exponent (▱), $\Delta SF_{final}$ (■), and Heckel-based SRS Index (□) values for each individual component. Data labels represent the average $SRS_{factor}$ value for each material.

Materials whose deformation behavior is predominantly plastic and/or viscoelastic (Lycatab® PGS and Starch 1500®) were more strain rate sensitive than
materials that consolidate by fragmentation (lactose grades and Emcompress\textsuperscript{®}) according to the rank ordered $SRS_{factor}$ values listed in Figure 45. The composite parameter, $SRS_{factor}$, is valuable for comparing the overall strain rate sensitivity of each material. This parameter provides a quantitative measure of how sensitive a material is to changes in tablet press speed. For example, Starch 1500\textsuperscript{®} which has an average $SRS_{factor}$ value of 0.75 is much more strain rate sensitive than lactose 316 which only has an average $SRS_{factor}$ value of 0.16. In practice, these $SRS_{factor}$ values can be used to understand which material is more susceptible to potential changes in deformation behavior upon scale-up. Starch 1500\textsuperscript{®} is highly sensitive, so it shouldn’t be unexpected to observe deformation behavior changes resulting from changes in the tablet press speed used to prepare tablets. Conversely, lactose 316 is generally insensitive and would be expected to exhibit nearly identical behavior at both slow and fast compression speed.

Another benefit of this analysis is the ability to obtain specific information about a material’s strain rate sensitive behavior by looking at the scaled values of each individual parameter. The quantitative contribution of each deformation behavior to the overall strain rate sensitivity was assessed by taking the ratio of the min/max scaled values for the Indentation Creep SRS Exponent and $\Delta S_{f inal}$, respectively (Table 22, on the following page).
In cases where a material is insensitive examination of the individual behaviors isn’t of that much value. However, in the case where a material shows some sensitivity, the individual parameter data can identify the contributing behavior, or behaviors. Relative sensitivity of these materials can be understood in terms of their viscoplasticity and viscoelasticity, considered separately.

Clearly, the deformation behavior of Emcompress® was not affected by changes to tablet press speed. In the lab-scale data, Emcompress® behaved similarly regardless of the speed used to compact each tablet. This was confirmed by the identical in-die mean yield pressures (Heckel-Based SRS Index) for this material at slow and fast speed. Emcompress® also showed essentially no viscoelastic recovery, and minimal creep displacement as indicated by having the smallest unscaled Indentation Creep SRS
The ability to dissipate applied stress occurs rapidly for a material like Emcompress® that cracks and breaks.

Sensitivity that was observed for Avicel® PH 200 appears to be due to its time-dependent plasticity with little contribution from its viscoelastic behavior. This was confirmed by the data presented in Table 22. Avicel® PH200 had a ratio of 2.35 when comparing its viscoplastic sensitivity to its viscoelastic sensitivity. Ratio values much greater than one indicate that viscoplastic behavior is the dominating time-dependent deformation mechanism. It was hypothesized that this phenomenon is due, in part, to the high percentage of intra-particle porosity reported for this material [48]. Agglomerated microcrystalline cellulose like Avicel® PH 200 can permanently deform on both the macro and micro scales [116]. Macroscopically the intra-particle pore structure can collapse, while dislocation due to the presence of slip planes in the crystalline lattice will induce permanent deformation on the microscale [117]. Both mechanisms contribute to the observed plasticity of this material. Lab-scale data collected for this material suggests that only a fraction of the observed plasticity is time-dependent. This was confirmed by comparing the Out-of-die Heckel Slope to the Indentation Creep SRS Exponent for this material (Section 3.2.2). The collapse of the intra-particulate pore structure results in a reduction in porosity. Particles are not fractured or broken, but deform as the entrapped air is released. It is reasonable to suspect that the collapse of the intra-particulate pore structure occurs rapidly compared to the time required to induce dislocation movement. As a result, Avicel® PH 200 will deform significantly during compression on both the macro and micro scale, but only a fraction of that deformation will be time-dependent.
For Lycatab® PGS, its plasticity was speed dependent, but its elasticity was also highly sensitive. This was quantitatively assessed by looking at the ratio of viscoplasticity (Indentation Creep SRS Exponent) to viscoelasticity ($\Delta SF_{\text{final}}$) in Table 22. The ratio for Lycatab® PGS was unity, confirming that both deformation modes contribute equally to the observed strain rate sensitivity of that material. Starch is a carbohydrate that consists of two different types of glucose polysaccharides, namely amylose and amylopectin. It is hypothesized that the viscoelasticity of this material is due to the chemical structure of these two units. Amylose is starch formed by unbranched chains of glucose monomers, whereas amylopectin is a branched polysaccharide. Because of the way the subunits are joined, glucose chains assume a helical structure [118]. Therefore, it was hypothesized that this structure is able to compress like a spring when subjected to an applied load. Stresses are stored but not dissipated. As a result, a large portion of this material's deformation is reversible. Upon ejection from the die, the stored elastic strain is recovered leading to its high degree of viscoelasticity.

Beyond specific information about the sensitivity of each deformation mode, the practical implications of strain rate sensitivity are of great importance to formulators and process development scientists. In the case of an insensitive and brittle material like Emcompress®, no changes to deformation behavior would be predicted under high-speed compaction conditions. The same cannot be said for Lycatab® PGS. Lycatab® PGS showed differences in its deformation behavior with speed. Tablets prepared under high-speed conditions will likely exhibit reduced strength when compared to tablets of the same material prepared under slower speed conditions. In cases where large differences
are observed, problems such as excessive friability and absence of pharmaceutical
elegance may result from a mechanically weak tablet product.

4.2.3 SRS$_\text{factor}$ : Mixtures

Overall strain rate sensitivity values ($SRS_{factor}$) for each of the fifteen mixtures
are provided in Figure 46. Data points are grouped according to the percentage of
Lycatab$^\text{®}$ PGS in each mixture. Individual component data are provided as a reference.

![Figure 46. SRS$_\text{factor}$ values for each mixture in combination with Lycatab$^\text{®}$ PGS](image)

As reported in Section 4.2.2, Lycatab$^\text{®}$ PGS was the most sensitive individual
component that was tested in this work. For that reason, it was used as a model
compound to simulate the presence of a strain rate sensitive active ingredient in combination with excipients expressing varied deformation behavior. In order to vary the strain rate sensitivity of each mixture, the amount of Lycatab<sup>®</sup> PGS was progressively decreased from 75% to 25% as indicated in Figure 46.

In general, as the percentage of Lycatab<sup>®</sup> PGS in each mixture decreased, so did the measured strain rate sensitivity. How much the sensitivity changed was dependent on the sensitivity of the other excipient in the mixture. At 75% Lycatab<sup>®</sup> PGS in the mixture, the largest reduction in overall strain rate sensitivity was observed for the mixture containing the least sensitive material on its own, Emcompress<sup>®</sup>. The $SRS_{factor}$ decreased from 0.86 for Lycatab<sup>®</sup> PGS by itself, to 0.52 for the mixture containing 25% Emcompress<sup>®</sup>. In comparison, the other mixtures at that same ratio had average $SRS_{factor}$ values that ranged from 0.60 - 0.66 and were not statistically insignificant from one another. For these mixture combinations, it was apparent that strain rate sensitivity was most affectively mitigated by including another component that was not strain rate sensitive. All average $SRS_{factor}$ values for the mixtures containing Emcompress<sup>®</sup> were less than the average $SRS_{factor}$ values for any of the other mixture combinations. Discussions regarding atypical mixture behavior are provided for each combination of excipient with Lycatab<sup>®</sup> PGS. Information related to the specific deformation behaviors that contribute to the observed sensitivity will be discussed.

4.2.3.1 Lycatab<sup>®</sup> PGS : Starch 1500<sup>®</sup> Mixtures

The first set of mixtures that were analyzed contained two highly strain rate sensitive materials based on their average $SRS_{factor}$ values. Lycatab<sup>®</sup> PGS was the most
sensitive, having an average value of 0.86 while Starch 1500\textsuperscript{®} had an average measured value of 0.75 (Figure 45). A $t$-test comparing group means indicated that no statistically significant difference between values was observed. Therefore, it was confirmed quantitatively that these two materials had equivalent overall strain rate sensitivity.

Summarized mixture behavior is provided in Figure 47. Plotted on the primary y-axis are the scaled values for each of the three individual parameters. The secondary y-axis represents the average of these three scaled values, or the composite parameter $SRS_{factor}$. Columns were grouped and labeled according to the weight percentage of Lycatab\textsuperscript{®} PGS in the mixture. The individual component data is provided for reference.

![Figure 47](image_url)

**Figure 47.** Scaled parameters: Indentation Creep SRS Exponent (■), $\Delta S_{final}$ (□), Heckel-based SRS Index ( ), and average $SRS_{factor}$ ( ) values for Lycatab\textsuperscript{®} PGS : Starch 1500\textsuperscript{®} mixtures
The $SRS_{factor}$ value at a composition of 75 % Lycatab® PGS : 25 % Starch 1500® decreased significantly compared to the $SRS_{factor}$ value of Lycatab® PGS alone. The remaining mixtures (50 % Lycatab® PGS : 50 % Starch 1500® and 25 % Lycatab® PGS : 75 % Starch 1500®) maintained a fairly constant sensitivity across all compositions. No statistically significant differences in average $SRS_{factor}$ values for those mixtures were observed when compared to the individual component values.

Mixture behavior in the literature has largely been categorized as being either ideal or non-ideal. Ideal mixtures follow a simple arithmetic relationship with respect to the mixture composition. In other words, when the deformation properties of a mixture’s components contribute to the overall behavior strictly according to their weight proportions in the mixture, it would be classified as ideal mixing behavior. Many reports of ideal behavior have been reported previously [78,119-123]. Non-ideal behavior is observed in mixtures that behave either more or less similarly to one component than would be predicted from the behavior of both components. This behavior is identified as having either positive or negative deviations from linearity [123-127].

Lycatab® PGS : Starch 1500® mixtures showed both positive and negative deviations depending on the mixture composition (Figure 48, on the following page).
Except for the 50:50 mixture, the $SRS_{factor}$ values could not be predicted from the properties of the individual constituents. For example, the predicted $SRS_{factor}$ value based on the linear mixture model for the mixture containing 75% Lycatab® PGS was 0.83 compared to the measured value of 0.68. Differences in sensitivity that were observed for each mixture appear to be influenced primarily by the viscoelastic component of their behavior. This was confirmed by comparing the mixture data for the Indentation Creep SRS Exponent and $\Delta SF_{final}$. The unscaled values for both of these parameters are provided in Table 23 along with their standard deviations based on the replicates listed for each measurement in Section 4.1.3.1.
Table 23. Lycatab® PGS : Starch 1500® mixture unscaled parameter values

<table>
<thead>
<tr>
<th>Mixture Composition</th>
<th>Indentation Creep SRS Exponent (S.D.)</th>
<th>$\Delta S_{F_{final}}$ (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lycatab® PGS (75 %) : Starch 1500® (25 %)</td>
<td>0.042 (0.003)</td>
<td>0.092 (0.004)</td>
</tr>
<tr>
<td>Lycatab® PGS (50 %) : Starch 1500® (50 %)</td>
<td>0.041 (0.002)</td>
<td>0.112 (0.004)</td>
</tr>
<tr>
<td>Lycatab® PGS (25 %) : Starch 1500® (75 %)</td>
<td>0.042 (0.003)</td>
<td>0.108 (0.004)</td>
</tr>
</tbody>
</table>

Each mixture appears to have very similar strain rate sensitivity based on the creep data, but are different in terms of the $\Delta S_{F_{final}}$ results. The viscoelastic response is more affected by strain rate in the mixtures with 25 % and 50 % Lycatab® PGS than it is in the mixture with 75 %. The difference in viscoelasticity of these mixtures is manifest in the relaxation of the tablets. The mixtures with 25 and 50 % Lycatab® PGS expanded to a greater extent than the mixture with 75 % Lycatab® PGS as represented by the $\Delta S_{F_{final}}$ values in Table 23.

4.2.3.2 Lycatab® PGS : Avicel® PH200 Mixtures

The next set of mixtures contained Avicel® PH 200, a material that has been shown in this work to be sensitive primarily due to its viscoplastic deformation behavior. Figure 49, on the following page, provides the compiled data for each of these three mixtures. Again, individual component data have been provided for reference.
Mixtures of the most sensitive individual component, Lycatab® PGS, with a highly plastic material, Avicel® PH 200 showed strain rate sensitivities intermediate to the sensitivity of each individual component. A reduction in sensitivity was not unexpected as the amount of Avicel® PH 200 in the mixture increased given the difference in sensitivity of the individual components. SRS\text{factor} values were approximated using a linear mixture model and the strain rate sensitivities of each individual component. Quality of fit was assessed by comparing the measured and predicted values (Table 24).
Table 24. Lycatab® PGS : Avicel® PH200 mixtures scaled and predicted $SRS_{factor}$ values

<table>
<thead>
<tr>
<th>Mixture Composition</th>
<th>$SRS_{factor}$</th>
<th>Predicted $SRS_{factor}$</th>
<th>Residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lycatab® PGS</td>
<td>0.86</td>
<td>0.86</td>
<td>--</td>
</tr>
<tr>
<td>Lycatab® PGS (75 %) : Avicel® PH200 (25 %)</td>
<td>0.64</td>
<td>0.72</td>
<td>-0.08</td>
</tr>
<tr>
<td>Lycatab® PGS (50 %) : Avicel® PH200 (50 %)</td>
<td>0.56</td>
<td>0.57</td>
<td>-0.01</td>
</tr>
<tr>
<td>Lycatab® PGS (25 %) : Avicel® PH200 (75 %)</td>
<td>0.38</td>
<td>0.43</td>
<td>-0.05</td>
</tr>
<tr>
<td>Avicel® PH200</td>
<td>0.29</td>
<td>0.29</td>
<td>--</td>
</tr>
</tbody>
</table>

For all the mixtures, the predicted $SRS_{factor}$ values were greater than the experimental values. In order, the differences were -0.08 for the mixture containing 75 % Lycatab® PGS, followed by -0.01 for the 50 : 50 mixture, and -0.05 for the mixture with the most Avicel® PH200. Negative residuals for all mixtures indicate a slight negative deviation. It is presumed that this behavior is due to the consistency in the trend of the individual parameters used to determine $SRS_{factor}$.

The contribution of viscoplasticity and viscoelasticity appear to be the same for the mixtures containing 75 % and 50 % Lycatab® PGS, but slightly different from the mixture containing 25 % as presented in Figure 50, on the following page.
Figure 50. Scaled parameters: Indentation Creep SRS Exponent (■) and $\Delta S_{\text{final}}$ (■) for the three Lycatab® PGS : Avicel® PH 200 mixtures.

In addition to plasticity being time-dependent for these mixtures, the viscoelastic component of their behavior was also a contributing factor. Based on the scaled values, viscoelasticity contributed nearly equivalently for the mixtures containing 75% and 50% Lycatab® PGS. The ratio of viscoplasticity to viscoelasticity was 1.02 and 0.98, respectively. As before, values close to unity indicate nearly equivalent contribution from both behaviors to the observed sensitivity. The mixture containing only 25% Lycatab® PGS showed sensitivity dependent more on viscoplastic behavior in the absence of sensitivity of the viscoelastic mode (Figure 50). This mixture exhibited behavior that favored the more abundant component in the mixture. This can be confirmed by
examining the trends for that mixture and Avicel® PH200 as an individual component in presented previously in Figure 49.

4.2.3.3 Lycatab® PGS : lactose 316 Mixtures

The third set of mixtures contained lactose 316 in combination with Lycatab® PGS. This mixture combination can be used to evaluate the behavior of a highly sensitive component with a material that had minimal observed sensitivity (Figure 46). The compiled data for each of these mixtures is provided in Figure 51, below. Individual component data has been provided for comparison.

Figure 51. Scaled parameters: Indentation Creep SRS Exponent (■), ΔSF_{final} (□), Heckel-based SRS Index ( ), and average SRS_{factor}(□-□) values for Lycatab® PGS : lactose 316 mixtures
A reduction in overall strain rate sensitivity of each mixture was not unexpected given the large difference in strain rate sensitivity of each individual component. The mixture containing 25 % Lycatab® PGS had an average $SRS_{factor}$ value of 0.38 which was significantly less than the average $SRS_{factor}$ value for the mixture containing 75 % Lycatab® PGS which was computed to be 0.64. The behavior of $SRS_{factor}$ was accurately predicted by the same linear mixing model applied to the mixtures of Lycatab® PGS with Starch 1500® and Avicel® PH200 shown in Figure 52.

![Figure 52. SRS_factor values for Lycatab® PGS : lactose 316 mixtures (-◊-). Linear mixture model data (◊) is provided](image)

The largest difference between the actual and predicted values was 0.05 for the mixture containing equal parts Lycatab® PGS and lactose 316. For all three mixtures, the
residual differences were less than the uncertainty in the measured $SRS_{factor}$ values.

Although the overall risk factor exhibited ideal behavior, it was interesting to observe that some of individual parameters did not (Figure 51). The most noticeable deviation was observed for the parameters evaluating viscoelasticity, $\Delta SF_{final}$. The unscaled $\Delta SF_{final}$ values for each mixture are provided in Table 25, below. The predicted values were calculated based on the linear combination of each component in the mixture.

<table>
<thead>
<tr>
<th>Mixture</th>
<th>$\Delta SF_{final}$ (S.D.)</th>
<th>Predicted $\Delta SF_{final}$</th>
<th>Residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lycatab® PGS</td>
<td>0.120 (0.004)</td>
<td>0.120</td>
<td>--</td>
</tr>
<tr>
<td>Lycatab® PGS (75 %) : lactose 316 (25 %)</td>
<td>0.095 (0.005)</td>
<td>0.093</td>
<td>0.002</td>
</tr>
<tr>
<td>Lycatab® PGS (50 %) : lactose 316 (50 %)</td>
<td>0.093 (0.005)</td>
<td>0.067</td>
<td>0.026</td>
</tr>
<tr>
<td>Lycatab® PGS (25 %) : lactose 316 (75 %)</td>
<td>0.043 (0.010)</td>
<td>0.040</td>
<td>0.003</td>
</tr>
<tr>
<td>lactose 316</td>
<td>0.013 (0.005)</td>
<td>0.013</td>
<td>--</td>
</tr>
</tbody>
</table>

For all mixtures, the viscoelastic recovery was greater than would be predicted based on the behaviors of the components. This is confirmed by positive residual values for each mixture. The largest residual was observed for the mixture containing 50 % Lycatab® PGS. A linear mixture model under predicted solid fraction by a value of 0.026 or ~ 28 %. It has been reported previously that softer materials can have a greater effect
on the deformation behavior observed in mixtures than more rigid components [128,129]. The behavior has been attributed to a particulate-level effect, where the softer particles deform preferentially and dominate the overall behavior. This would cause the softer material to contribute more to the overall behavior than its weight fraction would indicate. In this case, the softer material in the mixture is Lycatab® PGS which has a hardness value at the start of the hold region of 12.3 MPa compared to a hardness value under the same experimental conditions of 35.8 MPa for lactose 316. Although this rational seems reasonable, the effect appears to be only applicable to the 50 : 50 mixture since the residuals for the other mixtures are less than the uncertainty of the unscaled values.

4.2.3.4 Lycatab® PGS : anhydrous lactose Mixtures

An additional lactose grade was evaluated in mixtures with Lycatab® PGS at the same compositions as each of the previous three materials. Mixtures of Lycatab® PGS with anhydrous lactose exhibited overall strain rate sensitivity behavior intermediate to the behavior of the individual components. Figure 53, on the following page, provides a plot of the composite strain rate sensitivity parameter, \( SRS_{factor} \), overlaid with the linear mixture model predictions based on weight composition in the mixture. Individual component and mixture \( SRS_{factor} \) values are listed as data labels for reference.
The presence of a brittle material in the mixture effectively reduced the overall strain rate sensitivity, $SRS_{factor}$, progressively from 0.66 for the mixture containing 75% Lycatab\textsuperscript{®} PGS to 0.42 for the mixture containing 50% Lycatab\textsuperscript{®} PGS. The reduction in sensitivity for these mixtures corresponded favorably with the predicted behavior based on the contribution of each constituent. However, as the amount of Lycatab\textsuperscript{®} PGS in the mixture was decreased to 25%, atypical behavior was observed. For the mixture containing 25% Lycatab\textsuperscript{®} PGS, no reduction in sensitivity was measured even though an additional 25% of a non-sensitive material was added to the mixture. The nearly identical behavior of these two mixtures can be understood by comparing the scaled values of each of the three parameters used to determine $SRS_{factor}$. 

Figure 53. $SRS_{factor}$ values for Lycatab\textsuperscript{®} PGS : anhydrous lactose mixtures (-◊-). Linear mixture model data (◊) is provided.
Figure 54 provides the compiled data for each mixture of anhydrous lactose in combination with Lycatab® PGS. The parameters corresponding to viscoplastic, viscoelastic, and non-descriptive time-dependent deformation behavior are labeled accordingly.

As mentioned, for the mixtures containing 50 % and 25 % Lycatab® PGS, no change to the strain rate sensitivity was measured. This is confirmed by the identical average values for the Indentation Creep SRS Exponent (0.61) and ΔSFfinal (0.27). As a result, the corresponding ratio of those two parameters is also identical meaning that the contribution of viscoplastic to viscoelastic behavior is the same. In both mixtures, the dominating mechanism of the observed sensitivity was viscoplasticity. The ratio of the
Indentation Creep SRS Exponent to $\Delta S_{f_{final}}$ was 2.26. Compared to the mixture containing 75 % Lycatab® PGS, which had a ratio of the same parameters equal to 1.14, viscoelastic behavior contributed to a much lesser extent. The only difference observed for these two mixtures was in the Heckel-Based SRS Index. A slight reduction in the average value from 0.38 to 0.34 was measured as the amount of Lycatab® PGS in the mixture decreased from 50 to 25 %.

From a formulation prospective, the behavior of these two mixtures is compelling. Anhydrous lactose is able to accommodate an additional 25 % w/w of a highly sensitive material to its formulation with no changes to its sensitivity. For most of the other excipients in combination with Lycatab® PGS, there was a decrease in the strain rate sensitivity of the mixture as the amount of Lycatab® PGS decreased (Figure 46). The Starch 1500® mixtures were the exception, but the high strain rate sensitivity of those mixtures make them high risk when considering scale-up operations. The ability of anhydrous lactose to mitigate sensitivity in this manner is particularly valuable. For example, in instances where the drug load is high and/or the active is highly sensitive like Lycatab® PGS, anhydrous lactose can be used to mitigate sensitivity even when the sensitive material is present in relatively large amounts.

**4.2.3.5 Lycatab® PGS : Emcompress® Mixtures**

The final material that was mixed in combination with Lycatab® PGS was Emcompress®. Experimentally, Emcompress® tested as the least sensitive individual component of the six materials under investigation. As a result, these mixtures represent
the combinations of the most sensitive material with the least sensitive material. Figure 55 presents the compiled data for Emcompress® in combination with Lycatab® PGS.

![Figure 55](image)

**Figure 55.** Scaled parameters: Indentation Creep SRS Exponent (■), ΔSF<sub>final</sub> (■), Heckel-based SRS Index (■) and average SRS<sub>factor</sub> (■-□-) values for Lycatab® PGS : Emcompress® mixtures

The two materials principally consolidate by different mechanisms: Lycatab® PGS is plastic and viscoelastic and Emcompress® is highly brittle. As a result, the overall strain rate sensitivity, SRS<sub>factor</sub>, of mixtures of these two materials were intermediate to the sensitivity of each individual component. It was observed that the largest reduction occurred for the mixture containing 25% Emcompress® relative to the sensitivity of Lycatab® PGS alone. The SRS<sub>factor</sub> value decreased from 0.86 to 0.52. Further
reductions in strain rate sensitivity were observed for the remaining two mixtures, but to a lesser extent. For example, the change in $SRS_{factor}$ between the mixture containing 75% Lycatab® PGS and the mixture containing 50% Lycatab® PGS was 0.15. These reductions were not unexpected given the large difference in strain rate sensitivity of each individual component. More specific interpretations about the strain rate sensitivities of these mixtures can be gained by looking at the values of the three individual parameters used to calculate $SRS_{factor}$.

It was observed that Heckel-Based SRS Index values were under predicted for two of the three mixtures based on the composition of each component. The effect was particularly noticeable in the mixture containing 75% Lycatab® PGS. The unscaled Heckel-Based SRS Index values for each mixture are provided in Table 26, below.

<table>
<thead>
<tr>
<th>Mixture</th>
<th>Hecke-Based SRS Index (S.D.)</th>
<th>Predicted Hecke-Based SRS Index</th>
<th>Residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lycatab® PGS</td>
<td>13.5 (3.4)</td>
<td>13.5</td>
<td>--</td>
</tr>
<tr>
<td>Lycatab® PGS (75%) : Emcompress® (25%)</td>
<td>4.8 (2.6)</td>
<td>10.1</td>
<td>-5.3</td>
</tr>
<tr>
<td>Lycatab® PGS (50%) : Emcompress® (50%)</td>
<td>4.5 (2.7)</td>
<td>6.8</td>
<td>-2.3</td>
</tr>
<tr>
<td>Lycatab® PGS (25%) : Emcompress® (75%)</td>
<td>3.5 (3.0)</td>
<td>3.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Emcompress®</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Table 26. Lycatab® PGS : Emcompress® mixture unscaled and predicted Heckel-Based SRS Index values
Negative residuals indicate that the mixture was behaving more like the individual component with the lower Heckel-Based SRS Index value. Based on that parameter, alone, these mixtures would be classified as having limited strain rate sensitivity. For example, the Heckel-Based SRS Index values for these mixtures compares favorably to the same parameter value for anhydrous lactose as an individual component (Table 20).

However, when considering the strain rate sensitivity based on all three parameters, \( SRS_{factor} \) values were greater than the Heckel-Based SRS Index. This difference appears to be due to the viscoelastic behavior. Table 27 lists the unscaled \( \Delta S\bar{F}_{final} \) values for each individual component and their corresponding mixture. Predicted values are based on a linear mixing rule.

<table>
<thead>
<tr>
<th>Mixture</th>
<th>( \Delta S\bar{F}_{final} ) (S.D.)</th>
<th>Predicted ( \Delta S\bar{F}_{final} )</th>
<th>Residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lycatab\textsuperscript{®} PGS</td>
<td>0.120 (0.004)</td>
<td>0.120</td>
<td>--</td>
</tr>
<tr>
<td>Lycatab\textsuperscript{®} PGS (75 %) : Emcompress\textsuperscript{®} (25 %)</td>
<td>0.098 (0.004)</td>
<td>0.090</td>
<td>0.008</td>
</tr>
<tr>
<td>Lycatab\textsuperscript{®} PGS (50 %) : Emcompress\textsuperscript{®} (50 %)</td>
<td>0.077 (0.005)</td>
<td>0.061</td>
<td>0.016</td>
</tr>
<tr>
<td>Lycatab\textsuperscript{®} PGS (25 %) : Emcompress\textsuperscript{®} (75 %)</td>
<td>0.052 (0.004)</td>
<td>0.031</td>
<td>0.021</td>
</tr>
<tr>
<td>Emcompress\textsuperscript{®}</td>
<td>0.001 (0.002)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
The positive residuals for all three mixtures indicate an under prediction of $\Delta S_f^{\text{final}}$ based on the data collected for each individual component. These data offset the negative deviations observed in the Heckel-Based SRS Index data provided in Table 26. Post-ejection from the die, mixtures show viscoelastic recovery that was dominated much more so by Lycatab® PGS than it was by Emcompress®. For the combination of Lycatab® PGS with Emcompress® both constituents dominate the behavior of the mixtures, albeit differently.

### 4.3 Summary

A multi-dimensional parameter was used to identify the specific mechanical behavior/s responsible for a material’s observed strain rate sensitivity. The strain rate sensitive deformation behavior of six pharmaceutical excipients and fifteen mixtures was analyzed. Individual component sensitivity was rank-ordered from the most to the least sensitive. A detailed description of a materials time-dependent deformation behavior can be described in terms of plasticity and elasticity, considered independently (Table 28, on the following page).
<table>
<thead>
<tr>
<th>Individual Component</th>
<th>Strain Rate Sensitivity ($SRS_{factor}$)</th>
<th>Contributing Deformation Behavior/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-gelatinized maize starch (Lycatab® PGS)</td>
<td>High (0.86)</td>
<td>Viscoplasticity, Viscoelasticity</td>
</tr>
<tr>
<td>Partially pre-gelatinized corn starch (Starch 1500®)</td>
<td>High (0.75)</td>
<td>Viscoplasticity, Viscoelasticity</td>
</tr>
<tr>
<td>Microcrystalline cellulose (Avicel® PH 200)</td>
<td>Intermediate (0.29)</td>
<td>Viscoplasticity</td>
</tr>
<tr>
<td>Spray-dried lactose 316 Grade</td>
<td>Low (0.16)</td>
<td>--</td>
</tr>
<tr>
<td>anhydrous lactose 120 MS</td>
<td>Low (0.14)</td>
<td>--</td>
</tr>
<tr>
<td>Dibasic calcium phosphate dihydrate (Emcompress®)</td>
<td>Low (0.00)</td>
<td>--</td>
</tr>
</tbody>
</table>

Mixture behavior was assessed by changing the composition of the most sensitive individual component (Lycatab® PGS) in combination with five other excipients. The largest reduction in overall strain rate sensitivity, $SRS_{factor}$, of a mixture was observed when the second component in the mixture was highly brittle (i.e., Lycatab® PGS mixed with Emcompress®). The extent of reduction was dependent on the difference in strain rate sensitivity of each individual component. The further apart they were, the larger the reduction. Conversely, combining two viscoplastic/viscoelastic materials did little to mitigate the sensitivity of Lycatab® PGS (i.e., Lycatab® PGS mixed with Starch 1500®).

Several interesting mixtures were identified among the fifteen that were tested. First, when 75 % Avicel® PH 200 was mixed with 25 % Lycatab® PGS the behavior responsible for the observed sensitivity changed relative to the behavior of the other
mixture compositions. In that mixture, Lycatab\textsuperscript{®} PGS’s time-dependent elasticity was minimized. The behavior was controlled by Avicel\textsuperscript{®} PH 200 and as a result sensitivity was primarily due viscoplasticity. Second, are the mixtures of Lycatab\textsuperscript{®} PGS with 50 \% and 75 \% anhydrous lactose. No change to mixture sensitivity was observed when the amount of Lycatab\textsuperscript{®} PGS in the mixture was increased from 25 \% to 50 \%. This observation was unique since for all other mixtures, $SRS_{factor}$ increased as the amount of Lycatab\textsuperscript{®} PGS in the mixture increased. Anhydrous lactose was able to modulate the behavior of Lycatab\textsuperscript{®} PGS up to 50 \% in a mixture. Last, the mixtures of Lycatab\textsuperscript{®} PGS with Emcompress\textsuperscript{®} exhibited behavior that was dominated by each component, though differently. Mixtures showed relative insensitivity to compression speed based on the Heckel-Based SRS Index data, but were highly viscoelastic. During compression at two different speeds, the brittle component (Emcompress\textsuperscript{®}) controlled consolidation. However, post-compression the tablets demonstrated viscoelastic recovery that was dominated by the recovery of Lycatab\textsuperscript{®} PGS.

This multi-component approach proves valuable for assessing strain rate sensitivity. In cases where complicated behavior is observed, this technique can be used to identify the specific contributing deformation behaviors. Additionally, this method is also material-sparing only requiring gram level quantities of material. If only a small amount of raw material is available or where a large number of different materials are to be studied, this method allows for a detailed understanding of time-dependent deformation behavior to be learned.
Chapter 5: Conclusions

In addition to plastic deformation, the elastic response of a material to stress can be time-dependent. Since many pharmaceutical materials also demonstrate relatively large amounts of elastic deformation, it can be difficult to identify whether a material’s strain rate sensitivity is due to changes in elasticity or due to changes in plasticity at different speeds. A characterization method that is specific to individual deformation modes would be helpful for improving the understanding of the strain rate sensitivity of these materials. As a result, the experimentation presented in this dissertation was designed to test the hypothesis that a multi-component, lab-scale assessment of strain rate sensitivity enables overall sensitivity to be quantified, and identification of the specific mechanical behaviors contributing to the observed sensitivity.

The goal of the first specific aim was to establish the effect of compression speed on the tableting profiles (compressibility and tabletability) of three common pharmaceutical excipients with varied deformation behavior. High speed experiments were performed using a Huxley-Bertram compaction simulator. Material compressibility and tabletability was assessed. Emcompress® was insensitive to tablet press speed changes in both profiles. Avicel® PH200 and Lycatab® PGS both showed sensitivity, but that sensitivity was different for the two materials. Insensitivity in these commonly used profiles suggests that the compaction behavior of that material is unaffected by changes to tablet press speed. In instances where sensitivity is observed, nearly equivalent compaction behavior would not be expected as a result of changing the speed of the tablet
press. The observed sensitivity was dependent on the predominant deformation behavior of the material being studied.

The goal of the second specific aim was to introduce three lab-scale measurements that comprehensively describe the various aspects of strain rate sensitivity during powder compaction. These specific parameters were selected based on the need to improve current methods used to characterize strain rate sensitivity, and the complexity of time-dependent deformation. Strain rate sensitivity was assessed by combining three individual parameters: 1) Indentation Creep SRS Exponent, 2) ΔSF_{final}, and 3) Heckel-Based SRS Index. Materials with the largest experimental values for each of the three parameters (Lycatab® PGS and Starch 1500®), deform predominantly by plastic and/or viscoelastic mechanisms. Conversely, materials which had the lowest experimental values (Emcompress®) are highly brittle. The use of these three parameters, in combination, allows for more specific characterization of strain rate sensitivity.

Finally, the goal of the third specific aim was to quantify strain rate sensitivity, of several common pharmaceutical excipients and mixtures containing those materials, using a composite evaluation of time-dependent deformation. For the individual components, Lycatab® PGS was the most sensitive and Emcompress® was the least. Sensitivity of the materials can be understood in terms of viscoplasticity and viscoelasticity, considered separately. For example, any sensitivity that was observed for Avicel® PH 200 appears to be due to its time-dependent plasticity with little or no contribution from its viscoelastic behavior. For Lycatab® PGS, its plasticity is speed dependent, but its elasticity is also highly sensitive.
Mixture behavior was decidedly more complex. In general, strain rate sensitivity was reduced when a less sensitive material was added to the mixture. How significant that reduction was depended on the difference in strain rate sensitivities of each individual component. Of the fifteen mixtures that were analyzed, several stood out. For example, for two of the mixtures of Lycatab® PGS with anhydrous lactose no change to the mixture strain rate sensitivity was observed. The sensitivity of Lycatab® PGS was effectively mitigated as the amount of Lycatab® PGS in the mixture increased from 25 to 50 %.

Based on the data presented in this dissertation, it is evident that the combination of factors used to characterize time-dependent deformation allows for a more detailed characterization of strain rate sensitivity. Assessing the time-dependency of both plasticity and elasticity offers the potential to understand what role each deformation behavior plays in the overall sensitivity of a material upon scale-up.
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Appendix A: Material-Sparing Method for Deriving the Out-of-Die Heckel Slope from Data Collected During a Single Compression-Decompression Cycle

The purpose of the work described in Appendix A was to demonstrate a procedure by which the data collected during a single compression cycle can be used to derive out-of-die Heckel data. The data collected form a single compression-decompression cycle was used to generate a profile equivalent to a complete out-of-die compressibility profile that had been corrected for both elastic and viscoelastic recovery.

A.1 Data Correction

Unlike in-die Heckel analysis, out-of-die Heckel analysis requires generating a larger number of tablets to assess volume reduction behavior over a range of applied pressures. Typical in-die (Figure A.1) and out-of-die (Figure A.2) Heckel plots for Lycatab® PGS are shown on the following page, respectively.
Figure A. 1. In-die Heckel plot for Lycatab® PGS compacted at 0.04 mm/s

Figure A. 2. Out-of-die Heckel plot for Lycatab® PGS compacted at 0.04 mm/s
Although out-of-die Heckel analysis allows researchers to assess the consolidation behavior of a powder after elastic and viscoelastic deformation have been recovered, this method is time-consuming and requires a significant amount of raw material. To take advantage of the benefits of each method, a procedure that uses data collected during a single compression-decompression cycle (in-die, Figure A.1) was used to generate a profile equivalent to a complete out-of-die Heckel profile (Figure A.2). This procedure utilizes corrections to the in-die data for both elastic and viscoelastic recovery to generate a corrected Heckel profile that is indistinguishable from data collected using the out-of-die approach [114,115].

The derivation 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 solid fraction that occurs because of elastic deformation during compression up to the sample level of applied pressure, even if the pressure of interest is less than the maximum pressure used to compact the tablet. The second assumption is that the decrease in solid fraction due to viscoelastic recovery after ejection is not significantly dependent on the maximum applied pressure. These two assumptions allow correction for elastic recovery using the in-die data collected during decompression and correction for viscoelastic recovery using the solid fraction change after ejection.

Since this correction method relies on in-die data, proper corrections for machine part deformation were performed. Methods describing how that correction was performed can be referenced in Section 2.1.2.5. Prior to applying the solid fraction correction method used to obtain the Out-of-Die Heckel Slope, the raw data was transformed into
profiles of pressure (Eq.(16)) versus in-die solid fraction (Eq.(17)). The in-die compressibility profiles were acquired from the data recorded during the compression of each material at 0.04 mm/s outlined in Section 3.1.2.2.

An example in-die solid fraction versus compaction pressure profile for Lycatab® PGS prepared at 0.04 mm/s is provided in Figure A.3.

![Graph](image)

Figure A. 3. In-die solid fraction versus pressure profile for Lycatab® PGS compacted at 0.04 mm/s

It is assumed that 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. At every pressure between zero and the maximum pressure, the solid fraction measured during compression can be corrected for elastic deformation by
subtracting the change in solid fraction that occurred during decompression from the same pressure. This approach is applied even for pressures that are less than the maximum pressure used during the compression cycle. The corrected solid fraction ($SF_{c/d}$) associated with each applied pressure can be determined using Eq. (25):

$$SF_{c/d} = SF_c - [SF_d - SF_d(0)]$$

where $SF_c$ and $SF_d$ correspond to the solid fraction values measured at the same pressure during compression and during decompression, respectively. $SF_d(0)$ represents the solid fraction of the compact measured after the applied pressure has returned to zero but has not been ejected. This value is calculated using the thickness of the powder bed, in the die, at the moment the applied pressure returns to zero and reflects immediate elastic recovery in the axial direction but does not include radial elastic recovery or viscoelastic recovery.

Application of this correction to the pressure range over which in-die compressibility data were collected produces a function of elasticity-corrected solid fraction as a function of applied pressure (Figure A.4).
This figure shows how the corrected solid fraction ($SF_{c/d}$) relates to the measured in–die data. In this work, the $SF_c$ and $SF_d$ values were used when their corresponding pressure values differed by no more than 0.8 MPa. This creates gaps between $SF_{c/d}$ data points in cases where specific pressure values were unique to either the compression or decompression phase. Nevertheless, $SF_{c/d}$ data were obtained spanning the entire pressure range of each profile.

To assess the validity of this assumption, the amount of solid fraction change during decompression was compared between two tablets compressed using different maximum pressures. The change during decompression from 38 MPa was determined for
separate tablets compressed to maximum pressures of 38 and 264 MPa, respectively (Figure A.5).

![Graph of Pressure versus Displacement profiles for Lycatab® PGS compacted at 0.04 mm/s. Compression-decompression profiles for tablets compacted to 38 MPa (—) and 264 MPa (—) are labeled.]

For the 264 MPa tablets, this reflects only a fraction of the total decompression event, whereas it captures the entirety of decompression for the tablet compressed to 38 MPa. Nevertheless, the assumption is that the amount of decompression observed over the same range of pressure should be indistinguishable. The difference between the mean solid fraction change during decompression from 38 MPa, of the tablets formed using maximum pressures of 38 and 264 MPa, was less than 0.001 for Lycatab® PGS and no
more than 0.002 for all materials. The change in solid fraction due to elastic deformation during compression to 38 MPa appears to be the same as the amount of elastic deformation recovered during decompression from 38 MPa, even if the maximum applied pressure (264 MPa) is substantially higher. The consistency supports the assumption that the amount of elastic recovery only depends on the range of pressure considered and not on the maximum pressure used to prepare the compact.

A second correction was applied to the elasticity corrected in-die data ($S_{Fc/d}$) based on the assumption that the extent of viscoelastic recovery post ejection is relatively independent of the maximum applied pressure. This assumption allows for the change in solid fraction due to viscoelastic recovery after compression to one maximum applied pressure (264 MPa) to be used to correct for the time-dependent reversible deformation occurring at all other levels of applied pressure. The solid fraction change after ejection, referred to as $\Delta S_{final}$, represents the difference in solid fraction between $S_{Fc/d}$ and the measured out-of-die solid fraction (Figure A.6, following page).
Figure A. 6. Viscoelastic recovery versus pressure profile for Lycatab® PGS compacted at 0.04 mm/s. Data points represent average values (n = 6) and associated error bars represent standard deviation.

It is assumed that tablets compressed to lower pressures exhibit comparable recovery. Therefore, the SF_{c/d} value calculated at every pressure can be corrected for viscoelastic recovery by subtracting the same ΔSF_{final} value. Solid fraction values corrected for both elastic and viscoelastic recovery are referred to as SF_{corrected}, and are calculated using Eq. (26):

\[ SF_{corrected} = SF_{c/d} - ΔSF_{final} \] (26)
It should be noted that an applied pressure of 264 MPa is not of intrinsic significance, but was simply the largest pressure studied. Further application of this method only requires a tablet to be compressed to a pressure large enough to contain the pressure range of interest. Lycatab® PGS (Figure A.7) provides the best illustration for how this data correction is performed because of the relatively large contributions that elastic and viscoelastic deformation make to its behavior. The out-of-die solid fraction curve has been included for reference.

Figure A. 7. In-die (—), elasticity corrected (•••), viscoelasticity corrected (•••), and out-of-die solid fraction (□) versus pressure profiles for Lycatab® PGS compacted at 0.04 mm/s.
Prediction accuracy of $SF_{corrected}$ was assessed by comparing its value, at each of the seven pressures used to obtain the out-of-die compressibility profile, to the solid fraction values determined after complete elastic and viscoelastic recovery. These differences for Lycatab® PGS are presented in Figure A.8.

![Graph comparing predicted versus reference solid fraction values](image)

**Figure A. 8.** Predicted ($SF_{corrected}$) versus reference (Out-of-die SF) solid fraction values for Lycatab® PGS.

The difference in solid fraction at any pressure did not exceed 0.03. No difference was observed for tablets compressed to 264 MPa because this pressure was the reference pressure for determining $\Delta SF_{final}$. This small difference suggests that the applied corrections for elastic and viscoelastic deformation can be used to correct in-die solid fraction values with confidence. This comparison is also evident when Figure A.7 is
examined. The out-of-die data are indistinguishable from the $SF_{\text{corrected}}$ data in these plots. Next, corrected solid fraction data are converted to porosity using Eq. (7) and the natural logarithm transformed data are plotted as a function of pressure. Heckel plots for Lycatab® PGS are in Figure A.9.

![Heckel plots for Lycatab® PGS](image)

**Figure A. 9.** In-die (—we), elasticity corrected (•••), viscoelasticity corrected (•••), and out-of-die (□) Heckel plots for Lycatab® PGS compacted at 0.04 mm/s

At this point in the analysis, the next step was to determine the appropriate linear range in Figure A.9 for calculating the Out-of-Die Heckel Slope. As mentioned in Section 3.1.3.3, Heckel data in this work were considered linear when the first derivative showed less than 15 % variation. In order to compare yield pressure values, the same pressure range identified for the in-die curve was used for the remaining Heckel curves.
(i.e. $SF_{c/d}$, $SF_{corrected}$, and out-of-die). Table A.1, on the following page, provides a summary of the Heckel analysis results for each Lycatab<sup>®</sup> PGS curve.

Table A.1 Calculated yield pressure values using Heckel analysis

<table>
<thead>
<tr>
<th>Material</th>
<th>Uncorrected $P_y$&lt;sup&gt;a&lt;/sup&gt; (MPa)</th>
<th>$SF_{c/d}$ $P_y$&lt;sup&gt;a&lt;/sup&gt; (MPa)</th>
<th>$SF_{corrected}$ $P_y$&lt;sup&gt;a&lt;/sup&gt; (MPa)</th>
<th>Out-of-die $P_y$&lt;sup&gt;a&lt;/sup&gt; (MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-gelatinized maize starch (Lycatab&lt;sup&gt;®&lt;/sup&gt; PGS)</td>
<td>55 (5)</td>
<td>88 (10)</td>
<td>134 (13)</td>
<td>133 (14)</td>
</tr>
</tbody>
</table>

<sup>a</sup>$P_y$ represents the average of the reciprocal slope obtained from three replicate tablets compressed to 264 MPa.

The error reported for apparent yield pressure reflects the standard deviation of three replicate tablets. The predicted apparent yield pressure did not deviate significantly from measured values. Out-of-die Heckel slope values, $k$, can be calculated by taking the inverse of yield pressure, $P_y$, using Eq. (27):

$$k = \frac{1}{P_y}$$

For the data presented in Table A.1, the estimated out-of-die Heckel slope value using $SF_{corrected}$ is 0.00746 compared to 0.00751 for the measured out-of-die data. The applicability of this method to generate out-of-die compressibility curves that can be fit to the Heckel model with precision and accuracy is significant because this is one of the most commonly used pieces of data by formulation scientists to guide tablet development. Not only is this method computationally simple, but it is also material-
sparing requiring as little as one tablet worth of material. Characterization of powder compressibility using this simple approach can improve productivity and streamline tablet development studies; allowing more information to be obtained from fewer experiments. The proposed method offers the ability to assess plasticity, using the Out-of-Die Heckel Slope, quickly and independently. In cases where only small amounts of raw material are available or where a large number of different powders are to be studied, this method allows a detailed understanding of material deformation to be developed in a straightforward and reproducible manner.