Additional Shear Testers

Schulze ring shear and Jenike shear cell testers are used extensively due to their commercial availability, though other shear cells are available. Plate or "simplified" shear cells have also been designed, which consist of a thin sandwich of powder between a lower stationary rough surface and an upper rough surface that is movable.[18,51] Uniaxial, biaxial, and triaxial testers have also been used for flow analysis, and have been discussed in the literature. The measurement principle of the uniaxial tester is similar to that of shear cells.[35,52]

Dynamic Test Methods

Avalanche testers assess the flowability of powders by measuring their avalanching behavior, which is related to powder cohesivity and flowability. Unlike shear cell methodology, this type of assessment is dynamic in nature,[53] which may be more applicable to low-shear processes such as blending, in which avalanching behavior of powder promotes mixing. Avalanche testing can be carried out in different types of equipment, including rotating drums and vibratory feeders.[54,55] Avalanche testing has been shown to distinguish between freely flowing powders, blends, and granulations.[56,57]

One of the most widely used rotating drum avalanche testers is the Aeroflow® (TSI, St. Paul, MN). Powder is filled into a transparent drum, which is then rotated at a fixed speed. The stress applied to the powder sample as a result of rotation causes the powder to shear, resulting in avalanche events.[58] The avalanche events are monitored by an optical sensor system. From the detector response data, a frequency or mass distribution of the avalanche events can be generated which can be used to determine various flowability parameters. Hancock et al. used the mean time to avalanche (mean of the distribution), and the coefficient of variation of the avalanche events, to characterize powder flow.[54]

One limitation of the avalanche tester is the qualitative nature of determining the regimes of avalanche flow in the rotating drum. Boothroyd et al. argued that the ideal flow regimes necessary for meaningful data analysis for pharmaceutical powders were the "rolling" and "cascading" regimes.[59] Another limitation of the system is the method development required prior to analysis. Rotational speed, measurement duration, and sample size must be optimized, as they have a great degree of influence over the measurement results.[54] A third limitation is the amount of material required, which limits the use of this technique in a material-sparing approach to formulation development. Hancock et al. proposed a sample size of 50 mL.[54]

Bhattachar et al. developed a vibratory feeder method for assessing avalanche behavior that requires a smaller sample size than for the Aeroflow® (1.2 g). Results compared to those generated using the Aeroflow®.[60] Despite the small sample size requirements this method is not widely used. The instrument is not commercially available, and has not been extensively tested.

8.4 COMPACT (MECHANICAL PROPERTY) CHARACTERIZATION

Many investigations have demonstrated the importance and impact of the physical and chemical properties of materials on powder processing. Physical properties such as particle size and shape clearly influence powder flow for example. The previous sections of this chapter provide some recommendations for how to proceed with characterization using limited quantities of materials. However, compact mechanical properties (i.e., those properties of a material under the influence of an applied stress) are also of great importance for solid dosage form development and manufacturing—particularly for tablet formulation. This section describes the importance of the mechanical properties of materials, as well as some basic principles and methodologies that can be used to investigate the influence of these properties on compaction. For the purposes of this discussion, physical properties are considered to be those properties that are "perceptible especially through the senses" (i.e., properties such as particle size, and shape). In contrast, mechanical properties are those properties of a material under an applied load: elasticity, plasticity, viscoelasticity, bonding, and brittleness.

Table 8.4 lists some of the physical and mechanical properties that influence powder properties and compaction. For example, surface energy and elastic deformation properties influence individual particle true areas of contact. Plastic deformation likely occurs to some extent in powder beds depending on the applied load, and almost certainly it occurs during the compaction of powders into tablets. Certainly at asperities, local regions of high pressure can lead to localized plastic yielding. Electrostatic forces can also play a role in powder flow, depending on the insulating characteristics of the material and environmental conditions. Particle size, shape, and size distribution have also been shown to influence flow and compaction. A number of environmental factors such as humidity, adsorbed impurities (air, water, etc.), consolidation load and time, direction and rate of shear,

and storage container properties are also important. With so many variables, it is not surprising that a wide variety of methods have been developed to characterize materials. The focus of this chapter is on those useful methods that require limited amounts of material (bulk drug or formulation), and provide the most valuable information.

What holds particles together in a tablet? A detailed discussion is beyond the scope of this chapter, and excellent references are available in the literature.[61,62] However, it is important to realize that the forces that hold particles together in a tablet or powder bed are the very same forces discussed in detail in introductory physical chemistry texts. There is nothing magical about particle–particle interactions; the forces involved are London dispersion forces, dipole interactions, surface energy considerations, and hydrogen bonding. The consolidation of powders brings particles into close proximity, and these fundamental forces can begin to act effectively to produce strong particle–particle interactions (e.g., bonding). Particle rearrangement, elastic and plastic deformation of material can establish large areas of true contact between particles; if the resulting particle–particle bonds are strong, a strong and intact tablet is produced.

8.4.1 Important Mechanical Properties

Materials used in the pharmaceutical industry can be elastic, plastic, viscoelastic, hard, tough or brittle in the same sense that metals, plastics or wood are. The same concepts that mechanical engineers use to explain or characterize tensile, compressive or shear strength are relevant to pharmaceutical materials. These mechanical properties of materials can have a profound effect on solids processing.

The mechanical properties of a material play an important role in powder flow and compaction. These properties are critical properties that influence the true areas of contact between particles. Therefore, it is essential to characterize the properties. Reliable mechanical property information can be useful in helping to choose a processing method such as granulation or direct compression, selecting excipients with properties that will mask the poor properties of the drug or helping to document what went wrong, for example, when a tableting process is being scaled-up or when a new bulk drug process is being tested. Since all of these can influence the quality of the final product, it is to the formulator's advantage to understand the importance of the mechanical properties of the active and inactive ingredients, and to be able to quantify the properties.

Elastic Deformation

In general, during the initial stages of deformation, a material is deformed elastically. A change in shape caused by the applied stress is completely reversible, and the specimen will return to its original shape on release of the applied stress. During elastic deformation, the stress–strain relationship for a specimen is described by Hooke's law (Equation 8.8):

$$\sigma = E \cdot \varepsilon \tag{8.8}$$

where:

E is referred to as Young's modulus of elasticity
σ is the applied stress
ε is the strain $(\varepsilon = (l - l_o)/l_o)$.

The region of elastic deformation of a specimen is shown graphically in Figure 8.6. The reader is directed to standard texts in material science and engineering for detailed discussions of elastic deformation. As long as the elastic limit is not exceeded only elastic deformation occurs.

The elastic properties of materials can be understood by considering the attractive and repulsive forces between atoms and molecules. Elastic strain results from a change in the intermolecular spacing and, at least for small deformations, is reversible.

Plastic Deformation

Plastic deformation is the permanent change in shape of a specimen due to applied stress. The onset of plastic deformation is seen as curvature in the stress–strain curve shown in Figure 8.7. Plastic deformation is important because it "allows" pharmaceutical excipients and drugs to establish large true areas of contact during compaction that can remain on decompression. In this way, strong tablets can be prepared.

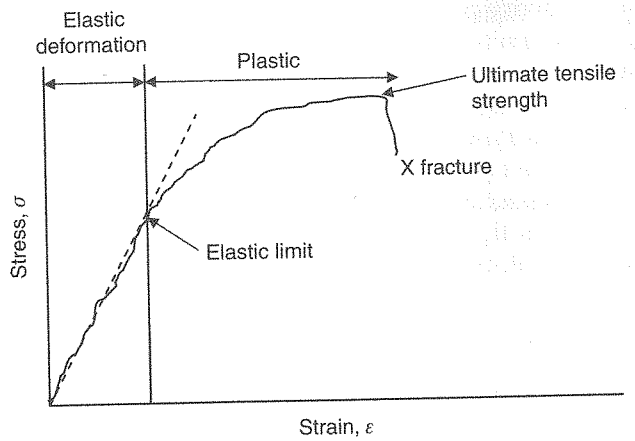

FIGURE 8.7 Stress–strain curve

Plastic deformation, unlike elastic deformation, is generally not accurately predicted from atomic or molecular properties. Rather, plastic deformation is often determined by the presence of crystal defects such as dislocations, grain boundaries, and slip planes within crystals. While it is not the purpose of this chapter to discuss this in detail, it is important to realize that dislocations and grain boundaries are influenced by factors such as the rate of crystallization, particle size, the presence of impurities, and the type of crystallization solvent used. Slip planes may exist within crystals due to molecular packing arrangements that result in weak interplanar forces. Processes that influence these (e.g., crystallization rate, solvent, temperature) can be expected to influence the plastic deformation properties of materials, and hence the processing properties. The reader is directed to standard texts in material science and engineering for detailed discussions of plastic deformation.

The plastic properties of a material are often determined by an indentation test.[63] Both static and dynamic test methods are available, but all generally determine the pressure necessary to cause permanent and non-recoverable deformation.

Brittle and Ductile Fracture

In addition to plastic deformation, materials may fail by either brittle fracture or ductile fracture; fracture being the separation of a body into two or more parts. Brittle fracture occurs by the rapid propagation of a crack throughout the specimen. Conversely, ductile fracture is characterized by extensive plastic deformation followed by fracture. Ductile failure is not typically seen with compacts of pharmaceutical materials. The characteristic snap of a tablet during hardness testing is indicative of brittle fracture.

Viscoelastic Properties

Viscoelastic properties can be important; viscoelasticity reflects the time-dependent nature of stress–strain. A basic understanding of viscoelasticity can be gained by considering processes that occur at a molecular level when a material is under stress. An applied stress, even when in the elastic region, effectively moves atoms or molecules from their equilibrium energy state. With time, the rearrangement of atoms or molecules can occur.

The stress–strain relationship can therefore depend on the time frame over which the test is conducted. In compacting tablets, for example, it is frequently noted that higher compaction forces are required to make a tablet with a given strength when the compaction speed is rapid. All pharmaceutical materials are viscoelastic; the degree to which their mechanical properties are influenced by rate depends on the material.

8.4.2 Overview of Methods

Characterizing mechanical properties has been an active area of pharmaceutical research for decades. The application of classic "engineering" methodologies to characterize pharmaceutical materials dates to the 1950s or before. With the advent of high-speed computer control, and monitoring of processes such as tablet compaction, the era of "dynamic" characterization of pharmaceutical materials was ushered in. Sophisticated instrumentation of rotary tablet presses and, in particular, the design of tablet compaction simulators with seemingly infinite control of the compaction process, has offered scientists an unprecedented opportunity to study the mechanics of materials at speeds representative of production tablet compaction. Yet, even today, both dynamic testing and the classic "quasi-static" engineering testing approaches offer opportunities to understand pharmaceutical materials. In this regard, dynamic and quasi-static testing are complementary tools. Both quasi-static and dynamic test methodologies will be discussed in the following sections. One key advantage of quasi-static testing is the ability to "independently" dissect out and investigate the various mechanical properties of a material. As stated previously, pharmaceutical materials can be elastic, plastic, viscoelastic, hard, tough or brittle. Ultimately, these individual components that cumulatively describe a pharmaceutical material determine its compaction properties in a dynamic compaction process.

The consolidation of powders into intact tablets is a process of reducing pores in a powder bed while creating interparticle bonds. During compression, materials experience complex stresses, the structure of the powder bed changes, and consolidation is brought about mainly by particle rearrangement, plastic deformation, and fragmentation.[64] The deformation of pharmaceutical materials is time dependent, and this dependency is related to the consolidation mechanism and dynamics of the consolidation process.[65,66,67,68,69] Under compression, for example, brittle materials are considered to consolidate predominantly by fragmentation; plastic materials deform by plastic flow. The time dependency of this process arises from stress relaxation for materials undergoing primarily plastic deformation. However, the compaction of brittle materials is often less influenced by speed, because fragmentation is rapidly achieved and prolonged exposure to the force has a limited effect on tablet properties.

Several researchers have previously identified the utility of solid fraction in describing tablet properties. Armstrong and Palfrey[70] concluded that differences in the tensile strength of tablets compressed at different speeds could be accounted for by differences in tablet porosity. Hancock and coworkers[71] found that tablet strength and disintegration time for tablets made on an eccentric press and a rotary press were comparable when considering a comparable solid fraction. Maarschalk and coworkers[72] found that tablet tensile strength of sorbitol as a function of tablet porosity was independent of compression speed. Finally, Tye and coworkers[64] extended this work to show that tablet solid fraction (SF) was the primary factor determining tablet strength for several pharmaceutical excipients (both brittle and ductile) over an extremely wide range of compaction speeds (dwell times from <10 msec to 90 sec).

The solid fraction (SF) of a compact can be calculated based on the true density (ρ_{true}) of the material (typically determined using pycnometry), the tablet volume (ν), and the tablet weight (Wt) (Equation 8.9):

$$SF = \frac{Wt}{\rho_{true} \cdot \nu} \tag{8.9}$$

The relationship between the solid fraction, also referred to as relative density, and porosity (ε) is:

$$\varepsilon = 1 - SF \tag{8.10}$$

8.4.3 Quasi-static Testing

Quasi-static testing typically applies variations of traditional engineering and material science testing methods to compacts (i.e., test specimens) of pharmaceutical materials. There are, for example, a number of variations of indentation, tensile, flexural, compression, and brittle fracture tests in the pharmaceutical literature.[73] The quantity of material required for testing varies from 1 to 100 grams. Methods for characterizing the elastic, plastic, and brittle properties of compacts of organic materials have, for example, been developed by Hiestand and coworkers.[74,75,76,77,78] These measures of tableting performance assess several key mechanical properties of compacted materials that have been shown to relate to tableting. Currently available methods typically require from 10 to 60 grams for complete mechanical property characterization using Hiestand's methods.

Test Specimen Preparation

It is important to properly prepare test specimens of pharmaceutical materials so quasi-static test results are not improperly influenced by "flaws" that may exist in the test specimen itself. Of the methods defined in the literature, the most refined method is to make square compacts using triaxial compression and decompression.[74] A split die (Figure 8.8) is used to make compacts that are substantially free of defects that may occur if a conventional compaction process were to be used. The split die permits triaxial decompression such that the pressure applied to all three axes is essentially equal during the decompression process.[74] This is achieved by computer control of the decompression process. The stresses in the compact are more uniformly relieved in three dimensions, and this minimizes the production and propagation of flaws within the compact.

Importance of the Solid Fraction

It is imperative to realize and address the fact that the mechanical properties of a compact are very much influenced by solid fraction. A change in solid fraction of 0.01 (i.e., a change in *SF* from 0.85 to 0.86) can result in a mechanical property change of 10% to 20%. For this reason, it is critical to compare the properties of a material at a "reference" solid fraction to ensure that one is "comparing apples to apples." Hiestand and coworkers[74] defined their reference solid fraction as 0.9 (i.e., porosity = 0.1 or 10%) while others have used a solid fraction of 0.85 or even extrapolated to a solid fraction of 1.0 (e.g., zero porosity). In comparing results from the literature, it is important to keep this in mind. It is recommended that a solid fraction in the range typical of tablet compaction be used. For compacts of organic materials, a reference solid fraction of 0.85 is in the midrange of those typically

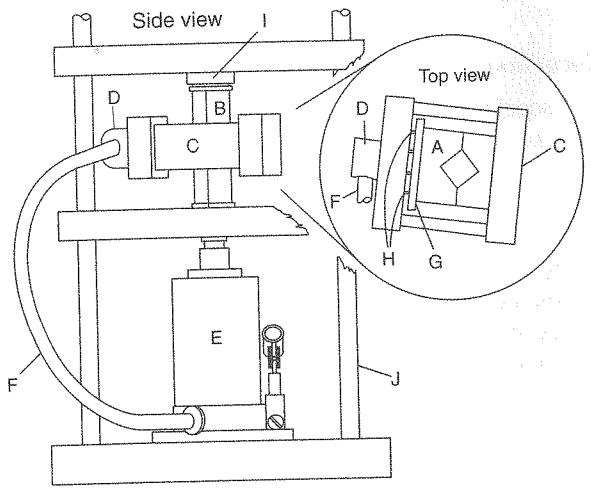

FIGURE 8.8 Schematic drawing of a simple triaxial press with a split die

observed. For inorganic materials (such as dicalcium phosphate) solid fractions in the 0.6 to 0.75 range are often observed for tablets. The wide range of mechanical properties observed means no ideal value can be identified for all materials.

Tensile Strength Determination

The tensile strength, σ_T, of a square test specimen provides extremely useful information. Several methods for determining it are available, and include traditional tablet hardness testing and transverse compression or square compacts. In transverse compression, specimens are compressed with platens 0.4 times the width of the compacts in the tensile testing apparatus.[74] The force necessary to cause tensile failure (tensile forces are maximum at the center of the tablet) is monitored by a load cell, and the magnitude of the force at fracture is determined. Testing of square compacts has advantages over the testing of circular compacts; however, circular compacts can be used. Conventional hardness testing of tablets can result in a measurement of tensile strength.[79] Similar results are obtained for round and square compacts when tensile failure is achieved. It is extremely important to compare measured properties such as tensile strength at the same solid fraction. Tensile strength values in excess of 1 MPa (typical range 0.1 to 4 MPa) are typically desired for tablets.

Pendulum Impact Device

A simple schematic of a pendulum impact device (PID) is given in Figure 8.9. This equipment permits the permanent deformation pressure of a compact of material to be determined under dynamic conditions.[74,75] Flat-faced, square tablets of the test substance are compressed at different compression pressures, and then subjected to impact with a stainless steel ball in the PID. The rebound height of the ball and the chordal radius of the dent are carefully measured, and used to calculate the permanent deformation pressure. In a simple sense, one is measuring the energy necessary to make the permanent deformation (the difference between the initial height of the ball and the rebound height). By measuring the volume of the dent, one can calculate the deformation pressure—the energy divided by the volume. The permanent deformation pressure is the pressure (i.e., stress) necessary to cause plastic deformation. This permanent deformation pressure, H, has been shown to be related to the yield pressure obtained using dynamic testing methods and Heckel analysis.[80] The dynamic hardness and tensile strength are shown in Figure 8.10 as a function of solid fraction for a common pharmaceutical excipient. One can clearly see the impact of solid fraction on the measured mechanical properties.

Tableting Indices

Using the methodology described above, several indices of tableting performance have been developed by Hiestand and coworkers.[61,76] These indices provide relative measures of properties (i.e, dimensionless numbers) that reflect the performance of materials during processing.

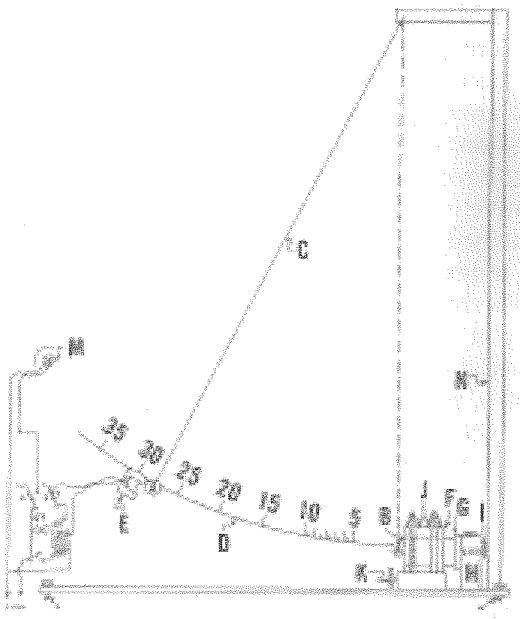

FIGURE 8.9 Pendulum impact device

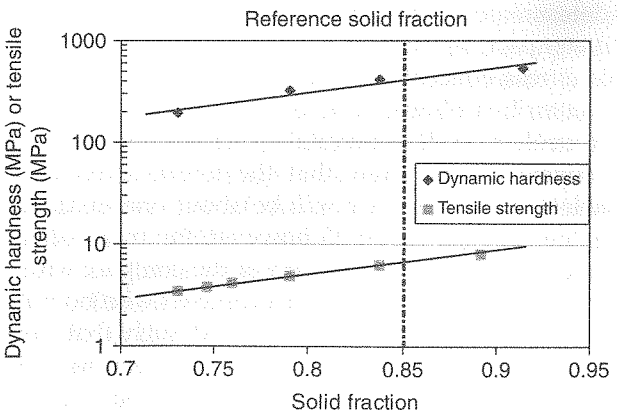

FIGURE 8.10 Dynamic hardness and tensile strength as a function of solid fraction

Bonding index

The purpose of the bonding index is to estimate the survival of strength during decompression;[76] it is defined in Equation 8.11:

$$BI = \frac{\sigma_T}{H} \tag{8.11}$$

where:

σ_T is the tensile strength of the compact at a given solid fraction (typically 0.85 or 0.9 as defined by the user)

H is the permanent deformation pressure (i.e., hardness) of a compact at the same solid fraction.

The bonding index (BI) is, in essence, a measure of the ability of a material, on decompression, to maintain a high fraction of the bond that was created during compression. At maximum compression pressure, the bonded areas are at a maximum, because the true areas of contact are maximized. During decompression, some of that area and bond is "lost" due to elastic recovery. A high bonding index indicates that, relatively speaking, a larger portion of the strength remained intact after decompression. A low bonding index indicates that less of the strength remains. The term bonding index, then, is a good description since it, in effect, characterizes the tendency of the material to remain intact after it has been compressed. Tablets made of materials with poor bonding characteristics may be quite friable. Compacts made of materials with good bonding indices may, conversely, make strong tablets. A bonding index in excess of 0.01 (range 0.001 to 0.06) is typically desired.

Brittle fracture index

The brittle fracture index is a measure of the brittleness of a material. It is a measure of the ability of a compact to relieve stress around compact defects by plastic deformation. The brittle fracture index (BFI) is determined[74,75] by comparing the tensile strength of a compact, σ_T, with that of a compact with a small hole (stress concentrator) in it, σ_{To}, using the tensile test described above. A hole in the center of a compact weakens it. If a material is very brittle, theoretical considerations show that the tensile strength of a tablet with a hole in it will be about one-third that of a "defect free" tablet. If, however, the material can relieve stress, then the strength of the compact with a hole in it will approach that of a compact with no hole. The brittle fracture index is defined such that very brittle compacts have a *BFI* of 1, and very nonbrittle materials have a *BFI* close to 0; it is calculated in Equation 8.12.[74] *BFI* values less than 0.3 (range 0 to 1) are indicative of relatively nonbrittle materials.

$$BFI = 0.5 \cdot \left[\frac{\sigma_T}{\sigma_{To}} - 1 \right] \tag{8.12}$$

Viscoelastic index

Hiestand and coworkers have further refined the concept of bonding index to include both a worst-case and a best-case bonding index.[76] The bonding index is determined under different experimental conditions: the rate at which the permanent dent is made in a compact is varied such that the viscoelastic properties of the material are assessed. If a material is very viscoelastic, there is substantial stress relaxation with time. It is reasonable to expect, then, that tablets that are slowly deformed during the determination of the hardness, H, may retain more of the bonded area than tablets that are rapidly deformed (i.e., as in the pendulum impact device), since some of the stresses developed during compaction will have a chance to be relieved. The dynamic bonding index (BI_d), sometimes called the worst case BI, is determined using a the pendulum impact device (PID) for measuring the indentation hardness (H_d), while the quasi-static bonding index (BI_{qs}), also sometimes referred to as the best case BI, is measured using a "quasi-static" or slow method for measuring indentation hardness (H_{qs}). The dynamic and quasi-static bonding index is calculated as previously described. The viscoelastic index (VE) is defined as the ratio of the dynamic to quasi-static indentation hardness:

$$VE = \frac{H_d}{H_{qs}} = \frac{BI_{qs}}{BI_d} \tag{8.13}$$

Application of Quasi-static Testing to Formulation Development

The application of quasi-static testing methods and interpretation has been discussed extensively in the scientific literature. In addition to the pioneering work of Hiestand and coworkers,[61,62,63,74,75,76,77,78] additional research discussing the application of this methodology is available.[33,64,81,82,83,84,85,86,87,88,89,90] Benefits of a complete characterization of the mechanical properties of both the active ingredient and the excipients used in the formulation include:

- fundamental understanding of critical mechanical properties of the active ingredient and excipients;
- identification of mechanical property deficiencies and attributes;
- selection of excipients that can overcome deficiencies of active ingredient;

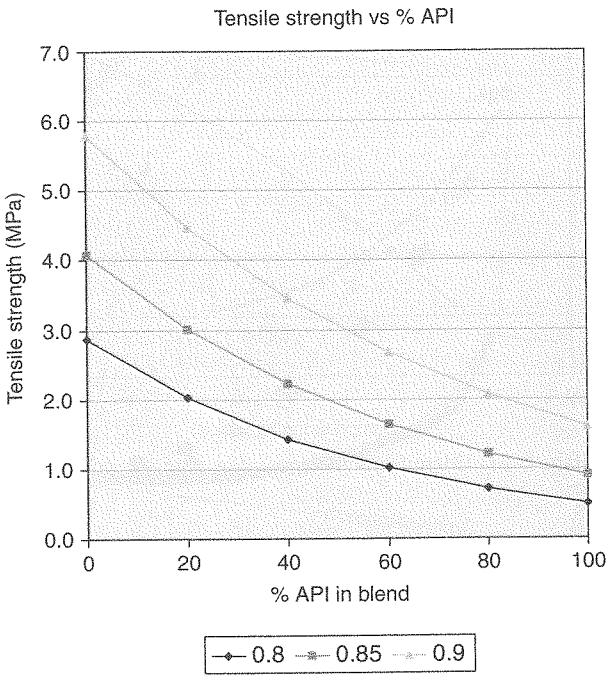

FIGURE 8.13 Predicted mechanical properties of a ternary blend of API, micro crystalline cellulose and lactose spray process.

conditions of the test is a measure of the deformability. In addition to yield strength, the shape of the Heckel plot has been used to distinguish volume reduction mechanisms.[105] Three types or families of curves are considered to reflect materials that undergo consolidation primarily by: (a) plastic deformation, (b) fragmentation, or (c) a variation of (a) which is plastic flow with no initial particle rearrangement.

Additional information regarding the compaction process may be obtained using dynamic testing conditions, including work of compaction, work recovered during decompression, work to overcome die wall friction, etc. A detailed discussion of these opportunities is beyond the scope of this chapter, and the reader is directed to the literature for further information. While very valuable as a research tool, the quantitative use of pressure–porosity measurements and analysis beyond the determination of yield pressure does not appear to be used routinely during formulation development and optimization.

Application of Dynamic Testing to Formulation Development

There are a number of reports of the use of dynamic testing of active ingredients and excipients in the literature. There are two key benefits of dynamic testing: (1) the properties can be determined under dynamic conditions representing those in a production environment; and (2) small quantities are typically required (2–10 g). In contrast, disadvantages include the difficulty of factoring out the individual mechanical property "components" that, combined, determine how a material behaves during compaction.

The relationships between compaction pressure, tensile strength, and solid fraction are critical to understanding and characterizing the compaction process. The relationship between these three parameters is described as:

- Compactibility: relationship between tensile strength and solid fraction;
- Tabletability: relationship between tensile strength and compression pressure;
- Compressability: relationship between compaction pressure and solid fraction or porosity;
- Manufacturability: relationship between tablet crushing force and compression force.

Representative compactibility, tabletability, compressability, and manufacturability profiles for a compactable excipient are shown in Figures 8.14 through Figure 8.17. The compactibility, tabletability, and compressability profiles form the three faces of a three-dimensional plot as shown in Figure 8.18.[64] The Presster™ compaction emulator was used for these studies, although other properly instrumented presses can also be used. The compaction emulator was set up to emulate a Killian RST tablet machine (250 mm compression rolls) with a 27 msec dwell time (corresponding to 28 800 tablets/hour) using 10 mm diameter flat-faced round punches with no precompression force.

Compactibility is the ability of a powder to be transformed into tablets with a resulting strength.[107] It is represented by a plot of tensile strength versus solid fraction. The compactibility is the most valuable of the three properties, since it reflects the two most important effects of applied pressure: tablet strength, and solid fraction. A representative compactibility profile of an excipient is shown in Figure 8.14. If one can achieve an acceptable tensile strength at an acceptable solid fraction with the application of pressure, a satisfactory tablet can be produced. Compactibility plots are largely independent of the process by which compacts are made, since only measured tablet properties (tensile strength and solid fraction) are involved. Compactibility plots are useful as a tool to compare formulations made on different equipment. If the formulations are the "same" then the "same" compactibility plots will be obtained.[64]

Tabletability is the capacity of a powder to be transformed into a tablet of specified strength under the effect of compaction pressure.[107] It is represented by a plot of tensile strength versus compaction pressure. Tabletability describes the effectiveness of the applied

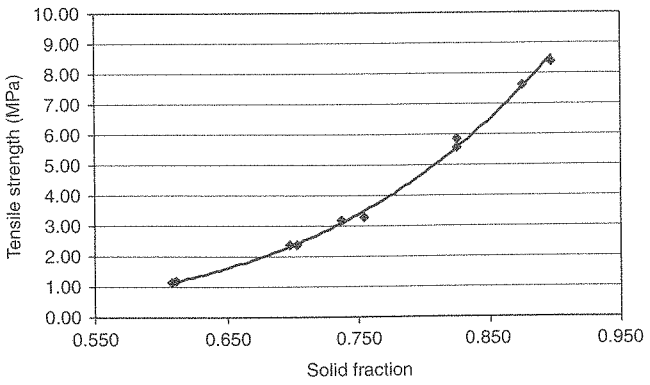

FIGURE 8.14 Compactability profile using a compaction emulator

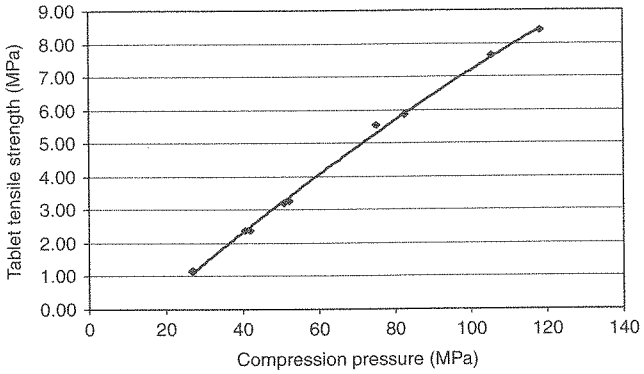

FIGURE 8.15 Tabletability profile using a compaction emulator

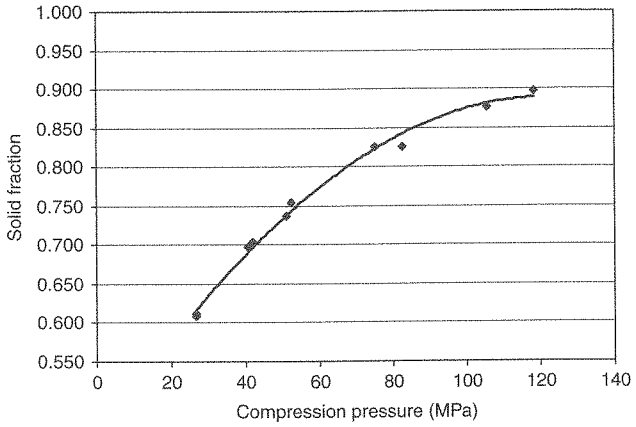

FIGURE 8.16 Compressibility profile using a compaction emulator

pressure in increasing the tensile strength of the tablet, and demonstrates the relationship between the cause (the compaction pressure), and the effect (the strength of the compact) (see Figure 8.15). Normally, a higher compaction pressure makes a stronger tablet. However, this relationship is often found to be speed

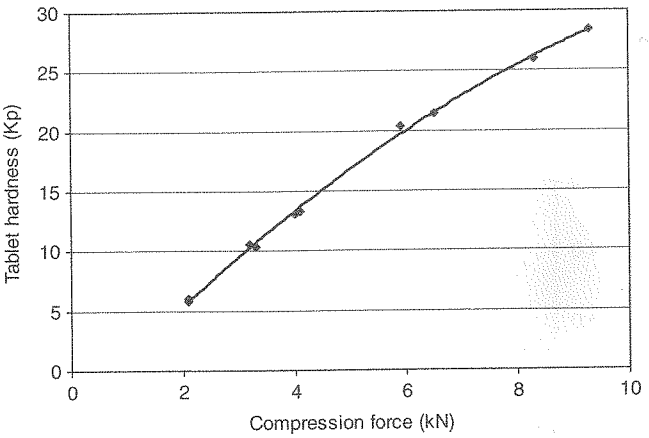

FIGURE 8.17 Manufacturability profile using a compaction emulator

dependent. Also, at high pressures, some materials may have lower tensile strength due to overcompaction.[106] Characterization of the tabletability provides excellent insight into the compaction process and mechanical properties of a material.

Compressability is the ability of a material to undergo a reduction in volume as a result of an applied pressure.[107,108] It is a measure of the ease with which a powder bed undergoes volume reduction under compaction pressure; it is represented by a plot showing the reduction of tablet porosity (i.e., the increase in solid fraction) with increasing compaction pressure (Figure 8.16). Compressability is often described by the Heckel equation.[109] Heckel plots, for example, have been widely used to assess the mechanism of deformation, and as a tool to estimate yield pressure. It is also well-known that tablet porosity is an important parameter, for example, in tablet disintegration and dissolution, since some porosity is often necessary to facilitate liquid penetration into tablets.[110,111]

Manufacturability, a plot closely related to tabletability, shows the relationship between the tablet crushing force (related to tensile strength), and compaction force (related to compression pressure). The manufacturability profile (Figure 8.17) is commonly considered by formulation scientists since it reflects the "measured" properties of a dosage form during manufacturing (tablet crushing strength and compression force). In general, however, pressure and tensile strength are preferred parameters to consider.

In summary, characterization of the compactibility, tabletability, compressability, and manufacturability of a formulation provides valuable information of the compaction process, and the prospects for a successful tableting process in manufacturing. Obtaining tablets with adequate tensile strength at a reasonable solid fraction with acceptable compression pressure is the

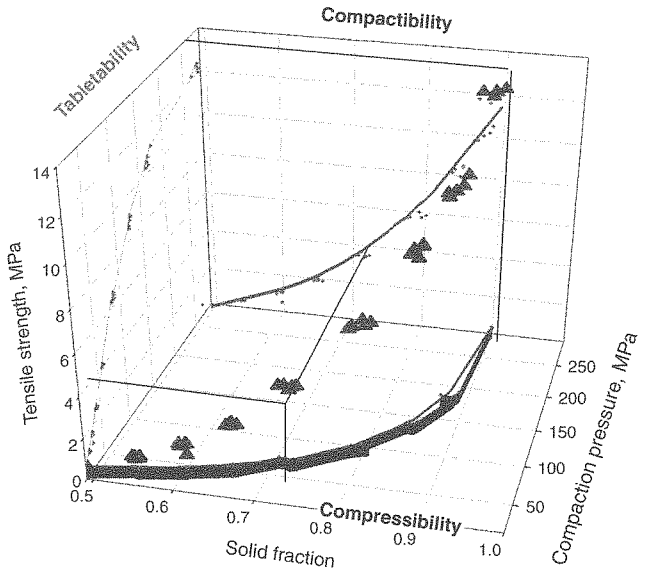

FIGURE 8.18 Three-dimensional tablet tensile strength, solid fraction, and compaction pressure curve

key to success. Robust formulations must not be on the "edge;" that is, they should provide the manufacturing scientist with the ability to adjust compression pressure to achieve the desired tensile strength and still maintain the solid fraction in a desirable range, such that the tablet performs as required.

8.5 CONCLUSIONS

As timelines become tighter and shortened, it has become more important than ever to quickly and efficiently characterize the critical properties of materials that will influence product development and performance. In this chapter, a discussion of those particle, powder, and compact properties that are most important in developing solid dosage forms has been discussed. The focus has been on methods that yield important information, yet require small quantities of materials. With a sound understanding of these properties, formulation development can proceed most efficiently and scientifically with greater success. Tomorrow's formulation and process scientists will require a sound understanding of these pharmaceutical material science principles, and must be able to apply them to the design and development of dosage forms in an efficient and scientifically rigorous way. The beauty of science is the knowledge and ability it gives us to reliably predict the future. As formulation and process scientists, the future we need to accurately predict is that of a consistent, reliable, manufacturable product that performs as expected.

References

1. Brittain, H. G. (2004). *Evaluation of the Particle Size Distribution of Pharmaceutical Solids. Profiles of Drug Substances, Excipients, and Related Methodology*, Vol. 31.
2. Allen, T. (1997). *Particle Size Measurement*, 5th edn. Vol. 1. Chapman & Hall, New York.
3. Stanforth, J. (2004). Particle-size Analysis, In: Pharmaceutics *The Science of Dosage Form Design*, M. Aulton (ed.). pp. 152–165.
4. US Pharmacopeia 27. (2006). US Pharmacopeial convention, Rockville, MD, pp. 2716–2717.
5. Newman, A. W. & Brittain, H. G. (1995). Particle Morphology: Optical and Electron Microscopies. In: *Physical Characterization of Pharmaceutical Solids*, H.G. Brittain, (ed.). Marcel Dekker, New York. pp. 127–156.
6. Operation and Maintenance Manual. (2004). Gilsonic Siever Model GA-8, Gilson Company, Inc., P.O. Box 200, Lewis Center, Ohio 43035-0200.
7. US Pharmacopeia 27. (2006). US Pharmacopeial convention, Rockville, MD. pp. 2720–2722.
8. Rohrs, B.R., Amidon, G.E., Meury, R.H., Secreast, P.J., King, H.M. & Skoug, C.J. (2006). Particle size limits to meet usp content uniformity criteria for tablets and capsules. Journal of Pharmaceutical Sciences 95(5), 1049–1059.
9. Dressman, J.B. & Fleisher, D. (1986). Mixing tank model for predicting dissolution rate control of oral absorption. Journal of Pharmaceutical Sciences 75, 109–116.
10. Higuchi, W.I. & Hiestand, E.N. (1963). Dissolution rates of finely divided drug powders I: Effect of a distribution of particle sizes in a diffusion-controlled process. Journal of Pharmaceutical Sciences 52, 167–171.
11. Hintz, R.J. & Johnson, K.C. (1988). The effect of particle size distribution on dissolution rate and oral absorption. International Journal of Pharmaceutics 51, 9–17.
12. Rohrs, B. R. & Amidon, G. E. (2005). Particle Engineering: A Formulator's Perspective. AAPS Arden House Conference. Harriman, New York.
13. US Pharmacopeia 27. (2006). US Pharmacopeial convention, Rockville, MD, pp. 2669–2670.
14. Mohanmmadi, M.S. & Harnby, N. (1997). Bulk density modeling as a means of typifying the microstructure and flow characteristics of cohesive powders. Powder Technology 92, 1–8.
15. Abdullah, E.C. & Geldart, D. (1999). The use of bulk density measurements as flowability indicators. Powder Technology 102, 151–165.
16. Suzuki, M., Sato, H., Hasegawa, M. & Hirota, M. (2001). Effect of size distribution on tapping properties of fine powder. Powder Technology 118, 53–57.
17. US Pharmacopeia 27. (2006). US Pharmacopeial convention, Rockville, MD, pp. 2638–2639.
18. Amidon, G.E. & Houghton, M.E. (1985). Powder flow testing in preformulation and formulation development. Pharm. Manuf. 2(7), 20–31.
19. Köhler, T. Influence of Particle Size Distribution on the Flow Behaviour of Fine Powders. Particle and Particle Systems Characterization, 8, 101–104.
20. Shinohara, K. (2000). Effect of particle shape on angle of internal friction by triaxial compression test. Powder Technology 107, 131–136.
21. Podczeck, F. (1996). The influence of particle size and shape on the angle of internal friction and the flow factor of unlubricated and lubricated powders. International Journal of Pharmaceutics 144, 187–194.
22. Kachrimanis, K., Karamyan, V. & Malamataris, S. (2003). Artificial neural networks (ANNs) and modeling of powder flow. International Journal of Pharmaceutics 250, 12–23.