A marketable drug must be stable under a wide range of conditions of temperature and relative humidity to ensure a satisfactory shelf life. For oral solid dosage forms, it is generally considered that 2-year storage at room temperature is the minimum acceptable shelf life. This allows sufficient time for manufacture of drug substance and drug product, shipping, storage, and finally sale to and use by consumers. Loss of potency and impurity growth are important considerations in determining the shelf life. While perhaps 5% loss of drug may be considered acceptable by regulatory agencies, the shelf life of a product is often limited by formation of a much lower level of degradation products. The International Conference on Harmonization (ICH) Q3B (R2)[33] specifies the reporting, identification, and qualification thresholds for impurities in new drug products. Depending on the maximum daily dose, a level of 0.1% to 1% of degradation products will likely require identification or qualification.[33]

Solution Stability

For oral solid products, it is important to test solution stability, because a drug has to dissolve in the gastric or intestinal fluids prior to absorption. The stomach is generally quite acidic for a majority of people, and the residence time in the stomach varies between 15 minutes and a few hours depending on food intake. Therefore, it is important to conduct stability testing under acid conditions over a period of a couple of hours at 37°C, to ensure no significant appearance of degradation products of unknown toxicity. Residence time in the small intestine is approximately 3 hours, while residence time in the large intestine ranges up to 24 hours. The intestinal pH may range from 5 to 7. If a drug molecule is stable in solution with the pH ranging from 5 to 7 at 37°C for up to 24 hours, significant decomposition in the intestine will not be likely to occur. For a majority of drug candidates, solution stability is tested in buffered aqueous solution at pH of 1.2 to 2, and in the range of pH 5 to 7. However, for a compound with known stability problems, a complete pH-degradation rate profile can provide valuable information regarding the degradation mechanism and degradation products.

Solid-state Stability

Solid-state decomposition may occur through several pathways, i.e., hydrolysis, oxidation–reduction, racemization, decarboxylation, ring cleavage, and photolysis.[16] Among these, hydrolysis and oxidation–reduction are most frequently encountered. Most solid-state degradation of pharmaceuticals has been analyzed with either zero-order or first-order kinetics.[34] Occasionally the Prout–Tompkins equation has been used.[35]

To speed up stability testing, accelerated stability studies are often carried out on drug substance and drug product at higher temperatures, such as 40°, 50° or even 70°C, under dry or humid conditions. It is a rule of thumb that the shelf life determined at 40°C/75% RH is about one-fourth of that at room temperature. Extrapolation of shelf life is based on the assumption that a solid-state reaction follows Arrhenius kinetics, and that an activation energy determined at higher temperatures can be used to calculate the rate and shelf life at room temperature. The assumption is valid if the reaction occurring at higher temperatures also occurs at room temperature, and follows the same degradation pathway. However, it is not uncommon that degradation products produced at temperatures such as 60°C and 70°C may never occur at room temperature. Generally though, according to the guidance document Q1A(R2), the FDA allows the projection of shelf life for New Drug Applications based on studies under accelerated conditions, but data at the recommended storage temperature is generally required to support the actual shelf life of marketed products.

18.3 MECHANICAL PROPERTIES

Oral pharmaceutical dosage forms are usually composed of multiple components, including an active ingredient that exerts pharmacological action, and inactive ingredients (or excipients) that enable processing of the active ingredient into a drug product, and facilitate disintegration and dissolution of the drug product upon ingestion. This multi-component system is quite complicated, because the drug and excipients may have widely differing density, shape, surface charge, particle size distribution, and crystal hardness, which significantly influence how well the material can be processed. Thus, it is important to understand how mechanical properties of a formulation and its individual components can influence common pharmaceutical unit operations, such as granulation, compression, milling, and mixing. This section will focus solely on oral solid dosage forms, which constitute the majority of marketed drug products.

18.3.1 Compression and Compaction

The processes of tableting, roller compaction, and extrusion all involve application of mechanical forces

to induce compression and compaction of solid particles to form a compact dosage form with sufficient strength. When external forces are applied to a powder mass, the powder bed initially undergoes volume reduction by rearranging solid particles to achieve minimum packing volume. Further compression induces volume reduction through particle deformation. Three common types of deformations are elastic deformation, plastic deformation, and brittle fracture. Elastic deformation is reversible, and typically undesirable, because a compact formed by elastic deformation tends to expand to its original volume during decompression, leading the compact to laminate. Plastic deformation, which is irreversible by nature, may occur when the applied forces reach beyond the elastic limit or yield point. During plastic deformation, materials undergo further volume reduction, and particles are brought to close contact for bonding to occur. Plastic deformation predominates in materials that are soft and pliable, such as microcrystalline cellulose and clays. Conversely, for hard and brittle materials, such as dicalcium phosphate and lactose, the materials may fragment into smaller pieces when the shear strength exceeds the tensile or breaking strength of the materials, a phenomenon known as brittle fracture. Extensive fragmentation creates large clean surfaces, which provide opportunities for bonding between particles to occur. Both plastic deformation and brittle fracture produce strong compacts by forming a large number of contact points where intermolecular attractive forces can develop. In principle, the following material properties favor formation of a strong compact:[36]

1. materials with limited elastic deformation;
2. materials that are highly fragmenting or very plastically deforming;
3. fine particulate materials that have large surface area;
4. starting materials possessing high surface roughness which is capable of forming a large number of weak attractive forces.

18.3.2 Mechanical Property Characterization

Tensile Strength

Compactibility reflects a material's ability to produce compact strength (tensile strength) as a function of solid fraction. Here, solid fraction is calculated by subtracting porosity from unity. Pharmaceutical powder compacts tend to be brittle. For this reason, a simple tensile test by stretching the specimen is rarely used. The most commonly used technique to test breaking or tensile strength of pharmaceutical compacts is a diametral compression test, more commonly known as hardness testing. Taking the Schleuniger hardness tester as an example, a tablet is placed between two opposing platens. A platen driven by an electric motor presses the tablet at a constant load rate against a stationary platen until the tablet breaks. The instrument reports the tablet "hardness value" in both kilopound and Strong Cobb units. Tablet hardness is not a very precise terminology since hardness has a specific meaning in material science, associated with indentation, which will be discussed in this section. Nonetheless, tablet hardness can be converted to tensile strength, which is independent of tablet shape and dimension. For a round tablet, tensile strength can be calculated as the following:

$$\sigma = \frac{2P}{\pi D t} \tag{18.14}$$

where:

σ = tablet tensile strength
P = fracture load or tablet hardness
D = tablet diameter
t = tablet thickness.

Indentation Hardness

Unlike tensile strength, which describes the global strength of a specimen, indentation hardness describes the "local" plasticity of a material. Hardness may be defined as the resistance of a material to plastic deformation. To measure a material's hardness, either a pendulum is allowed to strike it from a known distance or an indenter is allowed to fall under gravity onto the surface of the specimen, leaving an indentation. The resistance of the material to indentation or the dynamic indentation hardness can be calculated by dividing the energy of impact to indentation volume. Under the same impact energy, soft materials tend to have a larger indentation, and thereby lower hardness than hard materials. Rowe and Roberts have collected data from the literature on indentation hardness of a variety of common drugs and excipients measured on compacts and crystals.[37]

Young's Modulus

Tensile strength and dynamic hardness alone are not sufficient to describe a material's mechanical properties. For this reason, Young's modulus was introduced to describe the stiffness and toughness of a material. For elastic deformation:

$$E = \frac{\sigma_d}{\varepsilon} \tag{18.15}$$

where:

E = Young's modulus of elasticity
σ_d = deformation stress
ε = deformation strain.

Young's modulus of elasticity can be determined by several tests, including flexure testing using both four- and three-point beam bending, compression testing, and indentation testing on both crystals and compacts. Rowe and Roberts collected data from the literature on Young's modulus of elasticity of a variety of common drugs and excipients measured by flexure testing.[37] In general, the values of Young's modulus can vary over two orders of magnitude, ranging from high moduli for hard rigid materials (e.g., calcium phosphate) to low moduli for soft elastic materials (e.g., polymers).

Yield Stress from Heckel Plots

Compressibility reflects the ability of a material to undergo volume reduction under pressure. One of the most commonly used models to depict force–volume relationships is the Heckel equation:[38]

$$-\log E = K_y P + K_r \tag{18.16}$$

where:

E = porosity of the tablet
K_y = a material-dependent constant inversely proportional to its yield strength S ($K_y = 1/3S$) or mean yield pressure P ($K_y = 1/P$)
K_r = porosity of the powder bed where the pressure is zero. This relates to the initial packing stage.

The compression pressure, P, can be calculated by dividing the compression force with tablet surface area. For a flat round tablet:

$$P = \frac{4F}{\pi D^2} \tag{18.17}$$

where:

F = compression force
D = tablet diameter.

E can be calculated for any stage during compression. For a round tablet, E is calculated using the following equation:

$$E = 100 \times \left[1 - \frac{4w}{\rho_t \times \pi \times D^2 \times H}\right] \tag{18.18}$$

where:

w = tablet weight
ρ_t = true density of the tableting mass
H = thickness at the point of compression. It can be obtained from relative punch displacement measurement.

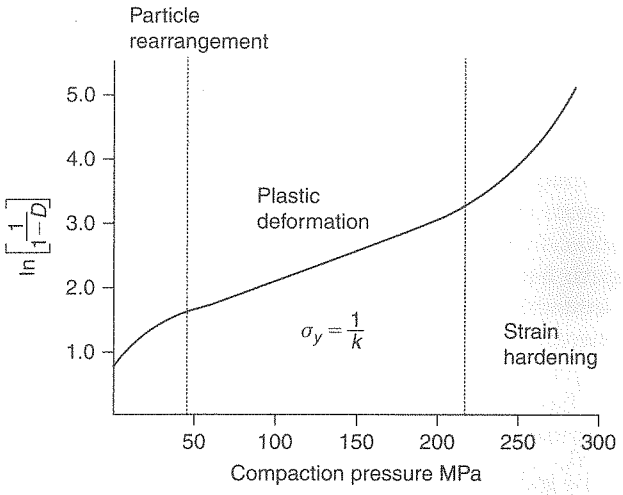

FIGURE 18.2 Schematic diagram of the Heckel plot (copied from Figure 5 in reference 38)

A unique feature of the Heckel plot resides in its ability to differentiate plastic deformation from brittle fracture. Materials that readily undergo plastic deformation have a relatively higher slope than those that undergo brittle fracture, implying the former has a lower yield pressure. Another advantage of the Heckel plot is that it depicts the physical significance of a compression event, shown in Figure 18.2.[38] Three events may occur—particle rearrangement at low pressure, plastic deformation (or fragmentation) occurs at medium to high pressure, and strain hardening at very high pressure.

Tableting Indices

A few decades ago, Hiestand developed a unique set of tableting indices that integrated some of the tests discussed earlier to characterize the mechanical properties of materials under careful experimental control.[39] Hiestand believed that a prerequisite to precise mechanical measurement was to produce compacts without internal fracture. Unfortunately, compacts made from the conventional uniaxial press tend to develop fracture lines, due to large die wall pressures developed during decompression. To solve this problem, he designed a triaxial press with a diagonally-split die to compress materials into square compacts. Unlike the conventional press, which can only relieve pressure vertically, the triaxial press can expand both horizontally and vertically, at a controlled rate, during decompression. Hiestand argued that if the mean die wall pressure and the mean punch pressures were held equal, the internal shear stresses should be less than the strength of the compact, in which case no fracture lines would be developed.

The three indices that Hiestand used to characterize the mechanical properties of materials are the bonding indices (*BI*), brittle fracture index (*BFI*), and strain index (*SI*). *BI* is calculated as the following:

$$BI_b = \frac{\sigma_T}{H_0} \tag{18.19}$$

$$BI_w = \frac{\sigma_T}{H_{30}} \tag{18.20}$$

where:

BI_b = best case bonding index
σ_T = tensile strength of the compact
H_0 = instantaneous indentation hardness where the indentation volume was obtained when the steel ball strikes the compact and immediately rebounds
BI_w = worst case bonding index
H_{30} = indentation hardness with a dwell time of 30 minutes. The indentation volume was obtained when the steel ball was held in contact with the compact for 30 minutes.

Hiestand believed that *BI* is a better indicator for a compact's bond strength than the conventionally used tensile strength, because tablets with excellent tensile strength may still have problems of capping and lamination. By incorporating the term of dynamic hardness, it is believed that *BI* more accurately reflects the actual bond strength of the compact. The higher the *BI*, the stronger is the bond strength of the compact. The value of dynamic hardness *H* depends on the dwell time over which an indentation is made. When the dwell time is really long, such as 30 minutes, the dynamic hardness H_{30} is lower than the instantaneous dynamic hardness H_0, and more so for viscoelastic materials. In theory, viscoelastic materials tend to produce stronger bonds than non-viscoelastic materials.[40] Therefore, both the magnitude of bonding indices, and the differences between BI_b and BW_b, should be considered. A large difference indicates the tablet strength can be dramatically improved by slowing down the machine speed.

The brittleness of a material may be measured by its brittle fracture index, calculated as:

$$BFI = 0.5 \times \left(\frac{\sigma_f}{\sigma_{f0}} - 1 \right) \tag{18.21}$$

where:

BFI = brittle fracture index
σ_f = tensile strength of a compact without a hole
σ_{f0} = tensile strength of a compact with a hole.

Two sets of square compacts were prepared using the triaxial press. One set contains a circular hole, whereas the other does not. The tensile strength of the compact with the hole (σ_f), is compared to that without (σ_{f0}). If the material is completely brittle, elastic theory predicts that the ratio of σ_f to σ_{f0} is close to 3. Most pharmaceutical materials are not completely brittle, and they are capable of relieving highly localized stress around the hole through plastic deformation. Therefore, the lower the *BFI*, the more plastic a material is. When *BFI* is less than 0.2, experiences teaches that there will not be a problem with tablet fracture on a rotary press unless the bonding (*BI*) is really weak.

The strain index, *SI*, may be used to reflect a relative value of the elastic strain following plastic deformation. It shows to what extent fracture of a compact is contributed to elastic recovery. *SI* is calculated as the following:

$$SI = \frac{H_0}{E'} \tag{18.22}$$

$$1/E' = \frac{\Sigma(1 - \upsilon^2)}{E} \tag{18.23}$$

where:

SI = strain index
E = Young's modulus
υ = Poisson's ratio.

E' can be determined from the same indentation experiment used to measure the dynamic hardness, H_0. Hiestand measured tableting indicies of several common excipients, shown in Table 18.1.[39]

18.3.3 Practical Implications of Mechanical Property Characterization

Mechanical properties of drug substances and drug products can have a significant impact on

TABLE 18.1 Examples of values observed for tableting indices (modified from Table 3 in reference 39)

Material ($\rho_r = 0.9$)	$BI_W \times 10^2$	$BI_b \times 10^2$	*BFI*	$SI \times 10^2$
Avicel[a]	3.4	13.5	0.03	2.3
Sorbitol	0.46	13.7	0.03	0.94
Lactose, spray dried	0.36	1.1	0.12	1.8
Sucrose	0.40	2.3	0.68	1.5
Ibuprofen[b]	0.76	4.1	0.06	0.6
Aspirin	2.1	5.1	0.19	0.7
Caffeine	1.4	4.5	0.47	1.3
Phenacetin	0.88[c]	1.4	0.43	1.0
$CaSO_4 \cdot 2H_2O$	0.79	1.3	0.08	1.2

[a]PH-101, microcrystalline cellulose
[b]Lot-to-lot variation regularly observed
[c]Compression pressure slightly $> H_0$

manufacturability in multiple unit operations, such as compression, milling, and granulation. For example, during compression, a compression blend needs to have adequate flow from the hopper to the feed frame, and from the feed frame into the die. Otherwise, it is difficult to obtain consistent tablet weight. In addition, the compression blend needs to have reasonable compactibility, so that it can form a strong compact on a high-speed rotary press. Characterization of mechanical properties of the drug substance will help select appropriate formulation excipients and manufacturing processes for development of a robust product. This is especially important for high drug load formulations, where the mechanical properties of a drug may significantly impact final properties of the drug product. In a high drug load formulation containing drug with poor flow and/or compaction properties, one may choose to wet granulate or roller compact the formulation to improve flow and compaction properties of drug product. Granulation technology may also be selected for low dose formulation (e.g., the drug loading is <1% w/w) to improve content uniformity. For a drug substance that has reasonable mechanical properties, the drug can be blended with appropriate excipients, and the resulting blend can then be directly compressed on the tablet press. Direct compression is the simplest and most cost-effective way to manufacture a tablet dosage form. Of course, selection of a manufacturing process also strongly depends on the type of dosage form to be manufactured. For compounds that require specialty formulation to enhance oral bioavailability, additional manufacturing steps may be needed prior to compression or encapsulation of a formulation into a final dosage form. For example, milling may be required to reduce the particle size of drug substance to facilitate drug dissolution. How the drug substance fractures under impact, cutting or shear action may determine the fracture energy required, and the extent of particle size reduction. Therefore, understanding the impact of mechanical properties of a drug and formulation on each unit operation at a relevant scale is a recipe for successful scale-up of a robust product.

18.4 BIOPHARMACEUTICAL PROPERTIES

18.4.1 The Biopharmaceutical Classification System (BCS)

It is often believed that the magnitude of the therapeutic response increases as the drug concentration in the body increases. A more rapid and complete absorption tends to produce more rapid and uniform pharmacological responses. Based on this premise, one of the key objectives in designing an oral dosage form is to facilitate rapid and complete oral absorption, which is influenced by a multitude of factors, including physico-chemical properties of the drug and dosage form components, and physiological aspects of the human digestion system. To simplify this complicated picture, Amidon proposed a Biopharmaceutics Classification System (BCS), which categorized drugs according to two key physico-chemical parameters—solubility, and permeability.[41] These two factors were selected because most orally administered drugs are absorbed via a passive diffusion process through the small intestine, where the extent of oral absorption is largely influenced by a drug's membrane permeability and solubility, as is evident from the following equation:[42]

$$M = A \cdot t_{res} \cdot P_{eff} \cdot C_{app} \tag{18.24}$$

The amount of drug absorbed (M) is proportional to the surface area available for absorption (A), the residence time (t_{res}) during which the drug stays within the site(s) of absorption, the effective membrane permeability (P_{eff}), and the apparent luminal drug concentration (C_{app}). As shown in Table 18.2, the BCS categorized drugs into four classes. Class I compounds have high solubility and high permeability; class II compounds have low solubility and high permeability; class III compounds have high solubility and low permeability; and class IV compounds have both low solubility and low permeability.

The Food and Drug Administration (FDA) has issued guidelines to define what is considered high solubility and high permeability.[43] According to this guideline, a high solubility drug is defined as one that, in the largest dose strength, fully dissolves in 250 mL of aqueous medium with the pH ranging from 1 to 7.5 at 37°C. Otherwise, drugs are considered poorly soluble. In other words, the highest therapeutic dose must dissolve in 250 mL of water at any physiological pH.

TABLE 18.2 The biopharmaceutics classification system[41]

		Permeability	
Categories		**High**	**Low**
Solubility	High	Class I	Class III
	Low	Class IIa (solubility limited)	Class V
		Class IIb (dissolution rate limited)	