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Article *in* Critical Reviews in Therapeutic Drug Carrier Systems · February 2006

DOI: 10.1615/CritRevTherDrugCarrierSyst.v23.i1.10 · Source: PubMed

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Compression Physics in the Formulation Development of Tablets

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ABSTRACT: The advantages of high-precision dosing, manufacturing efficiency, and patient compliance make tablets the most popular dosage forms. Compaction, an essential manufacturing step in the manufacture of tablets, includes *compression* (i.e., volume reduction and particle rearrangement), and *consolidation* (i.e., interparticulate bond formation). The success of the compaction process depends not only on the physico-technical properties of drugs and excipients, especially their deformation behavior, but also on the choice of instrument settings with respect to rate and magnitude of force transfer. This review discusses various properties of drugs and excipients, such as moisture content, particle size and distribution, polymorphism, amorphism, crystal habit, hydration state, and lubricant and binder level of the blend that have an influence on compaction. Tableting speed and pre/main compression force profile, also have a bearing on the quality of the final tablet. Mechanistic aspects of tableting can be studied using, instrumented punches/dies, instrumented tableting machines, and compaction simulators. These have potential application in pharmaceutical research and development, such as studying basic compaction

0743-4863/05/$35.00

mechanism, process variables, scale-up parameters, trouble shooting problem batches, creating compaction data bank, and fingerprinting of new active pharmaceutical ingredients (APIs) or excipients. Also, the mathematical equations used to describe compaction events have been covered. These equations describe density–pressure relationships that predict the pressures required for achieving an optimum density. This understanding has found active application in solving the analytical problems related to tableting such as capping, lamination, picking, sticking, etc. Mathematical models, force-time, force-distance, and die-wall force parameters of tableting are used to describe work of compaction, elasticity/plasticity, and time dependent deformation behavior of pharmaceuticals. Various indices of tableting performance such as the bonding index, brittle fracture index, and strain index can be used to predict compaction related problems. Compaction related physico-technical properties of commonly used tableting excipients have been reviewed with emphasis on selecting suitable combination to minimize tableting problems. Specialized tools such as co-processing of API and excipients can be used to improve their functionality.

KEY WORDS: compaction, consolidation, particle deformation, tablet instrumentation, force-displacement profile

I. INTRODUCTION

The use of pills and powders to administer drugs was reported as early as 1550 BC in Papyrus Ebers. The pill continued to be one of the most common dosage forms until the middle of the 20th century, when mass-production of tablets was introduced by the pharmaceutical industry following the invention of the tableting machine, patented in 1843 by William Brockedon.[1] Pharmaceutical products have historically been administered to the body using a relatively basic drug and excipient combination in suitable dosage form, usually resulting in rapid release and systemic absorption of the drug(s). Different delivery technologies and routes of administration have been used to ensure optimal administration of therapeutic agents. All along the history of pharmacy, oral route has been the most preferred way of drug administration and oral solid dosage forms have been widely used mainly because of their convenience of administration, ease of manufacturing, accurate dosing, and patient compliance.[2,3] Out of powders, granules, pellets, tablets, and capsules, tablets have been the dosage form of first choice in the development of new drug entities[4] and account for some 70–80% of all pharmaceutical preparations.[2,5] A flow-chart of the relationship between solid pharmaceutical dosage forms is shown in Figure 1.

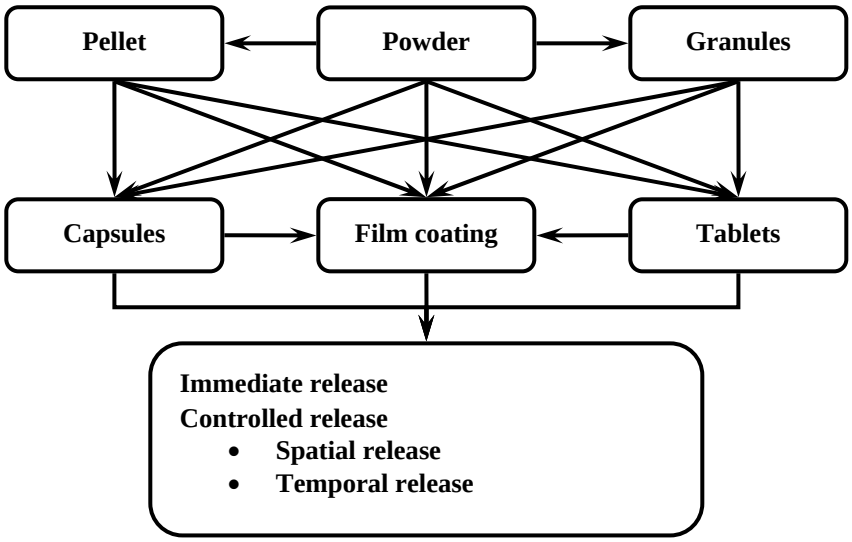

FIGURE 1. Relationship between the various solid dosage forms.

Tablets can be made directly from powders, granules, pellets, or film coated multiple units. The prerequisite, however, is that the material must have good compressibility to form a tablet.[6] In general, the tableting process involves, applying pressure to a powder bed, thereby compressing it into a coherent compact.[7] The simplest process for tableting is direct compression, in which the drug(s) and excipient(s) are dry mixed and then compacted. For this process to be successful, the powder mixture requires certain properties, such as high flowability, low segregation tendency, and high compactibility. Pharmaceutical powders often lack these properties and must, therefore, be pretreated with a particle modification process before compaction.[3] Generally, this pretreatment is a granulation step in which the primary drug(s) and the excipient particles are agglomerated into larger secondary particles (granules or agglomerates), usually of a higher porosity than the primary ones. Techniques to improve tabletability involve different granulation techniques, both wet and dry, and special wet granulation techniques, which yields almost spherical agglomerates, such as pelletization, or extrusion–spheronization.[8]

Compaction represents one of the most important unit operations in the pharmaceutical industry because physical and mechanical properties of the tablets, such as density or strength (hardness/friability), are determined during this process. Dosage form integrity and bioavailability is related to the tablet compression process. The production of compressed tablets is a complex process involving many variables and a number of engineering principles and the complete understanding of the physics of compression has been an ongoing proc-

ess.[9] Particle size, size distribution, crystal habit, crystallinity, polymorphism, pseudomorphism, amorphism, and crystal moisture are the most common elements that can change the compression properties.[10,11] Simple compression of a bulk material, either powder or granulate, into a robust tablet is also influenced by process variables such as force transfer, rate of force transfer, particle deformation behavior, and the adhesive forces between the particles.[12]

The study of compression physics is of special interest in cases of high-dose poorly compressible drugs that exhibit nonlinear relationship between compression force and tablet tensile strength. These show a propensity towards tableting problems such as capping, lamination, sticking, and picking during scale-up on high-speed tableting machines. As the deformation of pharmaceuticals is time dependant, so reduced dwell times on high speed tableting machines increases the chances of structural failure of tablets. In addition to varying the type and proportions of composition, process-related factors also affect tablet properties and quality.[6] Literature reports a number of high-dose and/or poorly compressible drugs including paracetamol,[13,14] ibuprofen,[15] mefenamic acid,[16] acetazolamide,[17] metformin,[18] and hydroxyapetite.[19] The identification of tableting-related problems and establishing their relation with compaction parameters such as compaction force, punch displacement, porosity, and tensile strength, helps in understanding such complications and minimize them. For pharmaceutical applications, the tablet ingredient mixtures are almost always complex and it is as yet impossible to preview the properties of the end-product tablet by knowing the exact composition of the powder mixture. Achieving the possibility of such predictions would be economic and time saving, and for this reason, the characterization of model excipients and drugs, as well as several mixtures of them, is an interesting and important research field.[20]

II. PROPERTIES OF POWDERS

Physicotechnical properties of pharmaceutical solids dictate the performance and processing of solid dosage forms, including their compressibility. These properties are inter-related and a change in one property is likely to affect the other.

II.A. Surface Properties

Surface properties of a powder material have a major influence on their flow and intermolecular attraction. Atoms or ions located at a surface have a different distribution of intermolecular and intramolecular bonding forces than those

present within a particle. This is caused by the unsatisfied attractive molecular forces that extend out to some small distance beyond the solid surface. This gives rise to *free surface energy* of solids, which plays a major role in interparticulate interaction.[21] Particulate attractive forces include those between like particles called *cohesion,* and those between un-like particles called *adhesion.*[22] The attractive forces resist the differential movement of constituent particles when subjected to an external force. Other types of resistance to relative movement of particles include the electrostatic forces, adsorbed moisture, and residual solvent on the surface of solid particles.[6]

II.B. Porosity

The porosity of powder (E) is defined as the ratio of total void volume (V_v) to the bulk volume (V_b) of the material.[4] The total void volume, V_v is given by $V_v = V_b - V_t$ where, V_t is the true volume.

$$E = V_b - V_t / V_b = 1 - V_t / V_b \quad (1)$$

One of the methods used to determine the compressibility of a powder bed is the degree of volume reduction owing to applied pressure, which is related to porosity and is assumed to be a first-order reaction.[23] Porosity–pressure relationship is also explained by the Heckel equation (discussed in Section VI.B.), and is commonly used as a measure of compressibility.[24]

II.C. Flow Properties

Good flow property of a pharmaceutical powder is essential to ensure proper die fill during compression, especially in direct compaction process. Reasons such as, high percentage of fines, excess moisture, lubricants, and electrostatic charge may contribute to poor flow of powders.[25,26]

Angle of repose is commonly used to measure flow of powders, and is the maximum angle (Φ) between the plane of powder and horizontal surface. The value of Φ less than 30° usually indicates free flowing material, up to 40° indicates reasonable flow potential, and above 50° the power flows with great difficulty.[27]

The increase in bulk density of a powder is related to its cohesivity. Bulk density and tap density relationship is another way to index flowability.[27] Indices such as the Hausner Ratio (H) and Carr's Index (CI) are based on tapped and bulk densities. Hausner ratio is the ratio of tapped density to bulk density,[27,28] and varies from about 1.2 for a free-flowing powder to 1.6 for cohesive powders.[27]

The percentage compressibility, also called as Carr's Index[29] is 100 times the ratio of the difference between tapped density and bulk density to the tapped density. Values of Carr's index of about 5–12% indicate free-flowing powder, 23–35% indicate poor flow, and >40% an extremely poor flow.[27]

Additionally, flow rate is used to determine the resistance to movement of particles especially for granular powder with poor cohesiveness. A simple indication of the ease with which a material can be induced to flow is given by compressibility index, *I*.

$$I = [1 - V_t / V_0] \times 100 \quad (2)$$

where, V_t is the tap volume and V_0 is the volume before tapping. Value of *I* below 15% indicate good flow properties but values above 25% mean poor flow.[6]

II.D. Compaction

Compaction can be defined as the *compression and consolidation* of a particulate solid–gas system as a result of an applied force.[30] Compression involves a reduction in bulk volume as a result of reduced gaseous phase. A closer packing of the powder particles as a result of rearrangement is the main mechanism for initial volume reduction. As the force is further increased, rearrangement becomes difficult and particle deformation sets in. Consolidation, which is a subsequent process, involves increase in the mechanical strength resulting from particle–particle interactions. As the particles move into closer proximity to each other during the volume reduction process, bonds are established between the particles. The nature of bonds formed is similar to those of the molecular structure of the interior of the particles, but because of the roughness of the particles surface, the actual surface area involved is small. Consolidation is the major reason for increase in mechanical strength of a powder bed, when subjected to rising compressive forces.[6] The various steps involved in powder compaction are illustrated in Figure 2.

Over the years, there has been considerable confusion in literature around tableting terminology. Different terms, e.g., *compressibility*, *compactibility,* and *tabletability*, have been used by different authors to describe the same type of relationship. The root cause of this confusion is that three variables, pressure, tablet tensile strength, and porosity, are not always studied simultaneously and the first systematic study of all three variables and definition of the terms was

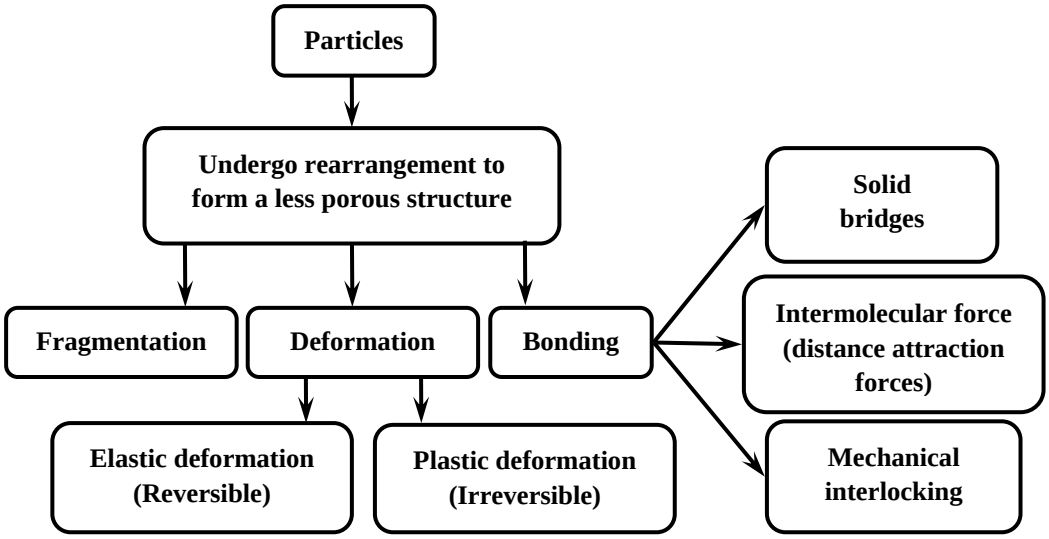

FIGURE 2. The various steps involved in compaction of powders under an applied force.

presented by Joiris et al.[7] They defined *compressibility* as the ability of a material to undergo a reduction in volume as a result of an applied pressure and is represented by a plot of tablet porosity against compaction pressure; *compactibility a*s the ability of a material to produce tablets with sufficient strength under the effect of densification and is represented by a plot of tablet tensile strength against tablet porosity; and *tabletability* as the capacity of a powdered material to be transformed into a tablet of specified strength under the effect of compaction pressure and is represented by a plot of tablet tensile strength against compaction pressure. The usage of this terminology is recommended, where all three variables are considered in a single study.

The compaction process mainly includes particle rearrangement, followed by deformation under pressure, although, smaller particles formed as a result of fracture of larger particles may undergo further rearrangement.

1. Particle Rearrangement and Volume Reduction

The nonisostatic compression of powder or granular material to produce a compact is a complex process, arising from the numerous internal processes that lead to consolidation. These events include particle rearrangement, fracture, and plastic deformation.[31] The first thing that happens when a powder is compressed is that the particles are rearranged under low compaction pressures to form a closer packing structure.[32] The finer particles enter the voids between the larger ones and give a closer packing arrangement. In this process, the en-

ergy is evolved as a result of interparticulate friction and there is an increase in the amount of particle surface area capable of forming interparticulate bonds.[33] As the pressure increases, further rearrangement is prevented and subsequent volume reduction is accomplished by plastic and elastic deformation and/or fragmentation of the particles.[31] The number of contact points known as potential bonding areas (inter- and intraparticulate) of the particles, are dependent on particle size, size distribution, density, surface properties, interparticulate voids, and process variables such as the moisture content, rate of flow, and the relationship between die-cavity diameter and particle diameter. Brittle particles are likely to undergo fragmentation, i.e., breakage of the original particles into smaller units resulting in increase in contact points. Plastic substances deform in an irreversible manner, resulting in a permanent change of the particle shape (irreversible process), whereas elastic substances when deformed resume their original shape (reversible process).

The degree of volume reduction that a pharmaceutical powder bed undergoes depends on the mechanical properties of the powder and the type of volume reduction mechanisms involved. Particle size and speed of compression will in turn influence the mechanical properties of the material.[34] For example, reduction in particle size has been related to a decreased tendency to fragment. Some materials appear to have a critical particle size at which a transition from brittle to ductile behavior occurs as the particles become smaller.[35] Brittle materials that undergo extensive fragmentation generally result in tablets of relatively high porosity because of the large number of bonding points that are created, which prevent further volume reduction. A ductile material, on the other hand, will often result in tablets of low porosity because the high degree of plastic deformation enables the particles to move very close to each other. Similarly, different crystal habits such as spherical, cubical, and acicular, have different tendencies to pack in a close structure.[10,13] Particles having regular shape appear to undergo rearrangement more easily as compared to irregular particles.

2. Deformation of Particles

As the upper punch penetrates the die containing the powder bed, initially there are essentially only points of contact between the particles. Application of the external forces to the bed results in force being transmitted in through these interparticulate points of contact, leading to development of stress and local deformation of the particles. Energy is lost at this stage as a result of interparticulate and the die-wall friction, as well as deformation. Based on their mechanical properties, powders are classified as plastic, elastic, and viscoelastic. However, under the influence of an applied pressure, the particles not only deform plastically or elastically, but also fragment to form smaller particles. The latter is

termed as brittle fracture. The type of deformation depends not only on the physical properties of the material but also on the rate and magnitude of the applied force and the duration of locally induced stress.[30]

As a result of the resistance of a material against deformation (strain), the stress inside the particles increases. If the applied stress is released before the deformation reaches a specific critical value, the particles deform elastically, i.e., the deformation is reversible and the particles inside the powder bed regain their original shapes. Until this critical value, the stress is linearly proportional to the deformation and is characterized by elastic or Young's modulus (E)[36] (Figure 3a). For the brittle materials, particles fragment into smaller units at a certain stress value (σ_f). This stress is the fracture strength (Figure 3b). For ductile/plastic materials, after a critical stress (σ_y), the particles yield and start to deform plastically. This critical stress is the yield strength of a material (Figure 3c). Material fracture eventually occurs at higher deformations. Elastic deformation is a reversible process, whereas plastic deformation results in a permanent change in the particle shape. The deformation mechanism for a few representative pharmaceuticals is presented in Table 1.

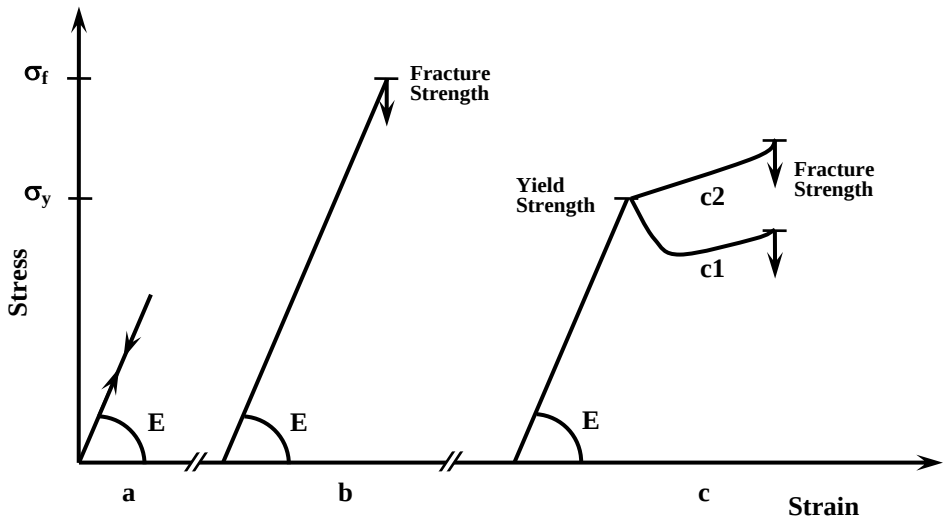

FIGURE 3. Macroscopic stress-strain relationships showing, (a) reversible elastic deformation; (b) brittle behavior; and (c) ductile behavior (c1 normal plastic flow, c2 strain-hardening). E is the Young's modulus.

TABLE 1. Deformation Mechanisms for a Few Representative Pharmaceuticals

Major deformation mechanism(s)	Material
Fragmentation	Ascorbic acid,[37] Dicalcium phosphate,[38] Maltose,[33] Phenacetin,[33] Sodium Citrate,[33] Sucrose[35]
Fragmentation and elastic deformation	Ibuprofen,[39] Paracetamol,[12,13,40]
Fragmentation and plastic deformation	Lactose monohydrate,[41,42] Microcrystalline cellulose[43]
Plastic deformation	Sodium bicarbonate,[44] Sodium chloride,[45] Pre gelatinized starch[3]
Elastic deformation	Starch[46]

3. Time Dependency of Compaction Process

Successful formation of a pharmaceutical tablet by the compression of solid particulate matter depends on interparticulate bonding across particle–particle interfaces. The areas of virtual contacts, during and after compression are expected to depend on the time-dependant flow of material, which occurs in conjunction with instantaneously responding elastic deformation.[14] Some deformation processes (e.g., plastic deformation) are time dependent and occur at various rates during the compaction sequence,[47] so that the tablet mass is never in a stress/strain equilibrium during the actual tableting event. This means that the rate at which load is applied and removed may be a critical factor. More specifically, if a plastically deforming solid is loaded (or unloaded) too rapidly for this purpose to take place, the solid may exhibit brittle fracture.[35] This is a contributing factor to structural failure of tableting as the machine speed is raised. Conversely, if the dwell time under the compression load is prolonged, then plastic deformation may continue, leading to more consolidation.[5]

Hence, the compact formation is determined by the time dependant viscoelastic behavior. Speed of the process (dwell time) can have marked effect on compactibility and on tendencies such as lamination, capping, and picking, which can occur during and/or after ejection.[48] Extended dwell time involves application of compression force for a longer period of time. This further allows plastic flow and absorbs the energy of elastic strain recovery before the force is released.[14] Coupling of these processes results in viscoelastic behavior being observed during the compression of the tablets at normal production speed and often at slower speeds. The viscoelastic parameters of the tablets and their components therefore are expected to be indicative of the relative sensitivity of tablet formation to the rates of compression and decompression and the rate and the nature of ejection from die.[49] This can lead to a situation, where a

formulation can produce a good tablet on a slow machine speed, but fails on a higher machine speed.[48]

III. MODELS FOR MECHANICAL STRENGTH OF TABLETS

Different theoretical models for describing the mechanical strength of tablets have been proposed in the pharmaceutical literature, some of which are reviewed below.

III.A. Bonding Mechanisms

The mechanical strength of a tablet depends on the dominating bonding mechanism between the particles and the surface area over which these bonds act.[33] When the surfaces of two particles approach each other closely enough, their surface energies result in a strong attractive force, a process called cold welding. This hypothesis is favored as a major reason for the increasing mechanical strength of a powder bed when subjected to compression force. On the macro scale, most particles have an irregular shape, so that there are many points of contact in the bed of powder. As the force is applied to the powder bed, this transmission may result in generation of considerable frictional heat. If this heat is not lost, the local rise in temperature could be sufficient to cause melting of contact area of the particles, which would relieve the stress in that particular region. In that case, the melt solidifies giving rise to fusion bonding.[6]

"Rumpf bond summation concept" is based on the following types of bonding mechanism, where the agglomerate strength is considered to depend on the interparticulate bond structure,[50]

a) Solid bridges (as a result of melting, crystallization, sintering, chemical reaction, and binder hardening)
b) Bonding as a result of movable liquids (capillary and surface tension forces)
c) Non freely movable binder bridges (viscous binder and adsorption layers)
d) Attraction between solid particles (molecular and electrostatic forces)
e) Mechanical interlocking (irregular particle size and size distribution)

However, dominating bond types for dry powders are solid bridges, mechanical interlocking and intermolecular forces. Intermolecular forces include Van der Wall's forces, hydrogen bonding, and electrostatic forces. These bonds are of a special importance for directly compressible binders such as microcrystalline cellulose (MCC), polyvinyl pyrrolidone (PVP), and lactose.

The strength of a given plane within a tablet is described by the sum of all

attractive forces between the particles in that plane. It is assumed that all interparticulate bonds in the failure plane break more or less simultaneously.[9] The application of fracture mechanics has also been studied in relation to the mechanical strength of pharmaceutical tablets.[51] The fracture mechanics concept stresses the importance of defects and flaws in the tablet, which can be considered as starting points for the fracture, and the subsequent propagation of the fracture. The propagation of fracture is considered to be a kinematic process.[52] A fracture may be regarded as either brittle or ductile. A brittle fracture generally propagates rapidly, whereas a ductile fracture is characterized as being preceded by plastic deformation.

III.B. Bonding Surface Area

Bonding surface area is often used to define the effective surface area taking part in the intermolecular attraction. In case of solid bridges, bonding surface area is the true interparticulate contact area, whereas for intermolecular forces the term is difficult to define. Considering the importance of the bonding surface area for the mechanical strength, it is desirable to measure the actual surface area participating in bonding. Hiestand described that the mixing of elastic drug with plastic deforming material (e.g., MCC), resulted in a harder compact as a result of plastic deformation increasing the bonding surface area.[53,54] Thus during recovery, the stored elastic energy is inadequate to separate extensive areas of contact, and strong bonding results. However, direct measurements of the bonding surface area are difficult. Instead, more indirect methods have been applied, for example to measure the surface area of the powder and compare it with the surface area of the tablet. Particle size, shape, fragmentation, deformation, and bond formation determine the bonding surface area in tablets.[33]

Various techniques have been used to determine the extent of consolidation and bonding mechanisms in pharmaceutical powders, such as stress relief under pressure, three dimensionless tablet indices (brittle-fracture index),[55,56] X-ray diffraction,[57] and multi-compression cycle.[58]

III.C. Percolation Theory

The concept of percolation covers wide range of applications in pharmaceutical technology and has been used with great interest in understanding the design and characterization of dosage forms.[59] Different types of percolation such as random-site, random-bond, random-site-bond, and continuum have been proposed.[9] In the percolation theory, the tablet is seen as consisting of clusters of particles forming a network. It has been used to describe the formation of the

tablet and the distribution of pores and particles within it. A number of tablet properties are directly or indirectly related to the relative density of a tablet and changes in tablet properties, such as mechanical strength, is related to percolation thresholds.[59] At a percolation threshold, one of the component percolates throughout the system and properties of tablets are expected to experience a sudden change. It is assumed that a tablet can only be produced with a certain minimal amount of a well compactable substance which is needed to build a percolating cluster in the tablet.

Besides the percolation threshold of the relative density, a threshold of the mass fraction also exists. An interpretation can therefore be provided for the dilution capacity of a direct tableting excipient with a poorly compactable drug. A direct tableting excipient has the ability to incorporate a certain amount of a poorly compactable drug. The dilution capacity is understood as a critical value of the mass fraction above which the compactibility of the tableting mixture vanishes. The problem of finding the dilution capacity seems to be related to the problem of elucidating a percolation threshold of the excipient. Theoretical tools can also be applied to mixtures of more than two substances[9] if they consist of a single well compactable excipient and several poorly compactable components. Such mixtures are relevant for the development of directly compressible tableting formulations.[60]

IV. COMPRESSION CYCLE AND EFFECT OF APPLIED FORCES

Compression is important for molding a drug-excipient blend into tablets. The compression cycle on a rotary tablet press includes precompression, main compression, decompression, and ejection phases. To study the mechanism by which powder materials are compressed, it is essential to study all stages of compression cycle and to understand how various formulation and compression variables affect the finished tablet.

IV.A. Precompression

Precompression is the stage where the tablets are partially formed and the precompression roller is usually smaller than the compression roller, so that the applied force is smaller in precompression stage. Optimal compression efficiency is achieved on a machine that offers multistage compression with high precompression and a desirable main compression force. Precompression plays a major role especially at high compression speeds.[40] For products that undergo brittle fracture, the application of precompression at a higher force than main compression results in higher tablet hardness. However, this is not the case for material with elastic property, because this product requires gradual application

of force to minimize elastic recovery and allow stress relaxation. Similar sizes for main and precompression rollers to apply similar forces are reported to result in optimal tablet formation.[6]

IV.B. Main Compression

Main compression is the phase in which compression and consolidation of powder bed occurs at high force. During main compression, the applied energy is transformed into formation of interparticulate bonds. When a force is applied in a die, the particles first undergo rearrangement to form a less porous structure at very low forces. Subsequently, the particles reach a state where further relative movement is impossible, and an increase in the applied force induces either particle fragmentation or deformation (or both). Viscoelastic properties that determine compression behavior are functions of compression conditions and thereby it may be useful to adjust compression conditions to avoid tableting problems.[61]

IV.C. Decompression

As the applied force is removed, a new set of stresses within the tablet gets generated as a result of elastic recovery. The tablet must be mechanically strong enough to accommodate these stress, otherwise the structure failures occur. The degree and rate of relaxation within the tablet is the characteristic of a particular blend. Recording of this phase provides insights into tableting problems. For example, if the degree and rate of elastic recovery are high, the tablet may cap or laminate. If the tablet undergoes brittle fracture during decompression, the compact may form failure planes as a result of fracturing of surfaces. Tablets that do not cap or laminate are able to relieve the stresses by plastic deformation. Since the plastic deformation is time dependant,[47] stress relaxation is also time dependant. The tablet failure is affected by rate of decompression (machine speed).[62] Addition of a plastically deforming agent (e.g., PVP, MCC) is advisable to reduce the risk of such structure failures.[6]

IV.D. Ejection

The last stage in compression cycle is ejection from die. Ejection phase also requires force to break the adhesion between die wall and compact surface and other forces needed to complete ejection of tablet.[6] Radial die wall forces and die wall friction also affect the ease with which the compressed tablet can be removed from the die. The force necessary to eject a tablet involves the distinctive peak force required to initiate ejection, by breaking of die wall–tablet adhe-

sion. The second stage involves the force required to push the tablet up the die wall, and the last force is required for ejection. Variation in this process are sometimes found when lubrication is inadequate and a *slip-stick* condition occurs between the tablets and die wall, with continuing formation and breakage of tablet die–wall adhesion.[6] Heat is generated during ejection as a result of friction from shear between the compact and the die wall, and absorption of this heat can aid in bond formation. The shear forces during ejection can produce additional plastic flow and afford consolidation not achieved during the compaction event. Lubrication usually assists in reducing the ejection forces, however it also has the negative effect on compact strength because of reduction in cohesion characteristics.[26] The unequal stress exerted on the compact during ejection can cause stress planes that break bonds and result in compact capping or laminating.[63] Lubricants minimize stress patterns so, they reduce the tendency for materials to cap or laminate.[64] The particle size of the powdered material also has an effect on ejection forces and shear. As particle size decreases, more of its surface may be in contact with the die wall.[65] This adds to increased friction forces and the generation of heat. If more particle surface is available for contact with the die wall, larger forces may be required to remove the compact.

V. INSTRUMENTATION

The production of compressed tablets is a complex process involving many variables and a number of engineering principles. Fundamental research concerning tablet manufacture has been ongoing for a number of years. Use of instrumented tablet machine is essential for basic research in compression physics, as it facilitates product development, optimization and scale up, and enables monitoring and control of production, by providing significant information about the compression and ejection forces involved in the tableting operation. Accurate measurement of these forces enables scientific designing of a tablet formulation with desired attributes. Research and product developmental work can be carried out to establish general relationships between the force of compression and the physical properties of tablets such as thickness, hardness, friability, density, disintegration, and dissolution times. The resulting data can be used to screen, and compare tableting excipients and their levels in formulations and also aid in developing in-process quality controls. The instrumentation available include those that are inbuilt or fixed in the compression machine, attachable ones such as instrumented punch die sets, and compaction simulators that mimic the tableting cycle.

V.A. Attachable Instrumentation

Instrumentation for rotary machines includes strain-gauge punches and displacement transducers for obtaining accurate measurement of the operational

characteristics of high speed tableting machines. These are inserted into punch guides, and a radio telemetry system is used to extract the force and displacement signals. The strain gauges are mounted as closely as possible to the tips of the punches to minimize errors resulting from longitudinal punch distortion during compression. The displacement transducer is mounted in a punch guide adjacent to a standard punch that is modified to couple it mechanically to a transducer. A battery powered transmitter rotating with the turret, and combined with an aerial bonded to the circumference of the turret, sends the signals to a receiver mounted on a tie bar of the machine.[66] The data is then accumulated or transmitted via telemetry to a computer. Several instrumented punches having strain gauges and other built-in instrumentation such as Portable Press Analyzer™ (Puuman Oy, Finland), Director™ (SMI Inc., New Jersey, USA), Presster™ (Metropolitan Computing Corporation, New Jersey, USA) are available commercially. Such devices are versatile enough to report compression force and punch displacement or acceleration. The instrumented punches are limited to one size and shape of tooling, and limited to one station, compared to the roll-pin instrument that reports data for all stations and any tooling. Presster™ is a versatile instrument designed to mimic a punch force-displacement profile and gives choice of interchangeable precompression/compression rolls and can fit different sizes and shapes of tooling to mimic the loading pattern of any tablet press. SMI punches report measurements in terms of punch acceleration, but that can not be integrated to produce a true punch displacement signal because the integration constants (zero point velocity) are not known. Attempts to calculate displacement from acceleration have not yet been validated.

V.B. Fixed Instrumentation

Telemetric systems such as those just described, although capable of operating at full factory speed, are inappropriate for monitoring routine production batches. Although, the full compression force/distance profile is of great value for research and development, it is not essential for routine monitoring. To obtain this measurement, strain gauges can be mounted at various positions on tablet presses to measure peak compaction forces on both the top and bottom punches. The most accurate and convenient position for such strain gauges is on the roll pin or the carriage pins.

In addition, there has been interest in measurement of the ejection force, which, however is more difficult to measure than the compression force. The exact position at which the head of a bottom punch makes contact with the ejection cam depends on the position of the bottom pressure roll and shape of the punch head. To measure the ejection force accurately using instrumented ejection cams, the system must be designed in such a way that the

force output is independent of the contact position of the punch. This can be achieved by inserting strain gauges in a metal platform that is then mounted below a modified ejection cam.[20] Instrumentation is also available to measure sweep-off force to predict the force of adhesion between a tablet and the lower punch.[6]

Die-wall instrumentation is another type of instrumentation that gives information about transmitted radial stress that can be used to assess lubricating properties of materials.[67] It is also useful for elucidating the friction phenomena during compaction and related tableting problems such as capping, lamination and tooling wear. In fact, capping and lamination often originate in the compression and decompression phases, but become evident at ejection phase.[68]

V.C. Compaction Simulator

Compaction simulators are designed to mimic the exact cycle of any tableting process and to record all important parameters during the cycle. The compaction simulators have certain advantages such as mimicing the cycle of many presses, and can be used for stress–strain studies. In addition to these advantages, compaction simulators have potential application in pharmaceutical research and development, such as studying basic compaction mechanisms, processing variables, scale-up parameters, trouble shooting problem batches, creating a compaction databank, and fingerprinting new drugs or excipients.[20,66]

VI. PHYSICS OF COMPRESSION

The mechanics of tablets is very complex and a great deal of scientific effort has been devoted to the analysis of the compaction of single component tablets. It is therefore not surprising that most studies on mixtures deal with simple binary systems rather than more realistic multi-component mixtures.[60] The use of instrumentation in tableting research offers an in-depth understanding of physical process of tableting. Force-time and force-displacement measurements can be obtained from instrumented punches and dies. Later, this data can be fitted to mathematical equations to elucidate the compaction behavior. The final quality attributes of a given blend can be understood better by using the parameters obtained from the mathematical treatment of compaction data.

VI.A. Compaction Profiles

Compaction data obtained from instrumented tableting machine are basically of two types—force-time and force-displacement profiles.

1. Force-Time Profile

Compression force-time profiles are used to characterize compression behavior of active ingredients, excipients, and formulations with respect to their plastic and elastic deformation.[38] Various attempts have been made to characterize compression force-time profiles from single punch and rotary tablet press. On a rotary tablet press, the force-time curves are segmented into three phases—compression phase, dwell phase, and decompression phase (Figure 4).[69] The force-time profile gives information about these phases as well as various characteristic parameters of the compression cycle. *Consolidation time* is the time to reach maximum force, *dwell time* is the time at which maximum displacement occurs, and *contact time* is the time for compression and decompression.[70] Pa

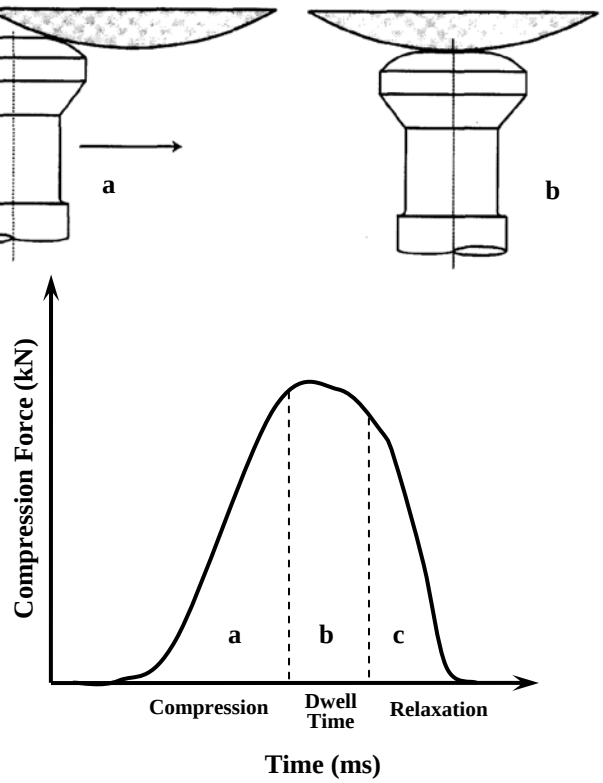

FIGURE 4. Phases of compression event on a rotary tablet press, (a) compression phase-horizontal and vertical punch movement; (b) dwell time-only horizontal punch movement as plane punch head area is under compression roller; and (c) decompression-both punches moving away from upper and lower surfaces, initial relaxation of the tablet. (Adapted from Ref. 38 with permission from Elsevier.)

rameters such as *compression area* (A_1) and the *compression slope* (S_{kc}) describe the initial phase;[38] the *area ratio* (AR),[71] and the *peak offset time* (t_{off}) characterize the dwell time;[72] and the *decompression area* (A_4) and the *decompression slope* (S_{kd}) describe the terminal phase. On a rotary tablet press, dwell time exists because the punches do not move actively in vertical position when they are with their plane punch-head area under compression roller[38] (Figure 4). The *total area* under the force-time curve (A_{tot}),[70] AR, t_{off}, S_{kc}, and A_1 are used for phase-specific allocation of the occurrence of plastic flow, which is found to be a function of compression force[12] and moisture content.[39] Tablet strength,[73] tablet porosity, and in-die bulk porosity[23] provide additional information for comprehensive interpretation.

In Figure 5 the compression force-time curve is shown divided into compression, dwell-time, and decompression phases. The area under the curve A_1 represents compression phase. For a constant tablet weight, A_1 is small for powder having high density, (e.g., dicalcium phosphate dihydrate (DCP)) and large for those having low density (e.g., MCC). Areas A_5 and A_6 are obtained by drawing a parallel line to *x*-axis from starting to the end point of dwell phase. Plastic materials show a decrease in force over dwell time, in contrast a plateau is observed for brittle materials (DCP, crystalline lactose), and therefore the

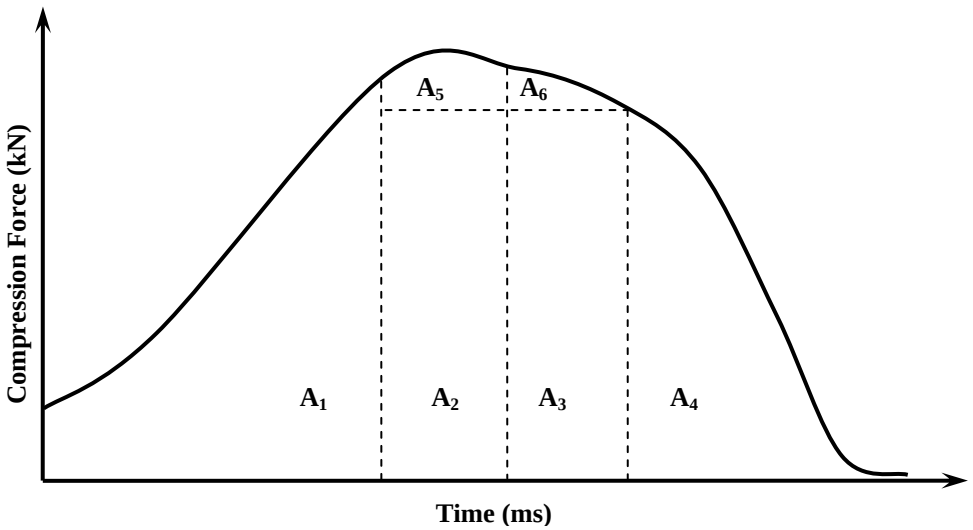

FIGURE 5. Compression force-time curve for microcrystalline cellulose (Avicel® PH102) showing, the compression phase (A_1), the dwell time phase (A_2+A_3), and decompression phase (A_4). Areas A_5 and A_6 are obtained by drawing a parallel line to X-axis from starting to the end point of dwell phase, and the ratio (A_6/A_5) can be used to measure the plasticity of a substance. (Adapted from Ref. 38 with permission from Elsevier.)

dwell-time coefficient (A_6/A_5) can be used to measure the plasticity of a substance mixture.[38,74]

Peak offset time, t_{off}[48,72] is the difference between the time of maximum pressure and the middle of the dwell time (Figure 6). The duration of t_{off} depends on the ability of the compacted powder to relieve stress (time dependant plastic flow)[70] and is an indication of the predominant mechanisms of particle deformation during consolidation. At a given F_{max}, short t_{off} values are characteristic of materials that consolidate mainly by brittle fracture whereas longer values indicate an increase in plastic flow.[72] Hiestand found that materials that are known to cap showed slow stress relaxation.[31] One of the reasons behind occurrence of tableting problems on high speed rotary machines is the decrease in the plastic flow[14,40] as indicated by a decrease in t_{off} at faster machine speed. However,

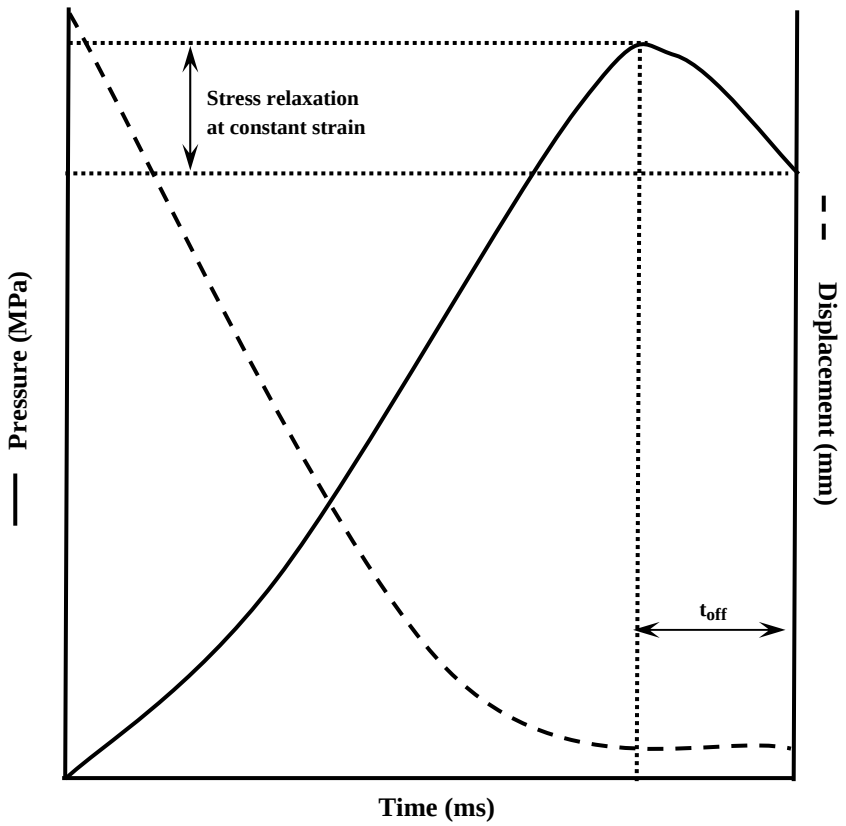

FIGURE 6. Pressure-time and displacement-time profiles for microcrystalline cellulose (Avicel® PH 102) showing peak offset time, t_{off}, an indication of stress relaxation at constant strain. (Adapted from Ref. 72 with permission from Pharmaceutical Press, UK.)

for brittle materials, stress relief does not depend on the rate of application of stress.[72] The difference between times, (t_{diff}) of maximum forces and the respective maximum densifications, and the occurrence of the maximum force before the maximum of volume reduction can only be attributed to relaxation by plastic flow (Figure 7). The area under the compression curve, *AI*, includes the increase in force caused by densification and the decrease in force at reducing rates of densification by relaxation. This area represents the compression phase and the first half of the dwell time. The area under the decompression curve, *AII*, is a measure predominantly of fast elastic expansion. Both the differences in time and in displacement have been proposed to be measures of relaxation.[70]

2. Force-Displacement Profile

Stress relaxation is observed to be minimal in case of plastic deformation; where as materials that undergoes elastic deformation tend to relax to a greater extent during and/or after decompression. However, it has been observed that

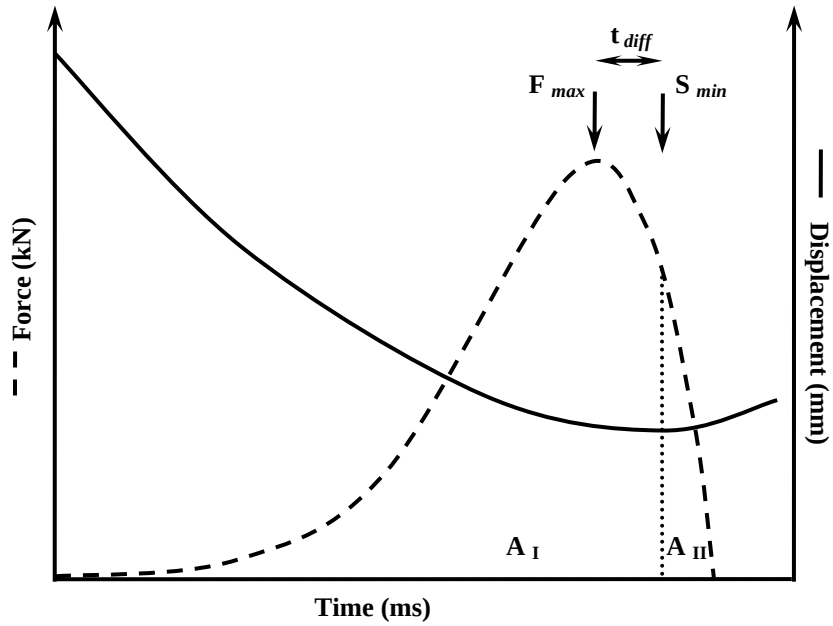

FIGURE 7. Force-time and displacement-time curves for sorbitol (Karion instant®) showing the time difference, t_{diff}, between maximum force, F_{max} and displacement at maximum densification S_{min}. The area AI includes the increase in force caused by densification and the decrease in force by relaxation, whereas the area under the decompression curve, AII, is predominantly a measure of fast elastic expansion. (Adapted from Ref. 70 with permission from Elsevier.)

most of the materials undergo both plastic and elastic deformation at different stages of compression, hence the work required for compression is the sum of work necessary to rearrange the particles, deform, and finally to fragment them.[48]

A common method for assessment of the compaction behavior of materials is the use of compression force versus punch displacement profiles,[71] from which the work involved during tablet compaction can be calculated[75] (Figure 8). Force-displacement profiles can be used for the determination of plastic and elastic behavior.[75] In a typical instrumented tablet machine, *net work of compaction* (*NWC*) is calculated by subtracting the *work of elastic relaxation* (*WER*) from the *gross work of compaction* (*GWC*). So *NWC* includes work against frictional forces and work required for deformation and/or fragmentation.[76,77]

$$NWC = GWC - WER \tag{3}$$

$$GWC = W_f + W_p + W_e + W_{fr} \tag{4}$$

where, W_f is *work against friction*, W_p is *work of plastic deformation*, W_e is *work of elastic deformation*, W_{fr} is *work of fragmentation*, with $W_e \approx WER$.

This information can be used to predict the compaction behavior of pharmaceutical materials as well as to explain the behavior of the material during compaction. However, to be able to characterize the inherent deformation properties of a material by force-displacement measurements, tableting should not be affected by particle interaction during compaction, i.e., friction and

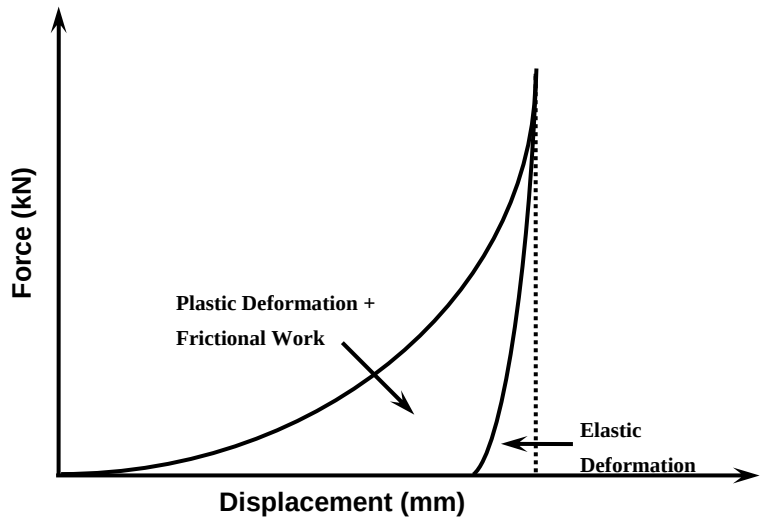

FIGURE 8. Force-displacement profile showing the plastic deformation and frictional work, and the elastic deformation areas.

TABLE 2. Mathematical Equations and Parameters to Study the Various Aspects of Compaction of Powders

Process	Parameter	Ref.
Compaction stages (compressibility and consolidation)	Heckel equation Kawakita equation Leuenberger equation Ge equation Balshin equation Work of plastic deformation	23,24,78
Elastic deformation, Elastic recovery, Capping/lamination tendency	Percentage elastic recovery Work on upper punch in recompression Elastic recovery index Plastoelasticity index Work of elastic deformation Radial die-wall and axial pressure	71,79,80
Interparticulate bonding	Brittle fracture index Bonding index	55
Plastic flow, Plastic deformation	Work of plastic deformation Yield pressure Yield strength	23,71,77,78
Lubrication efficiency	R value Force transmission ratio	6,81

bonding.[77] Higher the compressibility of a material, lesser is the amount of work needed to compress it to a certain final volume and vice versa. Hoblitzell established the relationship between force-displacement and force-time curves.[71] Moisture content of the blend also has a critical role in the energy involved in the compaction.[39] Mathematical equations and parameters used to study the various aspects of compaction of powders are summarized in Table 2.

3. Die Wall Force Profile

During tableting, friction arises between the material and the die (die-wall friction) and also between particles (interparticulate or internal friction). However, internal friction is significant only during particle slippage and rearrangement at low applied pressures. The friction between the powder mass and the die wall is of concern beyond a certain consolidation ratio, when a sufficient radial pressure gets generated.[82]

The coefficients of friction related to the tableting process are static friction coefficient (μ_l), which gives the force required to initiate sliding, and dynamic

friction coefficient (μ_2), which gives the force to maintain sliding between two surfaces.[83]

$$\mu_1 = \textit{maximum axial frictional force/maximum radial force} \quad (5)$$

$$\mu_2 = \textit{ejection force/residual die-wall force} \quad (6)$$

Friction phenomena can also be quantified by parameters calculated from upper and lower punch force and displacement. This includes the ratio of the maximum lower punch force to the maximum upper punch force (called the lubrication ratio or R value),[6] and the difference between the lower and upper punch force, F_d.[67]

Radial pressure is another useful parameter for predicting compaction behavior of pharmaceuticals.[84,85] Figure 9 shows the force and punch displacement profile corresponding to compression, decompression, and ejection. The die

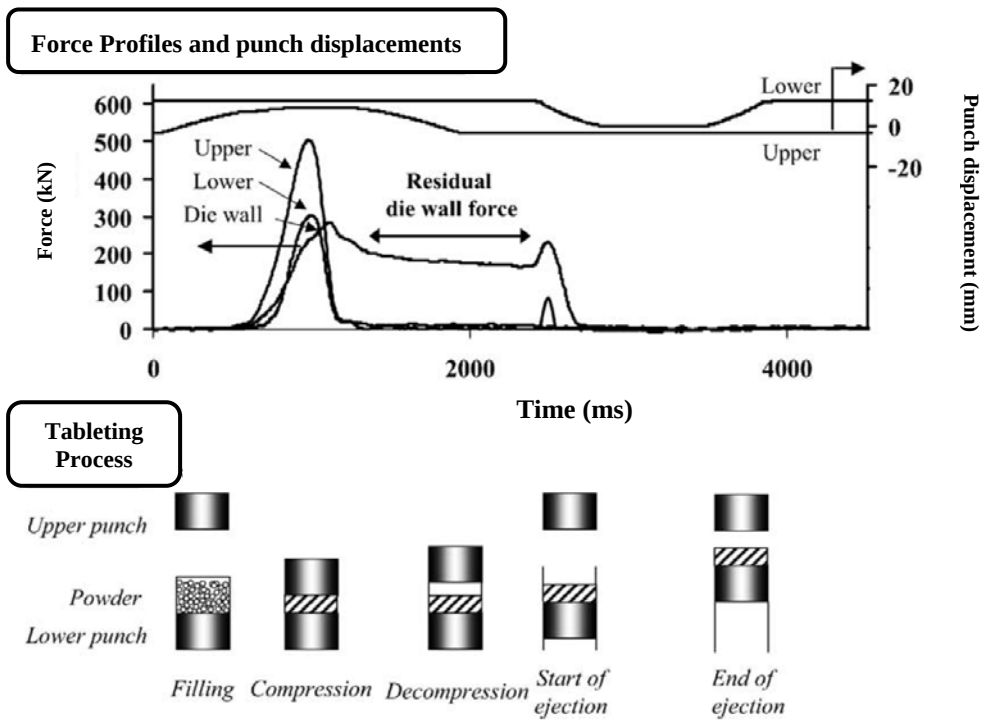

FIGURE 9. Force and punch displacements profiles during tableting process. (Adapted from Ref. 80 with permission from Elsevier.)

wall force reaches a maximum just after the maximum upper and lower force, and a constant residual value after upper and lower forces became zero, until the ejection process starts, when it again increases.[80] The residual die wall force is the average of values in the constant region at zero upper punch force, with the difference of displacement between upper and lower punch, giving a measure of the tablet area contact with the die wall. Residual die wall force depends on deformation behavior of particles under force. For materials that undergo plastic deformation,[86,87] a large residual die wall force is observed, in contrast to lower force for elastic materials as a result of their large relaxation behavior. Brittle materials show medium values of the residual die wall force as a result of considerable fragmentation and a large peak at ejection. The high die wall force during ejection is a sign of adhesion of powders to the die, and a reduction of this die wall force is effective in improving the tableting process.[80]

VI.B. Compaction Equations

A compaction equation relates some measure of the state of consolidation of a powder, such as porosity, volume (or relative volume), density, or void ratio, as a function of the compaction pressure. Since the recording of first-ever accurate compaction data in 1923 by Walker, a number of compaction-related equations have been proposed. However, the Heckel and Kawakita equations have been the most commonly used, as they relate the physical properties of the materials to applied pressure.[24]

1. Kawakita Equation

The basis for the Kawakita equation for powder compression is that the particles are subjected to compressive load in equilibrium at all stages of compression, so that the product of pressure term and volume term is constant.[88] The Kawakita equation is

$$Pa/C = [1/ab + Pa/a] \tag{7}$$

$$C = [V_0 - V/V_0] \tag{8}$$

where, Pa is the applied axial pressure, a is the degree of volume reduction for the bed of particles, and b is a constant proposed to be inversely related to the yield strength of particles. C is the degree of volume reduction, V is volume of compact at pressure, and V_0 is the initial apparent volume of powder.[89] This equation holds best for soft fluffy pharmaceutical powders, and is best used for low pressures and high porosity situations.[24]

2. Heckel Equation

The Heckel model[90,91] provides a method for transforming a parametric view of the force and displacement signals to a linear relationship for purely plastic materials. This makes the Heckel model a convenient method for interpretation and the most frequently used relationship between relative density and applied pressure.[92] The Heckel equation is based on the assumption that densification of the bulk powder under force follows first-order kinetics (Figure 10).

The Heckel equation is expressed as

$$\ln [1/1–D] = KP + A \qquad (9)$$

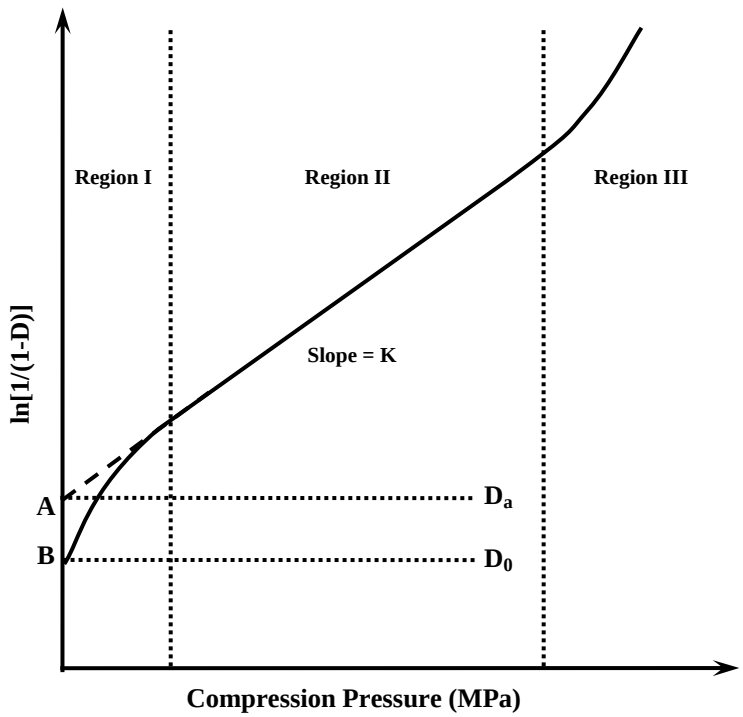

FIGURE 10. A typical Heckel plot derived from relative density and compaction pressure. Region I corresponds to particle rearrangement at low pressure, whereas region II, the linear part of the curve shows the ability of the material to deform plastically. At higher pressures, region III is observed due to work hardening. D_a gives densification due to initial particle rearrangement, whereas D_0 gives densification due to initial die filling. (Adapted from Ref. 13 with permission from Elsevier.)

where, D is the relative density of the tablet (the ratio of tablet density to true density of powder) at applied pressure P, and K is the slope of straight line portion of the Heckel plot. Reciprocal transformation of the slope gives mean yield pressure, P_y. In-die measurements of the tablet thickness give apparent mean yield pressure, and the intercept of linear portion A gives densification of the powder as a result of initial particle rearrangement (D_a)

$$A = \ln [1/1–D_0] + B \tag{10}$$

$$D_a = 1 – e^{-A} \tag{11}$$

where, $\ln [1/1–D_0]$ is related to the initial die filling and B is the densification as a result of slippage and rearrangement of primary and fragmented particles (D_B).

From the point B where the Heckel Plot intercepts the Y-axis, D_0 is obtained (zero pressure powder density), which is defined as the densification as a result of die filling or initial powder packing.

$$D_0 = 1 – e^{-B} \tag{12}$$

$$D_B = D_A – D_0 \tag{13}$$

In 1961, Heckel proposed a relationship between the constant K and the yield strength for a range of metal powders.

$$K = 1/3\ \sigma \tag{14}$$

where, σ is the yield strength of the material. K is inversely related to the ability of the material to deform plastically. Heckel studied mainly metal powders and the equation was only meant for materials that compact by plastic deformation. The term $3\sigma(=1/K)$ is often called the yield pressure. Heckel parameters have been shown to be more dependent on the compression–decompression cycle than on the size of die.[93]

Methods used to collect data for Heckel transformation are *in-die* or *at-pressure* and *out-of-die* or *zero pressure* after ejection of the compact. In the in-die method,[94,95] results can be influenced by an elastic deformation under pressure, which lowers the porosity. Therefore the *out-of-die* or *zero-pressure* measurement describes powder behavior more accurately,[96] and hence is a reliable method for obtaining yield strength and avoiding contribution of elastic deformation. However, the in-die method is still commonly used to derive the yield strength of powders because it requires less time and effort. Although important, a quantitative comparison between these two methods is not available.

Three regions for an in-die Heckel plot may be observed[97,98] (Figure 10). The first region corresponds to low-pressure, where the curvature arises from particle rearrangement before a plastic deformation takes place. The second region is the linear part of the plot in the medium pressure range representing material's ability to deform plastically under pressure. At the high-pressure region, the curvature has been attributed to work (strain) hardening[97,99] and to a

change in crystal density. However, Sun and Grant explained the curve behavior in the last region with an elastic deformation of the powder. This elastic deformation can even lead to a negative porosity and a value for relative density higher than one.[100]

Roberts and Rowe[74] proposed an additional study on the effect of punch velocity to understand the compression process. Strain rate sensitivity (*SRS*) was measured according to equation

$$SRS = [Py_2 - Py_1 / Py_2]\ 100 \tag{15}$$

where, Py_1 is the yield pressure at low speed and Py_2 is the yield pressure at high speed.[101] Although Heckel only applied pressures between 69 and 690 MPa, he postulated that extrapolation of the values to even higher pressures are justified, because linearity exists over nearly 80% of the pressure range.[97] Relative density is always influenced by determination of true density, tablet weight, and tablet volume. Therefore, data points at relative density more than 0.95 should be used with caution, because they can cause deviations from linearity.[96] Kuentz and Leuenberger[102] postulated a modified Heckel equation which allows the description of the transition between the states of a powder to the state of a tablet.

$$\sigma = \frac{1}{C}\left[\rho_c - \rho - (1-\rho_c)\ln\left(\frac{1-\rho}{1-\rho_c}\right)\right] \tag{16}$$

where, σ is the pressure, ϱ is the relative density, ϱ_c is the critical density, and C is a constant. Similar to the constant K in the Heckel equation, the constant C in the modified Heckel equation shows high values for plastic behavior and low values for brittle powder behavior.

Although Heckel plots are mostly used to characterize single materials, they can also be used for powder mixtures. Ilkka and Paronen[92] investigated binary mixtures and reported that all the mixtures behaved like intermediate materials between the bulk mixture components. Yet, no exact linear relationship in behavior between the mixtures and bulk components was seen. In most of the cases, one mixture component seemed to have more effect on the densification of the powder mixtures than the other.

3. Walker Equation

The Walker equation[103] is based on the assumption that the rate of change of pressure with respect to volume is proportional to the pressure, thus giving a differential equation

$$Log\ P = -L\ x\ V' / V_0 + C_1 \tag{17}$$

where, V_0 is the volume at zero porosity. The relative volume is $V'/V_0 = V = 1/D$, C_1 is constant. The coefficient L is referred to as the pressing modulus.[104]

The Heckel and the Walker equations transform the relative density in a different manner (Figure 11). The Heckel transformation is practically linear at intermediate densities, whereas Walker transformation is most curved in this region. At high densities the Walker equation approximates linearity whereas the Heckel transformation tends to infinity. Compared with the Walker equation the Heckel model is less reproducible and has less discriminative power as a general compression constant.[23]

VI.C. Tableting Indices

The evaluation of drug substances and pharmaceutical excipients for their physico-mechanical properties is of prime importance in the development of oral solid dosage forms. Apart from tensile strength and porosity–pressure rela-

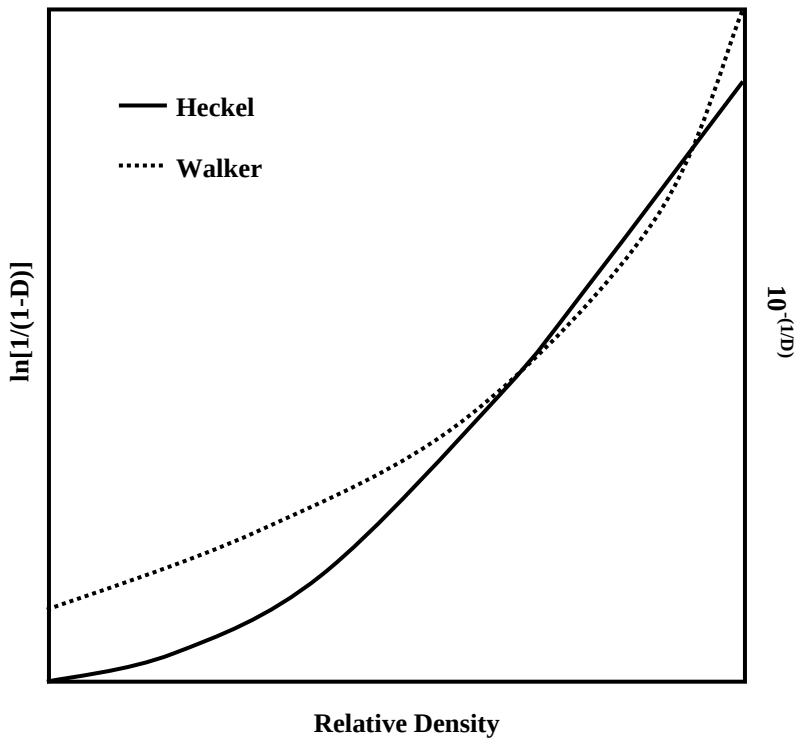

FIGURE 11. Heckel and Walker transformations of relative density. Heckel transformation is linear at lower densities, whereas Walker is linear in the high density region. (Adapted from Ref. 23 with permission from Elsevier.)

tionship, another approach to characterize the properties of compact is by dimensionless Hiestand's indices,[55] which gives insight about relative tableting performance of materials. Hiestand also defined and developed procedures for determining the indices of tableting performance such as *bonding index (BI), brittle fracture index* (*BF*), and *strain index* (*SI*).[55] The determination of these three indices involves measurements of indentation hardness and tensile strength of large compacts with a hole and without a hole in the center.[56]

BI estimates the survival of bonds during decompression. Materials with higher *BI* form stronger compacts which survive the die-wall and ejection forces. Conversely materials with low *BI* may produce friable tablets. The values of *BI* generally range from 0 to 0.04.[105] *BFI* indicates the ability (or inability) of material to relieve localized stresses within the compact by plastic deformation.[105] A *BFI* of 1 would correspond to purely brittle material, whereas a zero value indicates that stress at the whole had been completely relieved by plastic deformation.[27] Hiestand and Smith proposed that the materials with high *BFI* would be less able to relieve stresses during decompression and ejection and therefore be more susceptible to capping and lamination. Problems crop up when *BFI* is 0.8 or more.[55] *SI* indicates the relative strain energy change (or a change in size) during elastic recovery after plastic deformation. The values range from 0 to 0.04 and a high *SI* value shows potential structural failure in terms of capping and lamination as a result of high elastic recovery after decompression.[105] According to Hiestand, *special case* materials do not plastically deform and are believed to be exhibit poor tableting performance.[106] Such materials are identified when the compression stress required to form a compact (σ) is greater than its *dynamic indentation hardness* (H_0), i.e., σ/H_0 is greater than unity. For normal materials that show plastic flow, σ/H_0 is less than unity.[107]

Podczeck and Newton have criticized the concept of BFI and stated that the calculations as described by Hiestand et al.[31] with cubic compacts and applied to circular tablets from data using the value of the tensile strength of tablets with and without a central hole, are incorrect based on formula used to calculate the tensile strength of the tablets, which had a central hole. Hence, it is essential to know the stress conditions, which exist in the specimen.[56,108]

VII. FACTORS INFLUENCING THE COMPACTION OF PHARMACEUTICAL POWDERS

The identification and quantification of the numerous parameters that affect the compaction process are vital for product uniformity. Crystal habit, particle size, particle size distribution, polymorphism, amorphism, moisture content, salt form, tableting speed, (dwell time, lag time), mechanism by which particles undergo compaction, solid state of lubricants and their concentration, coproc-

essing of excipients or drugs, pre- and main-compression force profile, granulation methods, and ultrasonic vibration, all are known to affect the compaction of pharmaceutical powders. All these factors are interrelated to each other and cannot be considered in isolation. The various factors, by acting at the fundamental level, have the ability to influence the behavior of powder under compaction. For example, moisture level is a determinant of the plasticity of a blend; force profile may influence viscoelastic behavior; and solid state forms may dictate particle rearrangement based upon differential slip plane characteristics. Also, in the following discussion, at times certain conflicting results have been mentioned, this can be attributed to the different experimental designs and conditions used in one study to the other.

VII.A. Moisture Content

The study of moisture adsorption and absorption by excipients and solid dosage forms provides information for selecting excipients such as disintegrating agents, direct-compression carriers, binders, and for determining the humidity control required during production and storage.[109] Moisture affects the flow,[29] mixing rheology,[110] compaction,[39,111] true density,[43] and mechanical properties of granules as well as tablets.[73] Water plays a key role in all manufacturing steps, therefore, water–powder interaction is a major factor in the formulation, processing, and performance of solid dosage forms.[112] The amount of water associated with a solid at a particular RH and temperature depends on its chemical affinity, surface area, and available sites of interaction.[113]

Moisture plays an important role in interparticulate bond formation by enhancing the tensile strength of the powder bed and decreasing the density variation within the tablet. The reduction in tablet density variation is ascribed to the lubrication of the die wall, which allows more of the applied force to be transmitted through the compact onto the lower punch (*R* value).[67] Absorbed water decreases particle surface free energy and tablet adhesion to the die wall. Any water expressed during compaction also functions as a low-viscosity lubricant. Rees and co-workers found in their study that lower applied pressure is required in presence of moisture to improve powder compaction.[73]

MCC is an important excipient upon which, the role of moisture has been extensively investigated. Teng et al. reported that tablets containing MCC became harder as the moisture content increased,[114] whereas a lack of moisture was responsible for tablet lamination because of increased yield force and elastic recovery.[115] In another study, Pilpel and Ingham reported the effect of moisture in MCC on density, compaction, and tensile strength and related the changes in mechanical properties of MCC to the way in which water is sorbed into the cellulose structure.[116] A marked reduction in MCC tablet tensile strength was observed at 8% w/w water content by Fassihi and co-workers.

This effect was attributed to hydrostatic resistance to consolidation caused by the presence of water in a relatively unrestricted form.[117] The effect of moisture on the binary mixtures of MCC-PVP also has been investigated.[118] Pilpel and Ingham concluded that moisture is sorbed into the amorphous part of MCC[119] and most likely exists in at least three states—tightly bound to an anhydroglucose unit (one water molecule binding between two anhydroglucose units, followed by each anhydroglucose unit), less tightly bound, and bulk water.[120] Increases in the molecular mobility of MCC explained how water acted as a plasticizer in amorphous part of MCC. Also, MCC with low moisture content (1.1%) yields lower tablet strength than normal moisture content (4.9%). Commercial grade Avicel® PH-101 and Emcocel® MCC showed 20–30% increase in cohesiveness after addition of water, which did not increase further with addition of more water. Khan et al. also examined the effect of MCC's moisture content on the compression properties of formulations containing paracetamol and potassium phenethicillin and reported that the strongest compacts were produced with MCC having 7.3% moisture.[121] Table 3 gives examples of the effect of moisture on compaction for a few representative drugs and excipients.

An increase in tensile strength with increasing moisture content or RH has been explained by adsorbed water functioning as a surface-restructuring medium, thus increasing the amount of solid bridges.[122] Another possible explanation for increasing tensile strength is that immobile water layers sorbed at particle surfaces can enhance particle–particle interaction. According to this theory, an adsorbed water vapor layer can contribute in two ways-(i) tightly bound water vapor layers can be regarded as part of the particles that reduce interparticular surface distances and increase intermolecular attraction forces,[122] and (ii) adsorbed layers can touch or penetrate each other, thus increasing the attractive forces between neighboring particles.[123] Additionally, moisture in a material exerts the van der Waals' forces, and aids in the development of additional bonds by plastic deformation and/or melting or recrystallization of powder particles. A contrary effect of decrease in tensile strength upon increased moisture is attributed to the formation of water layers or the presence of free water at the surfaces, which reduces intermolecular attractive forces and allows separation of the particles.[39,122]

An alternative explanation for the effects of moisture on the compaction involves the glass transition temperature (T_g) of amorphous materials, which reduces due to the plasticizing effect of water and changes the viscoelastic properties of polymers.[124–126] At certain moisture content above the level consistent with the transition from the glassy to the rubbery state, significant changes occur in the mechanical properties of the polymer. At temperatures exceeding T_g, polymers exhibit highly increased chain mobility and plasticity, which have major consequences for compaction properties. Therefore, water is

TABLE 3. Effect of Moisture on Powder Compaction for a Few Representative Drugs/Excipients

Drug/excipient	Observations	Ref.
Maltodextrin (lower degree of polymerization)	Compact exhibited highest tensile strength at 8% moisture and above this level, tensile strength was decreased as a result of reduction in interparticulate adhesion.	111
Sodium chloride	10% Moisture exerted a hydrodynamic resistance to consolidation, which inhibited interparticulate shear forces and bonding	127-129
Paracetamol and paracetamol–cellulose	6% Moisture content in paracetamol, and 2–4% in paracetamol-cellulose formed stronger tablets than those without moisture	130,131
Ibuprofen	2.5% Moisture increased the particle interaction and allowed plastic flow under applied pressure.	39
β-cyclodextrin	β-Cyclodextrin lost its compactibility on removal of water, and about 14% appeared optimum for maximum compactibility.	132,133
HPMC* and HPMC-ibuprofen	At all compression speeds, an increase in moisture content reduced the elastic recovery of compacts due to greater tablet consolidation.	134,135
Anhydrous β-lactose	An increase in the moisture content reduced tablet hardness and greater pressure was required to achieve specified hardness values.	136

Key: HPMC = hydroxypropyl methylcellulose

needed to enhance the compressibility of starches and facilitate their plastic deformation.[137] Hence, moisture can increase plastic deformation and reduce elastic property of powder material and reduce the ejection force. Shotton and Rees reported an increased sodium chloride punch force ratio (R) at 0.55% moisture for low applied force. This effect was explained by reduced friction caused by the formation of moisture film acting as a die wall lubricant. Lower moisture contents provided less die-wall lubrication at all values of applied force.[134]

VII.B. Compression Force Profile

It is well known that speed of compression can have significant effect on the compaction properties of pharmaceutical powders and this is a challenge during

scale-up and technology transfer when tableting speeds increase significantly.[138] Altering the method of force application is beneficial for tablet production in order to increase tablet strength and prevent the incidence of capping and lamination. In all cases, for a given pressure, double compaction produces stronger tablets than single compaction. The ratio and magnitude of pre- and main compaction pressures can be varied depending on the deformation behavior of materials.[138] DCP/MCC and pregelatinized starch[139] tablets show no significant difference in crushing strength values regardless of whether the precompaction pressure is less than or greater than the main compaction pressure. However, both direct compression acetaminophen and ibuprofen were found to have increased crushing strengths and decreased capping/lamination when the precompaction pressure was less than the main compaction pressure**.** When the time interval between the pre- and main compaction events was varied from 30 to 500 msec, no significant difference in the crushing strength or capping/ lamination tendency was observed.[140]

For maize starch and polymeric materials (plastic), an increase in the yield pressure with punch velocity is attributable to a change from ductile to brittle behavior or a reduction in the amount of plastic deformation due to the time-dependent nature of plastic flow. However, for magnesium and calcium carbonates (brittle), no changes in yield pressures were observed with increasing punch velocity.[74] In another study, describing the reduction in porosity of substances that consolidated principally by fragmentation, relatively little velocity dependence was observed.[141] For pure lactose tablets, the porosity and tensile strength of compacts were less affected by compression rate, though they depended on the applied force.[138] The properties of MCC tablets varied with the tableting speed, in addition to the applied force, as a result of its time dependant plastic deformation.[142] However, Tye et al. reported that the tableting of MCC was reported to be speed independent.[138] Similar contrasting results have also been reported for DCP. The tabletability of DCP was reported to be independent of machine speed,[47,141] but the recent published literature by Tye et al. showed that tabletability of DCP increased as the compaction speed was increased. It is interesting to note that stronger tablets were formed at higher tableting speed (shorter dwell-time) under similar compaction pressure.[138] These differences could be explained by the range of compression pressure or tableting speed explored in various studies. Tye et al. had explored at much broader range, as compared to previous studies reported by Rees et al.[47] and Armstrong et al.[141] Higher tableting speeds, cause extensive fragmentations of DCP, resulting in larger number of new bonding sites available for the bonding.[138,34]

In case of maltodextrin, mechanical parameters and disintegration time increased as applied pressure was increased above 90 MPa, however, no differences were found above this limit.[101,143] Various grades of polyethylene glycol

(PEG) (molecular weight 1500 to 35000) showed that resistance to densification increased with molecular weight and compression speed. At any compression speed, low molecular weight PEGs undergo greater densification. For a given molecular weight, tablets made at 10 mm/s had better mechanical strength than those made at 300 mm/s. PEG 12000 gave the hardest tablets at all compression speeds, but compressibility was lesser than lower molecular weight PEGs.[144]

Vezin et al. described that adjustment of pre- and main compression reduced the loss of tablet tensile strength arising from lubricant over-mixing.[145] The duration of t_{off} depends on the ability of the compacted powder to relieve stress and is an indication of the predominant deformation during consolidation. Thus, at a given maximum pressure (P_{max}), short t_{off} values are characteristic of materials that consolidate mainly by brittle fracture whereas longer values indicate an increase in plastic flow. t_{off} decreases with increase in P_{max} as a result of the reduction in the porosity of the compact and consequent restriction of plastic flow into the void spaces.[72]

Blend of paracetamol and MCC (1:1) was compacted at different combinations of pre- and main compression of 320 and 240 MPa. Tensile strength decreased when compression speed was increased. Precompression played a major role at high compression speeds as the tensile strengths of tablets at precompression of 160 MPa followed by a main-compression of 80 MPa (at 390 mm/s) were similar to those compressed using a single compression of 320 MPa at the same compression speed.[40] Thus, combinations of lower pressures can be employed to compress the material to the same tensile strength as a high single compression.[146] Also, the tableting speed affects dwell time and lag-time, which ultimately affect the time dependent deformation behavior of the pharmaceuticals. Another study by same investigator reported that the application of higher dwell-time resulted in greater tensile strengths than lag-time, which had lesser effect on the compaction properties.[14]

VII.C. Solid-State Properties

Drugs and excipients used in tableting exist in a variety of solid-state forms. These forms often show difference in their physico-technical behavior, therefore, it is important to know their influence on pharmaceutical process including compaction.

1. Hydration/Solvate State

The need for optimal moisture content in the formation of strong tablets is indicated by crystal hydrates that compress well, but fail to form strong tablets

when water of crystallization is removed (e.g., ferrous sulfate heptahydrate).[147] The influence of water in the crystal structure on the compaction properties of structurally similar crystals, *p*-hydroxybenzoic acid anhydrate (HA) and monohydrate (HM) were investigated. Incorporation of water into the crystal lattice resulted in greater tablet strength and larger volume reduction as a result of improved plasticity. In case of HA crystal compression, the zigzag-shaped layers mechanically interlock, inhibiting slip and reducing plasticity. However, in the HM crystals, a water molecule played a space-filling role, which increases the layer separation and allows easier slip between layers and provides greater plasticity to HM crystals, which increases the interparticulate bonding surface area.[148]

In another study, the compaction properties of calcium lactate pentahydrate were found to be much better than calcium lactate trihydrate. Moreover, as a crystalline structure, calcium lactate pentahydrate showed compaction speed sensitivity. This meant that, in combination with its excellent flow properties, calcium lactate pentahydrate was a suitable filler-binder in tablets prepared by high-speed compaction.[149] Lactose monohydrate, however, showed improved tablet strength upon removal of water of crystallization by thermal or chemical means.[150] Organic solvents converted α-lactose monohydrate into a stable anhydrous product with increased binding capacity and flowability.

2. Crystal Habit

Isomorphic forms of drugs differ only in their crystal habit. Tableting behavior, flowability, and the tendency to stick to the punches can be affected by the crystal habit of the drug(s). Crystal engineering and particle design can be effectively used to improve compactibility.[10] In a study by Sun et al. on the influence of crystal shape on the tableting performance, prism and plate shaped crystals of L-lysine monohydrochloride dihydrate, were evaluated. Greater tabletability of plates when compared to prisms was a result of its better compactibility that overcame the negative effects by its lower compressibility. This was a result of favorable orientation of the slip planes in the plates, corresponding to greater plasticity under load.[11] In a study, polyhedral and thin plate-like crystal habit of paracetamol influenced the compression property, which was also investigated by the Heckel plots and their associated parameters. The correlation coefficient of the initial part of the Heckel plots, and also the values of *SRS*, were lower for thin plate-like crystals, indicative of greater fragmentation as compared to polyhedral crystals. Compacts made from thin plate-like crystals exhibited higher elastic recoveries as a result of lesser plastic deformation during compression than for polyhedral crystals.[13] Production of sintered-like crystals of paraceta-

mol for direct compression was prepared by recrystallization from a dioxane solution or suspension.[151]

Phenytoin crystals having varied habits were prepared by recrystallization from ethanol and acetone solutions under different conditions. The compacts of phenytoin crystals produced from alcohol or acetone had higher crushing strengths than untreated phenytoin as a result of the lower porosity and the lower elastic recovery.[152] The compaction characteristics of a new drug substance with two crystal habits and particle size fractions as well as its binary mixtures with MCC were studied. The three-dimensional hexagonal crystal habit or smaller particle size gave a slightly higher total work of compaction as compared to cubic brick habit or larger particle size, respectively.[153]

3. Polymorphism/Amorphism

Differences in the physical and chemical properties of various drug substance polymorphic forms are well documented. In a study on compression behavior of pure orthorhombic or monoclinic paracetamol, orthorhombic crystals exhibited better technological properties due to presence of sliding planes for crystal plasticity, greater fragmentation at low pressure, increased plastic deformation at higher pressure, and lower elastic recovery, thus avoiding capping even at high compression pressures.[7] In another study that related the effect of polymorphic structure of sulfamerazine on the tableting properties, form I showed highest tensile strength, where as form II(B) showed minimum values and the porosity at the same compaction pressure followed the order, I << II (A) < II (B). Greater plasticity and compressibility was attributed to the slip planes present in form I crystals.[154] Acetaminophen is known to exist in two polymorphic forms. The thermodynamically stable form I (monoclinic) gave unstable tablets with high capping tendency as a result of a stiff construction of the molecules inside the crystal, whereas, form II (orthorhombic) showed better compression behavior as a result of presence of sliding planes.[155]

The complete absence of long-range, three-dimensional, intermolecular order associated with amorphous materials might significantly modify the mechanical properties of a powdered amorphous drug substance.[124] Amorphous α-cyclodextrin,[156] spray-dried lactose,[157] showed improved in compaction behavior. The improvement in compaction behavior of amorphous materials can be attributed to higher plastic deformation than their crystalline counterparts.

4. Particle Size and Particle Size Distribution

The particle size and particle size distribution can affect both the particle rearrangement and compaction phases. Correlations between average particle size

and tablet tensile strength are important to select and design appropriately sized particles. Two particle size fractions (<90 micron and 105–210 micron) of paracetamol were examined for their compaction properties. Each fraction produced extremely weak tablets with capping. The 105–210 micron particles underwent more fragmentation than 90 micron particles. Heckel analysis confirmed that the larger size fraction of paracetamol produced denser compacts than the smaller fraction with lower elastic recoveries and elastic energies.[12]

Fichtner reported that the spread in particle size of paracetamol had no influence on the evolution in tablet porosity and tensile strength during compression, but had a significant and complex influence on the short-term postcompaction hardening. It was concluded that the distribution in size of free-flowing particles is not critical for the tablet porosity, but may give significant effects on tablet tensile strength as a result of postcompaction hardening.[158] A study related to the effect of particle size of L-lysine monohydrochloride dihydrate on compaction showed that compression of smaller particles at low compaction pressures resulted in tablets of greater porosity. At the same compaction pressure, tensile strength of tablets increased with decreasing particle size as a result of a larger number of contact points between smaller crystals and more homogeneous distribution of pores. Increasing yield strength with increasing particle size indicates greater apparent plasticity of the smaller particles. However, fragmentation of the larger particles tended to equalize the particle size and reduce its influence.[34]

Particle agglomeration behavior of a novel drug substance DPC 963 was affected by particle size, with smaller particle size giving higher pore volumes, suggesting lower densification tendency as compared to the larger drug particle size. Granule compressibility was increased by decreased in drug particle size. The effect of particle size on granulation growth was a result of increased densification propensity, as a result of increased drug substance particle size.[159] A recent paper by Sun et al. discussed about the reduced tabletability of roller compacted MCC as a result of granule size enlargement. This was attributed to lower surface area in larger granules, thus leading to lower tensile strength as compared to smaller granules.[8]

VII.D. Salt Form

Another important but rarely explored factor determining the compaction properties, is the salt forms of pharmaceuticals. Sun and Grant examined the effects of salt form of L-lysine with the following anions at various pressures-acetate, monochloride, dichloride, L-aspartate, L-glutamate (dihydrate), and L-lysine (zwitterionic monohydrate). Results indicated that different salts were differing in their compaction behavior and melting temperature of each salt was

found to be as an indicator of its tensile strength at zero porosity. Because a higher melting point indicates stronger intermolecular and interionic interactions in the crystals, the tensile strengths at zero porosity might be related to the melting points of the salts.[160]

VII.E. Granulation Method and Binder

As a result of poor flowability and compaction behavior, pharmaceutical powders are often subjected to granulation prior to tableting. The optimal granulation method is selected for production of porous and free-flowing granules, which enable formation of tablets with high mechanical strength at low compression pressures.

In an attempt was made to study the effects of different wet and melt granulations on compaction. In the wet granulation methods, the tensile strength was in the order of wet massing granulation > wet fluidized bed granulation > wet tumbling fluidized bed granulation > wet high-speed mixer granulation; and melt high-speed mixer granulation > melt fluidized bed granulation > melt tumbling fluidized bed granulation in melt granulation. These results indicated that the compactabilities of granules varied with the granulation method used.[161] In an independent study, melt granulations of lactose and PEG 4000 were made with a fluid-bed granulator and for comparison in a high-speed mixer with scraper. Remarkable differences in tablet properties such as hardness and disintegration time were found between the two different mechanisms (coalescence and layering) of granule formation.[162]

The effect of binder on the relationship between the bulk density and compactibility of lactose granulations was studied by comparing binderless granules (α-lactose monohydrate) with granules (β-lactose) containing hydroxylpropyl cellulose. The results showed that the effect of binder on tablet strength was independent of the type of lactose used, but was significantly influenced by the consolidation and compaction behavior of the lactose particles. The effectiveness of the binder increased with a decrease of the bulk density of the granule powder bed. Tablets with a high crushing strength could be prepared from porous granules, containing a binder.[163] The effect of wax (glyceryl behenate) on the deformation and compression characteristics of MCC and acetaminophen prepared by extrusion and spheronization were described. Beads made without wax required greater compression forces to form cohesive tablets. As the amount of wax in the bead formulation was increased, the beads became more plastic and compressible. The Heckel analysis showed that as the level of wax in the bead formulation was increased, the yield pressure decreased, indicating that the beads densify by a plastic deformation mechanism.[164]

VII.F. Use of Ultrasonic Vibration

Levina et al. found that coherent ibuprofen tablets could be prepared by ultrasound-(US) assisted compaction at pressures as low as 20-30 MPa. The breaking forces of the tablets produced with ultrasound applied during compaction were found to be consistently significantly higher than when compaction was performed conventionally, or with US applied before or after compaction. Application of US during compaction made it possible to increase tablet mechanical strength by 2–5 times.[165] In another study by the same author, it was reported that coherent paracetamol tablets could be prepared by US-assisted compaction at similarly low pressures. The breaking forces of the tablets produced with US applied during compaction were higher than those produced conventionally.[166] The explanation provided for enhanced compactibility was that US improves particle rearrangement and provides energy for partial melting and subsequent fusion of particle surfaces, which increases interparticulate bonding. Development of solid bridges between the particles during US-assisted compaction was thought to result in a reduction of void space.[166]

VIII. TABLETING PROBLEMS

Compression related tableting problems mainly include capping/lamination and sticking/picking. These problems stem from poor compactibility at the particulate level and thereby an in-depth scrutiny of the compaction behavior can aid in scientifically absolving the respective problem. Capping is a term used to describe the partial or complete removal of the top or bottom crown of a tablet from the main body whereas lamination is the separation of a tablet into two or more distinct layers. These tableting problems though usually arise immediately after compaction, may surface after a lag time. Friability test is the quickest way of revealing such a problem. The main reason behind these problems is the inability of materials to relieve stress after the removal of force.[55] Also, excess fines can trap air in the tablet resulting in capping and lamination. The inherent deformation properties of the material, such as plastic, brittle or elastic also affect these tableting problems. Density and stress are unequally distributed in a compact and elastic recovery is considered to be the most likely cause of capping in the areas of high density.[167] During compression, particles undergo sufficient plastic deformation to produce die-wall pressure greater than that can be relieved by elastic deformation. Sometimes die-wall pressure produces enough stress inside the compact that leads to cracking or surface fracture upon ejection. Tablets that do not fracture after decompression relieve internal stress by plastic deformation. As the plastic deformation is a time dependant phenome-

non,[47] therefore stress relaxation depends on dwell time and rate of force transfer to the powder bed,[14] with rapid compression and decompression more likely to result in tablet failure. Tablet capping or lamination problems are also associated with pre- and main compaction profile.[12] Measures such as, applying precompression, slowing tableting speed (longer dwell time), and reducing final compression force may help mitigate capping/lamination.[168]

The type of tooling used can also have an effect on capping or lamination.[169,170] Often deep concave punches give capping as a result of more radial expansion and shear stress in cap region than in body of the tablet. Flat punches produce less shear stress within compact.[171] Dies also develop a wear ring in the areas of compression and the tablets compressed in the ring have fewer diameters to pass through die wall, resulting in capping and/or lamination upon ejection. Incorrect set up of tableting press is another cause of capping/lamination and proper adjustment of lower punch and sweep off plate is essential. Moisture plays a key role in bonding mechanism and plastic deformation,[39,172,173] and therefore, granules or powder having less moisture tends to cap or laminate. Addition of hygroscopic substances such as methyl cellulose, sorbitol, and PVP can help to maintain proper moisture level in such cases.[4]

Picking is a term used to describe the removal of surface material of tablet by a punch. Picking is often a concern with punch having engraving or embossing. Some letters such as "A," "B," and "O" are difficult to manufacture cleanly. To reduce this problem, lettering should be as large as possible or tablet can be formulated in larger size.[4] Sticking refers to tablet material adhesion to die wall. Punch surface roughness,[169] compaction force and the blend composition are significant factors contributing to sticking. Chrome plating of punch faces increases sticking at a low compaction force but decreases it at higher forces.[170] Low melting substance either active ingredient (e.g., ibuprofen) or additive (stearic acid and PEG) may soften as a result of heat generation during compression. Addition of high melting additives in the formulation, refrigeration of granules, and cooling of tableting press can be used. Monitoring the moisture level is also important for controlling these problems, as increased moisture has been related to sticking and picking.

IX. IMPROVEMENT OF COMPACTION BEHAVIOR

Many of the pharmaceutical drugs and excipients per se exhibit poor compressibility. Depending upon what constitutes the major bulk of the blend, importance needs to be given either to improving the compaction behavior of either the API or the excipient(s). In addition, steps such as granulation and coprocessing may be required, to introduce satisfactory compactibility. Low dose drugs with poor compressibility rarely show tableting problems, because excipients contribute the required compressibility. However, for high dose drugs, improvement of the API and/or selection of excipients especially the

diluents, and binders are critical to minimize tableting problems. The selection and/or modification of blend components is dictated by their compression behavior, when present alone or in combination. An example of this approach is the choice of blend/coprocessing components based on their complimentary nature (plastic versus brittle).

IX.A. API Modification

Modification of the API is essential for high dose drugs because of the limited role excipients play in improvement of compactibility. Production of spherical crystals to improve compaction behavior and flow has recently received attention. Spherical crystals of acebutolol hydrochloride,[174] ascorbic acid,[175] bucillamine,[176] and propyphenazone[177] showed improved compactibility and flow properties. The improvement of static compression behaviors of the agglomerated crystals was due to higher stress relaxations and lower elastic recoveries of agglomerated crystals.[174] The excellent compactibility of agglomerates was also attributed to the fragmentation property and a greater degree of plastic deformation under compression.[176] Pawar et al. described some techniques for crystal coagglomeration to obtain ibuprofen-paracetamol agglomerates.[15,178] Optimization of tableting behavior of excipients was carried out by Staniforth and group. They examined alternative crystallization conditions in order to design a directly compressible mannitol and obtained a highly porous surfaced mannitol.[179]

IX.B. Excipient Modification/Selection

The type and amount of the excipient(s) selected influence the overall quality attributes of the tablets. From view point of their role in compaction, excipients may be classified as (i) those that have a positive influence, such as diluents and binders; and (ii) those with negative influence such as disintegrants, and lubricants. Various classes of excipients with emphasis on their respective roles in compaction are discussed in the following section.

1. Diluents

Diluents play the most critical part among all the excipients, because they are usually present in amounts greater, than other excipients. Diluents range from highly compressible materials such as MCC, to those with very low compressibility such as starch. As described previously, the main behavioral patterns of pharmaceuticals under compaction are plastic deformation, elastic deformation, and brittle fracture. Material having plastic deformation properties such as MCC[51] and amorphous binders exhibit higher number of attractive forces, which contribute to higher compact strength. Rough surface on the particles

contributes positively towards, compact strength, even in the absence of fragmentation. MCC has both the properties and is considered best diluent for direct compression. Materials undergoing extensive fragmentation acquire a large number of interparticulate contact points. The latter, despite a low compaction load per unit area, are sufficient to generate a strong compact by virtue of their large number. In contrast, less fragmenting materials such as crystalline lactose,[94] acquire only a small number of contact points that will give a good compact, only if interparticulate bonds are strong enough or solid bridges are formed.

Successful tablet production therefore depends upon optimum balance between brittle fracture and plastic behavior, as dictated by the compression characteristics of the API and excipients. The most commonly employed excipients ranked in ascending order of their brittleness are MCC, spray-dried lactose, β-lactose, α-lactose, α-lactose monohydrate, and DCP.[180] A compilation of commonly used tableting diluents and their compaction properties are given in Table 4.

Over the years, there has been a perceptible shift towards direct compression for manufacture of tablets. The term *direct compression* is used to define the process by which tablets are compressed directly from the powder blends of active ingredient(s) and suitable excipient(s). Direct compression is a simple and economical process in terms of fewer unit operations and fewer stability issues for heat or moisture sensitive compounds. However, not all pharmaceuticals are amenable to direct compression and it is estimated that only about 20% of pharmaceutical materials can be compressed directly into tablets.[181]

Although direct compression is a simpler process, it demands increased performance from the excipients, especially diluents. Ideal requirements of a directly compressible diluent include good compressibility, free flow, and low segregation tendency.[3,133] The suitability of a diluent for direct compression can be quantified in terms of its dilution potential, which is defined as the amount of an active ingredient that can be satisfactorily compressed into tablets with a directly compressible excipient. The dilution potential is generally expressed in terms of percentage of noncompressible material or as optimum drug to diluent ratio. Higher dilution potential can help in incorporation of high amount of poorly compressible drug(s)[182] and small tablet size. However, the dilution potential of a diluent is also influenced by how poor is the compressibility of drug(s). Also, directly compressible adjuvant should be capable of being reworked without loss of compressibility or flow.

Excipients, per se might not be amenable to direct compression, however, their properties can be modified by granulation, agglomeration, and coprocessing. Coprocessing has emerged as a popular way to generate directly compressible excipients. In the absence of a chemical change during processing, coprocessed excipients can be considered generally regarded as safe (GRAS) if the parent excipients are also GRAS-certified.[183] This ensures rapid commercialization without the need for rigorous safety testing.[184] Coprocessing is defined as

TABLE 4. Commonly Used Tableting Diluents and Their Compaction Properties

Diluent	Features	Ref.
Microcrystalline cellulose	▪ High plastic deformation ▪ Excellent compactibility at low pressures ▪ High dilution potential, most useful diluent for direct compression ▪ Self-lubricating property	32,116,186
α-Lactose monohydrate	▪ Undergoes brittle fracture with low fragmentation ▪ Not directly compressible, used in wet granulation	41,187
Anhydrous β-lactose	▪ Consolidates by particle fragmentation with low fragmentation ▪ Directly compressible, poor flowability, picks up moisture at elevated humidities ▪ Binding capacity of anhydrous form higher than monohydrate	187,188
Spray-dried lactose	▪ Plastic nature provides better compaction than crystalline lactose ▪ Requires high compression pressures ▪ Compressibility adversely affected below 3% moisture ▪ High dilution capacity and freely flowing ▪ Bonding not affected by addition of lubricants	94,185
Dibasic calcium phosphate dihydrate	▪ Deforms by brittle fracture with high fragmentation ▪ Lubricants, as MS, have practically no effect on binding	186,189
Dibasic calcium phosphate anhydrous	▪ Deforms by brittle fracture ▪ Unlike the dihydrate, anhydrous form exhibits capping/lamination at higher pressure	190
Starch	▪ Poorly compressible ▪ Highly sensitive to lubricants ▪ Good disintegrant, binder	46,95
Pregelatinized starch	▪ Next choice after lactose and MCC ▪ Good compressibility and high dilution capacity than native starch ▪ Extremely sensitive to the softening effects of alkaline stearates ▪ Higher concentrations of MS (above 0.5% w/w), can affect interparticulate bonding, stearic acid is the preferred lubricant ▪ Good binder, free flowing, good disintegrant properties	191-193
Sorbitol	▪ Deforms by fragmentation ▪ Different crystalline types (α, β, γ, and δ) and amorphous forms are known, δ form is most stable and has the best compaction ▪ 2% MS tablet formulation has no negative effects on tablet strength ▪ Hardening of tablets upon ageing caused by recrystallization of sorbitol can be prevented by adding pregelatinized starch	194-196
Mannitol	▪ Deforms by brittle fracture, nonhygroscopic, useful for moisture-sensitive drugs ▪ Several polymorphic forms such as β and γ differ in compression behavior	173,197
Dextrose and modified dextrose (Dextrates)	▪ Deforms by brittle fracture, used as a direct compression diluent ▪ Less hydroscopic and produces softer tablets than lactose ▪ Hydrous form incompatible with moisture sensitive drugs ▪ More browning of tablets in presence of amines than lactose ▪ Dextrates are made by addition of other carbohydrates at lower concentrations. Good for direct compression and free flowing.	198,199

Key: MCC, microcrystalline cellulose; MS, magnesium stearate

combining two or more excipients by an appropriate process, leading to formation of an excipient with superior physico-technical properties, without any associated chemical change. In general, coprocessing ensures that deformation can occur along any plane and multiple new surfaces are formed during the compaction process that combines the advantages of both wet granulation and direct compression.[185]

Coprocessing is generally conducted with a combination of a plastic and a brittle excipient. Maarschalk reported coprocessing with a large amount of brittle material and a small amount of plastic material.[200] This particular combination prevents elastic recovery during compression, which results in a smaller amount of stress relaxation and a reduced tendency of capping and lamination.[64] However, examples of the other extreme also exist e.g., silicified MCC has a large amount of MCC (plastic material) and a small amount of silicon dioxide (brittle material). Hence, coprocessing these two kinds of materials produces a synergistic effect, in terms of compressibility, by selectively overcoming their individual disadvantages. Commercially available and some literature reported coprocessed directly compressible excipients are reported in Table 5. These include examples of combination of diluent(s), and/or diluent(s)-binder(s).

2. Lubricants

As with other classes of pharmaceutical excipients, lubricating agents are added to the formulation of solid dosage forms to aid in the manufacture and ensure appropriate quality of the finished products. Lubricant is best identified as a suitable material, a small amount of which, when interposed between two rubbing surfaces, will reduce friction arising at the interface. According to the basic mechanism by which they act, lubricants are divided mainly into two types[201] (i) hydrodynamic or fluid lubricants, and (ii) boundary lubricants. The hydrodynamic or fluid lubricants act by completely separating the moving surfaces by forming a layer. Resistance to motion arises solely by the viscosity of the lubricant. Hydrodynamic lubrication is not a surface phenomenon and friction coefficient values lie around 0.001 and thus doesn't cause much wear of the tooling (e.g., mineral oil).[202] In boundary lubrication, die wall and the granular surfaces are separated by lubricant layer penetrated by the surface asperities of granules, which are the main cause for the production of friction. In contrast to the former, it is a surface phenomenon and friction coefficients are much higher (0.05–0.15), and thus wearing of tooling does occur. However, good boundary lubricants are tough enough in the form of films thus can resist and minimize wear. They have low shear strength and hence readily form a film that is able to reduce the contact area of granules with the die wall.

Commonly used lubricants include, water insoluble metallic stearates, stearic acid, talc, and waxes; and water soluble materials such as boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine, carbowax, sodium

TABLE 5. Commercially Available and Literature Reported Coprocessed Drug/Excipient(s)

Coprocessed drug/excipient(s)	Method of preparation	Trade name (Manufacturer)	Comments	Ref.
Lactose (93.4%), PVP (3.2%), Crospovidone (3.4%)	Spray drying	Ludipress® (BASF AG Ludwigshafen, Germany)	Good compaction and bonding property, good flowability, low degree of hygroscopicity, hardness independent of machine speed	207
α-Lactose monohydrate (75%), Cellulose (25%)	Spray drying	Cellactose® (Meggle GmbH & Co. KG Germany)	Highly compressible, good mouthfeel, low cost	208
Sucrose, Dextrin (3%)	Agglomeration	Di-Pac® (American Sugar, USA)	Directly compressible sugar	209
MCC, Silicon dioxide	Blending	Prosolv™ (Penwest Pharmaceuticals Company, USA)	Better hardness of tablet, reduced friability better flow, reduced sensitivity to wet granulation	210
MCC, Guar gum	Blending	Avicel® CE-15 (FMC Corporation, USA)	Improved compaction with enhanced bonding properties	211
Calcium carbonate (70%), Sorbitol (30%)	Spray drying	ForMaxx™ (Merck Chemicals Ltd, UK)	Improved compaction and flow properties	212
α-Lactose monohydrate (75%), Cellulose (25%)	Spray drying	Microcelac® (Meggle, Germany)	Capable of formulating high dose small tablets with poorly flowable actives	213
β-lactose anhydrous (95%), Lactitol (5%)	Milling	Pharmatose® DCL40 (DMV Veghel, The Netherlands)	High compressibility, low lubricant sensitivity	214
Lactose monohydrate (85%), native corn starch (15%)	Spray agglomeration	StarLac™ (Roquette, France)	Good compressibility and flow	215
Fructose (95%), Starch (5%)	Spray drying	Advantose™ FS 95 (SPI Polyols, Inc. USA)	Directly compressible powder	216
Maltose	Spray drying	Advantose™ 100 (SPI Polyols, Inc. USA)	Spray dried directly compressible maltose powder	217

TABLE 5. (Continued)

Coprocessed drug/-excipient(s)	Method of preparation	Trade name (Manufacturer)	Comments	Ref.
Calcium carbonate (90%), starch (10%)	Spray drying	Barcroft™ Cs 90 (SPI Polyols, Inc. USA)	Good compaction and flow behavior	218
Hydroxides of Al, Mg and sorbitol	Spray drying	Barcroft™ Premix St (SPI Polyols, Inc. USA)	Direct compression antacid powder	219
Xylitol, Sodium CMC	Spray drying	Xylitab® Danisco A/S, Denmark	Directly compressible xylitol	220
Lactose, Sodium alginate	Spray-drying	—	The tensile strength of composite particles is as high as spray-dried amorphous lactose, with less elastic recovery than alpha-lactose monohydrate	221
Rice starch, MCC	Spray-drying	—	Compressibility of composite particles was greater than commercial spray-dried Eratab®, Cellactose® and Tablettose®	222
MCC, Colloidal silicon dioxide, Lactose monohydrate, and DCP	Wet granulation	—	Good compressibility and flow	223
Lactose, MCC	Melt granulation	—	Directly compressible adjuvant	18
Powdered cellulose, Magnesium carbonate	Roller compaction	—	Improved compaction than physical mixture	224
Lactose, PVP, polysorbate 80	Spray-drying	—	Compression behavior and tablet-forming ability of spray-dried amorphous lactose was modulated by the addition of stabilizing polymers and surfactants	225

Key: MCC, microcrystalline cellulose; DCP, dibasic calcium phosphate; PVP, polyvinyl pyrolidone; Na-CMC, sodium cabroxy methylcellulose

oleate, and sodium lauryl sulfate. Magnesium stearate (MS) is the most widely used lubricant in tablet manufacturing because of its high lubrication potential. However, MS has a negative effect on tablet tensile strength[203] and dissolution profile[204,205] due to its hydrophobic nature which inhibits interparticulate bonding by coating around drug particles.[206] Colloidal silicon dioxide is often used as a flow enhancer and it eliminates the negative effect of MS on interparticular bonding while maintaining the lubrication action. This property of colloidal silicon dioxide is affected by its hydrophobicity/hydrophilicity and by the particle deformation properties of the excipient upon compression.[226] The choice of a type and amount of lubricant is influenced by the deformation behavior of the major component of the blend. Lubricated tablets show larger relaxation for plastic materials, as a result of the reduction of interparticulate bonding by the lubricant. While for brittle material, the lubricant film is destroyed by fragmentation, minimally affecting the interparticulate bonding, hence only a small or no effect on tablet relaxation is observed.[203] Optimizations of lubricant concentration in formulations are important to minimize problems related to dissolution and tensile strength. However, this has to be carefully balanced against the requirement of MS to lubricate the blend, tooling and prevent tableting problems. Optimization is done by creating ejection profile of each lubricant to reduce the stresses related to tablet compaction. Also, various hydrophilic lubricants are an alternative to eliminate dissolution and tablet hardness related issues. Granular MS has been suggested as a viable alternative to ordinary MS, as it does not affect the tensile strength, friability, disintegration, and dissolution.[227] Lubrication properties were also compared among glycerin fatty acid esters, MS and a sucrose fatty acid ester, and it was shown that lubricant characteristics were similar to MS, and tablets were superior to those with MS in terms of hardness, disintegration and stability.[228] Compretol® (glyceryl dibehenate) as a tablet lubricant showed similar performance at 0.5% concentration by hot melt coating as compared to simple blending at 3% lubricant level.[229]

3. Disintegrants

Achievement of desired dissolution rate of drug substance(s) from a tablet requires overcoming cohesive strength of tablet and breaking into primary particles. This is achieved by adding disintegrants into formulations. Commonly used disintegrants, along with their usage concentration in parenthesis include starch (3–15%), MCC (5–15%), pregelatinized starch (5–10%), croscarmellose sodium (1–5%), sodium starch glycolate (2–8%), and crospovidone (2–5%). The basic mechanism of disintegration is swelling in presence of water. The ability of these materials to take up moisture from surroundings and consequently swell can have a negative effect on tensile strength. Many of the commonly used diluents such as MCC and starch also possess disintegrant property.

MCC has excellent compressibility, whereas starch is poorly compressible and affects tensile strength of compact. This can be addressed by substituting starch with pregelatinized starch, which not only has better compressibility, but also affords an improved disintegration profile. Superdisintegrants such as sodium starch glycolate, crospovidone, and croscarmellose sodium can be used as they act at lower concentration and are less likely to change the compaction behavior of the blend. However, sodium starch glycolate at above 10% concentration is known to reduce tablet tensile strength as a result of its poor compressibility.[230] Optimization of the concentration of disintegrant is thus important to avoid their negative impact on compressibility of the tablet blend.

4. Granulating Agents/Binders

Granulating agents are used to form granules from powder. Water and organic solvents act as a granulating agent by partially dissolving the surface of the particles and forming solid bridges upon evaporation. However, these types of bonds are weak and lead to formation of friable granules. Therefore, it is usual to include binder to granulations to increase granule strength and tackle the problem of capping and lamination. Granulating agents are usually cohesive hydrophilic polymers that aid in granulation process and impart strength after drying.

Effective granulating agents form a film around particle surface. Rowe has suggested that binder should be selected on the basis of their spreading coefficients, which is the difference between 'work of adhesion' of binder-particle and 'work of cohesion' of the binder. Correlations have been found between the spreading coefficient of the binder and actual experimental measurements of granule friability, tablet strength and tablet capping.[231] Particle size, surface/surface structure, and plasticity of binders are known to influence binding. The ideal dry binder should have small particles, high plasticity, and a large surface area.[232]

Granulations with a more homogeneous distribution of binder generally produce tablets of a higher mechanical strength than with a peripheral localization of binder. Therefore, high granule porosity with homogeneous intragranular binder distribution is advantageous for the compactibility of a granulation.[188] The ability of the binder to fill the voids between the particles/granules is the determining factor for increasing strength and also the amount of binder added to the mixture affects the results.[44] Fine-particle ethyl cellulose[233] as a tablet binder in direct compression and the utility of fine-particle hydroxypropyl cellulose[234] as a roller compaction binder was shown to increase the contact area, resulting in greater bond formation, and reduced problem of capping in tablets containing highly elastic materials.

The strength of tablets containing a less plastic binder is governed by the inherent compactibility of the blend. The tablet porosity, bonding mechanisms

and volume reduction mechanisms of the compound are also influenced by the binders. For example, the plasticity and particle size of the binder has most significant effects on tablet strength when the tablet porosity is low, whereas, the plasticity and the compactibility of the binder determines the strength of tablets when the tablet is more porous.[44,235] *Binder toughness* is the property of binder that quantifies the ability of a material to resist the crack propagation under applied stress. In a study, hydroxypropyl cellulose was reported to be the toughest binder and had a very high degree of plasticity, when compared to methyl cellulose, PVP, and starch. PVP and starch showed very low strength and toughness with nearly nil to very little plastic flow.[236]

The choice of a suitable binder for a tablet formulation requires extensive knowledge of binder properties for enhancing the strength of the tablet and also the interactions between the various constituents of a tablet. Addition of a binder, which increases elasticity, can decrease tablet strength because of the breakage of bonds as the compaction pressure is released.[237] PEG is a ductile plastically deformable material with a moderate mechanical strength and its mechanical properties were found to relate to the average molecular weight.[144,238,239]

In a study using deformable binders, which did not fragment to any significant extent (e.g., PEG and amorphous lactose), the disintegration time was extended and was not substantially affected by the addition of a superdisintegrant. However, if the tablet was sufficiently porous, the negative effect of the binders was reduced. When less deformable binders which are likely to fragment were used, the effect of the superdisintegrant was substantial, and rapidly disintegrating tablets of high tensile strength were obtained.[240]

X. SUMMARY

Compaction is an integral step for the manufacture of tablets, and it is pertinent to understand the underlying physics of compaction. Complete understanding of compaction physics still eludes us, many variables such as inherent deformation behavior of drugs/excipients, solid-state properties, and process parameters are known to affect the final attributes of tablets. A due consideration to the variables of compaction process, can aid a pharmaceutical scientist to design optimum formulation devoid of problems such as capping, lamination, picking, and sticking. Availability of sophisticated tableting instrumentations has catalyzed the understanding of process, and the generation of compaction profiles such as force-time profile, force-displacement profile, and pressure–porosity relationships can help in deciphering the dynamics of the process. The compactibility of the drugs, especially in case of high dose systems, is critical for successful manufacturing of tablets. An appreciation of the contribution of tableting excipients to the compaction behavior of the tablet-matrix can enable

science-based selection of excipients. Similarly, optimization of process parameters such as granulation, moisture content, and rate and magnitude of force transfer, can help in achieving satisfactory tensile strength and desired biopharmaceutical properties in tablet drug products.

ACKNOWLEDGEMENT

Aditya M. Kaushal would like to acknowledge CSIR, India for providing senior research fellowship. The insightful comments and suggestions of the reviewer are gratefully recognized.

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