IJPSR (2012), Vol. 3, Issue 06 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 04 February, 2012; received in revised form 15 May, 2012; accepted 25 May, 2012

COMPRESSION PHYSICS OF PHARMACEUTICAL POWDERS: A REVIEW

Shailender Mohan

Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur- 302 022, Rajasthan, India

Keywords:
Compaction,
Compression,
Physics of Compression,
Tablet Manufacturing,
Tableting Problems,
Compaction Equations

Correspondence to Author:

Shailender Mohan

Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, Rajasthan, India-302022

ABSTRACT

Due to various advantages such as high-precision dosing, manufacturing efficiency and patient compliance helped making tablets the most popular dosage forms among all available dosages forms. Compaction, which is an essential manufacturing step in the manufacture of tablets, mainly includes compression (i.e. reduction of volume of the powder under consideration and particle rearrangement) and consolidation (i.e., formation of interparticulate bond to facilitate stable compaction). The success of the compaction process depends not only on the physico-technical properties of drugs and excipients, but also on the instrument settings with respect to rate and magnitude of force transfer. Tablet manufacturing speed and pre/main compression force profile also have an influence on the quality of the final tablet. Mechanical aspects of tablet formation can be studied using, instrumented punches/dies, instrumented tablet punching machines, and compaction simulators. These have potential application in pharmaceutical research and development, such as studying basic compaction mechanism, various process variables, scale-up parameters, trouble shooting problems, creating compaction data library, and fingerprinting of new active pharmaceutical ingredients (APIs) or excipients. Mathematical models, force-time, force-distance, and die-wall force parameters of tablet manufacturing are used to describe work of compaction, elasticity/plasticity, and time dependent deformation behavior of pharmaceuticals powder under consideration.

INTRODUCTION: 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 & patient compliance. Out of powders, granules, pellets, tablets, and capsules, tablets have been the dosage form of first choice in the development of new drug entities and account for some 70–80% of all pharmaceutical preparations [1-3].

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 [4].

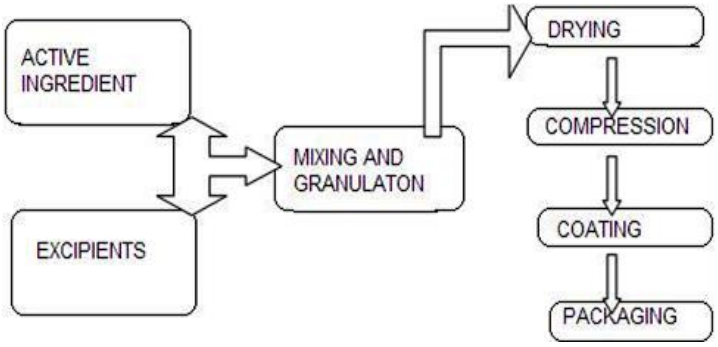

FIG. 1: GENERAL STEPS IN TABLET MANUFACTURING

In general, the tableting process involves, applying pressure to a powder bed, thereby compressing it into a coherent compact [5]. 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.

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 process [6]. Particle size, size distribution, crystal habit, crystallinity, polymorphism, pseudomorphism, amorphism, and crystal moisture are the most common elements that can change the compression properties [7].

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. Literature reports a number of high-dose and/or poorly compressible drugs including paracetamol, ibuprofen, mefenamic acid, acetazolamide, metformin and hydroxyapetite [8-13].

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.

Properties of Powders: Physical properties of pharmaceutical solids predict the performance and processing of solid dosage forms, including their compressibility. These properties are somewhat related to each other and a change in one property is most likely to affect the others.

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 [14]. 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 [4].

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 [1]. The total void volume, V_v is given by $V_v = V_b - V_t$, *where* Vt is the true volume.

$$E = \frac{(Vb - Vt)}{Vb} = \left\{1 - \frac{Vt}{Vb}\right\}$$

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 [16].

C. **Flow Properties:** Good flow property of a pharmaceutical powder is essential to ensure proper die fill during compression, especially in direct compaction process.

Angle of repose is commonly used to measure flow of powders, and is the maximum angle (θ) between the plane of powder and horizontal surface.

$$\text{Angle of Repose } (\theta) = \tan^{-1}\left\{\frac{h}{r}\right\}$$

Where, h is the height of the heap formed when the powder is allowed to fall through a funnel and r is the radius of the heap calculated using graph paper.

TABLE 1: ANGLE OF REPOSE

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

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 [16].

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, and varies from about 1.2 for a free-flowing powder to 1.6 for cohesive powders [16]. The percentage compressibility, also called as Carr's Index [17] is 100 times the ratio of the difference between tapped density and bulk density to the tapped density.

TABLE 2: SCALE OF FLOWABILITY

Compressibility Index (%)	Flow Character	Hausner Ratio
≤10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

*A Hausner ratio of <1.25 indicates a powder that is free flowing whereas >1.25 indicates poor flow ability. *The smaller the Carr's Index the better the flow properties. For example 5-10 indicates excellent, 11-15 good, 16-20 fair and > 23 poor flow.

D. **Compaction:** Compaction can be defined as the *compression and consolidation* of a particulate solid–gas system as a result of an applied force [18]. 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 occurs. Consolidation, a simultaneous occurring process, involves increase in the mechanical strength resulting from particle-particle interactions. As the particles move into closer propinquity to each other during the volume reduction process, bonds are established between the particles, the nature of which depends upon the nature of the bond in the molecular structure of the interior of the particles. It should be noted that consolidation is the major reason for increase in mechanical strength of a powder bed, when subjected to rising compressive forces [4].

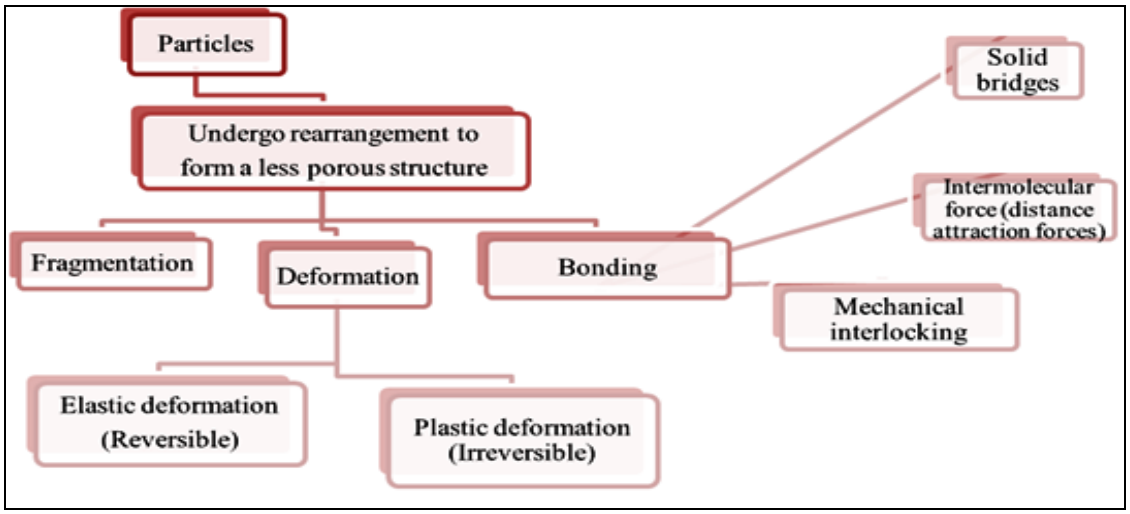

FIG. 2: STEPS INVOLVED IN COMPACTION OF POWDER UNDER APPLIED FORCE

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. When a powder is compressed initially the particles are rearranged under low compaction pressures to form a closer packing structure. The finer particles enter the voids between the larger ones and give a closer packing arrangement. In this process, the energy 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. 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 [19].

   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 pharmaceutical powder beds undergo will depend upon 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 [20].

   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 [7, 21].

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. The 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. Although, under the influence of an applied pressure, the particles not only deform plastically or elastically, but also fragment to form smaller particles (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 [18]. 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. After the critical value stress, the powder bed deforms plastically i.e. removal of applied pressure from the compressed powder will have no effect on the deformed particles and the particles will remain in the deformed state leading to compaction.

   * Elastic deformation is a reversible process and plastic deformation results in a permanent change in the particle shape.

3. **Time Dependence of Compaction Process:** Successful formation of a pharmaceutical tablet by the compression of solid particulate matter depends on interparticulate bonding across particle-particle interfaces. Some deformation processes (e.g., plastic deformation) are time dependent and occur at various rates during the compaction sequence [22], 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.

This further makes evident that if a plastically deforming solid is loaded (or unloaded) too rapidly for the purpose to take place, the solid may exhibit brittle fracture. This may be a contributing factor to structural failure of tableting as the machine speed is raised. And if the dwell time (compaction time) under the compression load is protracted, then plastic deformation may continue, leading to more integration.

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. The compact formation is determined by the time dependant viscoelastic behavior.

Thus, the viscoelastic parameters of the tablets and their components are expected to be revelatory of the relative sensitivity of tablet formation to the rates of compression and decompression and the rate and the nature of ejection from die [23]. 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.

Compression Cycle and Effect of Applied Forces:

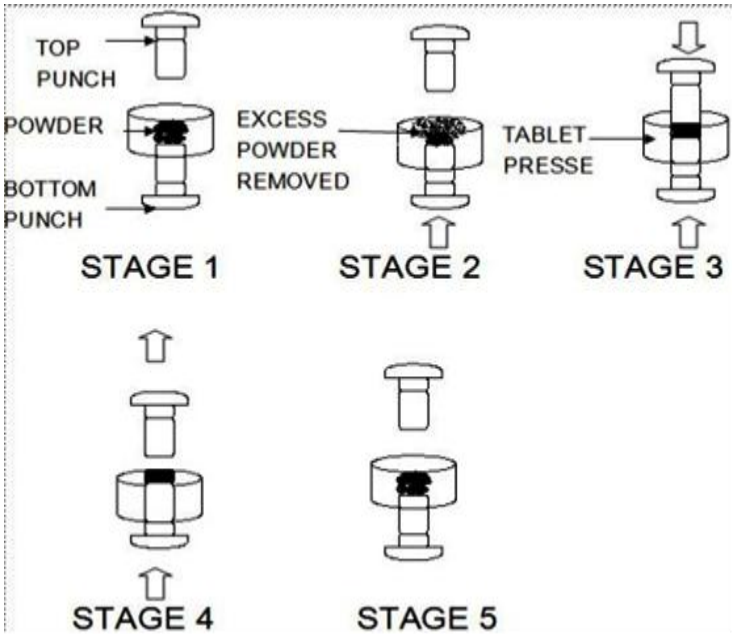

FIG. 3: VARIOUS STEPS INVOLVED IN COMPRESSION OF A TABLET

The compression cycle on a rotary tablet press includes precompression, main compression, decompression, and ejection phases.

1. **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. For products that undergo brittle fracture, the application of pre-compression at a higher force than main compression results in higher tablet hardness. Similar sizes for main and precompression rollers to apply similar forces are reported to result in optimal tablet formation [4].

2. **Main Compression:** During main compression, the applied energy is transformed into formation of interparticulate bonds. When a force is applied in a die, the particles firstly undergo rearrangement to form a less porous structure at very low forces. Afterwards, 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).

3. **Decompression:** As the applied force is removed, a 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 tablet structure failure may occur.

   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.

*The tablet failure is affected by rate of decompression (machine speed).

4. **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. The force

necessary to eject a tablet involves the distinctive peak force required to initiate ejection, by breaking of die wall–tablet adhesion. The second stage involves the force required to push the tablet up the die wall, and the last force is required for ejection. Variations in this process are sometimes found when lubrication is inadequate and a *slip-stick* condition occurs between the tablets and dies wall, with continuing formation and breakage of tablet die–wall adhesion. Lubricants minimize stress patterns so, they reduce the tendency for materials to cap or laminate [4].

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. 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 that can be used to elucidate the compaction behavior.

Compaction Profiles: Compaction data obtained from instrumented tableting machine are basically of two types:

- Force-time profiles.
- Force-displacement profiles.

- **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. On a rotary tablet press, the force-time curves are segmented into three phases-compression phase, dwell phase, and decompression phase. *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 [24].

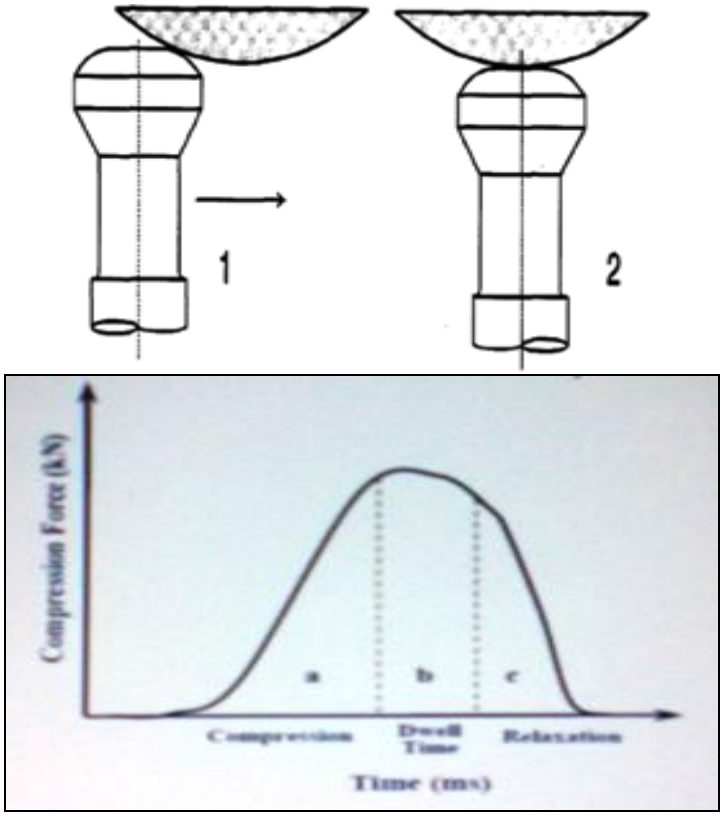

FIG. 4: PHASES OF COMPRESSION EVENT ON A ROTARY TABLET PRESS (a) Compression Phase-horizontal and vertical punch movement; **(b) Dwell Time**-only horizontal punch movement as plane punch head area is under compression roller; and **(c) Decompression**-both punches moving away from upper and lower surfaces, initial relaxation of the tablet.

- **Force-Displacement Profile:** Stress relaxation is observed to be less in case of plastic deformation; where as materials that undergoes elastic deformation tend to relax to a greater extent during and/or after decompression. Force-displacement profiles can be used for the determination of plastic and elastic behavior [25]. 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.

$$NWC = GWC - WER$$
$$GWC = W_f + W_p + W_e + W_{fr}$$

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.

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. Moisture content of the blend also has a critical role in the energy involved in the compaction [26].

- **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). The coefficients of friction related to the tableting process are static friction coefficient ($\mu 1$), which gives the force required to initiate sliding, and dynamic friction coefficient ($\mu 2$), which gives the force to maintain sliding between two surfaces [27].

μ1 = maximum axial frictional force/maximum radial force

μ2 = ejection force/residual die-wall force

Friction phenomena can also be measured by parameters that are calculated from upper and lower punch force and displacement. Radial pressure is another useful parameter for predicting compaction behavior of pharmaceuticals.

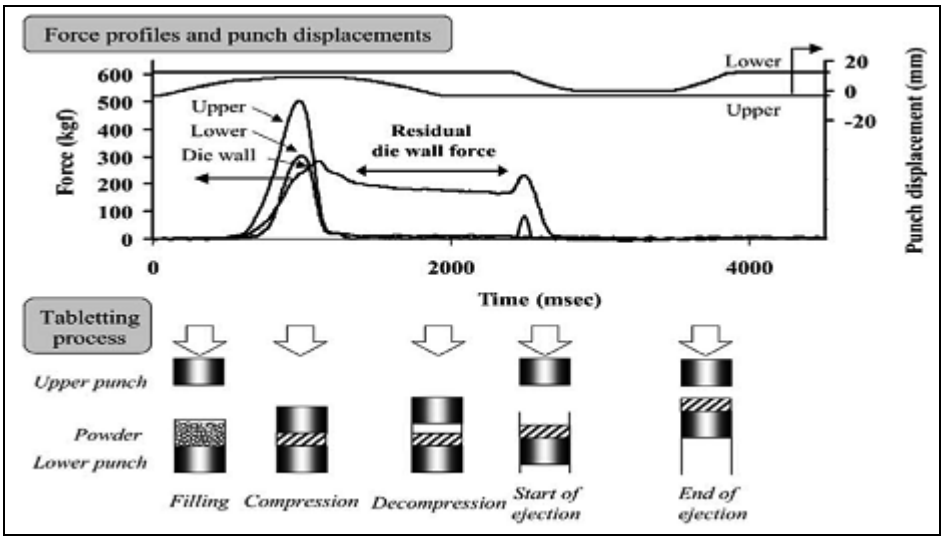

FIG. 5: FORCE AND PUNCH DISPLACEMENTS PROFILES DURING TABLETING PROCESS

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.

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.

1. **Kawakita Equation:** The basis for 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.

$$\frac{Pa}{C} = \left[\frac{1}{ab} + \frac{Pa}{a}\right]$$

$$C = \left[V0 - \frac{V}{V0}\right]$$

where, *Pa* is the applied axial pressure, *a* is the degree of volume reduction for the bed of particles, and *b* is a constant that is 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.

This equation holds best for soft fluffy pharmaceutical powders, and is best used for low pressures and high porosity situations.

2. **Heckel Equation:** The Heckel equation is based on the assumption that densification of the bulk powder under force follows first-order kinetics The Heckel equation is expressed as;

$$\ln\left[\frac{1}{1-D}\right] = KP + A$$

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.

Kuentz and Leuenberger postulated a modified Heckel equation which allows the description of the transition between the states of a powder to the state of a tablet [29].

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

Where, *σ* is the pressure, *ρ* is the relative density, *ρc* 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.

Hersey & Rees and York & Pilpel classified powders into three *types A, B and C*. The classification is based on Heckel plots and the compaction behavior of the material.

With type A materials, a linear relationship is observed, with the plots remaining parallel as the applied pressure is increased indicating deformation apparently only by plastic deformation. An example of materials that exhibit type A behavior is *sodium chloride*. Type A materials are usually comparatively soft and readily undergo plastic deformation retaining different degrees of porosity depending on the initial packing of the powder in the die. This is in turn influenced by the size distribution, shape etc. of the original particles.

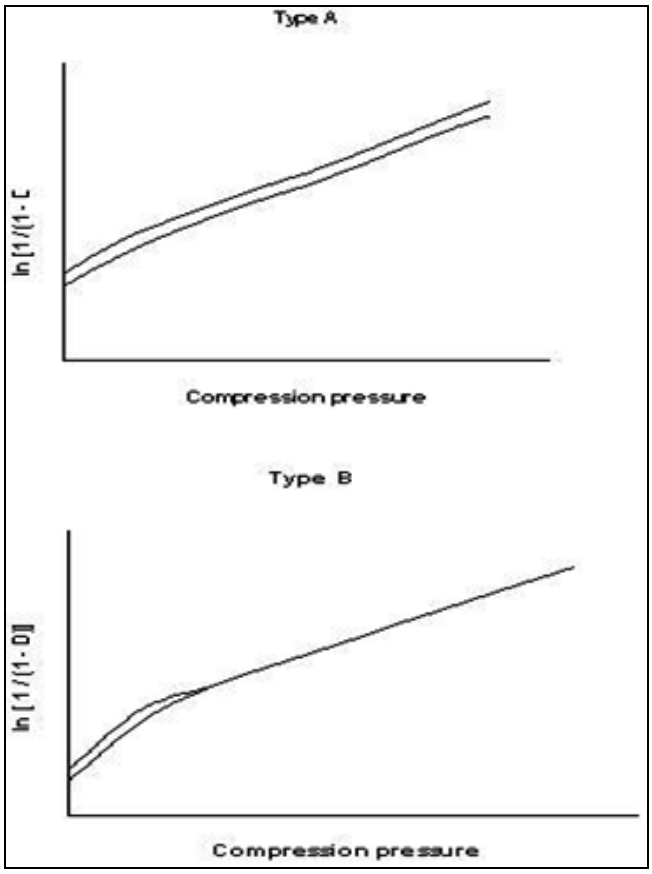

FIG. 6: HECKLE PLOT FOR TYPE A AND TYPE B MATRIALS.

For type B materials, there is an initial curved region followed by a straight line. This indicates that the particles are fragmenting at the early stages of the compression process i.e., brittle fracture precedes plastic flow. Type B Heckel plots usually occur with harder materials with higher yield pressures which usually undergo compression by fragmentation first, to provide a denser packing. Lactose is a typical example of such materials.

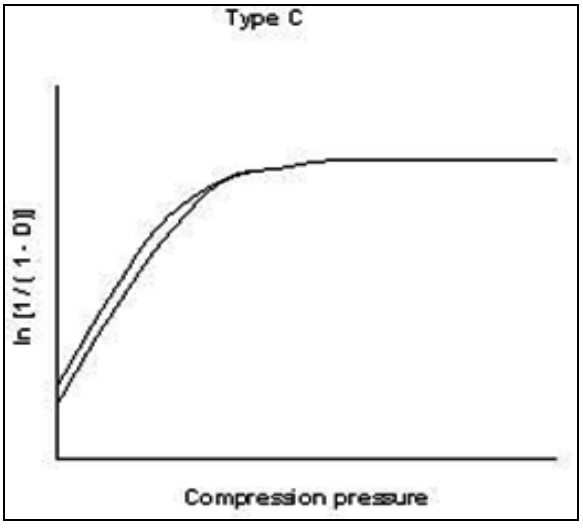

FIG. 7: HECKLE PLOT FOR TYPE C MATRIALS

For type C materials, there is an initial steep linear region which become superimposed and flattens out as the applied pressure is increased. York and Pilpel ascribed this behavior to the absence of a rearrangement stage and densification is due to plastic deformation and asperity melting.

Type A Heckel plots usually exhibit a higher final slope than type B which implies that the former materials have a lower yield pressure. This is so because fragmentation with subsequent percolation of fragments is less efficient than void filling by plastic deformation. In fact, as the porosity approaches zero, plastic deformation may be the predominant mechanism for all materials. The two regions of Heckel plots in type B are thought to represent the initial repacking stage and subsequent deformation process, the point of intersection corresponding to the lowest force at which a coherent tablet is formed. In addition, the crushing strength of tablets can be correlated with the values of k of the Heckel plot; larger k values usually indicate harder tablets. Such information can be used as a means of binder selection when designing tablet formulations. Heckel plots can be influenced by the overall time of compression, the degree of lubrication and even the size of the die, so that the effects of these variables are also important and should be taken into consideration.

3. **Walker Equation:** The Walker equation 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

$$Log\ P = -L\ x\ V'/V0 + C1$$

where, *V0* is the volume at zero porosity. The relative volume is $V'/V0 = V = 1/D$, $C1$ is constant. The coefficient *L* is referred to as the pressing modulus [30].

Factors influencing the compaction of Pharmaceutical Powders: 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, simultaneous processing 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.

1. **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. Moisture affects the flow, mixing rheology, compaction, true density, and mechanical properties of granules as well as tablets. 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. 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.

   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. Moisture can also increase plastic deformation and reduce elastic property of powder material and reduce the ejection force.

2. **Compression Force Profile:** The speed of compression can have significant effect on the compaction properties of pharmaceutical powders. [31]. 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.

3. **Solid-State Properties:** Drugs and excipients used in tablet manufacture 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 compaction.

   A. **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 [32].

   B. **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 [7].

C. **Polymorphism/Amorphism:** Differences in the physical and chemical properties of various drug substance polymorphic forms are well studied. In a study on compression behavior of pure orthorhombic or monoclinic paracetamol, ortho-rhombic crystals exhibited better technical 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].

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. The improvement in compaction behavior of amorphous materials can be attributed to higher plastic deformation than their crystalline counterparts.

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. 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 post-compaction hardening.

4. **Salt Form:** Another important factor determining the compaction properties is the salt forms of pharmaceuticals but these are rarely affecting the compaction profile.

5. **Granulation Method and Binder:** Due to poor flowability and compaction behavior, pharmaceutical powders are often subjected to granulation prior to tablet manufacturing. The optimal granulation method is selected for production of porous and free-flowing granules, which enables the formation of tablets with high mechanical strength at low compression pressures.

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 [34].

6. **Use of Ultrasonic Vibration:** 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 ultrasound during compaction made it possible to increase tablet mechanical strength by 2-5 times.

Tableting Problems: Compression related tablet problems mainly include capping/lamination and sticking/picking.

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 usually arise immediately after compaction but may occur after a lag time. *Friability test* is the quickest way to test such problem. The main reason behind these problems is the inability of materials to relieve stress after the removal of force. Also, excess fines that trap air in the tablet may results 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 bed and elastic recovery is considered to be the most likely cause of capping in the areas of high density.

Tablet capping or lamination problems are also associated with pre and main compaction profile [34]. Measures such as, applying precompression, slowing

tableting speed (longer dwell time) and reducing final compression force may help eliminating capping/lamination problems.

The type of tooling used can also have an effect on capping or lamination [35].

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. 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, which eventually results in capping and/or lamination upon ejection.

Picking is a term used to describe the removal of surface material of tablet by a punch. Picking is often a related with punch having engraving or embossing. To reduce this problem lettering should be as large as possible or tablet can be formulated in larger size [1].

Sticking refers to tablet material adhesion to die wall. Punch surface roughness [36], 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 [35] .

Monitoring the moisture level is also important for controlling these problems, as increased moisture has been related to sticking and picking.

Improvement of compaction behavior of Powder Bed: 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.

a. **API Modification:** Although its modification may not be permissible but modification of the API is essential for high dose drugs because of the limited role of the excipients that it can play in improvement of compactibility.

b. **Excipient Modification/Selection:** The type and amount of the excipient(s) selected do influence the overall quality attributes of the tablets. As per 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.

c. **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 and amorphous binders exhibit higher number of attractive forces, which contribute to higher compact strength. Rough surface on the particles contributes actively towards, compact strength, even in the absence of fragmentation.

   Successful tablet production therefore depends upon optimum balance between brittle fracture and plastic behavior, as indicated 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 [38]. Coprocessing has emerged as a popular way to generate directly compressible excipients.

d. **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 put in between two rubbing surfaces, will reduce friction arising at the interface. 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 oleate and sodium lauryl sulfate.

Optimizations of lubricant concentration in formulations are important to minimize problems related to dissolution and tensile strength and it can be done by creating ejection profile of each lubricant to reduce the stresses related to tablet compaction.

e. **Disintegrants**: Achievement of desired dissolution rate of drug substance(s) from a tablet requires overcoming cohesive strength of tablet and breaking itself into primary particles. This is achieved by adding disintegrants into formulations. Commonly used disintegrants includes 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 which causes a negative effect on tensile strength. Many of the commonly used diluents such as microcrystalline starch (MCC) and starch also possess disintegrant property. MCC has excellent compressibility, whereas starch is poorly compressible and affects tensile strength of compact.

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. Optimization of the concentration of disintegrant is therefore important to avoid their negative impact on compressibility of the tablet blend.

f. **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 counter the problem of capping and lamination. Granulating agents are usually cohesive hydrophilic polymers that aid in granulation process and impart strength after drying.

Addition of a binder, which increases elasticity, can decrease tablet strength because of the breakage of bonds as the compaction pressure is released. [38] Thus 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.

CONCLUSION: Compaction is an important integration step for the manufacture of tablets, and it is important to understand the underlying physics of compaction. Complete understanding of compaction physics still illustrates us, many variables such as inherent deformation behavior of drugs/excipients, solid-state properties, and process parameters which are known to affect the final attributes of tablets.

A due consideration to the variables of compaction process can assist a pharmaceutical scientist to design optimum formulation devoid of problems such as capping, lamination, picking, and sticking. The compactibility of the drugs is critical for the successful manufacturing of tablets. 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.

ACKNOLEDGEMENT: Shailender Mohan would like to acknowledge Mr. M. M. Gupta, Principal and Head of Department, Department of Pharmaceutics, Jaipur

College of Pharmacy, Jaipur, for his insightful support and encouragement. The author also would like to acknowledge Mr. H. M. Varshney, Assist. Prof., Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, for his constant support and encouragement.

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