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Compression, Consolidation, Compaction Physics of Pharmaceutical Powders: A Comprehensive Review

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Abstract

Tablets are the most popular dosage form of all those that are available because, among other advantages, they offer high-precision dose, efficient manufacturing, and patient compliance. Two of the most crucial manufacturing phases in the creation of tablets are compression (i.e., a reduction in consolidation) and volume of the powder under consideration (as well as particle rearrangement) (i.e., the development of an interparticulate connection to aid in compaction stability). The efficacy of the compaction process is influenced by the physico-technical properties of the pharmaceuticals and excipients as well as the instrument parameters for force transmission rate and magnitude. Pre/main compression force profiles and tablet manufacturing speed both have an impact on the finished tablet's quality. Instrumented punches/dies, compaction simulators, and instrumented tablet punching machines can all be used to study the mechanical elements of tablet production. These could be used, among other things, in pharmaceutical research and development to look into fundamental compaction mechanisms, various process variables, scale-up parameters, troubleshoot problems, create a compaction data library, and fingerprint new active pharmaceutical ingredients (APIs) or excipients. The work of compaction, elasticity/plasticity, and time-dependent deformation behaviour of the under-discussed pharmaceutical powder are characterized using mathematical models, force-time, force-distance, and die-wall force parameters of tablet manufacture.

Keywords: Compression; Consolidation; Compaction; Improvement of Compaction

Compression

Compression refers to a decrease in the bulk volume of materials as a result of the gaseous phase being displaced depicts the stages involved in powdered solids bulk reduction. The only forces that exist between the particles at the start of the compression process, when the powder is filled into the die cavity and before the upper punch enters the die cavity, are those that are related to the packing characteristics of the particles, the density of the particles, and the total mass of the material that is filled into the die cavity [1]. The packing qualities of the individual particles will determine the packing characteristics of the powder mass. When external mechanical forces are applied to a powder mass, the volume of the powder is usually reduced due to closer packing of the powder particles, and this is the primary mechanism of initial volume reduction in most circumstances [2]. However, when the stress grows, particle rearrangement becomes more difficult, and further compression results in particle deformation of some sort. The deformation is said to be elastic if it is reversible to a great extent after the load is removed, i.e. it behaves like rubber. When exposed to external forces, all solids deform elastically. Within the range of maximum force experienced in practice, elastic deformation becomes the major mechanism of compression with some medicinal compounds, such as acetylsalicylic acid [3, 4]. In some powdered solids, an elastic limit is reached, and loads over this level cause deformation that is not immediately reversible when the applied force is removed. In these circumstances, bulk volume reduction is caused by plastic deformation and/or viscous flow of particles, which are pressed into the remaining vacuum spaces, similar to how modelling clay behaves [5, 6]. When the shear strength is lower than the tensile or breaking strength, this process takes over. The greatest number of clean surfaces is said to be

created by plastic deformation. Because plastic deformation is a time-dependent process, applying more force at a faster rate should result in fewer new clean surfaces being formed, resulting in weaker tablets. Furthermore, because the development of fresh clean surfaces is required for tablet formation, high concentrations or overmixing of elements that form weak bonds results in weak tablets [7]. Magnesium stearate, for instance, forms a weak binding and is quickly moistened. As a result, excessive magnesium stearate mixing may result in weak pills. Particles may be preferentially fragmented in materials with a shear strength greater than the tensile strength, and the smaller fragments then aid to fill in the adjacent air gaps [8]. Brittle fracture is most likely to occur with hard, brittle particles, and sucrose acts in this fashion. The ability of a material to deform in a specific way is determined by its lattice structure, particularly the presence of weakly connected lattice planes [9]. Brittle fracture results on clean surfaces that are brought into close proximity by the applied load. Small particles can deform plastically through a process known as microsquashing, regardless of how large particles behave, and the amount of fine powders in a sample can be considerable. Asperities sheared off larger, extremely irregular particles may behave similarly; thus, particle form is a significant consideration [10]. During compression, four stages of events are encountered:

- Initial particle repacking.
- Particles are elastically deformed until the elastic limit (yield point) is achieved.
- Plastic deformation and/or brittle fracture then take over until all voids are almost completely filled.
- The solid crystal lattice is then compressed.

Consolidation

Consolidation is defined as a rise in a material's mechanical strength as a result of particle-particle interactions. The next sections go over several powder consolidation mechanisms. When the surfaces of two particles come close enough together (e.g., less than 50nm), their free surface energy combine to form a strong attractive force. This is known as cold welding. On a molecular scale, the nature of the bonds created is comparable to that of the molecular structure of the inside of the particle surface, but the surface area involved may be minimal. This theory is widely accepted as a primary cause for a bed of powder's growing mechanical strength as compressive forces increase [11]. On a macro scale, most particles encountered in practice have an irregular form, resulting in a bed of powder with several points of contact. Any load applied to the bed must pass through these particle connections. However, at significant stresses, this transmission may result in significant frictional heat build-up. If this heat is released, the local temperature rise may be sufficient to promote melting of the particle contact area, relieving stress in that particular region [12]. When the melt solidifies, fusion bonding takes place, resulting in an increase in the mass's mechanical strength. All of the deformation effects could be accompanied by the breaking and development of new bonds between the particles, resulting in consolidation as the new surfaces are forced together [13]. Another method for powder consolidation is aspartic melting of the powder particles' local surfaces. The temperature of the powder compact rises between 4 and 30 oC during compression, depending on friction effects, individual material features, lubrication efficiency, the magnitude and rate of application of compression forces, and machine speed. Stress relaxation and plasticity increase as the tablet temperature rises, whereas elasticity diminishes and powerful compacts form [14]. As a result, material compression at high temperatures combined with increased ductility should result in stronger tablets. Only with low melting point materials, where even very hard asperities are forced into a more pliable substance, is aspartic melting thought to be significant. The chemical nature of the powder, the surface area of the contact point, contamination (including film coating, such as magnesium stearate), and interparticulate distance all influence the final tablet qualities [15]. The compression event into a series of time intervals and suggested some useful concepts as a result [16]. These are the ones:

- Consolidation time: the amount of time it takes for the maximum force to be reached.
- Dwell time: the amount of time spent at maximal effort.
- Contact time: time spent compressing and decompressing, omitting the time spent ejecting.
- Ejection time: the duration of ejection.
- Residence time: the amount of time the produced compact spends inside the die.

Jones' definitions are shown in as a diagrammatic representation of the lower punch force trace from an eccentric press. Dwell time cannot be calculated in this circumstance because force reaches a maximum value and then rapidly falls, resulting in a peak with no plateau. However, in some studies, the maximum force is sustained for lengthy periods of time, and "dwell time" becomes relevant in these situations [17]. Furthermore, rotary presses have a distinct, albeit extremely short, dwell period.

Compaction

A particulate solid–gas system is compressed and consolidated as a result of an applied force. Compaction is a term used to describe the process of compacting soil. Compression results in a reduction in bulk volume due to the reduced gaseous phase. Closer packing of powder particles as a result of rearrangement is the fundamental process for initial volume reduction [18]. When the force is increased, particle deformation occurs, making rearrangement more difficult. Consolidation is characterized by an increase in

mechanical strength due to particle–particle interactions, which happens later. When particles get closer to one another during the volume reduction process, bonds are created between them. The nature of the bonds formed is similar to the molecular structure of the particles' insides, but due to the roughness of the particles' surface, the actual surface area involved is limited [19]. Consolidation is the primary cause of rising mechanical costs. The ability of a material to undergo a volume decrease as a result of an applied pressure is defined and is illustrated by a plot of tablet porosity against compaction pressure [20]. Compatibility is defined as a material's ability to produce tablets of sufficient strength under the effect of densification, as represented by a plot of tablet tensile strength vs tablet porosity; while tablet ability is defined as a powdered material's capacity to withstand densification [21]. This phrase is proposed when all three variables are addressed in a single study. Although smaller particles formed by the breakage of larger particles may be rearranged further, the compaction process typically consists of particle rearrangement followed by pressure deformation.

Powder properties

The physico-technical qualities of pharmaceutical solids determine the performance and processing of solid dosage forms, particularly their compressibility. These attributes are interconnected, and changing one will almost certainly affect the others.

Surface properties

Powder materials' movement and intermolecular attraction are highly influenced by their surface properties. Depending on whether the atoms or ions are on a surface, the distribution of intermolecular and present within a particle differs. This is caused by unmet attractive molecular forces that extend a short distance beyond the solid surface. As a result, free surface energy of solids is formed, which is significant in interparticulate interaction [22]. Two types of particle attractive forces are cohesion between like particles and adhesion between unrelated particles. The attractive forces resist the differential movement of constituent particles when an external force is applied [23, 24]. Residual solvent on the surface of solid particles, electrostatic forces, and adsorbed moisture are all examples of relative particle movement resistance.

Porosity

The porosity of powder is defined as the ratio of total void volume (Vv) to bulk volume (Vb) of a material (E). The full void volume, Vv, is given by Vv= Vb – Vt, where Vt is the true volume.

$1 - Vt / Vb = E = Vb - Vt / Vb = 1 - Vt / Vb$

One of the ways used to determine the compressibility of a powder bed is the degree of volume drop owing to applied pressure, which is related to porosity and assumed to be a first-order reaction [25, 26]. The porosity–pressure relationship, which is often employed as a measure of compressibility, is also explained by the Heckel equation.

Flow characteristics

The flow feature of a pharmaceutical powder is crucial for maintaining optimum die fill during compression, particularly in the direct compaction process. A high number of particles, excess moisture, lubricants, and electrostatic charge are all possible causes of poor powder flow. The maximum angle between the plane of powder and the horizontal surface, which is often used to analyse powder flow, is known as the angle of repose. A value of less than 30 degrees implies free flowing material, a value of 40 degrees offers fair flow potential, and a value of 50 degrees indicates difficult power flow. A powder's cohesivity is related to its bulk density. Another way to assess flowability is to examine the relationship between bulks and tap density. The Hausner Ratio (H) and Carr's Index are calculated using the tapped and bulk densities (CI) [27,28]. The Hausner ratio, which ranges from 1.2 for free-flowing powders to 1.6 for cohesive powders, is the percentage of tapped density to bulk density. Carr's Index is the ratio of the difference between tapped density and bulk density to the tapped density, which is 100 times the percentage compressibility. Carr's index values of 5–12% indicate free-flowing powder, 23–35% indicate poor flow, and >40% indicate extremely awful flow [29]. Flow rate is also utilized to determine particle resistance to movement, especially in the case of granular powders with little cohesiveness. The compressibility index, or I, is a simple measure of how easily a material may flow. Vt is the tap volume, and V0 is the volume before tapping.

$I = [1 - Vt/ V0] 100$

Where, Vt is the tap volume, and V0 is the volume before tapping. I value below 15% indicate good flow, whereas values above 25% indicate poor flow. The state of consolidation of a powder is plotted as a function of compaction pressure in a compaction equation [30]. Only a few examples are porosity, volume (or relative volume), density, and void ratio.

Compaction Equations

Since Walker's recording of the first-ever accurate compaction data in 1923, a number of compaction-related equations have been given. The most often used equations are the Heckel and Kawakita equations, which link the physical properties of the materials to applied pressure.

Kawakita equation

The Kawakita equation for powder compression is based on the notion that at all phases of compression, the particles are subjected

to compressive load in equilibrium, resulting in a constant product of the pressure and volume terms [31].

$[1/ab + Pa/a] = Pa/C$

$[V0 - V/V0] = C$

Where Pa is the applied axial pressure, an is the particle bed's degree of volume reduction, and b is a constant that is said to be inversely related to particle yield strength. V0 represents the initial apparent volume of the powder, C represents the degree of volume reduction, V represents the volume of the compact at pressure, and C represents the degree of volume reduction [32, 33]. Soft fluffy pharmaceutical powders and low pressures with high porosity work best with this equation.

Heckel equation

The Heckel model provides a mechanism for transforming a parametric representation of force and displacement information to a linear relationship for purely plastic materials. As a result, the Heckel model is the most widely used connection because it provides a simple approach to measure relative density and applied pressure. The Heckel equation is based on the assumption that when bulk powder densification is forced, it follows first-order kinetics.

The following is the Heckel equation:

$KP + A = \ln [1/1–D]$

Where D is the relative density of the tablet at pressure P, and K is the slope of the straight-line part of the Heckel plot. The mean yield pressure, Py, is calculated by reciprocally transforming the slope. In-die tablet thickness measurements determine the apparent mean yield pressure, and the intercept of linear component A represents powder densification as a result of initial particle rearrangement.

Walker equation

The Walker equation103 is a differential equation that assumes that the rate of change of pressure in relation to volume is proportional to the pressure. V0 is the volume at zero porosity, and $\text{Log } P = –L \times V' / V0 + C1$. $V'/V0 = V = 1/D$ is the relative volume, and C1 is constant. The pressing modulus is defined as the coefficient L [34].

Factors Influencing

Tableting speed (dwell time, lag time), particle mechanism, amorphism, polymorphism, moisture content, and salt form. The solid state of lubricants and their concentration, simultaneous processing of excipients or medicines, the pre and main-compression force profile, granulation techniques, and ultrasonic vibration all influence the compaction of pharmaceutical powders [35].

Moisture content

Studying moisture adsorption and absorption by excipients and solid dosage forms can aid in excipient selection, such as disintegrating agents, direct compression carriers, and binders, as well as determining humidity management requirements during manufacturing and storage. Moisture affects the flow, mixing rheology, compaction, real density, and mechanical properties of granules and tablets. Water–powder interaction is a critical issue in the formulation, processing, and performance of solid dosage forms since water is employed in every step of the production process. The amount of water associated with a solid is determined by its chemical affinity, surface area, and available sites of interaction at a certain RH and temperature [36]. Moisture promotes the formation of interparticulate linkages by enhancing the tensile strength of the powder bed and minimising density fluctuations within the tablet. Moisture can also cause plastic deformation, as well as a reduction in the elastic characteristics of powder materials [37, 38].

Compression force profile

The pace at which pharmaceutical powders are compressed can have a major impact on their compaction properties. In order to boost tablet strength and reduce the incidence of capping and lamination, it is beneficial to change the manner of force application.

Solid-state properties

Drugs and excipients used in tablet production come in a wide range of solid-state forms. Because these forms often differ in their physico-technical behaviour, it's crucial to understand their impact on compaction [39].

Hydration

When crystal hydrates are squeezed, the water of crystallization is eliminated, resulting in weak tablets. This highlights the importance of a sufficient moisture content in the development of strong tablets [40].

Crystal habit

The crystal habit of isomorphic and non-isomorphic drugs is the main distinction. The medicine's crystal habit can affect tableting behavior, flowability, and the tendency to stick to the punches. Crystal engineering and particle design can help to increase compactibility [41].

Polymorphism/Amorphism

Numerous pharmaceutical substance polymorphism forms have been widely studied in terms of their physical and molecular characteristics. Because of the existence of sliding planes, crystal plasticity is characterized by greater fragmentation at low pressure,

increased plastic deformation at higher pressure, and lower elastic recovery. In a study of compression behaviour of pure orthorhombic or monoclinic paracetamol, orthorhombic crystals showed excellent technical properties, avoiding capping even at high compression pressures [42]. The complete lack of long-range, three-dimensional intermolecular order in amorphous materials can significantly alter the mechanical properties of a powdered amorphous pharmaceutical molecule. The enhanced compaction behaviour of amorphous materials may be owing to higher plastic deformation than crystalline equivalents [43].

Particle Size and Particle Size Distribution

Particle size and particle size distribution have an impact on both the particle rearrangement and compaction stages. Average particle size and tablet tensile strength correlations are crucial for selecting and creating appropriately sized particles. While the size distribution of free-flowing particles is not critical for tablet porosity, it can have a significant impact on tablet tensile strength due to post-compaction hardening, according to the researchers [44,45].

Granulation Method and Binder

Due to poor flowability and compaction behaviour, pharmaceutical powders are commonly granulated prior to tablet manufacture. The optimum granulation process is chosen for the production of porous and free-flowing granules, enabling for the manufacture of tablets with good mechanical strength at low compression pressures. The order of tensile strength in wet granulation was wet granulation on a fluidized bed > wet granulation in a tumbling fluidized bed > wet granulation in a high-speed mixer. The order of tensile strength in melt granulation was melt fluidized bed granulation > melt tumbling fluidized bed granulation > granulation and melt high-speed mixer granulation [46, 47]. According to these data, granule compactabilities varied depending on the granulation procedure used.

Tableting Problems

The most prevalent compression-related tablet concerns are capping/lamination and sticking/picking. The separation of a tablet's top or bottom crown from the main body is referred to as capping, whereas the separation of a tablet into two or more layers is referred to as lamination. These tableting difficulties usually appear shortly after compaction, however they can also grow over time. A friability test is the most efficient way to test such a problem [48]. The fundamental cause of these problems is materials' inability to alleviate tension after force decrease. By trapping air in the tablet, excess particles can also induce capping and lamination [49]. The intrinsic deformation properties of the material, such as plastic, brittleness, or elasticity, can play a role in tableting concerns. Elastic recovery is regarded to be the most likely cause of capping in high-density zones in a compact bed, when density and stress are unevenly distributed [50]. Tablet capping and lamination difficulties are also linked to pre and primary compaction characteristics. Pre-compression, a slower tableting speed (a longer dwell time), and a lower final compression force may all help to eliminate capping/lamination problems. The type of tools used can have an impact on capping and laminating [51]. Deep concave punches usually produce capping because the cap region endures more radial expansion and shear stress than the tablet's body. Flat punches produce reduced shear stress within a compact. Dies produce a wear ring in compression areas, and the squeezed tablets have fewer diameters to pass through the die wall, resulting in capping and/or lamination upon ejection [52]. Picking is the process of removing surface material from a tablet with a punch. Picking is often associated with punching, engraving, or embossing. To address this problem, lettering should be made as large as feasible, or a larger tablet can be created [53]. Sticking is the process of attaching tablet material to the die wall. Sticking is affected by the surface roughness of the punch, the compaction force, and the mix composition. At low compaction forces, punch face chrome plating enhances sticking, while at higher compaction forces, it reduces it. Sticking and picking have been connected to increased moisture, therefore keeping an eye on the moisture level is also important for treating these concerns [54].

Improvement of Compaction Behaviours of Powder Bed

Compressibility is an issue with many pharmaceuticals and excipients. Depending on what makes up the majority of the mix, either the API or the excipient's compaction behaviour should be refined (s). Additional treatments such as granulation and coprocessing may be necessary to achieve adequate compactibility [55]. Low-dose medicines with weak compressibility rarely have tableting concerns since excipients contribute the required compressibility. In the case of high-dose drugs, however, enhancing the API and/or selecting the appropriate excipients, particularly diluents and binders, is critical to decreasing tableting difficulties [56].

API modification

Due to the limited role of excipients in enhancing compactibility, API modification is required for high-dose drugs, even if it is not allowed [57].

Excipient modification/selection

The type and amount of excipient(s) utilized has an effect on the overall quality of the tablets. Excipients are classified into two

groups based on how they aid in compaction. Diluents and binders, for example, have a beneficial impact; disintegrants and lubricants, on the other hand, have a negative impact.

Diluent

Diluents are the most important excipients since they are often present in higher concentrations than other excipients. Compressibility of diluents ranges from extremely compressible materials like MCC to extremely low compressible materials like starch. As previously indicated, the main behavioural patterns of medications during compaction are plastic deformation, elastic deformation, and brittle breakage. MCC and amorphous binders, which are capable of plastic deformation, have a higher number of attractive forces, resulting in improved compact strength [58]. The rough surface of the particles actively adds to compact strength even in the absence of fragmentation. The compression properties of the API and excipients point to an ideal balance of brittle fracture and plastic behaviour, which is necessary for effective tablet manufacturing. The most commonly used excipients, in order of brittleness, are MCC, spray-dried lactose, -lactose, -lactose monohydrate, and DCP [59].

Lubricants

Lubricants like other types of pharmaceutical excipients, are employed in the formulation of solid dosage forms to aid in production and ensure that the finished products are of acceptable quality. Lubricant is best characterized as a suitable material that, when a tiny amount of it is applied between two rubbing surfaces, lowers friction at the contact. Metallic stearates, stearic acid, talc, and waxes are often used lubricants, as are water soluble substances such as boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine, carbowax, sodium oleate, and sodium lauryl sulphate [60]. Establishing an ejection profile for each lubricant to alleviate stresses associated with tablet compaction is crucial for minimizing dissolving and tensile strength concerns in formulations [61].

Disintegrants

In order to achieve the appropriate dissolving rate of drug substance(s) from a tablet, the tablet's cohesive strength must be overcome and the tablet broken down into fundamental particles. To do this, disintegrants are utilized in formulations. Carbohydrates such as starch (3–15 percent), MCC (5–15 percent), pregelatinized starch (5–10 percent), croscarmellose sodium (1–5 percent), sodium starch glycolate (2–8 percent), and cross-povidone (2–5 percent) are among the most commonly used disintegrants [62]. The fundamental mechanism of disintegration is swelling in the presence of water. Certain materials' tendency to absorb moisture from their surroundings and swell as a result, lowering tensile strength. Many commonly used diluents, such as microcrystalline starch (MCC) and starch, are disintegrants. MCC has a high compressibility, while starch has a low compressibility and affects compact tensile strength. Because super-disintegrants such sodium starch glycolate, cross-povidone, and croscarmellose sodium work at a lower concentration, they are less likely to impact the blend's compaction behavior [63]. However, sodium starch glycolate in quantities more than 10% is known to reduce tablet tensile strength due to its low compressibility. The concentration of disintegrants must be optimized to avoid a negative impact on the compressibility of the tablet blend.

Granulating agents/binders

To turn powder into granules, granulating agents are utilized. Water and organic solvents operate as granulating agents by partially dissolving the surface of the particles and forming solid bridges during evaporation. On the other hand, these types of connections are weak and result in the formation of friable granules [64]. As a result, adding a binder to granulations to increase granule strength and avoid capping and lamination is typical practice. Granulating agents are hydrophilic, cohesive polymers that help in granulation and provide strength after drying. Because bonds are broken as the compaction pressure is released, a binder that promotes flexibility may lower tablet strength [65]. As a result, choosing a good binder for a tablet formulation needs a detailed grasp of binder properties for boosting tablet strength as well as interactions between the tablet's numerous constituents.

Conclusion

Compaction is a critical step in the creation of tablets, and understanding the physics behind it is critical. Because the intrinsic deformation behaviour of drugs/excipients, as well as process conditions, are known to alter variables such as solid-state characteristics, the end product is known to be affected. Despite the advances in tablet technology, a thorough grasp of compaction physics remains elusive. Understanding compaction profiles such as force-time profiles, force displacement profiles, and pressure–porosity correlations can help pharmaceutical chemists comprehend process dynamics and produce ideal formulations free of capping, lamination, picking, and sticking. If the compaction behaviour of the tablet matrix and individual excipients are researched, excipient selection can be based on science. Optimizing process and product parameters that affect the compaction process may also help achieve sufficient tensile strength and needed biopharmaceutical properties in tablet medicinal products.

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Consent for publication

Nil

Availability of data and material

Not Applicable

Authors' contributions

All the authors have contributed to the research work and preparation of the final manuscript.

Conflict of interests

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