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Physics of tablet with compaction and compression process for novel drug dosage form

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Abstract
Tablet is a unit solid dosage form, due to high precision dosing, manufacturing efficiency and patient compliance make tablet to most popular dosage forms. Compression (lessening in the bulk volume of material as a result of deracination of gaseous phase) and compaction (alteration of powder into coherent specimen) are the duet constitutive parts of tablet manufacturing. In this review discuss various types of excipients and their properties, including steps and mechanism of tablet compaction. Mechanistic aspects of tableting can be studied using several theories like mechanical theory, intermolecular theory, and liquid surface film theory. These all parameters have potential importance in various pharmaceutical research and development. Also, the mathematical equation used to characterize compaction and compression events. Compaction related physic-technical properties of commonly used tableting excipients have been reviewed with emphasis on selecting pleasantly combination to attenuate tableting problems. Specialized tools like co-processing of API and excipients properties like particle size & shape, surface area, density, strength and friability used to amend compression of tableting.

Keywords: tablet excipients, tablet compaction, compaction, compression, physics of tablet compression, equation of compaction

Introduction
The oral route of drug administration is the most convenient method of drug administration for systemic effects. It is mostly used for the neutral drugs. It may be in the form of tablets, capsules, syrups, emulsions, powders. Tablets and capsules act for unit dosage forms in which one usual dose of the drugs has been accurately placed. Pharmaceutical product have been administered to the body using drugs and suitable excipients, for rapid and systemic absorption of drugs [1, 2].

Of the two oral solid dosages forms commonly employed in this country, the tablet and the capsule, the tablet has a number of advantages. One of the major advantages of the tablet over capsule, which has recently proved significant, is that the tablet is an essentially tamperproof dosage form [3].

Tablets are made by compressing a drug or drugs with excipients on stamping machines called presses. Tablets presses are either single-punch or multi station rotary presses.

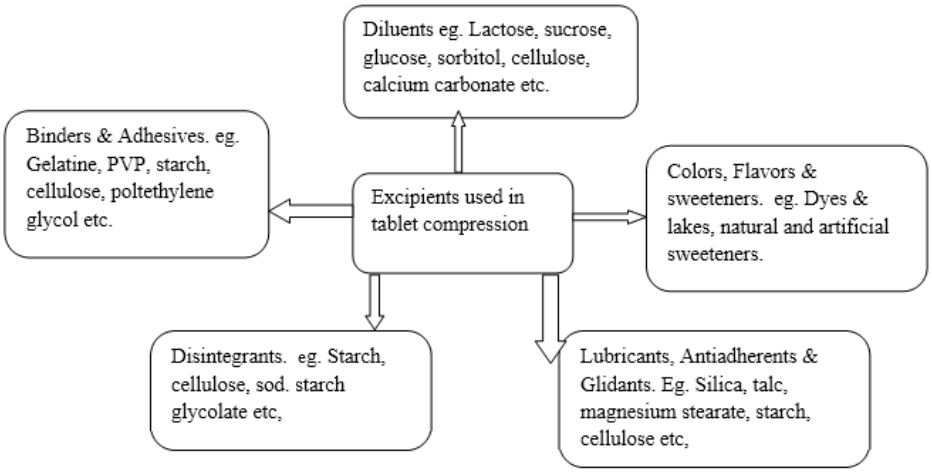

Fig 1: Excipients used in Tablet compression

Tablet Compaction [4-7]
Compaction: Compaction: compaction of a powder is a general term used to describe a situation in which powdered material is subjected to some level of mechanical force.

Compression: Compression: compression of a powder means reduction in the bulk volume of a material as a result of displacement of the gaseous phase under pressure.

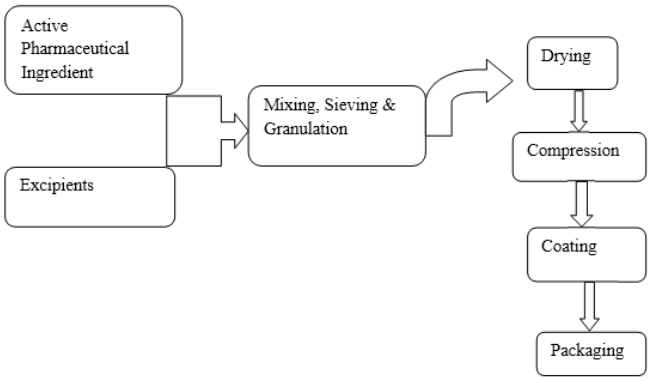

Fig 2: General steps in tablet manufacturing

The complete cycle of tablet compaction occurs in four steps-

- **Stage 1:** Top punch is withdrawn from the die by the upper cam. Bottom punch is low in the die so powder falls in through the hole & fills the die.
- **Stage 2:** Bottom punch moves up to adjust the powder weight. It raises and expels the excess powder.
- **Stage 3:** Top punch is driven into the die by upper cam and bottom punch is lowered by lower cam. Both punches heads pass between heavy rollers to compress the powder.
- **Stage 4:** Top punch is withdrawn by the upper cam. Lower punch is pushed up and expels the tablet. Tablet is removed from the die surface by surface plate.

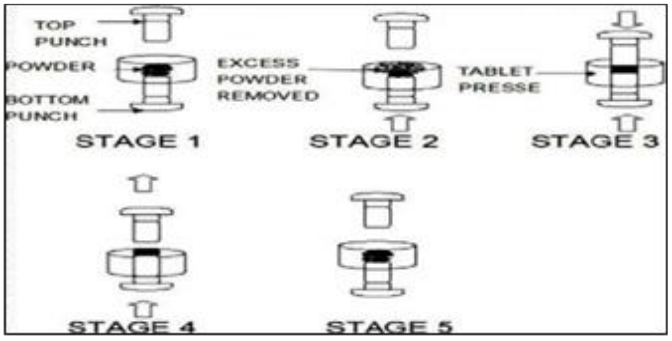

Fig 3: Steps involved in tablet compaction

Manufacture of Granulations

The manufacture of granulations for tablet compression may follow one or a combination of 3 methods [8].

Direct compression is a popular choice because it provide the shortest, most effective & least complex wat to produce tablets. The manufacture can blend an API with the excipient and lubricant, followed by compression, no additional processing steps are required. There are a few crystalline substances such as sodium chloride, sodium bromide and potassium chloride that may be compressed directly. Direct compression materials, in addition to possessing good flow and compressibility, must be inert, tasteless, rework able, able to disintegrate and inexpensive [9, 10].

Compression granulation has been used for many years, and is valuable technique in situations where the effective dose of a drug is too high for direct compaction, and the drug is sensitive to heat, moisture, or both. Many aspirin and vitamin formulations are prepared for tableting by compression granulation. Compression granulation involves the compaction of the components of a tablet formulation by means of a tablet press or specially designed machinery, followed by milling and screening, prior to final compression into a tablet. When a initial blend of powder if forced into a dies of a large capacity tablet press and is compacted by means of flat-faced punches, the compacted masses are called slugs, and the process is referred to as "slugging". The slugs are then screened or milled to produce a granular form of tabletting material [11-13].

Wet granulation processes involve the wet massing of the powders, wet sizing or milling and drying. Wet granulation forms the granules by binding the powders together with an adhesive, instead of by compaction [14, 15].

Granulation properties: There are many formulation and process variables involved in the granulation step, and all of these can affect the characteristics of the granulations.

1. **Particle size and shape:** The particle size of a granulation is known to affect the average tablet weight variation, disintegration time, granule friability, flow ability and drying rate of granules [16]. The exact effect of granule size and size distribution on processing requirements, bulk granulation characteristics and final characteristics of tablet depends upon the formulation ingredients and their concentrations, as well as the type of granulating equipment and processing conditions [17, 18].
2. **Surface area:** The determination of the surface area of finely milled drug powder may be of value for drugs that have only limited water solubility. Particle size and surface area of the drug, can have a significant effect upon dissolution rate [19].
3. **Density:** Density of granule may influence compressibility, tablet porosity, dissolution and disintegration rate. Dense, hard granules may require higher compressible loads to produce a cohesive compact [20]. The higher compression load, has the potential of increasing the tablet disintegration and drug dissolution time.

   Density is calculated from the volume of intrusion fluid displaced in the pycnometer by a given mass of granulation [21].

   $$D=M / V_p - V_i$$

   D= density, Vp= total volume of pycnometer, Vi= volume of intrusion fluid

   The equation of bulk density (ρ_b) is –

   $$\rho_b = M / V_b$$

   M = mass of particles, Vb = total volume of packing
4. **Strength and Friability:** A granule is an aggregation of component particles that is held together by bond strength. The strength of a wet granule is due to the surface tension and capillary forces. Upon drying, the granule has strong bond due to fusion or recrystallization of particles. The resultant strength of a granules depends on base material, the kind and amount of granulating agent used, the granulating equipment used [22-24].

5. **Flow properties:** The flow property of a material result from many forces. Solid particles attract to each other, and forces acting between particles when they are in contact. There are many forces that can act between solid particles; surface tension force, frictional force, mechanical force, electrostatic force, cohesive or van der waals forces. These forces can also effect granule properties such as particle size, particle size distribution, particle shape, surface texture, roughness and surface area [25, 28].
   Angle of repose is commonly used for the measurement of flow properties of powder and granules.

   $$\Theta = \tan^{-1}(h/r)$$

   Where
   Θ = is angle of repose,
   h = height of heap,
   r = radius of heap

Table 1: Angle of repose

Flow property	Angle of repose
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very Very poor	>66

6. **Compaction:** The process of consolidating and compaction of powder or granule material to form a tablet is complex. The basic tool that has been developed for studying the compression process is the instrumented tablet press [29].

Physics of tablet compaction

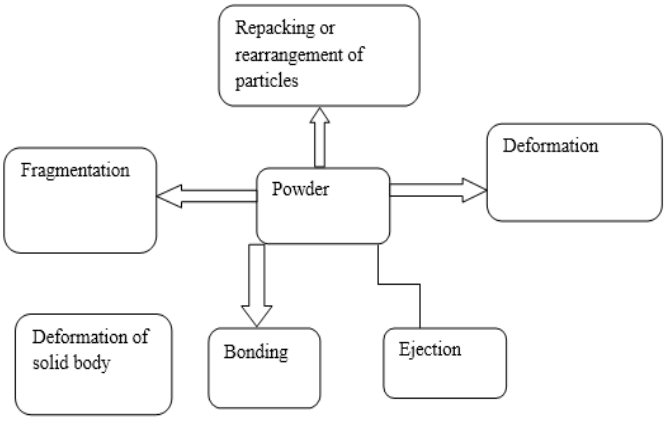

Fig 4: mechanism of tablet compaction

1. **Repacking or rearrangement of particles:** 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 [30, 31]. 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 inter particulate friction and there is an increase in the amount of particle surface area capable of forming inter particulate bonds [32]. 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 [33].
2. **Deformation:** 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 [34].
   As the upper punch penetrates the die containing the powder bed, initially there are essentially only points of contact between the particles [35]. 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) [36, 37]. The deformation is reversible and the particles inside the powder bed regain their original shapes.

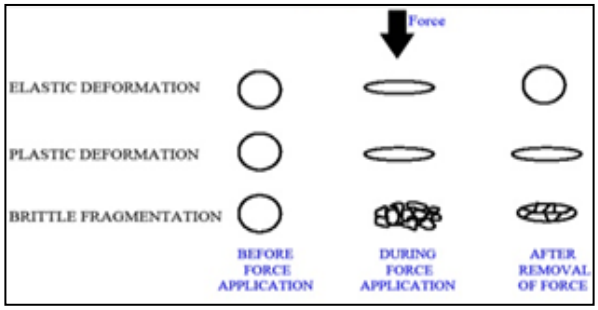

Fig 5: Mechanism of deformation

3. **Fragmentation:** As compression force increases deformed particles start fragmentation due to high load, particles breaks into smaller fragments leading to formation of new bonding areas. The fragment undergo densification with infiltration of small fragments into voids.
   Some particles undergo structural break down called as brittle fracture [38].
4. **Bonding of particles:** 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 [39]. This hypothesis is favoured as a major reason for the increasing mechanical strength of a powder bed when subjected to compression force. 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 [40, 41, 42].

Bonding of particles governed by several theories

a. **The mechanical theory:** Mechanics of a material deals with the behaviour of a solid body subjected to various types of loading. It occurs between irregular shaped bodies. Mechanical interlocking may increases the contact points between particles. The mechanical theory proposes that under pressure the individual particles undergo elastic/plastic or & brittle deformation & that the edges of the particles intermesh deforming a mechanical bond.
   - If only the mechanical bond exists, the total energy of compression is equal to the sum of the energy of deformation, heat & energy absorb for each constituent.
   - Mechanical interlocking is not a major mechanism of bonding in pharmaceutical tablet [42].

b. **Intermolecular theory:** Intermolecular forces are the forces which mediate interaction between molecules, including forces of attraction or repulsion which act between molecules and other types of neighbouring particles. e.g., atoms or ions. • The molecules [or ions] at the surface of solid have unsatisfied forces [surface free energy] which interact with the other particles in true contact [43, 44[.
   - Under pressure the molecules in true contact between new clean surfaces of the granules are close enough so that vender-walls forces interact to consolidate the particles.
   - Materials containing plenty OH groups may also create hydrogen bonds between molecules.

c. **Liquid surface film theory- T**his theory attributes bonding to the presence of a thin liquid film which may be the consequences of fusion or solution at the surface of the particles. This theory is a combination of Solid bridge, Hot welding and Cold welding theory [45].

5. **Deformation of solid body:** As the applied force /pressure is further increased the bonded solid is consolidated towards a limiting density by plastic/ elastic deformation of the tablet within the die [46].
6. **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 [47, 48].

Force distribution during compaction

$$F_A = F_L + F_D$$

F_{A-} force applied to upper punch, F_D- force transmitted to lower punch, F_D- reaction at die wall

Mean compaction force

$$F_M = (F_A + F_L)/2$$

Compaction equation

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;

$$\ln [1/1-D] = KP + A$$

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 [49].

The significance of Heckel plot [50]

1. The Heckel constant k has been related to the reciprocal of the mean yield pressure, which is the minimum pressure required to cause deformation of the material under compression.
2. The intercept of the curve portion of the curve at low pressure represents a value due to densification by particle rearrangement.
3. The intercept Obtained from the slop of the upper portion of the curve is a reflection of the densification after consolidation.
4. A large value of the Heckel constant indicates the onset of plastic deformation at relatively low pressure.
5. A Heckel plot permits an interpretation of the mechanism of bonding.

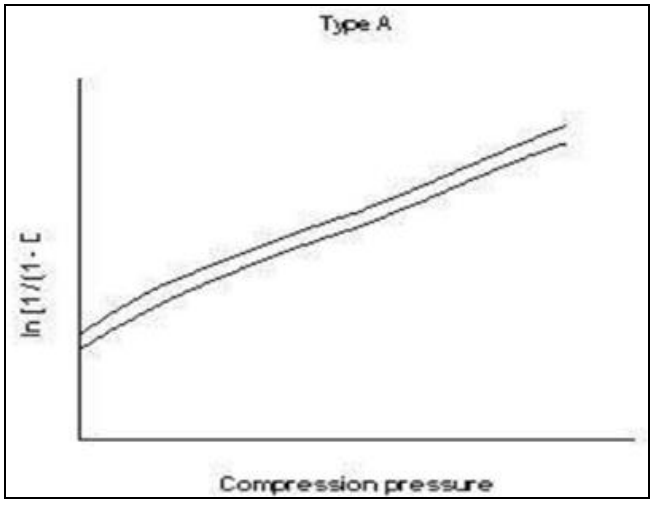

Fig 6: Heckel plots – For plastic deforming bodies

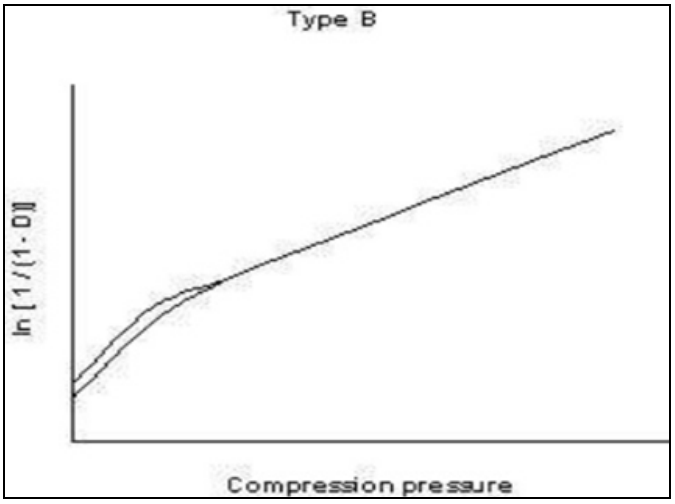

Fig 7: For fragmenting materials

Weakness of hackle plots [51]

Shape of the plot os very sensitive for small errors in the determination of powder true density.
Linear part of plot is sometime difficult to determine.
This plot determination need very accurate data.

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.

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

$$C = V0 - V /V0$$

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 [52-54].

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

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

Where, *V0* is the volume at zero porosity. The relative volume is *V'/V0 = V* = 1/*D*, *C*1 is constant. The coefficient *L* is referred to as the pressing modulus [55, 56].

Conclusion

Compaction and compression are an integral processes 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 behaviour 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. Various granulating steps, surface area, particle size & shape, strength & friability, density and flow properties can help in deciphering the dynamics of the process. Optimization of excipient, granulation and compaction forces & equations can help in achieving satisfactory tensile strength and desired biopharmaceutical properties in tablet drug products.

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