Particle Size Enlargement: Making and Understanding of the Behavior of Powder (Particle) System

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ABSTRACT

Particle size enlargement is the process of transforming fine particles into larger particles by the introduction of external forces, and is a value-added step in many processes involving powdered materials. There are many different reasons to enlarge particle size, including increased flowability and improved product shape and appearance. With the multitude of options available to achieve enlarged particle product, it can be difficult to narrow down the best method for the desired application. The main factor in selecting the right kind of method is to specify the type of end product required. In the pharmaceutical industry in particular, uniform flow of solid mixtures is one of the most important considerations in solid dosage manufacture. The particle size distribution, shape, hardness, and moisture content of the powder particles govern its flow and compactionability property. This article outlines making of enlarged particles and understanding their behavior.

Introduction

Powders are omnipresent and can be found in almost every industry. Particle engineering (design) and powder systems containing them is becoming increasingly important in pharmaceutical production and development. Still, among the several dosage forms, solid dosage forms are most popular and widely used. Particle design for solid pharmaceutical dosage forms involves improving the efficiency of the manufacturing processes and giving high degree of functionality to the drug or excipient particles.

Solid substances are characterized by three levels of solid state—the molecular, particle, and bulk level.[6] The molecular level comprises the arrangement of individual molecules in the crystal lattice and includes phenomena such as polymorphism, pseudo-polymorphism, and amorphous state. Particle level comprises individual particle properties such as size, shape, surface area, and porosity. The bulk level is composed of a group of particles and properties that govern it, such as flowability, compressibility, etc. Hence, making of particle or powder must begin with a particle design that is suited to deliver the desired function. Flow and compactibility of particles or powder are the most important consideration in the solid dosage manufacture.[2-4] Blending, transfer, storage feeding, compaction, and fluidization, all depends on good powder flow property.[5]

Particle Origin

Particles may be produced by different processes that can be regarded as constructive or destructive.[6] Constructive methods include crystallization, precipitation, and condensation. The method of manufacturing (origin) often dictates the particle structure and thus its properties. The properties include particle size, particle distribution, particle shape, specific surface area, true density, tensile strength, melting form, and polymorphic form. From these fundamental properties arises the other property such as solubility, dissolution rate, flowability, and compactibility.

The structures of particles are characterized in terms of crystal system and crystal habit. The crystal system can be defined by the lattice group spacing and bond angles in 3 dimensions. In practice, triclinic, hexagonal, trigonal, orthorhombic, and tetragonal are different crystal systems of powder. The phenomenon of crystal growth that occurs from solution inhibits any of the three dimensions. This inhibition results in the formation of different crystal habits. Inhibition of growth occurs due to differences in region of different polarity at the surface or charge density at the surface. Crystal growth thus gives rise to particle of different crystal habits that do not imply different lattice group spacing, as described
Particle properties affecting flow and compactibility

All particles show cohesion and adhesion properties. This is mainly due to the attraction between particles. The attraction between the particles influences the packing and flow of powders. On a molecular level, the characteristic surface roughness and real area of contact dictates the cohesion and adhesion properties of particles surface.[7-10] Sometimes, cohesive powders that exhibits poor flow property are formed due to increase in the humidity or as the weight or size of particle decreases (more prominent at sizes <100 μm). These cohesive forces are not present in all powders.[11]

A simple definition of powder flowability is the ability of a powder to flow. Flowability can never be presented as single value or index. Flowability is the result of the combination of material’s physical properties that affect material flow and the equipment used for the handling, storing, or processing the material. A more accurate definition of powder flow is the ability of powder to flow in a desired manner in a specific piece of equipment. For example, the movement of powders for tableting, encapsulation, and many other processes occurs through a constriction devices such as chute or hopper. The powder is discharged from hoppers or storage bins following either of the two flow regimes—mass flow or funnel flow.[8] In mass flow, all the powder in hopper or bin is in motion [Figure 1]. This regime is also referred to as “first-in-first out” flow, that is, the powder that enters the hopper first exit the hopper when it is opened.

In funnel or core flow, the central core of powder exits first, followed by remaining powder from the sides of container. This regime is called as “first-in-last-out” flow. If the material along the edges of the bin is in place and does not exit the container, a rat hole forms.[12] Rarely, a stable dome or arch is formed across the bottom of bin or hopper preventing any discharge.[13] When the dome of material is distributed, uncontrolled flow powder or flooding can occur.[14]

The specific bulk characteristics and properties of a powder that affect flow and that can be measured are known as flow properties. Examples of flow properties include density, cohesive strength, and wall friction. Finer powders tend to exhibit reduced flowability because of the greater surface area to mass ratio that allows cohesive surface forces to dominate over gravitational forces. Powder shape also influences flowability. Shape and size are related since shape is often described as a ratio of characteristic lengths.[15] Powder shape determines the number of contact points between individual particles, which affects interparticle forces. If the particle size is small (10 μm), the powder flow is restricted due to cohesive force between the particles. Particle with high surface to mass ratio are more cohesive than the coarser particle which are influenced by gravitational force. Particle size >250 nm are free flowing. Shear strength—Cohesion define as stress necessary to shear powder bed under zero normal load. Shear cell—apparatus measure the shear stress “τ” at different values of normal stress “σ.” Particle size, size distribution, crystal habit, polymorphism, and moisture content are the most common elements that can change the compression properties.[16]

A compaction process involves three basic steps—the application of consolidating stress to the powder, the removal of the stress, and then ejection of the compact. The understanding of the principles involved in compressibility and compactibility are required to represent the compaction profiles of enlarged particle materials. Both phenomena are important in the tableting of these materials.

Techniques of particle size enlargement

Particle size enlargement has become an important tool in modifying the flow properties of pharmaceuticals.[15] Literature survey reveals that particle size enlargement of drugs is a widely used technique in industrial processing. It can be carried out by techniques such as—melt extrusion,[17] melt agglomeration,[18] crystallo-co-agglomeration (CCA)[19] agglomeration,[20] ordered mixing,[21] and spherical crystallization.[22-24]

Agglomeration technique

Spherical agglomeration method proceeds in three steps. The first step is the selection of the crystallization method to precipitate crystals from solution, that is, thermal method (temperature decrease or evaporation), physicochemical methods (addition of another solvent, salting out), and chemical reaction. The second step is the choice of the wetting agent that will be immiscible with the solvent of crystallization. Finally, the third step is the hardening of the agglomerates.

There are several options available to produce an agglomerated product, and thus it can be difficult to narrow down the best method. There are four main categories of agglomeration—pressure agglomeration; tumbling agglomeration; extrusion agglomeration; and thermal agglomeration.

In pressure agglomeration, material masses are subjected to high forces. The application of high pressure causes partial crushing and realignment of the individual particles. The pressure can be high, in excess of 30 000 psi. This results in the particles being forced into close proximity, where interparticle forces result in binding. In tumbling agglomeration, material masses are combined with a binder and subjected to rolling or tumbling forces to form loose agglomerate structures. Agitation can be high or low shear, depending on the equipment. The feed to this type of system is typically a fine powder. Binding is generally accomplished by liquid bridges or chemical reaction. In extrusion agglomeration, material masses are subjected to forcespressing them through a die plate to form pellets. Pressure ranges from low to high depending on the type of extruder chosen. Feed to an extruder must be formable by the die, that is, it must be
a wet cake, paste, or dough, or form one through the mixing process in the extruder. Thermal agglomeration is a wide category focusing on agglomeration using heat transfer processes. These processes involve sintering through heat application, solidification through cooling, or coagulation through melting.

**Spherical crystallization technique**

**Solvent change method**

Spherical agglomeration has more importance than the other methods because it is easy to operate and selection of the solvents is easier than the other methods. In this method, the solution of the drug is in a good solvent is poured in a poor solvent under controlled condition of temperature and speed to obtain fine crystals. These crystals are agglomerated in the presence of bridging liquid. The poor solvent has miscibility with good solvent but low solubility with solvent mixture, so during agitation of the solvent system, the crystals are formed. The drawback of this system is that it provide low yield because the drug shows significant solubility in the crystallization solvent due to co-solvency effect. This method is not applicable for water-insoluble drugs. The most important parameters in spherical agglomeration are the selection and amount of the bridging liquid, the agitation rate, concentration of the solid, temperature, initial particle size, and feeding rate. Many studies have been done to optimize the amount of bridging liquid to be added into the system and found that less than the optimum amount of bridging liquid added produces plenty of fine particles and more than optimum amount produces secondary agglomerates. The choice of the bridging liquid has an influence on the rate of agglomeration and the strength of the agglomerates. An increasing stirring speed makes the agglomeration process less efficient. Bos and Zuiderweg found that at higher stirring rate, the final agglomerates tend to be less porous and more resistant.

**Quasi-emulsion solvent diffusion method**

Quasi-emulsion solvent diffusion is also known as transient emulsion method. In this method, only two solvents are required—a solvent that readily dissolves the compound to be crystallized (good solvent) and a solvent that act as an antisolvent generating the required supersaturation (poor solvent). It involves the formation of quasi—emulsion of solution of drug in good solvent with a nonsolvent. The crystallization of drug occurs by counter diffusion of good solvent and poor solvent. Residual good solvent in droplets acts as a bridging liquid to agglomerate the generated crystals. In this process, the emulsion is stabilized by the selection of suitable polymer which is required for proper crystallization. In the droplets, the process of solidification proceeds inward so the liquid is not maintained on the surface and the agglomerate is formed without coalescence. In this method, the shape and the structure of the agglomerate depended strongly on the good solvent to poor solvent ratio and temperature difference between the two solvents.

**Ammonia diffusion method**

Ueda et al. modified the spherical crystallization technique and developed a new agglomeration system, ammonia diffusion system (ADS), which is applicable to amphoteric drug substances like enoxacin. In this method, ammonia water act as a good solvent and bridging solvent, other components of this method are bad solvent and hydrocarbon/halogenated hydrocarbon (acetone). The hydrocarbon is miscible with the system but it reduces the miscibility of ammonia water with bad solvent. The counter diffusion process across the droplet involves movement of bad solvent into and ammonia out of the droplet. The droplet collects the crystals as a drug in ammonia water, precipitates slowly, and growth of agglomerates occurs. Pucchagut et al. prepared agglomerated crystals of norfloxacin and ampicillin trihydrate by a spherical crystallization technique using the ADS.

**Neutralization method**

Sano et al. reported spherical crystallization of antidiabetic drug tolbutamide by neutralization method. The drug was dissolved in a sodium hydroxide solution and hydroxypropyl ethyl cellulose aqueous solution. Hydrochloric acid was added to neutralize the sodium hydroxide solution of tolbutamide and crystallize out the same. The bridging liquid was added drop wise followed by agglomeration of the tolbutamide crystals.

**Melt granulation technique**

Melt agglomeration is a process by which agglomeration—or size enlargement by which fine particles are bound together to agglomerates or granulates—is obtained through the addition of either a molten binder liquid or a solid binder which melts during the process. Agglomerates are formed by agitation of the mixture. To obtain a stable, dry granule, a cooling to ambient temperature is necessary to solidify the binder. After the granulation, the binder crystallizes at room temperature.

**Melt congealing**

Processing of melttable materials by spray congealing involves spraying a hot melt of wax, fatty acid, or glyceride into an air chamber below the melting point of the melttable materials or at cryogenic temperature. Spray-congealed particles (10–3 000 μm in diameter) are obtained upon cooling. The congealed particles are strong and nonporous as there is an absence of solvent evaporation. Ideally, the melttable materials should have defined melting points or narrow melting ranges.

**Tumbling melt granulation**

A powdered mixture of melttable and nonmelttable materials is fed onto the seeds in a fluid-bed granulator. The mixture adheres onto the seeds with the binding forces of a melting solid to form the spherical beads. In preparing the spherical beads, both viscosity and particle size of the melttable materials should be kept at an optimum value. The particle size of a melttable material should be one-sixth or lower than the diameter of the seeds. High-viscosity melttable materials should not be employed, to avoid agglomeration of seeds and producing beads of low sphericity.

**Crystallo-co-agglomeration technique**

It is a modification of the spherical crystallization technique in which a drug is crystallized and agglomerated with an excipient...
or with another drug, which may or may not be crystallized in the system. The agglomeration is performed using bridging liquid. The process enables design of agglomerates containing two drugs or a low-dose or poorly compressible drug in combination with diluents.[5] To date, CCA has been used for size enlargement of low-dose bromhexine hydrochloride and talc,[33] ibuprofen-talc, [36] ibuprofen-paracetamol,[37,38] and naproxen-starch. [39] Studies have demonstrated that CCA generates spherical agglomerates having excellent micromeritic properties, satisfactory mechanical strength, and direct compressibility.

**Evaluation methods for enlarged particles**

**Powder size and shape (crystal habit)**

The most common particle-sizing methods for pharmaceutical dry powders and granules are sieve analysis, laser diffraction, and computerized image analysis techniques. Optical microscopy is used for larger particle sizes and using the scanning electron microscope (SEM), it is possible to obtain accurate and unambiguous data upon the shape, size, and surface topography of even small particles of 1 μ. Differential scanning calorimeter (DSC) and X-ray diffraction methods are used to determine quantitatively the amorphous fraction in crystalline-amorphous powder mixtures.

1. **Scanning electron microscopy**
   - The morphology (surface) of crystals can be examined using a SEM. The samples are sputter-coated with gold before examination.

2. **Optical microscopy**
   - The shape of the spherical crystals is studied by observing the powder under an optical microscope. The observations are made under 10X, 45X, 60X, etc., lens system.

3. **X-ray diffraction of powder**
   - X-ray diffraction powder (XRDP) analysis is a powerful method by which X-rays of a known wavelength are passed through a sample to be identified in order to identify the crystal structure. The wave nature of the X-rays means that they are diffracted by the lattice of the crystal to give a unique pattern of peaks “reflections” at differing angles and of different intensity. XRDP data can be recorded at room temperature on X-ray diffractometer at 40 kV, 30 mA and a scanning rate of 0.06° min⁻¹ over a range of 2-40 2. CuKα1 radiation of wavelength 1.5405Å. Samples can be measured on a low background quartz plate in an aluminum holder. The form of crystal in agglomerates is determined by using this technique. An amorphous form does not produce a pattern.

4. **Differential scanning calorimeter**
   - Thermograms of drug crystals can be recorded on DSC. Samples (4-5 mg) are placed in aluminum pans and the lids were crimped. The samples are heated ranging from 25 to 200°C at the rate of 40°C min⁻¹. Melting point can be automatically calculated. The increase in bulk density of a powder is related to its cohesiveness. Bulk density and tapped density relationship is another way to index flowability.[41]
   - Angle of repose of the test materials can be assessed by the fixed funnel method and computed as in Equation 6.
   
   \[
   \text{Angle of repose (°)} = \tan^{-1}(h/r)
   \]

   Powders are classified as “light” or “heavy.” Light powders have high bulk volume. Fines (up to 15%) increase angle of repose. Rough and irregular surface increases angle of repose. Lower the angle of repose, better is the flow property. Angle of repose is commonly used to measure flow of powders, and is the maximum angle 0 between the plane of powder and horizontal surface. The value of 0 less than 10° usually indicates free-flowing material, up to 40° indicates reasonable flow potential, and above 50° indicates the power flows with great difficulty.

**Porosity**

Porosity is the space between the particles. Volume occupied by powder is known as bulk volume. This can be derived from the values of true and bulk densities when fitted into the Equation:

\[
\text{Porosity} = (1 - \frac{\text{Bb}}{\text{Dt}}) \times 100
\]

Where, Bb is the bulk density, Dt is the true density, and e is the porosity.
Wettability

Wettability values are determined indirectly by measuring the densities and surface tensions of the saturated aqueous solutions of drug powder and its enlarged crystals. The densities are determined using a relative-density bottle. The surface tension values are determined using a stalagmometer.

Friability test

Friability can be investigated using Roche-type friabilator. Five grams of sieved sample (0.32 mm) is put into the apparatus and 100 revolutions are performed. It is rotated at 25 rpm for 4 minutes. Percent friability is calculated using the following equation:

Friability = \( \left( \frac{W_0 - W}{W_0} \right) \times 100 \)  

Where, \( W_0 \) is the weight of the tablets at time zero before revolution, and \( W \) is the weight of the tablets after 100 revolutions.

Moisture uptake study

Two grams of the sample material is accurately weighed and evenly distributed over the surface of a 70-mm tarred Petri dish. The samples are then placed in a large desiccator containing distilled water in its reservoir (RH = 100%) at room temperature and the weight gained by the exposed samples over a seven-day period is recorded and the amount of water absorbed is calculated from the weight difference.

Preparation of compacts

The compacts are prepared of the enlarged particles by direct compression method. The compacted tablets of approximately 200 mg of 8-mm diameter are prepared at different levels of pressure. The prepared compacts are evaluated for the following properties.

Tensile strength determination

The force required to fracture the compacts on hardness tester is measured to determine tablet crushing strength. The tensile strength of the compact can be calculated using the following equation:

\[ T = 2F / \pi Dt \]  

Where, \( D \) and \( t \) are the diameter and thickness of the compact, respectively, and \( F \) is the force fracturing the compact.

Crushing strength

It is measured by using 50-ml glass hypodermic syringe. The tip of the syringe barrel and the top end of the plunger are removed. The barrel is then used as hollow support and the guide tube with close fitting tolerances to the Plunger. The hollow plunger with open end served as load cell in which mercury could be added. A window was cut into the barrel to facilitate placement of granule on the base platen. The plunger acted as movable plates and set directly on the granules positioned on the lower platen as the rate of loading may affect crushing load (g). Mercury is introduced from reservoir into the upper chamber at the rate of 10 g/sec until the single granule is crushed; loading time should be <3 minutes. The total weight of the plunger and the mercury required to fracture a granule is the crushing load.

Porosity analysis of tablets

The porosity of tablets is calculated using true volume and bulk volume values of the tablets. The true volume of the tablets is analyzed using helium pycnometer. Bulk volume of the tablet is calculated by measuring the diameter and thickness of the tablet to \( \pm 10 \) \( \mu \)m. The total porosity \( \varepsilon \) of the tablet can be obtained using the following equation:

\[ \varepsilon = 1 - \frac{V_t}{V_b} \times 100 \]  

Where, \( V_t \) and \( V_b \) are true volume and bulk volume of the tablets, respectively.

Contact angles

The contact angles of the saturated aqueous solutions of drug and its enlarged crystals can be determined by measuring the height of a large drop when it was placed on a tablet surface. The contact angle is calculated using the following equation:

\[ \cos \theta = \frac{Bh^2}{\sqrt{3(1-h^2)}} V_b \]  

Where, \( B \) is the density of the saturated solution of the sample in water, dyne/cm; \( \gamma \) is the surface tension of the saturated solution of drug in water, g/cm; \( h \) is the height of the liquid drop, cm.

Compression behavior analysis

Good compactibility and compressibility are essential properties of directly compressible crystals. The compaction behavior of enlarged crystals and single crystals is obtained by plotting the relative volume against the compression pressure. Compaction behaviors of agglomerated crystals are evaluated by using the following parameters.

Heckel plots

To analyze the compression process of agglomerated crystals, and assess their compactibility, Heckel equation can be used. Heckel developed an equation by assuming similarity to the first order chemical reaction. Here, the concentration is substituted with porosity and time with pressure.\(^{[42]}\)

\[ \frac{dD}{dp} = k(1 - D) \]  

Where, \( D \) is a relative density of the compact at applied pressure (P) and \( K \) is a constant. This assumes that the rate of change in density with respect to pressure is directly proportional to the remaining porosity. Integration of equation gives,

\[ \ln \left( \frac{1}{1 - D} \right) = PK + 1 \]  

Where, “k” and “A” are constants. D and P are the packing fraction.
and pressure, respectively. The slope, $K$ of the Heckel plot gives a measure of the plasticity of a compressed material. The reciprocal of $K$ is known as the yield value. Yield value reflects the deformity of the material. The linear portion of the Heckel plot represents the densification process by particle deformation after interparticle bonding. The soft, ductile powders have lower yield value. The agglomerates with low yield value could be plastically deformed as a result of the rebonding of smaller primary crystals.[43] Thus, material exhibiting lower value of $Py$ has more tendency of plastic deformation.[44] Low value of $Py$ (steep slope) reflects low resistance to pressure, good densification, and easy compression. A large value of slope indicates the onset of plastic deformation at relatively low pressure.[45]

**Kawakita analysis**

Flowability is determined using the Kawakita analysis. The method involves pouring a 10 g of powder and formulations into a 50-ml glass measuring cylinder, and the bulk volume $V_{0}$ is accurately measured. Then, tapping is started mechanically and the change in volume of the powder column $V_{N}$ is noted after $N$ number of taps. The Kawakita equation, which is used for assessing the flow properties of powders, is given by:

$$\frac{N}{C} = \frac{a}{N} + \frac{1}{ab}$$  \hspace{1cm} (15)

Where, $a$ and $b$ are constants; $a$ describes the degree of volume reduction at the limit of tapping and is called compactibility; $1/b$ is called cohesiveness; $C$, the degree of volume reduction is calculated from the initial volume $V_{0}$ and tapped volume $V_{N}$ as:

$$C = \frac{(V_{0} - V_{N})}{V_{0}}$$  \hspace{1cm} (16)

Numerical values for constants $a$ and $b$ are obtained from the method of plots of $N/C$ vs number of taps $N$ ($N = 10$, 30, 100, and 300). The constant $a$ is equal to the minimum porosity of the bed prior to compression, whereas $b$, which is termed the coefficient of compression, is related to the plasticity of the material. The reciprocal of $b$ yields a pressure term, $Pk$, which is the pressure required to reduce the powder bed by 50%. The value of $Pk$ provides an inverse measurement of plastic deformation during the compression process.[46] Lower the value of $Pk$, the higher the degree of plastic deformation occurring during compression. Higher total plastic deformation would lead to more contact points for interparticulate bonding to produce stronger tablets.

**Determination of brittle fracture index**

The compacts are stored for 2 days before the test of diametral compression. Holes with diameters of 1.0 mm are bored through the tablets with a concentrated drill under very low rotational speed. Hiestand et al.[47] applied crack theory to develop a quantitative expression for the measurement of the brittle fracture tendency. Brittle fracture index (BFI) values of the final tablets were obtained from the expression derived by Hiestand et al., that is,

$$BFI = 0.5\left(\frac{T_{0}}{T} - 1\right)$$  \hspace{1cm} (17)

Where, $T_{0}$ and $T$ are the tensile strengths of tablets with and without a centre hole, respectively. The centre hole ($\leq 1.0$ mm) is a built-in model defect to simulate actual void formed in the tablet during compression. For brittle fracture to occur, the ratio $T/T_{0} = 3$. By subtracting 1 and multiplying by 0.5, the maximal BFI value is 1 (unity). The BFI value thus has a range of 0 (no fracture tendency) to 1 (maximal fracture tendency). Tablet samples with BFI values $\geq 0.5$ displayed a high fracture incidence during actual tableting.

**Tablet elastic recovery test**

Sample of size 150 mg is placed in a die with 8-mm diameter on a compression press to compress them up to 200 MPa at the constant speed of 10 mm min⁻¹. The thickness of each tablet under maximum pressure (Hc) and at about 24 hours after tablet ejection (He) is given by:

$$ER = \frac{[Hc - He]}{Hc} \times 100$$  \hspace{1cm} (18)

About 24 hours after the tablet is ejected, its weight, diameter, and thickness were measured, and its apparent density is calculated. The internal tablet porosity ($\varepsilon$) from true density ($\rho_{t}$) is measured with a pycnometer.

$$\varepsilon = 1 - \frac{\rho_{b}}{\rho_{t}}$$  \hspace{1cm} (19)

**Determination of tablets packing fraction**

The packing fraction of the tablets from each size fractions is calculated from the particle densities of the tablet compositions. The packing fraction, $Pf$, is computed using the following equation[48],

$$Pf = \frac{W}{\pi l^{2} t}$$  \hspace{1cm} (20)

Where, $W$ is mean weight of the tablets, $r$ is the radius, $t$ is the tablet thickness, and $I$ is the particle density using fluid displacement method. A high packing fraction is an indication of a high degree of consolidation of the particles in the tablet. This may be ascribed to the series of events that follows the compression processes, such as repacking, deformation, fragmentation, and bonding. There is a greater tendency for the larger granules to deform and fragment readily thereby creating a larger number of bonding points during compression compared with the smaller granules. Such plastic and elastic deformation and/or fragmentation of the larger granules is expected to bring about an increase in the surface area of the fragments which is also necessary for greater particle contact and bonding and hence a greater tendency for closer packing. In contrast to the smaller particles, there is a limited tendency to deform (that is, highly elastic) and fragment and hence they form less consolidated compact. It has also been reported previously that a reduction in particle size may be related to a decreased tendency to fragment.[49]

An increase in the granule sizes brought about an increase in the packing fraction of tablets, indicating that there is a higher degree of plastic deformation and fragmentation of the larger granules during compaction, with a resultant increase in the surface area of the fragmented particles necessary for particle-particle bonding; however, the smaller sized granules have limited sizes and were not prone to further deformation and fragmentation. General increase in the particle sizes brought about a decrease in the particle density and an increase in the percentage porosity of the tablets. The increase in percentage porosity displayed by the larger granules may be attributed to the presence of larger void spaces, a feature characteristic of larger particles and a limited surface area available for interparticulate bonding.

**Conclusion**

The intention of this work was to investigate the techniques used...
recently to enlarge the particle in powder system and to understand the evaluation of the formulation of the same. It should make a contribution toward formulation design of solid dosage form.

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