EFFECT OF SIZE REDUCTION AND DRYING TECHNOLOGY ON
GRANULES PRODUCTION

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ABSTRACT
Granulation is well known important unit operation in the Production of pharmaceutical solid oral dosage forms. Granulation process must be forwarded to improve from, compressibility of powder characteristic, improve the content uniformity, decreases isolation rate and avoided excessive fines practical. The result will be improve yields, reduction defects, increased productivity and reduce down time. The pharmaceutical Industry has employs several techniques like as direct compression, wet granulation, dry granulation methods for production of granules. The granules typically have a size rang between 0.2 to 0.4 mm bases on subseques several use. The aim of present work is focus on the factors affecting granulation like as size reduction and moisture contents. Also addition Information of drying technology and applicable use of granulation.

KEYWORDS: Granulation, Techniques, factors, Application, Production.

INTRODUCTION[1-4]
Granulation may be defined as a size enlargement process which converts fine or coarse particles. The process in which primary powder particles are made to adhere to form larger, multiparticle that’s called granules.

Reasons for granulation[5-7]
1. To prevent segregation of the constituents of the powder mixture.
2. To improve the flow properties of the mixture.
3. Increase the uniformity of drug distribution in the product.
4. Improve appearance of the product.
5. Improve compression properties of the mixture.
6. To improve the compaction characteristics of the powder.

The effectiveness of granulation depends on the following properties[^8-9]
1. Particle size of the drug and excipients.
2. Type of binder (strong or weak).
3. Volume of binder (less or more).
4. Wet massing time (less or more).
5. Amount of shear applied.
6. Drying rate (Hydrate formation and polymorphism).

Methods of granulation[^5-10]
Generally, there are three methods of granulation.
1. Dry granulation.
2. Direct compression.
3. Wet granulation.

1. Steps involved in dry granulation process are
   1. Milling of drugs and excipients.
   3. Compression into large, hard tablets to make slug.
   4. Screening of slugs.
   5. Mixing with lubricant and disintegrating agent.
   6. Tablet compression.

2. Steps involved in direct compression are
   1. Milling of drug and excipients.
   3. Tablet compression.

3. Important steps involved in the wet granulation are
   1. Mixing of the drug(s) and excipients.
   2. Preparation of binder solution.
   3. Mixing of binder solution with powder mixture to form wet mass.
   4. Course screening of wet mass using a suitable sieve (6-12 # screens).
5. Drying of moist granules.
6. Screening of dry granules through a suitable sieve (14-20 # screen).
7. Mixing of screened granules with disintegrant, glidant, and lubricants.

**FACTORS AFFECTING GRANULATION TECHNIQUE**\(^{[11-13]}\)

1. **Moisture Content**
   Moisture in the wet mass bring cohesiveness. High moisture contents lead to agglomeration of material. Low moisture content lead to generation of fines with large variation in size distribution.

2. **Rheological characteristics**
   The Rheological condition of the wet mass determines the flow ability in extruder optimum. Rheological condition leads to good flow ability in order to extrude the wet mass variation in rheology make improper and non-uniform extrusion.

3. **Solubility of excipients and Drug in granulating fluid**
   A soluble drug get dissolve in a granulating liquid. Thus increasing the volume of liquid phase lead to over wetting of system of agglomeration of pellet sand increase in wetting liquid increases plasticity but induces sticky mass.

4. **Composition of Granulating Fluid**
   Besides water, alcohol, water/alcohol mixture, Ethyl Ether, Dilute Acetic Acid, Isopropyl alcohol is also used as a granulating liquid.

5. **Physical Properties of Starting Material**
   Formulation variable such as type and content of starting material, type of filler and particle size of constituent have the effect on the pelletization process.

6. **Speed of the Spheronizer**
   The speed of the spheronizer affects the size, hardness, sphericity and density of pellets, high speed gives high sphericity, lower friability, smooth surface and higher crushing strength.

7. **Drying technique and drying temperature**
   It is important to get proper size, shape and flow of pellets and it must be reproducible and consistent in all the batches. Variation in pellet's size, shape and flow will lead to difference in physicochemical properties of final dosage form like weight variation, improper filling etc.,
which will further affect the therapeutic efficiency of the delivery system. Wider particle size distribution may lead to variation in the dose of drug delivery. Variation in shape may lead to variation in flow and compressibility.

8. Extrusion Screen
The quality of the Extradite/ pellets is greatly influenced by the characteristics of the orifice of the screen. An increase in orifice dimension resulted in increased mean pellet size.

9. Humidity
Humidity is the amount of water vapor present in the air. Water vapor is the gaseous state of water and is invisible.

10. Density and Porosity
The density of particles, powders, and compacts is an important property affecting the performance and function of many pharmaceutical materials. By definition, all density measurements involve the measurement of mass and volume.

11. Porosity
Porosity Tablet porosity determines the tensile strength (hardness) of tablets for a given composition. Tablet porosity may be regarded as a measure of the tableting process. Consists of volume of the pores relative to the envelope volume used to calculate envelope density.

12. Angle of repose

FORMULA FOR MEASURING ANGLE OF REPOSE

1. $\theta = \tan^{-1}(h/r)$
   here, $h =$height of pile
   $r =$radius of the base of the pile
   $\theta =$angle of repose.

2. $\theta = \cos^{-1} D / (l_1 + l_2)$
   here, $D =$diameter of base
   $l_1 + l_2 =$the opposite sides

Fig. No. 1: Angle of Repose.
GRANULATION MECHANISMS[14-18]

Particle bonding Mechanisms
To form granules, a strong bond must be formed between powder particles so that they adhere not easily breakdown in subsequent handling operations. There are five primary bonding mechanisms between particles: Adhesion and cohesion forces in the immobile liquid films between individual primary powder particles. Interfacial forces in mobile liquid films within the granules; The formation of solid bridges after solvent evaporation; Attractive forces between solid particles; Mechanical interlocking.

Fig. No. 2: Water distribution between particles of a granule during formation and drying.

Fig. No. 3: Mechanism of ball growth during granulation.
How to Factors affecting on granulation like as size reduction and drying

Size reduction
Wet granulation is the process by which powders are converted to granules with the desired properties to ensure good tablet production.

Important considerations are
Type and quantity of Binder
1. Compatibility.
2. Characteristics of drugs and other excipients.
3. Spreading of Binder.
4. Temperature and Viscosity.
8. Type of Granulator.
10. Apparatus Variables.
11. Impeller Movement.
12. Size reduction.

INTRODUCTION OF SIZING[12-17]
Sizing: The size reduction (size reduction, milling, and crushing, grinding, pulverization) is an important step in the process of tablet manufacturing. In manufacturing of compressed tablets, the mixing or blending of several solid pharmaceutical ingredients is easier and more uniform if the ingredients are about the same size. This provides a greater uniformity of dose. A fine particle size is essential in case of lubricant mixing with granules for its proper function. The sizing (size reduction, milling, crushing, grinding, pulverization) is an important step in the process of tablet manufacturing.

Size Reduction Mechanisms
1. Impact - Particle size reduction by applying an instantaneous force perpendicular to the particle/agglomerate surface. The force can result from particle-to-particle or particle-to-mill surface collision.
2. **Attrition** - Particle size reduction by applying a force in a direction parallel to the particle surface.

3. **Compression** - Particle size reduction by applying a force slowly (as compared to Impact) to the particle surface in a direction toward the center of the particle.

4. **Cutting** - Particle size reduction by applying a shearing force to a material.

![Size Reduction Mechanisms](image)

**Impact** — particle concussion by a single rigid force (hammer).

**Compression** — particle disintegration by two rigid forces (nutcracker).

**Shear** — produced when the particle is compressed between the edges of two hard surfaces moving tangentially.

**Attrition** — arising from particles scraping against one another or against a rigid surface (a file).

Fig. No. 4: DIG: Size Reduction Mechanisms.

**TYPES OF MILLS**

1. Ball mill
2. Hammer mill
3. Colloide Mill
4. Cutter Mill
5. Edge runner mill/Roller stone mill
6. Fluid energy mill/Pulverizer
7. Roller Mill

**DRIYING AFFECT ON GRANULATION**[^18-25]

Drying is a mass transfer process consisting of the removal of water or another solvent by evaporation from a solid, semi-solid or liquid. This process is often used as a final production step before selling or packaging products. To be considered "dried", the final product must be solid, in the form of a continuous sheet (e.g., paper), long pieces (e.g., wood), particles (e.g., cereal grains or corn flakes) or powder (e.g., sand, salt, washing...
powder, milk powder). A source of heat and an agent to remove the vapor produced by the process are often involved. In bio products like food, grains, and pharmaceuticals like vaccines, the solvent to be removed is almost invariably water. Desiccation may be synonymous with drying or considered an extreme form of drying.

**How to effect on granulation**

The influence of the drying temperature and granulation liquid viscosity on the inter and intragranular migration of a poorly water-soluble compound in a granulation mass and in a compact was quantitatively assessed. The wet granules were dried in a hot-air oven or compacted prior to drying. The drug concentration at different locations inside the granulated mass and the compacts after drying was determined spectrophotometric ally and by use of diffuse light reflectance measurements. The riboflavin distribution in the granulation masses and in the compacts was characterized by drug-enriched outer layers and drug-depleted inner regions, indicating a strong migration phenomenon. It was clear that the drying temperature had no influence on the inter- and intergranular drug distribution.

In some products having relatively high initial moisture content, an initial linear reduction of the average product moisture content as a function of time may be observed for a limited time, often known as a "constant drying rate period". Usually, in this period, it is surface moisture outside individual particles that is being removed. The drying rate during this period is mostly dependent on the rate of heat transfer to the material being dried. Therefore, the maximum achievable drying rate is considered to be heat-transfer limited. If drying is continued, the slope of the curve, the drying rate, becomes less steep (falling rate period) and eventually tends to nearly horizontal at very long times. The product moisture content is then constant at the "equilibrium moisture content", where it is, in practice, in equilibrium with the dehydrating medium. In the falling-rate period, water migration from the product interior to the surface is mostly by molecular diffusion, i.e. the water flux is proportional to the moisture content gradient. This means that water moves from zones with higher moisture content to zones with lower values, a phenomenon explained by the second law of thermodynamics. If water removal is considerable, the products usually undergo shrinkage and deformation, except in a well-designed freeze-drying process. The drying rate in the falling-rate period is controlled by the rate of removal of moisture or solvent from the interior of the solid being dried and is referred to as being "mass-transfer limited". This is widely noticed in
hygroscopic products such as fruits and vegetables, where drying occurs in the falling rate
period with the constant drying rate period said to be negligible.

**Methods of drying**[26-27]

1. Application of hot air
2. Indirect or contact drying (heating through a hot wall)
3. Dielectric drying (radiofrequency or microwaves being absorbed inside the material)
4. Freeze drying or lyophilization
5. Supercritical drying
6. Natural air drying

**DRYING EQUIPMENT**

**Classification and selection of dryers**

(a) Temperature and pressure in the dryer,
(b) The method of heating,
(c) The means by which moist material is transported through the dryer,
(d) Any mechanical aids aimed at improving drying,
(e) The method by which the air is circulated,
(f) The way in which the moist material is supported,
(g) The heating medium, and,
(h) The nature of the wet feed and the way it is introduced into the dryer.

**Types**

- Tray Dryers
- Tunnel Dryers
- Roller or Drum Dryers
- Fluidized Bed Dryers
- Pneumatic Dryers
- Rotary Dryers
- Trough Dryers
- Bin Dryers
- Belt Dryers
- Vacuum Dryers
- Freeze Dryers
CONCLUSION
Granules enhance the uniformity of the API, increase the density of the blend, facilitate metering or volumetric dispensing, reduce dust, and improve the appearance of product. The granules are formed by the following methods: solid bridges, sintering, chemical reaction, crystallization, and deposition of colloidal particles.

RESULT AND DISCUSSION
Granulation is a technique of particle enlargement by agglomeration in the production of tablets and capsules. During the granulation process, small fine or coarse particles are converted into larger agglomerates called granules. Granules are formed from the powder particles by wetting and nucleation, coalescence or growth, consolidation, and attrition or breakage. Granulation technique is broadly classified into two types, dry granulation and wet granulation, with wet granulation being the most widely used granulation technique. Currently available granulation technologies include roller compaction for dry granulation, and spray drying, supercritical fluid, low/high shear mixing, fluid bed granulation, and extrusion/spheronization for wet granulation. Recent progress includes pneumatic dry granulation technology for dry granulation, and reverse wet granulation, steam granulation, moisture-activated dry granulation or moist granulation, thermal adhesion granulation, melt granulation, freeze granulation, foamed binder or foam granulation for wet granulation.

REFERANCES
1. Shaik, Jayanth Kumar Reddy G. Department of Pharmaceutical Technology, East West College of Pharmacy, B.E.L. Layout, Bangalore- 560091, Karnataka, India.
2. Departments of Pharmaceutics, East West College of Pharmacy, B.E.L. Layout, Bangalore- 560091, Karnataka, India.
3. Department of Pharmaceutics, Satara College of Pharmacy, Degaon, Satara-415004 (MS) India.
4. Department of Pharmaceutics, Yashoda Technical Campus, Wadhe, Satara- 415011 (MS) India.
9. Michael Lavin, Granulation- End point determination and scale up.
11. Detiev Haak. The TOPO granulation technology used in manufacturing of effervescent tablet. HERMES PHARMA, Germany.


