A Review of the Fundamentals of Pharmaceutical Granulation Technology

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ABSTRACT

Powdered particles are glued together to create granules, which are big particle entities. This process is known as pharmaceutical granulation. The granulation technique generally preventssegregation; improvesthe flow property and compaction of the tablet dosage form. In the pharmaceutical industry; employing agglomeration or granulation techniques to create dust free environment and enhance the material's ultimate utility. Pharmaceutical granules are made by mainly two methods wet granulation and dry granulation. Recent and Modern techniques are used in both methods to make the production of qualitatively high and effective granules in pharmaceutical industries. Additives or excipients are chemically and physiologically inert, stable, and compatible with active pharmaceutical ingredients and are essential for the preparation of granules. Mostly the use of diluents, binding agents (for the wet granulation method), disintegrants, lubricants, and glidantsare preferred for the formation of granules. This review article gives fundamental and descriptive knowledge about the conventional technique used in the preparationsof granules as well as explainsthe advanced granulation technology such as wet granulation (reverse, steam, moist, thermal adhesion, melt, freeze, foam) and pneumatic dry granulation technology. The article also provides an overview of evaluation parameters for granules. Granules are evaluated by their morphological characteristics and other parameters like density, porosity, moisture content, friability, and flow property of granules. Moreover; these techniques are used in industries for large-scale production of solid dosage forms.

Key Words: Granules, Pellets, Fluid bed granulation, Thermal adhesion, Roller compactor, Pneumatic granulation

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INTRODUCTION

In the pharmaceutical industry, granulation is the process utilized to produce the big granules that are produced when powder particles stick together [1, 2]. Depending on the purpose for which they are designed, they might have sizes from 0.1 mm to 5.0 mm. These are formed by grouping particles and strengthening their connection. Either compression or the use of binding agents is used to create the bonds. Granules are a specific formulation made up of aggregates of powdered, dried solid particles that may or may not also contain other components called excipients and one or more active medicinal substances. Granules include two different sorts of bonds, slugging and employing binding agents [3].

The pharmaceutical sector used the granulation process in antiquity, but in the current era; most of the pharmaceutical industries have adopted this technique. The Latin term "granulatum," which means grain, is the root of the English word "granulated." Agglomeration procedures are used in several sectors to increase material utility, ease handling, and reduce dust. The process of creating the particles is called granulation. Granulation is necessary to enhance compaction, enhance flow characteristics, and prevent segregation.

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Need for granulation

The key points highlighting the need forgranulation arelisted below:

- To improve powder flow.
- To prevent weight fluctuation.
- To create a consistent combination.
- To prevent homogeneity with weak content.
- To make compactions better.
- To create an environment free of dust.
- To avoid segregation of the powder.
- To enhance the product's appearance.
- To enhance the tablet's compressing capabilities.

Ideal properties of granules

For any formulation; some minimum ideal characteristics or properties are required [4]. In the case of granules, the ideal properties include:

- For improved flow, it should be spherical;
- For content uniformity, it should have narrow particle size dispersion.
- It should be sufficiently dense and moist to fend off cracking and dust buildup during processing.
- It should have a good flow.
- It should have good compatibility.

Mechanism of granulation

Bonds between powder particles are necessary for them to adhere and coalesce into granules. These bonds need to be strong enough to stop the conversion of granules to powder during specific handling processes. The mechanism of granulation is shown in **Table 1**. There are four main types of bonding between particles [5]:

- The forces of cohesion and adhesion among different major particles in stationary liquid films.
- The force at the granule-mobile liquid film interface.
- The formation of solid bridges after a solvent evaporates
- Interlocking mechanisms.

Table 1. Mechanism of granulation

Mechanism of Granulation [6]			
S. No.	**Mechanism**	**Forces**	**Observation**
1.	**Immobile liquid films**	Adhesive forces Cohesive forces	Exist in the bonding of primary particles.
2.	**Mobile liquid films**	Interfacial forces	Required for Strong bonds, essential for solid bridges
3.	**Solid bridges**	Hardening of binder	It is responsible for functioning in wet granulation
4.	**Attractive forces**	Vander Waal and Electrostatics forces	No liquid is required
5.	**Mechanical interlocking**	Interlocking forces	Often fibrous or flat particles

Pharmaceutical pellets

Pellets are tiny (0.5-2 mm) free-flowing spherical units that are formed by pelletizing fine powder or granules of bulk medication and excipients. a tiny, sterile solid mass created by compression and molding that contains a highly purified medication (with or without excipients). a solid dosage form in which the medicine is present as granules to which variable degrees of coating have been applied. This dosage form allows for a reduction in dosing frequency compared to the drug's usual dosage form [6]. The comparison between pellets and granules is shown in **Table 2**.

Advantages of pellets

- They improved the aesthetic appearance of the product.
- They offer uniformity of dose.
- Pellets are used to control the release rate of drugs by coating drug pellets with different polymers.
- The chemically incompatible product can be formulated into pellets and delivered in single dosage form.
- Pellets provide less risk of dose dumping.

Disadvantage of pellets

- Pelletization is a complicated and time-consuming process.
- Difficult to compress pellets into tablets due to the rigid nature of pellets.
- Specialized types of equipment are required for pelletization which rise manufacturing costs.

Table 2. Comparison between granules and pellets

Comparison Between Granules and Pellets		
Characterization	**Granules**	**Pellets**
Definition	Adhesion of powder particles to each other to form large particle entities called granules.	Pellets are small sterile tablets used for implantations.

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Size	size ranges from 0.2 to 4.0 mm.	The size and shape of pellets are consistent and range from 0.5 to 2.0 mm.
Surface	Granules have a rough surface.	Pallets have smooth surfaces.
Porosity	About20-50%	About 10%

Excipient used in granulation methods

Granules are to be prepared for solid dosage forms. The excipients commonly used are diluents, binders, lubricants, glidants, and disintegrants [7-9]. **Table 3** enlists the excipient used in granulation along with their percentage.

1. Diluents

Diluents are also called filler or bulking agents. They may be water soluble or water insoluble. There are no separate diluents for any type of granulation method. Diluents are used in that case when a dose of active pharmaceutical ingredient is very small or the drug dose itself is not sufficient to produce in bulk. Diluents are inert ingredients that are added to enhance the bulk of a tablet to make it the right size for compression.

Example: Microcrystalline cellulose, Lactose, corn starch, Dicalcium phosphate, Kaolinetc.

Ideal properties of diluents

- It must be physically and chemically stable and medically inert.
- It ought to work well with the medication.
- It shouldn't impact the drug's bioavailability.
- It must not be harmful.
- It needs to be inexpensive.

2. Binders

Binders are materialsthatare used to produce granules when the binder isadded to the powder mixture, it hold the powder together and form granules. They are available in dry or liquid form. By creating desired size and hardness granules, they improve the granules' ability to flow freely. The type of tablet formulation affects the choice of binder. For instance, lozenges need a lot of binding agents, but tablets that need to dissolve fast utilize binders in lower concentrations. Examples: Gelatin, PVP, Starch paste, Povidone, Hydroxypropyl cellulose, etc.

3. Lubricant

The lubricant of granules is an equally important step of tablet manufacturing. Lubricants are used to lessen friction between the die chamber wall and the tablet as tablets are expelled from the tablet machine. They aid in preventing tablet formulation from adhering to dies and punches. Lubricants are mixed with granules basically for the purposes:

- To improve the granule flow property.
- To eject intact tablet from die without friction.
- To avoid sticking the tablet to the punch.
- To reduce weight variations during compression.
- To avoid excessive wear of punches and dies.

Examples: Talc, Magnesium stearate, Calcium stearate, Stearic acid, etc.

4. Disintegrants

When a tablet is placed in an aqueous solution, a disintegrant is added to the tablet formulation to speed up the disintegration process. These substances are added to tablet formulation so that tablets get breakup into small fragments after administration in the GIT.

Examples: Starches, Croscamellose sodium, Crospovidone, etc.

5. Glidants

The materials which can decrease the friction between particles and increase their flow characteristics are called glidants. When the flow property of the particle increases, the particle can flow easily from the hopper to the die cavity. The effectiveness of glidants depends on:

- The chemical interaction between the glidants and the powder or granules.
- The physical characterization like particle size, and shape of the components of granules.

Examples: colloidal silicon dioxide, Talcum, etc.

Table 3. Commonly used excipients in Granulation

Excipients Used in Granulation Method		
Function	**Excipient**	**% Used**
1.Diluent	MCC - Microcrystalline cellulose	15-30%
	Lactose monohydrate	Up to 85%
	Dibasic calcium phosphate	Up to 85%
	Mannitol	Up to 85%
2.Binder	Pregelatinized starch	1-5%
	Povidone	1-3%

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	Hydroxy Propyl cellulose	1-3%
	Hypromellose	1-3%
3.Disintegrants	Partly pregelatinized starch	5-20%
	Sodium starch glycolate	2-6%
	Croscarmellose sodium	2-6%
	Crospovidone	2-6%
4.Lubricant	Magnesium stearate	0.5-1%
	Sodium stearyl fumarate	0.5-1%
	Talc/Stearic acid	1- 3%
5.Glidant	Colloidal silicon dioxide	0.1-0.3%

Method for granulation

Generally, three conventional methods are used to prepare granules namely wet granulation, dry granulation, and direct compression [10].

1. *Wet granulation method*

Wet granulation entails combining dry primary powder particles with a granulating solution and rubbing the mixture together. To be removed by drying, the solvent in the granulating solution must be volatile. Common solvents include water, ethanol, and isopropanol, which can be used separately or in combination. In comparison to dry granulation, wet granulation has many more technical and technological advancements. The types of particles that require wet granulation include those with poor flow, low bulk density, and no binding characteristics. **Figures 1 and 2** depict the visual depiction and processes of wet granulation.

It is the oldest and most traditional method of manufacture of tablets. Among the methods, wet granulation is flexible, andis widely used. The method is expensive and requires more manpower and time. The powders are converted into granules through the binding property of liquid binderthe particles form aggregates using adhesive and cohesive forces. Cohesion refers to bonding between like particles and adhesion refers to bonding between unlike particles [11]. However, the fundamental principles involved in the aggregation of particles or enlargement of particles are:

- Intermolecular Forces
- Electrostatics Forces
- Bridging between solid and liquid (Binder solution)

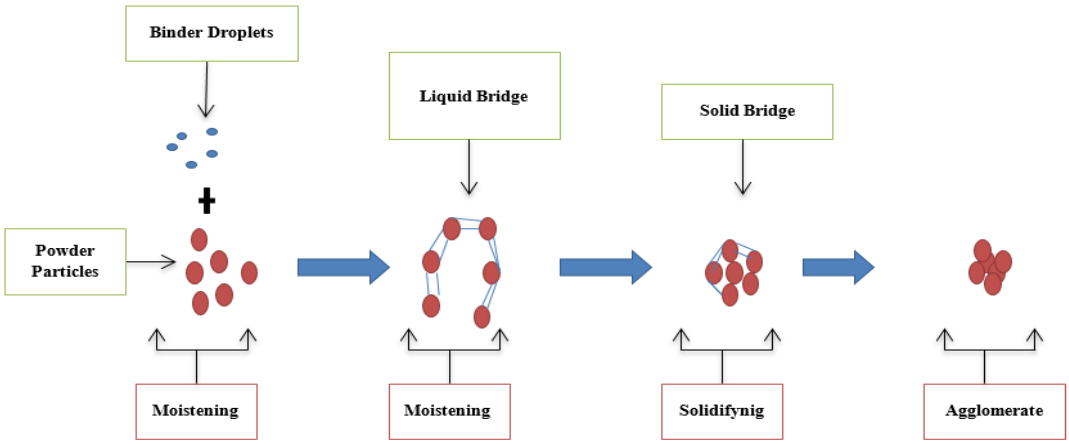

Figure 1. Visual representation of wet granulation

Steps involve in the wet granulation method

The wet granulation method involves the following processing steps:

Figure 2. Steps in wet granulation

1) *Weighing and mixing of formulation ingredients with excipients (excluding lubricant)*
In this stepweighing, and sifting of drug substance (API) and excipients (such as bulking agent, filler or diluents, and disintegrate) are mixed into a powder mixer. These ingredients are mixed using a mixer to get a uniform powder mix.
2) *Preparing the dump mass*
This step involvesa binder solution with the powder mixture to form the dump or coherent mass. While an excessive amount of binder solution results in hard tablets with slow disintegrating properties, an insufficient amount of binder causes poor adhesion, capping, and soft tablet production.
3) *Wet screening*
Use sieve no. 8 or 10 to screen the wet powder mixture. These can be carried out by hand or with the proper tools. The resulting wet granules are evenly distributed on a tray and baked to dry.
4) *Drying of moist granules*
In a hot air oven set to 60°C, the moist granules are dried. Additionally modified are the drying temperature and drying time.
5) *Sizing the granules by dry screening*
To obtain granules of a consistent size, the dried granules are run through sieve no. 20.
6) *Lubrication of granules*
Granules and the appropriate amount of lubricant are combined. At this point, the remaining disintegrant is also added.
7) *Compression of granules into tablets*
The combined grains are compressed in a tablet with a single punch or many stations that areequipped with the proper punches and die.

Advantages of wet granulation
- It allows for the mechanical handling of the particles without affecting the blend's quality.
- Increasing particle size and sphericity improves a powder's flow characteristics.
- Increases and enhances the powder's density homogeneity.
- Both during and after compaction, cohesion is improved, and air entrapment is reduced.
- Less dust and cross-contamination.

Disadvantage of wet granulation
- The procedure is expensive since it requires a lot of people, time, resources, equipment, energy, and space.
- Material loss throughout different processing phases.
- Not suited for medications that are thermolabile or moisture-sensitive.
- Validation and control are challenging because of the various processing steps, added complexity, and difficulty.

- Component incompatibility in formulations is made worse.

Types of wet granulation technique

Wet granulation is a technique thatis used sinceancient times for the preparation of granules followed by compression into tablets. This wet granulation is broadly divided into two types namely – conventional and advanced. The convention method is further subdivided into 3 types i.e. low shear granulation, high shear granulation, and fluid bed granulation. The advanced wet granulation technique as the name suggests uses advanced equipment to achieve improved yield and efficiency. It is further divided into seven sub type's viz. reverse wet granulation, steam wet granulation, moist wet granulation, thermal adhesion wet granulation, melt wet granulation, freeze wet granulation, and foam wet granulation [12]. The description and steps of all these methods are discussed below. The diagrammatic representation of types of wet granulation is shown in **Figure 3**.

Granulators used for wet granulation

The mechanism used to accomplish wet granulation is as follows:

- Binder distribution, nucleation, and wetting
- Growth and consolidation
- Attrition and breakage.

The granulators used are:

- Fluidized bed granulator
- Tumbler granulator
- Drum granulator
- Disc granulator
- Mixer granulator

The description ofthe method of granulation and its application in various fields is listed in **Table 4**.

Table 4. Granulators used in wet granulation technique [13-15]

Sr. No	Name of method	Types	Application
1.	Tumbling granulator	• Drums • Disc	Fertilizers Agricultural chemicals
2.	Mixer and planetary granulator	• Continuous high shear • Batch high shear	Chemicals Detergent Ceramics Pharmaceuticals
3.	Fluidized granulator	• Fluidized bed • Spouted bed • Wurster coater	Chemicals Detergent Ceramics Fertilizers Agricultural Pharmaceuticals
4.	Centrifugal granulator	• Spray drying • prilling	Foods Detergent Ceramics
5.	Compression agglomeration	• Extrusion • Roll press • Tablet press • Molding press • Tablet mill	Pharmaceuticals Catalyst Organic and inorganic chemicals Metals Ceramics

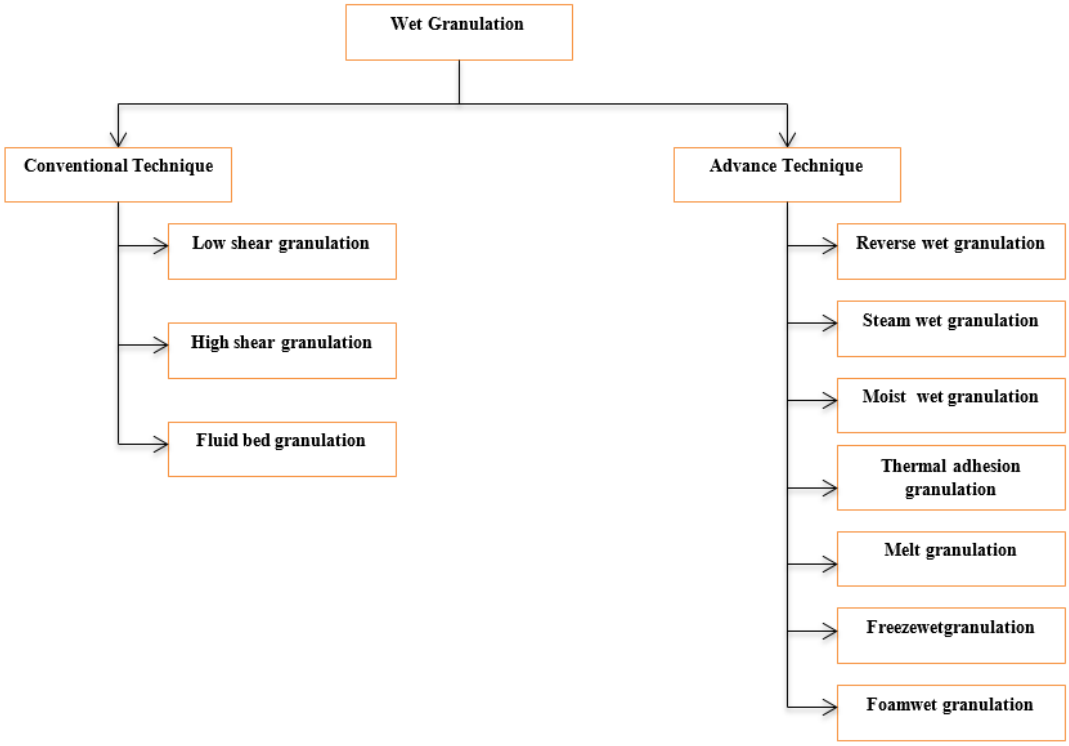

Figure 3. Types of wet granulation Technique

- *Conventional wet granulation technique*

Conventional wet granulation involves generally three following techniques [12, 16]:

Low shear granulation

Utilizing low-speed planetary or trough mixers, the medication and intragranular excipients are typically granulated along with a binder solution. The resultant damp material is screened to create separate granules, which are usually dried in a tray dryer. After being rescreened or milled to the necessary size, lubricated, and compressed, the dry granules are combined with extragranular excipients.

In this scenario, four equipment components are primarily used:

- When a formulation calls for two to three ingredients in the same amount, a planetary mixer can be used in place of a mixer machine to mix the ingredients.
- A planetary mixer creates the paste or wet mass.
- To create the wet grains, an oscillating granulator.
- Dryer to dry the grains that are damp (Tray dryer or fluidized dryer).

Advantage

- The method is not unduly sensitive to changes in the constituent properties of the granules.
- Inspection is frequently able to pinpoint the process's conclusion.

Disadvantage

- In this process having multiplesteps.
- It is a long-duration technique.
- In this technique, several pieces of equipment are needed.
- The substantial material loss that may result from transfer steps.

High shear granulation

High-shear mixes are frequently used in the blending and granulation processes in the pharmaceutical industry. Combining blending and wet massing with high mechanical agitation induced by a chopper and an impeller is used. Two mixing blades are used in high-shear mixer granulators, which is how they are identified. The moist mass is continuously broken up as granulation progresses by a high-speed chopper and an impeller that revolves in the mixer's base. In comparison to low shear granulation, this combination enables very efficient component mixing while using a smaller amount of water.

Advantage

- It is a short processing time technique.
- This method requires fewer amounts of liquid binders compared to a fluid bed.
- The high-shear granulation technique can be used to granulate very cohesive materials.

Disadvantage

- When compared to low-shear granulators, high-shear granulators create less compressible granules.

- Granules that have been overly wetted may develop rather huge lumps.
- When temperatures rise, thermo-labile materials may experience chemical degradation.

Fluid bed granulation

Fine solids are converted into a fluid-like state through the process of fluid bed granulation, which involves interaction with a gas. Spraying a binder solution onto a fluidized powder bed results in fine, homogenous, free-flowing granules through an air suspension process. In this state, it is simple to access individual particles. The liquid is sprayed onto the fluidized powder using spray nozzles (water, binder solution, etc.). Granules are created when particles cling together as a result of surface wetness and, occasionally, the presence of a binder. **Figure 4** depicts the diagrammatic representation.

Advantage

- It is a single-unit system;
- It is a single-unit system;
- Granulation optimization requires substantial development work and is initially costly.
- Fluidized bed systems might not mix powder components thoroughly enough.
- Granulating agents on the surface of particles make them more likely to adhere to equipment filters.

Disadvantage

- Granulation optimization requires substantial development work and is initially costly.
- Fluidized bed systems might not mix powder components thoroughly enough.
- Granulating agents on the surface of particles make them more likely to adhere to equipment filters.

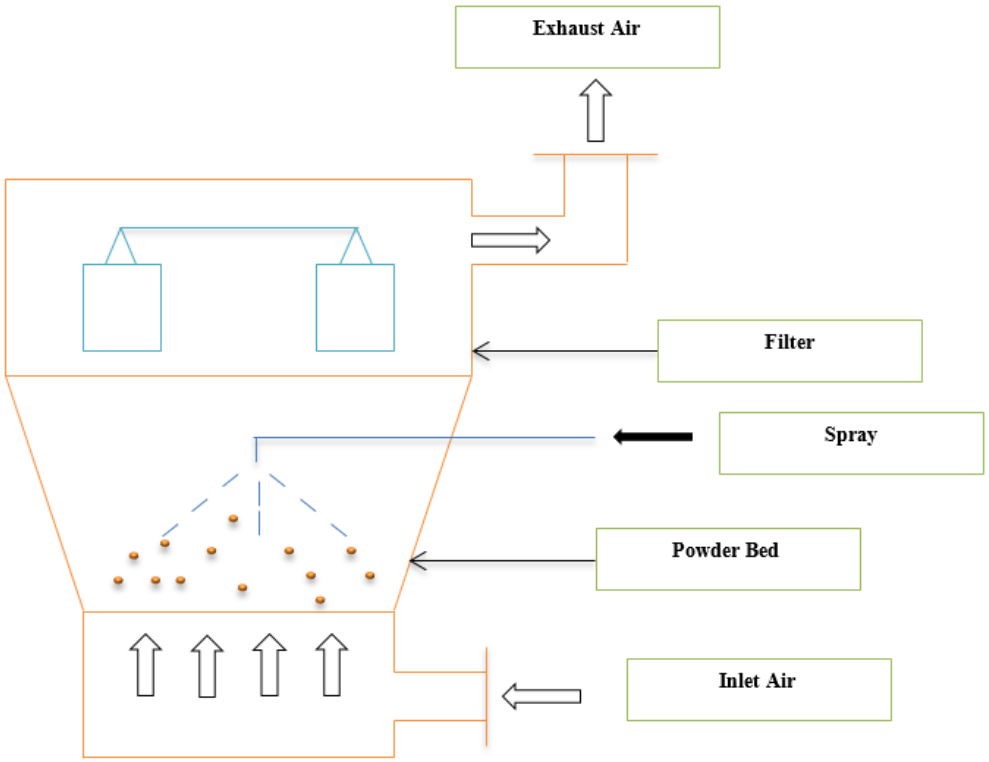

Figure 4. Fluid Bed Granulation Technique.

Advanced wet granulation technique

Reverse wet granulation technique

The traditional granules nucleation method has been superseded by the reverse wet granulation process, which was created and studied and involves dipping dry powder into the binder liquid. The risk of uncontrolled growth and batch loss is lowered as the reverse-phase process moves in the direction of reduced liquid saturation. By enabling consistent binder distribution, it enhances the features of the dissolution of drugs that are only marginally water soluble. The primary mechanisms of the reverse-phase granulation process were the mechanical dispersion of the binder liquid throughout the powder formulation and the breaking up of large wet agglomerates. The liquid saturation and impeller speed regulate the size and porosity of reverse-phase granules.

Advantage

- It enhances the qualities of drug dissolving for poorly water-soluble compounds by facilitating uniform distribution of the binder.

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- Powders with better flow properties.
- This raises the possibility that the medication and hydrophilic polymer will come into appropriate and uniform contact, leading to better dissolution.
- The consistent wetting and disintegration of the granules.

Steam wet granulation

Simply stated, this procedure is a variation of the traditional wet granulation approach. Water vapor is employed as a binder in this method. Pure steam is a clear gas that has a greater rate of particle diffusion and a more favorable thermal balance throughout the drying process. Pure steam takes up around 1,600 times the volume of an equivalent mass of liquid water at ordinary pressure and temperature. After the steam condenses, water forms a thin, heated coating on the powder particles, which evaporates more quickly and with no extra energy required. The diagrammatic representation is shown in **Figure 5**.

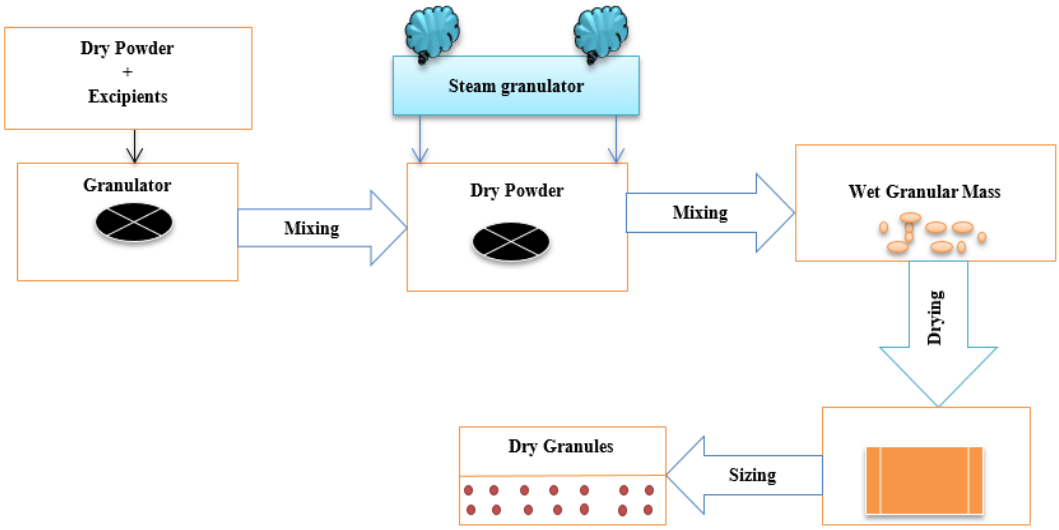

Figure 5. Steam wet granulation process

Advantage

- Evenly distributed throughout the powder's particles.
- More spherical granules form at higher diffusion rates.
- No risks to health.
- Maintain sterility.

Disadvantage

- Requiresspecialized technology for the production and transportation of steam.
- Significant energy inputs are necessary.
- Thermolabile materials are not good candidates.
- More safety measures are required.
- Not suitable for all binders.

Moist wet granulation

Moisture activates dry granulation is another name for moist wet granulation. This method is a variant of the traditional wet granulation method. The granulation of active medicinal compounds that are moisture-sensitive makes extensive use of this technology. Through the use of moisture-absorbing substances like microcrystalline cellulose and a negligibly large amount of granulating fluid, the drying processes are bypassed in this technique. In the moist granulation method, a planetary mixer activates a binder with the least amount of liquid possible. The addition of a moisture-absorbing material then absorbs any extra moisture. The two main steps of this process are aggregation and moisture dispersion.

It comprises using granulating fluid to produce a wet mass, which is then dried using materials that absorb moisture. The moist granulation procedure appears to have the potential to produce formulations with controlled release. **Figure 6** depicts the diagrammatic representation.

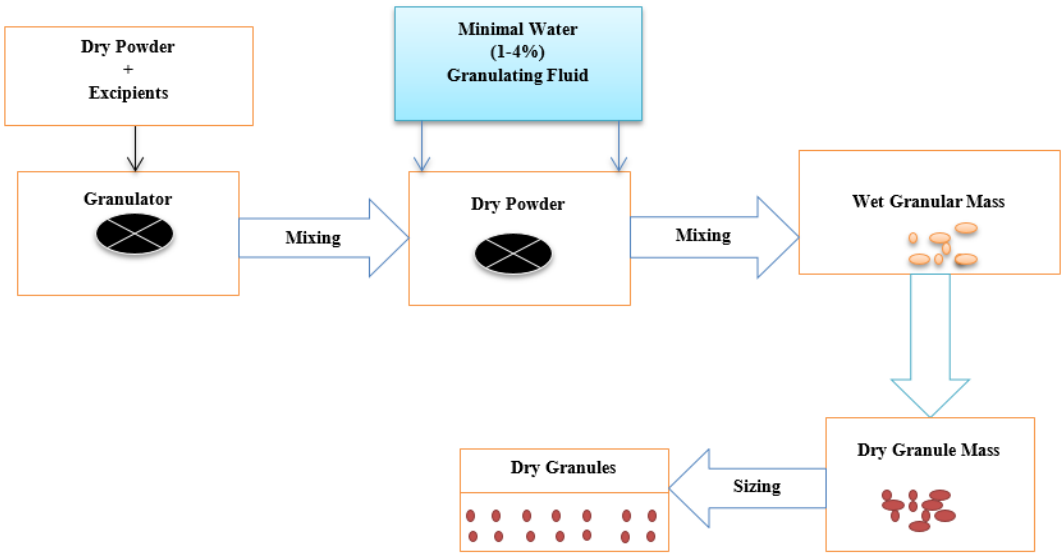

Figure 6. Moist Wet Granulation Process

Advantage

- Suitable for more than 90% of the industry's granulation requirements, including those in the food, pharmaceutical, and nutritional sectors.
- Time-saving.
- Conducive to continuous processing.
- Processing requires less energy.

Disadvantage

- APIs that are highly moisture-absorbing or moisture sensitive are poor candidates.

Thermal adhesion granulation

Taiwan's Taipei-based Wei-Ming Pharmaceutical Company invented this technique. The mixture must be granulated while utilizing very little water or solvents. This approach, which is simple and useful with low moisture and binder concentrations in a closed environment, can be used to produce highly compressible materials or to enhance the undesired qualities of excipients. As granulating liquids, both water and organic solvents are employed. Additionally, heat is used to hasten the granulation process. To aid in the agglomeration of the powder particles, the drug, and excipient mixture is heated in a closed system with tumble rotation to a temperature of 30-130° C. By adding a small amount of granulation liquid, which is primarily absorbed by the powder particles during agglomeration, this approach removes the drying stage. After freezing and filtering, granules with the specified particle size can be produced [12]. It can be used to generate direct tablet formulations. **Figure 7** depicts the diagrammatic representation.

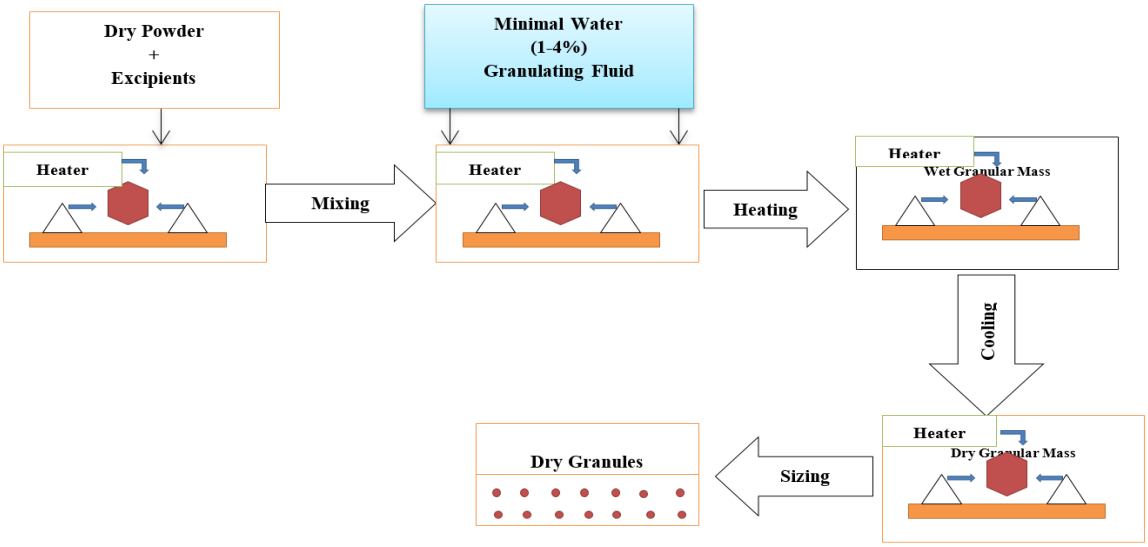

Figure 7. Thermal Adhesion Granulation Process

Melt granulation

Pharmaceutical powders are effectively agglomerated by the melt granulation technique, which uses melted binder components. In this method, binders that melt or soften at temperatures between 50 and 90 °C are used to aggregate powder particles. In the presence of a molten binding liquid, agitation, kneading, and stacking combine solid tiny particles into agglomerates. By cooling the clumped powder and then solidifying the molten or softened binder, granule formation is complete. The absence of water and organic solvents makes this approach superior to conventional granulation. The method is speedier and more energy-efficient than standard wet granulation because there is no drying step. Melt granulation is a viable replacement for existing wet granulation methods for materials that are water-sensitive. A wide variety of dosage forms and formulations, including immediate-release and sustained-release pellets, granules, and tablets, are produced by pharmaceutical companies today using melt granulation technology. **Figure 8** depicts the diagrammatic representation [16].

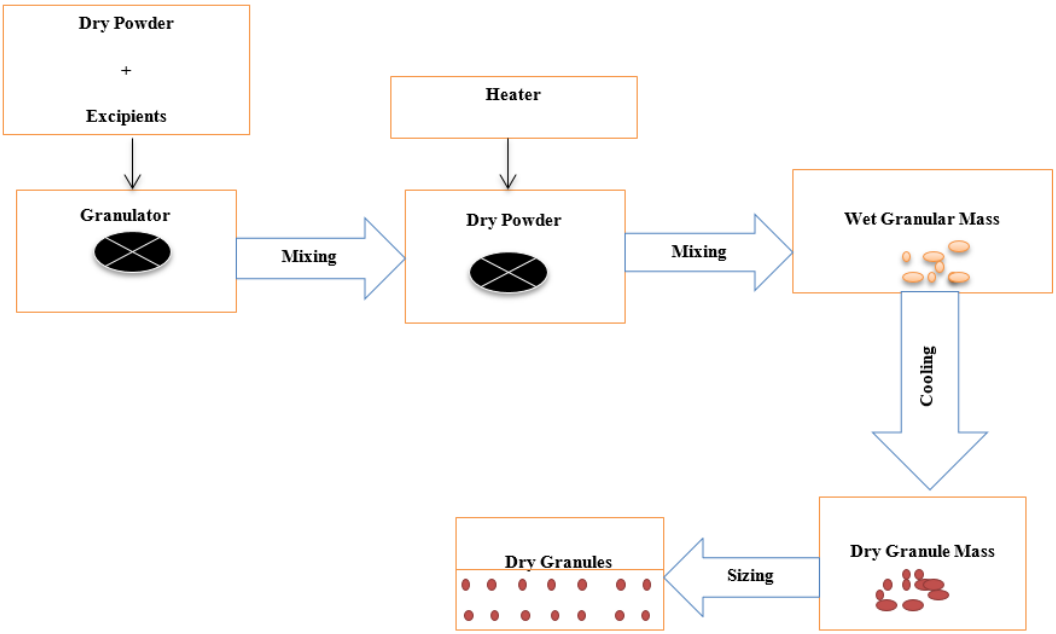

Figure 8. Melt Granulation Process

Advantage

- Time and money-saving method.
- Modifying and controlling medication release.
- Drugs that are water sensitive are suitable candidates.

Disadvantage

- Materials that are sensitive to heat are not good candidates.
- Binders with a lower melting point may melt while being handled or stored.

Freeze granulation

Liquid slurry or suspension droplets are sprayed into liquid nitrogen freeze, followed by freeze-drying to produce freeze grains. Spraying a powder solution with liquid nitrogen causes the droplets to swiftly condense into granules, which are then frozen by ice sublimation and dried by freeze-drying without causing any segregation effects. The diagrammatic representation is shown in **Figure 9**.

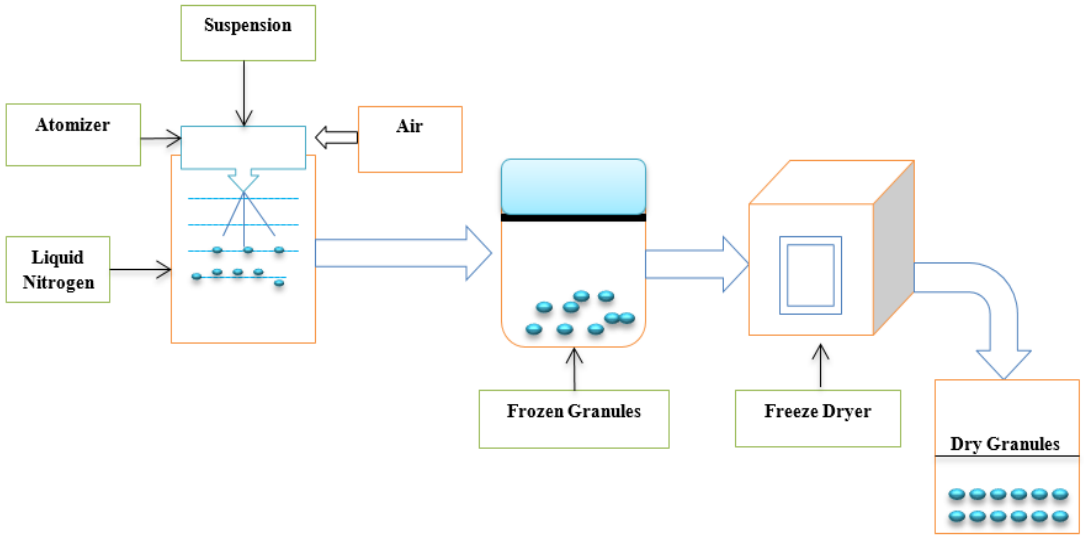

Figure 9. Freeze Granulation Process

Advantage

- Capable of controlling the granule density by preparing granules without voids and adding solids to the suspension.
- Useful for producing granules from suspensions whose homogeneity and particle size must be preserved.
- Improve stability and solubility while minimizing harm to organic compounds.
- Low material waste leads to high product output. Organic solvent recycling

Foam granulation

Foam granulation is adding liquid or an aqueous binder as foam as opposed to spray agglomeration, which involves spraying or pouring liquid over the powder particles. Inconsistent and unexpected binder distribution, which can impact tablet hardness and drug release, is prevented by administering the binder solution as foam as opposed to a spray. In the binder solution tank, a foam generator with a high-shear granulator or fluid bed granulator is employed instead of spraying or pouring the binder onto the moving powder particles.

Advantage

- There is no spray nozzle present.
- Increase the process's resilience.
- Granulation requires less water.
- Time-saving drying, monetary efficient.
- Even distribution of the binder.

- *Dry granulation method*

Slugging and double compression are some names for it. Dry granulation is a straightforward and inexpensive process that is gaining popularity due to these qualities. Using neither heat nor solvent, the powder mixture is compacted during the dry granulation process. The basic powder particles are gathered under great pressure. The dry granulation technique is used to produce granules without the use of a liquid solution due to the probable sensitivity of the substance to be granulated to heat and moisture. The processing steps for the dry granulation method are depicted in **Figure 10**.

Advantage

- It requires less space and equipment and does away with the need for binder solutions, large mixing vessels, and the pricey and time-consuming drying process necessary for wet granulation.
- Since there is no binder holding powder particles together, slugging can be advantageous for materials that are sensitive to heat, moisture, and both, as well as for enhanced disintegration.
- When alternative granulation techniques result in granules with poor flow or compression qualities, this technique is also used.

Disadvantage

- It requires a specialized heavy-duty tablet press to create a slug;
- It does not allow for consistent color dispersion as may be achieved with wet granulation, where the dye can be absorbed into binder liquid.
- When compared to wet granulation, the method tends to produce more dust.
- Relatively high initial capital expenditure for heavy-duty presses or compactors.

Figure 10. Steps in Dry Granulation

1) *Weighing of formulation Ingredients*
The appropriate quantities of ingredients and excipients are weighed on an analytical balance.
2) *Mixing of formulation ingredients*
The formulation components are mixed in a powder mixer until a homogenous powder mix is produced. This stage's application of a half-amount of lubricant enhances powder flow during slugging and prevents crushed powder from sticking to the die.
3) *Compression of mixed powders into slug*
Slugging or precompression are two terms for this phase. The pressure applied to create the slug is typically lower than the pressure applied during final compression.
4) *Milling and sieving of slugs*
In this step, slugs are broken down into smaller bits using a hammer mill or other common milling tools. Screening the mill slugs creates homogeneous grains.
5) *Mixing with disintegrants and lubricant*
Lubricant and other excipients are gently combined after screening to create a consistent mixture.
6) *Compression of granules into tablets*
The mixed granules are compressed into a tablet machine.

Types of dry granulation

Dry granulation is divided into two type's namely conventional and advanced techniques **(Figure 11)**. Conventional dry granulation is further subdivided into two types i.e. slugging and roller compaction. Whereas the advanced dry granulation technique is further divided into one type namely pneumatic dry granulation. The description and steps of these methods are discussed below.

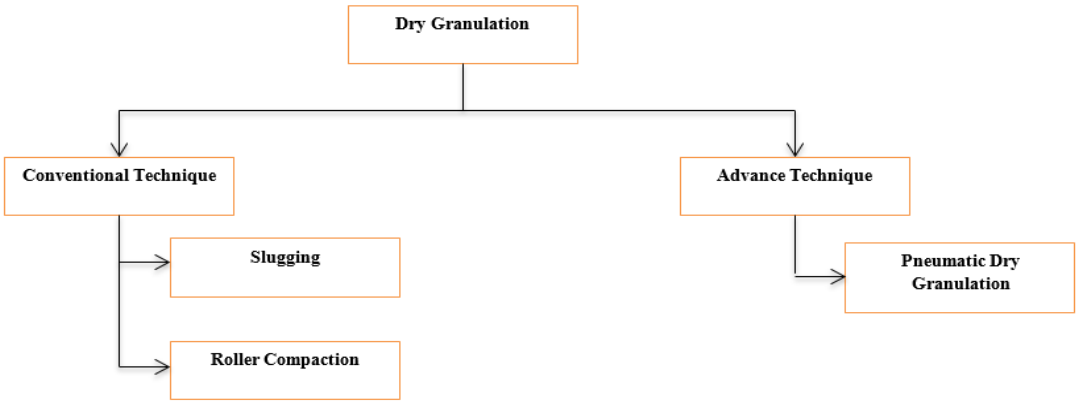

Figure 11. Type of Dry Granulation

➢ *Conventional techniqe*

Slugging

When the dry powder is compressed into tablets using a tablet press with a die chamber that has a large enough diameter to quickly fill it, the process is known as granulation by slugging. The slug's precision or other attributes are not crucial. Only apply the pressure necessary to compact the powder into uniform slugs. Slugs are produced, and their size is then reduced to the right granule size for final compression. The factors that affect a material's slugging capacity

- The matter's cohesion or compressibility.
- Powder compression ratio.
- The powder's density.
- Type of machine.
- Size of punches and dies.
- Slug width.
- Compression speed.
- The pressure used to make the slug.

Roller compaction

A device known as a chilsonator can also be used to condense powder using pressure rolls. In contrast to a tablet machine, a chilsonator continuously and steadily produces compressed material. A spiral auger feeds the powder into the compaction zone by forcing it from the hopper down between the rollers. To create granules, the aggregates are either filtered or crushed. The diagrammatic depiction is shown in **Figure 12**.

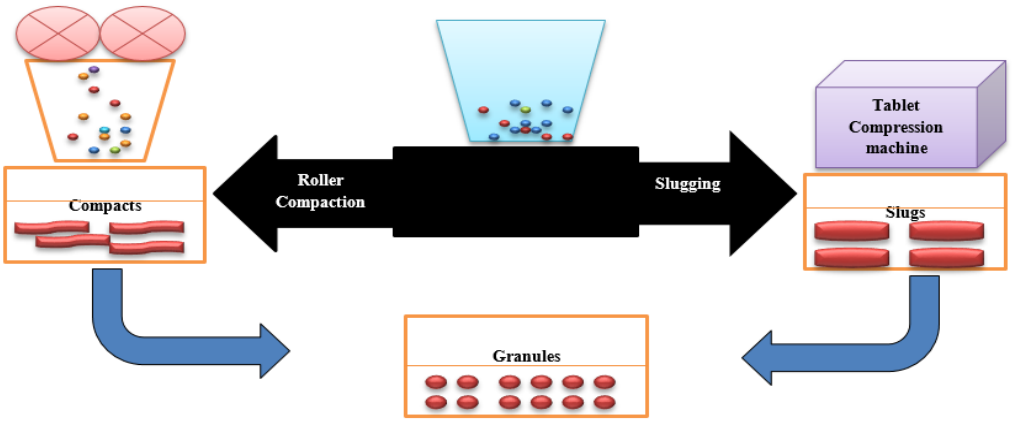

Figure 12. Dry Granulation Techniques

➢ *Advanced technique*

Pneumatic dry granulation

A patent application has been submitted for a new method called pneumatic dry granulation. The granulation process is based on the use of a special air classification technique, very mild compaction force roller compaction, and. Using this method, granules with a remarkable balance of flow ability and compressibility can be created. **Figure 13** depicts the diagrammatic representation. High drug loading can be accomplished with the pneumatic dry granulation technique, even when using challenging APIs and excipient combinations. It serves to hide the taste and has Very Good Stability.

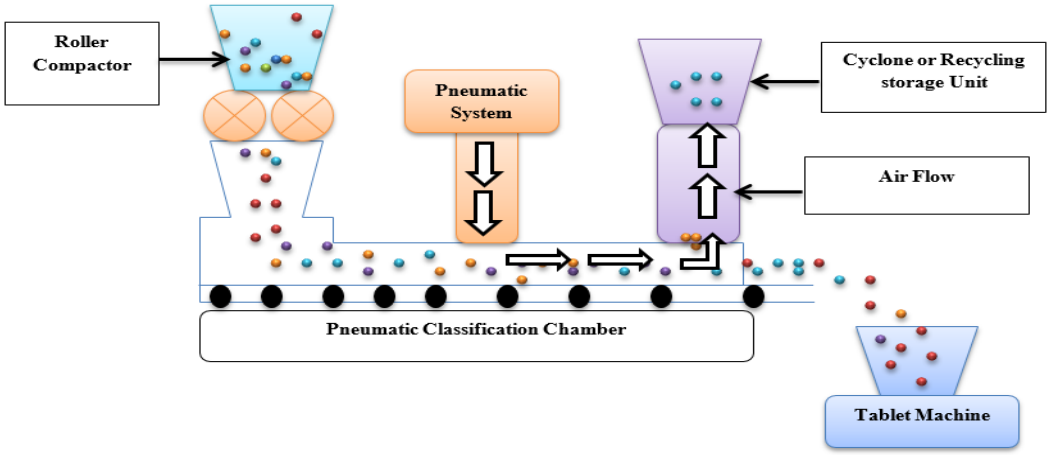

Figure 13. Pneumatic Dry Granulation Process

Advantage

- The closed system is safer than wet granulation because it has lower dust levels, allows for the sterile production or handling of hazardous materials, and produces goods more quickly and at a lower cost. The finished items have a highly stable shelf life.
- Minimal or no material waste.
- Scaling up is simple.
- The generated granules and tablets exhibit quick disintegration characteristics, providing the possibility of fast-release dosage forms.

- *Direct compression*

The process used to make tablets is called direct compression. When it is possible to create a tablet by blending materials and putting them in a tablet press without changing any of the contents, this method is utilized. This is not a very common occurrence since many tablets contain active pharmaceutical ingredients that are either too concentrated to allow for direct compression or because the excipients used in formulation do not contribute to direct compression [11, 12]. The following steps are involved in the direct compression method-

- Weighing and pre-milling of the ingredients used in formulation (API + Excipients).
- Combining the powdered excipients, such as lubricant, with the active pharmaceutical ingredient
- Using a rotary press to compress the combined powders into tablets.

Advantage

- Due to the direct compression's minimal operation requirements, it is more economical.
- A better fit for medicines that are susceptible to heat and moisture.
- Direct compression tablets dissolve notably more quickly, need fewer equipment requirements and processing processes, and have a lower risk of contamination.

Disadvantage

- Direct compression is not suitable for high-dose drugs if it is not easily compressible by itself.
- Low-dose drugs may be uniformly blended.
- Air entrapment during direct compression is sometimes linked to capping, laminating, breaking, or layering of tablets.

Characterization/evaluation of granules

The granules are characterized by their morphological characteristics. Granules morphology can be analyzed conveniently with the help of computer supported imaging system. There is a good correlation between the compressibility of granules and their shape, flow property, packing property, frictional property, and coatability. Some of these correlations are volume shape factor, shape coefficient, and morphological descriptors. The following parameter is used to characterize and evaluation of granules:

1) *Particle size and shape determination*

Granule size has an impact on average weight, weight variation, friability, flow capacity, and drying rate. The processing needs during granulation determine the size and form [16, 17]. The following techniques are used to determine size and shape:

- Sieving and sedimentation rate
- By light scattering and microscopy (SEM).

2) *Density*

Compressibility, porosity, and dissolutions may all be impacted by density. To limit the numberof loose grains visible on the tablet surface, cohesive compacts made of dense, hard granules may require a larger load [18].

Tools for calculating density-

Pyknometer

- Mercury-infused liquid (any solvent of low surface tension)
- Granules' solubility in liquid and ability to infiltrate pores shouldn't be concealed by it.
- By providing the mass of the granulation, density is then calculated from the volume intrusion fluid displaced in the pycnometer.
- Density (D) = $M/V_p - V_i$

Where V_p=Total volume of pycnometer

V_i= Volume of intrusion fluid containing mass (M) requirement to fill pycnometer.

3) *Granules strength and friability*

The Strongness and friability of granules are important because they affect:

- Modifications in granulations' particle size distributions.
- The ability to compress into a cohesive tablet.
- Compressive strength is used to determine the strength and friability of granules by applying the friability measurement.

4) *Flow properties*

For uniform tablet production, the grains must be allowed to flow from the hopper to the die cavity. Granules' flow characteristics are a function of several forces [19, 20].

- Forces of friction
- Mechanical forces brought on by the collision of particles with asymmetrical shapes.
- Forces of electrostatics
- Vander Waals/cohesive forces

Additionally, forces have an impact on the granules' surface area, shape, surface texture, roughness, and

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particle size distribution. When powder particles are 150 m in size, frictional and van der Waals forces dominate.

5) Moisture content

The term "moisture content" refers to how much moisture is found in granules. The granules' typical moisture content is 2%. During compression in the die cavity, the powder or grains must adhere to one another. The amount of moisture is calculated using IR balance or moisture balance. Simple balance makes up IR Balance. A little sample was retrieved from the oven to determine its moisture level, and it was then placed in the moisture balance [21].

Notes on the initial reading should be kept. The moisture in the grains is then evaporated by heating, and we start the IR light. We then record the final reading.

Percent moisture is calculated by-

% moisture content = Initial weight – Final weight

6) Percentage fines

Percentage fines indicate how much powder is still present in the granules. The amount is typically 15% of the fines. If 100% granules are utilized, it will be difficult to retain the hardness of the tablet since there will be free space in the cavity after compression, which will cause the tablet to shatter owing to air [13, 22]. The sieve method can be used to calculate the percentage of fines. The percentage shouldn't exceed 15%.

Application of granules

- In the development of sustained-release dosage forms like tablets and capsules.
- In the development of micro-encapsulation.
- In gene therapy by targeting transgenic proteins.
- Applicable in food industries' formation of egg yolk granules.
- In the manufacturing of polyherbal ayurvedic preparations.

CONCLUSION

Granulation is an important step for drug discovery and formulation of solid dosage forms. These contribute towards 75% of any dosage form which is further compressed to achieve tablets. Their resemblance and similarity with pellets make it difficult to separate. However, some critical parameters can differentiate them. Process ability and product formulation quality may both benefit from technical and technological advances that simplify and improve existing procedures.

In addition to having a significant impact on the economy, time, and product development; there is no doubt that pharmaceutical granulation methods and technology have advanced throughout time. However, pharmaceutical businesses have always had a strong interest in efficient and economical manufacturing techniques, which has accelerated the interdisciplinary scientists of pharmaceutical corporations across the globe in their search for new and improved technologies. During the formulation development process, each drug material presents a unique problem that the formulation development scientists must consider at the method selection stage.

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REFERENCES

[1] Martinez Faller E, Hernandez MT, Hernandez AM, San Gabriel JR. Emerging roles of pharmacist in Global Health: an exploratory study on their knowledge, perception and competency. Arch Pharm Pract. 2020;11(1):40-6.

[2] Soboleva MS, Loskutova EE, Kosova IV, Amelina IV. Problems and the Prospects of Pharmaceutical Consultation in the Drugstores. Arch Pharm Pract. 2020;11(2):154-9.

[3] Sharma S. A textbook of Industrial Pharmacy, 1st Ed. published by S. Vikash and Company (Medical Publisher); 2019. pp.35-44.

[4] Jannat E, Abdullah AA, Md MH, Abdullah BZ, Harun AR. Granulation techniques & its updated modules. Pharm Innov J. 2016;5(10, Part B):134-5.

[5] Divya K, Vamshi G, Vijaykumar T, Sandhya Rani M, Kiahore B. Review on Introduction to Effervescent Tablets and Granules. Kenkyu J Pharmacol. 2020;6:01-11.

[6] Tripathi DK. A textbook of Industrial pharmacy: AComprehensive Approach. Published by Pharma Med Press; 2015. pp.71-102.

[7] Ratul D, Ahmed AB. Pellets and pelletization technique: A critical review. Int Res J Pharm. 2013;4(4):90.

[8] Patil N, Khadse SC, Ige PP. Review on novel granulation techniques. World J Pharm Res. 2016;5(7):1-16.

[9] Iveson SM, Litster JD, Hapgood K, Ennis BJ. Nucleation, growth and breakage phenomena in agitated wet granulation processes: A review. Powder Technol. 2001;117(1-2):3-39.

[10] Hasan MM, Rashid HA, Chadni SH, Alam MJ, Hasna R, Islam MM. Gastro retentive: an innovative drug-delivery system. Int J Biol Pharm Res. 2016;7(5):262-72.
[11] Solanki KH, Tarashankar B, Thakur JH, Patel CA. Recent advance in granulation technology. Int J Pharm Sci Rev Res. 2010;5(3):48-53.
[12] Aulton M. Pharmaceutics: The Science of Dosage Form Design. Edinburgh: Churchill Livingstone; 2000. pp.15-32.
[13] Sahoo CK, Satyanarayana K, Ramana DV, Panda KC. Formulation and evaluation of controlled release tablets of aspirin. AJPTech. 2017;7(4):229-33.
[14] Muley S, Nandgude T, Poddar S. Extrusion–spheronization a promising pelletization technique: in-depth review. Asian J Pharm Sci. 2016;11(6):684-99.
[15] Patel HK. Formulation and Evaluation of Effervescent Tablet of Paracetamol and Ibuprofen. Int J Pharm Res Scholars. 2012;1(I-2):509-20.
[16] Nsel HC, Popovich NG, Allen LV Jr. Pharmaceutical Dosage Forms and Drug Delivery Systems. B. I. Waverly Pvt. Ltd., New Delhi, 1999;6:469-71.
[17] Bandeline FJ. Granulation. In: Liberman HA, Lachman L, Schwartz JB, editors. Pharmaceutical Dosage Forms: Tablets. New York: Marcel Dekker Inc; 1989. pp. 287-92.
[18] Maurya SD, Rawal RK, Jha S, Chauhan PS, Kumar A. Drug Loaded Beads: Current Status. Am J Pharm Tech Res. 2013;3(1):331-7.
[19] Bhusan SY, Sambhaji SP, Anant RP, Kakasaheb RM. New drug delivery system for elderly. Indian Drug. 2000;37(7):312-8.
[20] Patidar A. A Review on- Recent Advancement in the Development of Rapid Disintegrating Tablet. Int J Life Sci Pharm Res. 2011;1(1):7-16.
[21] Sinha VR, Agarwal MK, Agarwal A, Singh G, Ghai D. Extrusion-spheronization: process variables and characterization. Crit Rev Inther Drug Carrier Syst. 2009;26(3):275-331.
[22] Shanmugam S. Granulation techniques and technologies: recent progresses. BioImpacts. 2015;5(1):55-63.