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Comprehensive Review of Modern Techniques of Granulation in Pharmaceutical Solid Dosage Forms

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Comprehensive Review of Modern Techniques of Granulation in Pharmaceutical Solid Dosage Forms

ABSTRACT

This comprehensive review explores modern granulation techniques in pharmaceutical dosage forms along with conventional methods, focusing on dry granulation and wet granulation. Dry granulation techniques, including slugging, roller compaction, and pneumatic dry granulation, are dissected with thorough analyses of their processing methods, advantages, disadvantages, and diverse applications. The article delves into eleven wet granulation techniques, offering insights into high-shear granulation, low-shear granulation, fluidized bed granulation, reverse wet granulation, steam granulation, moisture-activated dry granulation, melt granulation, freeze-dry granulation, foam granulation, thermal adhesion, and twin screw wet granulation. Each method is scrutinized, providing a comprehensive understanding of its processing steps, merits, drawbacks, and practical applications in pharmaceutical manufacturing. The article serves as a valuable resource for researchers, pharmaceutical professionals, and students, offering a nuanced exploration of diverse granulation techniques vital in drug formulation. This synthesis of information aims to enhance the understanding of granulation processes, facilitating informed decision-making in pharmaceutical development and manufacturing.

INTRODUCTION

The term "Granulated" is derived from the "Granulatum", a Latin word denoting a grained mixture. In the pharmaceutical industry in the granulation process, the term "granules" denotes finely powdered particles that aggregate to create a larger, intricate structure.[1] These formations usually range from 0.2 to 0.4 mm. Generally, particles are produced in the range of 0.2 to 0.5 mm., making them well-suited for compression or mixing before compaction.[2] Pharmaceutical granulation plays a crucial role in enhancing drug quality by effectively dispersing agglomerates. Industries employ agglomeration processes not only to minimize dust, to improve handling, but also to optimize the material's overall functionality. The key components of granulation include wetting and nucleation, coalescence or growth, consolidation, and attrition or breakage.[3,4]

Granulation involves the assembly of particles by creating bonds between them through compression or the use of binding agents. For instance, granulated sugar is easier to compress into tablets compared to powdered sugar due to its better flow and compression characteristics.[5] It is crucial to have sufficient fines to fill the void spaces between granules, promoting better compaction, along with optimal moisture and hardness to prevent breakage and dust formation during processing.[6]

Granulation serves the purpose of preventing segregation. The granules encompass a rounded shape to improve flow properties, and enhance compaction.[7]

The key components of granulation are influenced by factors such as spray rate or fluid distribution, as well as the properties of the feed powder and existing granules. The choice of a granulation process hinges on factors like drug physiochemical properties, excipients, desired flow, and release properties.[8]

The pharmaceutical industry witnesses continual evolution in granulation techniques, including roller compaction, spay drying, supercritical fluid, low/high shear blending, fluid bed granulation, extrusion or spheronization. The ongoing advancements and innovations further shape the landscape of granulation processes. Granulation serves various crucial processes.[9] The types of Granulations are showed in the figure1.

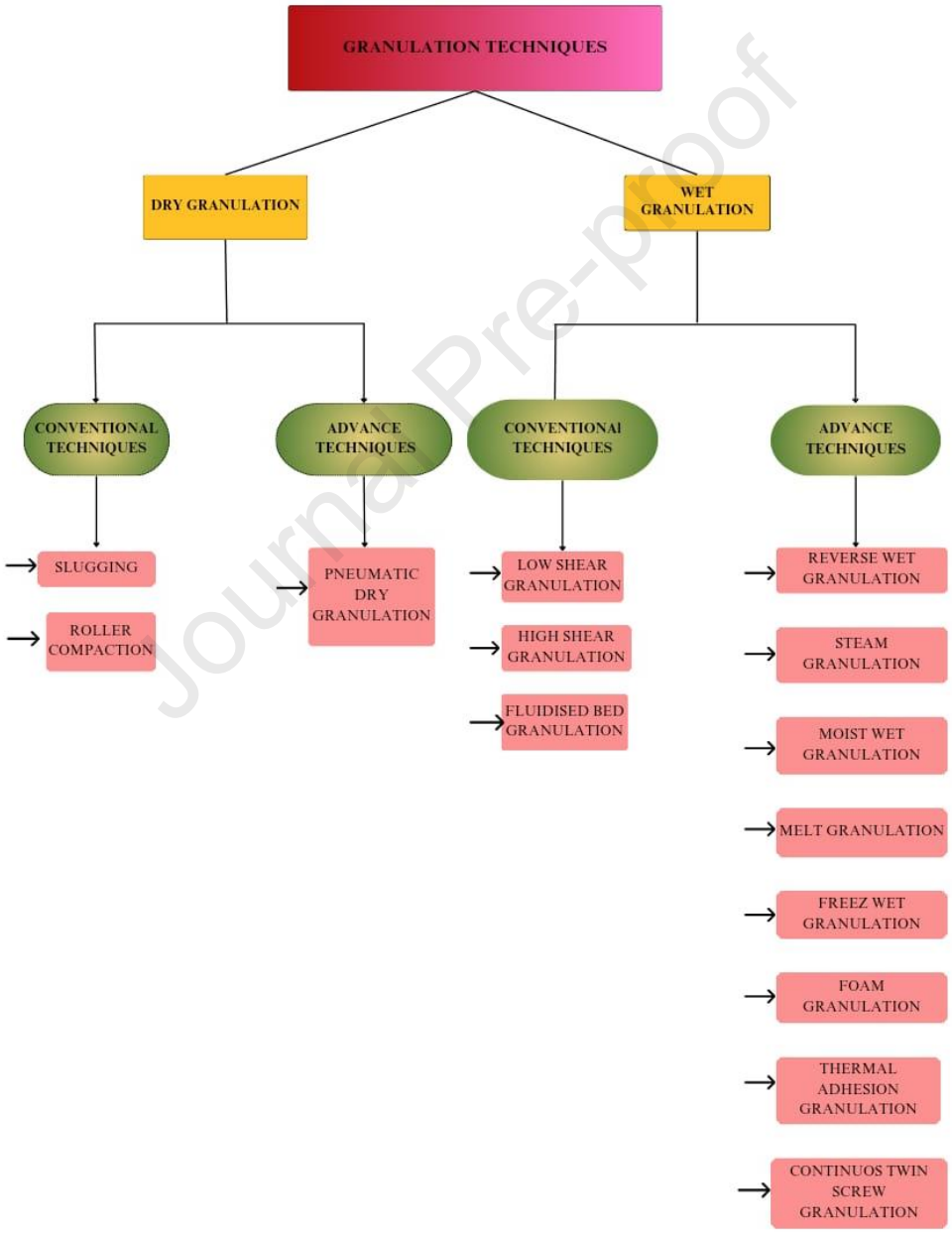


Figure 1 : Types of Granulation Techniques

REASONS FOR GRANULATION [7,8,9]

1. Segregation Prevention
2. Improved Flow Characteristics
3. Optimized Compaction
4. Safety
5. Dust Reduction
6. Consistent Medicine Distribution
7. Mechanical Toughness
8. Compressive Qualities
9. Hygroscopic Risk Reduction
10. Aesthetic Enhancement
11. Space Efficiency

1.DRY GRANULATION

Dry granulation in pharmaceutical manufacturing is a moisture-free process which compresses powdered particles into granules, offering advantages such as preventing moisture-induced degradation in active pharmaceutical ingredients and formulations. This method is an alternative to wet granulation that avoids the use of liquid binders, contributing to product quality and
stability.[10] In the dry granulation process, slugging is employed for tablet formation, especially when ingredients are sensitive to moisture or cannot withstand high temperatures. Referred to as dry granulation, pre-compression, or double compression, this method involves the manufacturing of large tablets known as slugs, which are then compressed through a mesh screen or pressure rolls. The granulated slugs are blended with lubricants and subsequently compressed into tablets. Another approach involves pre-compression.[11]

CONVENTIONAL DRY GRANULATION TECHNIQUE

1.1.SLUGGING

Slugging granulation, is a dry manufacturing technique in pharmaceuticals which is employed to create granules from powdered particles or excipients. This process involves compressing dry powder into uniform slugs, subsequently reducing them to achieve the appropriate granule size for final compression. The primary objectives include enhancing powder flowability, minimizing dust, and attaining the desired particle size distribution.[11]The pros and cons of slugging are illustrated in the figure 3.

1.1.1 Characterization of Slugs: For each batch of the 10 slugs, measurements of individual slug weight and thickness were conducted using a digital micrometer. Subsequently, compaction characteristics were derived. To assess the strength of five of the slugs, a motorized tablet hardness tester was employed.[12]

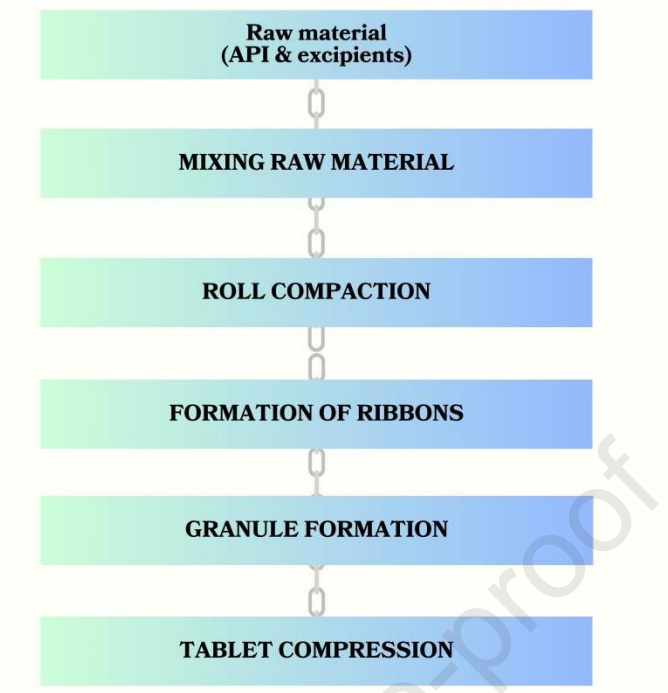


Figure 2: The process of slugging

1.1.2 Procedure

Slugging, is a pre-compression method that is utilized to generate extra-large tablets known as slugs. These slugs often have variable weights due to the poor flow of medication powder. Interestingly, The state of the slug is not a crucial determinant in this approach. The process involves applying the necessary pressure to compact the powder into even slugs. Subsequently, these slugs are reduced in size through screening and milling to achieve the appropriate granule size for final compression. This technique finds application in the dry granulation of hydrolyzable medications like aspirin and metformin, particularly when wet granulation is unsuitable. These medications are recompressed during the process to produce the final tablet.[13]The detailed process of slugging is shown in the figure 2.

1.1.3 APPLICATIONS OF SLUGGING GRANULATION:

1. Aspirin and Maize Starch Mixture:

A Manesty solitary impact tablet press was utilized to compress a mixture of aspirin powder (50 g) and cornstarch (6% w/w) into slug forms at an arbitrary load of 45 units. Subsequently, these slugs were diminished to granules and filtered through a sieve with an opening of 710 micrometers.[14]

2. Lactose Powder Compression:

A large punch and die set were employed to compress lactose powder at pressures of 50, 150, and 270 MNm-2, resulting in cylindrical slugs with a diameter of 38.1 mm. After being removed from the die, the slugs were crushed on a reciprocating granulator before undergoing sieving. This process demonstrated a reduction in lactose slug porosity as the slugging pressure
increased.[15]

3. Alginic Acid, Microcrystalline Cellulose, and OTC Particles:

A typical formulation comprising 1% alginic acid, 78% microcrystalline cellulose, and 21% OTC (oxytetracycline) particles was created using particle residues from the slugging
process.[16]

4. Potassium Phenethicillin :

For the creation of a slug, potassium phenethicillin batch 4277, microcrystalline cellulose (MCC), and magnesium stearate were combined using a planetary mixer. Subsequently, these ingredients were compressed on a single tablet punch instrumented machine.[17]

5. Disulfiram Immediate Release Tablets with Polymers:

Disulfiram immediate-release tablets were developed using the slugging granulation method, incorporating a variety of hydrophilic and hydrophobic polymers. Perceived medication and intragranular materials were prepared in precise amounts, including microcrystalline lactose, silicon dioxide, stearic acid, sodium starch glycolate, and cellulose. The slugs were blended, passed through a multi-mill display (1.5"), and underwent filtering through #20 sieves. Extragranular material was used to combine the final granules. The tablet press involved the use of concave round flat punches on a 12-station rotary machine.[18]

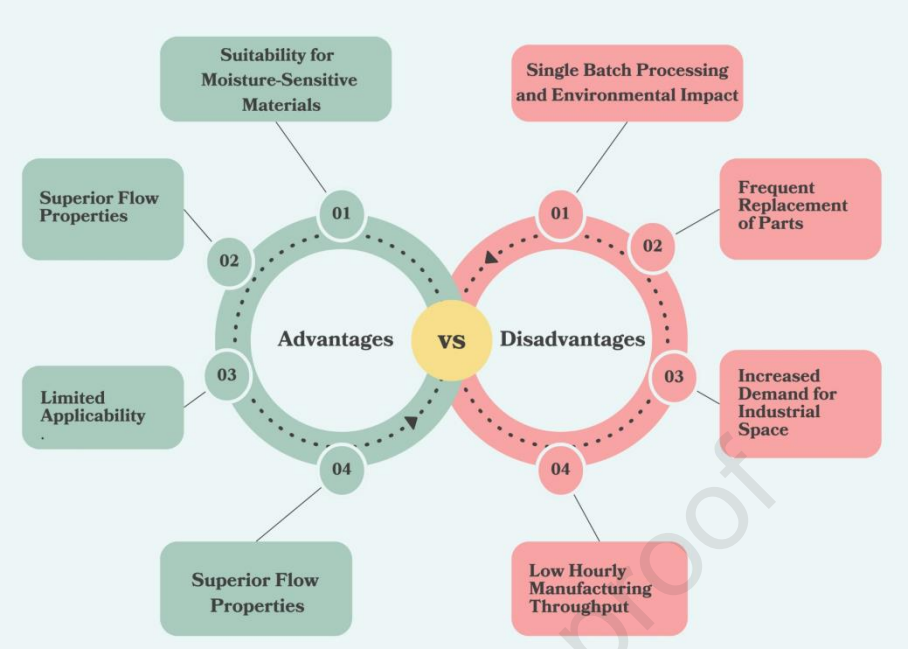


Figure 3: Advantages and Disadvantages of Slugging(19)

1.2 ROLL COMPACTION IN DRY GRANULATION

Roll compaction dry granulation (RCDG) is an agglomeration method utilized across various industries, with a particular emphasis on the pharmaceutical industry. The process involves compressing granules by passing or slugging them between two rolls rotating in opposite directions. Notable advancements in this technique include increased production capacity, enhanced control over operational conditions, and a reduced need for powder lubricants. The intense pressure applied in the roll gap transforms the powder into a condensed structure. When the rolls exhibit smooth, fluted, or knurled surfaces, the substance undergoes compression, forming compact ribbons (flakes, sheets, or strips). In the case of pocket-shaped rolls, the result is briquettes.

The area between the rolls is segmented into 3 zones:

- feeding zone
- compaction zone
- extrusion zone.[19]

Roll compaction stands as a well-established continuous granulation technique, particularly suitable for components that are vulnerable to heat and water exposure or those with inadequate blending mobility. The characteristics of the granules produced are significantly influenced by compaction force, roll gap width, and roll speed.

Understanding this relationship early in the roller compaction process is crucial for designing robust medicinal formulations. Recent years have witnessed a growing interest in drug development process and have shown the importance of refining and optimizing roll compaction techniques.[20]

1.2.1 Roller Compaction Process for Microcrystalline Cellulose: The roller compaction process for creating microcrystalline cellulose involves utilizing Dicalcium phosphate dihydrate, Emcompress Premium, and Ligamed MF-2-V magnesium stearate.

Here's a detailed breakdown of the process:

1. Equipment Used:
A Gerteis Nano-Polygran roller compactor was applied to produce strips using a celestial granulator. Ribbons were generated utilizing a compaction emulator and an oscillating grinder.
The resulting striplets were then treated through a Frewitt Oscillo Witt-Lab.
2. Granule Collection:
Granules from each manufacturing process were gathered using a Medel-Pharm Styl'One Evolution and a Micromeritics Geopyc 1365. Each sample of mass was calculated using a Mettler Toledo high precision balance.

3. Granule Size Determination:
Laser diffraction was utilized to determine the granule size distribution. Three duplicates of the experiment were carried out to ensure accuracy. The sample size distribution was determined using a Malvern Panalytical Mastersizer for laser diffraction, with a predicted dry powder dispersion rate of 50%.

4. Additional Analysis:
To further analyze the granules, they were subjected to a laser scanning electron microscope. This step helped determine the apparent density of the granules and their size distribution.[21] This comprehensive approach ensures a thorough understanding of the characteristics of the microcrystalline cellulose produced through the roller compaction process.

The Complete Procedure is shown in the Figure 4.

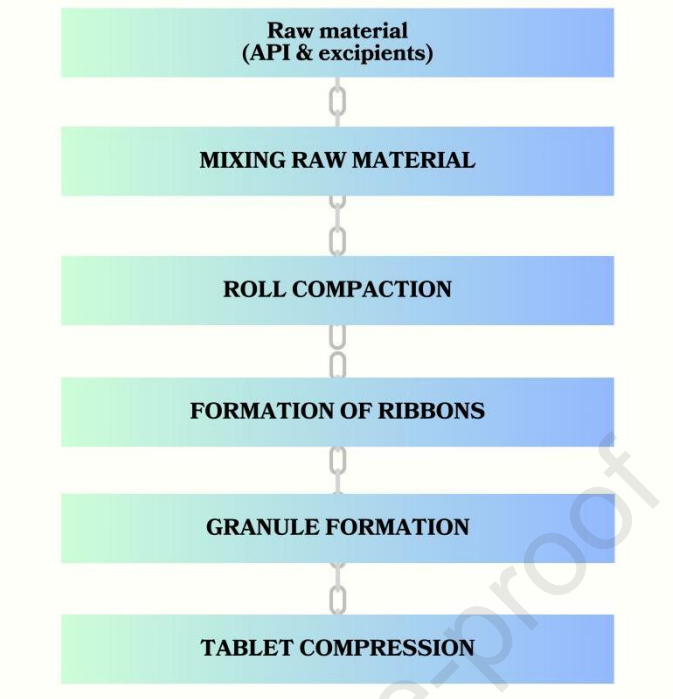


Figure 4: The Procedure of Roller Compaction

1.2.2 APPLICATIONS OF ROLLER COMPACTION

1.Binder Effects on Properties (1966):

Jaminet and Hess conducted a study on the influence of various binding agents on briquettes, granules, and tablets. The introduction of ethylcellulose enhanced strength, while carbowax 4000 had a reducing effect. The particle size distribution of the granules was impacted by the process parameters employed during dry granulation.[22]

2.RCDG Application to Pharmaceutical Powders (2007):

Parrott employed RCDG on eight distinct pharmaceutical powders utilizing a concavo-convex roll compactor at a pressure of 140 kg/cm2. The roll compacting system utilized in this instance demonstrated superior compression uniformity compared to traditional roll compressors. Funakoshi et al. investigated the variables influencing the distribution of compacting pressure throughout the procedure.[23, 24]

3.Employment of Acoustic Emission for Detecting Overcompaction (Preparation of Excipients):

Hakanen and Laine utilized acoustic emission in roll compaction to identify overcompaction in microcrystalline cellulose. They observed a 'capping' phenomenon at a compaction force of 30 kN.[25]

4.Influence of Roll Compaction on Granule Friability(Compaction of Lactose):
Inghelbrecht and Remon investigated the effects of roll compaction on the granule friability of four lactose variations, employing a second-order polynomial model. Optimal quality resulted from high pressure and low horizontal screw speed, but the compaction of spray-dried lactose posed challenges.[26]

5.Compaction of Pharmaceuticals and Formulations:
Inghelbrecht and Remon compared seven microcrystalline cellulose (MCC) types with ibuprofen as a model drug for fragmentation. The addition of 25% ibuprofen enhanced granule quality, and higher concentrations further improved it. The study revealed that a minimal amount disrupted MCC binding properties, but higher concentrations compensated for it.[27]

6.Granulation of Herbal Dry Extracts:
In their research, Rocks Loh and team delved into improving the crushing strength and disintegration time of tablets containing high-dose plant extracts. They explored the use of different fillers, disintegrants, lubricants, and glidants for optimization. The study included a comparison of tablets made from distinct plant extracts and granulated plant extracts. Interestingly, the findings highlighted that artificial neural networks (ANN) proved more effective in characterizing the factors influencing crushing strength and disintegration time compared to the conventional multivariate method (PLS), which showed limited predictive ability. This underscores the significance of innovative approaches in pharmaceutical research.[28] The Figure 5 Highlights the Advantages and Disadvantages of the Roller Compaction.

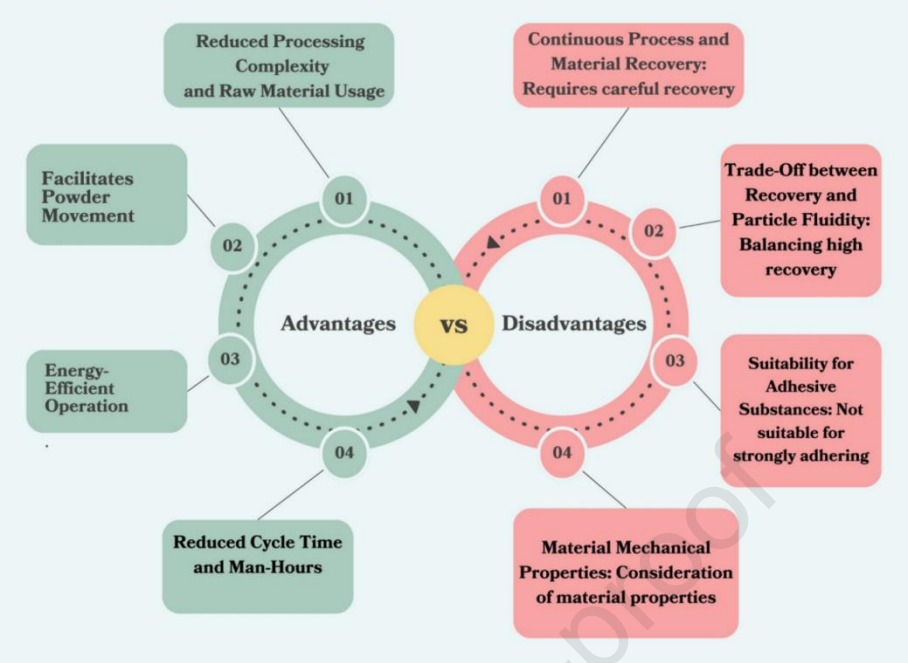


Figure 5: Advantages and Disadvantages of Roller Compaction(29,30)

ADVANCED DRY GRANULATION TECHNIQUE

1.3 THE PNEUMATIC. DRY GRANULATION (PDG)

The pneumatic dry granulation (PDG) process stands as an creative and patented technology utilizing Roller compaction and a distinctive technique of air classification. This approach yields granules with remarkable Flow characteristics and compressibility. PDG Technology offers adaptability in adjusting drug loading, disintegration time, and tablet hardness, catering to the requirements of heat-labile and moisture-sensitive drugs. The technology generates porous granules with outstanding compressibility and flowability, applicable to a wide range of pharmaceutical solid dosage ingredients [31].

While wet granulation remains the most prevalent method, its limitations become apparent with moisture and heat-sensitive drugs, coupled with cost-intensive, laborious, and time-consuming processes. PDG Technology emerges as a solution to these challenges, showcasing superior properties compared to wet granulation and dry granulation. The resulting granules exhibit notable compressibility and flowability without the need for exotic and costly excipients.

PDG Technology stands as a pivotal solution for pharmaceutical companies grappling with challenges in developing solid oral dosage forms. It presents advantages of accelerated development and enhanced quality. Rooted in classical rotary granulation (RC),PDG (Pre-Drying Granulation) substantially expands the possibilities of dry granulation by attaining improved flowability at a low ribbon density, consequently enhancing the compatibility of the resulting dry granulation. This paper provides a glimpse into PDG technology, highlighting its potential advantages through an experimental illustration [32].

1.3.1 Pneumatic Dry Granulation (PDG) Process:

In PDG, a roller compactor delicately compresses powder particles, forming a cohesive mass comprising fine particles and granules. A pneumatic system is then employed to segregate grains within the desired size range in a fractioning chamber. Remarkably, PDG allows for substantial drug loading, ranging between 70% and 100%.The Process of PDG illustrated in Figure 6.

The sequential unit operations integral to the dry granulation process encompass:

1. Milling APIs and Excipients: Creating powdery substances.
2. Combining Powder Mixture: Blending the powder components.
3. Consolidation: Forming thick, rigid Solid dosage forms.
4. Ribbons: Achieving the correct size of the particle.
5. Blending with Lubricants and Diluents: Enhancing flowability.
6. Compression of Tablets: Finalizing the tablet formation [33].

The PDG is very useful and its advantages and disadvantages are discussed in Figure 7.

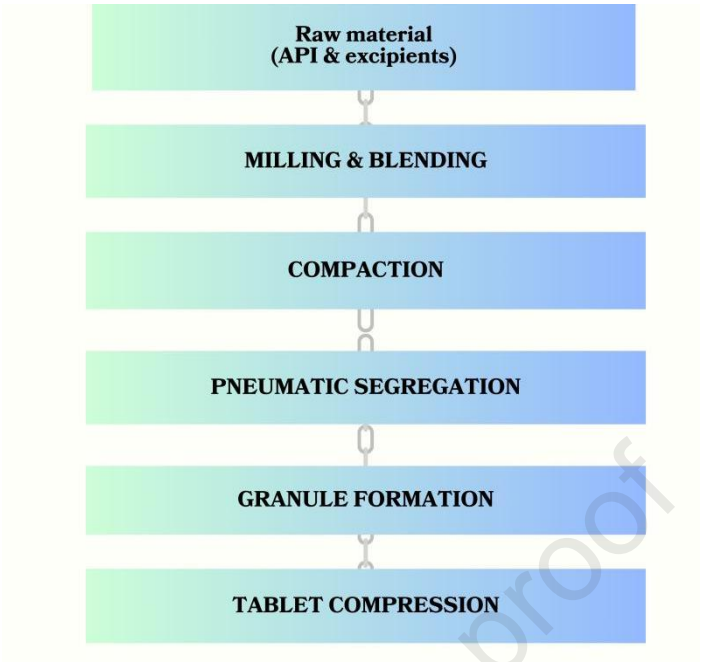


Figure 6: Schematic diagram of the Pneumatic Dry Granulation Process

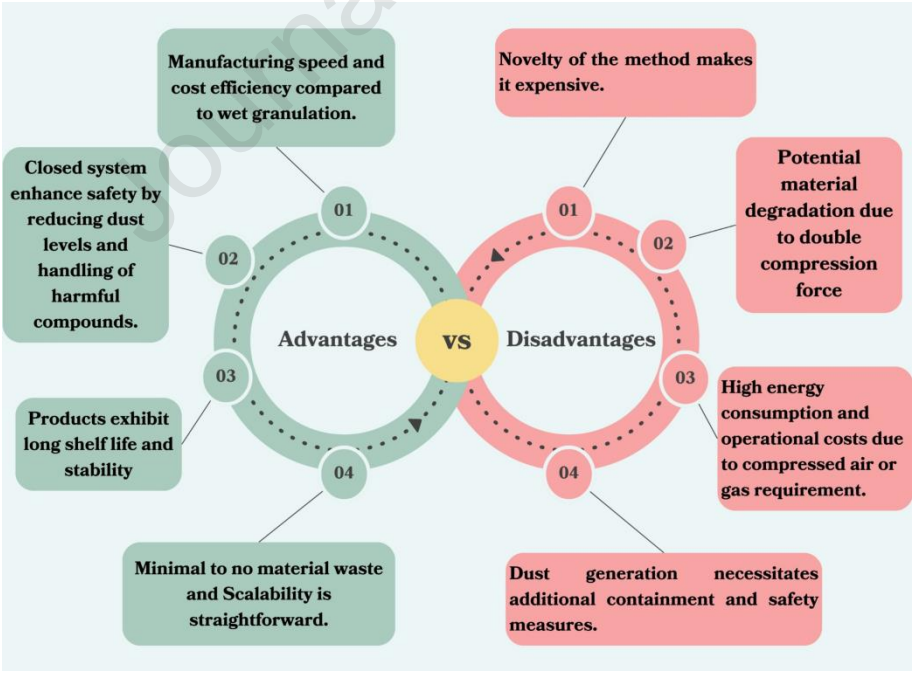


Figure 7: Advantages and Disadvantages of Pneumatic Dry Granulation [34,35]

2. WET GRANULATION

Wet granulation, a widely followed procedure in pharmaceuticals and nutraceuticals, aims to improve the technological characteristics of powders, including flowability, compressibility, and dosage precision. This technique involves introducing a liquid binding agent to the powder through apparatus like tumbling granulators or fluidized bed granulators, fostering through particle agglomeration. The physical alterations of powder particles, instigated by nucleation, agglomeration, and breakage occurrences, impact granule features such as density and size distribution. In the primary phase, nucleation involves wetting a dry powder bed as the binder is sprayed, culminating in the formation of small granules. Subsequently, agglomeration encompasses collisions between granules, increasing their compaction and size. Breakage transpires when sizable or fragile granules undergo deformation or rupture due to shear and impact forces, giving rise to minute particles that reintegrate into the cycle. These operations simultaneously unfold in the granulator vessel, under the sway of formulation variables (binder viscosity, liquid-solid surface tension, particle size distribution, and friction) and process variables (equipment type, binder volume, flow rate, method of binder addition, impeller rotation speed, and process time).[36]

Stages in Wet Granulation Process:

a. Blending pharmaceuticals and excipients.
b. Creating a binding solution.
c. Combining the binding solution with the powder amalgamation to generate a wet mass.
d. Preliminary screening of the wet mass utilizing an appropriate sieve (6-12 # mesh).
e. Desiccating the damp granules.
f. Sifting the dry granules through an appropriate sieve (14-20 # mesh).
g. Blending sifted granules with disintegrates, glidant, and lubricant [37]. The General Mechanism of Wet granulation is shown in the figure 8.

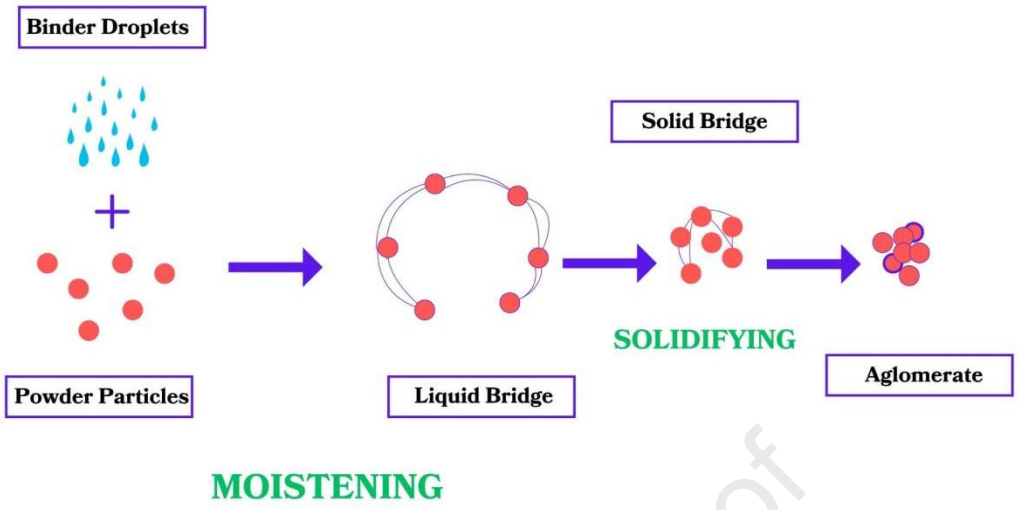


Figure 8 : Schematic diagram of wet granulation

CONVENTIONAL WET GRANULATION TECHNIQUE

2.1 HIGH SHEAR MIXTURE GRANULATION.

High shear mixture granulation is a Globally employed process in the pharma industry, serving purposes like blending, granulation, and densification. These processes are achieved through mechanical agitation facilitated by an impeller and chopper. This method stands out for its ability to handle wet, sticky materials, spread thick binders effectively compared to tumble granulators, and its resilience to operating conditions. Moreover, it excels at producing small, high-density granules with dimensions less than 2 mm. The powder motion in high shear granulation can be observed in both batch and continuous operations, categorized into horizontal axis and vertical axis granulators. The Figure 9 presents the Advantages and disadvantages of the High shear granulation.

A) Horizontal Axis Ploughshare Mixers:

Forrest et al. conducted a study on particle motion within horizontal axis ploughshare mixers, utilizing plate-shaped calcium hydroxy-phosphate and resin beads. They observed that particle state is influenced by ratio of relaxation time to blade time. A lower ratio causes the bed to rest, while a higher ratio induces movement. In addition, a low speed circulator zone was identified, where uncarried material falls into the blade's space. Laurent et al. conducted PEPT experiments using a horizontal axis mixer,

observing axial circulation zones through a 600 micrometres radioactive resin tracer and a 600 micrometers cylindrical shell stirred by a single blade.

B) Vertical Axis Ploughshare Mixers:

Wellm's study on a 0.3m diameter high shear mixer granulator revealed that the powder moves in the direction of the running blade, albeit at a slower pace. The particulate mass displayed a toroidal vortex motion, rising and falling near the mixer's axis. Fast Fourier transform analysis indicated that the speed of solids is dependent on blade speed, design, properties of the solids, & fill level. Interestingly, the speed of disc impeller did not significantly affect powder movement [38].

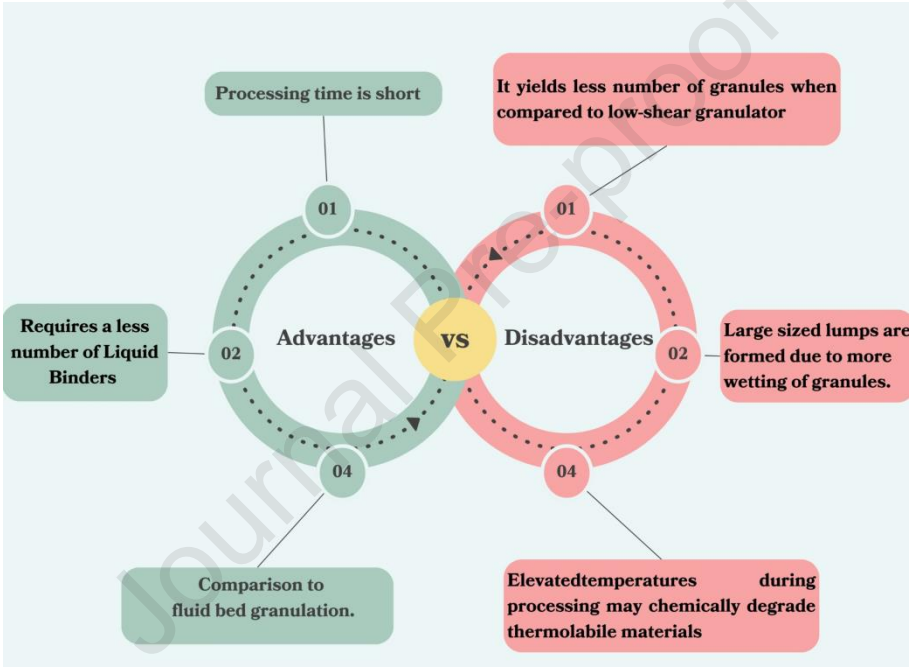


Figure 9 : Advantages and disadvantage of high shear mixture granulation.

2.1.1Applications

1.In practical studies, condenser microphones were strategically positioned on a PMA-10 high-shear granulator, targeting various sound sources such as air exhaust, bowl, and motor [39].

2.Microcrystalline cellulose (MCC), recognized for its high hygroscopicity, is extensively used as a pelletization agent. Simultaneously, lactose, a common excipient in the pharmaceutical sector, contributes plasticity to the mixture [39].

2.2 LOW SHEAR GRANULATION

In the landscape of wet granulation, diverse apparatus assumes unique roles. The integral mixer machine is pivotal for achieving a thorough blend of ingredients; nevertheless, it can be excluded in formulations where two to three components are in equal proportions. The versatile planetary blender comes into play for the formation of a wet mass or paste, contributing significantly to the granulation process. An essential component, the oscillating granulator, finds application in the actualization of wet granules. Following this phase, a dryer takes center stage, playing a vital role in the drying process of wet granules, offering alternatives such as tray dryers or fluidized dryers. [47] The Advantages and Disadvantages are visualized in the Figure 10.

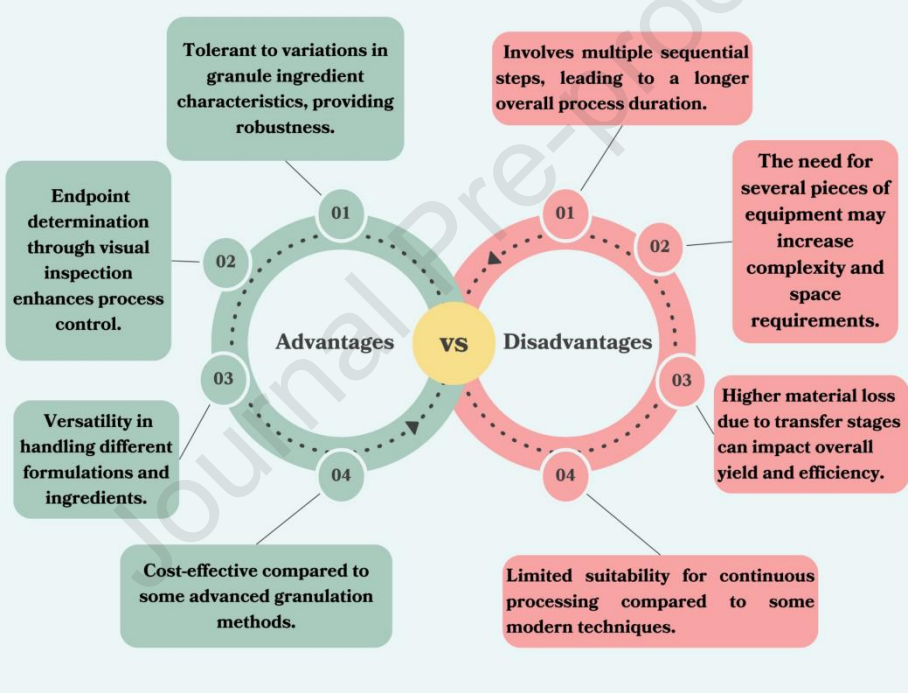


Figure 10: Advantages and disadvantage of low shear Granulation

2.2.1 Application : According to literature, Hydroxypropyl methylcellulose (HPMC) granules were produced by applying distilled water as a liquid binder on powders using a low-shear
granulator.[42]

2.3 FLUIDIZED BED GRANULATION

Fluidized bed granulation is a widely employed technique in the manufacturing of solid pharmaceutical Dosage forms, providing efficient blending, high thermal & mass transfer rates, and maintaining a uniform temperature throughout the bed. This process involves the spraying of droplets of a granulating solution onto the surface of fluidized granules. The particles undergo conversion into solid bridges, adhering to each other and forming agglomerates or granules. The schematic representation of Fluidized bed granulation shown in the figure 11. One of the primary advantages of fluidized bed granulation is the uniform and consistent formation of granules, ensuring homogeneity in the final product. The Complete Advantages and disadvantages of Fluidised Bed Granulation is shown in the Figure 12. The technique also facilitates the efficient mixing of ingredients, contributing to the overall quality of the granulation. Additionally, fluidized beds offer high heat and mass transfer rates, promoting desirable granule properties. The controlled temperature maintenance prevents localized overheating, and the process reduces agglomeration issues through the formation of solid bridges with the granulating solution. Fluidized bed granulation is versatile and adaptable to various formulations, proving particularly effective for solid dispersion manufacturing. However, it comes with challenges, including the potentially high cost of equipment acquisition and maintenance, the requirement for skilled operators, limited scalability, dust generation necessitating additional safety measures, unsuitability for heat-sensitive materials, and relatively higher energy consumption compared to some alternatives.[40]

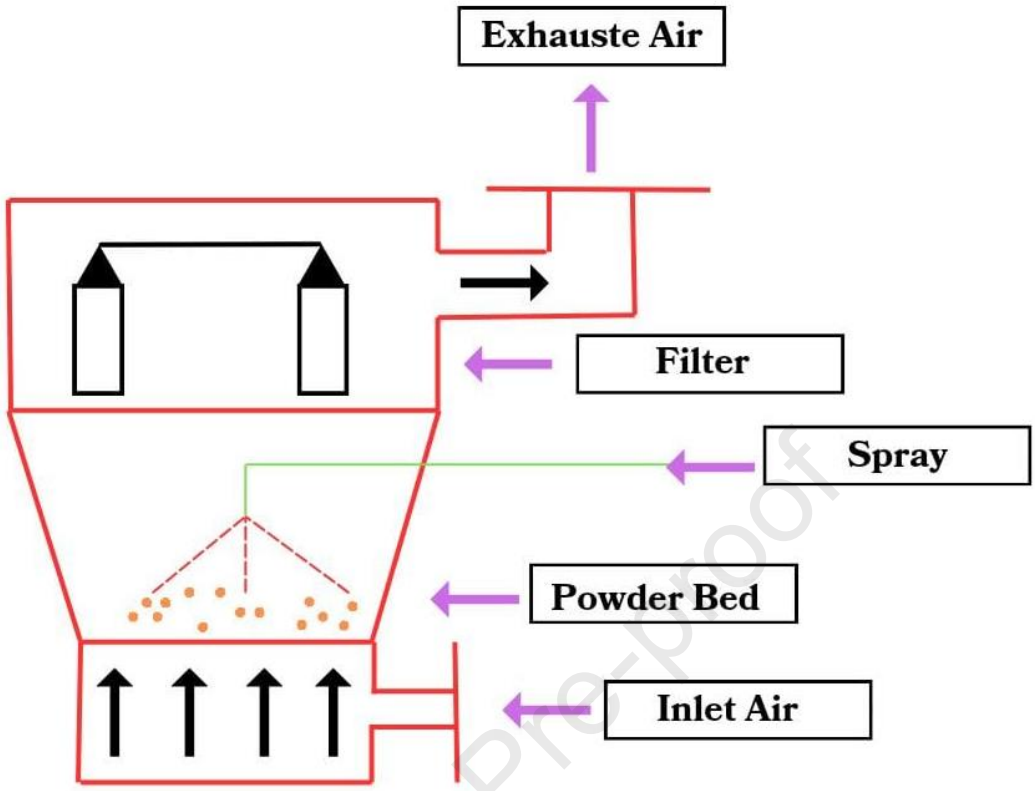


Figure 11: Fluidized bed Granulation

2.3.1 Principle:

Fluidized bed granulation is an integral part of tablet manufacturing, encompassing coating, drying, & granulation processes in a continuous manufacturing line. The technique involves the spraying of a binder solution onto a powder bed, where particles are suspended in an air stream, becoming wetted by granulating or binder solution and subsequently colliding. This process operates through two key mechanisms: surface tension at the interface and hydrostatic suction.

Fluid bed granulation serves to enhance the solubility and dissolution rate of poorly water-soluble drugs. However, controlling critical factors such as bed moisture level and granule microstructure poses challenges. Excessive granulating solution can result in wet quenching, while overly pronounced particle growth may lead to dry quenching. The procedure demands continuous pre-blending, wetting, and drying of particles, making it a complex process.

2.3.2 Types of Fluid Bed Granulation:

1. Top Spray Granulator:

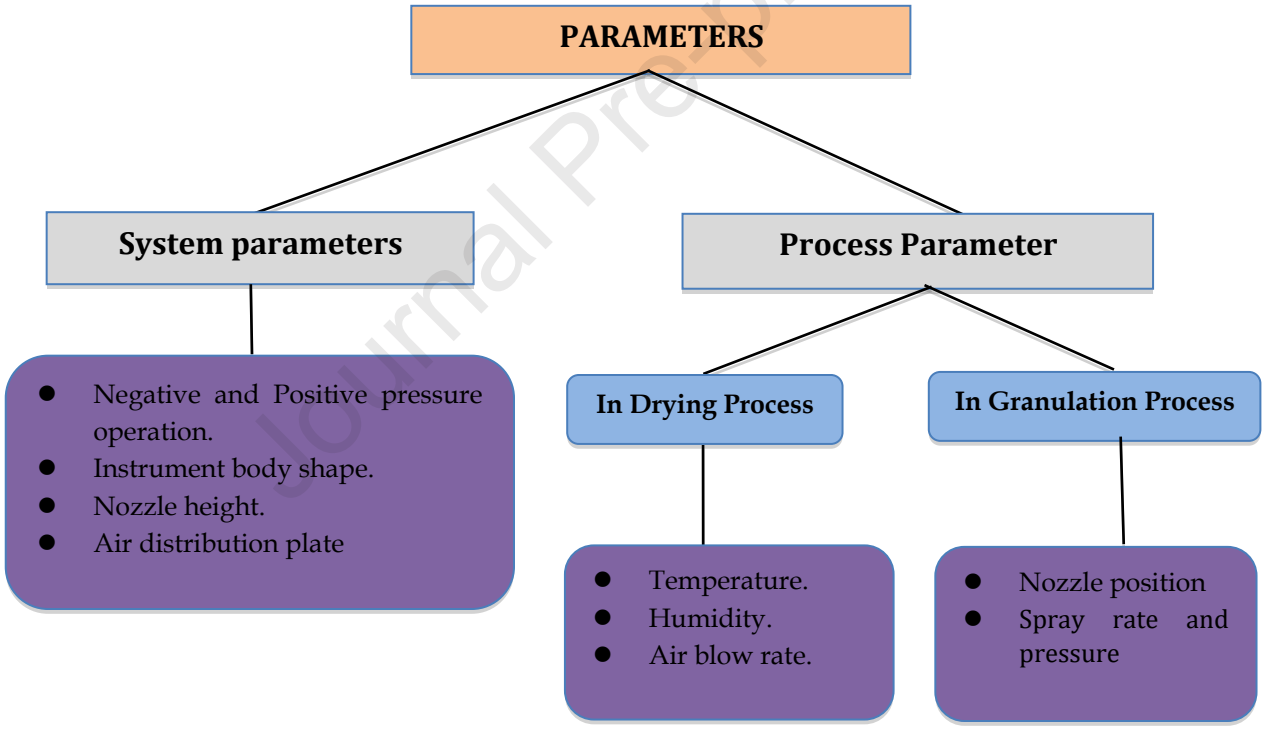
Utilizes two Methods—hardening binder and crystallization. The powder material is loaded into a product container through a spray nozzle and fine mesh retention screen. Controlled spraying of the binding solution allows for proper drying.

2. Rotating Disk Granulator with Dryer Option:

Combines layering techniques with a coater & rotating disk granulator, providing independent control of air velocity and volume. Fluidizing patterns in the rotor chamber are regulated by centrifugal force, gravity, and fluidization. A spray nozzle applies the solution tangentially to particles, employing the layering technique for pallet manufacturing.[40]

2.3.3 Parameters Affecting Fluidized Bed Granulation:

Several parameters influence the final product in a fluidized bed processor, categorized as apparatus and process parameters and those are shown in Flowchart 1.



Flowchart 1: Parameters Affecting Fluidized Bed Granulation

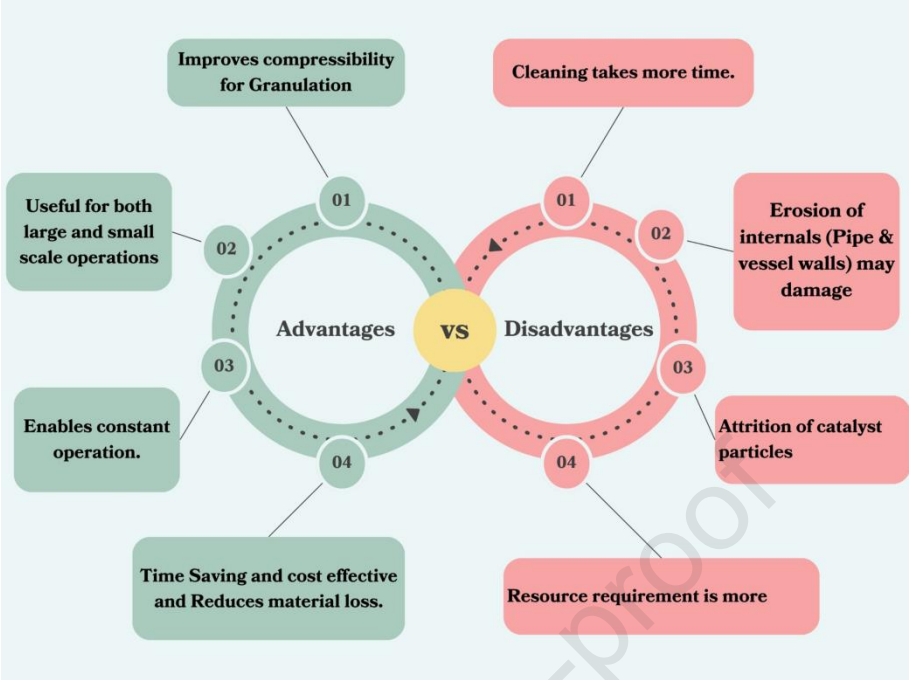


Figure 12: Advantages and Disadvantages of Fluid Bed Granulation

2.3.4 Applications of Fluid Bed Granulation:

1. Granulation of Milk Products:

Milk composition: 85-91% water, 3.4-6.1% fat, 2.8-3.7% proteins, 4.5-5% lactose, and 0.68-0.77% minerals. Skim milk fluidized-bed granulation creates storable, hydrophobic animal feed using hackled milk granulates or casein particles as hold-up material.

2. Granulation of Fertilizers:

Urea, a vital nitrogen fertilizer and animal food, traditionally produced 2mm diameter particles in prill towers. Fluidized bed granulation achieves 90-95% solid content, producing 4mm diameter particles suitable for airplane fertilization, with a clay coating for solubility.

3. Granulation of Microbial Products:

Rye Starch: Microorganisms preservation through granulating rye starch with a solid suspension of 0.145% within a specific temperature range.[41]

ADVANCED WET GRANULATION TECHNIQUE

2.4 REVERSE WET GRANULATION

Reverse wet granulation is an innovative process that deviates from the conventional granulation approach by immersing fine dry powder into a binder agent, eliminating the need for ancient granule nucleation. This method significantly reduces liquid

saturation, thereby minimizing the chances of undesired growth & potential batch loss. The primary advantage of reverse wet granulation lies in its ability to improve the dissolution characteristics of less water-soluble drugs. This improvement is achieved by ensuring a uniform distribution of the binder throughout the mixture, facilitating better contact between the drug and the hydrophilic polymer. The process parameters, such as liquid saturation and impeller speed, play crucial roles in controlling the size and porosity of the granules produced through reverse wet granulation.[67] The process Of Reverse wet Granulation is discussed in Figure 13.

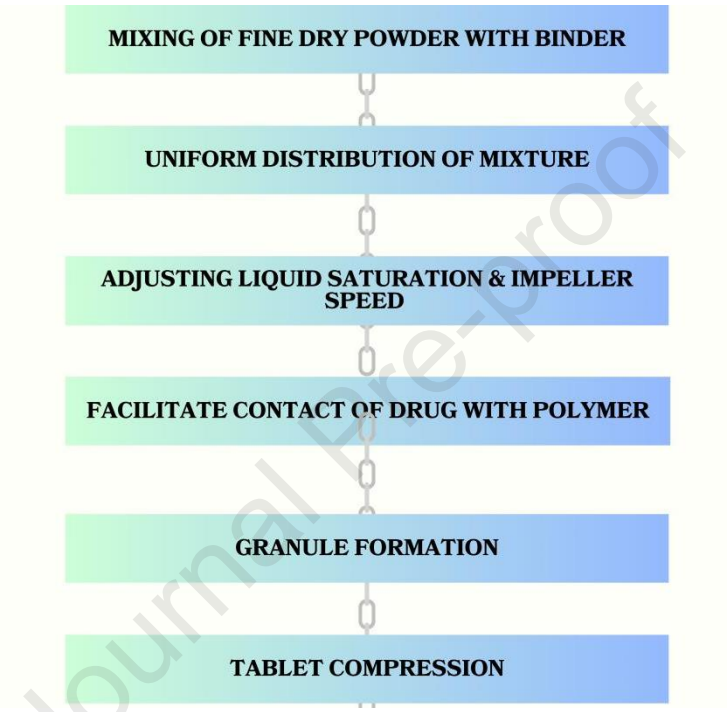


Figure 13: Process of Reverse Wet Granulation.

2.4.1 Applications of reverse wet granulation are evident in various pharmaceutical formulations:

1. Solubility Enhancement of simvastatin: Reverse wet granulation proves to be a successful technique for enhancing the solubility of simvastatin, a critical aspect in pharmaceutical formulations.

2. Granule Preparation: The process involves the preparation of granules by incorporating SIMVASTATIN into a granulating solvent, where water serves as the solvent. Excipients such as povidone, lactose, sodium starch glycolate, & aerosil are utilized in this granulation process.

3. Granule Evaluation: The resulting granules are subjected to a thorough evaluation, covering aspects like flow properties, solubility studies, x-ray diffraction, & Fourier-

transform infrared spectroscopy (FTR) analysis.[43] The Advantages and Disadvantages of Reverse wet granulation are shown in Figure 14.

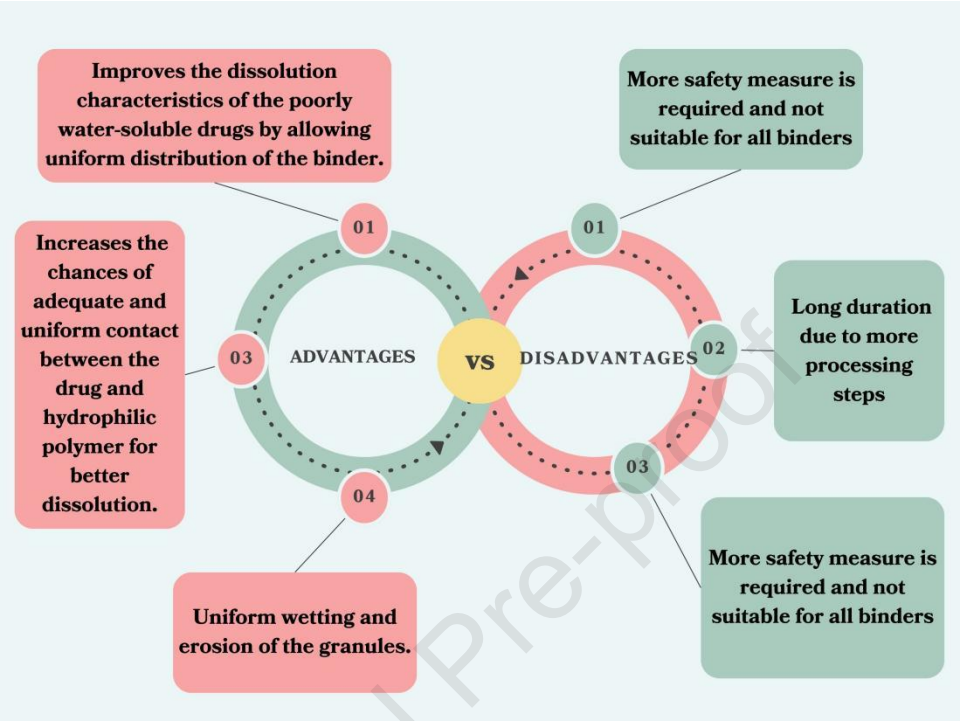


Figure 14: Advantages and Disadvantages of Reverse Wet Granulation.

2.5 STEAM GRANULATION

Steam granulation presents a modified approach to traditional wet granulation by utilizing steam as a binder instead of water. In this process, liquid is injected into the formulation alongside steam. The steam injection occurs at approximately 150 °C, resulting in localized overheating and condensation near the steam nozzles. This unique method can lead to the Agglomeration into lumps in the granule Pharmaceuticals due to the intense localized heating and moisture introduction during the process.[44] Figure 15 deals with a Schematic diagram of steam granulation.

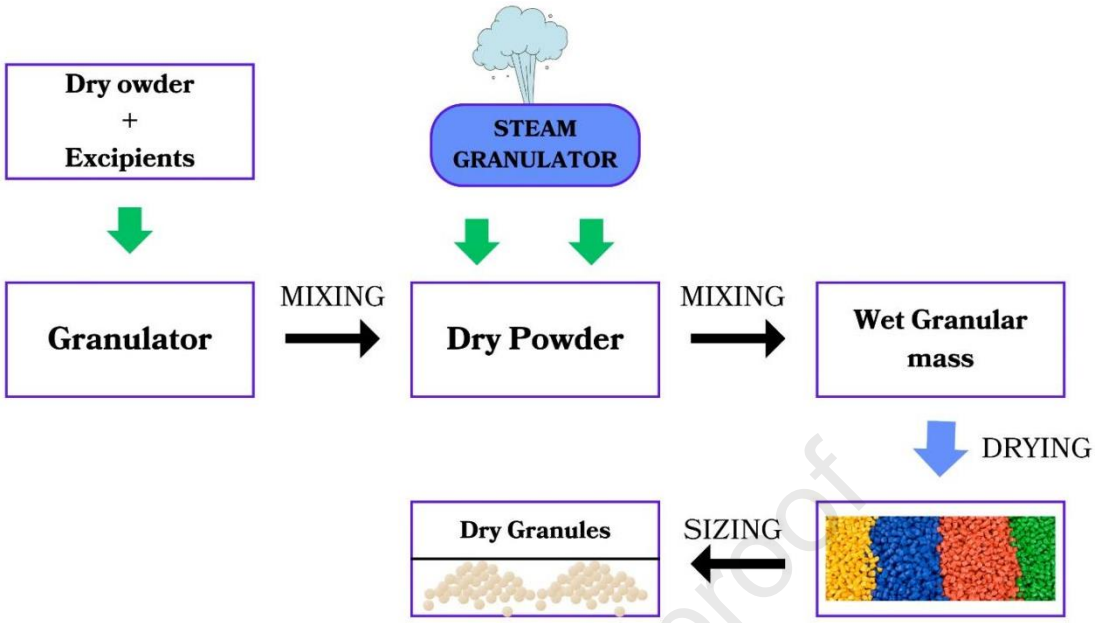


Figure 15: Schematic diagram of Stream Granulation

2.5.1 Apparatus and Method:

- The present invention addresses granulating challenges by introducing improved methods for fluidized bed apparatuses.
- Steam jets are injected into the apparatus, enveloped by corresponding gas jets to prevent premature condensation, ensuring lump-free and uniform wetting.
- Jets can be injected transversely or axially, allowing flexibility in the process.
- This method produces granulated products with no lumps.[45]

The Advantages and Disadvantages of steam granulation are listed in Figure 16.

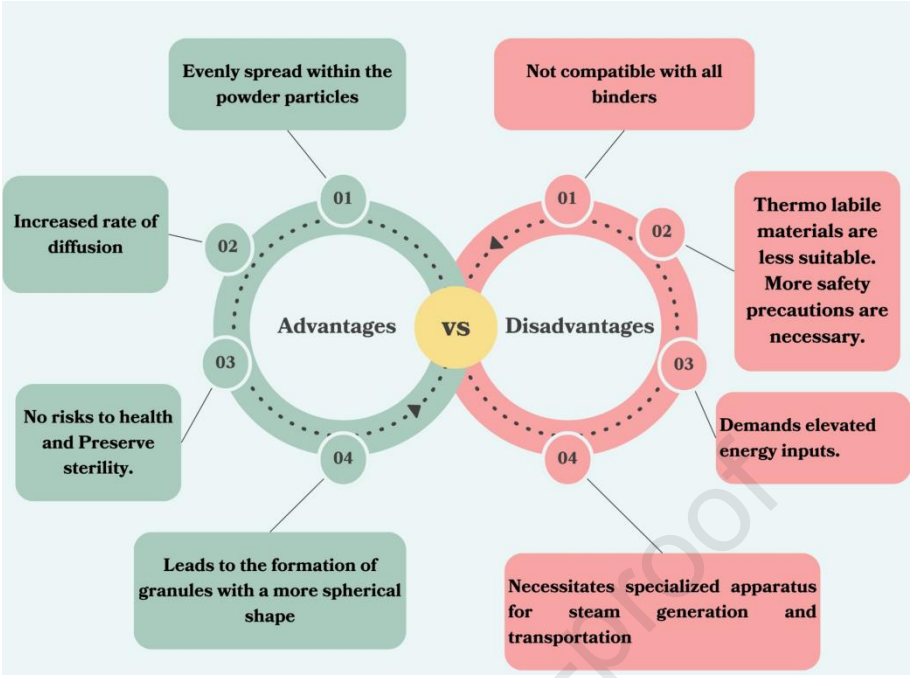


Figure 16: Advantages and Disadvantages of Steam Granulation

2.5.2 Applications :

1. **GranulEvaluation:** Utilized for assessing beta-lactose and Polyvinylpyrrolidone (PVP K12, PVP K90) as excipients in the preparation of piroxicam granules.

2. **Water Quantity in Steam Granulation:** The quantity of water employed for the Px/beta-lactose mixture was 15 mL in the steam granulation process.

3. **Steam-Induced Granule Formation:** Steam was utilized for granule formation, with water amounts of 10 mL and 15 mL for PVP K12 and PVP K90, respectively.[46]

2.6 MOISTURE ACTIVATED DRY GRANULATION(MADG)

Moisture Activated Dry Granulation (MADG) presents a solution to issues encountered in wet granulation processes, such as challenges in determining endpoints, the drying phase, and milling. Figure 17 shows the schematic diagram of MADG. Wet granulation often faces sensitivity to time and shear, while the resulting dried granules may exhibit undesirable bimodal distribution. MADG, on the other hand, involves the creation of granules through a process that utilizes water and a binder, omitting the need for heat drying or subsequent milling.[48] The Pros and cons of Moist Activated Dry Granulation are listed in Figure 18.

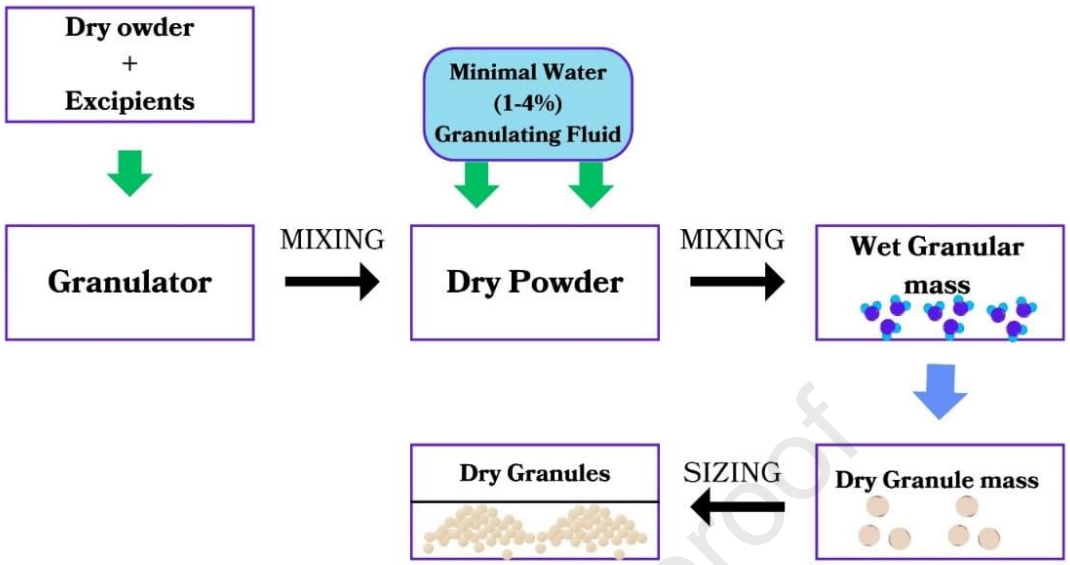


Figure 17: Schematic diagram of Moisture activated dry granulation

2.6.1 Stages of MADG:

Moisture Activated Dry Granulation (MADG) comprises 2 key stages:

A) Agglomeration: In this stage, the drug is mixed with diluents & a binder liquid, forming a homogeneous mixture.

B) Moisture Dispersion: Introduce moisture-absorbing substances, such as microcrystalline cellulose or silicon dioxide. This step activates granule formation without the need for heat. The outcome is granulation with a more consistent particle size distribution, minimizing the occurrence of larger lumps and ensuring uniform granulation results.[49]

2.6.2 Applications :

1. Development of IR tablets with cohesive, fluffy, and high-dose drugs using the MADG method.

2. Model compounds including metformin hydrochloride, acetaminophen, & ferrous ascorbate, along with binding agents like maltodextrin DE16, PVP K 12, etc. are used.
3. Formulation trials involved sifting drugs through a mesh screen, blending with low-viscosity binders, and granulating with the addition of moisture-absorbent Aeroperl and lubricant magnesium stearate. Blending continued for 0.5 minutes at 300 rpm.[50]

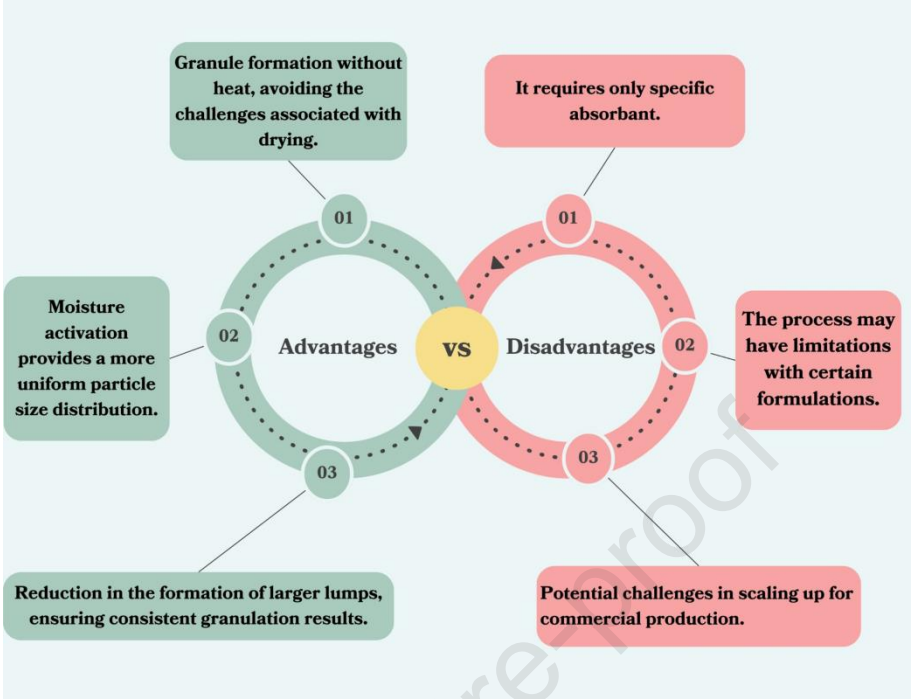


Figure 18: Advantages and Disadvantages of Moisture-activated Dry Granulation

2.7 MELT GRANULATION

Melt granulation, also known as thermoplastic granulation, involves obtaining granules by adding either molten or solid binders that melt during this process. The method, also termed thermoplastic agglomeration, consists of 3 phases: wetting and nucleation, coalescence, and attrition and breakage.

2.7.1 Wetting and Nucleation:

During the phase, the binder liquid contacts the powder bed, forming liquidized bridges and leading to the creation of small granules. The 2 nucleation mechanisms introduced by Schaffer & Matheson include immersion and distribution. Immersion nucleation occurs when the molten binder droplet size exceeds that of fine solid particles, while distribution involves distributing molten binder liquid onto the surface of fine solid particles, forming nuclei through collision. Conditions favoring nucleation by the distribution method include small binder droplet size, low binder viscosity, & high shearing forces.

2.7.2 Attrition and Breakage:

Attrition and breakage refer to the granulation fragmentation phenomenon, solidified by tray cooling to ambient temperature without requiring drying through a tumbling process.

2.7.3 Requirements:

In the context of melt granulation, it is common to incorporate 10-30% w/w of a meltable binder along with fine solid particles. A meltable binder, characterized by a melting point within the range of 50-100°C, proves suitable for this procedure. Immediate-release dosage forms typically utilize hydrophilic meltable binders, whereas hydrophobic meltable binders are favored for prolonged-release formulations.

2.7.4 Types of Meltable Binders:

1. The binder should be in a solid state when at room temperature and undergo melting within the temperature range of 40–80°C. The schematic visualization of Melt Granulation is figured out in Figure 19 and Table 1 discusses Meltable binders and their Melting ranges.
2. Two categories of meltable binders include:
   - Meltable binder with hydrophilic properties.
   - Meltable binder with hydrophobic characteristics.[51]

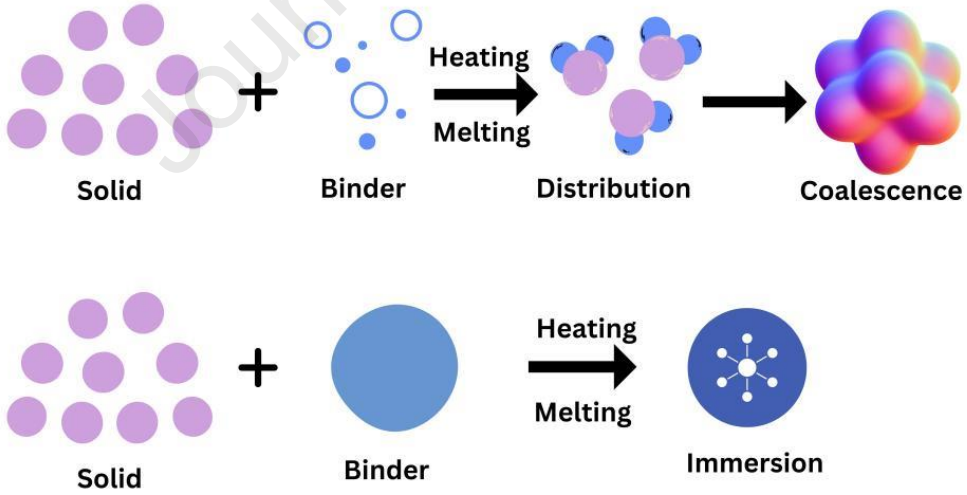


Figure 19: Process of Melt Granulation

Table 1: Hydrophobic meltable binders used in the melt granulation

Hydrophobic Meltable Binder	Typical Melting Range
Bees(wax)	329–333 K
Carnauba (Wax)	348–356 K
Hexadecyl Hexadecanoate	320–323 K
Glyceryl Octadecanoate	327–336 K
Hydrogenated Castor Oil	335–359 K
Microcrystalline (Wax)	331–345 K
Paraffin (Wax)	320–338 K
Stearic (Acid)	319–342 K

To compare the processes, tablet hardness and friability were assessed under identical compression forces. The results showed that the tablets' hardness followed the order MG > SG >WG, while the friability exhibited the pattern MG < SG < WG.[52]
The Pros and cons of the Melt Granulation are discussed in Figure 20.

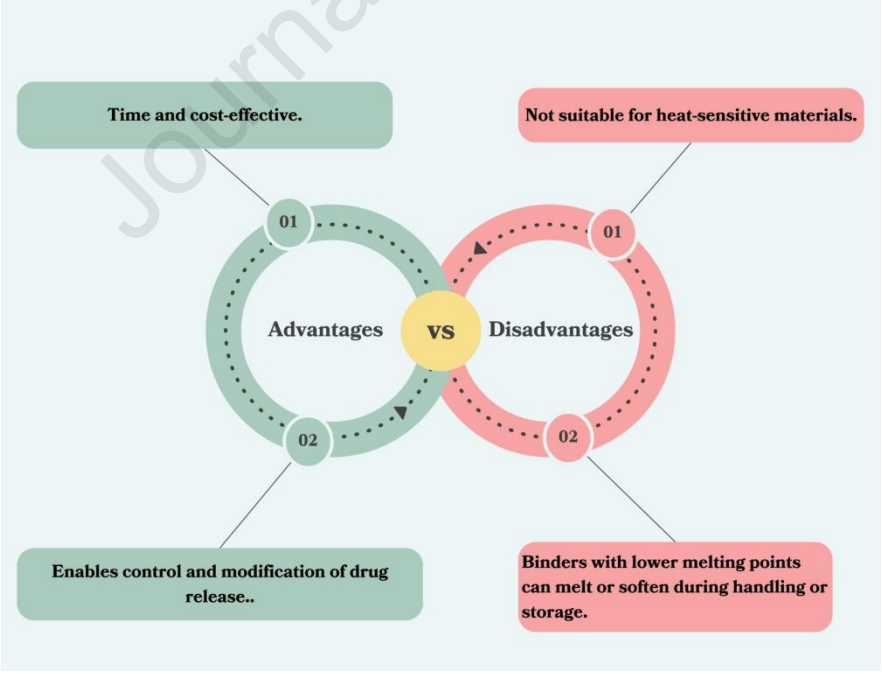


Figure 20: Advantages and disadvantages of Melt Granulation

2.7.5 Applications:

1. Enhancing Compatibility of High-Dose Drug Substances:

- Model Drug: Metformin HCl
- Polymeric Excipient: Hydroxypropylcellulose (HPC)
- Process: Utilizing a twin-screw extruder for the process of melt granulation.
- Objective: Improve the compatibility of poorly compatible high-dose drug substances.

2. Drug–Polymer–Powder Mixtures:

- Mixture Components: Drug, Polymer (HPC), Powder
- Granulation Temperature: Above glass transition of HPC (130°C) but below the melting point of metformin HCl (224°C).

2.8 FREEZE DRYING

Freeze drying, a meticulous process involving three key stages, begins with freezing the material. Typically accomplished in a freeze-drying flask within a shell freezer, cooled by mechanical refrigeration or substances like dry ice and liquid nitrogen, the material must be cooled below its eutectic point to ensure proper sublimation in subsequent steps, with freezing temperatures ranging from −50°C to −80°C. The critical freezing phase is vital to prevent spoilage, especially for amorphous materials without a eutectic point. Moving on to the primary drying phase, pressure is reduced to a few millibars, and heat is applied to facilitate water sublimation. The heat required is calculated using the latent heat of sublimation for the molecules undergoing sublimation. Approximately 95% of the material's water content is sublimated during this phase, where pressure is controlled by partial vacuum application. A cold condenser chamber aids in re-solidifying water vapor, with condenser temperatures typically below −50°C (−60°F). The schematic diagram of freeze drying is shown in Figure 21.

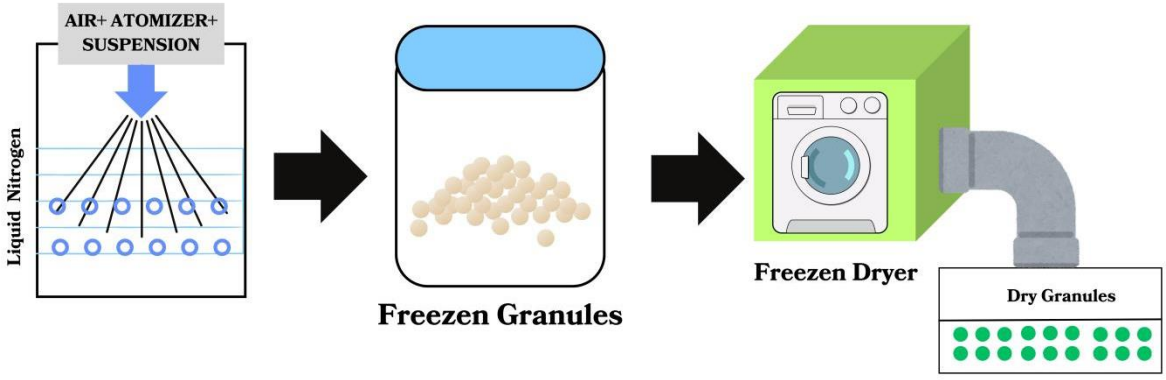


Figure 21: Schematic Diagram of Freeze Granulation.

Freeze Drying

Finally, the secondary drying phase targets the removal of unfrozen water molecules, following the elimination of ice in the primary drying phase.it is governed by the material's adsorption isotherms, this phase involves raising the temperature beyond the primary drying phase, potentially exceeding 0°C. The objective is to disrupt any physicochemical interactions formed between water molecules and the frozen material. Upon completion of the freeze-drying process, an inert gas such as nitrogen is introduced.

2.8.1 Principle:

Freeze-drying operates on the principle of sublimation, wherein a solid substance directly transforms into its gaseous state. Similar to evaporation, sublimation occurs when a molecule gains enough energy to separate from its neighboring molecules. Notably, water undergoes sublimation, transitioning from a solid (ice) to a gas (vapor), even when environmental conditions do not favor liquid formation. The state (solid, liquid, or gas) of a substance is primarily dictated by two factors: heat and atmospheric pressure.[53] Advantages and Disadvantages of Freeze Granulation are observed in Figure 22.

2.8.2 Applications:

1. The utilization of freeze-granulated powders serves as a viable industrial alternative to loose powder sintering, particularly in the production of transparent polycrystalline alumina (PCA).[54]

2. Freeze Granulation of Nonporous UiO-66 Nanoparticles for the Capture of Volatile Organic Compounds[55]

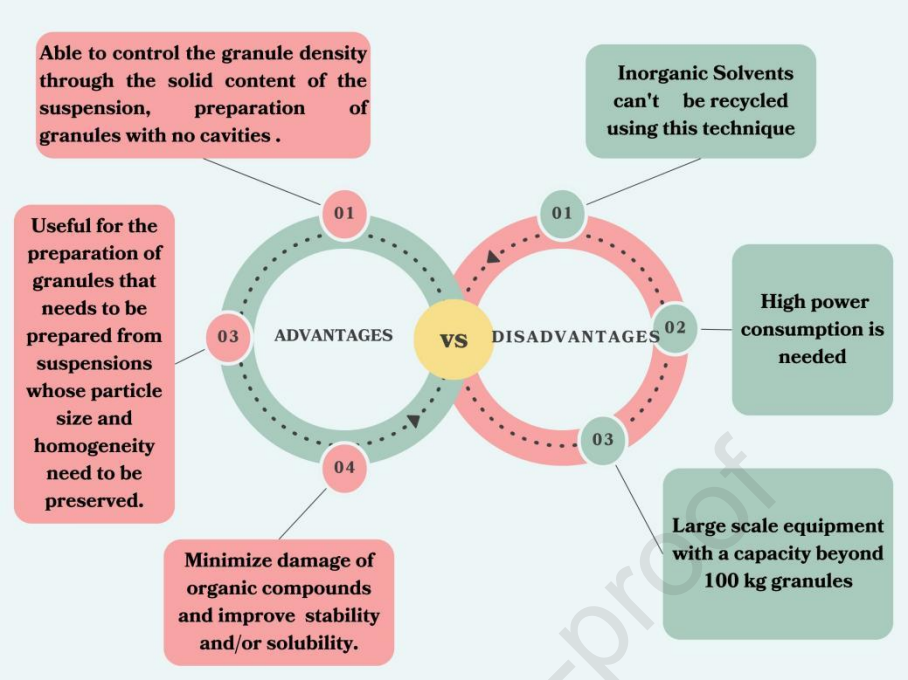


Figure 22: Advantages and Disadvantages Of Freeze Granulation

2.9 FOAM GRANULATION

Foam granulation technology involves the addition of a fluid glidant in the form of aqueous foam, a technique borrowed from the chemical industry. This method simplifies, enhances safety, and accelerates the wet granulation process. Utilizing well-established polymer methods, this state-of-the-art art technology improves the uniform distribution of binders in the formulation mix, resulting in superior outcomes., providing significant process benefits. In comparison to traditional spray processes, foamed binder technology reduces process time and water requirements, improving productivity with consistent binder distribution. Furthermore, it eliminates nozzle spray variability in the granulation process apparatus. The foam process enhances endpoint determination and reduces equipment cleanup time. Despite the numerous benefits, The inventive foamed binder technology removes the necessity for introducing new equipment or making substantial changes in processing techniques.[56]

2.9.1 How Foam Binder Granulation Works:

Foam granulation proves highly efficient by leveraging the substantial increase in the liquid surface area and volume of polymeric binder foams. The foam granulation process is illustrated in the figure 23.

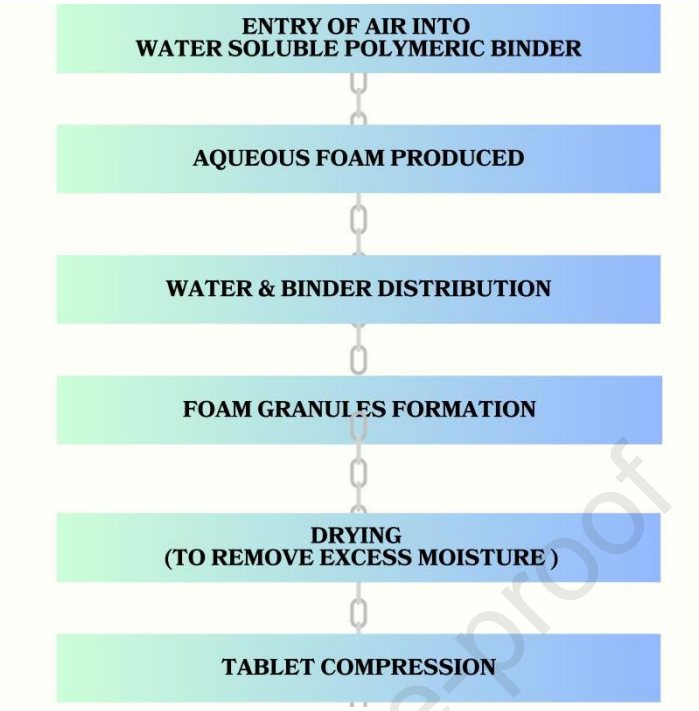


Figure 23: Foam granulation Process

This optimization enhances the distribution of the water/binder system throughout the powder bed in a solid-dose pharmaceutical formulation. Using a straightforward foam generation apparatus, the air is introduced into a conventional water-soluble polymeric excipient binder like methodical hypromellose (hydroxypropyl methylcellulose), yielding exceptional results. Widely acknowledged as a transformative approach in the pharmaceutical industry, this technique has seen extensive and successful application.[57] The Pros and Cons of this Technique are illustrated in figure 24.

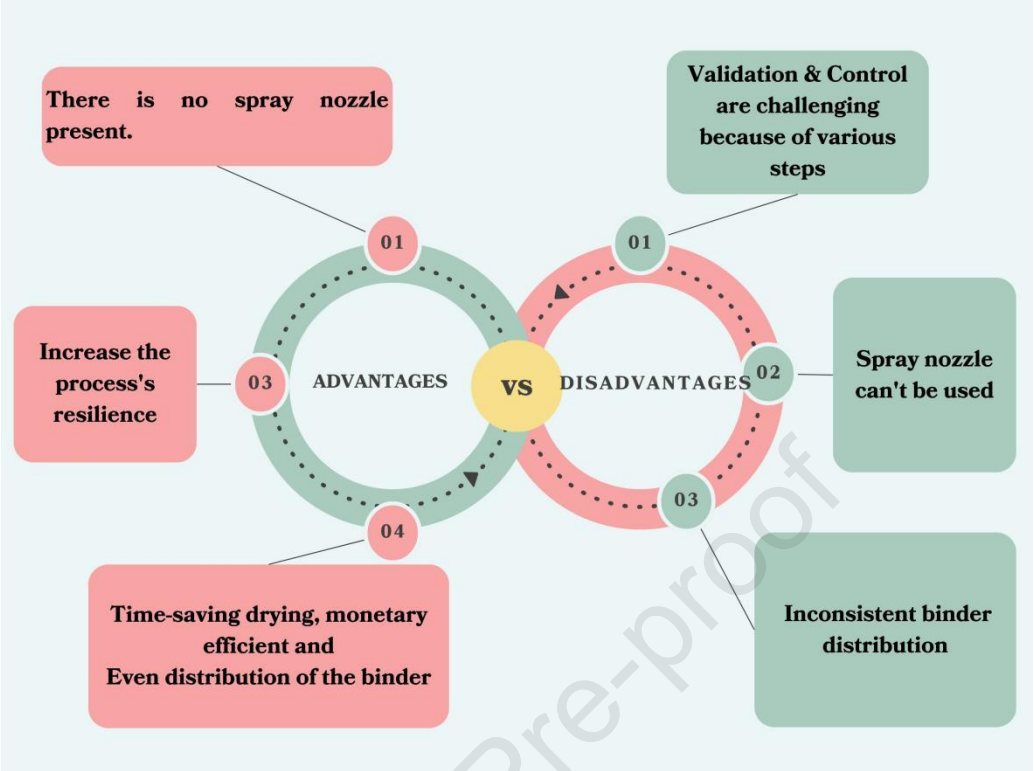


Figure 24: Advantages and Disadvantages of Foam Granulation

2.9.2 Applications:

1. Configuring a twin-screw extruder for foam granulation and subsequently contrasting this innovative method with liquid injection in the granulation process of α-lactose monohydrate using a methylcellulose binder.[58]

2.10 THERMAL ADHESION GRANULATION

Thermal Adhesion Granulation (TAG) functions akin to damp granulation, employing warmth and a limited quantity of granulation fluid to coalesce particles. Both water and solvent can act as the granulation fluid in this procedure. Heat expedites the granulation process, as the amalgam of the drug and excipient is heated within a sealed system, rotating at a temperature ranging from 30-130°C. Through the inclusion of a minimal granulation liquid, predominantly absorbed by the powder particles during agglomeration, this technology obviates the necessity for a drying phase. Following cooling and sieving, granules with the intended particle size can be acquired, rendering them apt for directly formulating tablets.[59] Figure 25 explains the schematic representation of Thermal adhesion granulation.

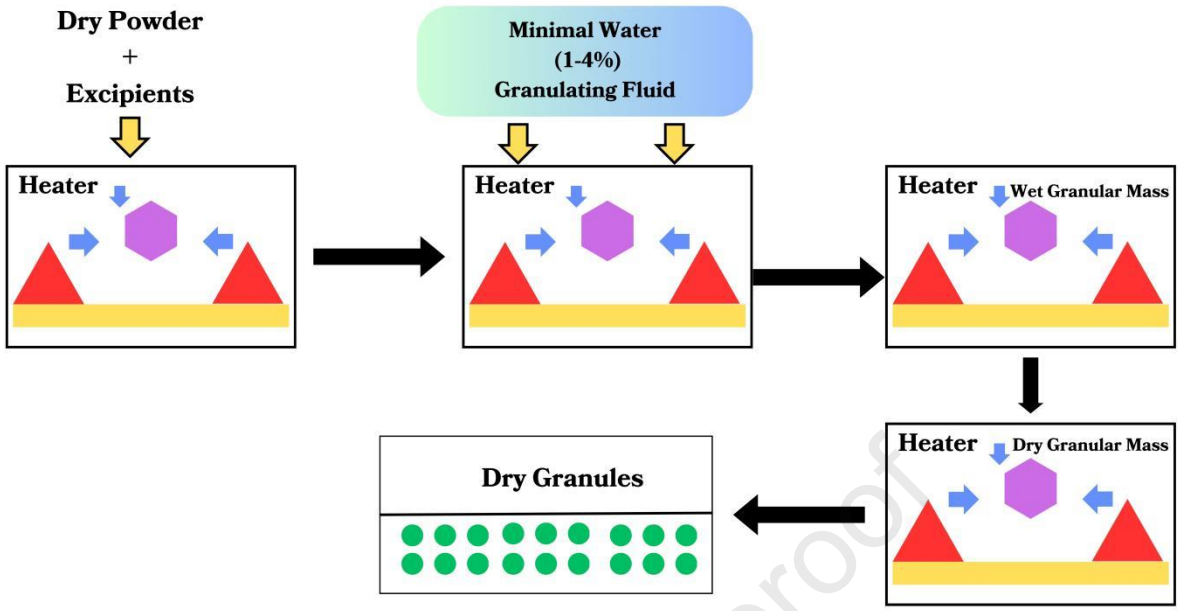


Figure 25: Schematic diagram of Thermal Adhesion Granulation.

2.10.1 Factors Affecting TAD:

1. **Material Characteristics:** The inherent properties of the materials involved play a crucial role.

2. **Selection of Excipients:** Choosing excipients based on the wettability and solubility of the drug powder is vital. For instance, if the powder is fine, loose, dry, and exhibits poor viscosity and low solubility in water, a more viscous adhesive should be utilized, with a relatively larger quantity.

3. **Stirring Speed:** The speed at which stirring occurs influences the process.

4. **Feed Flow:** The flow of feed materials is a factor that impacts Thermal Adhesion Granulation (TAG). Thermal Adhesion Granulation has many Advantages and Disadvantages, some of which are represented in Figure 26.

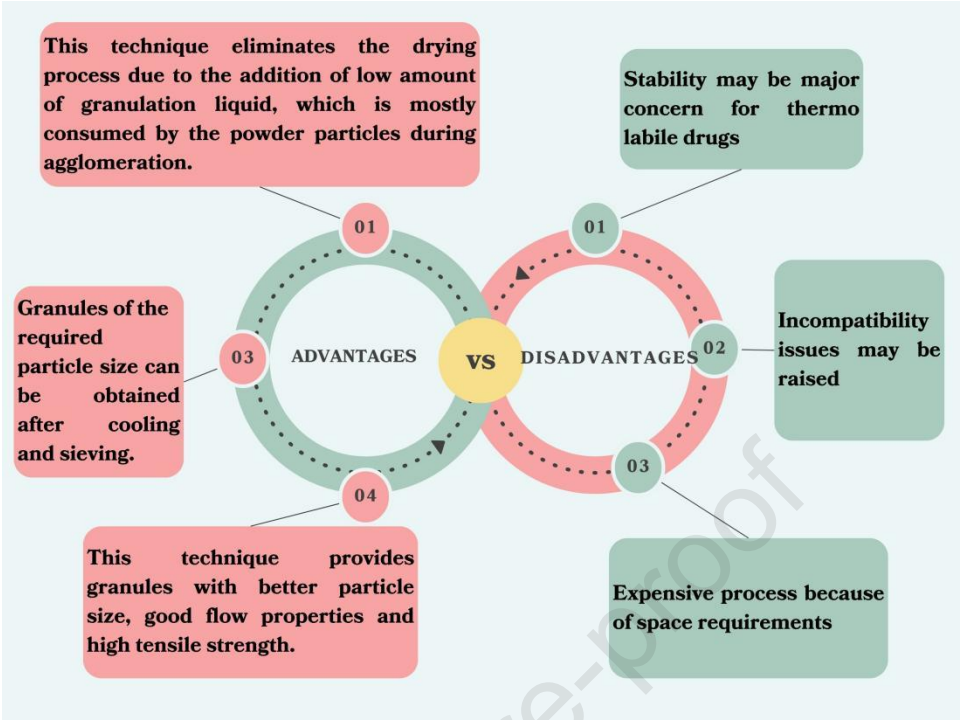


Figure 26: Advantages and Disadvantages of Thermal Granulation.

2.10.2 Applications:

1. The TAG technique entails exposing a blend comprising excipients such as microcrystalline cellulose (MCC), lactose, starch, or dibasic calcium phosphate (DCP) to heating while mixing under sealed conditions with low moisture content and a minimal polyvinyl pyrrolidone (PVP) binder. This results in the formation of highly compressible granules.[60]

2. The physical characteristics and dissolution profiles of cilostazol solid dispersions, formed through hydrophilic/lipophilic additives (Kollidon® VA64, tocopheryl polyethylene glycol succinate (TPGS), vitamin E), using both hot-melt and thermal adhesion granulation (TAG) techniques to absorb Fujicalin® and Microcel®, were examined.[61]

2.11 CONTINUOUS TWIN SCREW WET GRANULATION

The Twin Screw Wet Granulation (TSWG) approach proves to be a highly advantageous method for granulation, presenting various merits. It involves Continuous Manufacturing by the introduction of a physical blend containing the active ingredient, binder, and other excipients into the extruder through either a gravimetric hopper or a force feeder.

Within the kneading zone, materials undergo softening and even dispersion in the extruder barrel due to generated temperature and shear forces. Consequently, this yields high-quality granules, which are then conveyed and collected at the discharge point.
Furthermore, the TSWG method stands out for its efficacy in enhancing the stability of medications sensitive to heat and solvents. With a low binder content of 10%, the process enhances the drug-loading capabilities of formulations, making it a preferred choice for pharmaceutical companies.

In summary, the TSWG method emerges as a valuable technique with numerous advantages for the pharmaceutical industry. Its application not only improves the quality and stability of medications but also streamlines production, reducing both time and costs.
In order to assess the blending residence within the extruder, introduce blue food color powder into the feeding zone subsequent to filling the barrel with a physically blended mixture. Granules are then collected 15-20 minutes into the process, ensuring uniform quality is maintained throughout.[62]

2.11.1 Twin. Screw Wet Granulation Process

The Twin Screw Wet Granulation (TSWG) process involves feeding a physical mixture containing the active ingredient, binder, and other excipients into the extruder via a gravimetric hopper or force feeder. The feed material is moved into the mixing or kneading zone while maintaining a temperature below the glass transition temperature (Tg) or melting point (MP) of the formulation components to keep them in a dry condition.

Granule production occurs as materials soften and disperse uniformly in the extruder barrel due to the shear generated in the kneading zone. Produced granules are then transported and collected at the discharge site. This method proves beneficial for enhancing the stability of medications sensitive to heat and solvents, Notably, the TSWG process employs a low binder content (10%), enhancing the formulations' drug-loading capabilities.

The Continuous Manufacturing Process of Granulation relies on heat energy and shear in the mixing zones as the key driving forces. Granule formation is influenced by the compressible material percentage and medication load percentage in the physical mixture. Satisfactory granulation is indicated by good compression characteristics observed in the formed granules.[63] The Process of TSWG is shown as a schematic diagram in Figure 27.

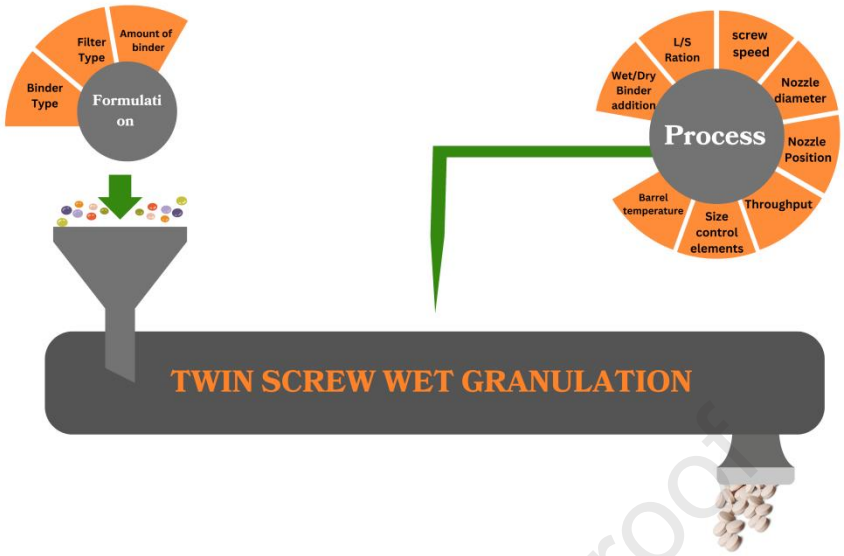


Figure 27: Schematic Diagram of Twin screw wet granulation.

2.11.2 Applications of Twin Screw Wet Granulation

1. Majumder et al. (2018):

- Utilized twin screw granulation to produce amorphous granules of Benzyl-methoxy-methyl indole-acetic acid (BMA). The amorphous nature of the granules was confirmed through solution calorimetry (SolCal).
- These granules exhibited a particle size smaller than 115 µm and demonstrated flow properties comparable to Neusilin®US2.
- Characterization techniques such as DSC, XRD, SEM, and optical microscopy confirmed the granules' amorphous nature.
- Dynamic vapor sorption (DVS) revealed the extrudates' hygroscopic nature, requiring careful storage.[64]

2. Upadhye et al. (2017):

- Conducted granulation on a mixture of Sildenafil citrate and polymers, including Klucel™ HF, Natrasol®, and Aqualon™ N7.
- Tested under various conditions, including 100-200 rpm, 65°C, and 3-5 g/min feed rate.
- The addition of magnesium stearate helped overcome material degradation and extruder noise.
- Highlights the use of low temperatures for heat-sensitive drugs.[65]

3. Richter's Study (2017):

- Explored the impact of process temperature on granulation using lactose, Kollidon VA64, Soluplus®, and MCC.

- Kollidon VA64 granulation resulted in poor granulation due to insufficient temperature.
- Soluplus® granulation was successful at 130-150 ℃, 0.5 kg/h, and 70-130 rpm.
- Decrease in processing temperature led to reduced fines and increased agglomerates.
- Highlights the importance of process parameters and API interaction in granulation for producing granules suitable for heat-sensitive drugs.[66]

Figure 28 explains the Advantages and disadvantages of the TSWG

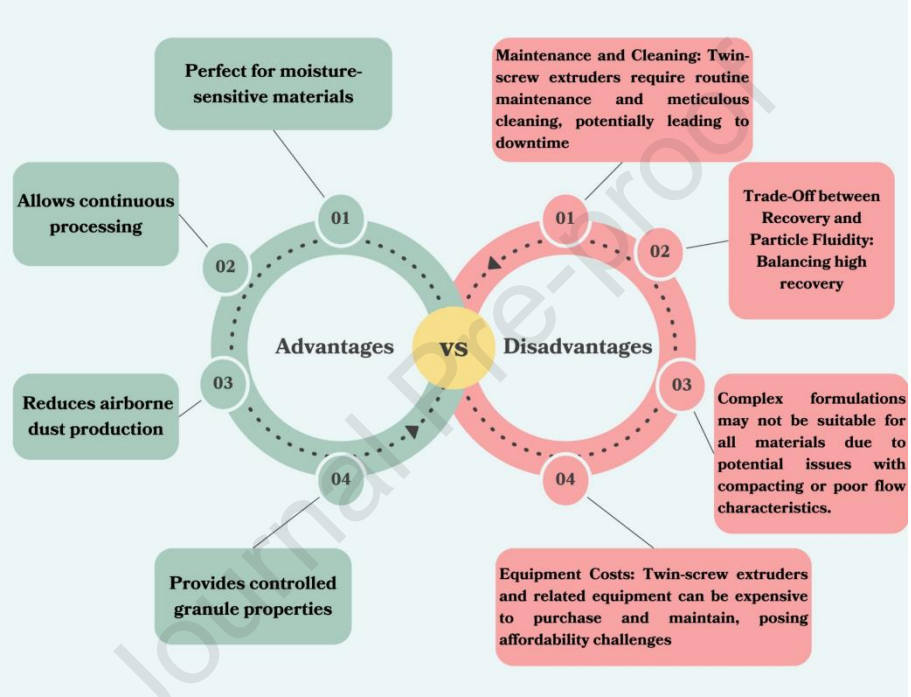


Figure 28: Advantages and disadvantages of Twin Screw Wet Granulation

CONCLUSION

Our detailed review delves into the complex world of Conventional and Advanced granulation techniques in pharmaceutical dosage forms, exploring both dry granulation and wet granulation methods. In dry granulation, we examine three main techniques: Pneumatic dry granulation, Roller compaction, and Slugging. We discuss how each method works, their benefits, drawbacks, and practical uses. For wet granulation, we explore eleven different techniques, ranging from High shear granulation to Twin screw wet granulation. Each method is explained in detail, highlighting how they work, their advantages, disadvantages, and specific applications. From the efficiency of High shear

granulation to the innovation of Twin screw wet granulation, our article provides valuable information for pharmaceutical professionals. This review serves as a comprehensive guide for researchers and practitioners, showcasing the various granulation techniques and helping with informed decision-making in the development of pharmaceutical dosage forms.

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Data Availability Statement

Comprehensive review on Modern Techniques of Granulation in Pharmaceutical Solid Dosage forms

Data sharing is not applicable to this article as no new data were created or analyzed in this study. This review relies entirely on previously published data and literature.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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