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(RESEARCH ARTICLE)

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A review on the wet granulation technique and its modules

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Abstract

Wet granulation is a processes that involves adding a liquid to a powder to create granule of a desired size and shape. Its used in many fields, including pharmaceutical, neutraceutical and zootechnics to improve the flowbility, compressibility, and dosage of powders. Their are different technique of wet granulation.

Low shear wet granulation, which is a form of wet granulation, is an important unit operation in the pharmaceutical, detergent and food industries. The granulation mechanism for wet granulation include wetting and nucleation, consolidation and growth and attrition and breakage. High shear wet granulation is considered a complicated and multivariate pharmaceutical process that is influenced by large number of variable derived from equipment, formulation, and processing. Fluid bed granulation is an important process within a drug product manufacturing framework since it sets the properties of the intermediate product the make the final drug product.

Keyword: Wet granulation; Granulation processing; Practical technology; Granulation design

1. Introduction

Granulation processes has been widely used in the pharmaceutical industry for the preparation of material (1). Granulation may be defined as a size enlargement processes which convert fine or course particles into physically stronger and larger agglomerate having good flow property, better compression characteristics and uniformity (2).

Dry granulation involve granule formation without using liquid solution as the product may be sensitive to moisture and heat. In this process dry powder particles may be brought together mechanically by compression into slugs or by roller compression to obtained flak. The granulation is the most widely used processes of granulation in the pharmaceutical industry. It involve addition of a liquid solution (with or without binder)to powders, to form a wet mass or it form granule by adding the powder together with an adhesive instead of by compaction (3). Wet granulation is a size enlargement process of powder particles used in many field, such as pharmaceutical, neuraceutical,and zootechnical, to improve technological properties of powder such as flowability, compressibility, dosage form. Wet granulation, the physical transformation of the powder particles due to the nucleation, agglomeration and breakage phenomena, control the granule final properties as the density and size distribution (4). The purpose is to improve the properties of very fine cohesive powders. The phenameno normally occur simultaneously in granule for vessel and depend on process variable and formulation variable (5,6,7,8). The drawback of this technique are the production of large amount of fines, which can be reduced by adding dry binder (10) and the high densification of the granulated material, which may lead to particle loss on tabletability (11,12,13). Nucleation is the initial step in wet granulation in which dry powder bed and liquid binder is sprayed onto the powder mass, forming initial nuclei of two or more particles, that are small particles. Agglomeration (consolidation and growth) is the granule collide on each other and increase of compaction and size of granulation(5,6,15,16).

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2. Wet granulation technique

Wet granulation is most used process of granulation in pharmaceutical industry during tablet manufacturing. The formulation of granules also helps to reduce segregation and improve the content uniformity of the final product. The effect of formulation and process variable on powder behavior in the granulator can be better understood once the main phenomena involve in the granulation are determined (5). Tablet represent the most popular drug delivery system (14). It has been reported that wetting and nucleation and thereby granule attributed were influenced by parameters like nature and amount of liquid binder and its properties like viscosity, density, wettability solid-liquid contact angle, liquid droplet size (17,18).

- Merits
    - It improve flow property and compression characteristics and increase density of granule.
    - Better distribution of color and soluble drug if added in the binding solution.
    - It reduce dust hazards.
    - Prevent segregation of powders.
    - Makes hydrophobic surface more hydrophilic (1).
- Demerits
    - Processes is expensive because of labor, space, time, special equipment and energy requirement.
    - Multiple processing steps involved in the process and complexity.
    - Loss of material during various stages of processing.
    - Moisture sensitive and thermolabile drugs are poor candidate.
    - Any incompability between the formulation components is aggravated during the processing.
- Steps

Mixing of API (active pharmaceutical ingredient) And excipient

Preparing a damp mass using binder solution

Screening – granulation and drying

Sizing this granulation by dry screening

Lubricant and compression.

Flowchart 1 Wet granulation

It is following are the different major technique which are used for wet granulation processes:

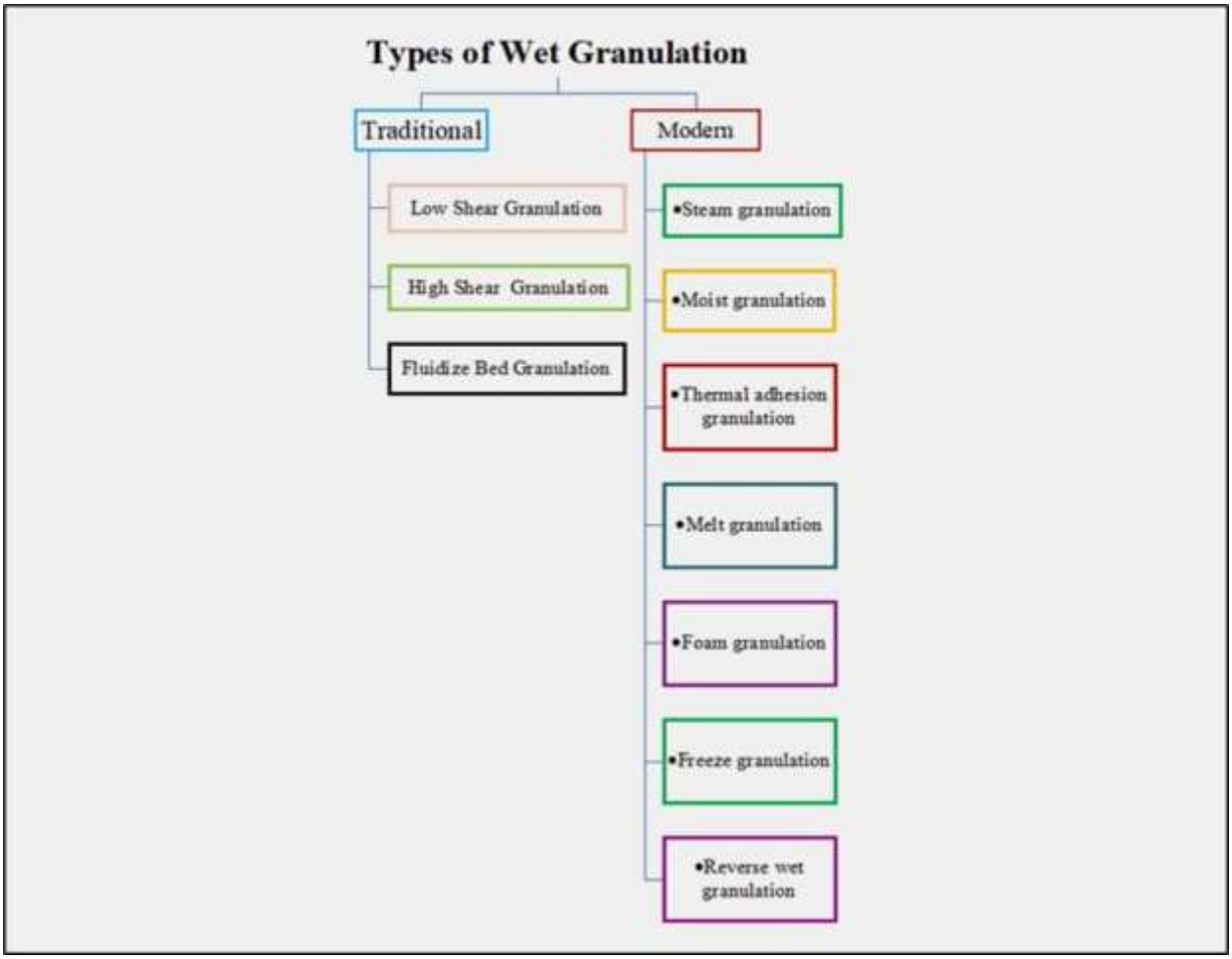

Figure 1 Types of wet granulation

2.1. Conventional technique

Conventional wet granulation involve generally three following technique -

2.1.1. Low shear granulation

Low shear is the traditional granulation process performed using low speed planetary or trough mixer in which the drug and excipient are granulated with a binder. The importance of a uniform distribution with in pharmaceutical granulation cannot be under estimated as it affect the final product uniformity and therefore the quality,safety,and efficacy of the product (19,20). Low shear wet granulation is a common unit operation in the pharmaceutical,food and detergent industries. Fine particles are difficult to handle, transport, feed and store and are therefore often agglomerated into required sizes and shapes. This is an important steps in many industries such as pesticides and pharmaceuticals,which require the particle to be finally divided for processing but were improper granulation can cause problems with downstream tableting (21). A large variety of techniques are available for granulation and the selection of the correct piece of equipment is currently based on which parameter are critical to the process or required in the product (22). The resultant damp material is screened to create separate granules, which are usually dried in tray dryer. After being rescreened or milled to the necessary size, lubricant and compressed the dry granules are combined with extragranular excipients.

Advantages

The method is not unduly sensitive to changes in the constituent properties of the granules.

- Inspection is frequently able to pinpoint the process conclusion.
- Low-shear mixing uses less energy than other mixing method.
- Low-shear mixing uses quieter than other mixing method.

Disadvantages

- In this process having multiples steps.
- It is long duration technique.
- In this technique, several piece of equipment are needed.

2.1.2. High shear granulation

High shear mixture has been widely used in pharmaceutical industries for blending and granulation. High shear granulation is considered and multivariate pharmaceutical process that is influenced by a large number of variables derived from equipment, formulation and processes. Granulation is well-known technology used to prepare granules of certain shapes and sizes from materials in the state a powder, melting liquid,or aqueous solution, which has been widely also used in agriculture,chemistry and food production (23). In comparison to low shear granulation, this combination very efficient component mixing while using a smaller amount of water.

Advantages

- Short processing time.
- Less amount of liquid binders required compared with fluid bed.
- Their ability to produce granules with a consistent size distribution.
- Fast powder granulation process.
- Highly cohesive material can be granulated.

Disadvantages

- High-shear granulator produces less compressible granules when compared to low-shear granulator.
- Over wetting of the granules may lead to formation of large sized limps.
- Themolabile material could be chemically degraded due to increase in temperature.

2.1.3. Fluid bed granulation

Fluidization is the operation by which fine solids are transformed into a fluid like state through content with gas. Fluidized bed granulation is an important powder production process,such as spray drying or high-shear granulation. The progress of drying is related to the outlet air and granule bed temperature combined with the drying time. Process endpoint is reached when a preset exhaust air temperature is obtained (24). Next a better understanding of granule formation mechanism and modeling of the process, adequate granulation control is necessary to shift from a granulation art to a granulation science(25). The system involve the heating of air and then directing it through the material to be processed(26). Spraying a binder solution onto a fluidized powder bed results in fine, homogenous, free-flowing granules thro1ugh an air suspension process.

Figure 2 Fluid bed granulation

Advantages

- 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.
- It reduce a lot of operation links and saves production practice.
- Fluidized beds have good temperature distribution, and high mass and heat transfer rates.

Disadvantages

- Initially expensive and optimization of granulation needs extensive development work.
- Fluidized bed system may not provide adequate mixing of powder component.
- Particle with granulating agent on their surface tend to stick to the equipment filter

2.2. Advance technique

Advance wet granulation involves seven following technique –

2.2.1. Steam granulation

Steam granulation is a technique that uses a jet of steam to create granule from a bed of fluidized particles. Its granulation process that can be used to produce spherical granules with a large surface area. This process is simply a modification of conventional wet granulation method. Here steam is used as a binder instead of water. Process offers several advantages and disadvantages (27).

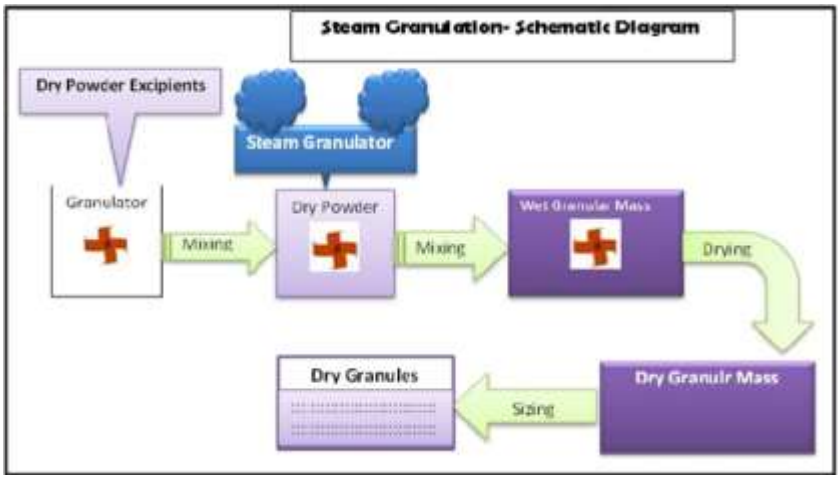

Figure 3 Steam granulation

Advantages

- High diffusion rate.
- Environmental friendly.
- No risk to health.
- Maintain sterility.
- Evenly distributed through the powder's particles.

Disadvantages

- Requires specialized technology for the production and transportation of steam.
- Steam is breakdown easily.
- Steamer can use a lot of water.
- Not suitable for all binder.

2.2.2. Moist granulation

Moist granulation is the process of adding a granulating fluid, such as water or ethanol, etc. to dry powdered materials to create a mixture that is then forced into a granulating extrusion cylinder where the material is compacted and cut off by a scraper to form larger size granules. Moisture activated dry granulation is another name for moist wet granulation.

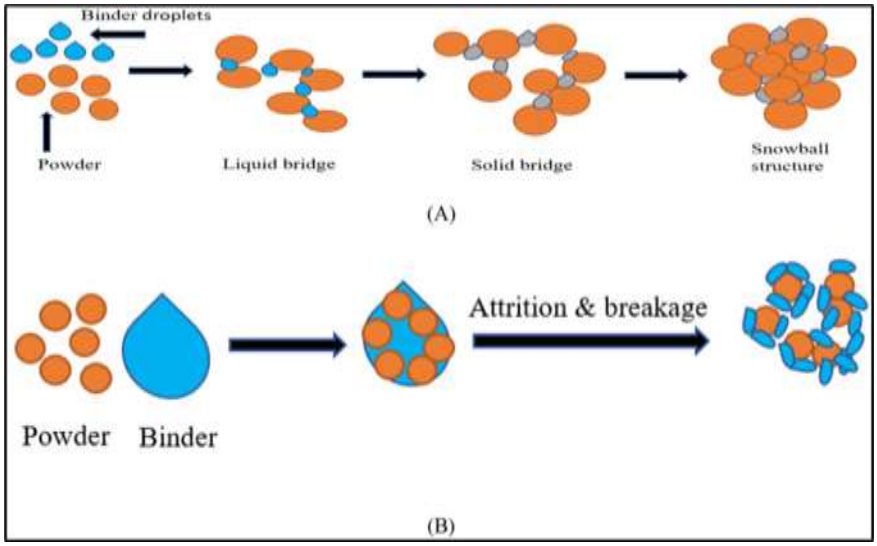

Figure 4 Moist granulation

Advantages

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

Disadvantages:

- Moisture sensitive and high moisture absorbing APIs are poor candidates.

2.2.3. Thermal adhesion granulation

Thermal adhesion granulation is a granulation that uses heat and a small amount of granulation liquid to agglomerate powder particles. This process uses both water and solvent as granulation liquid. To aid in the agglomerate of the powder particle,the drug,and excipients mixture is heated in a closed system with tumble rotation to a temperature of 30-130^{0}c. By adding a small amount of granulation liquid, which is primarily absorbed by the powder particle during agglomeration, this approach removes the drying stage. After freezing and filtering, granules with the specified particle size can be product (28).

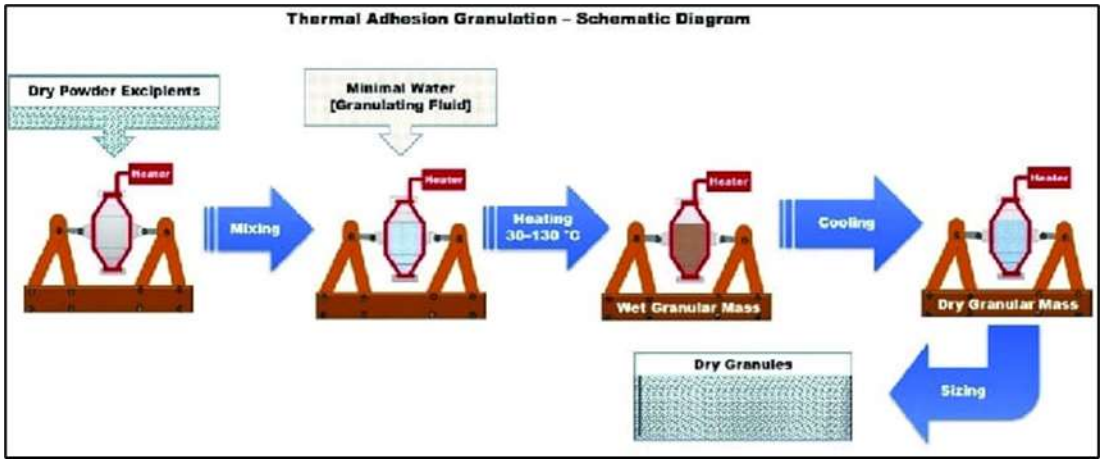

Figure 5 Thermal adhesive granulation

2.2.4. Melt granulation

Melt granulation or thermoplastic granulation is a technique that facilities the agglomeration of powder particles using meltable binders, which melt or softens at relatively low temperature (50-90^0 C). By cooling the clumped powder and then solidifying the moiten or softend binder, granule formation is complete. The absence of water and organic solvents makes this approach superior to conventional granulation.

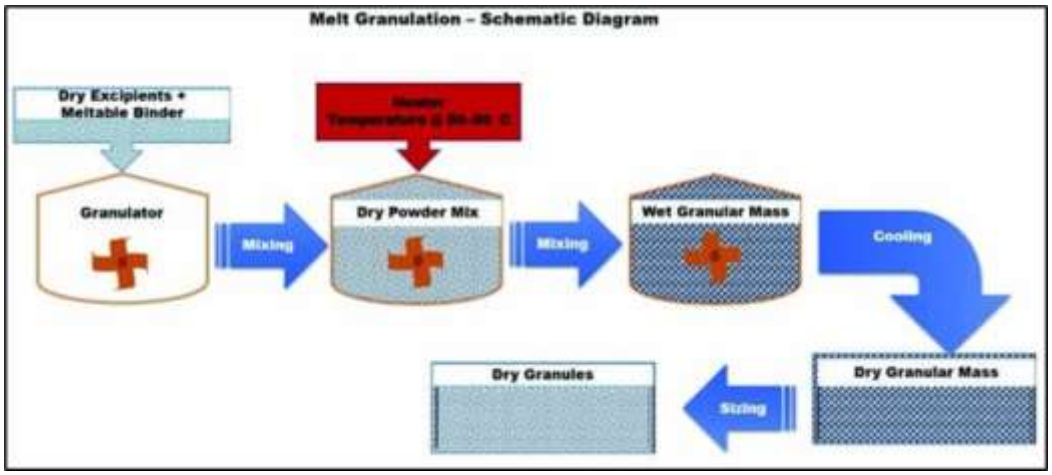

Figure 6 Melt granulation

Advantages

- Time and cost effective.
- Controlling and modifying the release of drugs.
- Water sensitive drugs are good candidates.

Disadvantages

- Heat sensitive materials are poor candidates.
- Lower melting point binder may melt/soften during handling or storage.

2.2.5. Foam granulation:

Foam granulation technique that uses foam to distribute binders to powder particles instead of spraying or pouring the liquid directly onto the powder. The advantages of foamed binder addition conventional binder addition method include-

- No spray nozzle is used

- Improve process robustness
- Less water required for granulation
- 4. Time efficient drying
- Cost effective
- Uniform distribution of binder
- No over wetting (29).

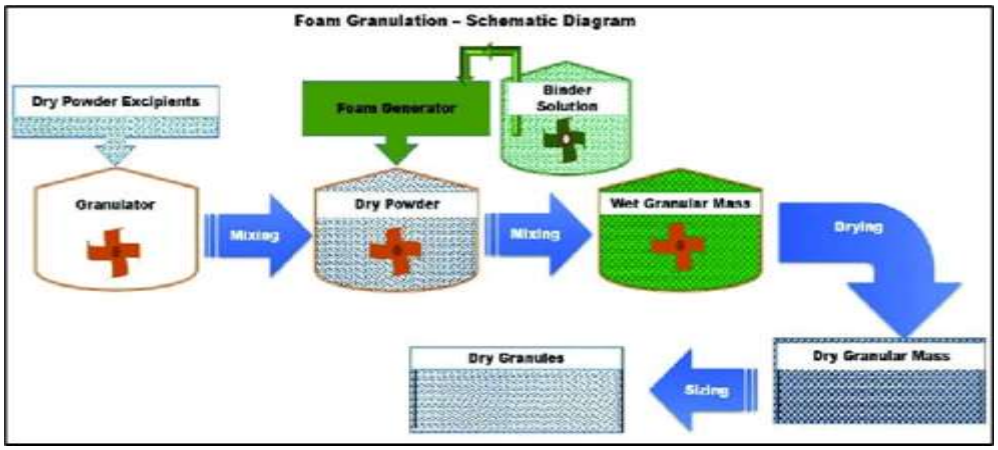

Figure 7 Foam granulation

2.2.6. Freeze granulation

Freeze granulation is a commercial process spherical granules from liquid materials by spraying them into a very cold environment(30). The process involve the following steps:

- 1. Spraying: A liquid material is sprayed into both of liquid nitrogen, which freeze the droplet instantly.
- Freeze drying: The frozen droplets are then freeze-dried to remove the solvent, such as water or an organic solvent.

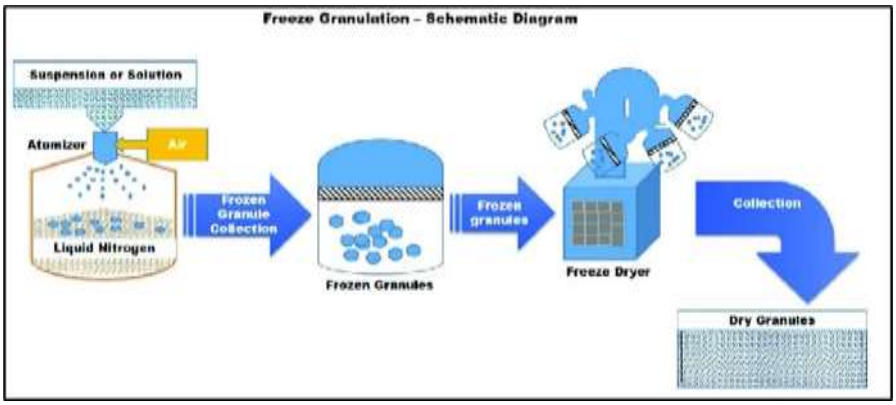

Figure 8 Freeze granulation

Advantages

- The granules density can be controller.
- No migration of small particles and or binder gives a high degree of granule homogenacity.
- No cavities in the granules.
- The equipment is easy to clean.
- Possibility of recycling organic solvents.

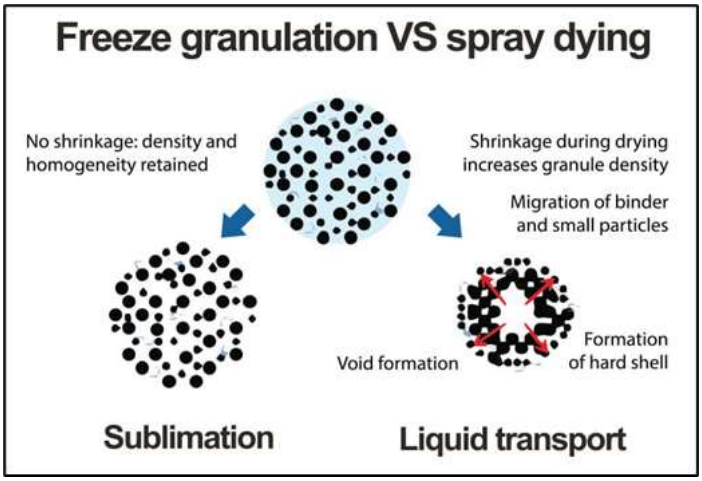

Figure 9 Process of freeze granulation

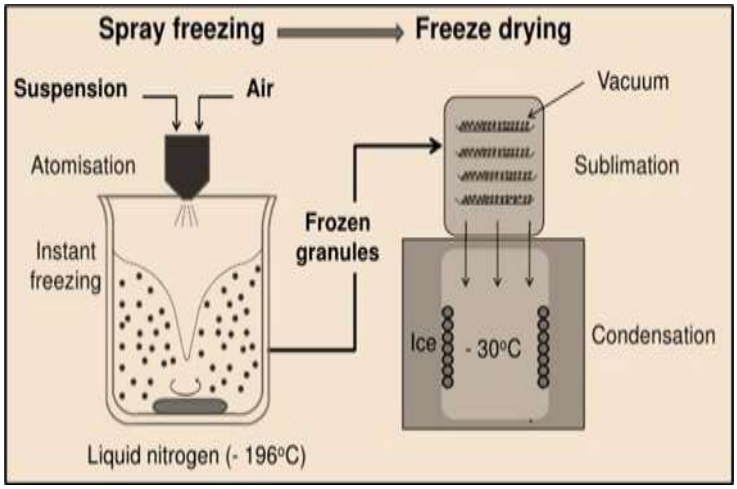

Figure 10 Process and temperature detective of freeze granulation

2.2.7. Reverse wet granulation

Reverse wet granulation or reverse-phase wet granulation is a new development in the wet granulation technique that involve the immersion of the dry powder formulation into the binder liquid followed by controlled breakage to form granules (31). It improve dissolution characteristic of poorly water soluble drugs by allowing uniform distribution of binder (32).

Advantages:

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.

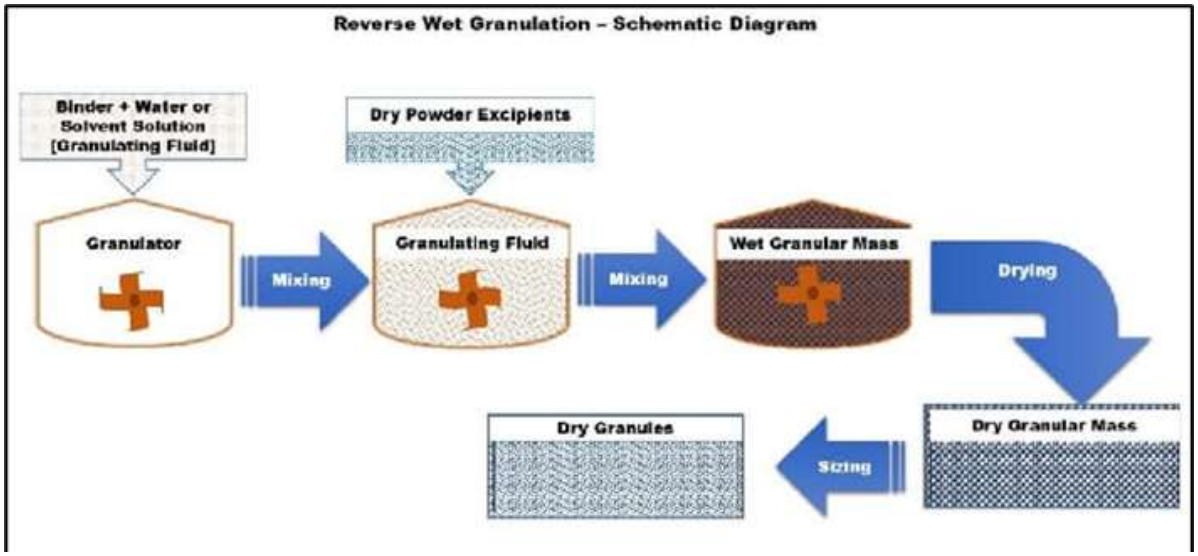

Figure 11 Reverse wet granulation

3. Conclusion

Tablets of good quality fulfilling the official specification with regard to drug content, hardness, friability, and disintegration time could by prepared by both the methods. The tablets prepared by direct compression method disintegrated very rapidly when compared to those prepared by wet granulation method. Technical and technological progress and ease other facilities is always desirable. The pharmaceutical granulation technique and technologies have improved over the years. This review discussed the recent development in granulation technology for conventional release dosage formulations only.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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