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Review Article

Beyond Traditional Methods: Novel Granulation Approaches for Enhanced Functionality in Pharmaceuticals

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ABSTRACT

Granulation, a cornerstone process in many industries, has seen significant advancements in recent years. This abstract explores these novel techniques, highlighting their potential to improve the functionality and efficiency of granule production.The traditional wet and dry granulation methods are addr essed, outlining their limitations, such as solvent usage and challenges with moisture-sensitive materials. The abstract then delves into innovative approaches that address these limitations. Techniques like pneumatic granulation, reverse granulation, foam granulation, steam granulation, and moisture-activated dry granulation (MADG) are discussed, emphasizing their advantages. Foam granulation offers improved binder distribution and reduced water requirement, while steam granulation eliminates organic solvents and promotes faster drying. Improved granule properties, including folowability, compressibility, and controlled release characteristics, are highlighted. Additionally, the reduction of solvent usage and drying times translates to increased environmental sustainability and production efficiency.The abstract concludes by emphasizing the ongoing development of novel granulation techniques. It underscores the potential of these advancements to revolutionize various industrial processes, particularly in the pharmaceutical industries, by ensuring the production of high-quality granules with improved functionality and at a reduced environmental cost.

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INTRODUCTION

Granulation is a process where small, coarse, fine particles agglomerate to produce a large mass called granules. Granulation is an essential step in the preparation of tablet and capsule. Theoretically particle size range for a granule is 0.2-4mm but most granules have a diameter of 0.2-0.5mm. Ideally granules must be spherical in shape, with sufficient fines to fill void space. Granulation depends on particles size of drug and excipients, concentration and volume of binder, type of granulator and drying rate temperature, time etc[1].

Mechanism of granulations

- **Particle bonding Mechanism-** particles need to bond with one another in order to stick together and form granules. The bonds must be strong enough that they don't break during handling. The 5 type of bonding mechanism between the particles are shown in Figure1.
- **Adhesion and cohesion forces in the immobile liquid films between individual powder**- when sufficient liquid is present in a powder inter-particle distance will decrease and there is increase contact area between the particles. When moisture is absorbed by powder particles it lead to adhesion. Pressure is applied during dry granulation to enhance contact area and reduce inter particle distance.
- **Interfacial forces in the mobile liquid film**- liquid that is used in wet granulation process dispersed as a film around and between the particles. Three types of liquid distribution between particles.
    i. **Pendular state**- Adhesion of particles occurs by lens shaped liquid.
    ii. **Funicular state-** It is intermediate step of pendular state and capillary state.
    iii. **Capillary state-**when all air is removed between the particles it is called capillary state. Continue kneading of wet mass gradually convert pendular state to capillary state.

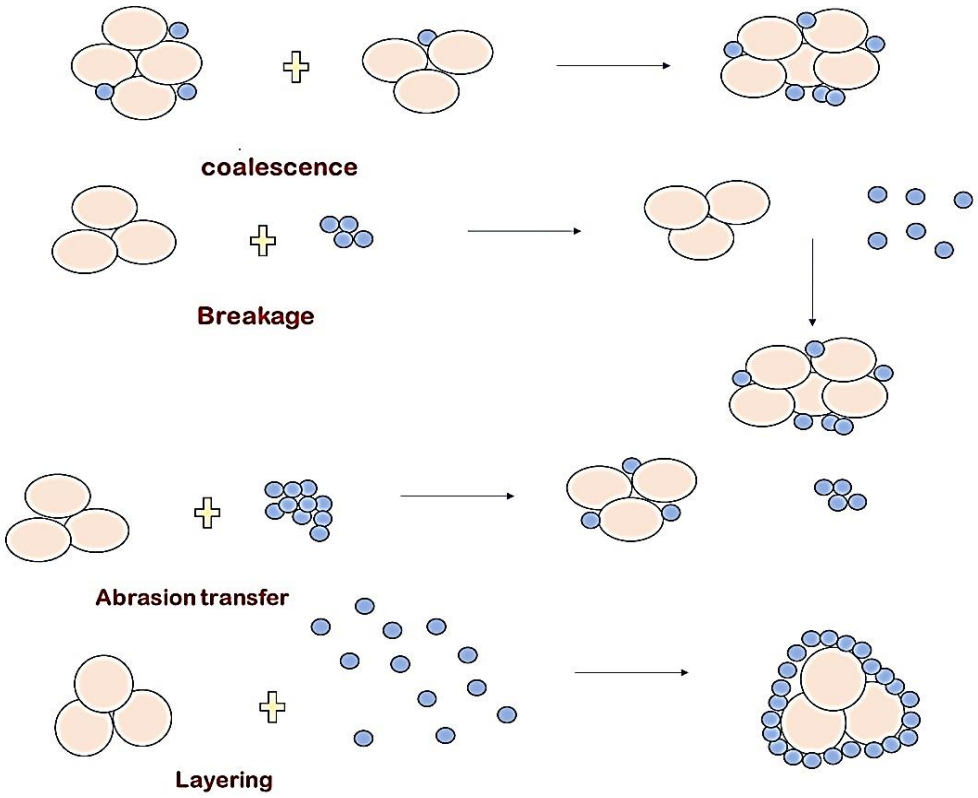

Figure 1: Mechanisms of granulation

Formation of solid bridge after evaporation of solvent- solid bridges are formed by 3 steps

- **Partial melting**- Pressure used in dry granulation may cause melting of low melting point substance when pressure is removed crystallization take place and bond is formed.
- **Hardening of binder**- This takes place when binder is added to granulating solvent. Liquid will form liquid bridge but adhesives i.e. added crystalize to form bridges. Adhesive include- PVP, CMC
- **Crystallization of dissolved substances**- One of the powder component is permitted to partially dissolve in the solvents used in the wet granulation process. This component crystalizes and act as hardening agent when the granules are dried. Ex- lactose added to powder blend granulated with water. In the absence of above solid and liquid bridges, two forces significantly act i.e. electrostatic and vanderwal forces. Electrostatic force is of low strength may be created due to mixing whereas Vander Waal forces are four times

greater than electrostatic force affecting bonding of particles[1].

Attractive forces between solid particles-Solid particles can attract one another even in the absence of liquid because of innate characteristics including electrostatic and van der Waals forces. Although electrostatic forces are usually small, they might promote cohesiveness during the first mixing of the material. When powders are compressed, these forces—which are greater than electrostatic forces—increase as the distances between particles get smaller.

Mechanical interlocking-This occurs often between fibrous or flat particles, where the physical shape of the particles leads to a form of mechanical bonding.

Granule formation divided into three stages Nucleation, transition, and ball growth coalescence. Mechanism of granulation can be varied according to the equipment used.

Nucleation: It occurs due to particle contact and adhesion due to liquid bridges. Particles aggregate to form pendular state which then gradually converts to capillary state. These bodies act as nuclei.

Transition: There are two ways to develop nuclei. Pendular bridges can add a single particle to the nuclei, or they can merge two or more nuclei, in which case the bed will be agitated and the nuclei will change shape. It is characterised by large number of small granules.

Ball growth: Large spherical granules are produced by continued granule growth, and granulation's mean particle size increases over time. Four potential ball growth mechanisms

- **Coalescence:** Two or more granules join to form large granules.
- **Breakage:** Granules break into fragments which adhere to large granules.
- **Abrasion transfer:** Agitation of granule bed causes attrition of material which lead to granule formation.
- **Layering:** A batch of powder increases the size of the granules by forming a layer on top of the granules.Use of slow process mixer like planetary mixture is preferred in layering because granulator end point control can be done easily[2, 3].

TYPES OF GRANULATIONS

Granulations are broadly categorised into two types i.e. Dry granulation and Wet granulation. A detailed description of Dry and wet granulation are shown in Figure-2.

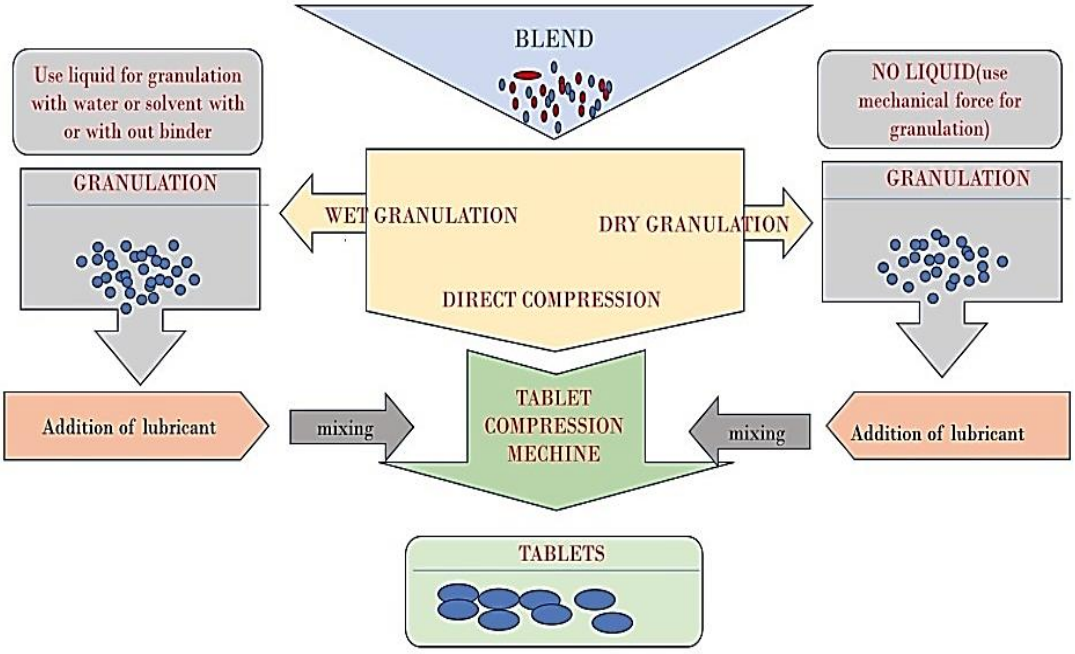

Figure 2: Types of granulation

Dry granulations:

Dry granulation is applied for drugs which are sensitive to moisture, not compressible after wet granulation. The two primary processes for producing dry granulations are slugging, which involves creating a big tablet (slug) using a heavy-duty tableting press, and roller compaction, which involves squeezing powder between two rollers to create a sheet of material. In each case, slugs are ground in a suitable mill and then sieved to produce the required granule size[1]. Figure -3

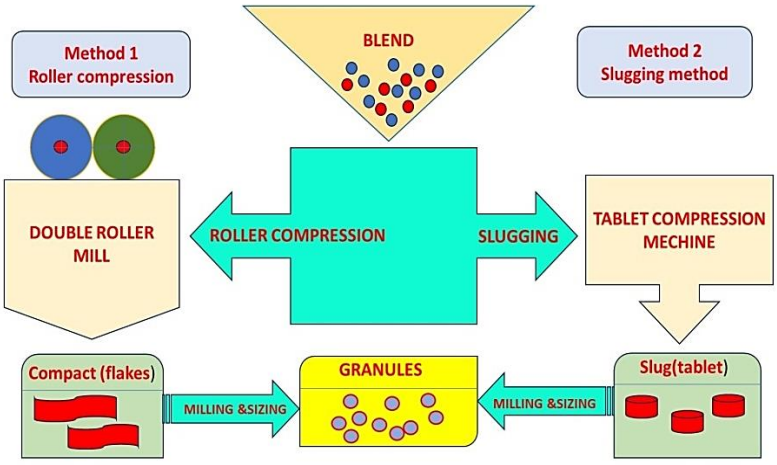

Figure 3: Dry granulation process

Progress in dry granulation:

Slugging or roller compaction could be used to create dry granulation. The schematic figure in Figure-3 depicts the two distinct kinds. Compared to wet granulation, the dry granulation technique and technology have not advanced as much, with the exception of one significant advancement known as pneumatic dry granulation[3].

Pneumatic dry granulations:

Pneumatic dry granulation (PDG) is a revolutionary dry granulation technology which combines air separation approach with roller compaction to create granules with a superior combination of flow ability and compressibility[4]. To produce a compacted mass with a mixture of small particles and granules, a light compaction force is first applied to the powder particles using a roller compactor.The required size granules are separated from the fine particles and/or smaller granules by entraining in a gas stream inside a fractioning chamber, where the desired size granules pass through to be compacted into tablets. (Pneumatic system).After being entrained, the fine particles and/or small granules are transferred to a device similar to a cyclone. There, they are either immediately reprocessed (recycling or recirculation process) or placed in a container to be processed later to produce the desired size granules.)[1]The pneumatic granulation process is shown in Fig-4.

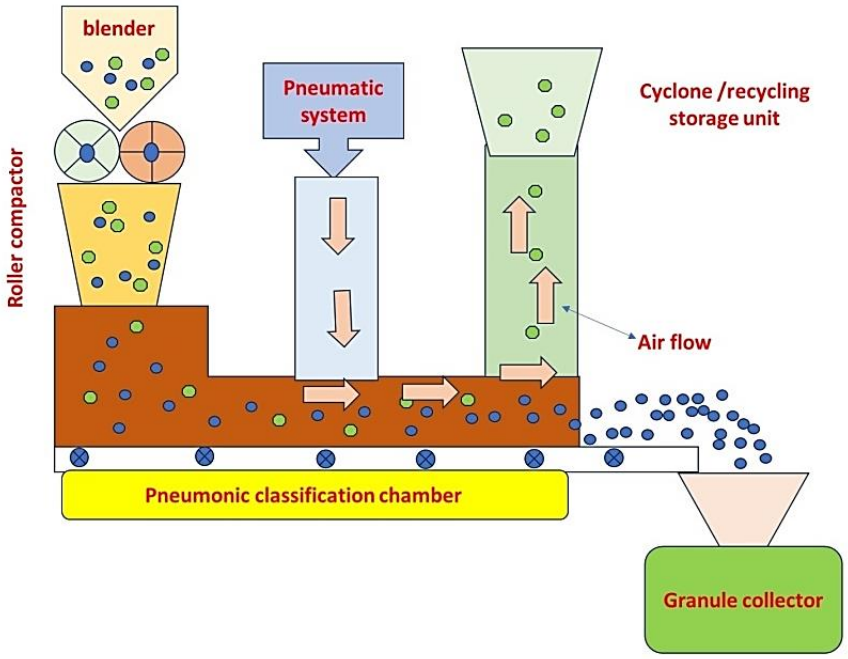

Figure 4: Pneumatic dry granulation process

WET GRANULATIONS:

It is a process of accumulating dry powder to form a wet mass using granulating fluid. Granulating fluid must be volatile in nature while drying it must be removed easily from the granules. Ex- water, ethanol, isopropyl alcohol. Granulating fluid may be singly used or it contains binder which help in aggregation of powder[1]. Steam granulation, moisture-activated dry granulation, also known as moist granulation, thermal adhesion granulation, melt granulation, freeze granulation, foamed binder or foam granulation, and reverse wet granulationare few of the technical and technological advancements that have been occurred in wet granulations. Schematic diagram of wet granulations shown in fig-5.

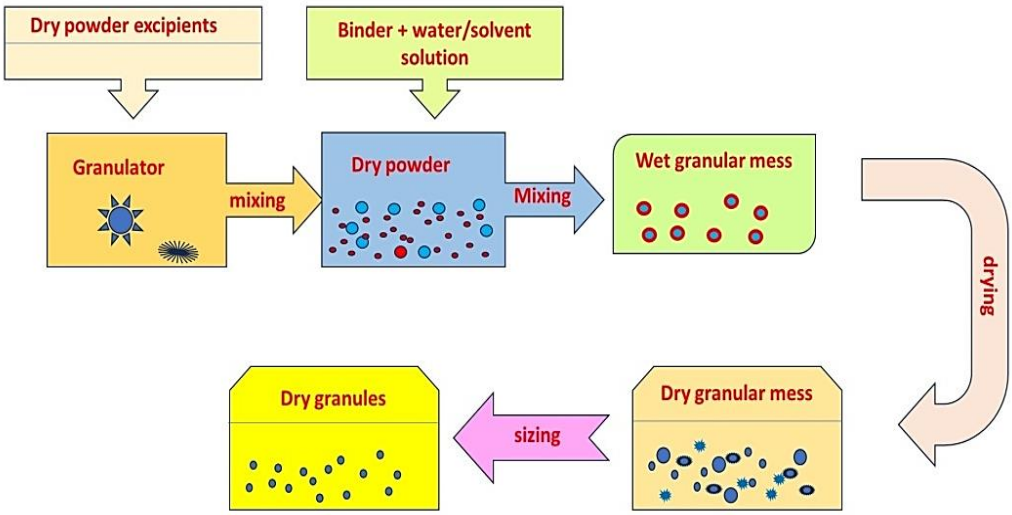

Figure 5: Conventional wet granulation Process

Reverse wet granulation:

Reverse wet granulation sometimes referred to as reverse phase wet granulation is a more recent development in the wet granulation technique. To create granules, the dry powder formulation must first be soaked in the binder liquid and then gently broken aparts[5]This procedure involvespreparing the binder solution first, and then adding the powder mixture to the binder solution in the granulator. Alternatively a drug polymer/binder slurry was prepared by mixing the drug with a granulating fluid containing a hydrophilic polymer or binder solution.

The drug-polymer/binder slurry was then submerged in a combination of additional dry excipients to create granules. After drying, the resulting moist granules were milled.

The handling and flow characteristics of the granules produced by this technique are equivalent to those produced by wet granulation process[6]. Reverse wet

granulation tablets show better dissolving than tablets manufactured using conventional wet granulation process. This technique enhances dissolution of poorly water soluble drugs by causing uniform distribution of binder and enables adequate wetting of drug substance and uniform contact between hydrophilic polymers for better dissolution[6]. This method produces small spherical shaped granules with improved flow property, uniform wetting and erosion of granules. Fig-6.

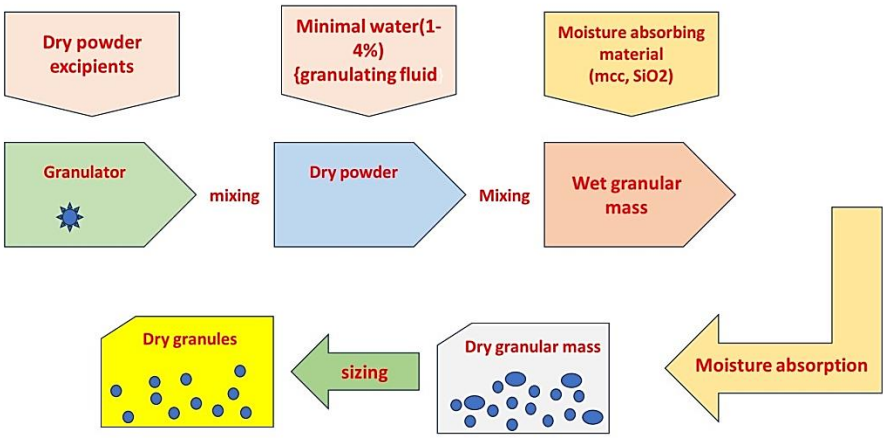

Figure 6: Reverse wet granulation Process

Steam granulations:

In this method pure steam is used as binder rather than one liquid. Additionally at standard temperature and pressure the volume of the steam will be approximately 1,600 times that of an equivalent quantity of liquid. Steam in its pure state act as transparent gas that promotes better thermal balance throughout the drying process and cause faster rate of diffusion into powder. Following condensation, steam forms an easily evaporative film around the powder paricles.[7]. The process of steam granulation is presented in Fig-7.

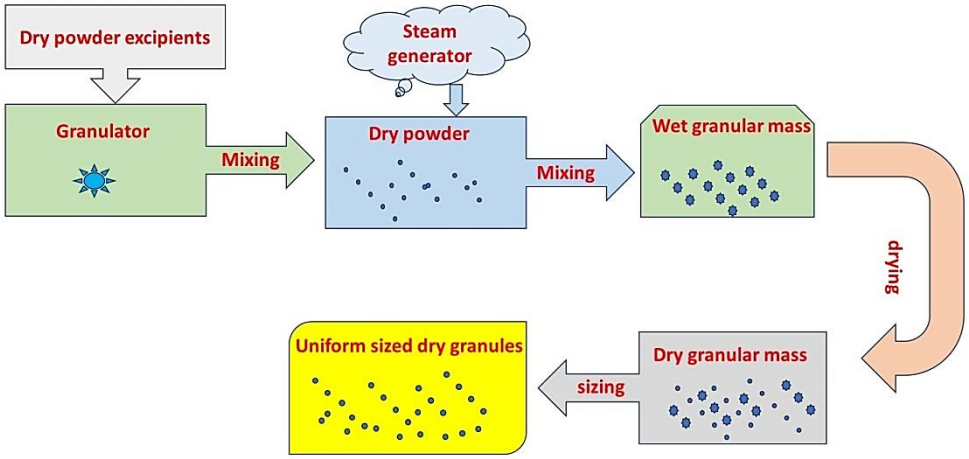

Figure 7: Steam granulation process

Moisture activated dry granulations:

This technique uses very little water to initiate the agglomeration process and activate a binder (Figure-8). A high shear mixer combined with spraying is suitable equipment for Moisture activated dry granulation. Wet agglomeration of powder particle, moisture absorption/distribution is principle of Moisture activated dry granulations.

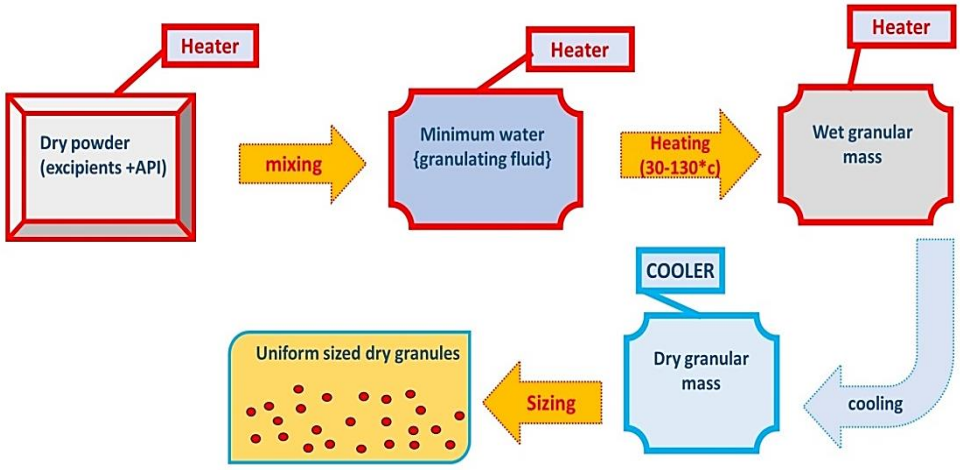

Figure 8: Moisture activated dry granulation Process

Usually, little amount water (1-4%) added to mixture of drug and excipient. Granulating fluid activates binder and it lead to agglomeration. After agglomeration moisture absorbing substance like MCC, Silicone dioxide applied to help absorb surplus moisture. The outcome is a dry granule mixer. It results in dry granule mixer. During this drying process some granules break and some remain as it is. This step prevents expensive drying step. This method offers following advantages such as no lump formations as less amount of water added, size range of agglomerates (150-500 µm). MADG is suitable for immediate release, controlled release tablet, it increase flow properties, compressibility, less energy input, continuous process. Due to instability, this approach is not appropriate for medications that are sensitive to moisture or hygroscopic substances[8-18].

Thermal Adhesion Granulations:

Like Moisture Activated Dry Granulation (Thermal Adhesion Granulations) uses granulating agent and heat for agglomeration[19]. It is shown in fig-6. It uses water as solvent/ granulating fluid. Furthermore the granulation process is carried out by the uses of heat[20]. In order to provide drug particles agglomerate the excipient mixture is heated in a closed system with tumble rotation to a temperature between 30 to 130c[21]. Here less amount of granulating fluid is used i.e. used in agglomeration hence no drying is

required. Granules of required particle size can be obtained by cooling and sieving shown in (Figure-9). This technique provides granules of desired flow property, high tensile strength that could be directly compressed[21].

Limitation-considerably high energy input special heat generating and regulation equipment is required. It is not for thermo labile drugs and not all binder can tolerate this high temperature[22].

Melt granulation:

It is also called thermoplastic granulation. In this process binder that melts at low temperature (50-90c) is used[23]. It is shown in figure-9. By cooling the agglomerated powder and solidification of binder final granules is produced.The binder can be introduced as molten liquid that may or may not contain a dispersion agent, or as solid particles that melt during the process (insitu granulation).It include heating a mixture of drug, binder other excipient to the temperature at or above melting range of the binder. While spray on process involves spraying of molten binder optionally contain the drug on to the heated powder[24-28]. Melt granulation is an alternative method to water sensitive material[29]. Aqueous or organic solvents are not required for melt granulation which eliminates the environmental need for organic solvent collection and recycling. This is one of the many benefits for melt granulation vs. wet granulation. Because it does not require water, less energy is used during wetting and drying phases.[30-34]. It improves stability of moisture sensitive drugs and improve physical properties[35]. Disadvantage of the process are during the procedure, high temperatures might damage or produce oxidative instability in certain ingredients. Granulator must be a high shear fluidized bed dryer[36].The steps in the process of melt granulation are present in Figure-9.

Freeze granulation:

It involves spraying droplets of a slurry/suspension into liquid nitrogen followed by freeze drying[37]. When a powder suspension is sprayed into liquid nitrogen the droplet quickly solidifies to granules (Figure-10). The granules are then dried by sublimating ice in the process of freeze drying that provides segregation. In this process water based or solvent based slurries are used to yield spherical free flowing granules. The structure and uniformity of the granules are maintained in the slurry or suspension. Any type of material can be made into granules but fin powder with proper additives are desired for the process[37]. It is useful for preparation of granules that is used in suspension, parenteral formulation Nano materials, self-emulsifying medication.

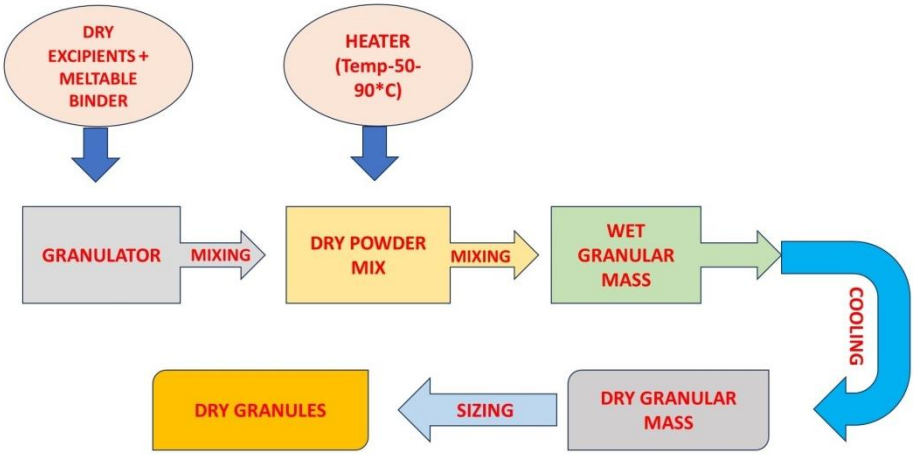

Figure 9: Thermal adhesion granulation Process

The freeze granulation creates proteins particles that are lighter and more porous than spray drying and due to this advantageous aerodynamic features. This technique produces better aerosol performance powder. Various advantages are granule density can be controlled. Due to lack of tiny particles mobility granules without cavity have high level of homogeinity[38].High product yield since there is little material waste and potential to recycle organic material exist. While a solvent with a frezzing point of (25±10c) can be utilised, water is the ideal solvent for this method because it dissolves any type of excipient and drug. . This methods was 1st created in late 1980 by Swedish ceramic institute. At present powder pro AB, a Swedish ceramic institute develops freeze granulation equipment[39]

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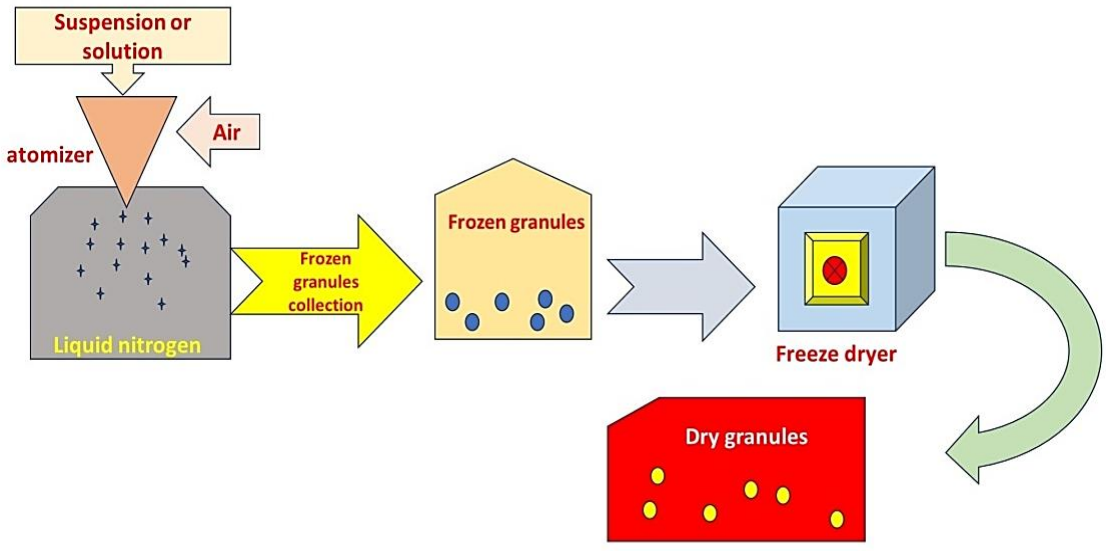

Figure 10: Freeze granulation Process

Foam granulation:

Foam is entrapment of gas in a solid liquid. Foam granulation is also called foamed binder granulation (Figure-11). This technique involves liquid/ aqueous binder as a foam. It is described in fig-(11)[40]**.** Foam generator is introduced to binder solution tank with high shear granulator or fluid bed granulator to add the binder in the form of foam. Addition of foam binder eliminates problems of in consistent binder distribution. Foam binder distribute well among the powder. Furthermore the sprayed liquid droplets requires a lot of water and binder since they have poor spread to soak ratio[41]. The spread to soak ratio means they tend to soak into powder and create over wetting rather than spreading on the particle surface. Eventually drying will remove surplus water. Conversely a foamed granules use less binder and has higher spread to soak ratio. Since the binder are coated on the particle rather than soaked. These elements save processing time and increase reproducibility. Most significant benefits of this technology is removal of spray nozzles along with associated processing variables and clogging issue. Because this technology can distribute drugs evenly it could be helpful for high potent/ low dose drugs. This technology is used to manufacture water sensitive formulations. In additions immediate release/ controlled release formulation also prepared because of small amount of water used and quick processing time[42, 43]. High/ low shear mixture, fluid bed granulator along with foam generator could be used for it. Despite many benefits of this technology further research is required to fully comprehend foam quality, process variables equipment, flow patterns, mixing behaviour etc[43]. In addition getting regulatory permission would be a significant challenge that need to be meet[44].

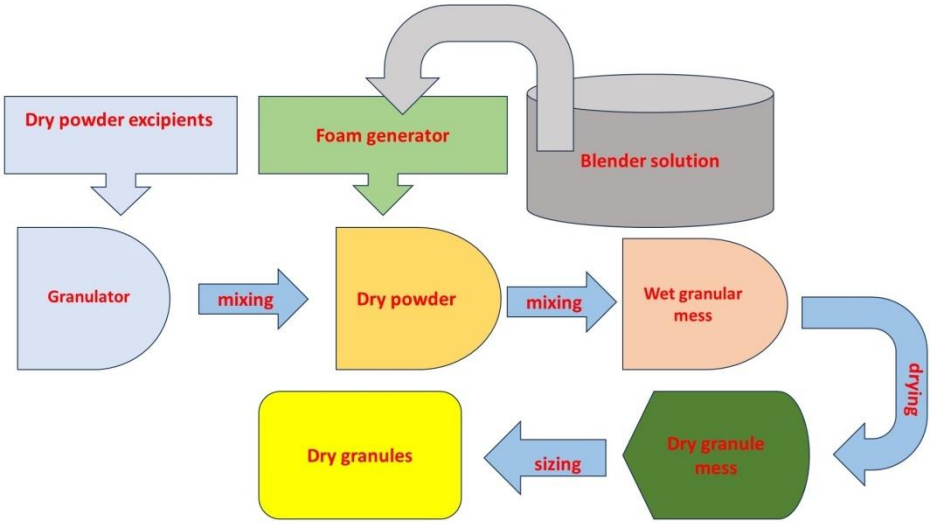

Figure 11: Foam granulation Process

Conclusions:

Technological and technical advancements that facilitate and enhance current procedures may have a significant impact on the economy, time, and development of new products as well as the process ability and quality of product compositions. It is evident that advances in pharmaceutical granulation technology and procedures have occurred over time. Nonetheless, the pharmaceutical industry has always had a keen interest in cost-effective and efficient production methods, which encourages multinational multidisciplinary scientists employed by pharmaceutical companies to conduct research and develop new and improved technologies. During the formulation development process drug material provides a unique set of challenges. Scientists must take into account at the method selection stage. Every approach has advantages and disadvantages of its own, thus choosing the right technique is requires complete knowledge about the physicochemical properties of drugs, excipients. According to the author, successful industrialization of the novel methods and technologies included in this review would require improvements in machinery, procedures, etc.

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