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A Review: Novel Granulation Technology

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Abstract

All the pharmaceutical Active pharmaceutical Ingredients (API) and Pharmaceutical excipients will have different particle size. While formulating a dosage form, particles from raw materials will tend to separate from other due to their rheological properties. There could be a condition where fine particles separate from the larger particles causing demixing or uneven distribution of active with its excipients leading to tablet content uniformity issue. To overcome this problem, particle enlargement or particle cohesiveness with or without additional aid is necessary, which could be achieved by granulation. Hence granulation technology is important in the formulation of pharmaceutical oral solid dosage form. Granulation is the process of adhering fine particles agglomerate into a large particle using two most common methods i.e. wet granulation and dry granulation/compaction. Day by day technological innovation is happening in all fields and pharmaceutical granulation process is also not an exemption. The objective of present review is to focus the novel granulation technology and how it is differing from the conventional granulation technology.

Keywords: Novel granulation, Excipients, Active pharmaceutical ingredients, Conventional tablet

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1. Introduction

Active pharmaceutical Ingredients are pharmacologically active chemical substances that are used to treat disease and symptoms. (1) Excipients are vehicle that plays a huge role in formulation. Earlier, it was thought that excipients are inert in the formulation, but nowadays excipients are modified synthetically which can greatly modify the intended effect of a drug and release characteristics from the dosage form. (2)

Selection of excipients and processing (method of Granulation) of drug and excipients mixture is a very important in the formulation. Success of formulation depends on the selection of excipients and the order in which the formulation ingredients are mixed with the drug, as well as how the process is carried out. (3)

Granulation is universal unique unit operation in pharmaceutical oral solid dosage form formulation. It is known for enlargement of particle size or process of conversion of fine powders into dust free large free-flowing powders. Still novel granulation process eliminate excessive amount of fine particles and will improve compression character, flow property of powder and blend uniformity. Generally, granules can be in the size range of 0.2 to 0.5 mm depending upon the process employed. Overall the purpose of granulation is to enhance content uniformity of API in final product and to increase the density of blend to occupy less volume in the unit dosage. It also plays a part in better shipment, storage. (4-5)

Ideal characters of granules:

Granules are spherical shaped smaller particle in the range of 0.2 to 0.5 mm with sufficient fines property to fill void spaces present between granules. The granules should have adequate moisture (between 1-2%) with good compressibility flow and sufficient hardness.

Strength and size of granules depend on the

- Drug and excipients particle size
- Binder and solvent volume
- Binder type
- Wet massing time

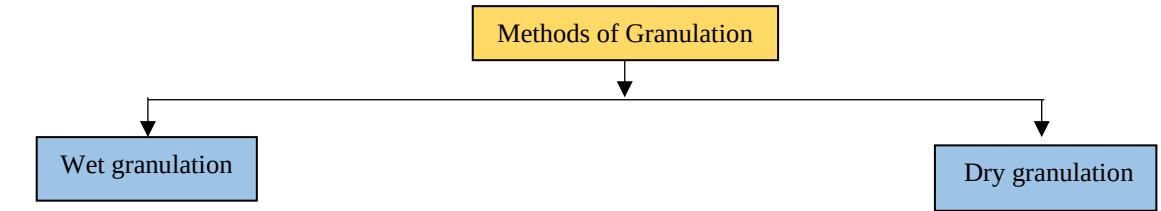
- Binder addition rate and amount of shear applied
- Time of drying (Polymorphism)
- Type of granulator (6)

Reason for granulation:

- ✓ To enhance the property of powder flow
- ✓ To enhance the strength of granule.
- ✓ To improve compression ability.
- ✓ To improve drug stability.
- ✓ To regulate the drug release from its dosage form.
- ✓ To prevent the formation of dust during process of granulation (7)

Methods of granulation:

API and excipients can be compressed into tablets from blend of powders processed either by wet granulation or dry granulation [Figure 1]. Granulation technique is broadly classified as two types, dry granulation and wet granulation, a type of method used to facilitate the agglomeration of powder particles. Physico-chemical property of API and excipients helps to select the method of granulation. i.e. if API is heat sensitive dry granulation is suitable and incase of bulk amount of API in a formulation, Wet granulation is one of the methods for processing.



Steps involved

- Mixing of the drug(s) and excipients
- Preparation of binder solution
- Mixing of binder solution with powder mixture to form wet mass.
- Coarse screening of wet mass using a suitable sieve (6-12 screens)
- Drying of moist granules
- Screening of dry granules through a suitable sieve (14-20 screens)
- Mixing of screened granules with disintegrant, glidant, and lubricant.

Steps involved

- Shifting of drug(s) and excipients
- Mixing of shifted powders
- Compression into large, hard tablets to make slug
- Screening of slugs
- Mixing with disintegrating agent and lubricants.

Figure 1 : Above diagram representing conventional granulation steps

Schematic diagram of conventional granulation technology

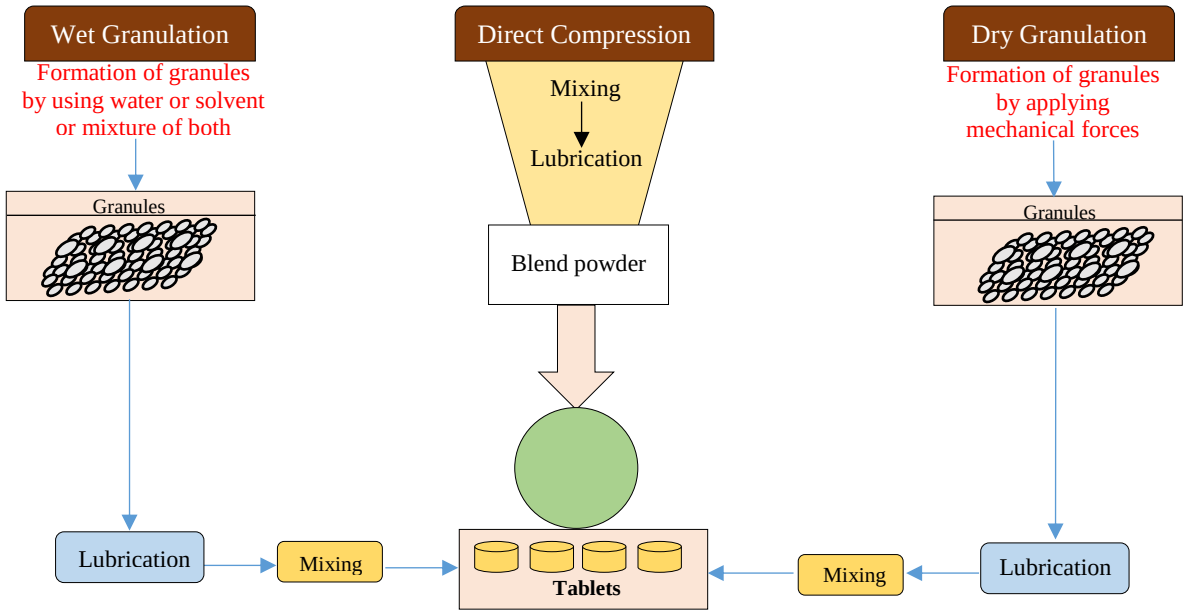


Figure 2. Diagram representing process and steps in conventional granulation technology

Novel Granulation technology

In the past one decade and at present, due to technological improvement, various newer granulation technologies have been evolved to improve commercial output such as:

- ✓ Reverse Wet Granulation
- ✓ Moisture Activated Dry Granulation (MADG)
- ✓ Thermal Adhesion Granulation Process (TAG)
- ✓ Steam Granulation
- ✓ Melt Granulation
- ✓ Foam Binder Granulation
- ✓ Freeze Granulation
- ✓ Pneumatic Dry Granulation
- ✓ Twin Screw Granulation (TSG) (9-10)

Reverse phase wet granulation or Reverse wet granulation

Reverse-phase wet granulation is a reverse process of conventional wet granulation technique. It is a new development in the wet granulation and the process invloves immersion of dry mixture powder into the binder solution followed by continuos controlled breaking produces granules. According to this method, initially the binder solution was prepared by adding the binder and API into the solvent such as water or isopropyl alcohol to form a slurry. This slurry act as a granulating fluid. Granules are formed by immersion of dry powder mixture containing excipients into the granulating fluid. Formed granules size were reduced by milling after drying, granules were produced by this process found to be a good flow, good compression character, more uniform erosion on dissolution media, compared to conventional wet granullation technology. Diagramatic representation of reverse phase wet granulation was shown in figure [Figure 3]. (9-11)

Schematic diagram of Reverse wet granulation

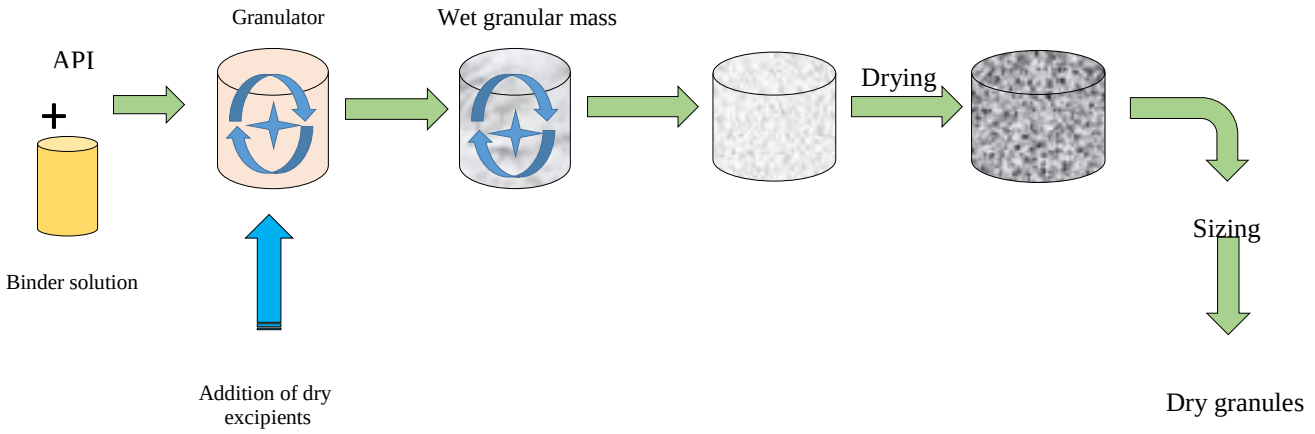


Figure 3. Diagram representing process involved in reverse wet granulation

This novel granulation technique is helpful to increase the dissolution behaviour of poorly water soluble drug by uniform distribution of API with binder solution and it act as wetting agent. It enables wetting of API during granulation process so as to produce enhanced drug release during dissolution compared to the conventional granulation. By this technique granules were produced with lower intragranular porosity and greater mass mean diameter when compared to the conventional wet granulation even at low concentration of binder. (12-13)

Moisture activated dry granulation (MADG):

In MADG process, granules are formed by moisture. Hence, drying step is not necessory because of moisture absorbing material such as micro crystalline cellulose, silicon dioxide, potato starch was added after wet mass formation. Moisture absoring material absorb excessive moisture, so drying step is eliminated. After that the granules were involved into lubrication process resulting powder mixture was compressed into tablet. By MADG process small quantity of water is enough to activate binder in pre-mixed powder blend and initiate granulation process. (14)

MADG process involve two step to form granules.

Wet granulation of powder.

Moisture absorption.

Step 1 : agglomeration of particle

By initially adding small quantity of water (usually less than 5%) into the powder particle triggers agglomeration with small wettability. The formataion of agglomerates are small spherical shaped because of less quantity of water used, compared to conventional wet granulation method.

Step 2 : Addition of moisture absorbing materials

After completion of agglomeration particle addition moisture absorbing materials is carried out inorder to facilitate the excess quantity of moisture from agglomerates.

Advantages of the MADG process is less water or solvent required to form granules so large lumps (particle growth) formation was prevented by this process and particle size of agglomerates is 150 to 500 µ. Actual processing time of MADG process is 15-20 minutes. It is continuous process, time efficency, very less energy input, fewer process variable. However this method is not suitable if

the granules have high drug load, moisture sensitive drug and hygroscopic drug.(15)

Granules produced by MADG method is useful for immediate release and controlled release because granules obtained by this method have increased particle size, enhanced flow property with good compressibility. High shear mixture coupled with spray gun is suitable equipment for moisture-activated dry granulation process.(9) Venkateswara reddy et al, reported that the MADG process is robust and creates granulation with good physical properties and finished products with satisfactory quality attributes. It is also an economical, energy-saving, and efficient manufacturing process.(16)

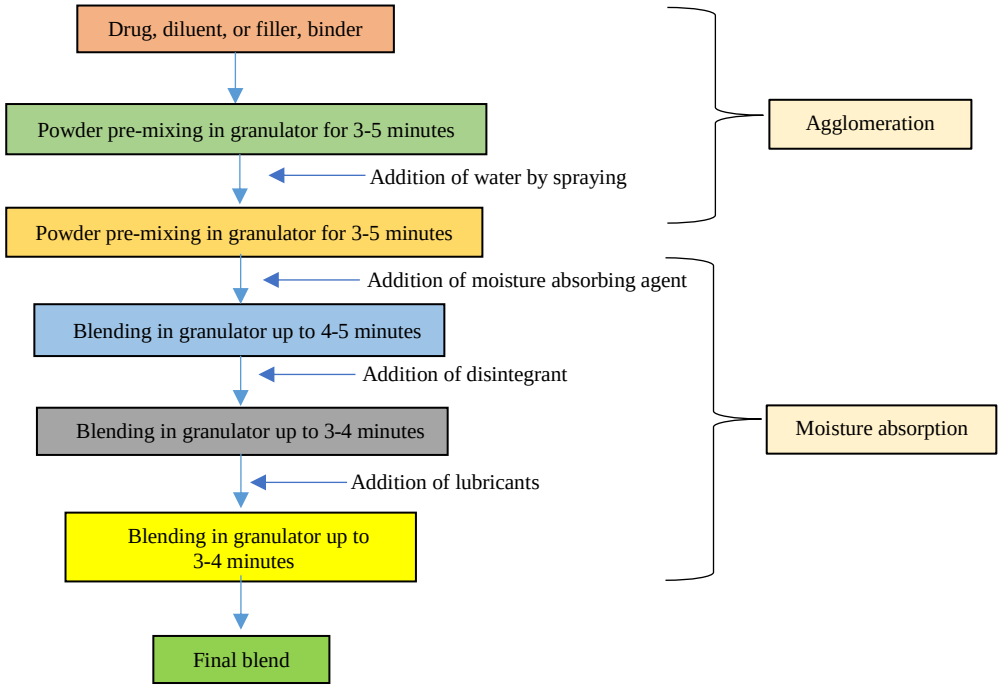


Figure 4. Diagram representing Moisture Activated Dry Granulation(MADG) process

Thermal adhesion granulation (TAG):

This technique was developed by Wei-Wing Pharmaceuticals, Taiwan. TAG process is suitable for direct tableting formulation and it is performed under low moisture content and with low pharmaceutically acceptable solvents such as water, isopropyl alcohol, etc by introducing one or more excipients. This process is not like moisture activated dry granulation process because in MADG process water alone used as granulation agent. In TAG process, water and solvent both used in granulating process, in addition to this heat is used to facilitate the granulation process. In TAG process drug and excipient mixture is heated to 30°C to 130°C in closed system under tumble rotation to facilitate agglomeration of granules formation, followed by cooling process to produce required size of granules through sieving. Advantage of this type of process is to prevent dust during formation of granules because it is a closed system.(17-18) The TAG process is was clearly presented in [Figure 5].

Steam Granulation:

Steam granulation is the modified method of conventional wet granulation process. This process is ecofriendly because in this novel method no organic solvent used but instead of that pure steam is used. Pure steam will have good penetration power compared to conventional granulation fluid such as water and other organic solvent. Pure steam act as binding agent instead of water and it diffuse uniformly into powder particle and it forms thin hot film on the surface of powder particle, causes adhersion of particle that results in larger particle in a short time period. This novel method is good to improve dissolution behavior of poorly water soluble drug because increased surface area obtained by this steam granulation method. However this method may not be suitable for certain thermolabile API, since hot steam is used. Equipment such as high-shear mixer coupled with a steam generator would be enough for this technique. This method was clearly presented in diagram [Figure – 5].(19-20) Cristina et al observed increased dissolution rate of poorly water soluble drug of piroxicam by steam granulation technique.(21)

Melt Granulation:

Melt granulation is the type of novel granulation process. In this process granules are obtained by adding meltable binder to the dry powder excipient and API mixture under continuous heating. Melting point of binder should be in the range of $50^{O}C$ - $100^{O}C$. This method is suitable for moisture sensitive API and the binders are added in a form of solid material. All the excipients, binders and API are added in the granulator. Heating is initiated inside the granulator with continuous rolling to produce the melting of solid binder into liquid cause agglomeration of powder particle by liquid bridge. It is formed between the powder particle followed by cooling process producing small size dry granules with good compressibility property. In this

method, drying step is eliminated. This melt granulation process is less time consuming and reliable. Meltable binders such as polyethyle glycol, stearic acid, cetyl alcohol, stearyl alcohol, mono- or di-, or tri-glycerides and polyoxy stearates are used.(22)

The equipment that could be used for melt granulation is high-shear mixer and fluidized bed granulator. So many formulators are showing interest in melt granulation process in recent years because this technique has numerous merits over conventional wet granulation technique.(23) Process of melt granulation was clearly represented in diagram [Figure 6].

Foamed Binder Granulation (FBG)

Foamed binder granulation is otherwise called as foam granulation. In this process, binder is used in the form of foam. FBG process invloves addition of binder solution on moving powder particle in the form of foam instead of coventional pouring method. Dow chemical company (Midland, MI) was first introduced and patented the Foam binder Granulation technology in 2003. Dr. Colinkeary and Dr. Paul Sheskey was the inventor of foam granulation technology. Foam is a colloidal dispersed system consists of liquid continuous phase and gaseous dispersed phase. It will consume fewer amounts of binder solution and less cleaning time.(24-25)

A foam generator is used to create foam binder; the resulted foam is very consistent like shave cream. Hydroxyl propyl methyl cellulose is cellulose derivative polymer which is soluble in water. Binder solution was prepared and poured into foam generator tank; dry powder excipient with API was placed in a rotating blender at the same time foam was generated resulting the agglomeration of particle followed by continuous break mixing. Tablet prepared by this granulation process, have enough hardness with less disintegration and dissolution time. This method is suitable for highly potent drug, because blend uniformity is improved by FBG technology.(26)

Schematic diagram representing steam granulation:

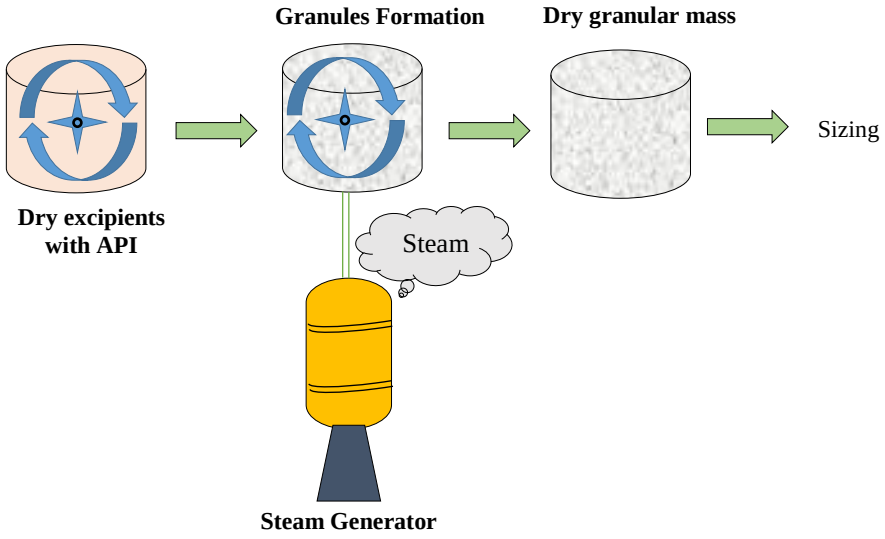


Figure 5. Diagram representing process and steps involved in steam granulation method

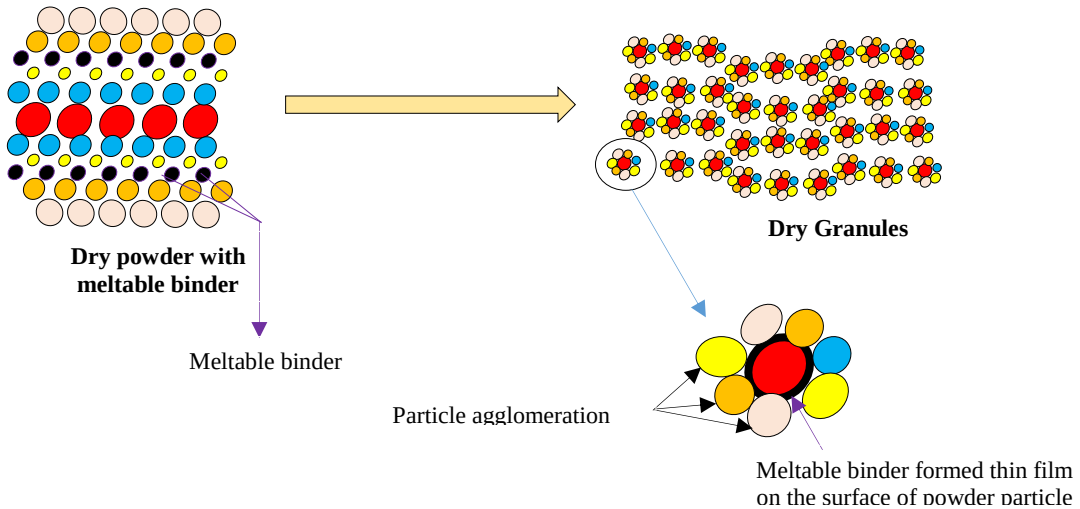


Figure 6. Diagram representing process involved melt granulation

Schematic diagram representing foam binder granulation

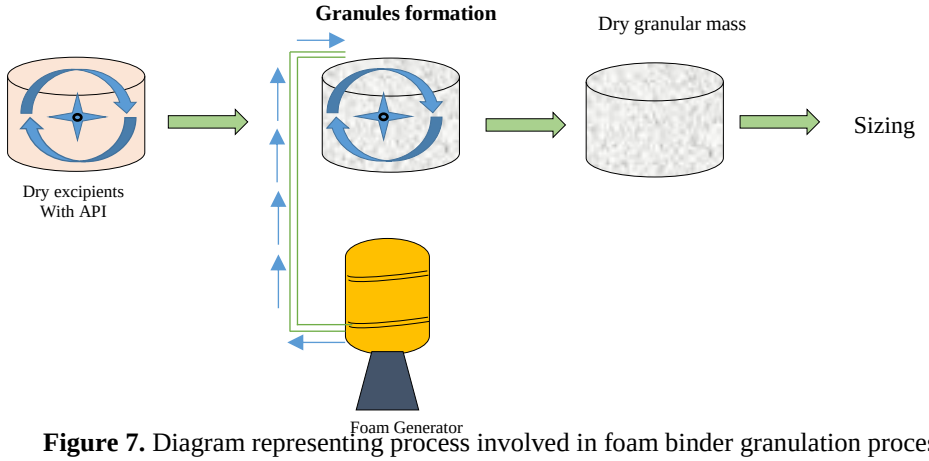


Figure 7. Diagram representing process involved in foam binder granulation process

Freeze Granulation (FG):

Swedish Ceramic Institute was adopted and developed by freeze granulation technology. The FG process involves the preparation of suspension or slurry by mixing all powder excipients and API in a suitable liquid medium and the slurry was sprayed in the liquid nitrogen containing medium. In that medium the slurry was converted from slurry into frozen powder particle. Finally all the, frozen granules was collected and dried by sublimation using ice without any segregation of granules. (27) The resulted granules was spherical and free flowing with optimal homogeneity. Granules size depends on the spray rate, pump speed, air pressure and pore size of spray nozzle and solid content of suspension. FG granulation is suitable for formulation of heat sensitive material and formulation of proteins substance because proteins have astringent property (proteins precipitation). This method is suitable to formulate re-dispersible parenteral powder, nano material, micro particle etc., Granules obtained by this process like spherical shaped particle with better free-flowing property and no cavities are observed. (28) Process of freeze granulation was simply given in flow chart [flow chart 1]

Merits of freeze granulation:

- Mild drying prevents oxidation of materials.
- Particle size controlled by spray rate and solid content of suspension.
- It prevents low material waste.
- No cavities observed in granules.
- Possible re-use of liquid nitrogen.
- Less time consuming, easy to clean.(29)

Flow chart of Freeze Granulation

Preparation of slurry
↓
Spraying of slurry into liquid nitrogen
↓
Freezing of droplets in liquid
Nitrogen medium
↓
Followed by sublimation of frozen
Particle without segregation
↓
Collection of granules

Flow chart – 1. Freeze Granulation

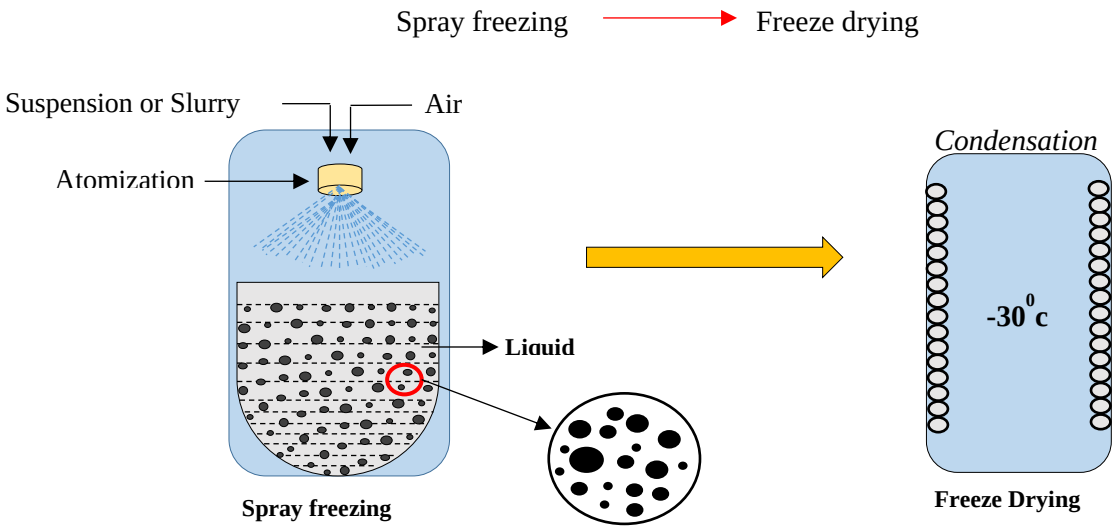


Figure 8. Diagram representing process and step of freeze granulation process

Flow chart 2: Schematic diagram representing pneumatic dry granulation

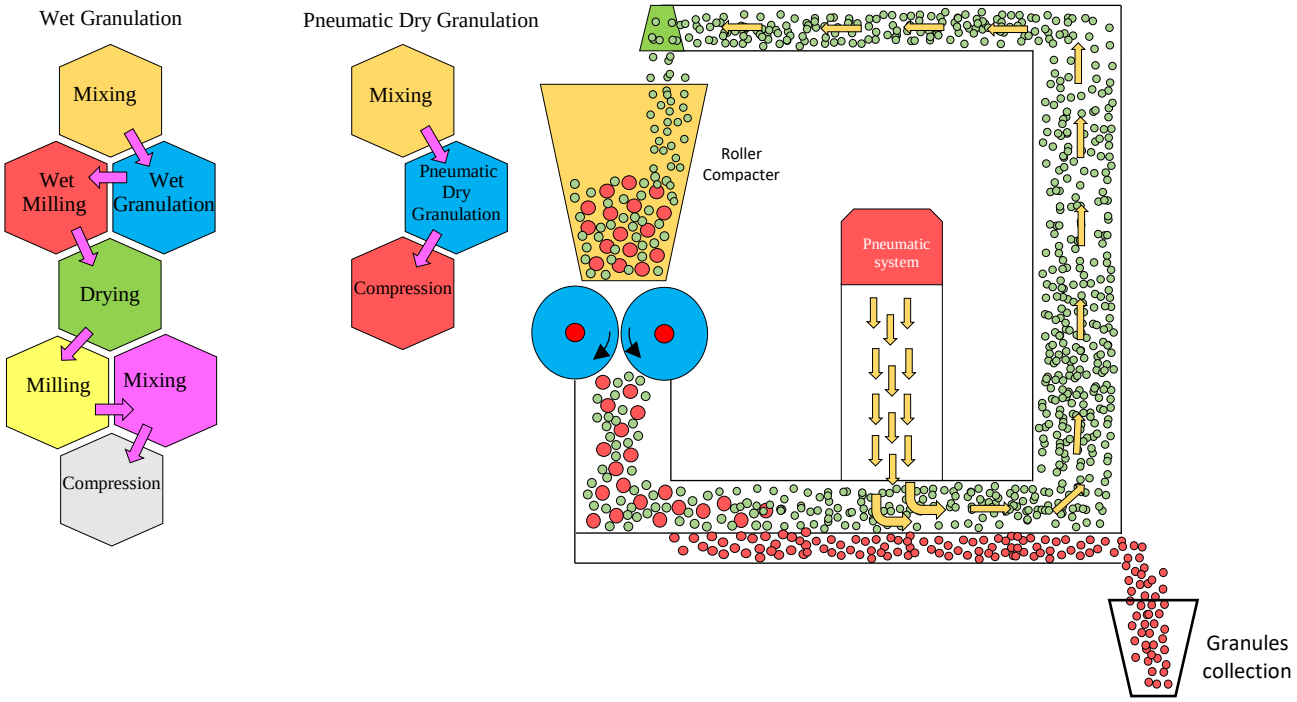


Figure 9. Diagram representing pneumatic dry granulation process

Twin Screw Granulation (TSG):

TSG has continuous and open (without die) granulation process implemented by pharmaceutical company switch from batch process to continuous process to overcome batch to batch variation, product loss by process, cost effect, and flexibility. The merits of TSG were improved product quality with low environmental impact. Replacing conventional wet granulation process by using TSG process. Additionally continuous process was encouraged by regulatory authority. More studies are conducted in TSG but limited numbers of researcher addressed the process parameter. In TSG process, granulating powder loaded in hopper, continuously placed binder adding nozzle or hopper, it consist of two closely arranged long screw, granules where formed by mechanical force produced by twin screw followed by addition of liquid binder resulted slightly wetted granules with good granular shape finally kneaded granules where obtained by TSG process. (33-34) TSG process is shown in [Figure 10]. Dhenge et al reported that more spherical granules produced by increasing the length of screw and size of granules depend on the length of screw.(35) Michael et al formulated sustained release tablet of ondansetron by twin screw granulation technology in the aspect of ready to compress.(36) Vanhoorne et al formulated controlled release formulation with various grade versatile matrix polymer of Hydroxy Propyl Methyl Cellulose by twin screw granulation technology, the resulted granules showed good compressibility and flow property with tablet showed good drug release pattern.(37)

Conclusion

In these article various advance techniques such as reverse phase wet granulation, moisture activated dry granulation, thermal adhesion granulation, steam granulation, melt granulation, foam binder granulation, freeze granulation, pneumatic dry granulation, and twin screw granulation were enlighten in detail. From the information available although observed various advanced technologies are available for granulation processes, right now in the pharmaceutical industry, only a few methods have emerged and implemented successfully. One rightly can understand the same could be due to diverse factors like regulatory impacts, investments time factor, quality, etc. However the objective of this article is to create awareness or once again emphasis on the advanced technologies, so that by referring this in future some may interest to focus on the novel technologies. The same could be either for betterment from the existing 'monotonous' conventional technologies or to bring novelties in the formulation process keeping aside the criticality factors that are creating a barrier for switching over to the recent advancements.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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