



Advanced technology of granulation

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ABSTRACT :

The granulation technology are used for pharmaceutical product Development. It is the most useful unit operation in the production of pharmaceutical dosage forms mostly tablets and capsules. The granules are used in the industry have their particle size range is 0.2 to 4mm. The various methods are used to develop the granules such as Dry granulation, Moisture activated dry granulation, Pneumatic dry granulation, Wet granulation, Melt granulation, Thermal adhesion granulation, Steam granulation and Foam granulation method etc. This review are focuses on the Advanced technology and techniques of granulation

Keywords :Dry granulation, Pneumatic dry granulation, Wet granulation, Melt granulation, Steam granulation.

Introduction :

The granulation process, small fine particles or coarse particles are converted in huge agglomerates called as granules. The granules are used in the pharmaceutical industry have their particle size range is 0.2 to 4 mm. They are first delivered as a intermediary with a size range of 0.2 to 0.5 mm to be either collect as a measurement structure or be blended in with other excipients previously tablet compaction(1,2). The existing techniques are performing granulation in the industry such as improving flow ability, blending properties and granules appearance to improve physico substance properties of fine powder incredible(3). The type of process selection necessitates in-depth understanding of the drug's physicochemical qualities, excipients, necessary flow and release properties, etc. For many years, a variety of pharmaceutical dosage forms have been successfully prepared using granulation techniques such as roller compaction, spray drying, supercritical fluid, low/high shear mixing, fluid bed granulation, extrusion/spheronization, etc. Pharmaceutical granulation technology is always evolving, and new, enhanced, and modified methods and tools have come to light along the way. The purpose of this review is to provide the reader with an overview of the most recent methods and tools for pharmaceutical granulation.

Ideal characteristics of granules

1. Spherical or round shape
2. Small molecule size
3. Appropriated with adequate fines to occupy void spaces between granules
4. Adequate dampness (between 1-2%)
5. Great stream property
6. Great compressibility
7. Adequate hardness

Types of granulation technology

The various types of granulation techniques such as,

1. Dry granulation
2. Moisture activated dry granulation
3. Pneumatic dry granulation
4. Wet granulation
5. Melt granulation
6. Thermal adhesion granulation
7. Steam granulation
8. Foam granulation
9. Direct compression process
10. Freeze granulation technology

11. Spray drying granulation
12. Fluidized bed granulation
13. Extrusion-Spheronization granulation

1. Dry granulation

This granulation technique is inexpensive and appropriate for materials that are sensitive to water. Granules are made using this approach without the use of heat or a binding solution. There are two steps in this process. One is slugging, or the preparation of big particles. Slugs are milled and screened into tiny granules as the second step.

Diagram:

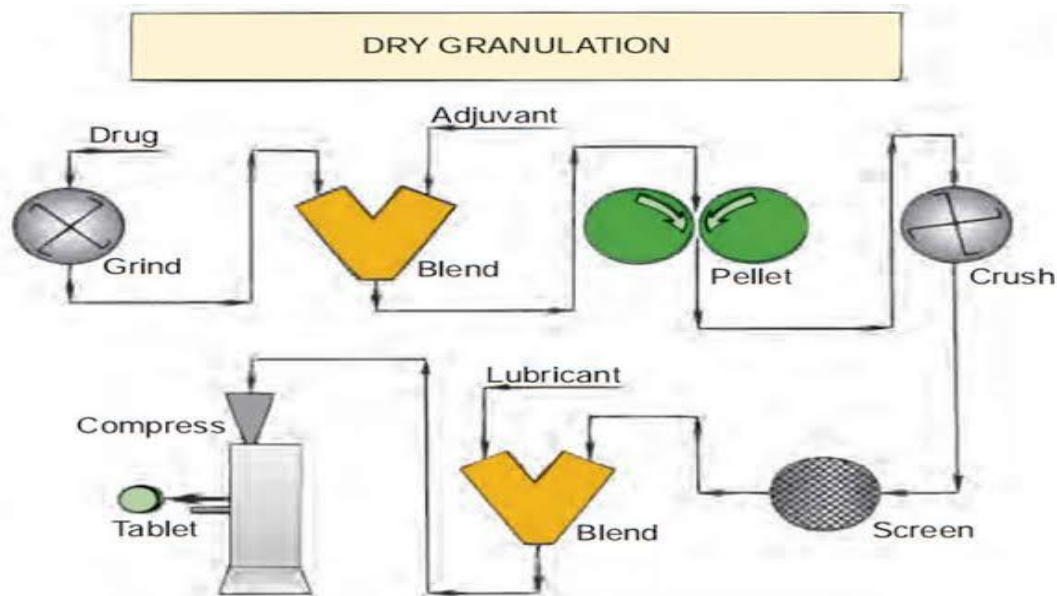


Photo credit: Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Philadelphia: Lippincott Williams and Wilkins.

Diagram⁽⁴⁾. (Dry granulation)

Advantages:

1. Less equipments are needed
2. Eliminate binding solution process
3. It eliminates the need for a binder solution, does not require any heavy mixing equipment, and does away with the time-consuming drying step necessary for wet granulation.
4. It is also effective for moisture-sensitive materials

Disadvantages:

1. It requires a particular hard core tablet press machine to frame slug.
2. The process create more dust than wet granulation
3. It will not permit uniform color distribution as we achieved with wet granulation where the dyes can be incorporated into binder liquid
4. Does not permit uniform colour distribut

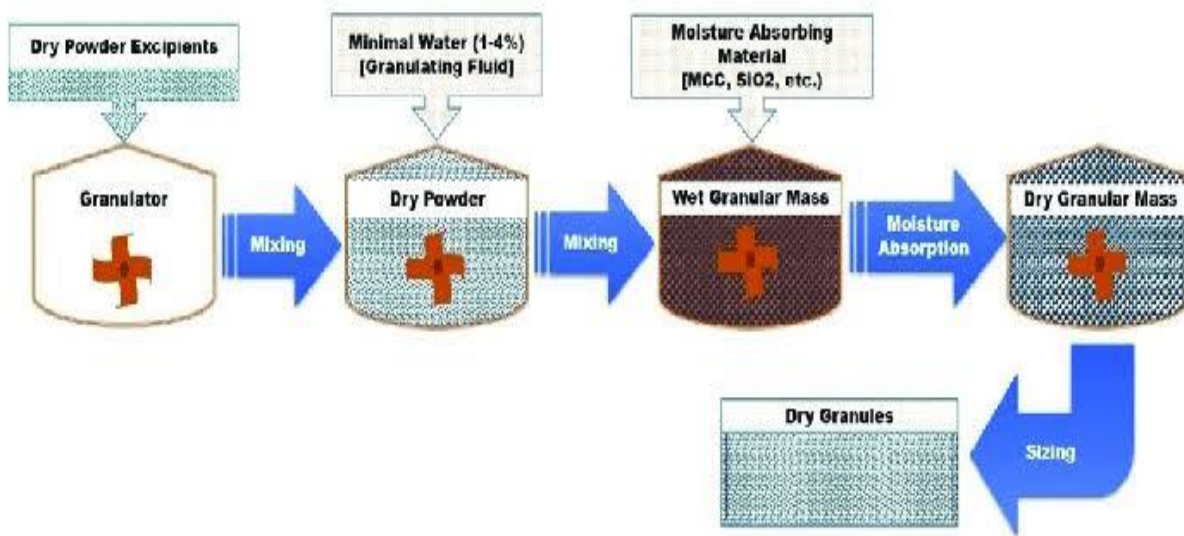
2. Moisture activated dry

granulation:

MADG is additionally called as 'Single-Pot' granulation . Here drying step is dispensed with on the grounds that exceptionally less measure of restricting specialist is utilized to initiate restricting cycle and additionally dampness engrossing specialists like microcrystalline cellulose (MCC), potato starch, a combination of MCC and potato starch (half w/w), silicon dioxide, Maltrin® maltodextrins 18, Spress® B818 Pregelatinized Corn Starch NF 17, and so forth. these are utilized to eliminate dampness present in the granules(5,6). This innovation includes wet agglomeration of the powder blend to shape a tasteless mass followed by dampness retention to dry the granules. In this innovation limited quantity of water (1-4%) is added to agglomerate the powder mix(7,8).

Diagram:

Moisture-Activated Dry Granulation - Schematic Diagram



2) Diagram⁽⁹⁾.(Moisture activated dry granulation)

Advantages :

1. A basic, spotless, lean cycle that consume tiny crushing liquid.
2. Produce granules with more uniform particle size distribution (particle size range of 150-500 μm) and having excellent flowability⁽¹⁰⁾.
3. Suitable for continuous processing, and preparation of floating and sustained release products.

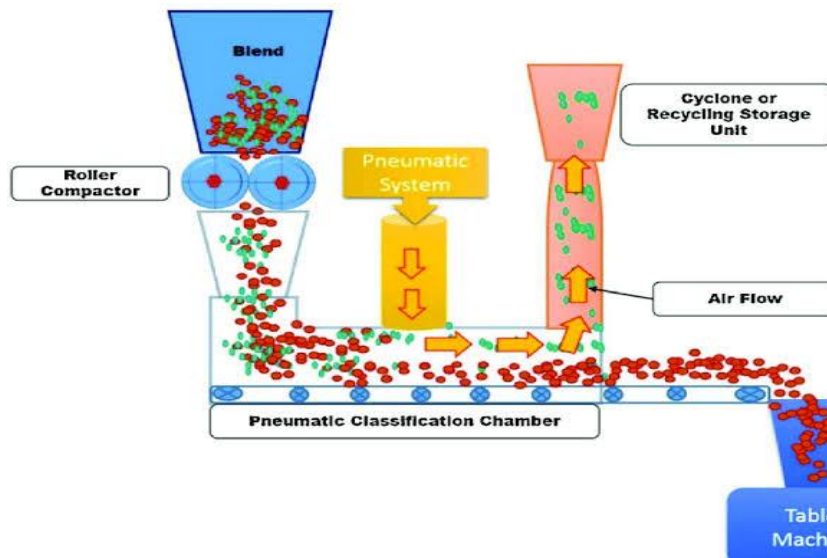
Disadvantage

1. Challenging to develop plans with high medication stacking.
2. Moisture sensitive and high moisture absorbing APIs are poor candidates

3.Pneumatic dry granulation:

This innovation produces permeable exceptionally compressible and free streaming granules. The granules created are reasonable for different applications like supported discharge, prompt delivery or covering. The tablets delivered have an upgraded drug stacking limit, crumbling time and tablet hardness. This technique is an uplifting news for heat delicate excipients and dynamic drug fixing. PDG Innovation has been demonstrated in different sorts of tablet applications including prompt delivery, controlled discharge also, orally crumbling tablets. This granulation innovation essentially is reasonable for all strong dose drug product. This innovation gives many benefits, for example, diminished creation cost through decreased squander by means of reusing and higher medication stacking through great granulation in any event, for those materials that are known to be hard to handle all things considered. Additionally, it offers potential for quick discharge measurements structure as the granules and tablets delivered showed quick deterioration properties. Further, discharge time can be custom fitted to prerequisites. What's more, the framework offers wellbeing benefits through lower dust levels as it is a shut framework and this is a potential for the development of sterile items and treatment of poisonous materials. Correlation among PDG and wet granulation showed that PDG granules have amazing properties and less advances^(11,12).

Diagram:



3) Diagram⁽¹³⁾. (Pneumatic dry granulation)

Advantages:

1. High drug loading of challenging material with a long history is possible.
2. Quicker advancement even with generally demonstrated troublesome materials.
3. enhanced shelf life and excellent stability.

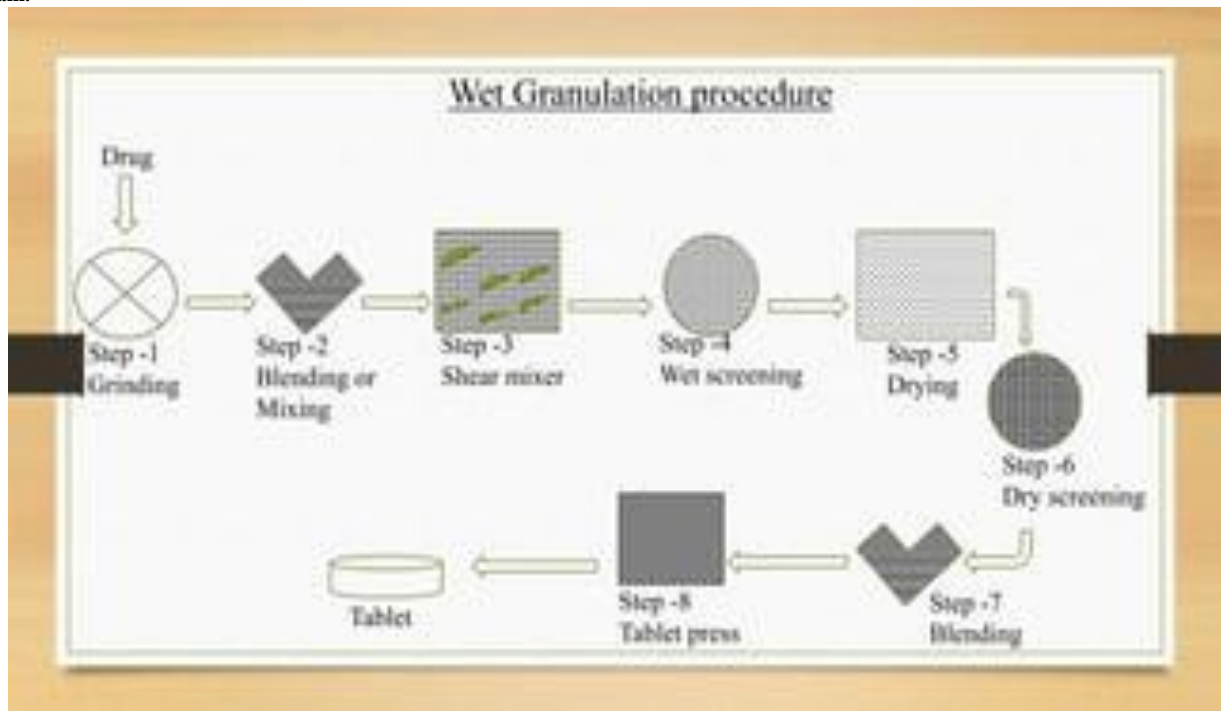
Disadvantages:

1. use of twofold pressure force materials utilized it might go through debasement.
2. Significant expense process because of curiosity.

4. Wet granulation:

Wet granulation is a way for size broadening which includes any cycle by which little particles are agglomerated into bigger, moderately long-lasting designs with the assistance of fluid folio. The wet granulation process should for the most part accomplish the ideal granule properties planned for explicit purposes Granule voidage controls strength, and controls case and tablet disintegration conduct, as well as compaction conduct and tablet hardness. In wet granulation strategies, fluid added to dry powders must be appropriated through the powder mix by the mechanical unsettling made in the granulator. The particles stick to each other in light of fluid expansion, and further tumult as well as fluid expansion causes more particles to stick.

Diagram:



4) Diagram⁽¹⁴⁾. (Wet granulation)

Advantages:

1. increases and enhances the powder density's homogeneity.
2. Limit air entanglement between granules.
3. reduces cross contamination and dust levels.

Disadvantages:

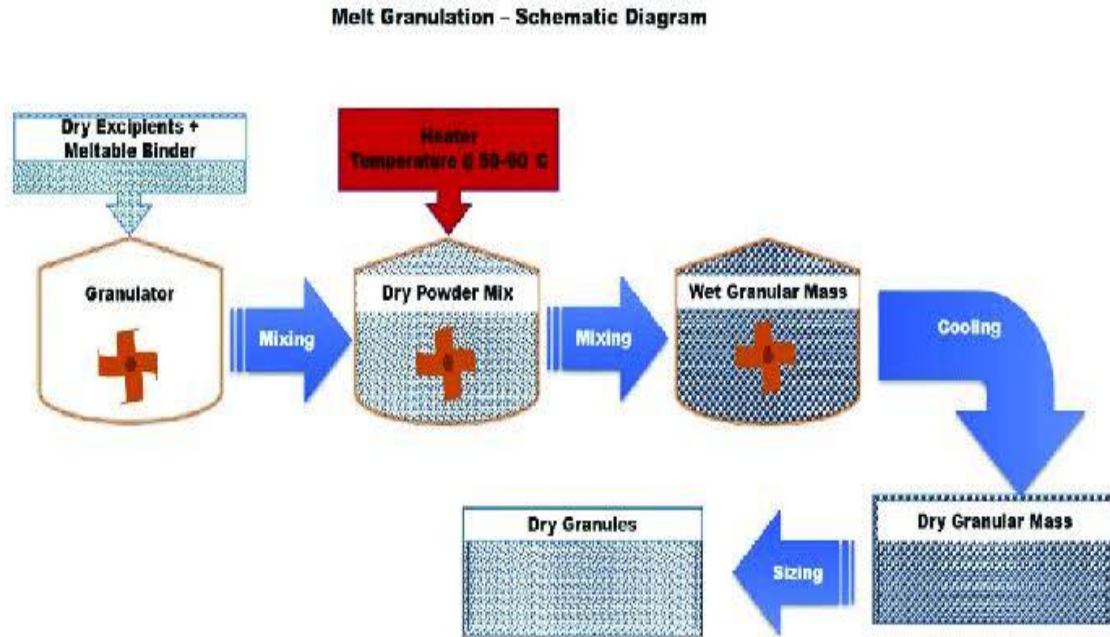
1. Losses during handling are higher since processing phases are longer.
2. It is a costly cycle on account of work, time, gear, energy and more space requires.

5.Melt granulation:

Liquefy granulation is a procedure help to accomplish agglomeration of powder particles through adding of either a liquid folio or on the other hand meltable fastener which can liquefy inside temperature range between 50-80 °C. Diminishing agglomerated powder temperature prompts drying the liquid folio to make it prepared for estimating the granular mass, to acquire last dry granules. Soften granulation has a few advantages over wet

granulation, for example, reasonable for moister delicate materials, set aside time and cash since there is no expansion of fluid what's more, drying method. Notwithstanding, the principal downside is that this procedure isn't reasonable for heat touchy medications⁽¹⁵⁾.

Diagram:



5) Diagram⁽⁹⁾. (Melt granulation)

Advantages:

1. Less processing stages are required, which eliminates time-consuming drying steps.
2. Uniform scattering of fine molecule happens.
3. Great security at different pH and dampness levels.

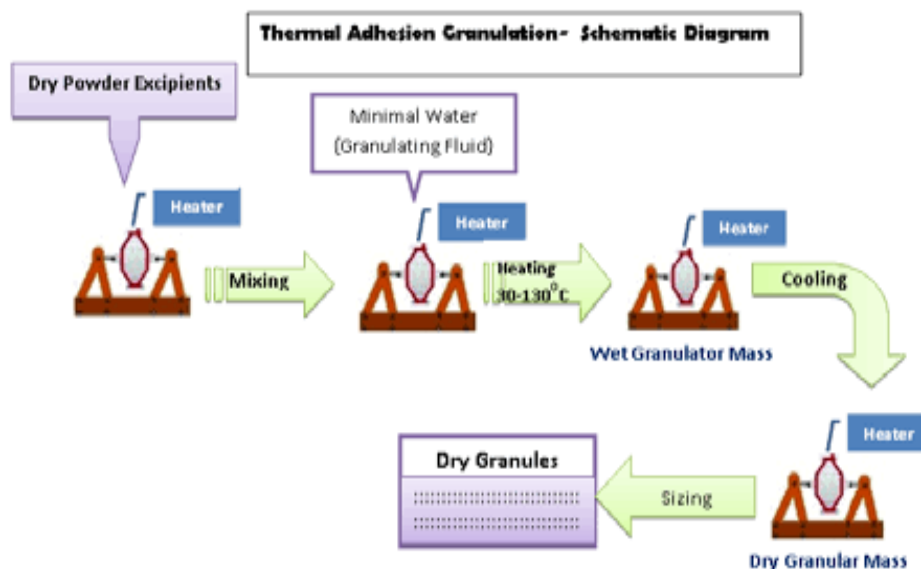
Disadvantages:

1. Heat touchy materials are unfortunate applicants.
2. Binder with a lower melting point could melt or soften while being handled or stored.

6. Thermal adhesion granulation:

An original granulation technique includes granulation by adding extremely less measure of granulation liquid. In this interaction the binder&/diluent combination is first wetted by pouring water or ethanol (2.0-3.6%). Then this mix is set in a prewarmed glass bottle, fixed and afterward warmed by an IR light to increment surface temperature of the hardware upto 900C-1050C for water as dissolvable, 700C-900C for ethanol as a limiting specialist and blended under tumble turn for 3-20 min until granules are shaped. Come about granules were quickly filtered with legitimate sifter 22(16,17).

Diagram:



6) Diagram⁽¹³⁾. (Thermal adhesion granulation)

Advantages:

1. Requires extremely less measure of granulation liquid and structures granules with awesome stream property.
2. decline the residue age during powder handling.

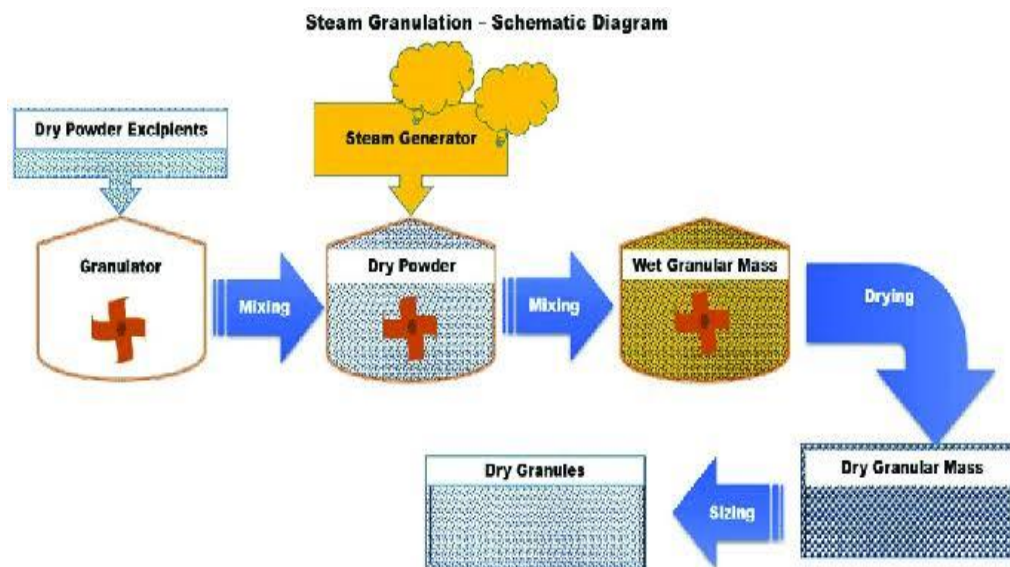
Disadvantages:

1. Not suitable for materials with a melting point of more over 1300C or for materials that bond, such as ethanol and water.

7. Steam granulation:

Wetting granulation is comparative. However, the distinction here is the cover utilized is an unadulterated steam rather than fluid. Moreover, this steam will involve multiple times the volume of an equivalent mass of the fluid, under standard temperature and pressure. Principal process in steam granulation is infuse the wanted measure of fluid as steam. The reason for steam infusion is to give a reasonable intensity and wet to the particles, thus lead to shape masses in the granulated item⁽¹⁸⁾.

Diagram:



7) Diagram⁽¹³⁾. (Steam granulation)

Advantages:

1. Higher circulation consistency.
2. Higher dispersion rate into powders.
3. Steam granules are more round.

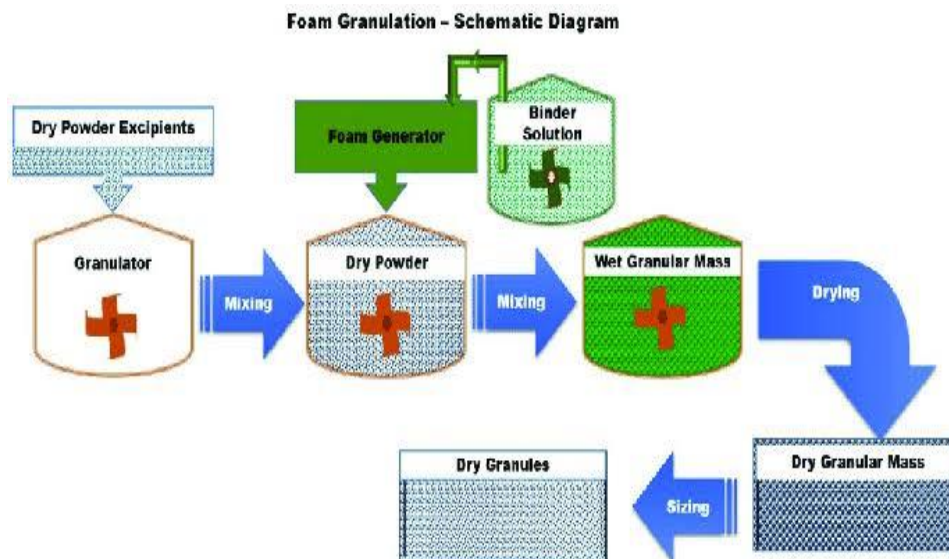
Disadvantages:

1. need unique machine to create steam
2. thermolabile items are not suggest and it isn't suitable for all covers.

8. Foam granulation:

Froth granulation is an innovation involving fluid cover as watery froth as opposed to showering or pouring fluid onto the powder particles . Contrasting and wet granulation, it enjoys many benefits, for instance less folio expected as contrasted with shower granulation, less water required thought about to wet granulation, abbreviate handling times by diminishing water prerequisites, end of the utilization of shower spouts what's more, hence no stopping issues as well as no over wetting issues. In addition, this technique is appropriate for dampness touchy material by abbreviate drying and producing time generally speaking. It works on the dispersion of cover homogeneously all through the powder bed with lesser folio is expected for strong dose structure⁽¹⁹⁾.

Diagram:



8) Diagram⁽¹³⁾. (Foam granulation)

Advantages:

1. gets rid of the need for plugging effects and spray nozzles.
2. Ensures uniform distribution of binder materials.
3. Financially savvy, quick, vigorous and reproducible handling

Disadvantages:

1. The best burden of froth granulation is it's expense.
2. It is a costly cycle in view of work, time, hardware, energy and space necessity.

9. Direct compression process:

This technique is utilized when every one of the fixings can be mixed and set in a tablet pressure to make a tablet with next to no of the fixings being changed. This isn't so normal on the grounds that numerous tablets have dynamic drug fixings which will not consider direct pressure because of their focus in mix or the excipients utilized in plan are not contributory to coordinate pressure.

Diagram:

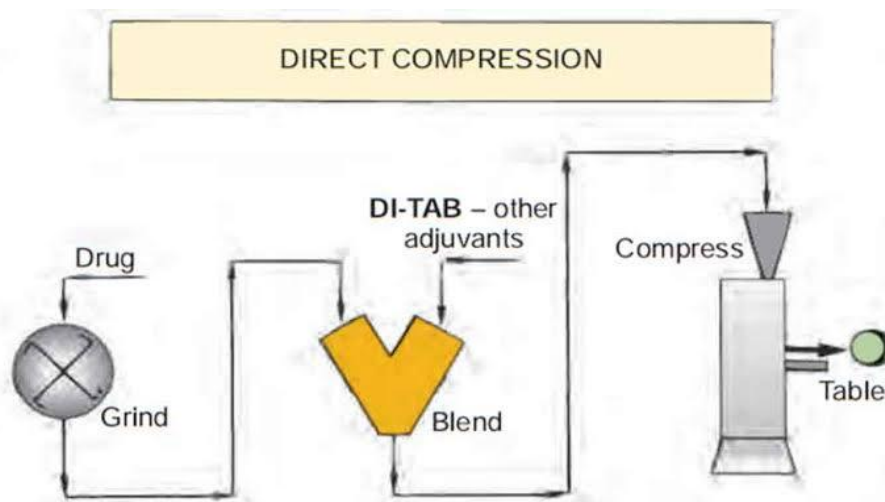


Photo credit: Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lippincott Williams and Wilkins

9) Diagram⁽⁴⁾. (Direct compression process)

Advantages:

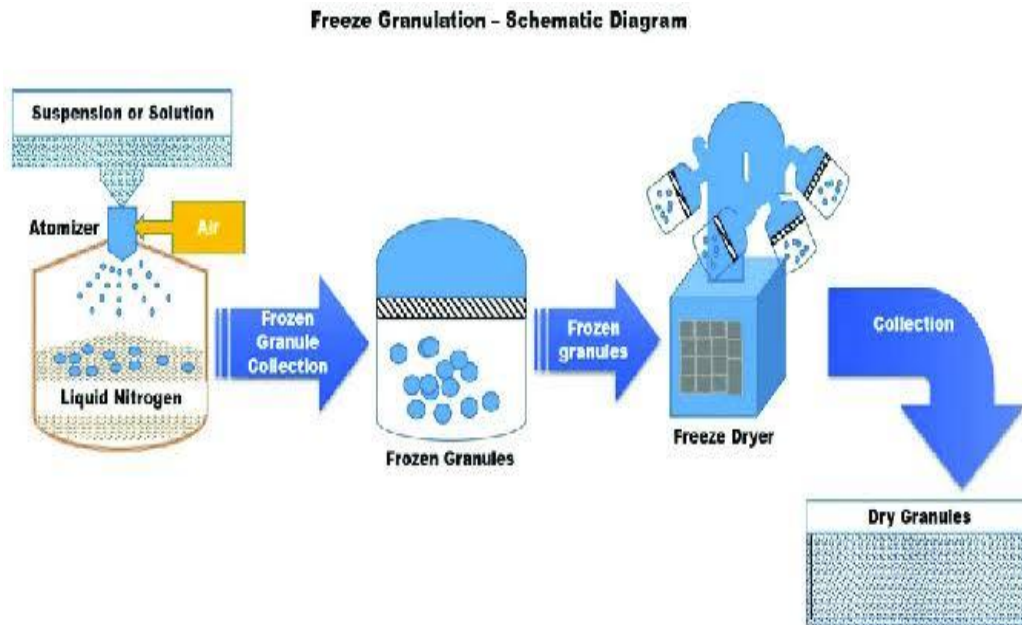
1. Monetary interaction
2. Accomplishes quicker disintegration when contrasted with other technique.

Disadvantages:

1. Variety in working⁽²⁰⁾.

10. Freeze granulation technology:

Coordinated Biosystems, had protected freeze granulation technique that outcomes in roundabout and free streaming granules with extraordinary homogeneity. freeze granulation incorporates showering of suspension comprise powder into fluid nitrogen where the drops were immediately stuck to frame granules which upon freeze-drying yields dry granules⁽²¹⁾.

Diagram:

10) Diagram⁽¹³⁾. (Freeze granulation)

Advantages:

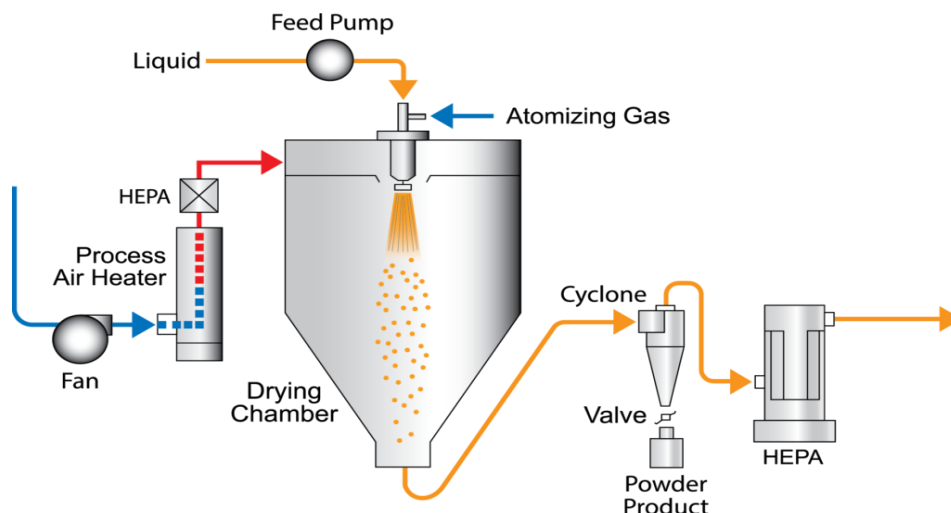
1. Granule thickness constrained by the strong items in the suspension.
2. metals and Non-oxides can be dealt with as gentle drying forestalls serious oxidation.
3. Results strong granules without any pits.

Disadvantages:

1. There might be an opportunity of debasement of medication because of purpose of temperature which is under 0 degree.

11. Spray drying granulation:

It is a nonstop cycle wherein a dry granular item is gotten by taking care of a limiting arrangement or a suspension of Programming interface no matter what excipients to the drying framework where the taking care of is atomized and dried with a hot gas stream then resulting division of granular item from the gas stream. On the other hand molecule agglomeration is achieve by showering the arrangement of fastener onto power bed particles in fluidized state accomplished with the section of air followed by drying utilizing hot air^(11,21).

Diagram:

11) Diagram⁽²²⁾. (Spray draying granulation)**Advantages:**

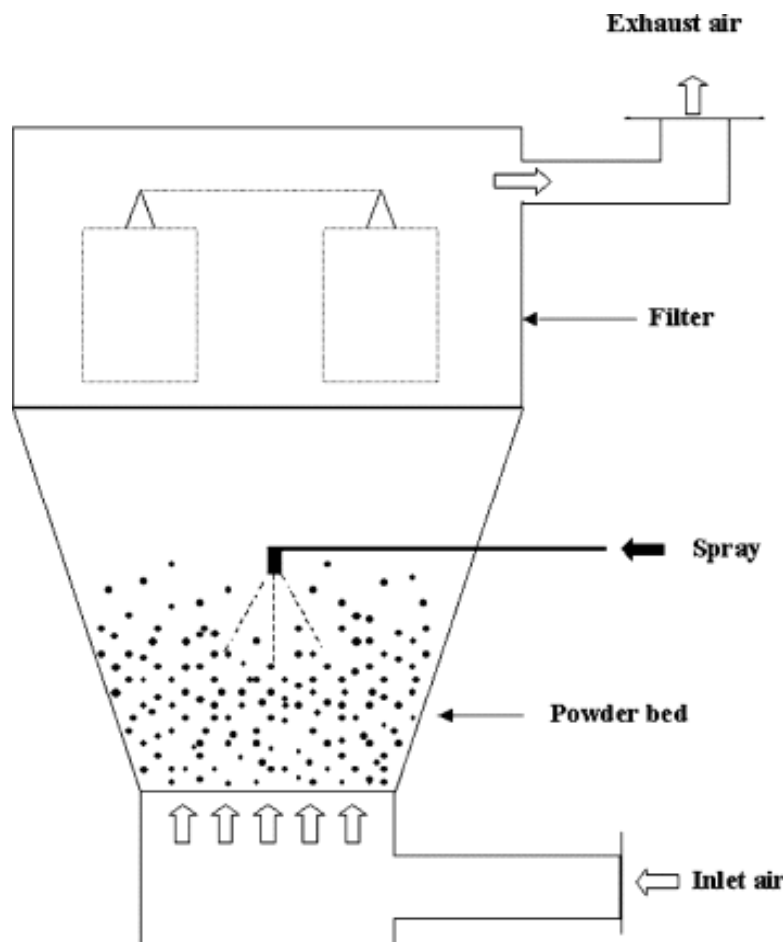
1. It is a quick and ongoing procedure.
2. Cheap and efficient.
3. lowers the exposure of operators to dust.

Disadvantages:

1. Heat-sensitive materials are not good choices.
2. A poor spray job resulted in particles that were too small.

12. Fluidized bed granulation:

Is an air suspension technique , of drugs was first utilized by Wurster to cover tablets that are subsequently utilized for grinding and drying of molecule/granule covering. 17 FBD process incorporates showering of cover arrangement onto the FPB to acquire better granules , free streaming granulation and homogeneous granules utilizing only one hardware known as FBP. FBP incorporates air-dealing with unit, item compartment and air wholesaler, control framework, withdrawal region and cycle channels, splash spout, exhaust blower or fan,solution conveyance framework.

Diagram:**12) Diagram⁽²³⁾. (Fluidized bed granulation)****Advantages:**

1. decline dust arrangement during handling.
2. Increment housekeeping and specialist security.
3. compatible for resulting covering and controlled discharge items and decreases item misfortune.

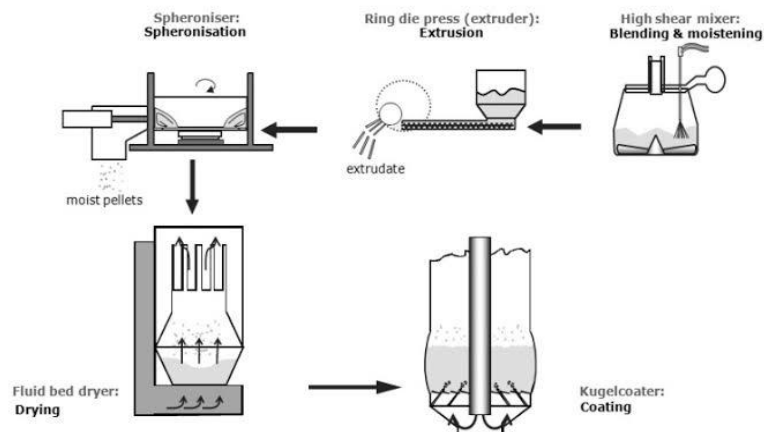
Disadvantages:

1. Cleaning needs more labor, tedious and guaranteeing reproducibility.

13. Extrusion- Spheronization granulation:

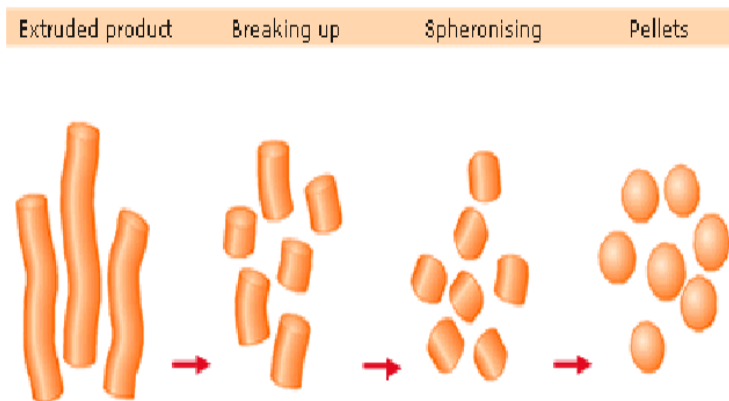
A various step process includes five-steps fit for making same measured round particles with restricted size dissemination that were compatible for controlled discharge plans by expelling the shabby mass through extruder and resulting pelletization utilizing pelletizer . 17,18 Pellets are made by utilizing wet or hot liquefy expulsion strategies. Wet expulsion method incorporates expulsion of wet agglomerate of the powder blend in to the extruder. Hot soften expulsion strategy remembers expulsion of thermoplastic materials for to the a thermostatically controlled extruder. Handling boundaries like extruder pore size, spheronization speed ,functional circumstances should be streamlined which impacts size dissemination ,molecule size, and morphology of granules 18.

Diagram:



13) Diagram⁽¹³⁾. (Extrusion- Spheronization granulation)

Different steps involved in the Extrusion- Spheronization granulation:



14) Diagram⁽¹³⁾. (Steps of Extrusion- Spheronization granulation)

Advantages:

1. Incorporates more elevated levels of dynamic without creating unreasonably bigger particles.
2. Simple to blend at least two dynamic specialists inside a similar unit, in any proportion.
3. Adjustment of actual attributes of the Programming interface and excipients.

Disadvantages:

1. Needs more labor and time for granulation.
2. Can't be utilized for hygroscopic and thermo-labile materials.

Application :

1. Additionally, because the method uses less water per granulation, it requires less drying time and has a smaller environmental impact.
2. Froth innovation has been demonstrated to scale without any problem for both quick delivery and framework controlled discharge tablets.
3. This innovation seems to assist with addressing the issues that individuals have been having with wet granulation of profoundly water dissolvable and, surprisingly, exceptionally unfortunate water solvent drugs.
4. Because foam granulation is an effective compound carrier that can carry active ingredients at very low concentrations as well as the liquid and polymer, it solves problems with dispersing a very low concentration drug level, such as milligram (or) micro gram per tablet in a powder bed.
5. The innovation appears to give a superior and a more extensive end guide in which toward grind to each with some very troublesome exercises that we work with, including normal fixings in the nourishing enhancements.

Conclusion:

The review works mainly focus on the advanced technology of granulation. Every technique has advantages and disadvantages of its own. The specific properties of the ingredients and their capacity to flow, compress, eject, and disintegrate correctly determine which method is used. It is necessary to thoroughly research every constituent in the formula, their combination, and their interactions with one another before deciding on a procedure.

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