Review Article

Fluidized Bed Granulation: A Promising Technique

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Received: 18-06-2020; **Revised:** 25-09-2020; **Accepted:** 02-10-2020; **Published on:** 20-10-2020.

ABSTRACT

The fluidized bed processing technology is the potential tool to develop newer trends and implication within the area of formulation and development with improve therapeutic efficacy. The fluidized bed processor is employed for coating, drying, layering and granulation. It is current capturing the market leaps and bounds with recent trends and development with its revolutionary techniques. fluidized bed granulation technique is most rising and upcoming face of granulation technology of pharmaceutics. In pharmaceutics fluidized bed granulation is a key technique which improves the powder properties for preparing pharmaceutical dosage form with enhance the functional properties i.e, solubility, dissolution. Understanding and controlling the critical process parameters obtained high quality granules. This article reviews the fundamentals of fluidized bed processor, fluidized bed granulation and detailed information regarding with principle, advantages, latest technology and troubleshooting were also described.

Keywords: Fluidized bed granulation, granulation, fluidization, particle growth, drying.

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DOI:
10.47583/ijpsrr.2020.v64i02.022

DOI link: http://dx.doi.org/10.47583/ijpsrr.2020.v64i02.022

INTRODUCTION

In the manufacturing of pharmaceutical dosage form, one of the significant and important unit operation is granulation, mostly in the tablets manufacturing and capsules filling. During the process of granulation, very fine or coarse particles are converted into large agglomerates known as granules. Generally, granulation starts after initial preblending or dry mixing of powder ingredients and active pharmaceutical ingredient with the help of these we can achieve uniform distribution of all ingredients throughout the mixture. They are primarily produced as an intermediary to be either packed as a dosage form or be mixed with other ingredients before tablet compaction and capsule filling.[1-4]

The process granulation utilizes the granulation fluid which is made up of dry powder materials and a liquid. Binders may be by combining dry materials such as powders and perhaps crystals with granulation fluid also known as binder solution. which are mixed in dry ingredients to achieve uniform distribution of the granulating solution. which allows the particle particle interactions. The formation of stable granules, inter-particle forces are responsible. [5-7,29]

Purpose of granulation: [1,2,7,8,15-18]

- ✓ Increased the density of blend so that it occupies the less volume per unit weight for better storage and shipment,
- ✓ To facilitate volumetric and metering dispensing ,
- ✓ To improve the appearance of the formulation,
- ✓ To improve dispersibility
- ✓ To reduce the dust formation during process of granulation,
- ✓ To reduce the exposure of toxic substances and to reduce the process related hazards.
- ✓ Spherical shape of granules is formed to improved flow properties of powder,
- ✓ Sufficient fines to fill void spaces between granules for better compaction,
- ✓ Narrow particle size distribution for content uniformity and volumetric dispensing
- ✓ Compression characteristics, adequate moisture and hardness to prevent the breaking and dust formation during process.
- ✓ While powders are very fluffy and very fine, will not stay blended or will not compress, then they must be granulated, fluffy isn't a technical term but it suits the trouble well, it means that the specified amount of powder physically will not fit into the die cavity on the tablet press. The volume of fill (bulk density) is more than that which is mechanically allowed.

Granulation fundamentals:[1,2,7,8]

Granulation is the physical operation which is design to the formulate large agglomerates by the fine powder particles, pellets and grains. In the granulation process mainly used granulation fluid i.e. binder solution or dry binder incorporating in granulating solution. these granulating fluid are incorporated in dry powder blend. Agglomerates are formed by combing the granulating solution and dry powder blend. uniform distribution is achieved by continuous mixing and allowing formation of bridge or particle- particle interaction. Stable granules are formulate by the inter particle forces.

Types of liquid state of granules: [2,8,15-17]

1. Pendular State:-

This type of granulation is express as "too dry" In which particles have been exposed to granulating solution for liquid bridges to form.

2. Funicular state :-

Liquid bridges joining adjacent particles are interspersed less frequently by air. As moisture content increases, surface coverage by the granulation liquid also increases. Agglomerates are characterized by greater strength than agglomerates formed in the pendular state.

3. Capillary state:-

Incorporation of granulation fluid leads to complete liquid coverage of solid phase surface agglomerates formed in these phase have good strength and demonstrate minimum attrition on further processing.

4. By continuously incorporation of granulation fluid leads to complete wetting of all solid surface. If any small quantity of liquid added beyond this point has very less possibility of adhering to solid surface and becomes associated with the part of the liquid film that covers the surface of particles in the granulator.

Mechanism of granule formation: [8]

1. Nucleation
2. Transition
3. Ball growth

Classification of Granulation Technologies: [2,7,8]

Classified on the basis of type of processing:

1. Conventional methods
   - (i) Dry granulation
   - (ii) Wet granulation
     - (a) High-shear wet granulation
     - (b) Low-shear wet granulation
2. Novel/advanced methods
   - i. Moisture activated dry granulation
   - ii. Thermal adhesion granulation
   - iii. Pneumatic dry granulation
   - iv. Melt/thermoplastic granulation
   - v. Fluidized bed granulation
   - vi. Extrusion-spheronization granulation
   - vii. Spray drying granulation
   - viii. Freeze granulation
   - ix. Foam binder granulation
   - x. Steam granulation

FLUIDIZED BED PROCESSOR [7-16,27]

The concept of fluidized solids actually invented in the field of catalytic cracking method. In the process of fluidization the standard oil development has many benefits and contribution. The Prof. W.K Lewis and E.R Gilliland carried out individualistic research on flow properties of solid suspended particles in gases and developed the Fluid bed process. The fluid solid technique principle was the first industrial plant implemented into operation in 1930 for non pharmaceutical application but this process was first invented by Wruster in 1960. In 1953 Dale Wruster invented the coating of tablets by spraying the coating solution on tablets bed stream of warm air suspended in warm air in 1953 this process also known as wruster process. In 1960 Dr. Dale Wruster carried out the granulation of powders. Then in 1980s have seen an explosion in the research, application and commercialization of fluid bed process.

Application of such equipment helps to reduce the cost, time and also the processing steps included in manufacturing of formulation. The latest technology known as fluid bed processing technology. Fluid bed processing involves coating, granulation, drug layering and drying of powder material. The most commonly known fluid bed process for coating in the pharmaceutical industry is the bottom spray (wurster) process.

Principle of fluidized bed processor: [8,10,27]

The fluid bed it is the bed of powder material or solid particle bed. The hot air passed at high pressure through the air distribution plate which is place in bottom then particles are lifted from bottom and suspended in air stream this process known as fluidization process. Granulating solution or coating solution is sprayed with the help of spray nozzles to formulate granules or coating of the particles, respectively those coated particles or granules are dried simultaneously because of hot air.

Concept of Fluidization[8,10,27,28]

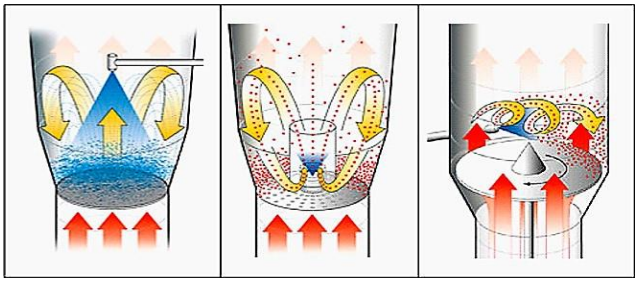
The concept involved in such technique may be either by top spray or bottom spray or tangential spray process. Those principle depends on the spray gun poisoning in equipment . The top spray positioning helps in obtaining the uniform granulation and pelletization. And the bottom

spray positioning process utilizes wurster coating unit for the spray.

- Lighter particles or objects float om top of the bed.
- The solid substances can flow through an opening in the vessel.
- The bed have a static pressure head because of the gravity.
- It has a zero angle of repose.

The three patterns of the fluid bed processor could be characterized by the position/location of the spray nozzle i.e.,

- a. Top Spray
- b. Bottom Spray
- c. Tangential spray



a. Top Spray b. bottom Spray c. Tangential Spray

Figure 1: Concept of Fluidization

Fluidized bed processor elements:

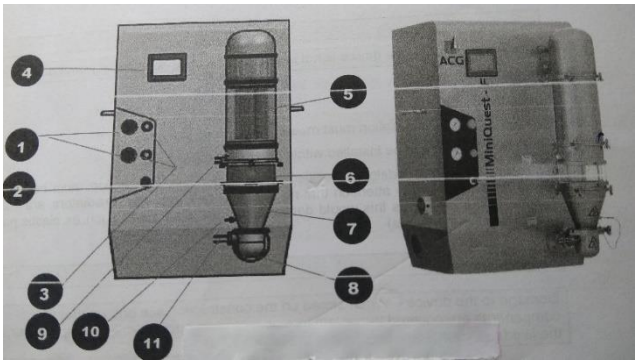


Figure 2: Indicating and control elements of FBP

1. Dial Gauge
2. Atomization Air Nipple
3. Control Switch (Regulator) for inlet airflow & atomization air.
4. HMI (4")
5. Filter Housing Assembly
6. Expansion Chamber
7. Product Container
8. Lower Plenum
9. Port for Top Spray Nozzle
10. Temperature Sensor
11. Port for Bottom Spray Nozzle

Table 1: FBP parts and their function:

Sr. No	Parts	Function
1.	**Nozzle**	The droplet size and distribution of granulating or coating solution
2	**Air distribution plate**	Distributing the fluidized air between outer and inner portion
3	**Plenum \ draft tube**	Air enters, equalized pressure for more even distribution
4	**Cylinder**	Particles are actually sucked through the partition gap
5.	**Filter bags**	filter bags is used for the continuous fluidization
6	**Expansion chamber**	For recurring the flow of the particles

FLUIDIZED BED GRANULATION [8,10,13-30]

Introduction

Process of granulation is converting fine size solid particles into large particles by continuous mixing in presence of granulating fluid. The process of granulation is very vast and multistep process have many disadvantages and such drawbacks overcome by the novel technique i.e, fluidized bed granulation and drying in fluidized bed processor. Fluidized bed granulation [FBG] is one of most widely used technique in manufacturing of solid pharmaceutical products such as Granulation is also known as agglomeration. Fluidized bed granulator (FBG), a highly economical and efficient one pot process, is a popular technique in the pharmaceutical.

Fluidized bed granulation is one of the many techniques i.e, drum granulation, pneumatic dry granulation, high shear granulation, and so on to produce agglomerates. Fluidized bed granulation technique is preferred over other techniques because it provides properly mixing, high heat and mass transfer rates, continues the bed more or less at uniform temperature.

In operation of fluidized bed granulation fine droplets of granulating solution are sprayed at the surface of fluidizing particles. when particles are wetted and collide to each other and formation of liquid bridges are converted into solid bridges. When they received adequate amount of heat form the fluidizing air, to drive off the solvent present. Hence the particles are adhere to each other to form agglomerates/ granules.

Fluidized bed granulation technique Recently, a method for preparation of solid dispersion using fluid bed granulation process. Solid dispersion using fluidized bed granulation process has been attracting attention as a manufacturing process because it overcomes so many

drawbacks and problems arising in other multistep granulation and solid dispersion manufacturing processes.

Principle of Fluidized bed granulation process [8, 9,13,25-29]

In the tablet manufacturing process, a continuous production line, involving several operations like coating, drying and granulation, can be performed in fluid bed equipment. Fluid bed granulation process involves the spraying of binder solution, suspension or dispersion onto a physical mixture i.e powder bed, where particles are suspended in air stream. These particles are wet by granulating or binder solution and when they collide to each other then formation of the liquid bridges which leads to acquisition of granules. The liquid bridge that adhere the particle to each other in two mechanism.

1. By surface tension at interface
2. By hydrostatic suction

Bed moisture level and Granule microstructure can be affected by many conditions, such as the primary particle size, Fluidizing air velocity, concentration and spray rate of binder solution, manufacturing processes which can leads minimizes the rate of granule breakage. However despite the recognized application of the fluid bed granulation for improving the solubility and dissolution rate of poorly water soluble drugs. The solidification of liquid bridges are dried then formation of cluster of solid particles such as granules or agglomerates. fluidized bed granulation it involves continuously preblending of dry excipients, wetting and drying of particles. Hence, the factors controlling in fluidized bed granulation process technology becomes difficult process. If the granulating solution is excess or if it is maldisributed, large region of the bed may defluidize and particle adhered to each other to form a large lumps of particles, such process is known as wet quenching. On the other hand minimum fluidization velocity occurs because of excessive particle growth minimum fluidization velocity is proportional to square of particle diameter which will exceeds the operating velocity, which leads to fluidization, known as dry quenching.

Granulators[8]

The density of each granule increase by increasing the quantity of granulating solution as well as the mechanical action of the mixer. Consequently, controlling the amount binder, granulating solution and mechanical action allows one to control the density and strength of the agglomerates/ granules. Equipment or machines that are applicable for this method are known as granulators. Granulators may be low shear, medium shear or high shear. Shear is term describes the amount of mechanical force of the granulators. A low-shear granulators utilizes very low mechanical force to mixing powders and binding solution.

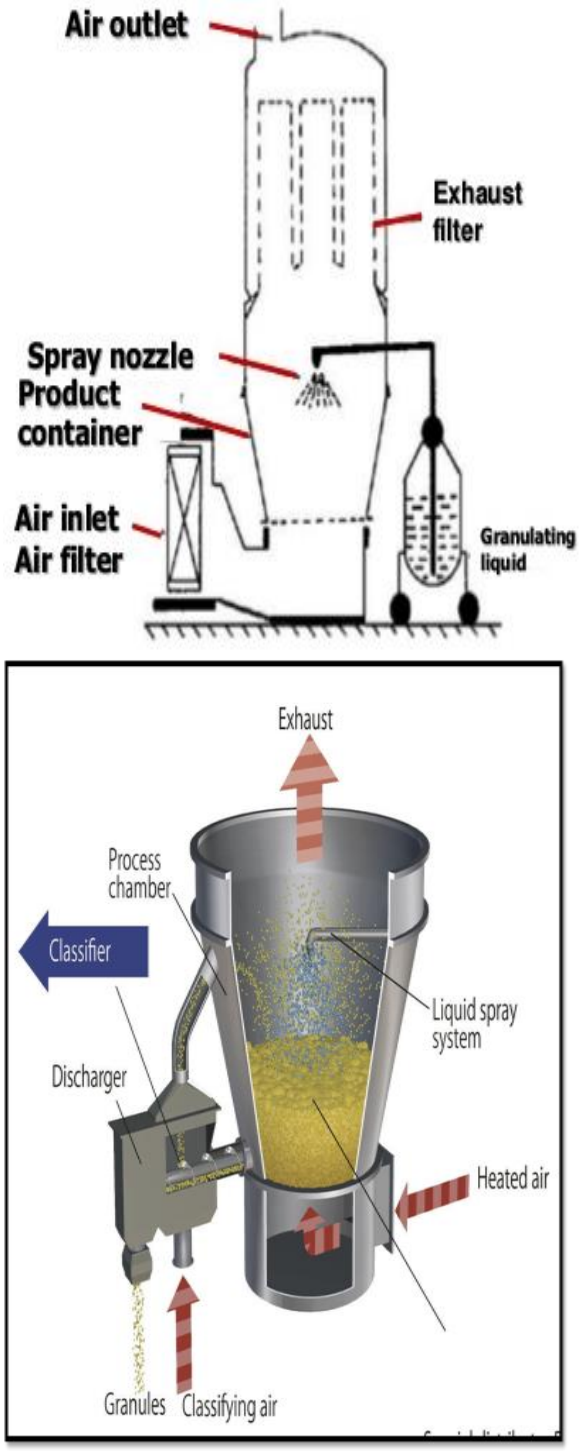


Figure 3: Fluidized bed Granulator

Fluidized bed Granulation[8,13,25]

The fluidized bed granulation, the low shear granulator are most commonly use form the porous granules, uses a high volume of air flow to powders are lifted in vessel while a granulating solution is sprayed onto the particles to form light bond. A fluidized bed granulators does not impart mechanical energy but instead relies on the powder properties and the binder solution to form the lightly held powders into agglomerates. A high shear granulators will not formulate light granules.

Steps in Fluidized Bed Granulation[8]

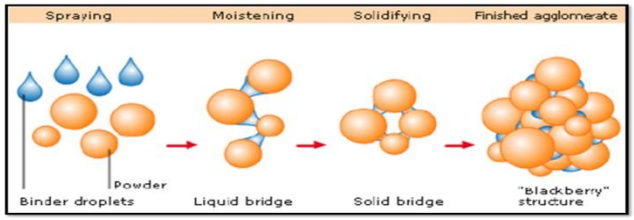


Figure 4: Steps in fluidized bed granulation

Both dry and wet granulation process can achieved in fluidized bed granulation.[23]

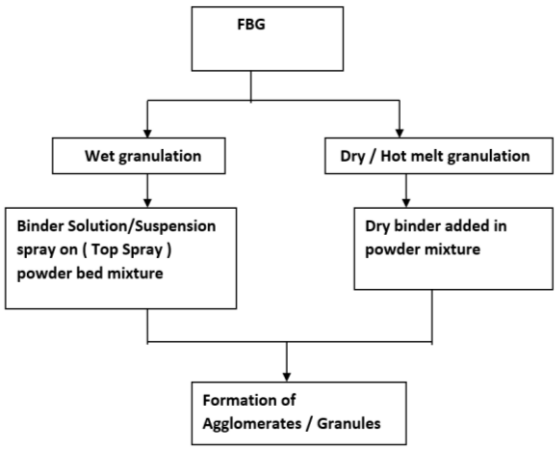


Figure 5: Types of fluidized bed granulation

Types of Fluidized Bed Granulator:

1) Top Spray Fluid Bed Granulator-

In the Top Spray Fluid Bed Granulator involves two technologies i.e. hardening binder and recrystallization. At the top of equipment spray nozzle is located and at the base the powder material is loaded into product container is equipped with fine mesh retention screen to allow small particles. In the lengthen expansion chamber above the static bed the nozzle spray is mounted. Fluidized bed granulator is operated by binding solution is spray on powder bed material at controlled rate. After appropriate agglomeration the powder material is allowed to dry after liquid spray is cut off after moisture content is achieved.

2) Rotating Disk Fluid Bed Granulator-

Rotating Disk fluid bed Granulator With Dryer Option Layering technology carried coater and rotating disk granulator. The unit is combined with expansion chamber to form coater fluid bed device and rotating disk granulator due to these granulation technique is extended with coating technology. Variable slit opening between the outer perimeter of the disk and side wall of container these will be created when rotating disk is moving up or down. This allows independent control of air velocity over air volume, air is drawn through the slit into the product container under negative pressure. Product move under centrifugal force to outer position when the disk is rotated at variable speed when it is lifted into the expansion chamber by fluidizing air stream. As the material fall to the center of the rotating disk and continuously repeat the processes. Around the inside the rotor chamber the fluidizing patterns are described as rope like pattern or spiraling helix. Various forces like centrifugal force, gravity, and fluidization are controlled the motion of fluidization of the particle. Spray nozzle is located into the fluidization bed and spray applied on particles into tangential position. Layering technique is applicable for the manufacturing of pallets in this process started material seed material having particle size diameter 250 mm. Several layers of solutions and suspension of binder or granulating solution and drug can be applied. Drug can be applied at controlled rate as a dry powder fed, so that bed expands into both ways i.e. horizontal as well as vertical. Up to 1000% at starting weight can be used. So that uniformed and coated for controlled release of drug pallets can be formed. Layer of powder on the particle substrate can be formed using layering technique in which dry powder can be fed into wet bed this leads to formation of layers. Liquid spray cut off at the end of process the material present in unit is dried by increasing the temperature and fluidization air volume.

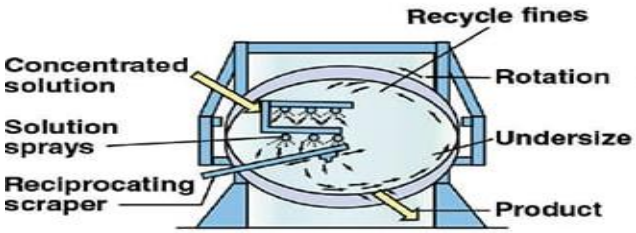


Figure 6: Rotating Disk Fluid Bed Granulator

PARAMETERS AFFECTING AND CONTROLLING IN FLUIDIZED BED SYSTEM[8-12, 18-25,30]

The number of parameters are affects final product which is processed through the fluidized bed processor:

1. Apparatus Parameters

- 1 Positive and negative pressure operation
- 2 Shape of instrument body- The Annular shape base gives better fluidization and products
- 3 Nozzle height- nozzle height it plays a significant role in process of granulation and coating. The atomized coating solution should not get dried before reaching the tablet surface.
- 4 Air distribution plate- The airflow pattern affected by the position of air distribution plate inside the body.

2. Process Parameters

In Drying Process

Inlet air parameters are critical, and applicable in all process like granulation, drying and coating.

1. Temperature:-

Rate of drying is directly proportional to inlet air temperature, as inlet air temperature increase the rate of drying is also increases and vice a versa. This approach to increase the rate of drying cannot be used always because some materials are harmed by high temperature.

E.g. Ibuprofen, above 60 °C temperature of inlet air should be optimized without any affects on product quality, If temperature is low soft spot can be formed and if temperature is high, it leads to blistering.

2. Humidity:-

Dehumidified air should be used for faster drying rate, Drying rate is inversely proportional to humidity of inlet air, as humidity of inlet air increases rate drying is also ultimately decrease. Hence it is important that during the process humidity of inlet air should be as low as possible.

3. Air blow rate:-

Air blow rate should be controlled properly for the proper use of drying air. As rate of increases because of increases in air flow rate which results in increases in cost of drying. If drying air is allowed for sufficient time to remain in contact with drying material, mass transfer is takes place by transferring heat and that results into decrease in cost of drying. Air flow rate should be optimized for sufficient drying, it should not be too fast and too slow.

In Granulation Process

Related to Spray Nozzle -

- Nozzle position:- Nozzle position should be decided in relation with material height and it should be placed suitably for better contact between material and binder solution. In fluidized bed granulation process nozzle is place on top position .
- Spray rate:- Spray rate should be optimized otherwise poor wetting and agglomeration of the product may happen hindering the fluidization and good quality granule formation.
- Spray pressure:- Optimization of spray pressure is important for the proper quality granule formation.

Miscellaneous -

- Outlet gas temperature
- Pressure drop across exhaust filters.

The above two parameters which gives denoted the efficiency of the fluidization process. There are two parameters for optimizing system's level of efficiency

3. Product Parameters

In Drying Process

- Initial moisture content of drying material, for the purpose of increase in drying time increase moisture content should be high.
- Batch size: Batch size should be small and it should be optimized based on the feasibility.

In Granulation Process

- Granulating agent.

For the proper granulation process it is important that selection of right granulating agent which is based on the solvent used in binder solution. Mostly aqueous solvent is preferred but organic solvent cause explosions. Solvent should be used in optimum concentration For obtaining good quality of granules. If the temperature of solvent then binder solution will be dry before reaches to powder material.

- Starting material

For better contact of starting materials with granulating agent fluidization should be optimized. Hydrophilic granulating agent is used for hydrophobic starting material for the better contact and granulation of material.

COMMON PROBLEMS ARISES IN FLUIDIZED BED GRANULATION [8, 10-15, 18, 22, 25]

1) Excessive fine

- In sufficient quantity of binder
- Air flow or high fluidized velocity
- Too low Binder spray rate
- Atomization air pressure is high
- Weak binder or low concentration of binder solution.
- High Inlet temperature
- Fine droplet size of the binder.

2) Excessive coarse granulation –

- High binder spray rate.
- Inlet air temperature is low
- Low fluidization velocity or air flow
- Nozzle position is too low
- Stronger binder or higher concentration of spraying liquid

3) Final moisture inconsistency

- Temperature probe out of calibration
- Fluidization is improper
- Outside air humidity

4) Fluidization is poor

- Air velocity is low
- Processor fan does not have adequate pressure drop
- No proper cleaning of air distributor
- High quantity of product in product container
- Air distribution plate is incorrect

- Exhaust is blocked
- Porosity of exhaust is small

5) Finished product non uniformity

- spraying time is Insufficient
- Lumps in raw material
- insufficient Filter shaking
- Product homogeneity before granulation is not adequate

6) Low yield

- At the end of process filter bag is not shake
- Material sticks to expansion chambers
- Wrong porosity exhaust filter
- Air distributor with coarser screen opening

into the bed of suspended particles granulating solution or solvent are sprayed. The quality and performance of final product based on the various factors like rate of addition of binder or solvent, spray rate, concentration binder, distance between spray nozzle and material bed, Temperature of air, volume of air, moisture content of air etc. Density of particles produced in fluidized bed granulation technique is more than other conventional methods.

Advantages [8,9,11-15]

- To improve compressibility for tableting.
- Applicable for large or small-scale operations
- Continuous operation
- Time and cost effective.
- Reduce product loss.
- To reduced dust formation operator and environmental safety.
- Improve housekeeping and workers safety.
- Saving labour cost

Disadvantages [8-15]

- Cleaning was labour intensive and time consuming
- Erosion of internals. Pipe and vessel walls erode due to collisions by particles
- Attrition of catalyst particles.
- Hot melt granulation method required more attention because sometimes product degradation by excess heat
- Due to the complexity of fluidized bed behaviour, there are often difficulties in attempting to scale-up from smaller scale to industrial units

CONCLUSION

Very fine and small size particle have a negative impact on the flow properties of powders.

And will not stay blended or will not compress in die cavity for tablet manufacturing. To overcome this problems, they must be granulated, granulation is used to improve the functional properties of the powders. During the granulation process, powder particles are adhered to each other and formation of cluster , increasing the particle size. Numerous agglomeration methods can be employed depending on the end use properties of granules. The fluidized bed granulation technique is widely used in the industry because it produces granules with high porosity and homogeneity. To overcome all possible problems and achieve the desired products and controlling and understanding mechanism of the parameters affecting granulation process and properties of granules; e.g., mixing rate, binder property, moisture content, inlet air temperature etc such a properly investigated and controlled.

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Source of Support: None declared.

Conflict of Interest: None declared.