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# Novel technique of Granulation

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**ABSTRACT**

Granulation is an essential unit method withinside the manufacturing of pharmaceutical dosage bureaucracy like tablets, tablets and different dosage bureaucracy. Granulationmethod will increase flow, compressibility and content material uniformity of the powders. It inhibits the separation of mixture additives and decreases excessivequantity of pleasant particles. This method enables to attain progressed yields with much less pill production defects. Particle length of granules relies upon on theamount and feeding fee of the granulating liquid. Selecting a technique of granulation calls for complete have a look at of every component withinside the formula,the mixture of elements and their compatibility with every different is checked after, which suitable granulation method may be applied. Thecurrent technology used for granulation encompass steam granulation, moisture activated dry granulation (MADG), wet granulation technique (MGT),extrusionspheronization granulation, fluidized mattress granulation, thermal adhesion granulation method (TAGP) and foam granulation etc. have theirpersonal benefits and triumph over the risks of traditional granulation method along with dirt technology or deteriorating impact of warmth as dryingstep. The goal of gift paintings is to consciousness on the radical granulation technology.

**Key words:** Granulation, Granulation technology, Advances, Pharmaceutical industry.

## INTRODUCTION

Granulation is technique making separate powder debris in to ainstitution with the aid of using the use of granulating fluid. Granulating fluid can also additionally bewater inclusive of or water heating, this rely on the character ofdrug and different excipients used. The technique of creating ofgranules is granulation and method and system used isgranulation technology.

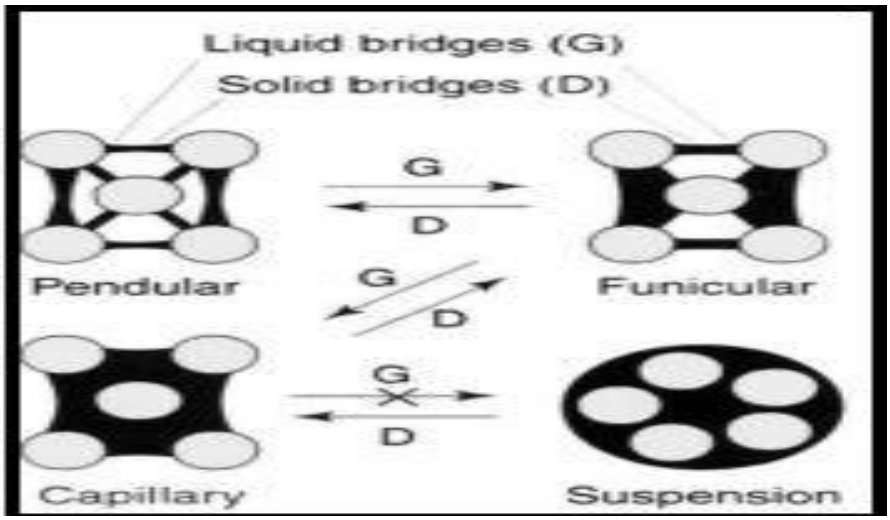
**Stages of granulation:**

a) **Pendular degree:** This is preliminary degree simply after addition ofbinding agent.

b**) Funicular degree:**This is 2nd degree in which adequatebinding answer integrated among the debris.

c**) Capillary degree:**In this degree binding answer entrapped with the aid of usingcapillary action. This is an ideal degree in which right granulesmay be obtained.

d) **Droplet degree:**Here over wetting, debris can also additionally form. Thisdegree isn't applicable degree (Shown in Figure 1).



## Classification of Granulation Technologies

Basing upon the sort of processing, that were involved, GTmay be labelled as follows:

1. Conventional methods
· Dry granulation
· Wet granulation
a) High-shear moist granulation
b) Low-shear moist granulation
2. Novel/superior methods
· Moisture activated dry granulation
· Thermal adhesion granulation
· Pneumatic dry granulation
· Melt/thermoplastic granulation
· Fluidized mattress granulation
· Extrusion-spheronization granulation
· Spray drying granulation
· Freeze granulation
· Foam binder granulation
· Steam granulation

**Dry Granulation**

This approach is most inexpensive approach of granulation and appropriate forhydro-touchy products. In this approach granules are preparedwithout binding answer and heat. This approach entails twosteps. One is making ready big debris known as slugging. Secondone is milling and screening of slugs into small granules.

**Advantages**

a) Less equipments are needed
b) Eliminate binding answer process

**Disadvantages**

a) Requires specialised heavy responsibility pill press.
b) Does now no longer allow uniform color distribution.
C) Tends to create greater dirt with appreciate to moistgranulation.
d) Increases the potentiality of pass contamination.ApplicationsSuitable for hydrophobic andoily substances.

**Wet granulation**

This technique includes numerous steps. Initially with the aid of using the addition ofbinding agent (hydrophilic or hydrophobic) to get moist mass.This moist mass is exceeded thru the sieves observed with the aid of usingdrying.

**Advantages**

Easy method and no want of experts.

**Disadvantages**

Time consuming, Labor fee is greater, numerous steps are involved.

**Moisture Activated Dry Granulation (MADG)**

MADG is likewise acknowledged as **`Single-Pot`** granulation or **moist**granulation. Here drying step is removed due to the fact very much lessquantity of binding agent is used to set off binding method andfurthermore moisture soaking up marketers like microcrystallinecellulose (MCC), potato starch, a aggregate of MCC and potatostarch (50% w/w), silicon dioxide, Spress® B818 PregelatinizedCornStarch NF 17, Maltrin®maltodextrins 18, etc. used toget rid of moisture gift withinside the granules. This generationincludes moist agglomeration of the powder aggregate to shape acheesy mass observed with the aid of using moisture absorption to dry the granules.In this generation small quantity of water (1–4%) is brought toagglomerate the powder combination.

**Advantages**

· A simple, clean, lean method that makes use of very littlegranulating fluid.
· Produce granules with greater uniform particle lengthdistribution (particle length variety of 150-500 μm) andterrific flowability.
· Economical and time efficient, as calls for much less power andremoves drying step.
· Suitable for non-stop processing, and for coaching offloating and sustained launch products.

**Disadvantages**

· Unsuitable for thermo-labile, moisture sensitive, excessivemoisture soaking up substances.
· Difficult to increase formulations with excessive drug loading.

**Applications**

· Suitable for eutectic and hydro-phobic substances.

**Thermal Adhesion Granulation (TAG)**

It is a singular GT, patented with the aid of using Wei-Ming PharmaceuticalCompany (Taipei, Taiwan) that includes granulation with the aid of using adding very much less quantity of granulation fluid. In this method thebinder&/diluent aggregate is first wetted with the aid of using pouring water orethanol (2.0–3.6%). Then this combination is positioned in a prewarmedglass bottle, sealed after which heated with the aid of using an IR lamp toenhance floor temperature of the system to 90°C-105°C forwater as solvent, 70°C–90°C for ethanol as a

binding agent andcombined below tumble rotation for 3–20 min till granules areformed. Resulted granules have been straight away sifted with propersieve 22.[21-23]

**Advantages**

· Requires much less quantity of granulation fluid and formsgranules with top waft property.

· Reduces the dirt era at some stage in powder processing.

**Disadvantages**

· Not appropriate for materials with greater than 130°C meltingfactor andfor substances with binding solvents different thanwater and ethanol.

**Applications:** Applicable in R&D systems.

**Pneumatic Dry Granulation (PDG):**

It is a singular dry granulation technique evolved with the aid of using Atacama Labs(Helsinki, Finland). It includes manufacturing of compact mass with the aid of usingthe use of curler compaction technique with little compression pressure.This fabric is brought right into a newly innovated fractionatingtool that separates the granules and recycles rejectedfraction.[24-28]

**Advantages**

· Can gain excessive drug loading of historically testedtough substances.

· Faster development (inside weeks) despite historicallytested tough substances.

· Decreases price of product with the aid of using minimizing waste throughrecycling and manufacturing price.

· Excellent balance with more suitable shelf-life.

· Compatible with different technology like coating, sustainedlaunch, rapid launch.

· Suitable for thermo-labile and moisture touchy pills.

· Taste covering and tailoring of launch charge and time can beachieved.

· Produce gentle and porous granules with excessive compressibilityand Flowability.

· Possesses potentiality to deal with sterile merchandise or toxicsubstances

· Lowers scale-up price and problems.

**Disadvantages**

· Due to utilization of double compression pressure substances usedmight also additionally gothrough degradation.

· High price because of novelty in process.

**Applications**

· Applied broadly due to praise with regulatorybodies.

· Suitable for pills with excessive melting factor.

**High Shear Mixture Granulation**

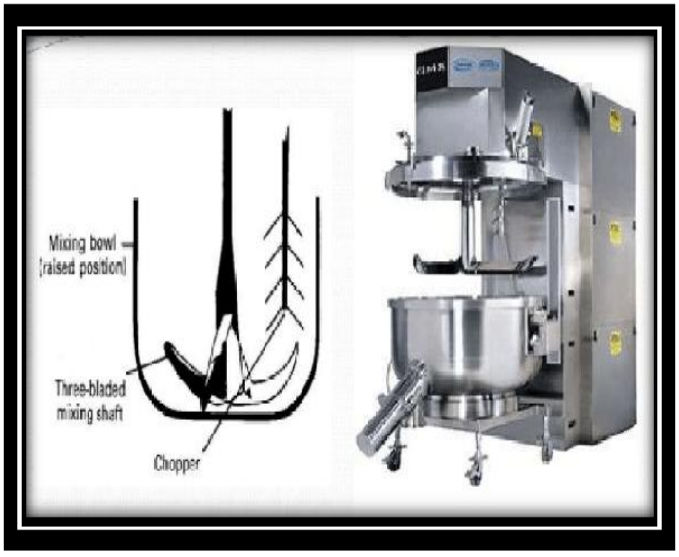



**Figure 2: Rapid mixture granulator**

Rapid combination granulator(RMG) is a easy and effortlessly cleanablegadget advanced according to Good ManufacturingPractice requirements, to lessen the cross-infection and theenvironmental dangers and to get round and well-compactedgranules in a exceedingly brief time. This device may beoperated in a closed unit and it includes mixing, number one andsecondary granulation, drying steps. Primary granulation stepincludes spraying of the binding agent onto the powder mattressat the same time as the secondary granulation includes kneading of the wetproduct to provide and to amplify the granules. Subsequentdrying of very last fabric is achieved certainly below low stress atmild temperature. [29,30,31,32]

Impeller speed, chopper speed, water addition approach and rate,massing (mixing) time, load of the RMG, feed fabriccharacteristics, drug substance particle length are the granulationmethod parameters that calls for tracking to get granules withfavored characteristics. Volume of load in RMG must be much lessthan two-thirds of its capacity (proven in determine 2)[4].

**Advantages**

· It includes Short processing time.

· Requires much less quantity of liquid binders required with respectto fluidized mattress granulation technology.

· Highly cohesive fabric may be handled.

**Disadvantages**

· Mechanical degradation ought to take area in case of fragileparticles.

· Results withinside the choppy distribution of binder solutionduring transferring powder mattress throughout high-sheargranulation.

· Unsuitable for thermo-labile fabric.

· Over wetting ends in formation of lumps and massive lengthgranules.

**Applications**

· Used in pharmaceutical enterprise and in addition to in paint,beauty industries.

**Fluidized Bed Granulation**

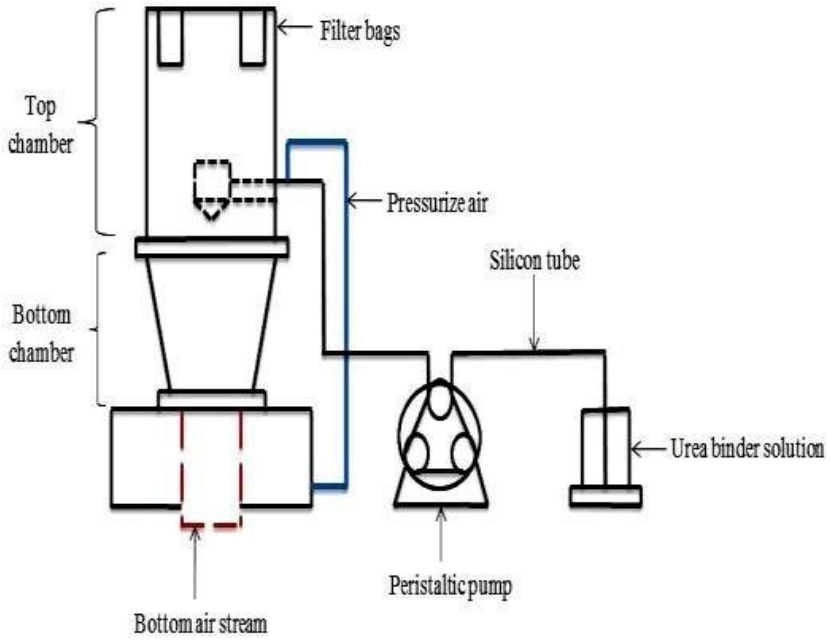



**Figure 3: Fluidized bed granulator**

It is an air suspension technique, of prescribed drugs become firststated with the aid of using Wurster to coat drugs which are later used forgranulating and drying of prescribed drugs and particle/granulecoating. [31-34]

Fluidized mattress granulation method includes spraying of binderanswer onto the fluidized powder mattress (FPB) to get finer, freeflowing and homogeneous granules using unmarried equipmentcalled FBP. FBP consists of air-managing unit, productbox and air distributor, spray nozzle, disengagement areaand method filters, exhaust blower or fan, manipulate system,answer shipping system (proven in determine 3)[4].

**Advantages**

· Reduces dirt formation for the duration of processing.

· Improves home tasks and employee safety.

· Suitable for next coating and managed releasemerchandise and decreases product loss.

**Disadvantages**

· Cleaning become labor-intensive, time eating and assuringreproducibility become troublesome.

**Applications:** Applicable for granulation, drying, coating,mixing, etc.

**Extrusion-SpheronizationGranulation**

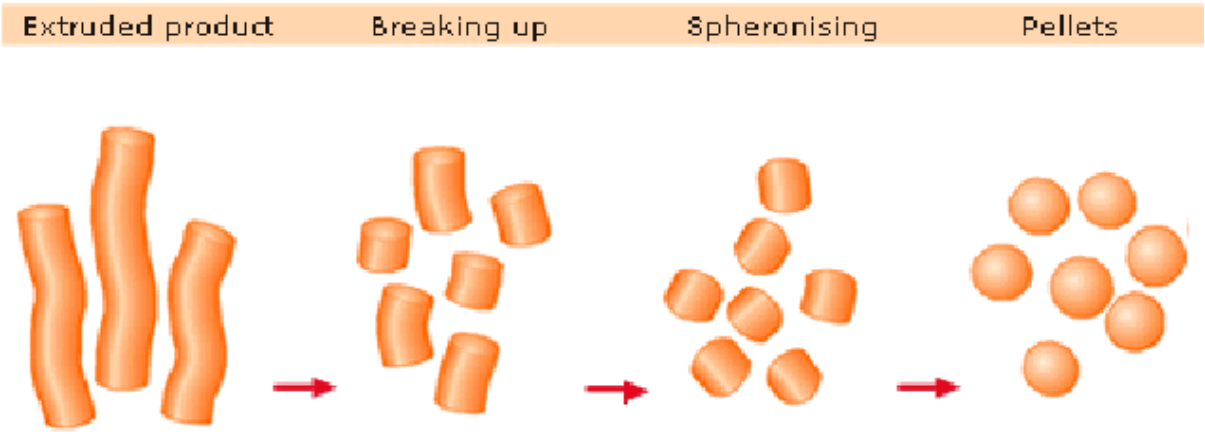



**Figure 4: Extrusion-Spheronization Granulation process**

A more than one step method entails five-steps able to makinguniform sized round debris with slim length distributionthat have been appropriate for managed launch formulations with the aid of usingextruding the cheesy mass thru extruder and subsequentpelletization or spheronization the use of pelletizer or spheronizer. [31-34] Pellets are organized with the aid of using using moist or warm soften extrusiontechniques.

Wet extrusion method entails extrusion of moist agglomerate(cheesy mass) of the powder combination thru extruder. Hot softenextrusion method entails extrusion of thermoplasticsubstances thru a thermostatically managed extruder.Processing parameters like extruder pore length, spheronizationpace and operational situations want to be optimized whichimpacts particle length, length distribution and morphology ofgranules (proven in determine 4)[35]

**Advantages**

· Incorporates better ranges of energetic with out producingexcessively large debris.
· Easy to mix or extra energetic dealers inside the sameunit, in any ratio.
· Modification of bodily traits of the energeticsubstances and excipients.
· Can produce round debris with excessive bulk density, lowhygroscopicity, slender particle length distribution andsmoother surface.

**Disadvantages**

· Needs extra exertions and time for granulation.
· Cannot be used for moisture touchy and thermo-labilematerials.

**Applications:** Used inpreparation of granules for tablets,capsules, suspensions and for dry powders.

**Spray Drying Granulation**

It is a non-stop system wherein a dry granular product isacquired through feeding a binding answer or a suspension of energeticagent without or with excipients to the drying gadget wherein thefeed is atomized and dried with a heated fueloline move observed throughnext separation of granular product from the fueloline move.Alternately particle agglomeration changed into delivered approximately throughspraying the binder answer onto mattress of powder debris influidized kingdom done with the passage of air observed throughdrying the usage of warm air. [19,20,27,28]

**Advantages**

· It is a quick and non-stop system.
· Low cost.
· Reduces operator publicity to dust.

**Disadvantages**

· Substances that are touchy to warmness are negative candidates.
· Improper spray results in insufficient sized particles.

**Applications:** Applicable withinside the coaching of dry syrups anddusting powders.

**Freeze Granulation**

Integrated Biosystems, Inc. (California, USA) had patentedfreeze GT that consequences in round and loose flowing granuleswith gold standard homogeneity. FG entails spraying of suspensioncontaining powder into liquid nitrogen in which the drops wereright away frozen to shape granules which upon subsequentfreeze-drying yields dry granules. [12-17]

**Advantages**

· Granule density may be managed via way of means of the stable contents ofthe suspension.
· Non-oxides and metals may be dealt with as slight dryingprevents critical oxidation.
· Results stable granules with out a cavities.
· High yield with low fabric waste.

· Low to excessive portions of granules may be produced withreproducibility.
· Equipment may be without problems wiped clean up and Organic solventsmay be recycled.

**Disadvantages**

There can be a threat of deterioration of drug because of use oftemperature that's much less than 0°C.

**Applications:** In the formation of injectable granules.

**Foam Binder Granulation**

FBG is a easy and more secure moist granulation processing ofsubstances and employs excessive shear or low shear RMG, or FBP ineach laboratory-scale and manufacturing-scale settings usinghydroxypropylcellulose or hypromellose as binder. Thisera includes non-stop addition of liquid binders in theshape of aqueous foam both onto the formerly blendedmattress contained in RMG with variable speeds of impelleror chopper or in FPB contained in FBD. After attaininggranulationendpoint the moist granules are dried in FBP tillfavored moisture content material became achieved.

Wet foam hasphysical traits and float just like liquidand dry foam has excessive air-to-liquid ratio that movements greater like asolid,are used for granulation; at the same time as dry foam is recommended.Foam first-rate became calculated from penetration time andnucleation ratio and the facts is used to decide the variety ofsuited foam first-rate that may be used to get granulatedproduct with favored first-rate.[11,13,15,19,20,28,33]

**Advantages**

· Eliminates use of spray nozzle thereby removes pluggingeffects.
· Requires low quantity of the water and the binder forgranulation.
· Improves procedure robustness.
· Binder distribution is uniform.
· No over wetting.
· Cost powerful as reduces drying, manufacturing, anddevice clean-up time, and does now no longer require newdevice or drastic adjustments in processing techniques.
· Immediate launch and matrix controlled-launch merchandisemay be without problems scaled-up.

**Disadvantages:**

This procedure is achievement complete in scale-up however it ishard for manufacturing scale.

**Applications**

· Suitable for merchandise with very low attention or druglevel (in mg or µg according to tablet) as generated foam can carryenergetic elements at a totally low attention.
· Suitable for water touchy formulations, distinctly watersolubleor even very poorly water soluble drugs.
· Can take care of traditionally demonstrated hard substances includingherbal elements utilized in dietary supplements.

**Steam Granulation**

This era is a easy change of traditional moistgranulation technique wherein steam became used as binder insteadof water and includes injection of a jet of steam into the mattress offluidized debris to be granulated.[28,33,34]

**Advantages**

· More round granules with huge floor vicinity are formedthereby will increase dissolution fee of the drug from granules.
· Rapid drying.
· Time green procedure.
· This Possess is supplement to regulatory bodies.
· Minimizes general microorganism count.

**Disadvantages**

· Special equipments are required for steam era and its transportation.
· Requires excessive power inputs.
· Unsuitable for thermo-labile material.
· More protection measures are required.
· Unsuitable for binders that can't be activated with the aid of using contactwith stem.
· Use of temperature results in degradation and physicalchanges.

**Applications:** Applied withinside the method of sterile merchandise.

**Advanced Granulation Equipment**

Semiautomatic or absolutely computerized instrumentation structures hadbeen advanced and are used for optimizing every unit operationlike granulation, slugging, compaction, and compression.Combining all or maximum of the unit operation in a single device areadditionally superior procedures in granulation device erathat operates with best reliability. [12,13,16,21,34]

## CONCLUSION

The advances in granulation era cause the methodof higher dosage bureaucracy in phrases of content material uniformity andbalance aspects. Still lot of studies paintings and look at has to beaccomplished for the advertising of content material uniformity, balance now no longer onlyin drugs and pills however additionally in dry syrups and numerous otherformulations in Pharmaceutical industries.

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