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Chapter No. 2

PELLATIZATION TECHNOLOGY GRANULATION TECHNOLOGY COATING OF MULTIPARTICULATE

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Pellets

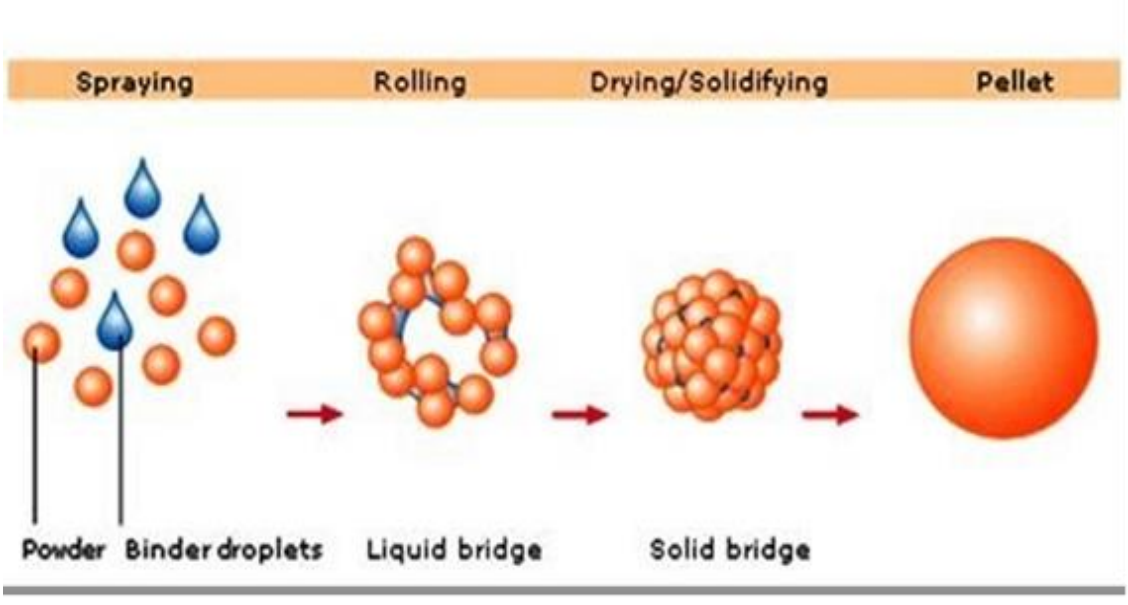
- Agglomerate obtained from diverse starting materials using different processing conditions.
- Spherical or semi-spherical solid units
- 0.5 mm to 1.5 mm

Advantages & Disadvantages of Pellets

Advantages	Disadvantages
• Easy to flow • Formulate control release products • Manage separation of incompatible drugs • Improve esthetic appeal of product • Disperse freely through GIT • Improvement of hardness and friability • Uniformity of dose	• Expensive • Complicated

Palletization

Pelletizing is a method of agglomeration, or particle size enlargement, in which material fines are processed into pellets or granules.



Requirements

Following requirements to be fulfilled for Palletization.

- Sufficiently fine particle size
- Sufficient moisture

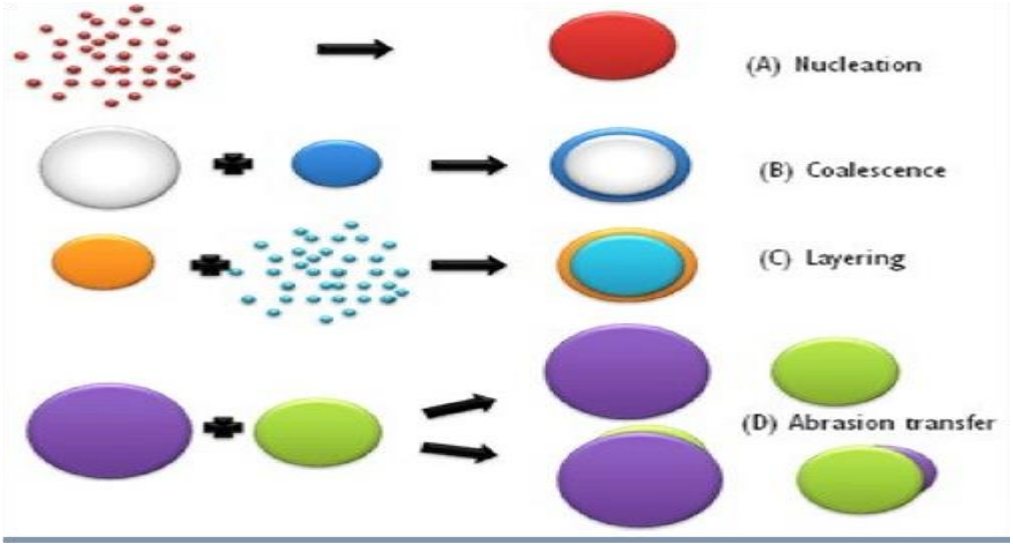
A binder **Reasons for Palletization**

- Prevention of segregation of co-agglomerated components, resulting in an improvement of the uniformity of the content.
- Prevention of dust formation, resulting in an improvement of the process safety, as powders can cause dust explosions.
- Increasing bulk density and decreasing bulk volume.
- Defined shape and weight improves the appearance of the product.
- Improvement of the handling properties, due to the free-flowing properties.
- Improvement of the hardness and friability of pellets.
- Controlled release application of pellets. Due to the ideal low surface area-to- volume ratio that provides an ideal shape for the application of film coatings.

Theory of Pellet formation

The theory of Palletization can be described by four steps:

a) Nucleation
b) Coalescence
c) Layering
d) Abrasion transfer



Nucleation

- Wetting of powder with solvent
- Held together by liquid bridges

COALESCENCE

- Formation of large particles by collisions of well-formed nuclei
- Slightly excess moisture is required
- No of nuclei decrease
- Total size remains constant

Layering

- Is a slow growth mechanism and with the successive addition of

fragments and fines on an already formed nuclei

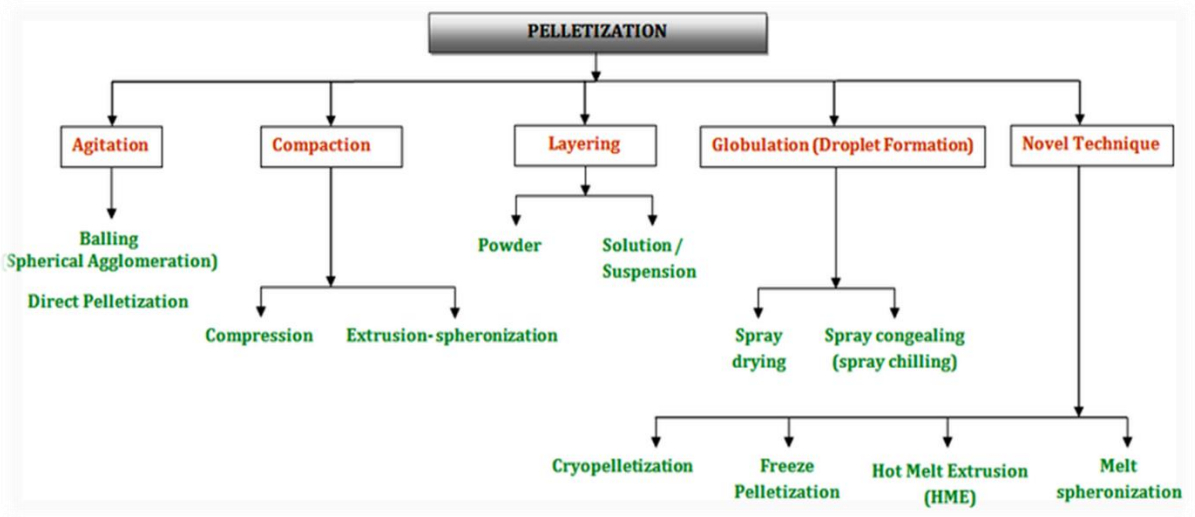
- No. Of particles remains constant
- Mass of system increases

Abrasion transfer

- Involves the transfer of materials from one granule form to another without any preference in either direction.
- Not any change in the total number or mass of the particles.
- However, the particles undergo a continuous change in their size as long as the conditions that lead to the transfer of material exist.

Techniques of Palletization

Following different techniques are used for the Palletization of drugs.



1. **Agitation**

- Fine powders can readily be formed into granular masses by admixture with a liquid phase followed by suitable agitation.
- The liquid and solid phases are thus brought into intimate contact to develop binding forces and cause agglomeration. The most common wetting phase is water or an aqueous solution with capillary binding forces being developed in the agglomerates.
- Other liquids and binding mechanisms may be utilized, however, with attendant development of viscous liquid, solid, van der Waals and other binding mechanisms.

  Most common agitation means is tumbling or Balling.

Balling

It is Palletization process in which pellets are formed by a continuous rolling and thumbing motion in pans, discs, drums or mixtures. The process consists of conversion of finely divided particles in to spherical particles upon

the addition of appropriate amounts of liquid.

2. Compaction

(a) Compression

- In this process mixtures of active ingredients and excipients are compacted under pressure to generate pellets of defined shape and size.
- At high pressure, elastic and plastic deformation can take place and create strong inter particle contact.

(b) Extrusion-Spheronization

This process is used as method to produce multiparticulate for controlled release application.

Principle:

In this process, the powder is formed into a wet mass, which is forced through restricted area (extrusion) to form strands of extrudate that are broken into short lengths and rounded on a rotating plate with in a cylinder. The resulting spherical granules or pellets are of uniform shape, size and density.

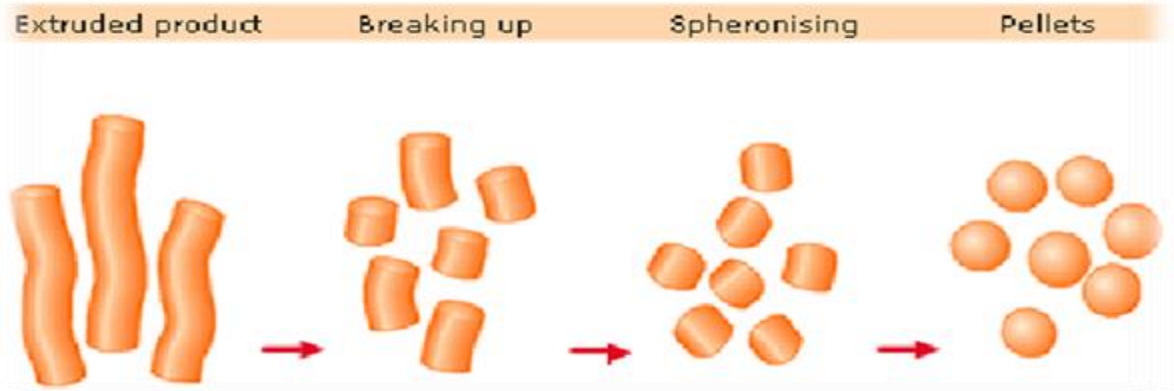
Extrusion/ Spheronization

Multistage process to obtain uniform size pellets using wet granules

Steps

1. Dry mixing of ingredients
2. Wet massing to form plastic mass
3. An extrusion stage to convert wet mass into cylindrical shape
4. Spheronization stage to convert small cylinders into solid spheres
5. Drying of spheroids
6. Screening

Extrusion process

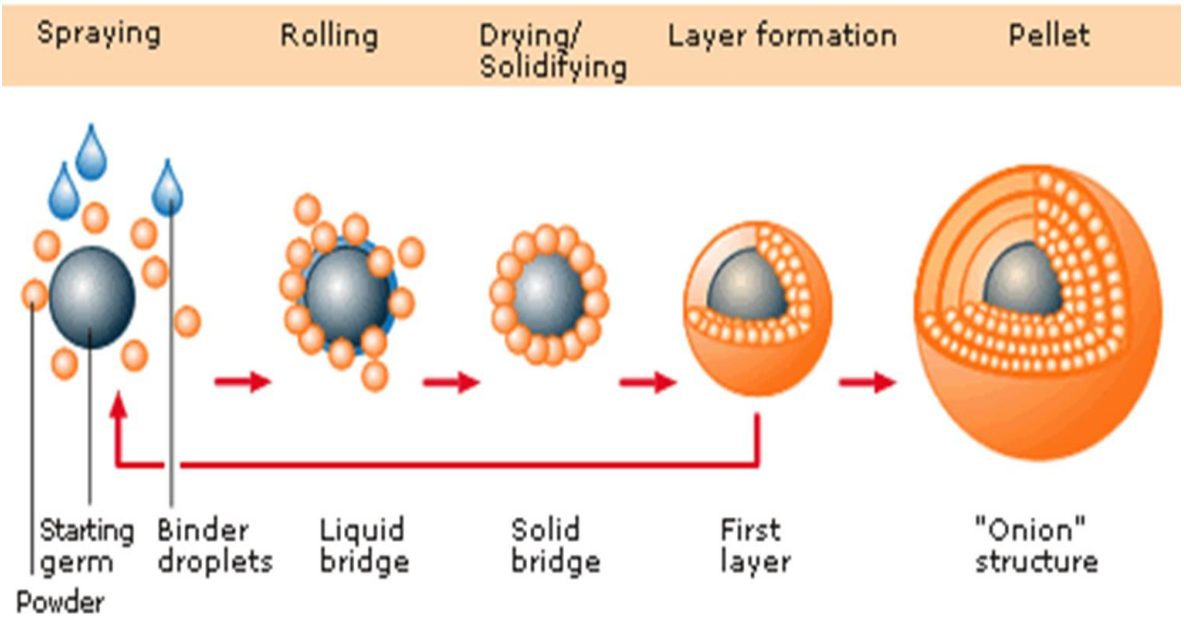


3. Layering

Deposition of successive layers of drug entities from solution, suspension or dry powder on nuclei which may be crystals or granules of the same material or inert starter seeds.

1. Dry powder layering
2. Solution/suspension layering
   a. **Powder layering**
      - Low liquid saturation
      - Binder solution is first sprayed onto the nuclei, followed by the addition of powder.
      - The most nuclei tumble in the rotating pan of disc, pick up powder particles, and form layers of small particles that adhere to each other
      - As additional bonding, liquid is sprayed, layering of more powder on the nuclei continues until the desired pellet sizes are obtained.

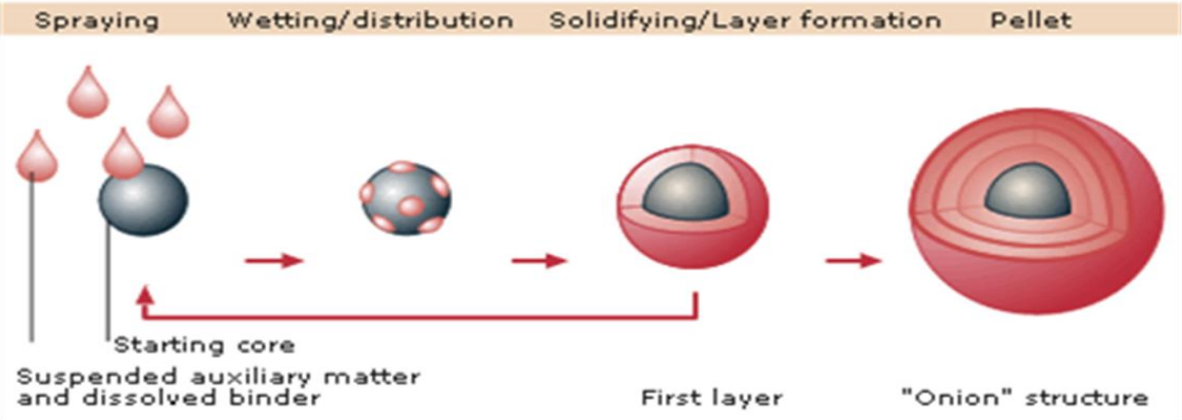
Principles of powder Layering



Solution/Suspension layering

- Involve the deposition of successive layers of solutions and suspensions of drug substances, and binders on starter seeds.
- As the solution or suspension is sprayed onto the product bed, the droplets impinge on the starter seeds or cores and spread evenly on the surface.
- This is followed by drying phase which allows dissolved materials to crystallize and form solid bridges between the core and initial layer of the drug substance as well as among the successive layers of drug substance. The process continues until the desired layers of drug is obtained.

Solution or Suspension Layering process:



4. Globulation

a) Spray drying

During spray drying, a drug solution or suspension is sprayed, with or without excipients, into a hot-air stream generating dry and highly spherical particles.

b) Spray Congealing

A process in which a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes, fatty acids or other melting solids. The dispersion is then sprayed into stream of air and other gases with a temperature below the melting point of formulation components.

Cryopellatization

- It involves freezing of the material being processed.
- Pellets can be produced by allowing droplets of liquid formulation such as solution, suspension or emulsion to come in contact with liquid nitrogen at -160˚C.
- Pellets are then dried in freeze dryers.

Freeze Palletization

- Molten-solid carrier/matrix is introduced as droplets into an inert column of liquid in which the molten solid is immiscible.
- The molten solid moves in the liquid column as droplets and solidifies into spherical pellets.

Hot melt extrusion

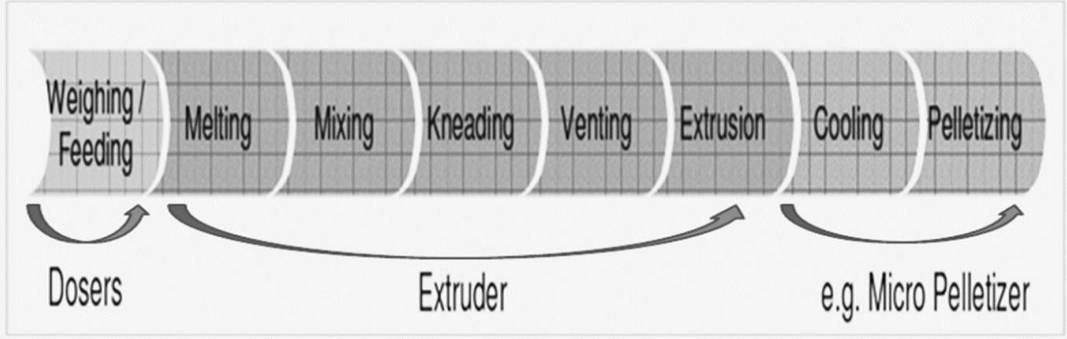
- It is process of pumping raw materials with a rotating screw under elevated temperature through a die into a product of uniform shape.
- Rotating screw impose mixing and agitation result in the de-aggregation of suspended particles in the molten polymer resulting in the more uniform dispersion.

Principle

- During hot melt agglomeration process, the melt able binder may be added as molten liquid, or as dry powder or flakes.
- In the latter, the binder may be heated by hot air or by a heating jacket above the melting point of the binder. Typically, the melting points of

melt able binders range from 50 to 80°C.

- A lower-melting-point binder risks situation where melting or softening of the binder occurs during handling and storage of the agglomerates



Advantages	**Disadvantages**
A continuous process No organic solvent or water are needed Shorter and more efficient processing time.	Not suitable for heat labile drugs Must be moisture free

Advantages and Disadvantages of Hot Melt Extrusion:

Palletization products

Formulation type	example
Sustained release pellets	omeprazole
Sustained release pellets	pantoprazole
Immediate release pellets	tramadol
Matrix pellets	atenolol
Extended release pellets	Verapamil hydrochloride

Granulation technology

***Granulation**:*

It is the process of forming grains or granules from a powdery or solid substance, producing a granular material. It is applied in several technological processes in the chemical and pharmaceutical industries.

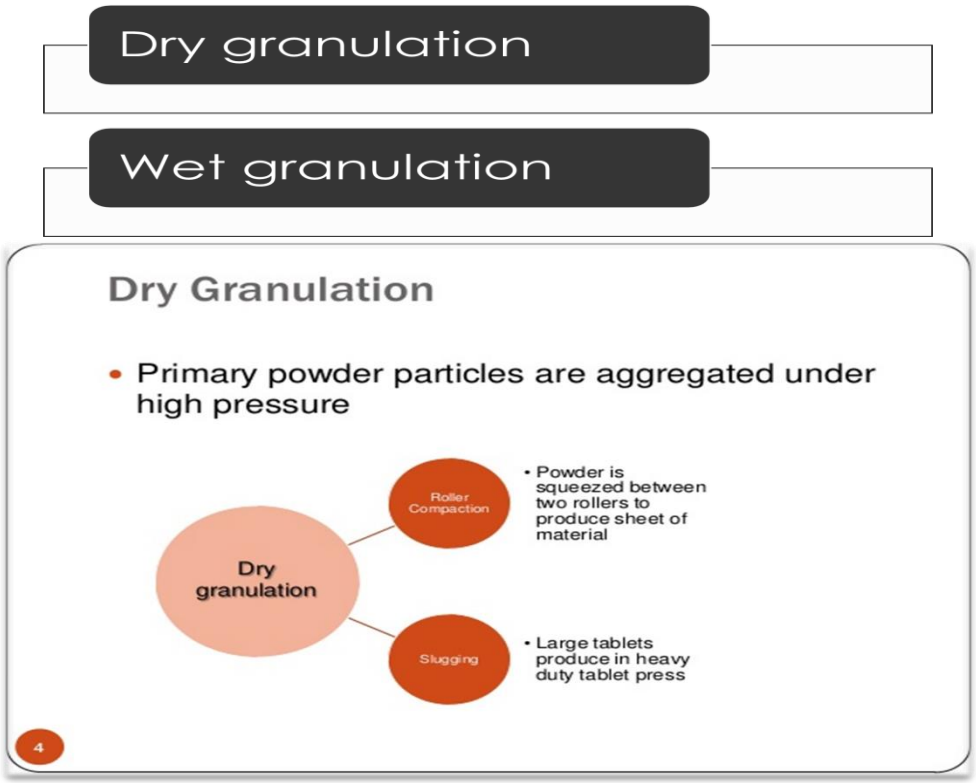
Why we prepare granules?

To avoid powder segregation-- Segregation may result in weight variation

To produce uniform mixtures

To eliminate poor content uniformity

Types of Granulation:



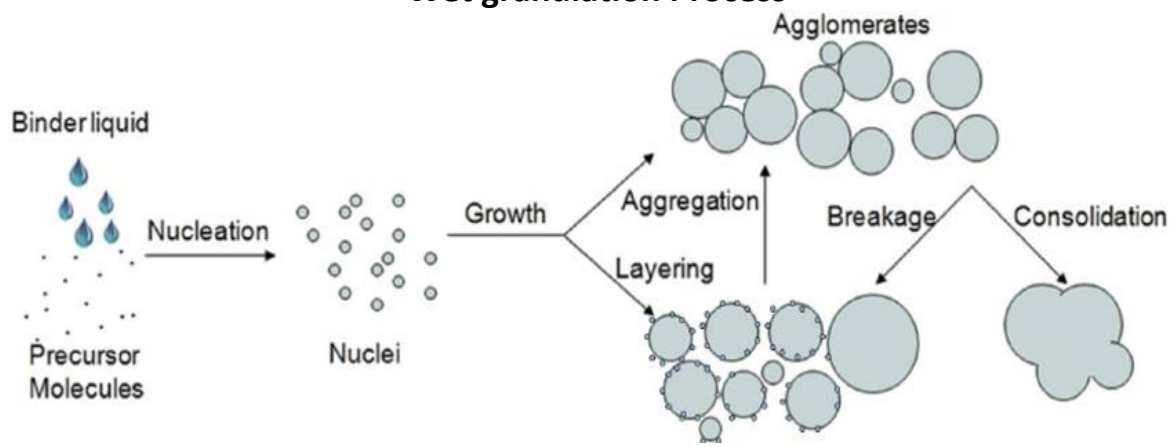
a) Wet Granulation:

Wet granulation involves the massing of a mix of dry primary powder particles using a granulating fluid (the process of adding a liquid solution to powders). The fluid contains a solvent which must be volatile so that it can be removed by drying, and be non-toxic.

It consists of six steps

- Dry Mixing
- Wet Mixing
- Milling of the wetted mass
- Drying
- Milling of dried mass
- Final Blending

Wet granulation Process

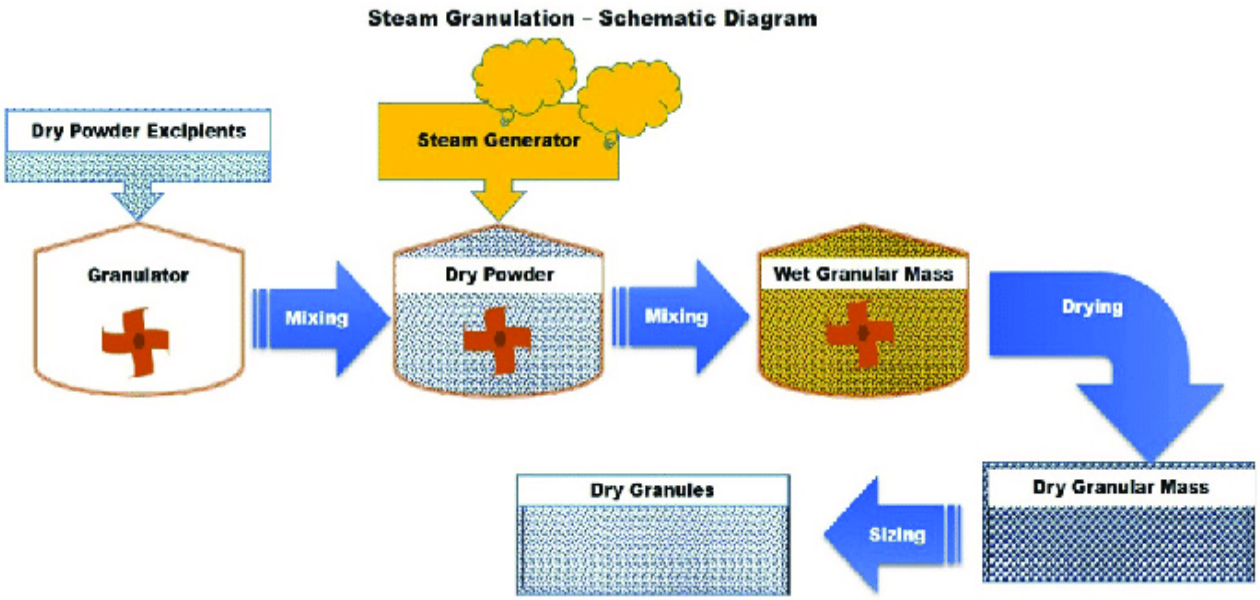


Granulation technologies

a) Steam granulation
b) Fluid bed granulation
c) Moisture activated dry granulation
d) Melt granulation
e) Foam granulation
f) Freeze granulation
g) Pneumatic dry granulation

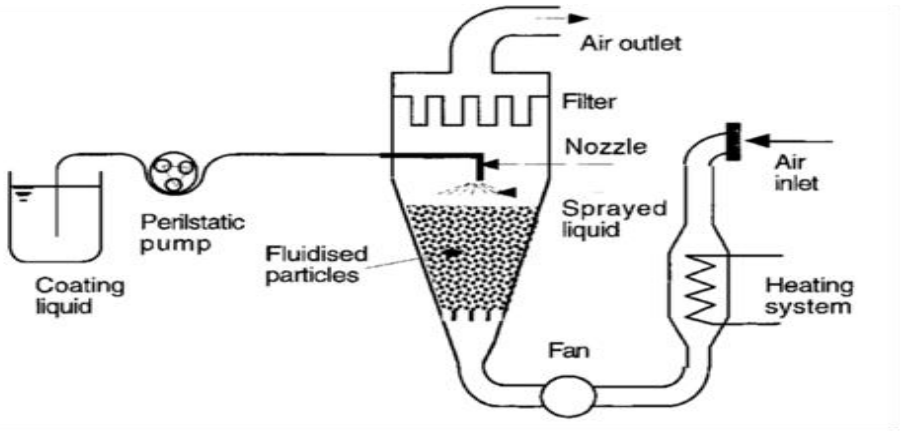
a) Steam Granulation

- A steam granulation technique involves the injection of a jet of steam into a bed of fluidized particles to be granulated.



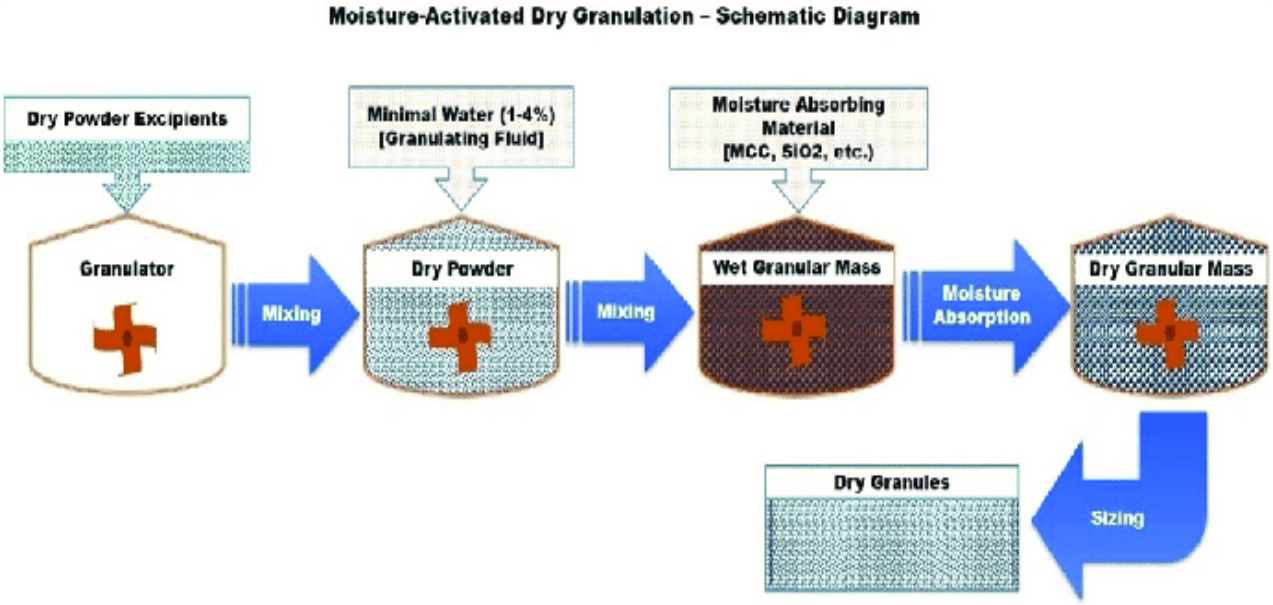
b) Fluid bed granulation

- It is the operation by which fine solids are transformed into a fluid like state through contact with a gas.
- Fluid bed granulation is a process by which granules are produced in single equipment by spraying a binder solution onto a fluidized powder bed.
- The system involves the heating of air and then directing it through the material to be processed. Later, the same air exit through the voids of the product.



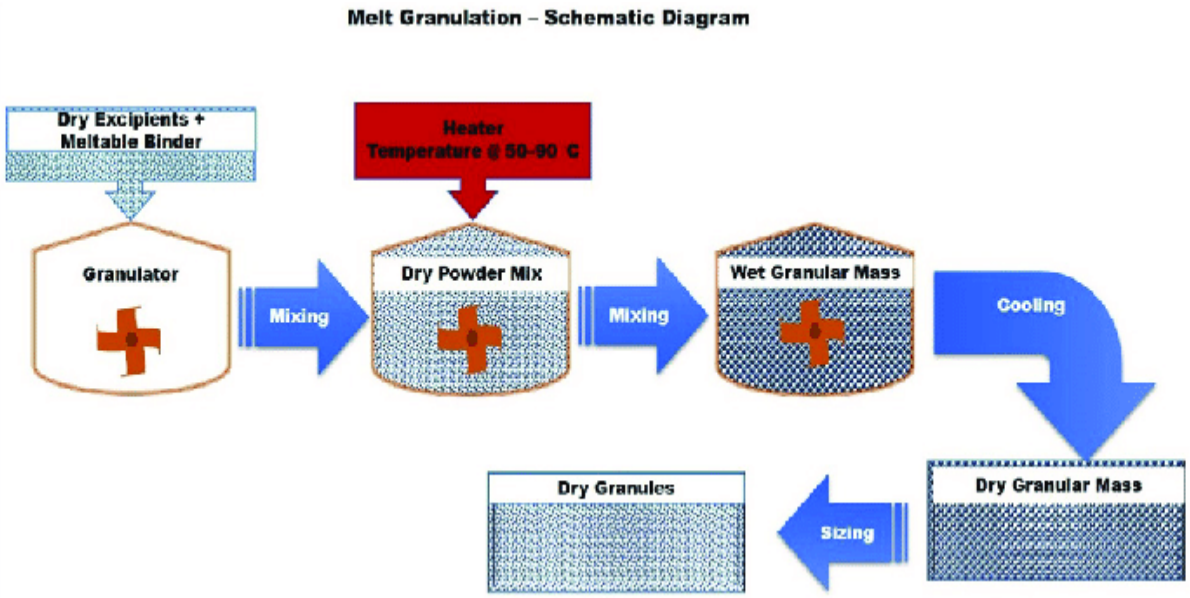
c) Moisture activated dry granulation

Moisture-Activated Dry Granulation (MADG) is a very simple and innovative process where granules are created with water and a granulating binder, as in wet granulation, but are not heat dried or milled. This process helps to minimize endpoint sensitivity.



d) Melt granulation

Melt granulation is a size enlargement process in which the addition of a binder that melts or softens at relatively low temperatures (about 60°C) is used to achieve agglomeration of solid particles in the formulation.



e) Foam granulation

- Involves the addition of liquid/aqueous binder as foam instead of spraying or pouring liquid onto the powder particles.
- No spraying nozzle is used, less water required and cost effective.
- A simple foam generation apparatus is used to incorporate air into a conventional water soluble polymeric excipients binder such as METHOCEL.

f) Freeze granulation

- It involves spraying droplets of a liquid slurry or suspension into liquid nitrogen followed by freeze-drying of the frozen droplets.
- By spraying a powder suspension into liquid nitrogen, the drops are instantly frozen into granules, and in the subsequent freeze drying process, the granules are dried by sublimation of ice without any segregation effects

g) Pneumatic dry granulation

- A dry granulation technology, utilizes roller compactor technology.
- Granules are produced from powder particles by applying mild compaction.
- Fine particles are separated from the intended size granules in fractionating chamber.
- Then these particles enter the cyclone and are returned to roller compactor for immediate reprocessing.
- Granules are obtained .

COATING OF MULTIPARTICULATE

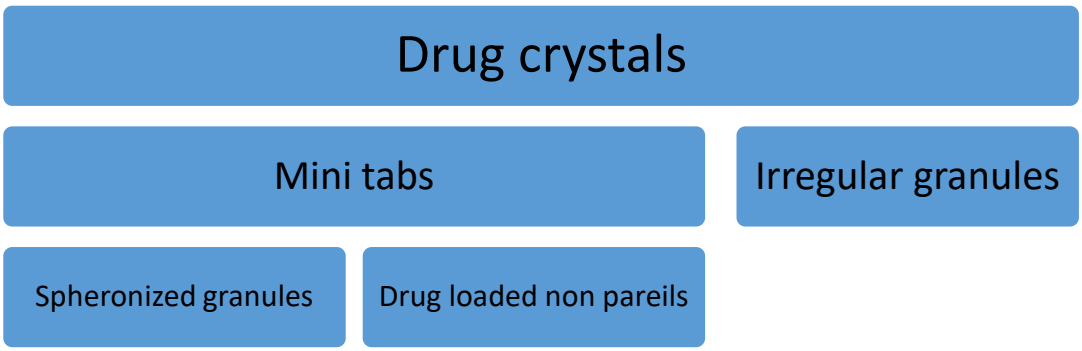
- Multiparticulate or multiple unit dosage forms are the discrete, small, repetitive units of drug particles which may or may not possess similar drug release pattern.

- They can be tailored for pulsatile, controlled and or delayed, targeted drug release depending upon the polymer employed in fabrication.
- Coating a process by which essentially dry outer layer of coating material is applied to the drug substance in order to confer specific benefits.

Why we need coating of multiparticulate?

- Protecting drug substance from environment.
- To mask the taste of drug.
- To get ease in swallowing.
- To make the dosage form appealing.
- Imparting modified release characteristics to drug product.
- To identify the product. i.e. colored coating

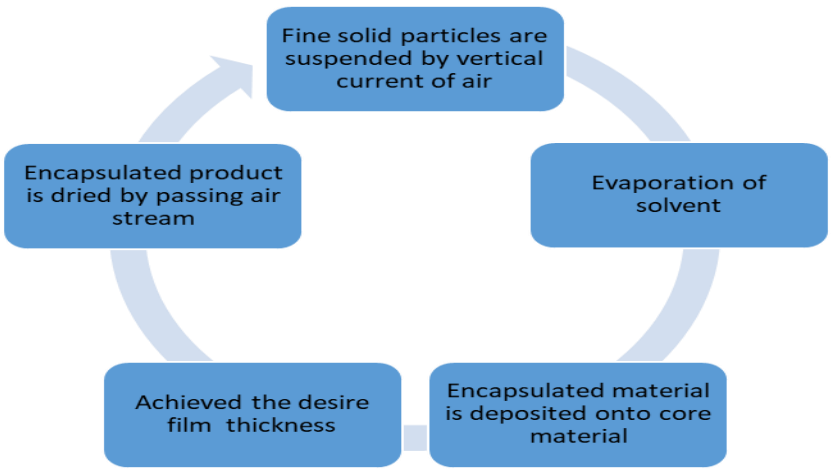
TYPES OF MULTIPARTICULATE



Types of Coating of Multiparticulate

a) Air suspension coating
b) Spray drying and spray congealing
c) Microencapsulation
d) Film coating
e) Sugar coating
f) Hot melt coating

a) Air Suspension Coating:



b) Spray Drying:

Spray drying is a process in which fluid (containing drug to be encapsulated and coating solution) is dispersed as fine droplets in to moving stream of hot gases.

Process:

- Operation in closed system comprising 4 phases;
- Atomization of feed
- Mixing of spray & air
- Solvent evaporation
- Product separation

c) Spray Congealing

- It can be applied by spray drying equipment when protecting material is applied as a melt.
- The core material is dispersed in a coating material melt.
- Coating solidification is accomplished by spraying the hot mixture into cool air stream.
- e.g. Microencapsulation of vitamins with digestible waxes for taste masking.

d) Microencapsulation

A process by which very tiny particles of solid or liquid are surrounded or coated with a continuous film of polymeric material.

Techniques of microencapsulation

i. Coacervation
ii. Solvent evaporation

i. Coacervation

A process in which aqueous colloidal solution separates upon alteration of thermodynamic conditions of state into two liquid phases one rich in colloid i.e. the coacervate & the other containing small colloids

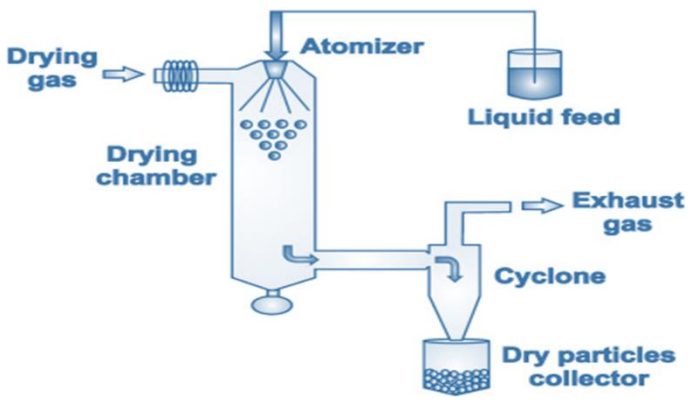
Steps of Coacervation:

It include following steps:

- Formation of immiscible phase.
- Disposition of coating.
- Rigidization of coating

Types of Coacervation

- Aqueous Phase Separation
- Non aqueous Phase Separation



Aqueous phase separation	Non aqueous phase separation
The hydrophilic coating, such as gelatin or gelatin-gum acacia. Water-insoluble core particles. The resulting microcapsules may contain payloads of 85-90% and can release their contends by pressure, hot water or chemical reaction. Used to encapsulate citrus oil, vegetable oils, and vitamin a	The coating is usually hydrophobic The core may be water-soluble or water immiscible. This process has been investigated for the encapsulation of solid food additives such as ferrous sulphate.

Methods for Coacervation

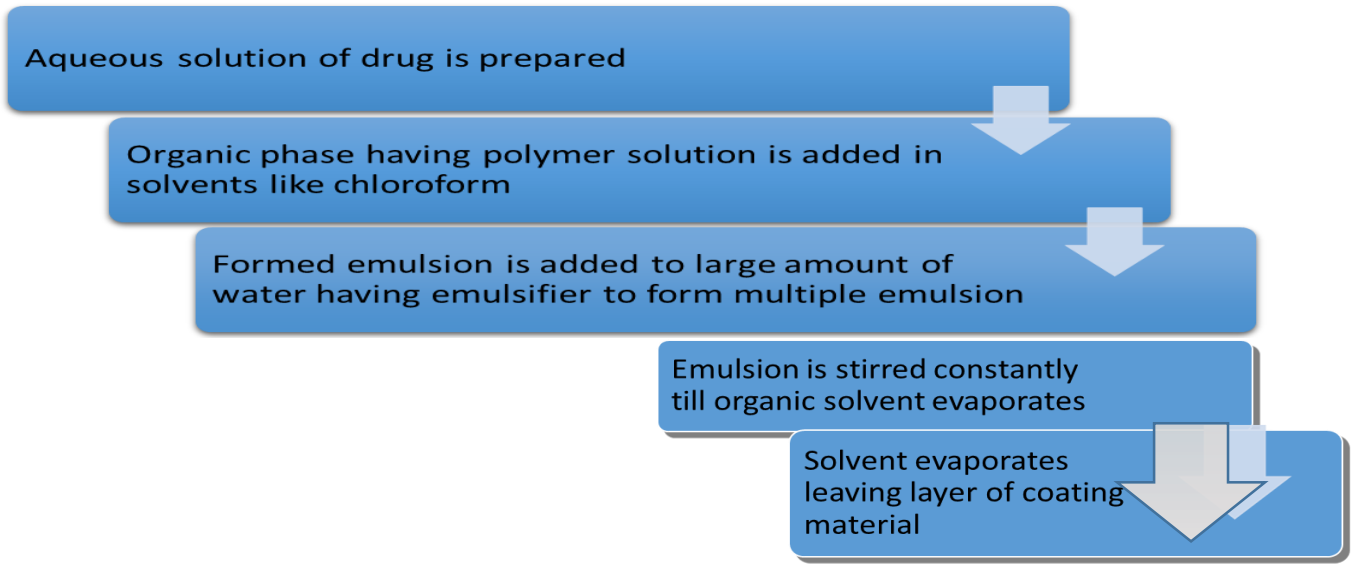
Choice of method depends on polymer and set of conditions being used. Methods include;

- Temperature change
- Salt addition
- Non-Solvent addition
- Incompatible polymer addition
- Polymer- polymer interaction

ii. Solvent Evaporation

Solvent evaporation involves emulsification of polymer in aqueous phase and dispersion in a volatile solvent like dichloromethane, chloroform, and ethyl acetate. Then the solvent is evaporated using high temperature, vacuum, or by continuous stirring.

Steps of Solvent evaporation:



e) Film coating

A film coating is a thin polymer-based coat applied to a solid dosage form.

Components

- Polymer
- Plasticizer
- Colorants
- Solvent

Procedure of coating

- The seed may be first coated with one layer of active drug
- Then coated with one layer of polymer.
- The processes are repeated until multiple layers are formed.

Types of film coating

1. **<u>Immediate release</u>**

   They don't affect biopharmaceutical properties of drug. They are readily soluble in the drug.

2. **<u>Modified release</u>**
   - They allow the drug to release in specific manner
   - Delayed release. I.e. enteric coating
   - Extended release .i.e. enteric coating

f) Hot melt coating

- It is the application of a layer to a substrate by pre-melting the desired material and then allowing or forcing the material to cool, solidifying the layer.
- The process is widely used in industry, particularly for pressure-sensitive adhesives on thin substrates- self-adhesive labels.
- Coating materials are mostly waxes.

g) Sugar Coating

It involves the application of sugar solution with color for several times to give uniform and elegant film.

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