

INDUSTRIAL PHARMACY-I**UNIT III-CAPSULES****CLASS:25****TOPIC****Pellets: Introduction, formulation requirements, pelletization process, equipments for manufacture of pellets****Definition**

Pellets can be defined as small, free flowing multiparticulate dosage forms manufactured by the agglomeration of fine powders or granules of drug substance and excipients using appropriate processing equipment

Ideal properties of the pellets

Spherical shape and smooth surface.

The particle size of pellets should be in range of 600-1000 μ m.

The quantity of the active ingredient in pellets should be maximum in order to maintain size of pellet

Advantages:**Technological advantages:****1. Uniformity of dose:**

Extrusion and layering techniques offers great accuracy with uniform drug in pellets

Spheres have excellent flow properties useful in automated process like tableting, moulding, capsule filling

2. prevention of dust formation:

Fine powders may cause dust explosion and respiration of fines may affects the health so these can be avoided by pellets

3. **Deliver incompatible bioactive drugs** simultaneously with different release profiles at the same or different sites of GIT

Therapeutic advantages

4. Pellets disperse freely in G.I.T. and invariably **maximize drug absorption** and also reduce peak plasma fluctuation
5. It **reduces accumulation of drugs** especially proven advantageous in the case of irritating drugs
6. Pellets are less susceptible to dose dumping.
7. Pelletization offers flexibility into the dosage form design and development.

Disadvantages

1. Difficult to compress pellets into tablets as they are rigid. So they are encapsulated into hard gelatin capsules
2. Demands sophisticated equipment thereby increases cost of manufacture

Theory of pellet formation and growth:

It involves three consecutive regions:

nucleation,

Coalescence and transition

ball growth

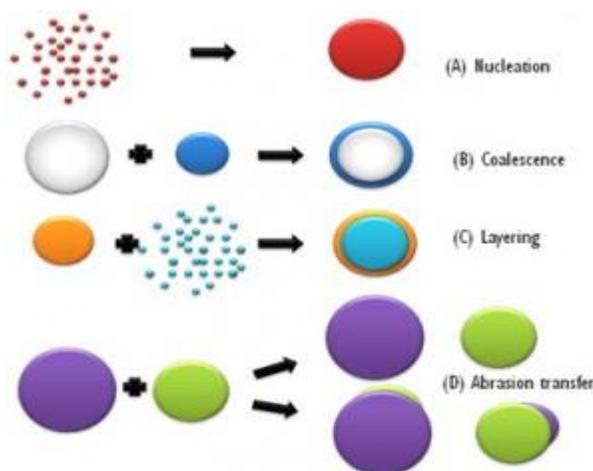
Nucleation

- It is a stage of Pelletization process that occurs whenever a powder is wetted with solvent system.
- The primitive particles are drawn together to form three-phase air-water-liquid nuclei system which are held together by liquid bridges that are pendular in nature.
- The reduction of particle size will improve the bonding strength between them.

- Further the size, the rate and the extent of nuclear formation depends upon the size of the particles, the moisture content, the viscosity of the binding particles, the wettability of the substrate and the processing conditions, such as tumbling and drying rates.

Coalescence and layering

- Nucleation is followed by a transition phase where the growth mechanisms affecting are coalescence and layering.
- Coalescence is defined as the formation of large-sized particles by random collision of well-formed nuclei, this mechanism require slightly excess moisture on the surface of the nuclei although the number of nuclei is progressively reduced even though the total mass of the system remains unchanged during this operation.
- Layering is a slow growth mechanism and with the successive addition of fragments and fines on an already formed nuclei.
- In the layering step, the number of particles remains constant while the total mass of the system increases due to increasing particle size as a function of time.
- The fragments or fine particles can be formed by particle size reduction



PELLET GROWTH MECHANISM

The fines and the fragments produced through size reduction are taken up by larger pellets. Production of fines and subsequent coalescence and layering continues until the number of

collisions declines rapidly, thereby leading to a reduction in the rate of growth of the pellets. At this point the third phase, the ball growth region, is reached.

Ball growth

- The main mechanism in the ball growth phase is the abrasion transfer which involves the transfer of materials from one granule formed to another without any preference in either direction.
- This phase does not result in 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.

Methods of preparation

Pelletization techniques

1. Compaction -extrusion and spheronization
2. Drug layering
3. Melt pelletization
4. Globulation
5. Balling
6. Compression

1. Pelletization by extrusion and spheronization

Wet mass extrusion spheronization also called cold-mass extrusion spheronization has become the method of choice when one is desirous of having dense spherical pellets of uniform size and shape.

It involves the following steps;

(a) Dry Mixing: Dry mixing of ingredients is done to achieve homogeneous powder dispersion using twin shell blender, planetary mixer, high speed mixer and tumbler mixer

b) Wet Massing:

- Wet massing is done to produce a sufficient plastic mass for extrusion, by employing normal equipment and processes as employed in wet granulation for compaction.

- The most commonly used granulator is planetary mixer or Hobart mixer or sigma blade mixer and high shear mixer.
- Evaporation of the fluid phase is a major problem with high shear mixers as they introduce a high amount of energy into the wet mass which is partly transformed into heat and induces evaporation of the granulation liquid thus changing the extrusion behavior of the wet mass. Cooling of the granulation bowl may avoid this problem.

c) Extrusion:

- This is the third step in the process, which produces rod shaped particles of uniform diameter from the wet mass.
- The wet mass is forced through dies and shaped into small cylindrical particles with uniform diameter.
- Such shaping of the wet mass into long rods, commonly termed 'extrudate.' The extrudate particles break at similar length under their own weight. Thus, the extrudate must have enough plasticity to deform but not so much that the extrudate particles adhere to other particles when rolled during spheronization process.
- Extruders are classified into three categories namely,
-Screw feed extruder (axial or end plate, dome and radial),

In the axial type, the screen is placed at the end of the screw, while in radial type the screen is placed around the screw discharging the extrudate perpendicularly to the axis of the screw.

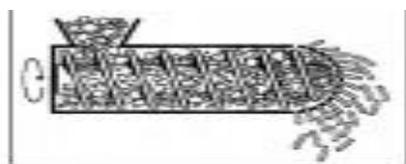


FIG. 5. AXIAL SCREW FEED EXTRUDER

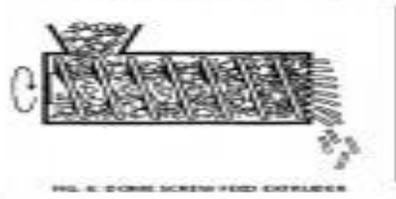


FIG. 6. DOUBLE SCREW FEED EXTRUDER



FIG. 07. RADIAL SCREW FEED EXTRUDER

-Gravity feed extruder (cylinder roll or gear roll) include

1. rotary cylinder and rotary gear extruders, which differ mainly in the design of the two counter rotating cylinders. In the rotary cylinder extruder, one of the two counter rotating cylinders is hollow and perforated, whereas the other cylinder is solid and acts as a pressure roller



FIG. 08. CYLINDER ROLL TYPE



FIG. 09. GEAR ROLL TYPE

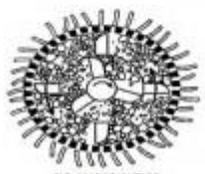


FIG. 10. RADIAL TYPE

In the rotary gear extruders there are two hollow counter rotating gear cylinders with counter board holes.

-Piston feed extruders (ram) which are probably the oldest type of extruders a piston displaces and forces the material through a die at the end. Ram extruders are preferentially used in the development phase, because they can also be used to measure the rheological properties of the formulations

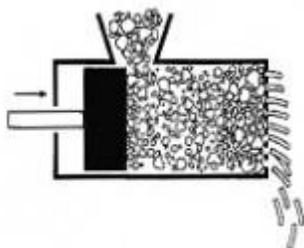


FIG. 11: AXIAL PISTON EXTRUDER



FIG. 12: RADIAL PISTON EXTRUDER

(d) Spheronization:

The spheronization technology was first introduced by Nakahara in 1964. A spheronizer also known as merumerizer consists of a static cylinder and a rotating friction plate where the extrudate is broken up into smaller cylinders with a length equal to their diameter and these plastic cylinders are rounded due to frictional forces. During spheronization process different stages can be distinguished depending upon the shape. The friction plate, a rotating disk with a characteristically grooved surface to increase the frictional forces, is the most important component of the equipment.

Two geometric patterns are generally used

- a cross-hatched pattern with grooves running at right angle to one another
- a radial pattern with grooves running radially from the center of the disc.

The rotational speed of the friction plate varies from 100- 2000 rpm. Spheronization process involves transition from rods to spheres that might occur in various stages which

usually take 5 to 30 minutes provided mass should not be too dry wherein no more spheres are formed and the rods will transform as far as dumbbells only



SCHEMATIC REPRESENTATION OF DIFFERENT PELLET FORMATION STAGES DURING SPHERONISATION

(e) Drying:

- A drying stage is required in order to achieve the desired moisture content.
- increased drying rate gave more porous pellets due to decrease pellet densification
- The pellets can be dried at room temperature or at elevated temperature in a tray drier/oven or in a fluidized bed drier
- If solute migration occurs during drying of the wet mass, this may result in an increased initial rate of dissolution, stronger pellets with modified surfaces, which might reduce adhesion of any added film coats.

(f) Screening:

- Screening may be necessary to achieve the desired size distribution and to avoid pellets having high size polydispersity index
- sieves are used.

Process parameters for the extrusion-spheronization techniques

a) Starting Material:

- ✓ The nature of the starting material influences the size, hardness and sphericity of the particle, as well as the release rate of the loaded drug.
- ✓ The material used in the formulation causes difference in pellet quality produced from different compositions.
- ✓ The use of similar products manufactured by different suppliers also showed changes in the characteristics of the pellet produced.

Eg. Pellets prepared with three types of microcrystalline cellulose (MCC) from different manufacturers featured differences in size and roundness even though processed under the same conditions

b) Extruders:

- ✓ According to Reynolds and Rowe
 - an axial screw extruder produces a denser material
 - radial screw extruder gives higher output and greater heat production during the processing.
- ✓ Pellet quality is dependent on
 - thickness of the screen -thin-rough and loosely bound extrudate
 - thicker screen forms smooth and well-bound extrudate
 - diameter of the perforations .

c) Extrusion Speed:

increasing speed causes at surface impairments, such as roughness and shark-skinning which leads to pellets with lower quality because the extrudate will break up unevenly during the initial stages of the spheronization process, resulting in a number of fines and a wide particle-size distribution

d) Extrusion Temperature:

The extrusion cycle during the operation may lead to rise in the temperature which could cause the granulating liquid to evaporate from the granules which causes difference in the quality of the extrudate right in the beginning of the batch itself. Extrusion temperature control is especially taken into the consideration when processing a thermolabile drug formulation

e) Spheronizer Specifications:

Pellet quality is also dependent on spheronizer load which affects the particle-size distribution, bulk and tap density of the final pellets

The increase in the spheronizer speed and a low spheronizer load will result in wider particle size distribution with less yield of pellets, whereas it increases with extended spheronization time at a higher spheronizer load. Barrau *et al.*, reported that an increasing spheronizer load decreased the roundness and increased the hardness of pellets.

the bulk and tap density increased and the size of the pellets decreased with an increasing spheronizer load

2. Drug layering: The layering process comprises the 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. In solution/suspension layering, drug particles are dissolved or suspended in the binding liquid. In powder drug layering, a binder solution is first sprayed onto the previously prepared inert seeds, followed by the addition of powder.

Conventional pan coaters have been used from the very beginning of the history of drug layering



.fluid bed processor is also employed.

Fig. DRUG LAYERING BY USING SOLUTION

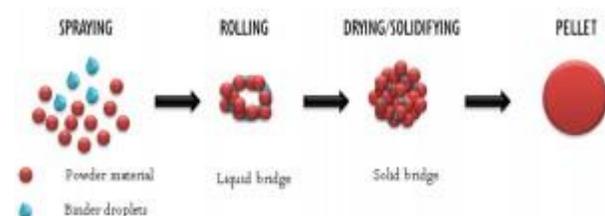


FIG. DRUG LAYERING BY USING SUSPENSION

3. Direct pelletizing: Sample material is blended and solvent or binder system is added to it. The material bed is then subjected to a centrifugal motion. The centrifugal forces act on the material in this process resulting in the formation agglomerates, which get rounded up into uniform sized dense pellets. The size, density and shape of the pellets formed are influenced by the speed of rotation. The moist pellets formed are then dried up in the fluid bed. Organic solvents can also be used if required.

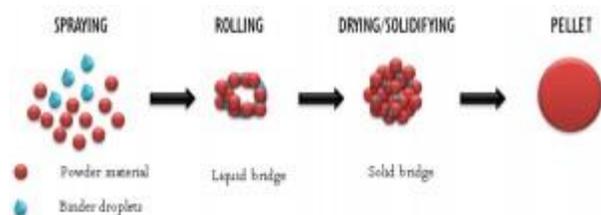


FIG. : DIRECT PELLETTIZATION PROCESS FOR PREPARATION OF PELLETS

Pelletization in fluid bed system:

- ✓ Making uniform spherical pellets in the Fluid Bed System is possible only in the Tangential Spray Attachment or Roto-Processor attachment.
- ✓ The major advantage is that all the operations from mixing to bead formation to bead drying to bead coating all can be done in one machine.
- ✓ The top-spray attachment can be used for making granules and bottom spray attachment is used for coating.
- ✓ A fluidized bed is a bed of solid particles with a stream of air or gas passing upward through the particles at a rate great enough to set them in motion.
- ✓ As the air travels through the particle bed, it imparts unique properties to the bed simulating a liquid form. It is possible to propagate wave motion, which creates the potential for improved mixing.

Other pelletization methods:

Other Pelletization methods such as globulation, cryopelletization, balling, and compression are also used, although a limited scale in the preparation of pharmaceutical pellets.

Globulation droplet formation consists of two related processes, spray drying and spray congealing:

Spray drying: It is the process in which drugs in the suspension or solution without excipients are sprayed in to a hot stream to produce dry and more spherical particles. This process is commonly used for improving the dissolution rates; hence bioavailability of poorly soluble drugs

Spray congealing:

- It is the process in which a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes or fatty acids, and is sprayed into an air chamber where the temperature is kept below the melting point of the formulation components, to produce spherical congealed pellets.
- Both immediate and sustained released pellets can be prepared in this process depending on the physiochemical properties of the ingredients and other formulation variables

Cryopelletization:

In aqueous-organic solution suspension or emulsion are dropped into liquid nitrogen to form frozen particles, these particles are then freeze-dried or lyophilized to remove water or organic solvents .

Compression:

- Pellets of definite sizes and shapes are prepared by compacting mixtures or blends of active ingredients and excipients under pressure .
- The formulation and process variables controlling the quality of pellets prepared are similar to those used in tablets manufacturing.

Balling:

- It is the Pelletization process in which pellets are formed by a continuous rolling and tumbling 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

Melt-Extrusion Technology:

- Earlier technique utilise water as granulation fluid which cause stability problem
- A novel hot-melt extrusion and spheronization process has been recently reported to produce spherical pellets without the use of water or other solvents eliminating instability problems during processing
- Pellets require film coating to control release where as pellets produced by melt extrusion do not require additional film coating since the drug release is diffusion controlled.

- This technique is being approved in the USA, and it is a fast, simple, continuous, solvent-free process with fewer processing steps.

Melt extrusion process consists of three basic steps:

melting or plasticizing a solid material,

shaping the molten material and

solidification of the material into the desired shape.

A hot melt extrusion line consists of

1. material feed hopper- holds the material and continuously feeds it into the extruder, which has a heated barrel containing the rotating screw
2. extruder- The extrudate is then cut into uniform cylindrical segments
3. spheronizer- cylindrical segments are spheronized to generate uniform sized pellets. The temperature maintained in the spheronizer should be high enough to soften the extrudate partially and facilitate its deformation and eventual spheroid formation.

Freeze Pelletization:

- In this technique, a 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.
- The molten-solid droplets can move upward or downward in the liquid column depending on the droplets' density with respect to the liquid in the column.
- If the density of the molten-solid carrier/matrix is more than that of the liquid in the column, then the droplets are introduced from the top of the column and pellets solidify in the bottom portion of the column .
- Conversely, if the density of the molten-solid carrier/matrix is less than that of the liquid in the column, then the droplets are introduced from the bottom of the column and pellets solidify at the top portion of the column.

Product characteristics of the Pellets:

1. Round pellets.

2. Good flow behavior.
3. Easy to dose.
4. Good dispensability.
5. Compact structure.
6. High bulk density and
7. Dense surface.

FORMULATION OF PELLETS

CLASS-30

Pellet Coating Process: The coating process for pellets is carried out primarily in order to modify the release of the drug from the pelletized drug delivery systems. Following are the some of the Coating equipments used for this purpose

Most of the coating processes use one of three general types of equipments.

1. The standard Coating pan
2. The Perforated Coating pan
3. The Fluidized bed coater

Conventional Pan System

a) **The standard coating pan:** The standard coating pan system consists of a circular metal pan mounted somewhat angularly on a stand, the pan is rotated on its horizontal axis by a motor, the hot air is directed into the pan and onto the bed surface, and is exhausted by means of ducts positioned through the front of the pan .Coating solutions are applied by spraying the material on the bed surface

b) **The perforated Coating Pan:** Perforated pan coaters are efficient drying systems with high coating capacity, and can be completely automated for both sugar coating and film coating processes.

There are four different type of coaters available

Acela-Cota,

Hi-Coater,

Driacoater,

Glatt coater.

In all four of these perforated pan systems the coating solution is applied to the surface of the rotating bed of pellets through spraying nozzles that are positioned inside the drum .

c) **The fluidized Bed Coater:**

The Fluid Technology offers a very efficient coating ,granulation and pellet formation with gastro resistance or controlled release system .

- Fluid bed dryer technology is commonly employed in the film coating of pellets. The coating suspension is sprayed as a atomized droplets onto the fluidized pellets. A film coat is formed around the pellet with successive disposition of spray droplets accompanied by solvent evaporation due to the heat supplied by the fluidizing air. Fluid bed pen coater called Mini Wet

Formulation:

1) Active Pharmaceutical Ingredient:

The different API's can be used to develop immediate release, sustained release pellets with diversified applications in different areas (subcutaneously and intramuscularly) depending on the size variations where the size range is maintained below 600 microns and are called as micropellets. Pellets technology is widely used to delivery GIT drugs at a specific site to release drug in a controlled manner.

2) Binder:

- They are also called as agglomerating inducers or bridging agents.
- These are adhesive materials(solution form than dry form) that can be incorporated into pellet formulations to bind powders and maintain integrity on pellet formation
- The mechanism of action of the binder involves formation of liquid bridge that holds the particles together; but as the liquid evaporates the precipitating and hardening of binder takes place leading to main bonding force and with a possibility of the soluble constituents to crystallize and contribute to the bonding mechanisms
- In drug layering process, the drug is layered onto the surface of the starter material along with the binders. Sequential layering of binder in the desired manner with the drug allows the formation and growth of pellets.
- In the spray-drying process, the binder is intimately mixed as suspension or solution form with the drug to provide a fairly cohesive mixture which results in the pellets with

appreciable strength after drying The binders are commonly used in the range of 2-10% w/w or v/v and should be optimized so that the pellets are durable and not friable

3) Granulating fluid:

- it imparts the required plasticity and cohesiveness to the wet mass to extrude it and spheronize it to give a perfect spherical shape.
- excess moisture content leads to agglomeration of pellets during the preparation process due to the presence of excess solvent system on the surface of pellets
- less quantity leads to generation of fines with large size distribution of pellets.
- In the case of soluble drug, it gets dissolved by the granulation liquid, thus, resulting in increase of the volume of the liquid phase which leads to over wetting of the system and agglomeration of pellets

E,g alcoholic or hydroalcoholic systems, ethyl ether, dilute acetic acid, isopropyl alcohol

4) Spheronizing Enhancer: Spheronization enhancers are formulation aids that improve the production of spherical pellets, mainly during spheronization and balling processes. They not only impart plasticity onto the formulation, but also impart binding properties that are essential for pellet strength and integrity.

5) Filler: These are the excipients used to form the bulk of the material, in the process of pelletization 70 to 80% of the excipients is formed by fillers.

Eg. microcrystalline cellulose, Avicel PH 101, Glyceryl mono stearate, Starch RX1500, spray dried lactose.

6) Plasticizer:

- Plasticizers improve the flexibility of polymers by reducing the tensile strength and glass transition temperature of the material
- The plasticizer selection will depend upon its compatibility with the polymer and also solvent employed in the casting of strip.
- The flow of polymer will be improved with the use of plasticizer that enhances the strength of the polymer.

E,g Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, Citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil

7) **Lubricant:**

During compression and Extrusion-Spheronization, lubricants do play a crucial role in the successful manufacture of pellets. Their use reduces the friction between the die wall and material mix either during the compression process or in ejection phase. They also play a significant role in smooth discharge of the pellets from the Spheronizer .

8) **Separating Agents:**

- Separating agents are materials which are adsorbed on the surface and promote the separation of pellets into individual units during a pelletization process, which are incorporated initially in the formulation or externally during processing to prevent pellets attracting one another due to surface charge development during the process, binding the pellets together leads to the formation of aggregates due to subsequent addition of binding agents, and agglomeration of pellets due to the wetness of the surface of the pellets coupled with the local concentration of the binding agents.
- The amount of separating agent used differs with the type of formulation and the manufacturing process and they are used in dry form during spheronization to prevent adhesion of the spheres to the friction plate and the cylindrical wall of the Spheronizer .

9) **Surfactant:**

- In most pelletization processes, the initial pellet formation and subsequent growth into fully fledged smooth surfaced spherical pellets depends on the liquid bridges that hold the primary particles together, therefore, liquid (water in most cases) wetting the particles effectively is given more attention.
- Surfactants are added to the liquid to improve wettability by lowering the interfacial tension between the liquid and drug particles.
- Surfactants help to weaken the liquid bridges and results in more friable pellets.
- In extreme cases, excess fines might be produced which brings in the focus to the addition of surfactants for pellet formulations.

- Care should be taken to avoid using surfactants unless it is absolutely essential for the production of pellets that possess specific properties.

10) pH adjusters:

- The pH adjusters influence the microenvironment of drug molecules used for many reasons.
- acid-labile drugs are protected from the pH conditions of the GIT by giving an enteric coating.
- Buffer systems may also be added to the core formulation to maintain the stability, to enhance the dissolution rate of drugs whose solubility's are influenced by changes in the pH this is particularly referred with pellets whose release rates are membrane-controlled as the solubility of the drug plays a major role in determining the rate of release.
- Therefore, specific buffer systems or dual buffer systems are incorporated in pellet formulations to adjust the solubility of drugs to fit a particular process.

11) Release modifiers:

- Th specific release profiles in a single step which can be achieved by the incorporation of release modifiers along with drug during the core formulation. .

E,g 1. soluble low molecular weight excipients, surfactants and disintegrants are incorporated in formulations to enhance the drug release kinetics,

1. water insoluble polymers, hydrophobic substances, inorganic salts, and hydrophilic polymers that swell and/or form gels are incorporated in pellets that retard release kinetics.

12) Flavoring agent:

- The choice for the flavors changes from individual to individual depending upon the age, ethnicity and liking which plays a significant role in the taste fondness.
- geriatric population like mint or citrus fruit flavors while younger generation like flavors like fruit punch, raspberry etc.
- The flavor selection for the particular formulation also depends upon the drug to be incorporated in the formulation

Eg, Mint flavor is generally added for gastric related ailments like indigestion.

The amount of flavor needed to mask the taste depends on the type and strength of the flavor. Preferably up to 10% w/w flavors are added in the formulations.

Cooling agents like monomethyl succinate, menthol can be added to improve the flavor strength and to enhance the mouth-feel effect of the product. Other cooling agents' like WS3, WS23 and Utracoll II can also be used in conjunction with flavors

RECOMMENDED FLAVOUR FOR THE PARTICULAR TASTE

Taste sensation	Recommended flavor
Salt	Butter scotch, Apple, Apricot, Vanilla, Peach
Bitter	Wild Cherry, Walnut, Chocolate, Mint, Passion fruit
Sweet	Berry, Vanilla.
Sour	Citrus Fruits, liquorice, Root beer, Raspberry

13) Sweetening agent:

- The sweet taste in formulation is more preferred especially in case of pediatric population. Natural sweeteners as well as synthetic sweeteners are used to improve the palatability of the formulations.

Examples

- The traditional source of sweetener is sucrose (derived from cane or beet in the form of liquid or dry state), dextrose, fructose, glucose, liquid glucose and maltose.

(fructose is dissolved rapidly in the saliva compared to sucrose and dextrose and also sweeter than sorbitol and mannitol)

- Polyhydric alcohols such as sorbitol, mannitol, isomalt and maltitol can be used in combination for good mouth-feel and cooling sensation
(. Polyhydric alcohols are considered less carcinogenic and do not have bitter after taste which is a vital aspect in formulating oral preparations.)

- The sweetness property of the polyols is less than half of that of sucrose except xylitol and maltitol which have similar sweetness as that of sucrose (scale of 0.8- 1.0).
- Saccharin, cyclamate and aspartame are the first generation synthetic sweeteners
- acesulfame-K, sucralose, alitame and neotame are second generation artificial sweeteners. **(Acesulfame-K and sucralose have more than 200 and 600 time sweetness. Neotame and alitame have more than 2000 and 8000 time sweetening power as compared to sucrose.)**
- Rebiana which is a herbal sweetener, derived from plant *Stevia rebaudiana* (South American plant) has more than 200–300 time sweetness but these synthetic sweeteners carry a disadvantage of after taste effect which can be reduced by mixing or blending the natural and synthetic sweeteners.
- Generally sweeteners are used in the concentration of 3 to 6 %w/w either alone or in combination.

14) Coloring agents: Coloring agents are generally used in order to improve the appearance and make it more patient compliance. Pigments such as Titanium dioxide or FD&C approved coloring agents are used either in the dry form or mixed with the granulating fluid during the formulation.

TABLE : SHOWING DIFFERENT POLYMERS USED IN THE PELLETTIZATION PROCESS

Polymer used in pelletization	Formulation	Applications
Carbopol 974P,NF, Resin.	Beads containing Weakly basic drugs.	Slower release of the salt basic drugs.
Crosscarmellose sodium or sodium starch glycolate.	Super-disintegrants in avicel pellets.	Increase dissolution rate, pellet micropore volume
Eudragit RS PO and RL PO.	Polymer (with combination) based pellets.	Better characterization li modulus of the pellets, s

		characteristics, sphericity
Eudragit RL 30D, RS 30D, NE 30D.	A multiple- unit floating drug delivery system.	Prolong the gastric residence time, increase the overall bioavailability of the dosage form.
Gelucire.	Lipidic –matrix pellets.	Controlled drug release.
Methocel-E5 (HPMC) or AMB, Eudragit L 30D-55.	Enteric coated pellets.	Improved film formation, reduced coalescence.
Microcrystalline cellulose, Ac-Di- Sol.	Floating pellets with bacterial antagonist.	Improving floating properties.
Microcrystalline cellulose and hydroxypropyl methyl cellulose.	Pellets with water insoluble drugs in self-emulsified form.	Controlling the drug release in various dosage forms.
Pectins or alginates.	Polysaccharide gel coated pellets.	Oral administration of the drug in the form of coated pellets.

Evaluation of Pellets:

1.Size distribution: The sizing of pellets is necessary because it has significant influence on the release kinetics. In most of the cases particle size determination is carried out by simple sieve analysis using sieve shaker. Vernier calipers used to determine the size of pellets.

Sieving method: The prepared pellets were estimated by sieving method. Sieving method directly gives weight distribution. Sieves were arranged in a nest with the coarsest at the top. A sample (5 gm) of the dried pellets was placed on the top sieve and subjected to mechanical agitation. The sieve set was fixed and shaken for a certain period of time (10 minutes). The pellets retained on each sieve were weighed. Frequently, the pellets were assigned the mesh number of the screen through which it passed or on which it was retained. It was expressed in terms of Arithmetic mean of the two sieves.

SXi Fi

Mean particle size = -----

S Fi

Where, SXi Fi = Weight size; S Fi = Percent weight retained.

The size analysis of the pellets was done by carrying out the sieve analysis of the prepared batches. The cumulative particle size distribution was plotted, from which the 50% value (median) was obtained.

2. Pellets shape:

Sphericity of the pellets is the most important characteristics and various methods have been used to determine it. The pellets were mounted on a light microscope fitted to a Camera Lucida and the images of the pellets were drawn manually on a graph paper.

The shape factor estimates the amount by which the projected image of particles deviate from a circle and it is calculated by means of the projected area of the pellets and its circumference.

For acceptable quality of pellets the roundness index/shape factor should be between 1 and 1.2. For perfectly circular projected image, the shape factor should be 1 while a value of 0.6 describes a particle of good sphericity .

Visual inspection of pellets by microscope and stereomicroscope are another method to determine shape of pellets. An angle at which a plane has to be tilted before a particle begins to roll is called to be One plane critical stability, is one of the important methods used for determining shape.

The angle of repose is an indirect indication of the circularity of pellets and is calculated by the ratio of double the pile height and pile radius by fixed funnel method measured after a certain amount of pellets are allowed to flow through a specific orifice from a given height .

3.Surface morphology: Scanning electron microscopy is used to examine the surface morphology and cross section of pellets . The sampling pellets are mounted onto the aluminum stub, sputter-coated with a thin layer of Platinum using sputter coater (Polaron, UK) under Argon atmosphere, and then examined using SEM. The use of optical microscopy to examine the microstructure of pellet surface was first reported .While the SEM pictures collected to observe the influence of

different fillers and concluded that MCC and corn- starch gives best quality pellets with smooth surface

4. Specific surface area: Surface area of pellets is directly related with size and shape of the pellets. Knowledge of the surface area is desirable especially if film coating is considered. Knowledge about the surface area is important even in case of uncoated pellets, since drug release is influenced by the surface area. Specific surface area of pellets is determined by gas adsorption technique

Mathematical calculations: A spherical pellet, which is smooth and dense, has minimum surface area per unit volume and can be characterized by its diameter. Since surface area is equal to πr^2 . True density measurements can also be used to determine the specific surface area.

Gas adsorption technique: In this technique, the volume of nitrogen that is adsorbed by the substrate contained in an evacuated glass bulb is determined at various pressures, and the results are interpreted using a linear plot of the BET equation for the adsorption of nitrogen on a substrate.

5. Hardness and Friability: The mechanical properties of pellets are important for processing. Pellets flake off during handling, shipping, storage coating process and other unit operations thereby resulting in formation of dust. Variations in the formulation and/or process of pellets, as well as variability in the raw materials, can potentially result in significant variations with hardness and/or friability of pellets.

Hardness of pellets can be determined using Kahl pellet-hardness tester but might not be accurate.

Friability of pellets are determined by using Erkewa type tablet friabiliator or turbula mixer for a fixed period of time combined with glass beads of certain diameter in order to generate abrasion and to generate friability index

Friability can also be determined using fluidized bed with Wurster insert by using stream of air

6. Mechanical tests:

Tensile Strength: The tensile strength of the pellets is determined by using tensile apparatus with a 5 kg load cell, the pellets are strained until failure occurs. The load is recorded and the tensile strength is calculated applying the value for the failure load and the radius of the pellets .

Cushing strength: The crushing strength (the load needed to break the pellets) and elastic modulus of 15 pellets (850–1000mm size fraction) were determined using a Material Testing Machine. The

speed of the upper mobile platen fitted with a 1 kN load cell was set at 1 mm/min. Elastic modulus and force–displacement graphs were obtained by a computer system attached to the apparatus .

7.Density: Density of pellets (bulk and tapped) can be affected by change in the formulation or process which may affect other process or factors such as filling and packaging characteristic during capsule manufacture and tablet compression, and is determined simply by USP density apparatus.

The bulk density of pellets can be measured by using an automated tapper, while the true density of pellets can be determined by an air-comparison pycnometer or by solvent displacement method. Bulk density is indicates the packing properties of pellets or spherical seeds which provide higher bulk densities due to small intraparticle porosities . True density indicates the extent of densification or compactness of pellets.

8.Porosity: The porosity of the pellets influences the release of drugs from the pellets by affecting the capillary action of the dissolved drug. The porosity of the pellets can be measured quantitatively by mercury porosimetry. The porosity of the pellets can also be determined qualitatively by SEM with image analysis and quantitatively by using optical microscopy rarely .

Pore radius is given by Washburn equation;

$$R = 2 \gamma [\cos \theta] / P$$

Where; $\gamma = 480 \text{ ergs/cm}^2$, $\theta = 140^\circ$, $r = \text{pore radius}$, $p = \text{mercury-intrusion pressure}$.

Thus, determination of the porosity of pellets by mercury porosimetry is a very well-established method showing reproducible results.

9.Disintegration time: Disintegration of pellets is one of the main characteristics for immediate release pellets. Done by reciprocating cylinder method (USP Apparatus 3) **10.In vitro dissolution studies:**

Release of drug from solid dosage form often constitute a determining step in the *in vivo* absorption process and used in conjunction with *in vivo/in vitro* correlation to establish quality control parameter. Release of the drug from pellet mainly depends on the composition, hardness and size of pellets and it is determined by using USP Apparatus I or by USP Apparatus II. The drug release profiles from pellets also depends on the Polymer and binder used, aqueous solubility of the drug, physical state of the drug in the pellet, drug loaded into the pellet and the presence of additives such as surfactants. In case of wax based freeze dried pellets, the drug

release decreased as the hydrophobicity of wax increases and the drug release increased as the aqueous drug solubility increased.

Applications: Pellets have varied applications in a number of industries and an innovative use of it's could achieve maximum profitability.

1. Taste masking:

various technique have been utilized to mask the bitter taste of a drug such as the -addition of sweeteners and flavors,

- filling in capsules,
- coating with water insoluble polymers or pH dependent soluble polymers,
- complexing with ion-exchange resins,
- micro- encapsulation with various polymers,
- complexing with cyclodextrins and
- chemical modifications such as the use of insoluble prodrugs,

The pelletization technique solves difficult taste masking problem while maintaining a high degree of bioavailability due to their high surface area, especially for oral products.

Furthermore, because of the special design of the manufacturing process, dust fractions that representing an uncoated fragments which could cause taste problems are absent in pellets. Many products, such as antibiotics (clarithromycin, roxithromycin and cephelexin) and anti-inflammatory drugs with a bitter taste, can now be formulated in products with high patient compliance, thus increasing the sales potentially in the pharmaceutical markets for the product.

2.Immediate release: Administering drugs in pellet form leads to an increased surface area as compared to traditional compressed tablets and capsules which would considerably reduce the disintegration time and have the potential for use in rapidly dispersible tablets.

3.Sustained release: The pellet form provides a smoother absorption profile from the gastrointestinal tract as the beads pass gradually through the stomach into the small intestine at a steady rate. Pellets are being increasingly used in the manufacture of sustained release dosage form of drugs. The advantages of the dosage form is well known

4.Chemically Incompatible Products: At times such ingredients are required to be delivered in a single dose. In the compressed tablet dosage form separate tablets would have to be administered, but the pellets can be administered in a single capsule.

5.Varying dosage without reformulation: Pellets have excellent flow properties, due to this, they can be conveniently used for filling capsules and the manufacturer can vary the dosage by varying the capsule size without reformulating the product

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