Exploring Pallets: A Cost-Effective Carrier for Pharmaceutical Applications

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Abstract— Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free flowing, spherical or semi-spherical units, referred to as pellets. This review outlines manufacturing of spherical pellets. The manufacturing techniques include Drug layering, Extrusion-Spheronization, Cryopelletization, Compression, Balling, Hot-Melt Extrusion Technology, Freeze pelletization, Spray-drying & Spray-congealing. Factors affecting pelletization technique and advantages, disadvantages of pellets are discussed.

Index Terms- Pelletization, Pellets, Extrusion-spheronization.

I. INTRODUCTION

The term "pallet" is etymologically derived from French palette or blades, a small shovel; it is the name of several tools in various materials (wood, brass, iron, plastic, etc.) used to collect or dig. Considering loading, the pallet is recognized worldwide as a portable platform, used as a base onto which various goods are loaded. Pallets are commonly made of wood, consisting of rectangular strips interspersed and superimposed on strips also spaced between them to enable the forklift to uplift and move the unit load. Pallets are developed for efficient material handling and are used globally to store, transport, and handle goods. About 1.8 × 109 pallets are in service in the United States, and about 4 × 109 pallets are in service in the European Union. Pellets are spherical or nearly spherical, freeflowing granules with a narrow size distribution, typically varying between 500 and 1500 µm for pharmaceutical applications. They are generally produced via a pelletization process whereby a powder blend consisting of an API and excipient particles is agglomerated into spherical granules. [1]

After being processed, pellets are usually filled into hard gelatin capsules or compressed into tablets. Furthermore, they can be formulated as immediate release dosage form or in sustain drug release over a long duration time or can be coated also to deliver a drug to a specific site of action in the gastrointestinal tract. Pellets provide the development scientist with a high degree of flexibility during the design and development of oral dosage forms. They can be divided into desired dose strengths without formulation or process changes, and also be blended to deliver incompatible bioactive agents simultaneously or particles with different release profiles at the same site or at different sites within gastrointestinal tract. Pellets provide development of formulation with high degree of flexibility due to free flowing characteristic. So they are packed easily without any difficulties. The spherical shape and a low surface area to volume ratio of pellets made uniform film coating. Pellets eliminate the dose dumping effect, which gives smoother plasma concentration profile and gradual absorption of drug than tablet, which further decrease the adverse effect of drugs. [2]

Advantages of pellets [3]

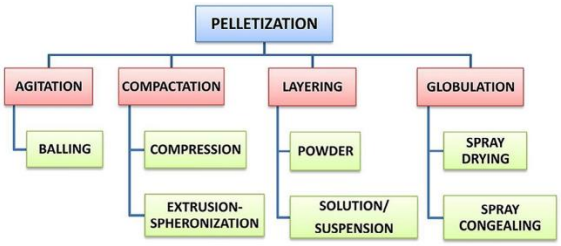
- Pellets show excellent flowing properties, due to its elegance.
- Extrusion Spheronization technique gives uniformity of dose with excellent accuracy.
- Pellets provide safety by preventing dust formation which can cause health issues because of fine powders due to its dust explosives.

- The product appearance is improved.
- The efficacy of product is improved due to the safety of the active ingredient.
- It shows less abrasion, decreased friability with uniform size.
- Pellets prevent from dose dumping and cause lesser side effects when prepared in sustained release form.
- They disperse freely in gastric intestinal fluids due to small in size, which gives a larger area for drug absorption and reduces peak plasma fluctuation.
- Reduces accumulation of drugs which mucosal Irritation.
- The incompatible drugs or recipients can be prepared as a single dosage form.
- Used for masking the bitter taste of unpalatable drugs.

Disadvantages of pellets [4]

- Sometimes pellets are too rigid in nature which is difficult to compress as a tablet, therefore have to be encapsulated into a capsule.
- The process of pelletization is a highly sophisticated method because specialized equipments are used.
- The cost of manufacturing is high.
- It involves number of formulation variables and process variables which leaves the manufacturing process complicated.

Pelletization technique [5]



Agitation [6]

Agitation involves the conversion of finely divided particles into spheroidal particles by the addition of required liquid by a continuous rolling or tumbling motion. The liquid can be added at the beginning of the process, or during the agitation process. Pans, discs, drums or mixers may be used to produce pellets by the balling process. It is the oldest and less efficient technique for production of pellets.

- Balling

It can be done either by adding the required volume of liquid into powder or by applying a high temperature. Spherical agglomeration can be divided into two categories, such as liquid- induced agglomerations and melt-induced agglomerations. Instruments like conventional horizontal drum pelletizers, inclined dish pelletizers or tumbling blenders, rotary fluid-bed granulators. This technique is popularly used in iron ore and fertilizer industries. The rate and extent of agglomeration formation depend on formulation variables such as particle size, the degree of liquid saturation, viscosity of liquid phase and solubility of powder. It is pelletization 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.

Advantages:

- Suitable for large-scale production.
- Produces pellets of uniform size.
- Good for handling fine materials like iron ore or fertilizers.
- Cost-effective for mass production.

Disadvantages:

- Equipment maintenance can be expensive.
- May require additional processing, such as drying or hardening.
- High energy consumption.
- Limited to materials that can adhere during the rolling process.

Compaction:

Agglomeration of drug particles or granules takes place in presence of pressure which gives out well-defined shape and size of pellet.

- Compression [7]

It is one type of compaction technique for preparing pellets. 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.

Advantages:
- Simpler and more cost-effective than other methods.
- Suitable for pelletizing coarse particles.
- Requires fewer processing steps.
- Can handle materials that cannot be agglomerated by wet methods.

Disadvantages:
- May not produce pellets of uniform shape or size.
- Limited to materials that can withstand compression without disintegrating.
- Poor control over pellet hardness and density.

- Extrusion-spheronization [8]

Produces pellets with high loading capacity of active ingredient without producing extensively larger particles and particles of uniform size distribution with good flow properties. Steps involved in Extrusion-spheronization

a) Dry Mixing- Dry mixing of ingredients is done to achieve homogenous powder dispersion using Twin shell blender, Planetary mixer, High speed mixer and Tumbler mixer.
b) Wet massing- It is done to produce a sufficient plastic mass for extrusion, by employing normal equipment and process as employed in wet granulation for compaction.
c) Extrusion- It produces rod shaped particles of uniform diameter from wet mass. The wet mass is forced through dies and shaped into small cylindrical particles with uniform diameter. Such shaping of wet mass into long rods, commonly termed ‘extrudate’.
d) Spheronization- It is 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. Two geometric patterns are generally used. It includes a crosshatched pattern with grooves running at right angle to one another, a radial pattern with grooves running radially from the center of the disc.
e) Drying- A drying stage is required in order to achieve the desired moisture content. An increase in drying rate gives more porous pellets due to decrease pellet densification during drying process.
f) Screening- It is necessary to achieve the desired size distribution, and for this purpose sieves are used.

Advantages:
- Produces highly uniform pellets in terms of size and shape.
- Suitable for pharmaceutical applications where precise dosing is required.
- Can handle various materials, including drugs or other fine powders.
- Effective for controlled-release formulations.

Disadvantages:
- Requires specific and costly equipment.
- Can be time-consuming due to multiple steps (extrusion, spheronization, drying).
- Not ideal for large-scale industrial use outside specialized sectors like pharmaceuticals.

Layering [9]

Pellet formation by layering involves the deposition of successive layers of drug molecules from dry powder or granules, suspension, a solution of drug particles.

Powder layering technique [10]

Various steps involved in this technique are as follows.
- Sifting/milling
- Loading of non-pareil seeds
- Drug coating
- Drying
- Sizing
- Functional coating
- Encapsulation

Solution/suspension layering technique [11]

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- Encapsulation

Globulation [12]
It is also known as droplet formation, it contains two process, spray drying and spray congealing. It works by atomization of hot melts, suspensions or solutions to form pellet particles.

Spray drying [13]
In this process, drug substances in solution or suspension are sprayed with or without excipients into hot stream of air to generate dry spheroids. When atomized droplets come in contact with hot air, evaporation of the application media takes place, this drying process continues through a series of stages where the viscosity of the droplets continuously increases until the entire application medium is evaporated and finally solid particles are obtained. The spray-dried powder particles are homogenous with uniform size. The design and operation of the spray drier can improve the characteristics of final pellet such as particle size, particle distribution, bulk density, porosity, flow ability, moisture content, and friability.

Spray congealing [14]
It is another globulation technique, where a melt material is sprayed and pellet formation occurs. And it solidifies through a fluid stream of gas or liquid material at a suitable temperature lower than the melting point of the carrier or drug molecule. This method is best suitable for coating of beads and also for small size beads.

Advantages:
- Ideal for heat-sensitive materials since the process occurs at lower temperatures.
- Capable of producing very small pellets or microspheres.
- Suitable for producing pellets with complex internal structures, such as drug formulations.

Disadvantages:
- High energy consumption.
- Requires complex and costly equipment.
- May not be suitable for large-scale industrial production of non-specialized materials.

Factors affecting pelletization technique [15-20]

1. Moisture content Moisture in the wet mass brings cohesiveness to powder so that the wet mass can be extracted and spheronizer to give spherical shape. High moisture contents lead to agglomeration of pellets during the process of spheronization.
2. Physical properties of Precursor Quality of pellets depend not only composition but also on different grades of the same product. The swelling property of material used in pelletization technique decides the release rate of drug in pellets.
3. Speed of Spheronizer It affects the size, hardness, sphericity and density of pellets. The high speed gives high sphericity, lower friability, smooth surface and higher crushing strength.
4. Extrusion screen The quality of pellets is greatly influenced by the characteristics of orifice of the screen. And increase in orifice dimension resulted in increased mean pellet size. The increase in orifice depth decreased with the presence of water at the extrudate surface.
5. Rheological characteristics The optimum rheological condition leads to good flow ability in order to extrudate the wet mass. The rheological variations make improper and nonuniform extrudate.
6. Solubility of excipients and drug in granulating fluid Soluble drug get dissolve in a granulating liquid. Thus increasing the volume of liquid phase leads to over wetting of pellets. But increase in wetting liquid increases plasticity but includes sticky mass.
7. Composition of granulating fluid Besides water, alcohol, water/alcohol mixture, ethyl ether, dilute acetic acid, isopropyl alcohol is used as a granulating liquid. Aqueous polymer dispersion containing HPMC, PVP, etc can also be used as granulating fluid.

Pharmaceutical applications of pellets [16]

1) Pellets have Excellent flowing properties in formulations.
2) Pellets provide less risk of dose dumping.
3) They improved aesthetic appearance of product.
4) Pellets in fast dissolution system: For immediate release like fast disintegration and fast dissolving pellets can be prepared for conventional oral drug delivery system.

5) Pellet combination as control release drug delivery System: Different pellets of incompatible chemicals can be combined in the same dosage form.
6) Pellets for Inhalation: Non-irritating soft pellets are designed for inhalation with a maximum particle diameter of approximately 1 mm in size for treating respiratory disorders.
7) Pellets as Implants: Polymeric spheroidal particles can be used as implants for release of "Active Pharmaceutical Ingredients" over a longer period of time. Several methods of pelletization are used for pellet implant production, but widely used is an extrusion.
8) Pellets as Solid Self Emulsifying Drug Delivery System: Used for lower aqueous solubility drugs to improve the in vivo behavior of drug by achieving dose proportionality by reducing inter, intra-subject

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