



Pharmaceutical Pellets: A Versatile Carrier for Oral Controlled Delivery of Drugs

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ABSTRACT:

In pharmaceutical industries, pellets are multiarticulate dosage form which was formed by the agglomeration of fine powdered excipient and drugs together that leads to the formation of small free flowing spherical or semi spherical particles. This technique is called as pelletization process. Pellets are typically varied between 500-1500 μm in size for pharmaceutical applications. It is of great interest over other similar techniques due to its uniformity of dose, less susceptibility of dose dumping, less friability etc. With the advent of controlled release technology, drug loaded pellets have been widely investigated for its control release property in gastrointestinal tract. This review will provide an insight into previous studies on pelletization techniques, investigation of various pelletization techniques namely: layering, extrusion spheronization, Cryopelletization, hot melt extrusion. It also gives a brief idea about the evaluation of pellets; parameters affecting pelletization, the different available marketed pellet formulation.

Key words: Cryopelletization, Extrusion, Fluidized bed Processor, Layering, Spherization.

I. INTRODUCTION:

Oral sustained- and controlled-release formulations are used to modify the release rates of active substances among sustained-release dosage forms, those based on multiarticulate systems have attracted much attention due to their various benefits

1. Historically, the most convenient and commonly employed route of drug delivery has been by oral ingestion. The original controlled release of pharmaceuticals was through coated pills, which dates back over 1000 years. Coating technology advanced in the mid- to late 1800s with the discovery of gelatine and sugar coatings. A major development in coating technology was the concept of coating drugcontaining beads with combinations of fats and waxes. Since the mid-1900s, hundreds of publications and nearly 1000 patents have appeared on various oral-delivery approaches encompassing delayed, prolonged, sustained, and, most recently, controlled release of the active substance 2. Pelletization is a technique that enables the formation of spherical beads with a mean diameter usually ranging between 0.5 and 2 mm 3.

Pelletization Techniques

1. Extrusion spheronization
2. Layering Technique
3. Cryopelletization
4. Hot Melt Extrusion
5. Freeze Palletisation

1.EXTRUSION SPHERONIZATION:

Extrusion is a well-known processing technology that has been developed over the last century. The unit operation of pelletization takes place in three steps

- Feed preparation
- Pellet production



➤ Pellet curing

Feed preparation constitutes mixing of drug-excipient with desired additives such as solutions of binding agent(s). The second and most important step, agglomeration, is taken place in a pelletizer, where desired size pellets are formed. The final step is where wet pellets are cured either by thermal drying or by simple stockpiling. An extrusion spheronization process takes place in the following steps- Formation of plastic mass; Formation of extrudates; Breaking up of extrudates; Spheronization; Spherical pellets 4.

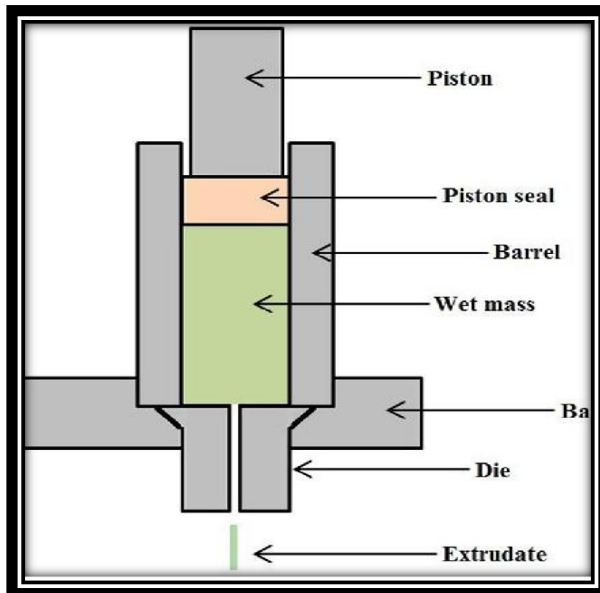


Figure 1. Extrusion-Spheronization a promising pelletization technique

2.LAYERING TECHNIQUE:

Another most commonly employed technique to produce spherical pellets is layering. This technique is further of two types: solution/suspension layering and powder layering 5,6. In solution or suspension layering, powder feed material and other components are dissolved or suspended in the solvent. This solution or suspension is sprayed on the surface of the starter core and spread evenly as soon as it impinges on its surface7. Spraying is followed by drying phase which allows dissolved material to get crystallized and thus between core and coating layer of the drug substance and among the consecutive layers of drug and polymers a solid bridges forms 8,9.It has been demonstrated that drying method affects the structural and functional properties of pellets. Like fluidized bed drying increases the dissolution rate of pellets due to increase pore diameter whereas

lyophilized pellets show increase dissolution due to increase porosity of pellets.

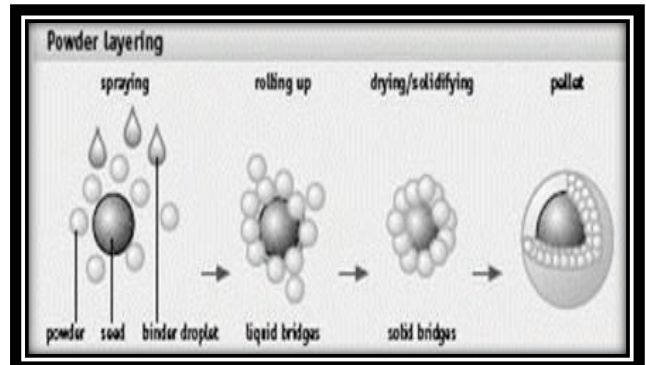


Figure:2 Steps of pellet formation by powder layering process

3.CRYOPELLETIZATION:

Pellets were prepared by the utilization of Freeze-drying method in this technique. Firstly, this technique was utilized in the nutrition industry to develop lyophilized bacterial suspension in order to produce drug loaded pellets. Here in this technique liquid nitrogen at -196°C is used as a fixing medium which causes freezing of droplet of liquid formulations into solid spherical particles which were then lyophilized to provide pellets. In this technique material gets freeze immediately and uniformly as a result of rapid heat transfer between the droplets and liquid nitrogen. The frozen pellets prior to drying were transported into storage container that is maintained at -60°C. In cryopelletization droplet formation is a critical step which is influenced by various factors such as formulation related variables (viscosity, surface tension and solid content), equipment design11.

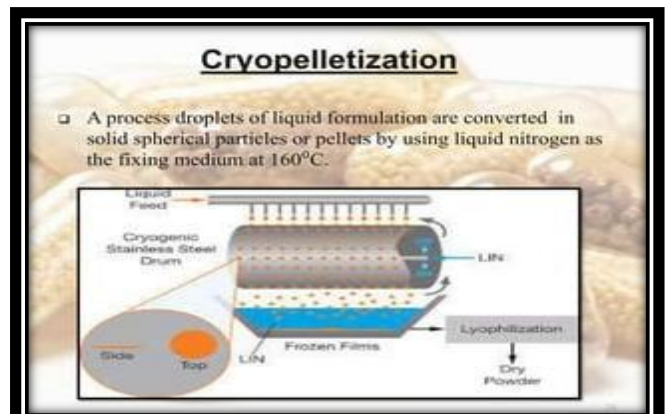


Figure:3 Cryopelletization



4.HOT MELT EXTRUSION (HME):

HME is a robust and novel technique used in pharmaceutical industries for producing various drug delivery systems. It is a widely used process in plastic, rubber and food industries. This technique is applicable to the manufacture of variety of dosage forms like granules, pellets, tablets, implants etc. Melt extrusion process by utilizing polymers with high glass transition temperature (such as Polyvinyl Pyrrolidone) was firstly applied by BASF SE to pharmaceuticals. Later this technology was commercialized and several drugs were subsequently launched by Solids, the drug delivery business unit About GmbH and Co KG12.

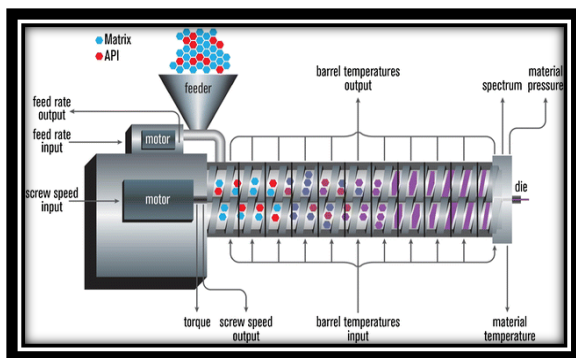


Figure:4 Hot-Melt Extrusion

5.FREEZE PELLETIZATION:

In this technique, a molten-solid carrier in which the drug is uniformly dispersed is allowed to enter as tiny droplets into an inert column of liquid in which the molten solid carrier is totally immiscible. This droplet gets solidifies into spherical pellets. These pellets can move in either direction i.e., move upward or downward depending upon the density of the molten solid carrier with respect to the liquid in the column. If the density of the molten-solid carrier is less than that of the liquid in the column then droplets are introduced from the bottom of the column, which then gets converted into solid pellets at the top portion of the column. The optimum viscosity of the liquid in the column should range between 4 and 40 cups at 20°C to obtain spherical pellets. If the viscosity is much lower, molten solid droplets move rapidly in the column and lose their spherical shape. If the viscosity is greater, then the pellets move too slowly and they may form agglomerates.

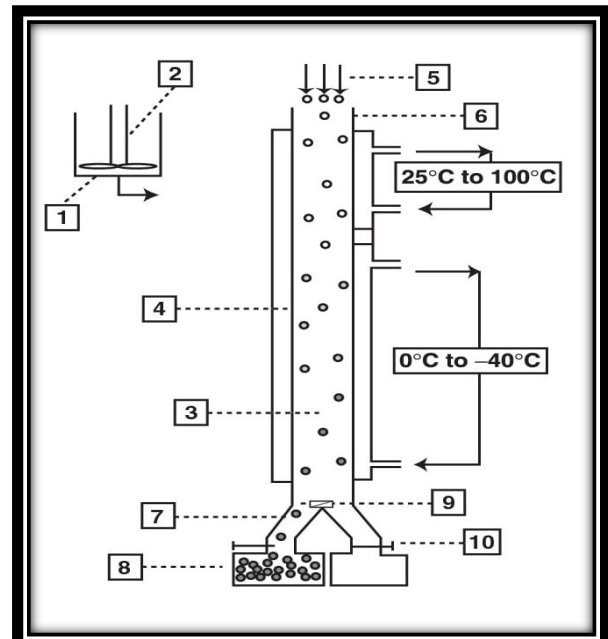


Figure:5 Freze Pelletization

CHARACTERIZATION OF PELLETS:

Pellets are evaluated for certain quality measures, which reflect the suitability and endurance of material during various operations like filling, transportation and handling.

The most common physical characteristics evaluated are:

1. Pellet size and sizedistribution:Determined by sieve analysis which is simple and economical; microscopy methods like Scanning electron microscopy (SEM) and laser diffraction 14,15. This characteristic feature of pellets affects coating and rate of drug release. Another method to determine the size of pellets is estimation of fret diameter obtained from four different angles. In all cases, the size data was best fitted by a normal distribution.

2. Shape:Influences flow of pellets during coating, filling into capsules and dies. The most common method of analysis is by ring gap analyser; scanning electron microscopy (SEM) for qualitative and quantitative analysis 16. Visual inspection of pellets by microscope and stereomicroscope also determines shape of pellets. Another method to determine spherical shape (sphericity) is by taking optimum size pellets, stained with dye solution in a petri dish and dried on a hot air oven. Each pellet is recorded for two-dimensional image i.e., length and width using camera lucida fixed to an optical microscope and circulatory factor(s) was calculated using the equation $S = P2 / (12.56 * A)$;



3. Surface area: Has an effect on drug release and results in batch-to-batch variability. To ensure the production of consistent shape pellets, surface area is analysed by particle size distribution, gas adsorption (BET method Brunauer, Emmett & Teller) and air permeability method. Surface roughness is analysed by fractal geometry of particle obtained by microscopy with image analysis and SEM. This property influences flow and packing of pellets 16.

II. CONCLUSION:

In conclusion, attempts to use pellets as controlled release drug delivery system offers certain advantages over the conventional drug delivery system, still pellets as controlled release drug delivery system requires certain consideration such as which controlled release system should be used, which polymer and excipients should be used, which technique should be selected for pellet formulation. Hence, more work is needed to explore the potential of this formulation tool. In conclusion, pellet formulation can be of great value in developing new controlled formulations for a variety of drugs and their potential is not yet fully explored. This is an area with very high research and development value in near future.

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