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Pellets Andpellitization Techniques

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ABSTRACT :
Pelletization as gained interest in recent years due to its various advantages over other similar techniques such as uniformity of dose and flexibility and dosage form design. There are number of pellitization techniques currently used by pharmaceutical industries among extrusion spheronization and suspension layering are most commonly used in pharmaceutical industries. Other novel techniques including balling compression cryopellitization, dry powder layering, hot melt extrusion etc. Extrusion spheronization process involved in dry mixing,wet granulation,extrusion, drying, and screening. It involves depositionof successive layers of drug and binder suspension on started seeds (materials or granules). Every technique has their own advantages and limitations.
Keywords: Pellitization techniques, extrusions, spheronizations,solutionlayering,suspension layering.

I. INTRODUCTION:

[1]. The word pellet has been used by various industries to describe a variety of agglomerates produced from different and diverse raw materials. Many industries have been utilizing pelletization techniques since the turn of 20th century but pharmaceutical industry started showing keen interest in this technology only in the early 1950s due to increased demand of sustained release preparations. The research scientists of Smith Kline & French realized in 1949, about the potential and developed tiny drug pellets for capsule filling. With the extensive research, more and more faster, efficient and cheaper pelletization techniques were developed. [2] Pellets for pharmaceutical applications are defined as spherical/ semi-spherical, free flowing units with a narrow size distribution, typically varying in diameter between 500and 1500 µm.Pellets for pharmaceutical use are defined as small, discrete, free flowing spherical units prepared from fine powders by a variety of size agglomeration processes. Their size distributions are usually relatively narrow with mean particle sizes ranging from about 0.5 to 1.5 mm. However, some applications require the use of smaller pellets, for example, pellets used for preparing oral dispersible tablets are generally of smaller particle sizes (<0.3 mm) in order to reduce gritty mouth feel. [3] As controlled release multiparticulate dosage forms, pellets have a number of therapeutic advantages, including less risk of local irritation due to wider area of drug distribution, less susceptibility to dose dumping, optimization of drug absorption, and independent of gastric emptying rate.

ADVANTAGES

Pellets offer a significant number of advantages overconventional unit-dose systems2-5 uniformityof dose.

Technological Advantages:

- Uniformityof dose. Layering techniques and extrusion-spheronization technique offers great accuracy with uniform drug delivery to the pellets.
- Spheres have excellent flow properties. This becomes very useful in automated processes or in processes where exact dosing is required, e.g. tableting, moulding operations, capsule filling, and packaging.
- Prevention of dust formation, resulting in an improvement of the process safety, as fine powders can cause dust explosions and the respiration of fines can cause health problems.
- 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.
- They can be blended to deliver incompatible bioactive agents simultaneously and/or to provide different release profiles at the same or different sites in the gastrointestinal (GI) tract.

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Therapeutic Advantages[4] :

- Pellets can disperse freely throughout the GIT after administration and consequently the drug absorption is maximized.
- The wide distribution of spherical particles in the gastrointestinal tract limits localized build-up of the drug, avoiding the irritant effect of some drugs on the gastric mucosa.
- Reduce inter- and intra-patient variability.
- Modified-release multiparticulate delivery systems are less susceptible to dose dumping than single-unit dosage forms.

PELLETIZATION:

[5]. Sometimes, granulation and pelletization terms are used synonymously. If a size-enlargement process produces agglomerates in size range of 0.1-2.0 mm and about 20-50%porosity, such process may be called granulation. Whereas, Pelletization is a size enlargement process of manufacturing agglomerates with a relatively narrow size range of 0.5-2 mm called pellets.Pelletization can be defined as an agglomeration process for converting fine powders or granules of bulk drugs or excipients into small, free flowing, spherical or semi-spherical units, referred to as pellets. Pellets are oral dosage forms consisting of multiplicity of small, discrete units, each exhibiting their desired characteristics.

PELLETIZATION TECHNIQUES

1. Pelletization by extrusion spheronization
2.Drug layering (dry powder layering & solution and suspension layering)
3. Cryopellitization
4. Freeze pelletization
5. Globulation
6. Compression
7. Balling

Extrusions spheronization:

[6]. Extrusion spheronization technique was developed as a pelletization technique in the early 1960s. For the purpose of formulating controlled or modified release, a consistent smooth surface is required with a narrow size distribution in order to ensure uniform coating and free flowing property.Extrusion spheronization technique can be used to achieve this. The main objective of this technique is to produce pellets/spheroids of uniform size with high drug loading capacity. Extrusion spheronization is a multiple process involving a pre-consolidation stage by extrusion followed by spheronization to produce uniform size spherical particles, called as spheroids, pellets, beads or matrix pellets depending upon material as well as process used. These days this technology has gained attention because of its simple and fast processing and high efficiency. Hence good extrudates will have to possess the desirable attributes to be broken down into regular fragments that can be rounded into pellets of a narrow size distribution. The method involves the following main steps

Dry mixing, of ingredients, to obtain homogenous powder dispersions, using different type of mixers like twin shell blender, high shear mixer, tumbler mixer and plantermixer

[7] Wet massing, in which powders are mixed to form a sufficiently plastic mass. Mostly planetry mixer is used routinely for both mixing and granulation operations.

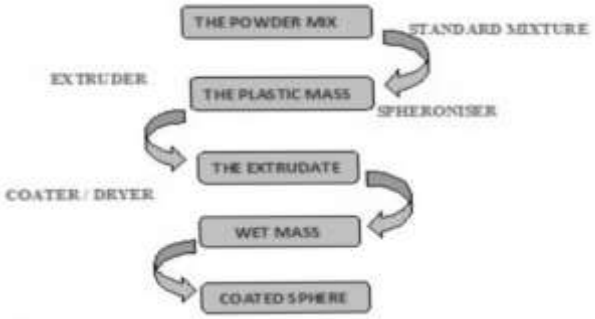

Figure 1: Extrusion and Spheronization

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Hot melt extrusion:

[8]. In order to overcome the problems associated with the pellets produced by layering and extrusion spheronization technique, melt agglomeration and hot melt extrusion technique are in used in pharmaceutical industries. This method eliminates instability problem during processing and storage due to presence of water. Furthermore, pellets produced by these techniques do not require additional film coating since drug release is diffusion controlled. There is slight differencebetween these two methods. Melt agglomeration is a process by which the solid fine particles are bound together into agglomerates, by agitation, kneading, and layering, in the presence of a molten binding liquid. Dry agglomerates are obtained as the molten binding liquid solidifies by cooling.

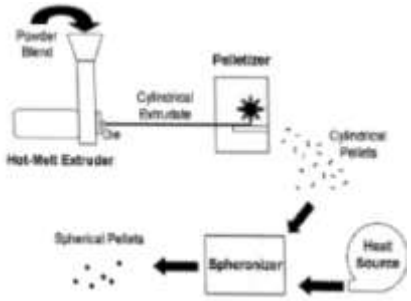

Figure no 2: Process of HME

Layering techniques

Solution and Suspension Layering

Layering a suspension or a solution of a drug on a seed material (usually, a coarse crystal or nonpareils) can produce pellets that are uniform in size distribution and generally posess very good surface morphology. These characteristics are especially desirable when pellets willbe coated for the purpose of achieving a controlled release.

Dry Powder Layering

[9] This process is similar to the solution or suspensions layering. Instead of these dispersions, the layering is performed using a drug powder.Usually, the process is carried out in conventional coating pans.Initially, the nonpareils or starter seeds (neutral or innert pellets, beads, spheres) are charged into a rotating pan, then wetted by spraying an adhesive solution.

Compression:

Compression 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 tablet manufacturing.[10]. Kadaretalprepared sustained release pellets of poly (lactic acid) with increasing bovine serum albumin (BSA) load and studied the in-vitro release pattern of theophylline from prepared pellets. They reported that theophylline release was driven by leaching through channels and not by polymer degradation. The release rate was found to be dependent on BSA loading and annealing.

Balling:

Balling otherwise known as spherical agglomeration, is a pelletization technique in which powders are converted into spherical pellets by a continuous rolling or tumbling motion. This can be done either by adding an appropriate amount of liquid into the powder, or subjecting it to high temperature. Spherical agglomeration can be divided into two categories—liquid-induced agglomerations and melt-induced agglomerations

Globulation:

Globulation, or droplet formation, consists of two related processes, spray drying and spray congealing. They involve atomization of hot melts, solutions, or suspensions to generate sphear**.**

SPRAY DRYING:

Drug entities in solution or suspension are sprayed, with or without excipients, into a hot stream of air to generate dry and highly spherical particles. As the atomized droplets come in contact with hot air, evaporation of the application medium occurs. This drying process continues through a

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series of stages whereby the viscosity of the droplets constantly increases until finally almost the entire application medium is evaporated and solid particles are obtained.

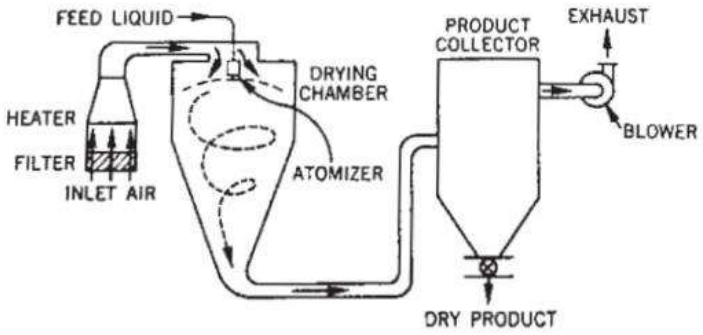

Figure 3: Schematic diagram of spray drier

Spray- congealing :

Spray-congealing is 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 a stream of air and other gases with a temperature below the melting point of the formulation components. Under appropriate processing conditions, spherical congealed pellets are obtained.

Cryoprelletization:

[11].Cryopellitization is a process whereby droplets of a liquid formulation are converted into solid spherical particles or pellets by using liquid nitrogen as the fixing medium. The technology, which was initially developed for lyophilization of viscous bacterial suspensions, can be used to produce drugloaded pellets by allowing droplets of liquid formulation such as solution, suspension or emulsion to come in contact with liquid nitrogen at -1600°C.

Evaluation of Pellets:

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. Wiwattaapatapee, 2004 reported the use of Vernier calipers 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.

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.

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

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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 by Sood, 2004.

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 techniques.

Applications:

Immediate release:

[12] 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.

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 are well known.

Chemically Incompatible Products:

[13] 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. 4. Varying dosage without reformulation: Pellets have excellent flow properties

TABLE 1 : Showing different polymers used in Pellitization process

Polymer used in pelletization	Formulation	Applications
Carbopol 974P,NF, Resin	Beads containing Weak basic drugs	Slower release of the salts of weakly basic drugs
Crosscarmellose sodium or sodium starch glycolate	Super-disintegrants in avicel pellets	Increase dissolution rate, increase the pellet micropore volume
Eudragit RS PO and RL PO	Polymer (with combination) based pellets.	Better characterization like elastic modulus of the pellets, surface characteristics, sphericity
Eudragit RL 30D, RS 30D, NE 30D	A multiple-unit floating drug delivery system.	Prolong the gastric residence time and to 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	Improved film formation and polymer coalescence
Microcrystalline cellulose, Ac-di-sol	Floating pellets with bacterial antagonist	Improving flowing property
Microcrystalline cellulose and hydroxypropyl methyl cellulose	Pellets with water insoluble drugs in self-emulsified form	Controlling the drug release from the oral dosage form
Pectins or alginates	Polysaccharide gel coated pellets.	Oral administration of theophylline

II. CONCLUSION:

This brief review on the pelletization technology hereby concludes with a note that they are considered as a most promising drug delivery system today which is catching up with the pace of speed to have a high existence in the Pharma world. This system gain more popularity because of their easy portability improved patience compliance and ease of administration and flexibility in the fabrication as tablets or capsules or packed simply as a single dose packlets. They can be applied by both oral and buccal routes. This technology is growing in fast pace challenging most of the pharmaceuticals companies to develop pelletized dosage forms for wide range of active pharmaceuticals ingredient.

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REFERENCES:

[1]. Sovgren K. In: Sandell E,Industrial Aspects of Pharmaceutics Stockholm: Swedish Pharmaceutical Press; 2011;5(4);17-56.
[2]. GU L, Liew CV, Heng PWS. Wet spheronization by rotary processing - A multistage single-pot process for producing spheroids: Drug Dev Ind Pharm; 2004; 12(10); 88-95.
[3]. Thommes M, Kleinebudde P. Use of k-carrageenan as alternative pelletization aid to microcrystalline cellulose in extrusion/spheronization: Influence of type and fraction of filler.Eur J Pharm Biosphere; 2006; 63(89); 59-67.
[4]. Ramu S, Ramakrishna G, Balaji M,Kondala rao K, Haranadh reddy S and Pavan kumar D. Multiple Unit Drug Delivery System: Pelletization Techniques, American Journal of Advanced Drug Delivery: I Eur pharm;2013;1(1); 011-021.
[5]. Shajahan, A., Chandewar, A. V., & Jaiswal, S. B. A flexible technology for modified release drugs: multiple-unit pellet system (MUPS):Journal of Controlled Release;2010;3(8):25-38.
[6]. Pellets by extrusion spheronization:Eur J Pharm Biopharm;2004;33(8):220 248 Steckel H, Mindermann-Nogly F. Production of chitosan.
[7]. BhaskaranS., Lakshmi P.K. Extrusion spheronization: A Review.Int.J.Pharm tech res;2010;2(7):79-86.
[8]. David M. Jones.Solution and Suspension Layering, in Pharmaceutical Pelletization Technology:Ghebre-Sellasie I., Ed. Marcel Dekker Inc., New York;1989;57(63):340-397.
[9]. Schwartz JP, Nguyen NH, Schnaare RL.Compaction studies on beads: compression and consolidation parameters:Drug DevInd;1994;57(89):300-435.
[10]. Weyermanns G.Freezing and pelletizing process and device for pourable and flowing materials: US patent; 1997; 89(50): 456-560.
[11]. Golam Kibria, Reza-ul Jalil: In vitro Release Kinetics Study of Diltiazem Hydrochloride from Pellets using an Ethylcellulose Pseudolatex Coating System; J. Pharm Sci; 2007; 6 (2), 87-92.
[12]. Satoshi Iwamoto, Kei Nakagawa, Shinji Sugiura, Mitsutoshi Nakajima: Preparation of gelatin microbeads with a narrow size distribution using Microchannel Emulsification; AAPS Pharm SciTech; 2002; 3 (3) 25.
[13]. A., Kolter. K., Bodmeir. R: pH-independent release of a basic drug from pellets coated with the extended release polymer dispersion Kollicoat® SR 30 D and the enteric polymer dispersion Kollicoat MAE 30 DP; Eur. J. Pharm. Biopharm; 2004;58, 45-9.