AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

A Remunerative Pharmaceutical Technique for Pelletization: Extrusion Spheronization

Mohammad Kashif Iqubal*[1], Pranjal Kumar Singh[1], Mohd. Shuaib[1], Ashif Iqubal[2], Poonam Bharadwaj[1]

1. Department of Pharmacy, Kalka Institute for Research and Advanced Studies, Partapur by-pass, Meerut.

2. Translam Institute of Pharmaceutical Education and Research, Mawana Road, Meerut.

ABSTRACT

Oral pelletized drug delivery system gives more advantageous biopharmaceutical result in compared to single-unit dosage forms, like better distribution and transportation in the gastrointestinal tract (GIT). In the pharmaceutical industries many techniques are available for pelletization such as solution layering, suspension layering or powder layering, cryopelletization, freeze pelletization, spray congealing, extrusion-spheronization (ES), hot-melt extrusion process. ES technique is very acceptable and it has gained more attention because of its simplicity and fast processing. This technique is widely applied for the production of oral sustained release, controlled release drug delivery system and it also overcome the problems related to bioavailability and site specific drug delivery system. This review article discuss about the aspects of ES technique with their different steps involved in the process of pellets production. We also discussed about the factors which can influence the pellet quality and methods for evaluation of the quality of pellets.

Keywords: - Pellets, pelletization, extrusion, spheronization.

*Corresponding Author Email: mkashif.iqubal@gmail.com

Received 1 Februay 2015, Accepted 24 February 2015

Please cite this article as: Mohammad KI *et al*., A Remunerative Pharmaceutical Technique for Pelletization: Extrusion Spheronization. American Journal of PharmTech Research 2015.

INTRODUCTION

The oral drug delivery route has been one of the easiest, most convenient and widely accepted routes of various therapeutics agents. Pellets are now days gained more attention in pharmaceutical industries because of its better biopharmaceutical results as compare to conventional unit dosage form. It's also overcomes the problems related to the bioavailability of drug which produce poor bioavailability and site-specific drug delivery system. Pellets give the better absorption and distribution in GIT. Controlled release and sustained release dosage form needs consistent smooth surface with a narrow size distribution and it is maintained by pelletization technique. In the pharmaceutical industries numbers of pelletization techniques are available such as solution layering, suspension layering or powder layering, cryopelletization, freeze pelletization, spray congealing, ES, hot-melt extrusion process. Pellets consist of small spherical or semi spherical free flowing solid unit, the diameter of pellet can varied between 0.5 to 1.5 mm, and are intended for oral administration.

EXTRUSION SPHERONIZATION

ES method was first reported by Reynolds (1970) and by Hadley and Conine (1970)[1]. Due to the simplicity and fast processing, ES technique of pelletization is most popular in the pharmaceutical industries. ES method produces pellets of uniform size with more drug loading capacity. Criteria for controlled and sustained release dosage form are fulfilled by this technique, and there is also a possibility to prepare sustained pellets without coating[1]. For the production of pellets by ES four different steps are applying, different amounts of shear are used for granulation, planetary mixer, high-shear mixer and twin-screw extruder with two different screw assemblies. Extrusion is performed on a rotary ring die press. In ES method after the spheronization wet mass extrusion occurred which produce uniform size spherical particles, called as spheroids, beads or pellets, it is depending upon the material as well as equipment used. ES method is primarily used for the production of pellets for oral controlled drug delivery system[2]. ES method require more labour than other method, but it is useful when it produce uniform spheres, uniform size, good flow properties, high strength, low friability and smooth surface. By the ES method any pharmaceutical products effectively utilize pellets as a drug delivery system.

Advantages

The pellets produced by the ES have following advantages are found over conventional drug delivery system.

- It improves appearance of product.

- Low hygroscopicity.
- Bulk density is high.
- It gives uniform size particles with narrow size distribution and it have better flow property.
- ES gives spheroids with high loading capacity of active pharmaceutical ingredient (API) without producing large particles.
- They also reduce the accumulation of drug in GIT, therefore it reduced the chance irritation in mucosa.
- Pellets consist of two or more chemically compatible or incompatible drug that can be blended and formulated in single unit dosage form that produce their pharmacological action at the same or different site in GI tract.
- Pellets are extensively used in controlled release drug delivery system because it facilitates free dispersion of spheroids in the GI tract and produce flexibility for further modification.
- It improves the safety and efficiency of API.
- It enhances the bioavailability of drugs by controlling or modifying the release rate of drugs.

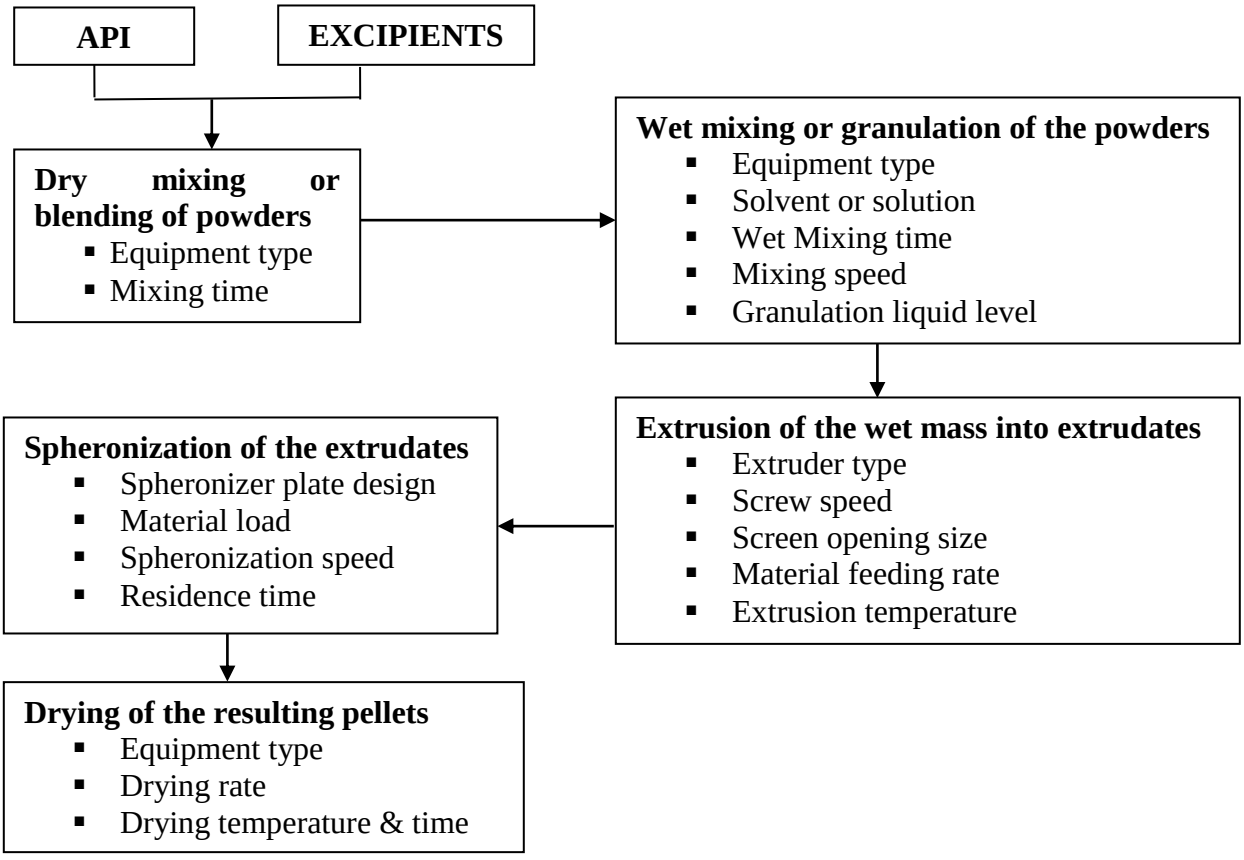


Figure 1: Flow Chart of ES Process with Individual Processing Variables.

Disadvantages

- The production of pellets is an expensive process because it requires highly specialized equipment and trained personnel.
- The control of production process is difficult because amount of water added and time play an important role in the quality of pellets because over-wetting can occur very easily.

Ideal properties of the pellets:

- Uniformity in shape, size and smooth surface, therefore it has good flow property.
- The range of pellets size should be in between 0.5 to 1.5 mm.[3]
- Pellets have high strength with low friability, therefore quantity of dust is reduced.
- The quantity of the API in pellets should be maximum in order to maintain size.

Steps Involve in the Extrusion Spheronization Process

Granulation

This is the first step of ES process which consists of the preparation of the plastic mass. Granulation consists of following steps:

Dry massing: Massing of API and excipients is done for achieving the homogenous powder mass dispersion using twin shell blender, planetary mixer, tumble mixer and high speed mixer.

Wet massing: In this process sufficient plastic mass has achieved for extrusion. Wet massing is same as wet granulation for compaction. Planetary mixer is frequently used for the wet massing in the pharmaceutical industry apart from this, sigma blender and high shear mixer is also used as granulator.

During the wet massing step the evaporation of fluid phase is major problem. This problem is generally occurred with the high shear mixer because it produce large amount of energy into the wet mass which is converted into the heat, therefore this heat induce evaporation of the granulation liquid thus altering the extrusion behavior of the wet mass. This problem can be overcome by the cooling of granulation bowl. Homogenous distribution of the liquid phase throughout the granulated mass is main feature of this step. This is achieved by left the wet mass for 12 hours in a sealed polyethylene bag.

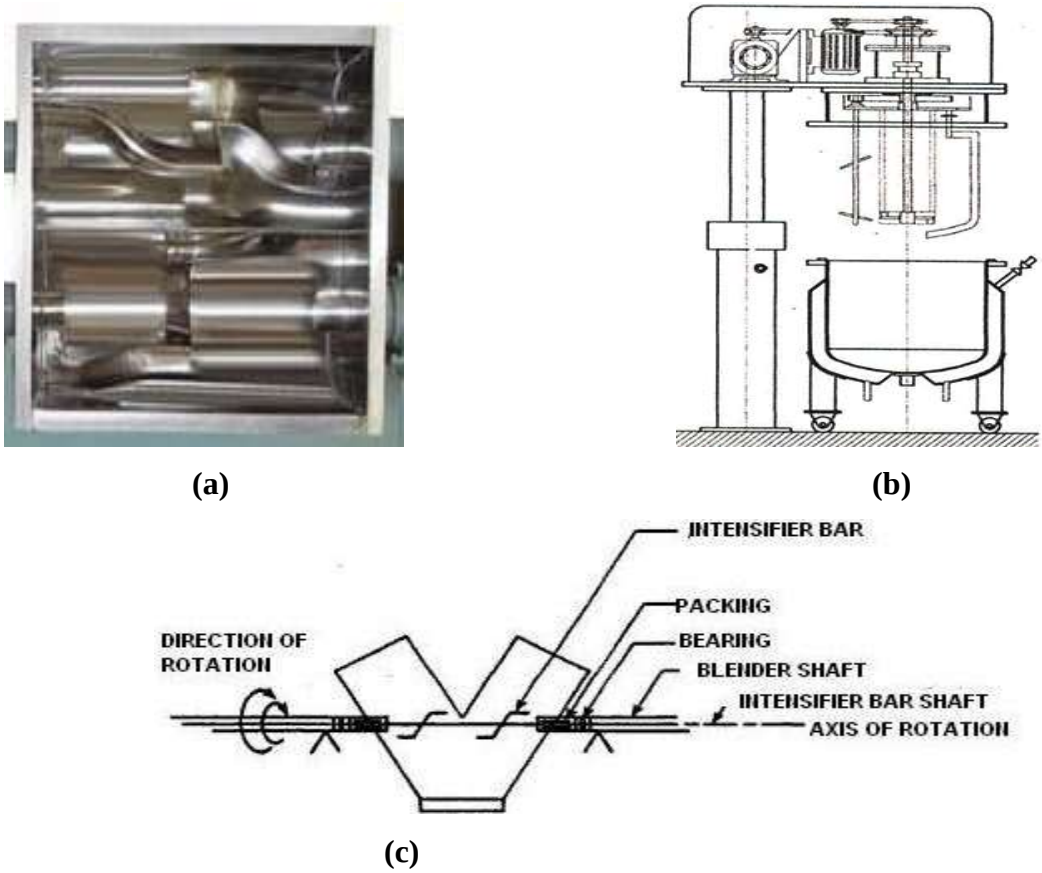


Figure 2: (a) Sigma blender, (b) Planetary mixer and (c) V-blender.

Extrusion

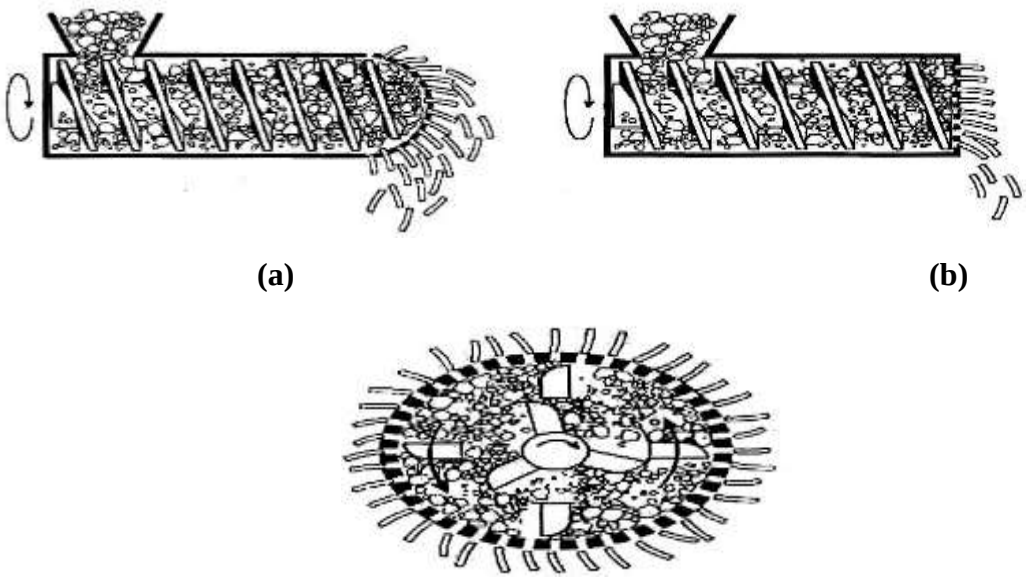
After granulation extrusion is performed. In this step long rod shaped particles of uniform diameter is achieved from the wet mass. These long rods are commonly known as extrudates. Extrudates is produced from the wet mass by forced through disc. The equipment which produced extrudates is commonly known as extruders. There are four main type of extruder occurs in the industry as follows:

Screw feed extruder:

It consist of one or two (twin-screw) screw feeding, the wet plastic mass is to an axial or radial extrusion screen. There are following types of screw extruder occurred such as axial or end plate, dome and radial type extruder.[3]

Axial or end plate screw extruder: The screen is placed at the end of the screw, perpendicular with the axis of the screw.

Radial type screw extruder: The die is placed around the screw, discharging the extrudates perpendicularly to the axis of the screw.



(a) **(b)**

(c)

Figure 3: (a) Axial screw feed extruder, (b) Dome screw feed extruder and (c) Radial screw feed extruder.

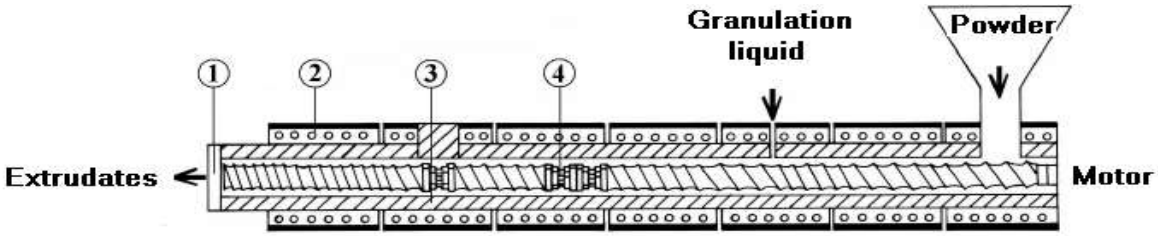


Figure 4: Schematic diagram of the twin screw extruder: (1) die plate (2) heating elements (3) barrel (4) screw. [31]

Sieve and basket extruder:

In this type of extruder the wet mass is fed by a screw or by gravity into the extrusion chamber. In this chamber the rotating or oscillating device pushes the wet mass through the screen. Sieve and basket type of extruder is only distinguished between the each other on the basis of the position of the screen. In the sieve extruder the screen is positioned at the bottom of the extrusion chamber, where as in the basket type the screen is positioned on the vertical wall of the extrusion chamber. [4]

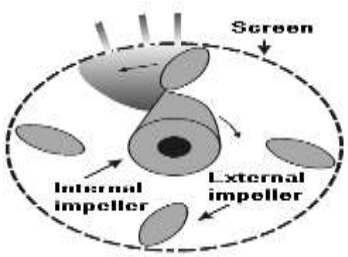


Figure 5: Basket-type extruder.

Roll extruder:

It is also known as gravity feed extruder. These are the different types of roll extruder, they can be distinguished on the basis of their design.[5]

I. An extruder equipped with one of the two counter rotating cylinders i.e., hollow and perforated and other cylinder is solid and it is acts as a pressure roller is known as rotator cylinder extruder (figure: 6).

II. An extruder with two hollow counter rotating gear cylinders and counter board holes is known as rotator gear extruders (figure: 7).

The above type of extruder used when mass is feed between the two wheels and the extruded mass is collected inside the extrusion

III. Other type of roll extruder contain perforated cylinder which rotates around one or more rollers, extrudated mass is collected outside of the cylinder (figure: 8).

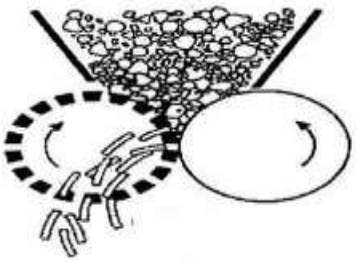


Figure 6: Rotator cylinder extruder.

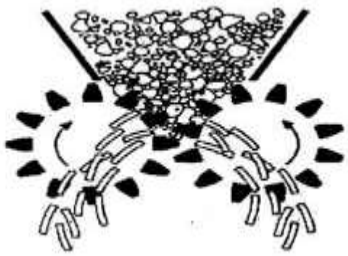


Figure 7: Rotator gear extruders.

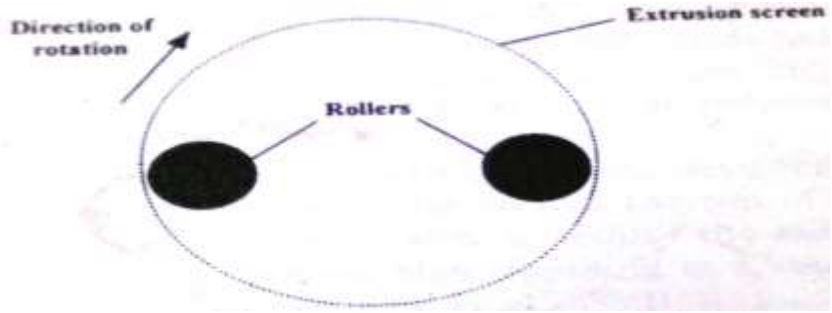


Figure 8: Roller extruder with the extrusion screen rotating around roller.

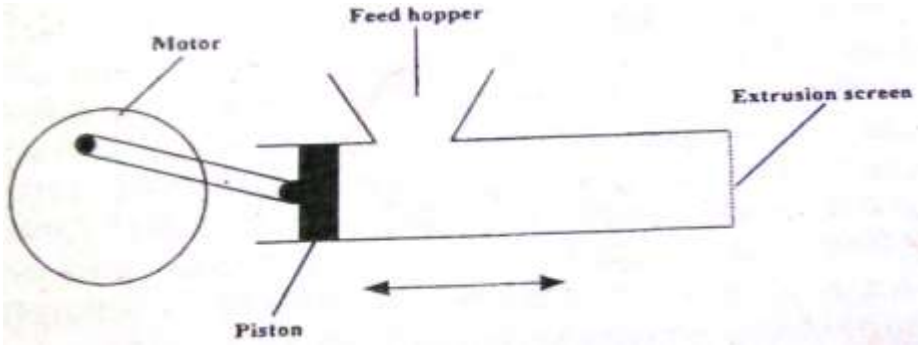


Figure 9: Ram extruder.

Ram extruder:

The principle of this extruder is based on a piston which pushes the wet mass through the screen situated at the end of barrel. It is oldest type of extruder also known as piston feed extruder. Ram extruders are mainly used in development phase, because they can play an important role in measurement of rheological properties of the products (figure: 9).[6]

Extruder choice

The selections of the extruders are based on the principal requirements of the extrudate. For the production of uniform granules it should be dried in a fluidized bed drier, a low condensed system, like that provided by the many types of screen extruders may be suitable. Gear extruders or cylinder type may be more suitable for a densified extrudate, such as that necessary for spheronization. Ram-extrusion systems that allow accurate control of extrudate, size, shape and density are ideal for the extrusion. Aspect should be given to the presence of small-scale equipment that is important for development work prior to scale-up on pilot- or production-scale equipment. The choice of equipment is not necessarily based on maximum flow capacity rate, through the subsequent processing steps such as cutting, spheronization, and drying is batch processes, and these are therefore, a rate limiting factor in production. Extrusion is a continuous process which allows sufficient production rates for most purposes with any of the above mentioned extruder types. The equipment must follow the code of Good Manufacturing Practice (GMP) standards within the pharmaceutical industry. Machines must be constructed of durable material with smooth surfaces to deprecate adhesion of adventitious material and facilitate cleaning. Equipment material should not be affecting the product. They must be corrosion resistant and able to withstand cleaning disinfectants.

Spheronization

During this process the extrudates mass which are occurred in cylindrical shaped dumped on to the spinning plate of spheronizer i.e., a friction plate where extrudates are broken up into smaller cylinders with a length of equal to their diameter. These equal plastic cylinders are rounded due to frictional forces. This spheronizer is also known as **merumizer**. This technology was first given by Nakahari 1964. The Spheronization step consists of different stage and i.e., distinguished depending upon shape of the particles. The shape of particles is starting from a cylinder over a cylinder with rounded edges dumbells and elliptical particles to eventually perfect spheres. There is another mechanism for the formation of pellets. In this mechanism cylinder are twisted after the formation of cylinders without rounded edge after that the cylinders are broke into the two distinct parts. Both parts have a round and flat sides during the spheronization the rotational and frictional

force are cirvehad the edge of the flat side. During the spheronization the rotational and frictional are involved, the edges of the flat side fold together like flower forming cavity observed in certain pellets. The spheronization of a product usually take 5-30 minute due to the conversions of rods into the spheres by crossing the different stages. A rotational speed of the friction plate in the range between 100-2000 rpm. During the spheronization the mass should not be too dry where in no more spheres are formed and the rode will transformation as far as dumbbells only.[1]

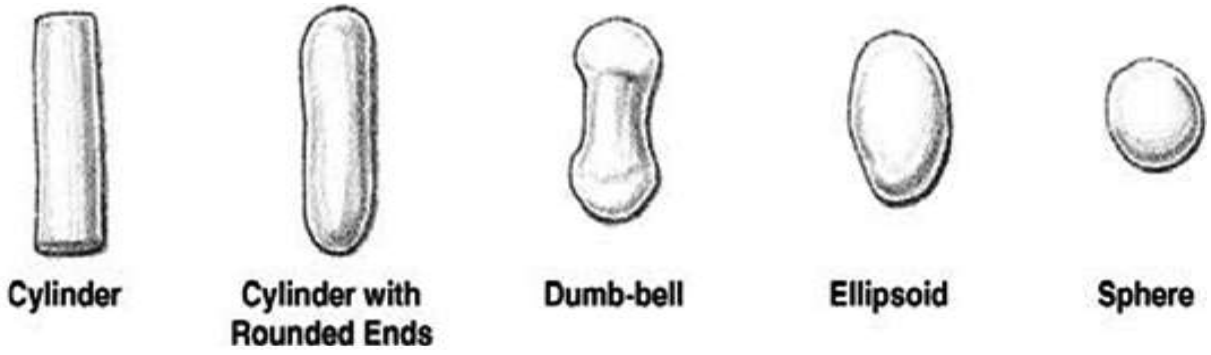


Figure 10: Schematic representation of different stages of pellet formation during spheronization.

Drying

In this stage drying of pellets occurs. This step is performed for achieving the desired moisture content. Rate of drying play an important role in pellets formation such as, increase the rate of drying gave more porous pellets due to decreasing the densification of pellets. The can be dried at room temperature or at elevated temperature in a hot air oven/ tray dryer or in fluidized bed dryer. Balaille *et al.,* at 1993, reported the use of microwave oven as dryer for the pellets.[1]

Screening

Screening is the final step of the process of ES, in this step the desired size distribution is achieved. For this purpose sieves are used. In the ES screening is most important step, in order to avoid pellet having size polydispersity index.

Parameters Which Enhance the Quality of Pellet

Granulation liquid

Mostly water is use as the granulating liquid. Sometimes alcohol or water /alcohol mixture has also been used as granulation liquid. The effect of granulation liquid is clearly explained by Melilla and Sclawartz in 1990.[1] For example minimum of 5% of granulation liquid is to be water for the production of pellets when processing a formulation of Avicel PH 101 and theophylline. Increase the water content in the granulation liquid lead to increase in the pellets hardness. This altered *in vitro* release rate of theophylline means decrease *in vitro* release rate of theophylline. [6]

Moisture content in the granulated powder mass

For maintaining the granulated powder mass, moisture content plays an important role. Moisture content help in extrusion process and maintenance of shape after wards. Therefore it is a major parameter for ES process. For achieving of acceptable pellets the moisture content of granulated liquid should be between the upper and lower limit. If the moisture is less than lower limit, a lot of dust will be formed during the spheronization process. Therefore large yield will be dust. In the other hand if the moisture content cross the upper limit leads to over wetted mass and agglomeration is formed of the individual pellets during spheronization, this is due to the presence of excess of water on the surface of pellets.[7]

Properties of the starting material

Properties of starting material such as particle size, solubility, type of material are play an important role in the size, hardness of pellets, sphericity as well as the release rate of the loaded drug. The starting material used in pellets production cause difference in quality of pellet produced from the different composition. Such as in 1988, Herman et al., showed the difference in rate of release in different types of dissolution fluid between pellets containing only microcrystalline cellulose and sodium carboxymethylcellulose. The particle size of the starting material is also affected the extrusion characteristics of the plastic mass and the size and sphericity of the resulting pellets. Characteristics of the pellets also changed when use of similar products from the different suppliers.[1, 8]

Extruder type

Reynold's 1970 and Rowe 1985 reported that more dense material was produced from the axial screw extruder in comparison to a radial screw extruder which had a higher output with the rise in the temperature of the mass during processing. The quality of extrudate and final pellets are mainly depend upon these two parameters i.e., length to radius ratio of extrusion screen used and difference in the shear rate or shear stress. In terms of radius the thinner screen yield a rough and loosly bound extrudate, whereas thicker screen produced smooth and well bound extrudate due to higher densification of wet mass. Size of the pellets depends upon the diameter of the perforations.[9]

Speed during extrusion

The extrusion speed and total output of the extrudate is directly proportional to the each other. The output should increase as possible for economical reason. But increasing the speed of extrusion affects the quality of final pellets like surface impairment such as roughness and shark-skinning. These surface defects lead to pellets of lower quality. Due to these problems extrudate will

breakup unevenly during the initial stages of the spheronization process, which yield a lot of fines and varying particle size distribution. These problems can be overcome by using the surfactant of high HLB value.[10]

The temperature of extrusion

In order to maintain the moisture content of granulated material and the formulation with thermolabile material, the control temperature during extrusion is very important. During the extrusion cycle increased temperature caused the alteration in moisture content by evaporation of the granulation liquid. This could lead to a difference in the quality of extrude from beginning to end of the batch. In the processing of a thermolabile drug, temperature should be maintained during extrusion cycle.[11]

The speed of spheronizer

The spheronizer speed affects the particle size of the pellets and its densification. With increasing the speed of spheronizer correlate with an increase mean diameter. The hardness, sphericity, bulk and tapped density, friability, flow rate and surface structure of pellets were also affecting by change in the speed of spheronizer. Rowe 1985, reported that speed of spheronizer should be optimized to obtain the desire densification. According to him low spheronizer speed would not provide sufficient densification and perfect spheres. In the other hand if the spheronization process is performed at higher speed agglomeration of the individual pellets was formed.

The spheronization time and spheronizer load

When the spheronization time is extended, following parameters are altered i.e., an increase in diameter, a narrower particle size distribution, a change in the yield of a certain size range. These alterations are mainly found when the formulation contained mixture of microcrystalline cellulose (MCC). When the spheronizer load is low with increased the spheronization speed, decreased the yield of pellets of specific range and it is increased with extended spheronization time at higher spheronizer load. When spheronization load is increased the mean diameter of the pellets is also increased. In the other hand size of pellet decreased and their bulk and tap density increased with an increasing spheronizer load. Barrau *et al.*, 1993, showed that increased the hardness and decreased the roundness of the pellets with increased the spheronizer load. Whereas the yield in the majority size range remained unchanged. [12]

Drying method

Bataille *et al.*, 1993, reported that when comparing a formulation dried in microwave oven or in an ordinary oven containing Avicel PH 101 and lactose. The pellets dried in microwave differed from those dried in the ordinary oven as their surface was rougher and those pellets were more porous

and lesser hardness.[13]

EVALUATION

Size determination of pellets

The size determination of pellets can be done by a variety of parameters such as: particle size distribution, mean diameter, geometric mean diameter, mean particle width and length. Particle size analysis is mainly carried out by a simple sieve analysis although the more advanced method of computer-aided image analysis has also been reported the Dietrich and Brausse, 1988 and Fielden *et al.,* 1992, 1993. In 2004, Wiwattaapatapee reported the use of varnier calipers for the determination of size of pellets. The pellets sizing is important because it has significance influence on the release kinetics.[3]

Weight distribution of pellets

Weight distribution can be directly determined by the sieving method. Sieves were arranged in a nest, coarsest sieve at the top. A sample (5 gm) of the dried pellets is placed on the upper most sieves and subjected to mechanical agitation. The sieves are set and fixed after that shaken for a certain period of time (10 minutes). The pellets retained on each sieve are weighed. Frequently, the pellets are assigned the mesh number of the screen through which it passed or on which it is retained. It is expressed in terms of arithmetic mean of the two sieves.[14]

$$Mean\ particle\ size = \frac{\sum XiFi}{\sum Fi}$$

Whereas, ∑Xi Fi = weight size, ∑ Fi = percent weight retained.

Sphericity of pellets

Pellets sphericity is the most important characteristics and determined by various method. The pellets are mounted on a light microscope in which Camera Lucida is attached and the images of pellets were drawn manually on a graph paper. The shape factor estimates the amount by which 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[14]. Visual inspection of pellets by microscope and stereomicroscope are another method for determination 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.[1]

Determination of surface morphology of pellets

Scanning electron microscopy (SEM) is used for the examination of the surface morphology and cross section of pellets. The sample 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. Sood *et al.*, 2004, reported that the use of optical microscopy for the examination of the microstructure of pellet surface. In 1991, Eurrkainea and Lindqvist give the information about 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. The analysis for surface roughness of pellets by applying a non-contracting laser profilometer was studied by Santosh *et al.*, 2004.[15]

Determination of specific surface area

Specific surface area of pellets is directly related with shape and size of the pellets. For the film coating knowledge of the surface area is important. Knowledge about the surface area is important even in case of uncoated pellets, since drug release is also influenced by the surface area. Specific surface area of pellets is determined by following method.[19]

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 of a pellets is equal to πr^2. True density measurements of pellets can also be used for determination of the specific surface area.[9]

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 (Brunauer–Emmett–Teller) equation for the adsorption of nitrogen on a substrate.[9]

Friability

Pellets have tendency to flake off during handling resulting in the formation of dust. It can be assessed by rotating the pellets in a friabilator or by shaking the pellets in a turbula mixer for a fixed period of time. In both techniques glass beads are use to increase the mechanical stress on the pellets.[21]

The pellet strength test

According to Reynolds in 1970, this characteristic of the pellets can be correlated with the friability or can be measured directly. The determination of hardness is performed by measuring the force required to break a pellet of well known diameter as the strength increases with

increasing diameter.[22]

Tensile Strength:

Using tensile apparatus with a 5 kg load cell is used for the determination of the tensile strength of the pellets, 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.

Crushing strength:

The crushing strength (the load needed to break the pellets) and elastic modulus of 15 pellets (850–1000mm size fraction) are determined by 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.[22]

Density

The bulk and tap densities of pellets are determined to gain an idea of the homogeneity of the particle size distribution. The true density of pellets evaluates the porosity of the pellets and can be determined by the displacement with He or Hg or by a pycnometer. Density of pellets such as 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.[9]

Porosity

The porosity 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 (Scanning electron microscopy) with image analysis and quantitatively by using optical microscopy rarely 80. Pore radius is given by Washburn equation;

$$R = \frac{2\gamma\,[\cos\theta]}{P}$$

Where; γ = 480 ergs/cm3, θ = 140o, r = pore radius, p = mercury-intrusion pressure.

Thus, determination of the porosity of pellets by mercury porosimetry is a very well-established method showing reproducible results.[1]

Disintegration time

Pellets disintegration is one of the main characteristics of immediate release pellets. In 2005, Huyghebaert *et al.,* state that reciprocating cylinder method (USP Apparatus 3) used for disintegration test. While tablet disintegration tester specially designed by Thommes and Kleinbudde in 2006, which consist of special inserting transparent tubes of certain diameter and

length with sieve of 710µm mesh size at the top and bottom of the tube. [1]

***In vitro* dissolution studies**

In vitro dissolution studies were performed for studying the release behavior of different formulations in different dissolution media and to establish a co-relation between *in vitro* release and *in vivo* absorption for the modified-release pellets. 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 pattern 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. Polymer and binder used in pellets, 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 also influence the drug release profile of pellets. 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.[9]

Flow properties

A final characteristic of pellets is their free flowing capacity. The flow capacity of the pellets is important parameter for a homogeneous filling of the hard gelatin capsules as well as for tablet compression.[1]

APPLICATION

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

Immediate release: By increasing the surface area in compared to traditional compressed tablets and capsules which would considerably reduce the disintegration time and have the potential for use in immediate release action.

Sustained release: The pellet form gives a smoother absorption profile from the GIT as the beads pass gradually through the stomach into the small intestine at a steady rate. Now pellets are being increasingly used in the manufacture of sustained release dosage form of drugs. The advantages of the dosage form are already understood.

Chemically incompatible products: Before the innovation of pellets 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.

Varying dosage without reformulation: Pellets have excellent flow properties, due to this, they are frequently used for filling capsules and the manufacturer can vary the dosage by varying the capsule size without reformulating the product.[28]

Taste masking: Pellets are ideal for products where perfect diminution of taste is required. The pelletization technique solves difficulties in taste masking problem while maintaining a high degree of bioavailability due to their high surface area, especially for oral products.[29,31]

CONCLUSION

This review focused on ES method recently reported to produce spherical pellet eliminate problem associated with other technique. By this method have many potential applications for preparing immediate and controlled release pellet. In addition, this method has provided a new platform to produce spherical particles of drugs those are not stable or having incompatibility in presence of solvents. In this technique not much excipients are used only spheronization aid one added such as-MCC and lactose etc.

REFERENCES

1. Vervaet C, Baert L, and Remon JP. Extrusion-spheronisation: A literature review. Int J of Pharmaceutics. 1995; 116: 131-146.
2. Rahman MA, Ahuja A, Baboota S, Bhavna, Bali V, Saigal N, Ali J. Recent Advances In Pelletization Technique For Oral Drug Delivery:A Review, Current Drug Delivery. 2009; 6: 122-129.
3. Kandukuri JM, Allenki V, Eaga CM, Keshetty V, Jannu KK. Pelletization techniques for oral drug delivery. Int J of Pharm Sc and Drug Res. 2009; 1: 63-70.
4. Bhaskaran S, and Lakshmi PK. Extrusion spheronization –A review. Int J Pharm Tech Res. 2010; 2: 2429-2433.
5. Supriya P, Rajni B, and Rana AC. Pelletization techniques: A literature review. Int. Res. J. Pharm. 2012; 3: 43-47.
6. Sinha VR, Agrawal MK, Kumria R, and Bhinge JR. Influence of operational variables on properties of piroxicam pellets prepared by extrusion-spheronization: a technical note. AAPS Pharm Sci Tech. 2007; 8: 1-5.
7. Sandler N, Rantanen J, Heinamaki J, Romer M, Marvola M, and Yliruusi J. Pellet manufacturing by extrusion-spheronization using process analytical technology. AAPS Pharm Sci Tech. 2005; 6: 174-183.
8. Akhgari A, Abbaspour M R, Pirmoradi S. Preparation and evaluation of pellets using acacia and tragacanth by extrusion-spheronization. DARU 2011; 19 (6): 417-423.
9. Lavanya K, V Senthil and Rathi V. Pelletization Technology: A Quick Review. Int J of Pharm Sci and Res. 2011; 2: 1337-1355.

10. Schmidt C, and Kleinebudde P. Influence of the Granulation Step on Pellets Prepared by Extrusion/ Spheronization. Chem Pharm Bulletin. 1999; 47 3: 405—412.

11. Patel HP, Patel JK, Patel RR, Patel MP. Pellets: A general overview; Int J of Pharm World Res. 2010; 2: 1-15.

12. Shajahan A, Anil V, Chandewar SB, Jaiswal. A flexible technology for modified-release drugs: Multiple-unit pellets system (MUPS). J of Controlled Release. 2010; 147: 2-16.

13. Dashevsky 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.

14. Podczeck F. A novel aid for the preparation of pellets by extrusion/spheronization. Pharm Tech Europe. 2008; 20: 1-10.

15. Sirisha KVR, Suresh K, and Reddy GK. Multiple unit pellet systems: A review. Int J Pharm. 2012; 2: 419-425.

16. Costa FO, Sousa JJS, Pais AACC, Formosinho SJ. Comparison of dissolution profiles of ibuprofen pellets. J Control Release. 2003; 8: 199-212.

17. Ghai D. Pelletization: An alternate to granulation. Pharma Times. 2011; 43: 13-15.

18. Heng PWS. Pelletization and Pellet Coating. 15th International Symposium on Microencapsulation Parma (Italy). 2005; (september):18-21.

19. S. Muschert F, Siepmann B, Leclercq B, Carlin J. Siepmann. Prediction of drug release from ethylcellulose coated pellets. J of Controlled Release. 2009; 135: 71-79.

20. Huyghebaert N, Snoeck V, Vermeire A, Cox E, Goddeeris MB, Remon. PJ. Development of an enteric-coated pellet formulation of F4 fimbriae for oral vaccination of suckling piglets against enterotoxigenic Escherichia coli infections. Eur J Pharm Biopharm. 2005; 59: 273-81.

21. Trivedi NR, Rajan MG, Johnson JR, Shukla AJ. Pharmaceutical approaches to preparing pelletized dosage forms using the extrusion-spheronization process. Crit Rev Ther Drug Carrier Syst. 2007; 24: 1-40.

22. Veena MC, Senthil KSK, Parthiban S. Pelletization technique in drug delivery system- A review. Int J Dev and Tech. 2013; 3: 13-22.

23. Jogad NP. A review: MUPS by extrusion spheronization technique. J of Pharmacy Res. 2010; 3: 1793.

24. Noche CR, Huct de Baroche B, Brossard C, Horvath S, Cuine A. Optimizing the manufacturing process for controlled release pellets. Pharm Tech. 1994; 42: 44-6.

25. Reynolds AD. A new technique for the production of spherical particles. Mfg Chem. Aerosol News. 1970; 41: 40-43.

26. Robinson IR, and Lee. Controlled Drug Deliver: Fundamentals and applications. 2nd edition, Marcel Dekker Inc, New York.

27. Santosh H, Veiga F, Pina M, Sousa JJ. A study on the effect of drying techniques on the mechanical properties of pellets and compacted pellets. Eur J Pharm Sci. 2004; 21: 119-29.

28. Sharma A and Chaurasia S. Multiparticulate drug delivery system: Pelletization through extrusion and spheronization. Int Res J Pharm. 2013; 4: 6-9.

29. Sinha VR, Agrawal MK, and Kumria R. Influence of formulation and excipient variables on the pellet properties prepared by extrusion spheronization. Current Drug Delivery. 2005; 2: 1-8.

30. Steckel H, Mindermann-Nogly F. Production of chitosan pellets by extrusion spheronization. Eur J Pharm Biopharm. 2004; 57: 107-13.

31. 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 Biopharm. 2006; 63: 59-67.