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RECENT ADVANCES IN PELLETS AND PELLETIZATION TECHNIQUES FOR ORAL SUSTAINED RELEASE DRUG DELIVERY

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ABSTRACT

Multiparticulate drug delivery systems are discrete particles that make up a multiple unit system. Although pellets have been used in the pharmaceutical industry for more than four decades, with the advent of controlled release technology, that the full impact of the inherent advantages of pellets over single unit dosage forms have been realized, not only has focused on refining and optimizing existing pelletization techniques, but also focused on the development of novel approaches and procedures for manufacturing of pellets. Pellets are especially suitable for achieving sustained release oral formulations with a low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. The present review outlines the manufacturing approaches and evaluation of pellets. Pelletization is a novel drug delivery system that converts fine powder particles into pellets and it is useful in order to develop a site specific drug delivery system. The manufacturing techniques include layering, cryopelletization, freeze pelletization, extrusion spheronization and hot melt extrusion have been discussed. Amongst various techniques, extrusion/spheronization is the most widely utilized technique due to its high efficiency and simple and fast processing. Characterization of pellets is discussed with reference to the particle size distribution, surface area, porosity, density, hardness, friability and tensile strength of pellets.

KEYWORDS: Multiperticulates, Drug delivery, Pellets, Pelletization technique, Sustained release.

INTRODUCTION

The oral route drug delivery is the most patient convenient means of drug administration. It is widely accepted approach of drug delivery system compared to conventional immediate release formulation of the drug. Traditional drug delivery system has been characterized by immediate release and repeated dosing of drug and that related to dose fluctuation and this creates the next door for sustained release drug delivery system which provides drug release for extended period of time , enhance bioavailability constant blood plasma concentration and that's results in patient compliance. Numbers of sustained release dosage forms are available as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic system. Sustained release formulation requires generally short half life of the drug. Consideration of various parameters before formulating sustained release dosage form like as, the GIT motility, various ph in GIT, The presence of enzyme system and its effect on dosage form, and the drug. Mechanism of action is diffusion, dissolution or combination of both. As like IV infusion, sustained release dosage form should release the drug by zero-order mechanism which maintains constant drug plasma concentration.[1, 2] Plasma drug profile for conventional formulation, SR formulation and zero-order SR formulation are as shown in figure1.

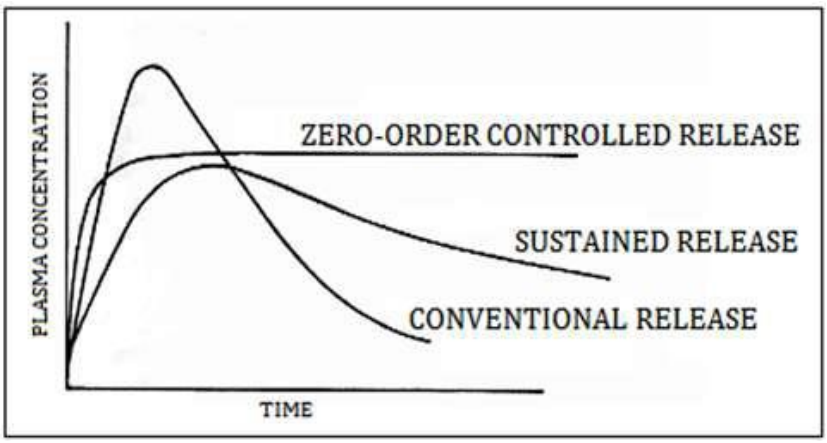

Figure 1: Plasma drug concentration profile for conventional release, a sustained release and zero order controlled release formulation

GOAL FOR DESIGNING SUSTAINED DRUG DELIVERY SYSTEM[3]

- To reduce the frequency of dosing.
- To increase effectiveness of the drug by localization at the site of action.
- To reduce the dose required.
- Providing the uniform drug delivery.

PROBLEM OCCURS DURING MULTIPLE DOSING

- If the dosing interval between the two doses is not proper according to the drug's biological Half-life, than it may result in the fluctuation of the drug plasma concentration.
- Drug plasma level will not remain in the therapeutic range due to inappropriate dosing, which may result in toxicity.
- Inconvenient for the patient and can result in missed doses and noncompliance with the regimen.

ADVANTAGES OF SUSTAINED RELEASE DELIVERY SYSTEMS

1) Decreased local and systemic side effects

- Reduced gastrointestinal irritation.

2) Better drug utilization

- Minimum drug accumulation on chronic dosing.
- Improvement in the bioavailability of some drugs.

3) Improved efficiency in the treatment

- More uniform blood concentration
- Maintenance of therapeutic concentrations.
- Reduced toxicity by slowing drug absorption
- Reduction in fluctuation in drug level and hence more uniform pharmacological response
- Increase the stability by protecting the drug from hydrolysis or other degradative changes in gastrointestinal tract.

4) Improved patient compliance

- Less frequent dosing
- Minimization in drug accumulation with chronic dosing.
- Reduced night-time dosing.

5) Economy

- Although the initial unit cost of sustained release products is usually greater than that of the conventional dosage form because of the special nature of these products, the average cost of treatment over an extended time period may be less.[4]

DISADVANTAGES OF SUSTAINED RELEASE DELIVERY SYSTEM

- Some differences in the release rate from one dose to another dose but these have been minimized by modern formulations.
- High cost of preparation.
- Sometimes the target tissue will be exposed to constant amount of drug over extended period results in drug tolerance.
- If the drug has short half-life, it has to be administered frequently, so there are chances of missing the dose.
- If the drug is not taken at periodic interval, peak valley plasma concentration time profile obtained is not steady.

  The fluctuations of drug plasma level that occurs during conventional release may produce under medication or over medication.

FACTORS AFFECTING THE ORAL SUSTAIN RELEASE DOSAGE FORM DESIGN

A) Pharmacokinetics and Pharmacodynamic factor

Biological half-life

Drug with biological half-life of 2-8 hours are considered suitable candidate for sustain release dosage form, since this can reduce dosing frequency. However this is limited in that drugs with very short biological half lives may require excessive large amounts of drug in each dosage unit to maintain sustained effects.

Absorption

Rate of absorption of a sustained formulating depends upon release rate constant of the drug from the dosage form, and for the drugs that are absorbed by active transport the absorption is limited to intestine.

Distribution

The distribution of drugs into tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending n the time course of drug disposition. Thus for design of sustain release products, one must have information of disposition of drug.

Metabolism

The metabolic conversion to a drug is to be considered before converting into another form. Since as long as the location, rate, and extent of metabolism are known a successful sustain release product can be developed.

B) Drug properties relevant to sustain release formulation

Dose size

A dose size of 500-1000 mg is considered maximal for a conventional dosage form. This also holds true for sustain release dosage forms. Since dose size consideration serves to be a parameter for the safety involved in administration of large amounts with narrow therapeutic range.

Ionization, pka and aqueous solubility

Most drugs are weak acids or bases and in order for a drug to get absorbed, it must dissolve in the aqueous phase surrounding the site of administration and then partition into the absorbing membrane.

Partition coefficient

Bioavailability of a drug is largely influenced by the partition coefficient, as the biological membrane is lipophilic in nature transport of drug across the membrane largely depends upon the partition coefficient of the drug. Drugs having low partition coefficient are considered as poor candidate for the sustain release formulation as it will be localized in the aqueous phase eg: Barbituric acid and vice a versa.

Drug stability

When drugs are orally administered, they come across acid-base hydrolysis and enzymatic degradation. In this case, if the drug is unstable in stomach, drug release system which provides medication over extended period of time is preferred, whereas in contrast the drug unstable in intestine will face problem of less bioavailability.[5]

MECHANISM OF DRUG RELEASE FROM MULTI-PARTICULATES

The mechanism of drug release from Multiparticulates can be occurs in the following ways:

Diffusion: On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

Erosion: Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle.

Osmosis: In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating.[6]

INTRODUCTION OF PELLETS

Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free-flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and are intended usually for oral administration. Implants of small, sterile cylinders formed by compression from medicated masses are also defined as pellets in pharmacy. Pellets can be prepared by many methods, the compaction and drug-layering techniques being the most widely used today. Regardless of which manufacturing process is used, pellets have to meet the following requirements.

- They should be near spherical and have a smooth surface; both considered optimum characteristics for subsequent film coating.
- The particle size range should be as narrow as possible. The optimum size of pellets for pharmaceutical use is considered to be between 600 and 1000 μm.
- The pellets should contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits.

In the last two decades, pellets have established their position for many reasons.[73] Pellets offer a great flexibility in pharmaceutical solid dosage form design and development. They flow freely and pack easily without significant difficulties, resulting in uniform and reproducible fill weight of capsules and tablets. Successful film coating can be applied onto pellets due to their ideal spherical shape and a low surface area-to-volume ratio. Pellets composed of different drugs can be blended and formulated in a single dosage form. This approach facilitates the delivery of two or more drugs, chemically compatible or incompatible, at the same sites or different sites in the gastrointestinal tract. Even pellets with different release rates of the same drug can be supplied in a single dosage form.[7]

The most important reason for the wide acceptance of multiple-unit products is the rapid increase in popularity of oral controlled-release dosage forms. Controlled-release oral solid dosage forms are usually intended either for delivery of the drug at a specific site within the

gastrointestinal tract or to sustain the action of drugs over an extended period of time. With pellets, the abovementioned goals can be obtained through the application of coating materials (mainly different polymers), providing the desired function or through the formulation of matrix pellets to provide the desired effect.

The advantage of multiple-unit products as a controlled-release dosage form is believed to be their behaviour in vivo because of their advantageous dispersion pattern in the gastrointestinal tract and their special size characteristics. The transit time of a gastrointestinal drug delivery system along the gastrointestinal tract is the most limiting physiological factor in the development of a controlled-release gastrointestinal drug delivery system targeted to once-a-day medication. Gastro-intestinal transit time, greatly affects the bioavailability of a drug from an orally administered controlled release preparation. Gastric transit of both single and multiple-unit solid dosage forms is prolonged in a fed stomach compared to a fasting one. Plastic spheres of 7 mm remained in the food-filled stomach even as food itself expelled steadily. Once the stomach had emptied, the spheres began to transit in clusters. It has been reported that pellets smaller than about 2.4 mm in diameter, are free from the digestive function of the stomach and the closing system of the pyloric sphincter to be emptied from the stomach. A maximum pellet diameter of 1.5 mm has been recommended for an optimal multiple-unit formulation clearly showed that the threshold size must be below 1 mm. According to there is no actual cut-off size for gastric emptying, but as the size of the pellets increase, predictable emptying from the fed stomach becomes uncertain and highly variable. However, it has been demonstrated that gastric emptying is not only dependent on the size but also on some other important factors, such as density of pellets, nature of food and inter-subject variation that both density and size of the pellets affect the gastrointestinal transit time. The higher density of the pellets prolonged the gastric transit time, while the larger size slightly prolonged the small gut transit time but not the gastric transit time. Controversial results have also been reported to the effect of pellets densities on the transit times through the gastrointestinal tract.[8]

IDEAL CHARACTERISTICS OF PELLETS

Due to free-flowing character of Pellets they are packed easily without any difficulties and hence flexibility in design and development a uniform solid dosage form.

The spherical shape and a low surface area-to- volume ratio of pellets made uniform film coating. Two or more drugs can be formulated in a single dosage form, chemically

compatible or incompatible, at the same sites or different sites in the gastrointestinal tract different release rates of the same drug can be supplied in a single dosage form.[9]

REQUIREMENTS OF PELLETS

- Pellets should be of spherical shape and the surface should be smooth so that desired uniform film coating can be done.
- Particle size of pellets should be in range 0.5-1.5 mm.
- The quantity of excipients should be maximum so as to maintain the particle size.

ADVANTAGES OF PELLETS[10]

- Gastric emptying is faster as the particles small in size and passes even if pylorus is closed.
- Avoidance of dose dumping.
- Better distributed and less likely to cause local irritation.
- Increased bioavailability as the surface area increases.
- Pellets are recommended for pediatrics and geriatric patient with difficulty in swallowing and dysphagia problem.
- Increased in flow property (smooth surface).
- Disperse freely in GIT and increase absorption of active drug.
- Incompatible drug and drugs with different property can be processed individually and later combined to form a modified drug delivery.
- Decreased the risk of systemic toxicity.
- Improved stability, patient comfort and compliance.

DISADVANTAGES OF PELLETS[11]

- The manufacturing of multiple unit dosage forms is more complicated and more expensive.
- The filling into gelatin capsules is difficult to accomplish, especially in the case where different subunits are involved.

FACTOR AFFECTING PELLETIZATION TECHNIQUE

➢ **Moisture Content**

It is one of the critical parameter for pellet growth in pelletization technique .Moisture in the wet mass bring cohesiveness to the powder so that the wet mass can be extracted and

spheronize to give spherical shape. High moisture contents lead to agglomeration of pellets during the process of spheronization which is one of the technique of pelletization due to excess of water in the surface of pellets and low moisture content lead to generation of fines with large variation in size distribution.

- **Rheological characteristics**

The Rheological condition of the wet mass determines the flow ability in extruder to optimum Rheological condition leads to good flow ability in order to extrude the wet mass variation in rheology make improper and non- uniform extrusion.

- **Solubility of excipients and Drug in granulating fluid**

A soluble drug get dissolve in a granulating liquid .Thus increasing the volume of liquid phase lead to over wetting of system of agglomeration of pellets and increase in wetting liquid increases plasticity but induces sticky mass.

- **Composition of Granulating Fluid**

Besides water, alcohol, water / alcohol mixture, Ethyl Ether, Dilute Acetic Acid, Isopropyl alcohol is also used as a granulating liquid. According to researcher like Millili and Schwartz, a minimum of 5 % of granulation liquid have to be water in order to produce pellets be water in order to produce pellets containing Avicel pH (101) and theophylline. Some researchers used water and dilute acetic acid in different powder to liquid ratio and concluded that mass fraction can be increased up to 100% by using dilute acetic acid for granulation step in place of demineralized water. Aqueous polymer dispersion containing Eudragit, Hydroxy Propyl Methylcellulose (HPMC), Poly vinyl pyrrilodine (PVP) and Gelatin is used in the moistening liquid.

- **Physical Properties of Starting Material**

Formulation variable such as type and content of starting material, type of filler and particle size of constituent have the effect on the pelletization process. 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 the drug in pellets.

- **Speed of the Spheronizer**

The speed of the spheronizer affects the size, hardness, sphericity and density of pellets, high speed gives high sphericity, lower friability, smooth surface and higher crushing strength.

➢ **Drying technique and drying temperature**

It is important to get proper size, shape and flow of pellets and it must be reproducible and consistent in all the batches. Variation in pellet's size, shape and flow will lead to difference in physicochemical properties of final dosage form like weight variation, improper filling etc, which will further affect the therapeutic efficiency of the delivery system. Wider particle size distribution may lead to variation in the dose of drug delivery. Variation in shape may lead to variation in flow and compressibility.

➢ **Extrusion Screen**

The quality of the extrudate/ pellets is greatly influenced by the characteristics of the orifice of the screen. An 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, increasing the extrusion force, and then had a negative effect on granulometric distribution and on shape.[11, 12]

REASON FOR PELLETIZATION

The pharmaceutical industry has developed a great interest in Pelletization due to a variety of reasons:

- Prevention of segregation of co-agglomerated components, resulting in an improvement of the uniformity of the content.
- 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.
- Increasing bulk density and decreasing bulk volume.
- The defined shape and weight improves the appearance of the product.
- Improvement of the handling properties, due to the free-fl owing properties
- Improvement of the hardness and friability of pellets.
- 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.

THEORY OF PELLET FORMATION AND GROWTH

In order to judiciously select and optimize any pelletization/granulation process, it is important to understand the fundamental mechanisms of granule formation and growth. Different theories have been postulated related to the mechanism of formation and growth of pellets. Some of these theories are derived from experimental results while others are

confined to visual observations. Results obtained from the experiments with some form of tracer technique are regarded as acceptable and convincing. As the conventional granulation, the most thoroughly studied, most classified pelletization process, which involves a rotating drum, a pan or a disc, has been divided into three consecutive regions: nucleation, transition and ball growth. However, based on the experiments on the mechanism of pellet formation and growth, the following steps were proposed: nucleation, coalescence, layering and abrasion transfer.[13, 14]

Nucleation (Figure 1A) is a common stage in all pelletization/granulation processes and occurs whenever a powder is wetted with liquid. The primary particles are drawn together to form three-phase air-water-liquid nuclei and are attached together by liquid bridges which are pendular in nature. The bonding strength is improved by reduction of particle size. The sizes of the primary 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, influence the size, the rate and the extent of nuclear formation . Both the mass and the number of nuclei in the system change as a function of time, which is an important feature of nucleation. Nucleation is followed by a transition phase, and the growth mechanisms affecting the transition region are coalescence and layering. Coalescence (Figure 1B) is defined as the formation of large-sized particles by random collision of well-formed nuclei, and the mechanism requires slight excess moisture on the nuclear surface. Although the number of nuclei is progressively reduced, the total mass of the system remains unchanged during this step. Layering (Figure 1C) is a slow growth mechanism and involves the successive addition of fragments and fines on an already formed nucleus. In the layering step, the number of particles remains the same, but the total mass in 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.

Large pellets pick up the fragments that are produced through size reduction. Production of fines and subsequent coalescence and layering continues until the number of favorable 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. In the ball growth phase the main mechanism affecting the slow growth of agglomeration is the abrasion transfer (Figure 1D), which involves the transfer of materials from one granule formed to another without any preference in either direction. This situation does not result in a change in the total number or

mass of the particles. The particles, however, undergo a continuous change in size as long as the conditions that lead to the transfer of material exist.[15]

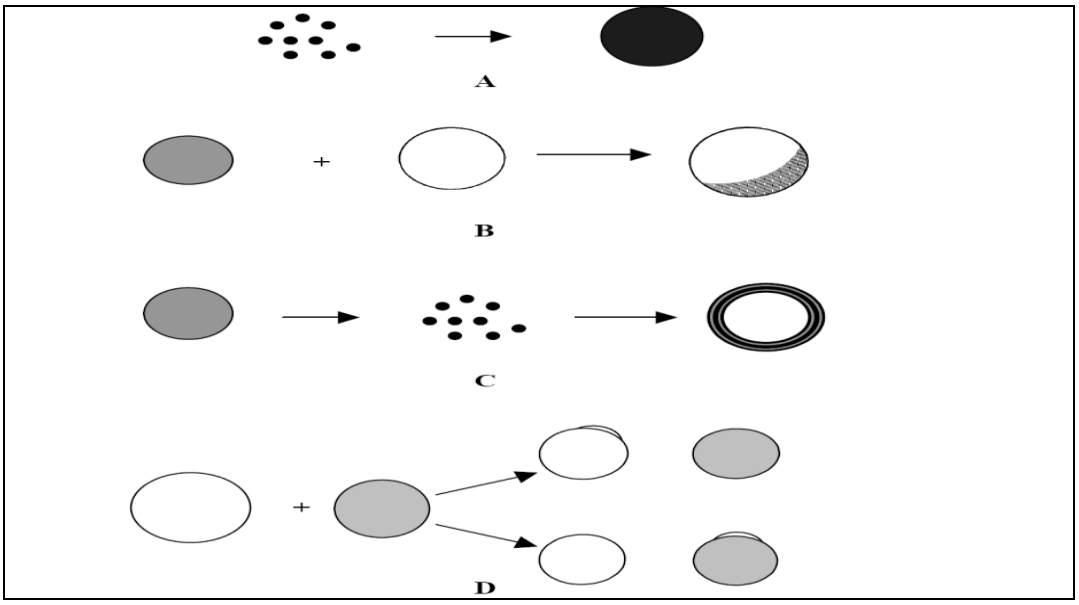

Figure No:-5 Pellet growth mechanisms. (A) Nucleation, (B) coalescence, (C) layering and (D) abrasion transfer.

PELLETIZATION TECHNIQUES

Pelletization methods are used in the pharmaceutical industry and it can be grouped by various criteria, e.g. by the type of equipment used, the intensity of the mechanical forces involved or the techniques employed for the production of pellets. The success of these methods depends on the complex relations between the equipment, the formulation and process variables.[16]

1) Extrusion / Spheronization
2) Powder layering technique
3) Suspension / Solution layering technique
4) Spherical Agglomeration
5) Spray Drying and Spray Congealing
6) Melt Spheronization
7) Cryopelletization

1) Extrusion / Spheronization

Extrusion / spheronization are a multistage process for obtaining pellets with uniform size from wet granulates (extrudate). The method involves the following main steps:

- The dry mixing of the ingredients, in order to achieve homogenous powder dispersions.
- Wet massing, in which the powders are wet mixed to form a sufficiently plastic mass.
- An extrusion stage, in which the wet mass is shaped into cylindrical segments with a uniform diameter.
- The spheronization stage, in which the small cylinders are rolled into solid, spheres (spheroids).
- The drying of the spheroids, in order to achieve the desired final moisture content.
- Screening (optional), to achieve the desired narrow size distribution.

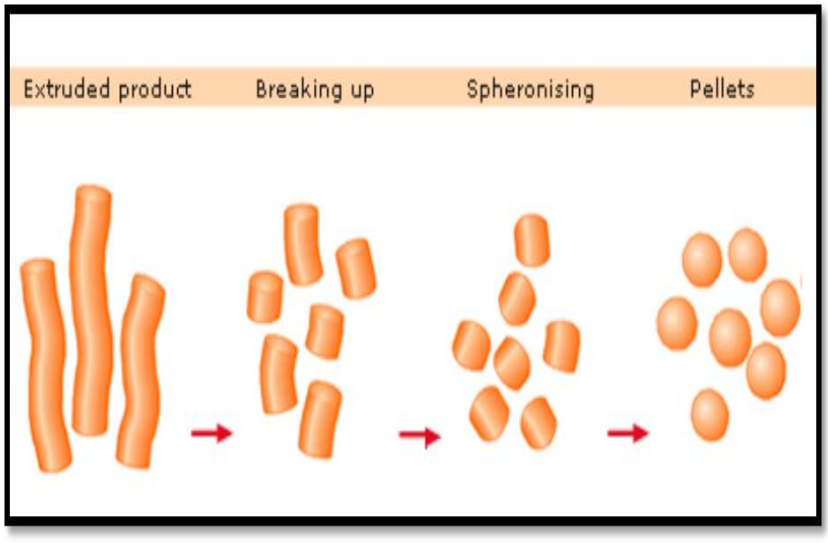

Figure 2: Principle of Extrusion–Spheronization process

Extrusion spheronization is a multi-step compaction process comprising of following steps;

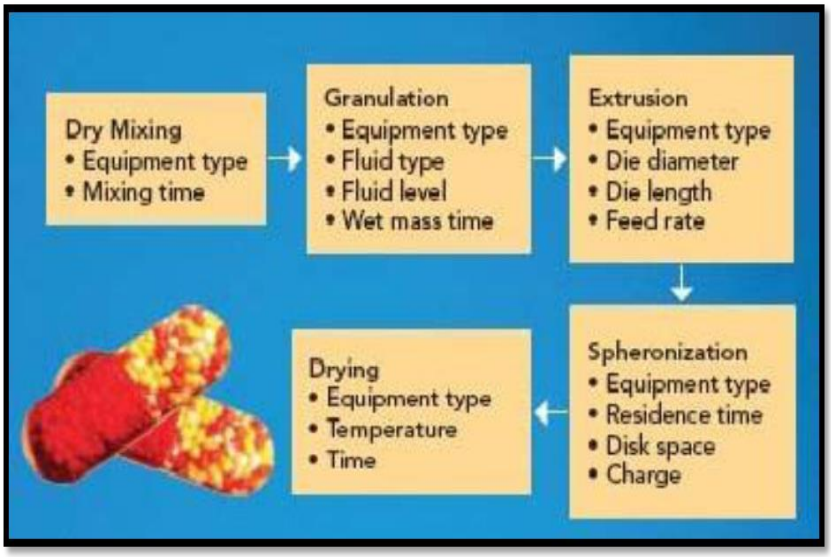

Figure: Process flow chart of the extrusion spheronization process, showing the process variables for each individual step

Extrusion spheronization was developed in the early 1960s as a pelletization technique. The extrusion-spheronization process is commonly used in the pharmaceutical industry to make uniformly sized spheroids. It is especially useful for making dense granules with high drug loading for controlled-release oral solid dosage forms with a minimum amount of excipients.

- **Dry mixing**

Dry mixing of all ingredients is done to get homogeneous powder dispersion or mixer using different types of mixers like twin shell blender, high shear mixer, tumbler mixer and planetary mixer.

- **Wet Massing**

This process of powder dispersion is done to produce a sufficient plastic mass for Extrusion. It is similar to the wet granulation method but the granulation and point is determined by the behavior of the wetted mass during the extrusion operation .The most commonly used granulator is planetary mixer or sigma blade mixer or high shear mixer and Horbat mixer.

- **Extrusion**

This is a method of applying pressure to a mass until it flows through an opening and determine two dimension of an agglomeration of particles .This operation is the major contributing factor in the final particle size of the pellets. In this process the wetted mass is passed through the extruder to form rod shaped particles of uniform diameter. The extrudate must have enough plasticity to deform but not so much that the extrudate particles adheres to other particles when rolled during spheronization process. The granulation solvent serves as the binding agent to form the granules and as the lubricating during the extrusion operation.

- **Spheronization**

This process is use to round up these rod shaped particles in to spherical particle in to spherical particle with narrow size distribution. The instrument used is called Spheronizer where the extrudate is rotated at higher speed by friction plate that breaks the rod shaped particles in to smaller particles and rounded them to form spheres.

- **Drying**

In order to get desired moisture content in pellets a drying stage is required the pellets are dried at room temperature or at a elevated temperature in a tray dryer or in a fluidized bed

dryer, according to DI.Wilsom et. Al, 2006 freeze drying method retains the shape and size and the granules whereas the oven drying produce rough granules.

➢ **Screening**

It is necessary to achieve the desired size distribution and for this purpose sieves are used. Based on the type of feed mechanism and to transfer the mass towards the die, Variety of extruders is used in the above mentioned technique. These extruders are classified in to following classes.[17, 18]

a) Screw fed extruders

The screw rotates along the horizontal axis and hence transports the material horizontally; they may be of two types:

- **Axial screw extruders:** These have a die plate that is positioned axially, consist of a feeding zone, a compression zone, and an extrusion zone.

- **Radial screw extruders**-The transport zone is short, and the material is extruded radially through screens mounted around the horizontal axis of the screws.

b) Gravity-fed extruders: These are of two types, which differ primarily in the design of the two counter-rotating cylinders. The rotary cylinder are two types including;

- **Two counter-rotating cylinders** is hollow and perforated, whereas the other cylinder is solid and acts as a pressure roller.

- **Rotary-Gear Extruder**: There are two hollow counter-rotating gear cylinders with counter bored holes.

c) Ram Extruders

This is probably the oldest type of extruders; a piston displaces and forces the material through a die at the end. These extruders are preferentially used in the development phase, because they can also measure the rheological properties of formulations.

d) Marumerizer

It consists of a two parts:

- Static cylinder or stator
- Rotating friction plate.

A typical friction plate has a crosshatch pattern, where the grooves intersect at a 900 angle. The rotational speed of the friction plate is variable and ranges from 100 to 2000 rpm; depending on the diameter of the unit and spheronizer friction plate with a cross hatch pattern.

2) Powder layering technique

This technique involves the deposition of successive layer of drug powder of drug and excipient or both on preformed nuclei or core with the help of a binding liquid. During powder layering the binding solution and finely milled powder are added simultaneously to a bed of starter seeds at a pre-determined controlled rate .In initial stages the drug particle are bound to the starter seeds of subsequently to the forming pellets with the help of a liquid bridges originated from sprayed binding liquid .These liquid bridges are replaced by solid bridges derived either from a binder in the liquid medium or from any material. Successive layering of a drug and the binder solution continuous until desired pellet size are reached. The first equipment used to manufacture pellets on commercial scale was the conventional coating pan but it has significant limitation that is the degree of mixing is very poor and the drying process is not efficient.

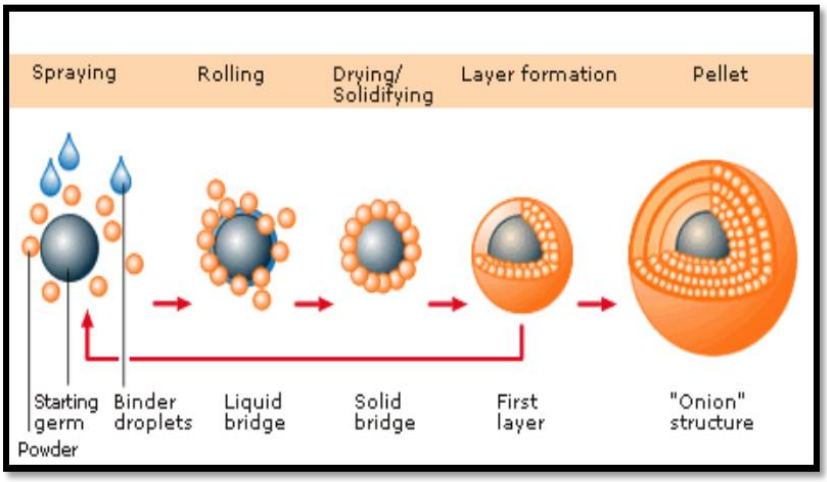

Figure 3: Principle of Powder Layering Process

Throughout the processes it is extremely important to deliver the powder accurately at a predetermine rate and in a manner that maintains equilibrium between the binder liquid application rate and powder delivery rate is not maintained ,over wetting or dust generation may occur and neither the quality nor the yield of the product can be maximized . More over the fines may be generated by inter particle and wall to particle friction and appear in the

yield. The above problem can be overcome if the application medium is sprayed on the cascading pellets at the end to increase the moisture level at the pellets surface and facilitate layering of fines on to the pellets. For this purpose now it is equipment like tangential spray granulator and centrifugal bed granulator are used.

3) Suspension / Solution layering technique

This technique involves the deposition of successive layer of solution and /or suspension of drug substances and binders on starter seeds which may be inert material or crystal of granules of the same drug. In this technique drug particles and others component are dissolved or suspended in the application medium .The droplets impringe on the starter seeds or cores and spread evenly as the solution or suspension is sprayed on the cores. Followed by drying phase allows dissolved material to crystallize and form solid bridges between the cores and initial layer of the drug substances and among the successive layer of drug substances or polymer. Continue this process until the desired layer of drug or polymer formed. Consequently conventional coating press, fluidized bed centrifugal granulator of Wurster coater has been used successfully to manufacture pellets. The most common configuration for bottom spray coating is known as the Wurster system. In this study solution/ layering of neutral pellets has been conducted applying novel fluidized bed technology from .This technology claims to improve the product movement in defined direction in all the equipment by the Disk jet gas distribution plate. Furthermore, a 3-component spray nozzle is used in order to improve the film formation on the pellets due to constant and reproducible drop size distribution. Accessibility of clogged nozzles without stopping and interrupting the process makes the equipment advantageous in respect to Wurster system. Hüettlin's three component nozzle is an air nozzle with an additional channel through which a second gas or component can be introduced to create a special microclimate around the nozzle which prevents excessive spray drying or clogging of the nozzle. Such microclimates near nozzle apertures are very useful when a film former with a relatively high minimum film-forming temperature (MFT) issued.[19-21]

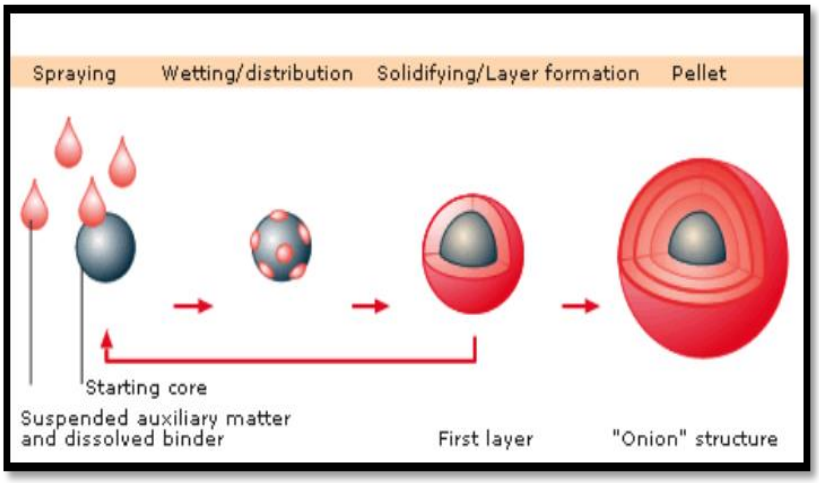

Figure: 4 Principles of Solution and Suspension Layering Process

4) Spherical Agglomeration

Spherical agglomeration, or balling, is a pelletization process in which powders, on addition of an appropriate quantity of liquid or when subjected to high temperatures, are converted to spherical particles by a continuous rolling or tumbling action. Spherical agglomeration can be divided into two categories:

- **Liquid-induced agglomeration**

During liquid-induced agglomeration, liquid is added to the powder before or during the agitation step. As powders come in contact with a liquid phase, they form agglomerates or nuclei, which initially are bound together by liquid bridges. These are subsequently replaced by solid bridges, which are derived from the hardening binder or any other dissolved material within the liquid phase. The nuclei formed collide with other adjacent nuclei and coalesce to form larger nuclei or pellets. At this point, coalescence is replaced by layering, whereby small particles adhere on much larger particles and increase the size of the latter until pelletization is completed.

- **Melt-induced agglomeration**

Melt-induced agglomeration processes are similar to liquid-induced processes except that the binding material is a melt. Therefore, the pellets are formed with the help of congealed material without having to go through the formation of solvent-based liquid bridges. If the surface moisture is not optimum, some particles may undergo nucleation and coalescence at different rates and form different sizes of nuclei admixed with the larger pellets. As a result, spherical agglomeration tends to produce pellets with a wide particle size distribution.[22]

5) Spray Drying and Spray Congealing

Spray Drying and Spray Congealing, also known as globulation process, involve atomization of hot melts, solutions, or suspensions to generate spherical particles or pellets. The droplet size in both processes is kept small to maximize the rate of evaporation or congealing, and consequently the particle size of the pellets produced is usually very small.

- **Spray Drying**

The drug entities in solution or suspension are sprayed, with or without excipients, into a hot air stream to generate dry and highly spherical particles. As the atomized droplets come in contact with hot air, evaporation of the application medium is initiated. This drying process continues through a series of stages whereby the viscosity of the droplets constantly increases until finally almost the entire application medium is driven off and solid particles are formed. Generally, spray-dried pellets tend to be porous.

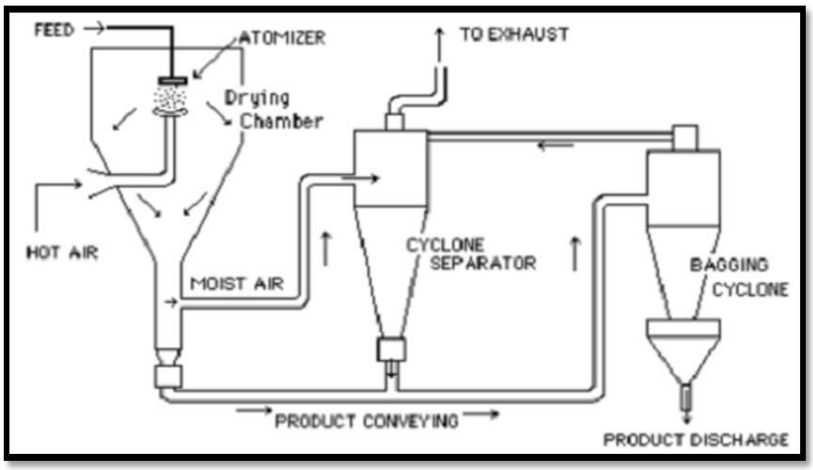

Figure 1: Spray drying process

- **Spray Congealing**

This process consists of suspending the particles in a molten coating material and pumping the resultant slurry into a spray dryer in which cold air is circulated. The slurry droplets congeal on contact with the air. The coating agents normally employed is low melting materials such as waxes. The congealing process require higher ratio of coating agents to active material than does the spray drying, because only the molten coating agent constitutes the liquid phase.

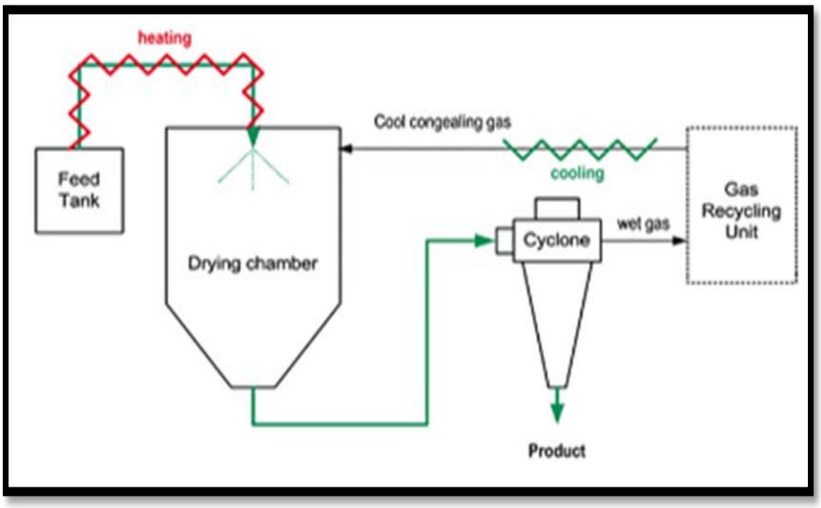

Figure1.8: Standard spray congealing step

6) Melt Spheronization

Melt Spheronization is a process whereby a drug substance and excipients are converted into a molten or semi molten state and subsequently shaped using appropriate equipment to provide solid spheres or pellets. The drug substance is first blended with the appropriate pharmaceutical excipients, such as polymers and waxes, and extruded at a predetermined temperature. The extrusion temperature must be high enough to melt at least one or more of the formulation components. The extrudate is cut into uniform cylindrical segments with a cutter. The segments are spheronize in a jacketed Spheronizer to generate uniformly sized pellets.[23, 24]

7) Cryopelletization

Cryopelletization 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 drug-loaded pellets in liquid nitrogen at -160^{0}C. The procedure permits instantaneous and uniform freezing of the processed material owing to the rapid heat transfer that occurs between the droplets and liquid nitrogen. The amount of liquid nitrogen required for manufacturing a given quantity depends on the solids content and temperature of the solution or suspension being processed. The equipment consists of a container equipped with: Perforated Plates a Reservoir Conveyor belt with Transport baffles Storage Container the perforated plates generate droplets that fall and freeze instantaneously as they come in contact with the liquid nitrogen below. The frozen pellets are transported out of the nitrogen bath into a storage container at - 60^{0}C before drying.[25]

EXCIPIENT FOR PREPARATION OF PELLETS

Various excipients have been used for formulation of pellets for different active ingredients. The most commonly used extrusion spheronization excipient is microcrystalline cellulose (MCC). It can be used for pellets to be filled in hard gelatin capsules or compressed into tablets. Various derivatives of celluloses have been used including different grades of Avicel (usually Avicel PH 101), Avicel with 5% methyl cellulose or 6-8% sodium carboxy methyl cellulose (SCMC) and mixtures of MCC with hydroxyl Propyl methyl cellulose (HPMC). MCC and cellulose derivative mixtures are used for pellets of high drug loading capacity upto 80%. Mixtures of corn starch and wheat starch with addition of 20% dextrin give high quality pellets with good shape and size distribution. Starch and other polysaccharides like dextrin are also mixed with MCC as excipients. A very low soluble derivative of pectin called pectinic acid is also a well suited for pelletization. Although it is not as universal as MCC, pectinic acid can be used with lactose in different ratios as excipient for pelletization. It is highly effective in combination with lactose, with concentrations ranging from 20-80%. Pectinic acid gives almost spherical pellets with good mechanical strength and solubility. Alginate and chitosan are also used with MCC. Chitosan imparts better disintegration profile to the pellets and 20% carrageenan with lactose. For spray dried pellets, excipients used include mixtures of MCC with HPMC, hydroxyl Propyl cellulose (HPC), SCMC and PVP with 20% lactose usually preferred, HPC and PVP being the most favored polymers due to maximum yield of pellets. Processes like spray congealing and melt or freeze pelletization require excipients like hydrophilic and hydrophobic meltable binders. Hydrophilic binders include Gelucire, Poloxamer, Polyethylene Glycol (2000, 3000, 6000, 8000, 10000, 20000) and Stearate. Hydrophobic binders include beeswax, carnauba wax, cetyl palmitate, glyceryl monostearate, glyceryl palmitostearate, glyceryl Stearate, hydrogenated castor oil, microcrystalline wax, paraffin wax, stearic acid and stearic alcohol.[26, 27]

APPLICATIONS OF PELLETS

Taste masking

Micro pellets are ideal for products where perfect abatement of taste is required. Although 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, microencapsulation with various polymers, complexing with cyclodextrin and chemical modifications such as the use of insoluble prodrugs, few reports have described the masking of unpleasant taste without

lowering of bioavailability especially for oral products. The micropelletization technique solves difficult taste masking problems 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 micro pellets. Many products, such as antibiotics (clarithromycin, roxithromycin and cephelexin) and anti-inflammatory drugs with a prohibitively bitter taste, can now be formulated in products with high patient compliance, thus markedly increasing the sales potential of the product.

Immediate release

Administering drugs in pellet form leads to an increased surface area as compared to traditional compressed tablets and capsules. This would considerably reduce the time required for disintegration 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 in to the small intestine at a steady rate. Pellets are being increasingly used in the manufacture of sustained release dosage form of drugs. The advantage of the dosage form is well known and some examples are given below:

- Extend day time and night time activity of the drugs,
- Potential for reduced incidence of side effects,
- Reduced dosage frequency of dosage forms,
- Increased patient compliance, patients who are required to take 2 or more doses of formulation a day are thought to be less likely to forget a dose then if they are required to take 3 or 4 times a day,
- Potential lower daily cost to patient due to fewer dosage units

In contrast the whole tablet is released at once in to the small intestine as the stomach empties itself, and Different type of polymers e.g. carboxymethylcellulose, ethyl cellulose, Eudragit etc., are utilized for coating of different drugs to enable the sustained release/controlled release rate of drugs. Pellets ensure improved flow properties and flexibility in formulation development and manufacture. If the pellet surface is smoother it allows thin or thick coat of the polymer on the surface of the pellets. The thickness of the coat determines the rate at which the drug is released from the coated pellets. The coating material may be colored with a dye materials so that the beads of different coating thickness will be

darker in color and distinguishable from those having fewer coating. It is widely used for frequently administered drugs having a half-life of 0.5-2 hr. The excellent reproducibility and homogeneity of the particle size and the round shape and smooth surface of the particles makes micro pellets with sizes smaller than 200mm a perfect match for powder injections. In addition, the very high drug substance load level of the micro pellets promotes lower injection volumes, thus increasing patient acceptance. Many drug substances, e.g. neuroleptics, peptides, hormones, therapeutic proteins; vaccines etc. in need of slow release formulations are product candidates for this technology. Micro pellets have thus opened a new dimension in parenteral depot technologies. Drug substance particles can either be coated with biodegradable polymers or embedded in a polymer matrix. Using these approaches, release profiles ranging from days to months and even pulsed release can be obtained at wish. The release rate of drugs from the polymer coat can be modified using various concentration of plasticizer and influence of pH. Even if they are useful as drugs, the necessity of frequent injection makes them inconvenient and often causes pain and trouble to patients.

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.

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.[28-30]

EVALUATION PARAMETERS OF PELLETS

Size Distribution

The sizing of pellets is necessary because it has significant influence on the release kinetics (Husson, I., 1992). Particle size distribution, mean ferret diameter, geometric mean diameter, mean particle width and length, are the parameters by which size of pellets can be determined. In most of the cases particle size determination is carried out by simple sieve analysis using sieve shaker.

Pellets Shape

Sphericity of the pellets is the most important characteristics and various methods have been used to determine it. 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 (Mezreb N., 2004). 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 is another method to determine shape of pellets (Lian-Dong H., 2006). One plane is critical stability, which an angle at which a plane has to be tilted before a particle begins to roll, is one of the important methods used for determining shape (Bornhoft M., 2005). 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 fall from a given height through a specific orifice.

Surface Morphology

Scanning electron microscopy is used to examine the surface morphology and cross section of pellets. Sood*et al.* in 2004 reported the use of optical microscopy to examine the microstructure of pellet surface (Sood A., 2004). Some researcher analyzed surface roughness of pellets by applying a no contracting laser profilometer (Santosh H. et al., 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 technique.

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. Today pelletization technology represents an efficient pathway for manufacture of drug delivery system. This review focused on frequently used pelletization techniques for producing pellets for oral drug delivery. Each technique has its own advantages and disadvantages. Layering processes have been used over the years for manufacturing of pellets. Most of the scientists

have focused research on refining and optimizing existing pelletization techniques and also focused on the development of novel approaches and procedures of manufacturing pellets employing innovative formulation and processing equipment. These pelletization techniques have great impact on the development of different type novel drug delivery systems. A number of pelletized products are being designed to maximize the in vivo performance of medications already in the market and to meet all regulatory requirements.

Friability

The mechanical properties of pellets are important for processing. Pellets flake off during handling and coating process resulting in formation of dust. In the case of subsequent coating it is desirable to have pellets with low friability. Friability of pellets are determined by using Erkewa type tablet Friabilator(Wiwattanapatapee R. et al, 2004) or turbula mixer (Mesiha M.S. and Valles J. ,1993) for a fixed period of time combined with glass beads of certain diameter in order to generate abrasion.[31, 32]

CONCLUSION

The recent market for novel drug delivery system has continued to grow at an impressive rate. Today's formulation design and development are the most promising and impending face of innovative pharmaceutical technologies in the current epoch for exploring newer formulations with high-quality. Development of pelletization has acquired the market of novel drug delivery involving both the controlled as well as immediate release. They are having simple design, high efficiency of producing spherical pellets, flexibility and robustness. Pelletization lays the scope for different oral immediate or controlled delivery system. Due to its simple design, greater flexibility, efficiency of producing spherical pellets and fast processing; it has found a special place in the Pharmaceutical industry. It can be concluded that due to their good technological and biopharmaceutical advantages, pelletization has gained an importance in modern pharmaceutical science.

ABBREVIATIONS

SR = Sustained release

MDP = Meltable dispersed phase

IER = Ion Exchange Release

CONFLICT OF INTEREST

The author declares no conflict of interest.

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