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PELLETIZATION AS MULTIPARTICULATE DRUG DELIVERY SYSTEM: A RECENT NOVEL APPROACH

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ABSTRACT:
Pharmaceutical research and development is placing more and more emphasis on administration methods that maximise therapeutic goals while reducing adverse effects. The active ingredient is present as a number of separate independent subunits in multiparticulate drug delivery systems, which are oral dosage forms made up of many small discrete subunits. Multiparticulate drug delivery systems (MPDDS) are suitable for both conventional as well as novel drug delivery system. Pelletization is a novel drug delivery which converts the fine powder into pellets. The current study is primarily concerned with all areas of formulation, evaluation and development of new techniques for pellets and pelletization which is useful in site-specific drug delivery system. This work also projects novel techniques for pelletization such as cryopelletization, freeze pelletization, Hot melt extrusion and melt spheronization.

KEYWORDS: Multiparticulate drug delivery, Pelletization, Pellets, Extrusion-Spheronization method, Spray congealing method.

INTRODUCTION:

With the advancement of the technologies in the pharmaceutical field, drug delivery systems have drawn an increasing interest over the last few decades. Because of the inherent challenges posed in the drug discovery and development process, pharmaceutical galenic research is now focused on creating more effective drug delivery methods using already existing molecules rather than aiming for novel drug discoveries. Pharmaceutical research and development started focusing on delivery systems which enhance desirable therapeutic objectives while minimizing side effects. Multiparticulate drug delivery systems are oral dosage forms consisting of multiplicity of small discrete units in which active substance is present as a number of independent subunits. Together, these characteristic units provide the overall desired controlled release of the dose. It is based on subunits such as granules, beads, microspheres, pellets, spheroids and Minitab. In MDDS, drug substances are divided into number of subunits, typically consist of thousands of spherical particles having diameter of about 0.05-2.00 mm. To administer or to recommend total dose these subunits are compressed into a tablet or filled into a sachet or encapsulated. The goal of designing a multiparticulate dosage form is to create a reliable formulation that has all the benefits of single unit formulations while being free from the risk of changes in the drug release profile and formulation behaviour caused by variation from unit to unit, changes in gastro luminal pH and changes in the population of enzymes.

ADVANTAGES AND DISADVANTAGES OF MPDDS:

Advantages

1. Predictable, reproducible and short gastric residence time.
2. Less variation between and within subjects.
3. Increase the bioavailability.
4. Increased tolerance and fewer side effects.

5. Modified release causes less dose dumping than reservoir and has a low risk of local irritation.
6. No possibility of dosage dumping.
7. Design flexibility.
8. Make stability better.
9. Boost patient satisfaction and compliance.
10. Develop a distinctive releasing pattern
11. Improved medication release in vivo and in vitro.

Disadvantages

1. A minimal drug load.
2. Significantly increased requirement for excipients.
3. Ineffective production, repeatability, and effectiveness.
4. There are numerous process factors.
5. Multiple steps in the formulation.
6. Higher production costs.
7. Demand for advanced technology.
8. A qualified staff is required for manufacturing.

DESIGN OF MULTIPARTICULATE DRUG DELIVERY SYSTEM:

The goal of creating multiparticulate dosage forms is to create a formulation that is reliable and free from the risk of changing the drug release profile or the behaviour of the formulation as a result of variation from unit to unit. Multiparticulate systems are formulated as:

Reservoir system with rupturable polymeric coating

In this technique, the coating is ruptured by several mechanisms such as swelling, disintegration, effervescent excipients or osmotic pressure in order to achieve the drug release. For instance, the polymer and aqueous solution were mixed with an effervescent mixture. The rupture of the coat and release of the medication are caused by fluid CO_2 production. The drug release and lag time are controlled by the mechanical properties of the coating layer, coating thickness and core hardness. Cross-carmellose sodium (CCS), Sodium starch glycolate (SSG) and low substituted hydroxyl propyl cellulose (L-HPC) are examples of swelling agents that swell, rupture and release medication.

Reservoir systems with soluble or erodible polymer coatings

In this technology, the burst release of the drug is caused by the polymer coat which either dissolves or erodes in aqueous fluid after a set lag time. Drug release and lag time are controlled by the polymer's thickness and pH sensitivity. It is essential to have a high ratio of drug solubility to dosage in order to prevent drug irritability due to burst release.

System with changed membrane permeability

One example of this kind of device is the osmotic MPDDS which releases the medication at predetermined intervals. The formulation consists of a medication core and a sodium chloride-based water soluble osmotic agent wrapped in an insoluble, water-permeable polymer film. In the dosage form, the film coating of each population of pellets is different from the coating of every other population of pellets in terms of how quickly water permeates to the core and how quickly drugs diffuse out of the core. As the osmotic agent disintegrates in the water, the pellet expands and the rate of medication diffusion into the environment of use is controlled.

MECHANISM OF DRUG RELEASE FROM MULTI-PARTICULATES:

Table 1.1: Mechanism of Drug Release from Multiparticulate

Diffusion	Erosion	Osmosis
Water diffuses into the interior of the particle when it comes into touch with aqueous fluids in the gastrointestinal tract (GIT). Drug solutions dissolve and disperse across the release coat to the outside as a result.	Some coatings can be made to gradually erode away over time, releasing the drug that is encapsulated inside the particle.	Under the correct conditions, an osmotic pressure can be created inside the particle by allowing water to enter. Through the coating, the medication is compelled from the particle and into the surrounding material.

PELLETIZATION:

Introduction

Pelletization, a process that turns small powder particles into pellets, is an attractive and novel drug delivery technology. With regard to predictable and even distribution and transportation in the gastrointestinal tract, ease of filling, improved flow properties of spherical pellets, sustained, controlled or site-specific drug delivery, ease of coating and uniform packing, these oral MPDDS offer biopharmaceutical advantages. Pelletization is the agglomeration (size-enlargement) process used to create small, free-flowing, spherical or semi-spherical units known as pellets from fine powder or particles of bulk medicines and excipients. Pellets come in sizes ranging from 0.5 to 1.5 mm.

Advantages

1. Pelletization creates spheroids with a high active ingredient loading capacity without creating a significant amount of large particles.
2. By using the pelletization technology, pellets have good flow and packing qualities and are more rounded than conventional nonpareil seeds.
3. Regardless of the stomach's level of filling or the size and density of chyme, particles smaller than 2-3 mm pass through the pylorus quickly.
4. Additionally, the size of the particles spread in the intestine is controlled by pelletization which also limits the spread of GI irritations.

Need of Pelletization

1. To enhance stability, compaction, solubility, flow and dispersion.
2. To transit through the GIT more consistently than single-unit dose forms such as tablets made by granulation and compression.
3. To create uniformly sized pellets with a high medication loading capacity.
4. To avoid dust and segregation.
5. Pellets can be put into capsules or compacted into tablets known as "pelltabs."

FACTORS AFFECTING PELLETIZATION:

Moisture content

Moisture makes powder more cohesive and produces wet extrudate, which is then spheronized to generate pellets. Due to an excess of water on the surface of the pellets, high moisture contents cause pellets to agglomerate during the spheronization process, whereas low moisture contents cause the production of fines with a wide range in size distribution.

Rheological characteristics

The ability of the wet material to flow in the extruder and during subsequent spheronization operations depends on its rheological condition. Therefore, rheological wet mass change causes inappropriate and uneven extrusion.

Solubility of excipients and Drug in granulating fluid

A granulating liquid dissolves a medication that is soluble in it. As a result, increasing the liquid phase's volume causes the pellets and agglomeration system to become excessively moist, which promotes flexibility but results in sticky mass.

Composition of Granulating Fluid

In addition to water, alcohol and water/alcohol mixtures other liquids employed as granulating agents include ethyl ether, diluted acetic acid and isopropyl alcohol. Water must make up at least 5% of the

granulation liquid in order to produce high-quality pellets.

Physical Properties of Starting Material

The parameters that affect the pelletization process include content, composition, varied beginning material grades, type of filler and filler particle size. The swelling characteristics of the material employed in the pelletization process determined the drug's release rate in the pellets.

Speed of the Spheronizer

The size, hardness, sphericity and density of the pellets are all influenced by the spheronizer speed; a high speed produces pellets with a high sphericity, low friability, smooth surface and a high crushing strength.

Drying technique and drying temperature

The final dosage form's physicochemical characteristics such as weight variation and inappropriate filling will fluctuate depending on the pellet's size, shape and flow which will further affect the delivery system's therapeutic effectiveness. A thorough drying process is necessary to produce optimum pellets since a wider particle size distribution may cause variations in the dose of medication administration.

Extrusion Screen

The features of the screen's orifice have a significant impact on the extrudate's/pellet's quality. Mean pellet size increased as orifice dimension increased. When water was present at the extrudate surface the rise in orifice depth decreased, increasing the extrusion force which then had a detrimental impact on granulometric distribution and shape.

THEORY AND PRINCIPLE OF PELLET FORMATION AND GROWTH:

When choosing the pelletization process, it is important to understand the underlying principle and mechanism of pellet creation and growth. There are numerous hypotheses that explain how pellets grow and are formed. Others are hypothesized based on visual observations, while some of them are generated from research. There are primarily three processes in the pelletization process: Ball Growth, transition and nucleation. However, the pelletization procedure phases that have been suggested based on experiments are: 1) Nucleation 2) Coalescence 3) Layering 4) Abrasion Transfer.

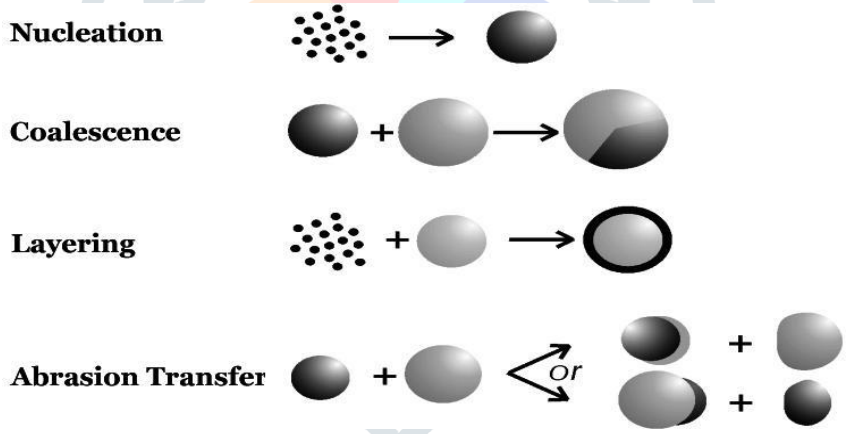

Fig. 1.1: Pellet Formation and Growth mechanism

Nucleation

In the beginning, the powder is moistened with a solvent solution to bring the first particles together to form a three-phase liquid that is composed of air, water and liquid to increasing the bonding strength and decreasing particle size. Additionally the size of the particles, moisture content, viscosity of the binding particles, wettability of the substrate and processing parameters such as tumbling and drying rates all affect the size, rate and degree of nuclear production. Following nucleation comes a transition period where coalescence and layering are the dominant growth mechanisms. The elimination of fines as a result of coalescence between the primary particles that have been wetted or the primary particles that have formed nuclei characterizes the nucleation phase. The resulting nuclei would experience consolidation as a result of the mechanical forces that were applied externally, gaining enough strength to withstand additional breakdown by impact forces and having the capacity to develop into larger agglomerates. To create moist nuclei the liquid is either slowly sprayed onto an area of dry powder or supplied to the primary particles all at once in a highly regulated manner. The fact that the mass and nature of the system's nuclei fluctuate over time as a function of time is an essential component of nucleation.

Coalescence

Coalescence is the process of creating large-scale particles after well formed nuclei randomly collides. The presence of a little excess of surface moisture is essential for optimal nuclei collision. Without a minor excess of moisture, coalescence needs additional mechanical stresses. The number of nuclei falls during this phase while the system's mass remains constant.

Layering

Layering is a gradual development method that builds up previously created nuclei with successive additions of fines and fragments. In the layering step the overall mass of the system grows as a result of the rising particle size as a function of time while the number of particles stays constant. By reducing the particle size the fragments or tiny particles can be created. Larger pellets absorb the particles and fragments created during size reduction. Up until the number of collisions begins to rapidly reduce, fines are produced which is followed by coalescence and layering that slows the rate at which the pellets expand. The ball growing region the third phase is now reached. Since only a small amount of material is ever supplied to the growing nuclei at any given time, the material deposited over the nuclei may be dry or moist and the development rate is always slow.

Abrasion transfer

Without regard for either direction materials are moved from one granule to another in this process. The overall number or mass of the particles remain unchanged. As long as the circumstances for the transfer of material are present and particles continuously fluctuate in size.

PELLETIZATION METHODS AND EQUIPMENT:

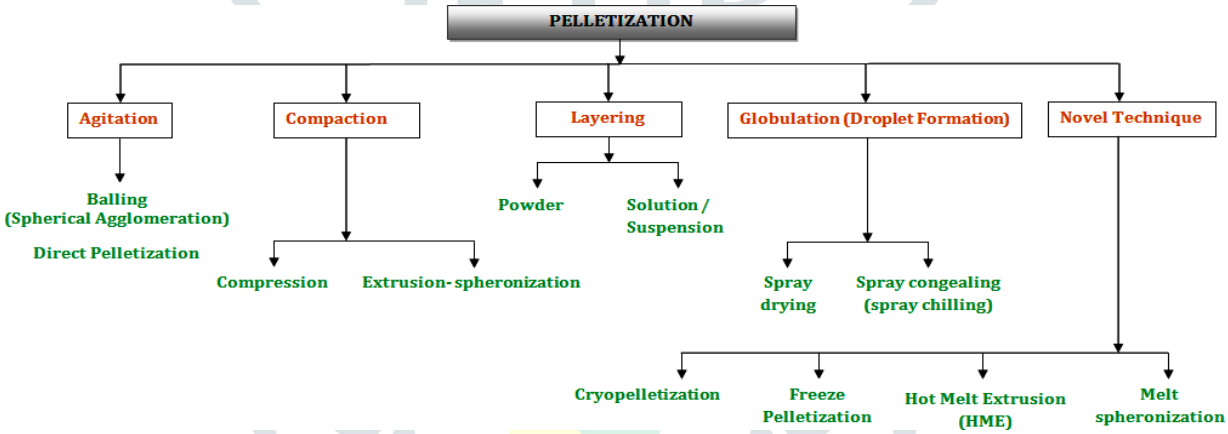

Fig. 1.2: Various Pelletization Methods

I. AGITATION

It is a pelletization process in which powders are transformed into spherical particles by a continuous rolling or tumbling action upon addition of an adequate amount of liquid or when exposed to high temperatures.

BALLING/SPHERICAL AGGLOMERATION

When liquid is added before or during the agitation stage, the finely divided powder particles are continuously rolled or tumbled into spheres. If a liquid is used to create a sphere this is known as liquid-induced agglomeration or if a liquid is heated to a high temperature this is known as melt-induced agglomeration. Balling can produce spherical pellets using rotary fluid-bed granulators, horizontal drum mixers and round curvature pans.

Mechanism of pellet growth by balling/spherical agglomeration

The addition of liquid creates agglomerates or nuclei that are linked together by liquid or melt bridges that are later replaced by solid bridges. The binder or melt is then hardened to create pellets.

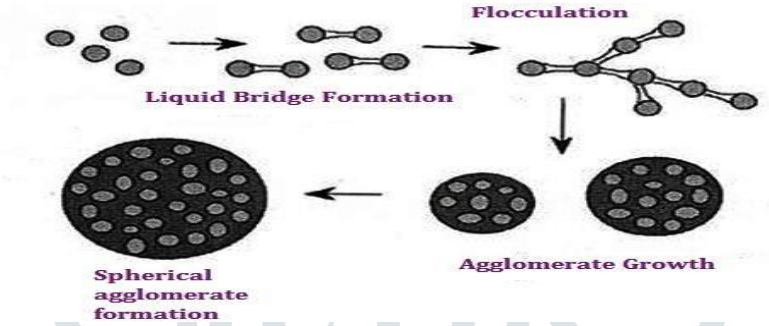

Fig.1.3: Pellet Growth Mechanisms in Spherical Agglomeration

DIRECT PELLETIZATION

In this system, the spherical agglomeration that results from centrifugal motion of the blended material and solvent (organic, any other) forms the uniformly sized dense pellets. Agglomerates are produced into pellets by accidental collisions. A substantial amount of surface wetness and/or a significant amount of mechanical pressure created by centrifugal motion promote this agglomeration.

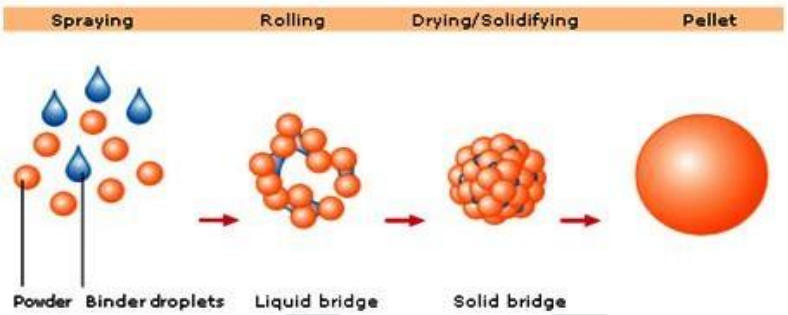

Fig.1.4: Principle of Direct Pelletization

This technology has several benefits including: 1. Effective procedure. 2. Product benefits (Compact, round pellets that are perfect for automatic dosing and even coating and pellets with diameters between 0.2 mm and 1.2 mm). The coexistence of many growth mechanisms which makes it challenging to manage the growth of the pellets is this technology's principal drawback. For this reason balling is rarely used to create pellets for medicinal applications.

II. COMPACTION

In the compaction process, a mixture of powder or granules is pressed together under pressure to create pellets of a specific shape and size. Mechanical interblocking increases the interparticulate contact and bonding forces like Vander-wall and electrostatic forces are used to make the adsorption layer effective.

COMPRESSION

It is a type of compaction technology in which the material is compressed mechanically to form pellets. The manufacture of tablets uses a similar formulation and process factors. In actuality, pellets created via compression are little more than tiny tablets with a roughly spheroidal shape. Theophylline's in-vitro release pattern was examined from produced pellets of the sustained release poly (lactic acid) with increasing

bovine serum albumin (BSA) load. They claimed that rather than polymer breakdown, the release mechanism was mediated by leaching through channels. It was discovered that annealing and BSA loading had an impact on the release rate.

Mechanism of pellet growth by compression

The particles in this method are prepared through blending or wet granulation followed by drying. They are then put under mechanical pressure which causes the pellets to develop into spherical shapes and mechanically interlock with one another.

EXTRUSION SPHERONIZATION

This method is used to create conventional, controlled or modified releases. In order to ensure a uniform coating and free-flowing properties a constant smooth surface with a restricted size distribution is needed. This method can also be utilized to create uniformly sized pellets or spheroids with high drug loading capacities. Extrusion Spheronization is a multi-step process that produces uniform-sized spherical particles that can be referred to as spheroids, pellets, beads or matrix pellets depending on the material and the procedure employed during pre-consolidation. In order to be broken down into regular fragments that may be shaped into pellets with a restricted size range, good extrudates must therefore possess the desired properties. When one wants to have dense, spherical pellets of uniform size and shape with high drug loading for controlled-release oral solid dosage forms with a minimal number of excipients, wet mass extrusion also known as cold-mass extrusion became known as the preferred method.

Extrusion

Applying pressure to a wet mass causes it to flow through precisely calibrated perforations in a screen or die plate of the extruder and then be further molded into tiny extrudate pieces. The liquid and powder material are combined to create a wet mass that is held together by capillary forces, solid bridges created by moisture loss, mechanical interlocking and to a lesser extent molecular forces. The mass finally breaks under its own weight as it moves through the extruder screen producing extrudates. The extrudates often have the same length. Extrudates must be sufficiently flexible to deform but too much plasticity could cause them to adhere to one another as they are collected and processed further in the spheronizer. The size of the openings in the extruder screen determines the diameter of the segments and the final size of the spheroids. Monitoring variables including feed rate, powder consumption, die temperature and compression chamber pressure is essential for getting reproducible results.

Spheronization

Spheronization is the process by which the tiny rods created by extrusion are transformed into spherical particles. The extrudates split into tiny cylinders with lengths corresponding to their diameters during the spheronization process. There are two mechanism put forth concerning how spheres form:

1. Frictional forces cause these plastic cylinders to curve into cylinders with rounded, dumbbell-shaped and elliptical particles that eventually form perfect spheres.
2. The cylinder is twisted which ultimately causes it to split into two separate pieces with a flat side and a round side. The flat side's edges fold together like petals to form the edges cavity as a result of the frictional and rotational forces.

The wet pellets need to be dried after spheronization in order to alter their size, density, hardness etc.

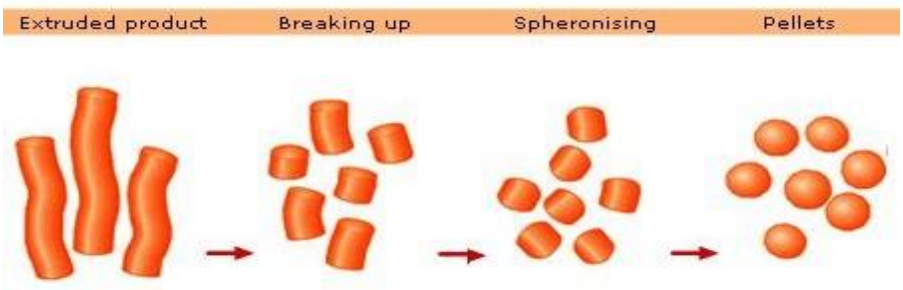

Fig.1.5: Extrusion-Spheronization Process

Table 1.2: Types of Extruder Systems

CATEGORY	TYPE
Screw feed extruder	Axial /end plate , Radial and Dome
Gravity / Roll feed extruder	Roatry cylinder, Rotary Gear and Radial
Sieve and Basket feed extruder	-
Piston feed extruder	RAM

III. LAYERING

Pelletization by layering involves placing successive layers of pharmaceutical substances from solution, suspension or dry powder on prefabricated nuclei that may be identical material crystals or granules, inert beginning seeds or crystals or granules of a different substance. The first components required for the layering process used to create pellets are the inert starting seeds over which the powdered medications have been deposited and maybe coated. Non-pareils are widely used in the laying process to prepare pellets as the initial substrate. Non-pareils main component, sucrose, has a number of well-known issues including negative impacts on diabetics and possible carcinogenicity. Most recently, microcrystalline cellulose (MCC) was used as a drug layering substrate.

SUSPENSION / SOLUTION LAYERING TECHNIQUE

On starter seeds, which could be inert materials or crystals/granules of the same drugs, successive layers of solutions and/or suspensions of drug compounds and binders are deposited. In order to achieve the proper viscosity during processing, all of the formulation's components are first dissolved or suspended in a suitable amount of application medium before being sprayed onto the product bed. If the drying conditions and fluid dynamics are ideal the sprayed droplets immediately impact the beginning seeds and distribute evenly on the surface. The formulation components would be held together as consecutive layers on the beginning seeds throughout the drying step that follows. Throughout this phase dissolved ingredients precipitate and create solid bridges. The procedure continues until the pellets reach the specified potency and the desired level of drug substance. In this the particle population stays constant, while the system's size and overall mass grow with time. The suspension layer is advised to use high viscosity binders to prevent drug particles from settling. API particle size for the suspension layering process should be between 10 to 50 μm. Consequently, the production of pellets has been effective when using traditional coating pans, fluid bed centrifugal granulators and Wurster coaters.

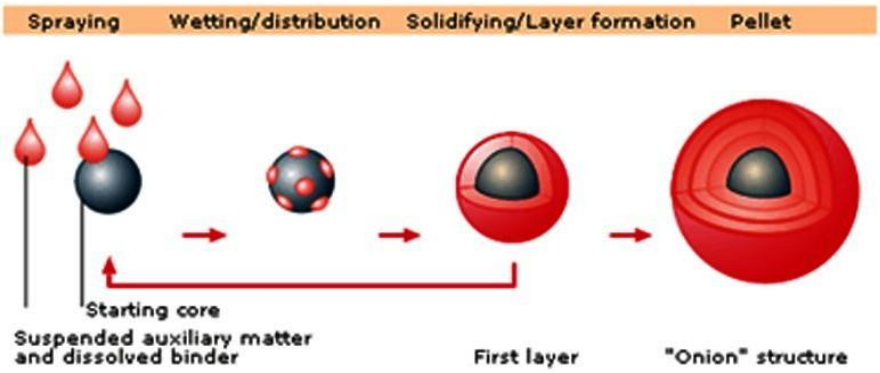

Fig. 1.6: Solution and suspension layering mechanism

Wurster coating process

The product chamber of a Wurster machine has a cylindrical partition as well as an aperture plate. High-velocity drying air can travel through the orifice plate, around the nozzle and through the barrier. The

particles enter the expansion chamber after leaving the partition. Here, the air's velocity is lower than the entrainment velocity. Particles land on the down bed-shaped partition's surrounding area. Particles from the down bed are drawn by suction into the space between the orifice plate and the wall. The height of the partition, which is the space between the orifice plate and the barrier, determines how quickly particles enter the spray zone. Since batch size is a significant variable, it is optimised for various batch sizes. Accessibility and nozzle blockage are severe drawbacks. Consequently, regular cleaning is required. Particle size, viscosity of the solution or suspension, binder content and solubility are critical factors that influence the process. This method is utilized when the drug load is minimal since it is not feasible economically to produce high-potency pellets from low solid content.

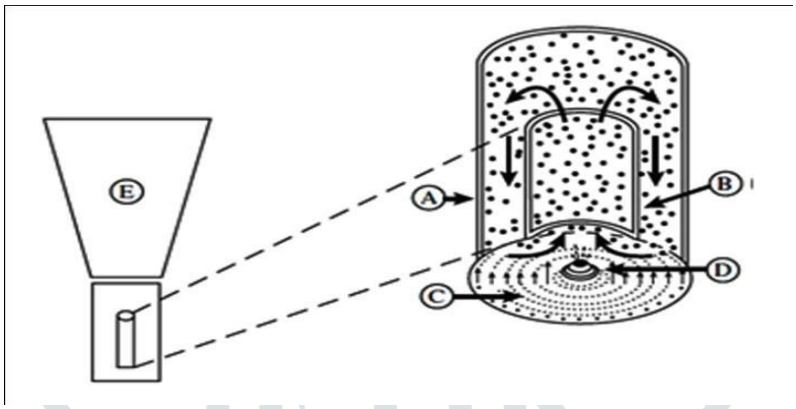

Fig. 1.7: Wurster Product Chamber and Process (A) Product chamber, (B) Partition, (C) Orifice plate, (D) Nozzle, (E) Expansion chamber

POWDER LAYERING TECHNIQUE

This uses a binding liquid to help add successive layers of powder and excipients on top of the starting seeds. The capillary forces generated in a liquid medium are what cause the tiny particles and nuclei to stick together. As long as the necessary pellet size is not achieved, the procedure continues. The main issue is fines generation at the conclusion of the process owing to friction between particles and between walls, which can be prevented by spraying the application medium. The final pellets moisture content must be carefully regulated. It is important to precisely distribute the powder at a set rate throughout the procedure and to do it in a way that maintains equilibrium between the addition rates of the powder and the binder liquid. Dust formation and over-wetting of the pellets are both possible with high powder addition rates and high liquid addition rates, respectively and neither the product's quality nor its yield is maximized.

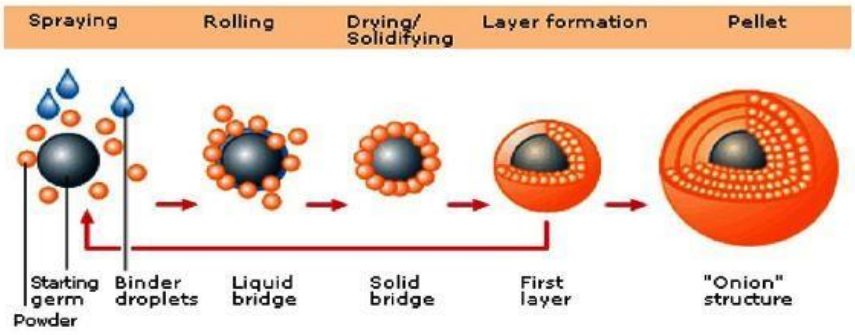

Fig. 1.8: Powder layering Mechanism

The coating pans (standard or conventional) and fluidized bed granulators bottom spray (Wurster coating and Continuous fluid bed), top spray and tangential spray (rotor pellet coating) are the most often used layering equipments.

IV. GLOBULATION / DROPLET FORMATION

The globulation process also known as spray drying and congealing, involves atomizing hot melts, solutions or suspensions to produce spherical particles or pellets. In globulation, atomization creates solid particles directly from the liquid phase by cooling or evaporating hot melts, solutions or suspensions before solidifying them. To maximize the rate of evaporation or congealing, the droplet size in both processes is kept small and as a result the particle size of the pellets generated is often quite small.

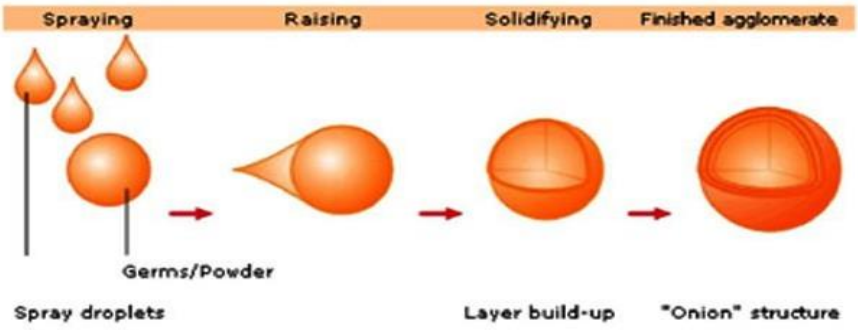

Fig. 1.9: Globulation Mechanism

SPRAY DRYING

To create dry, extremely spherical particles the drug entities are sprayed with or without excipients into a heated air stream. The application medium begins to evaporate as soon as the atomized droplets make contact with heated air. The viscosity of the droplets is continuously increased during the course of this drying process and at the end of each stage practically the entire application medium is driven off and solid particles are created. Spray-dried pellets typically have pores.

Mechanism of pellet formation

A hot gas stream contacts the atomized droplets during spray drying causing the liquid to begin to evaporate. This process involves simultaneous heat and mass transfer and is dependent on the temperature, humidity and transport characteristics of the air surrounding the droplet. When surface saturation conditions are attained and solid formation starts, more and more liquid evaporation occurs. These particles are first joined by capillary forces created by the liquid phase but solid bridges eventually take their place. This procedure is repeated until the desired size is reached. 1) Increased solubility & dissolution of poorly soluble drugs are two benefits of this method. 2) Generates homogenous, nearly spherical, homogeneous pellets. Particle size, size distribution, bulk density, porosity, moisture content, flowability and friability are all impacted by the design and use of a piece of equipment.

SPRAY CONGEALING / SPRAY CHILLING

Congealing is the process by which a melt changes from a flexible or fluid state to a stiff or solid one as a result of cooling. In order to create spherical congealed pellets, this method requires allowing the drug to melt, suspend or dissolve in hot melts of gum, fatty acids, waxes and other solids before spraying it into an air or steam chamber with temperature below the melting point of the formulation's components.

Mechanism of pellet formation

During spray congealing the atomized droplets are cooled below the melting point of the vehicle. The particles are held together by solid links formed by the congealed melts. Since solvent evaporation is generally prevented throughout the spray congealing process the particles are frequently non-porous, strong and retain their integrity when mixed. The design and development of pellet dosage forms should take into account the physical forces and fundamental growth principles that ultimately affect the strength and performance of pellets. For a spray congealing technique, the formulation components clearly defined, acute melting points or restricted melting zones are essential. Since there is no solvent evaporation throughout the process, the pellets are dense and non-porous. Because only the molten coating agent makes up the liquid phase, the congealing process necessitates a larger coating agent to active material ratio than does spray drying. One can make pellets for immediate release or prolonged release depending on the physico-chemical characteristics of the drug and other excipients.

V. CRYOPELLETIZATION

Cryopelletization, which uses liquid nitrogen as the solidifying medium produces pellets by enabling droplets of liquid formulation such as solution, suspension or emulsion to come into contact with liquid nitrogen at a temperature of -160°C. Due to the quick heat transfer that takes place between the droplets and the liquid nitrogen during the procedure the material being processed can be instantly and evenly frozen. The frozen pellets are moved into a storage container at a temperature of –60°C to come out before being dried in the freeze dryer. To get rid of any water or organic solvents the pellets are dried in standard freeze dryers. The apparatus comprises of a perforated-plate-equipped container below which is a reservoir of liquid nitrogen which has been immersed in a conveyer belt with transport baffles. The necessary residence time for freezing the pellets is provided by the conveyer belts variable speed. In the important procedure of cryopelletization droplet formation, equipment design and the relevant processing factors all play a role. Viscosity, surface tension and solids content are formulation-related factors. Droplet generation and size are also influenced by the liquid's surface tension. A surfactant is added which lowers surface tension and creates smaller particles. When pellets with a diameter of less than 2 mm are desired, the liquid nitrogen should be continuously agitated to avoid agglomeration. Initially utilized in the food industry to lyophilize bacterial solution this technology is now employed in the pharmaceutical sector to create drug-loaded pellets for both immediate and controlled release formulations. Drugs, fillers (lactose and mannitol) and binders (gelatin and PVP) are commonly included in immediate release formulations while crosslinked polymers of collagen derivatives are utilized in sustained release formulations. For the manufacture of 1 kg of pellets 3–5 kg of liquid nitrogen are typically needed.

VI. FREEZE PELLETIZATION

This method involves introducing droplets of a molten solid carrier and a dispersed active ingredient into a column of immiscible and inert liquid. In terms of pellet quality and process cost, the technology is superior to conventional pelletization processes since it uses fewer process variables. The pellets made with this method have a restricted size distribution and a spherical form. The pellets don't need to be dried because they are solid at room temperature. Droplets of molten solid carriers are added to the liquid column in which the molten solid is immiscible. Depending on their density in relation to the liquid in the column, these droplets can flow either upwards or downwards before solidifying into sphere-shaped pellets. Carriers are melted at a temperature 5–10° C over the melting point of the carrier solids depending on whether they are hydrophilic or hydrophobic in nature.

VII. MELT SPHERONIZATION

The technique known as "melt spheronization" requires heating a drug substance and excipients into a molten or semi-molten state which is then moulded using the right tools to produce solid spheres or pellets. Before being extruded at a specific temperature, the therapeutic component is first combined with the proper pharmaceutical excipients such as polymers and waxes. One or more of the formulation's components must melt at least partially at the extrusion temperature. With the use of a cutter the extrudate is divided into regular cylindrical segments. To create pellets of the same size, the segments are spheronized in a jacketed Spheronizer. Equipment like blenders, extruders, cutters (referred to as pelletizers in the plastics sector) and spheronizers are needed for the process. The procedure is similar to wet granulation but since the binder is molten it doesn't need to be liquified by water or another solvent. The interparticulate collisions that take place at random during the process result in vast particle size distributions in the pellets which is a characteristic of balling. In actuality the procedure is regarded as a variant of the balling process.

FORMULATION AIDS:

Active Pharmaceutical Ingredient

It is possible to create immediate release, sustained release pellets with a variety of uses in many fields using the various medications. As long as the size range is kept below 600 microns, pellets can be made with medications that can be administered subcutaneously and intramuscularly. These are known as micro pellets. Using pellet technology, GIT medications are frequently delivered to a specific location for controlled drug release.

Fillers

These are ingredients that are either water soluble or insoluble and are used to pellet formulations primarily to increase bulk. They can be selected based on physicochemical and pharmacological inertness and their range can be between 1-99%. In most cases, microcrystalline cellulose is employed for this. Also used are Avicel PH 101, Glyceryl mono stearate, Starch RX1500 and spray-dried lactose.

Binder

To bind powders and preserve integrity during pellet creation these adhesive compounds can be added to pellet compositions. The development of liquid bridges that hold initially followed by the liquid's evaporation, crystallization and formation of solid bridges is the binding mechanism. Commonly, binders between 2-10% w/w or v/v are utilized. Common ingredients include gelatin, HPC, PVP, sucrose and starch.

Granulating fluid

It retains moisture content and aids in the creation of wet material. The correct amount of granulating fluid must be used since adding too little results in the production of particulates during pelletization while adding too much leads to the agglomeration of pellets. As granulation liquids, alcoholic or hydro alcoholic systems, ethyl ether, diluted acetic acid and isopropyl alcohol have all been used in addition to aqueous forms. More cohesion is provided by the addition of binders.

Spheronizing Enhancer

They primarily aid in the spheronization and balling processes, which facilitate the creation of spherical pellets. They give the formulation binding qualities that are essential to pellet strength and integrity in addition to plasticity.

Plasticizers

By lowering the material's tensile strength and glass transition temperature, plasticizers increase the flexibility of polymers. Drugs and other excipients may occasionally be used as plasticizers. According to reports, some of the most frequently used plasticizer excipients include methyl paraben, glycerol, propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl, dibutyl phthalate and citrate derivatives like tributyl, triethyl, acetyl citrate, triacetin and castor oil.

Lubricant

They are introduced to lessen the coefficient of friction that exists between different particles or between the surfaces of the processing equipment and the particles. Additionally, they significantly contribute to the pellets smooth discharge from the spheronizer. Examples of lubricants frequently used in the production of pellets include glycerin, PEG, calcium stearate and magnesium stearate.

Separating Agent

In order to prevent pellets from sticking together due to the development of surface charges during the process, separating agents are substances that are adsorbed on the surface and encourage the separation of pellets into individual units during a pelletization process. They can be added initially to the formulation or externally during processing. It is typical to use pure talc.

Surfactant

Liquid bridges that bind the primary particles together are essential for the initial development and continued expansion of the pellets. Therefore, it's important that the liquid, which is often water, adequately wets the particles. Surfactants tend to weaken the liquid bridges and make the forming pellets friable by reducing the surface tension of the binding liquid. Sodium lauryl sulphate and Polysorbate are frequently utilized.

pH adjuster

The pH adjusters are additives used in pellet formulations to change the microenvironment of drug molecule. Typically, enteric coating is used to protect acid-labile drug from the pH conditions of the GIT. To keep the stability of the core within a desirable range, buffer systems may also be included in the

formulation of the core. Therefore, to modify the solubility of pharmaceuticals to suit a given process, appropriate buffer systems or dual buffer systems are included in pellet formulations. Most often, sodium carbonate is employed.

Release modifier

The drug release kinetics is changed by adding these substances to the drug and polymer. In order to improve drug release kinetics, formulations typically include water-soluble low molecular weight excipients, surfactants and disintegrants. In contrast, pellets often contain water-insoluble polymers, hydrophobic substances, inorganic salts and hydrophilic polymers that swell and/or form gels. Carnauba wax, shellac, ethyl cellulose and carbomers are examples of commonly used polymers.

Disintegrants

These are the compounds that encourage the disruption of solid dosage forms such as tablets, pellets, granules, capsules plug or any other agglomerated materials in the presence of liquid in order to regenerate the primary particles that were originally compacted or agglomerated to produce the dosage form.

Glidant

Because powder layering requires a carefully controlled powder feed rate to balance the simultaneous application of binder solution, it is critical that the powder not stick to the hopper's sides and create bridges. It is common to use talc.

Flavouring agents

These are important medications intended for children, elderly and those with bitter tastes (to mask taste). You can choose flavouring agents from artificial flavour oils, oleo resins, and extracts made from different plant components like leaves, fruits and flowers. You can use flavours individually or in combination. Examples of flavour oils include peppermint, cinnamon, nutmeg and spearmint, while fruity flavours include vanilla, cocca, coffee and citrus. Some examples of the fruit essence category are apple, raspberry, cherry and pineapple. The type and strength of the flavour will determine how much flavour is required to cover the taste. The formulations should include flavours up to 10% w/w, preferably. To increase the flavour intensity and the mouth-feel effect of the product, cooling substances such as mono methyl succinate and menthol may be used.

Sweetening agent

Some common examples of sweeteners such as liquid glucose, fructose, maltose, dextrose and glucose. However, these are useless for diabetic and health-conscious patients. Because of this, artificial sweeteners like saccharin and aspartame are employed, however they are carcinogenic. Rebiana, a natural sweetener made from the Stevia rebaudiana plant is also employed. Polyhydric alcohols such as sorbitol, mannitol, isomalt and maltitol can be used in combination as they additionally provide good mouth-feel and cooling sensation.

Coloring agents

Usually colouring compounds are employed to enhance the appearance and increase patient compliance. During the formulation pigments like titanium dioxide or FD & C approved colouring additives are either utilized in dry form or combined with the granulating fluid.

CHARACTERIZATION AND EVALUATION OF PELLETS:

Bulk density and tapped density

The prescribed amount of formulation is poured into the measuring cylinder, and the cylinder's volume is then calculated. The following formula is used to determine tapped density.

Bulk density = Weight of sample in g /Volume occupied by the sample in Ml

In order to obtain a constant volume, a predetermined amount of the formulation is transferred to the measuring cylinder and mechanically tapped till it is.

Tapped density = Weight of sample in g / Tapped volume in ml

It is easily determined using USP density equipment. An automated tapper can be used to estimate the bulk density of pellets but an air-comparison pycnometer or the solvent displacement method can be used to measure the real density of pellets. The packing qualities of pellets or spherical seeds which produce larger bulk densities because of small intraparticle porosities are shown by bulk density. The degree of pellet densification or compactness is indicated by true density.

Carr's compressibility index

The following equation was used to calculate the microparticles compressibility index (C.I.) or Carr's index value:

Carr's index = [Tapped density – Bulk density/Tapped density] X 100

A powder with a value below 15% typically has good flow properties, whereas a value exceeding 25% typically has poor flow capacity.

Hausner's ratio

Hausner's ratio of microparticles was calculated by using the following equation:

Hausner's ratio = Tapped density/Bulk density

Angle of Repose

The flow characteristics of solids have been described in terms of the angle of repose. An aspect of interparticle friction or the resistance to movement between particles is angle of repose. The surface of the powder or granule pile can only be angled away from the horizontal plane at this maximum angle. The graph paper is put on a flat horizontal surface and in the fixed funnel and free standing cone methods, a funnel is used with its tip set at a height, h, that is kept 2 cm above the graph paper. The following equation can be used to calculate the angle of repose with r representing the radius of the conical pile's base.

$$\theta = \tan^{-1} (h/r)$$

Where, θ is the angle of repose, *h* is the height and *r* is the radius.

Moisture content

Karl Fisher titration is used to measure the amount of moisture in a substance..

Content uniformity

Each batch's content uniformity (assay) is carried out in accordance with the instructions provided in the official pharmacopoeia.

Drug content

Both the final functional coated pellets and the drug-containing core were examined. Using a calibration curve, drug content was determined.

Surface morphology

In order to analyze the surface morphology and cross section of pellets scanning electron microscopy is performed. A small layer of platinum is sputter-coated onto the sampling pellets using a sputter coater (Polaron, UK) under an argon atmosphere and the pellets are then mounted onto an aluminium stub for SEM analysis. Optical microscopy is used to examine the microstructure of pellets.

Friability

The capacity to tolerate wear and tear during processing, transportation and storage is referred to as friability. For tablets friability is often recognized to be less than 0.08% while for pellets this value may be higher due to the higher surface area/unit and subsequent involvement of frictional force.

Table 1.3: Overview of Friability Testing Methods for Pellets

Method	Description
Erweka Friabilator, Roche Friabilator	Rotating drum like Friability testing Apparatus
Turbula	Turbula blender (closed test system)
Born Friabimat	Horizantal shaker (closed system)
Laboratory coating apparatus	Fluid bed device (open system)

Hardness

The Kahl Pellet hardness tester can be used to determine the hardness of pellets however it may not be accurate.

Tensile Strength

Utilizing tensile equipment with a 5 kg load cell, it is calculated. The pellets radius was noted and they were continuously strained till failure. Additional load is noted. Applying the value for the failure load and the radius of the pellets, the tensile strength is calculated.

Porosity

The porosity of the pellets affects the dissolved drug's capillary activity which in turn affects how quickly the pharmaceuticals are released from the pellets. Mercury porosimetry can be used to quantitatively determine the pellets porosity. Additionally, the porosity of the pellets can be assessed qualitatively using SEM and image analysis as well as quantitatively on a rare occasion utilizing optical microscopy. The Washburn equation yields the pore radius.

$$R = 2\,\gamma\,[\cos\theta] / P$$

Where; $\gamma = 480$ ergs/cm^3, $\theta = 140^o$, r = pore radius, p = mercury-intrusion pressure.

As a result, mercury porosimetry is a highly well-established technology with repeatable findings for determining the porosity of pellets.

Floating behavior

100 ml of the simulated gastric fluid (SGF, pH 2.0) was added with the proper amount of the floating microparticles and the mixture was mixed using a magnetic stirrer. Filtration was used to separate the layer of buoyant microparticles. Filtration divided the particles in the sinking particulate layer. Both kinds of particles were dried in a desiccator until they reached a constant weight. Both microsphere fractions were weighed and the weight ratio of the floating particles to the total of the floating and sinking particles was used to calculate buoyancy.

Disintegration time

In the case of pellets with immediate release, it is important. Utilizing a sieve with a 710 mm mesh size at the top and bottom of the tube, the reciprocating cylinder method (USP) is applied.

Dissolution test

In a dissolution apparatus of the basket type described in the United States Pharmacopoeia (USP) XXIII, the release rate of floating multiparticulate was assessed. A hard gelatin capsule (No.0) was filled with a weighed amount of floating multiparticulate equal to 50 mg of medication and placed in the basket of the dissolution rate equipment. A rotational speed of 100 rpm was used to maintain the dissolving fluid at 37 ± 1°. The drug release investigation was conducted in ideal sink circumstances. At every 30 minute interval, 5 ml samples were taken put through a 0.25 µm Millipore membrane filter and then their concentrations were determined using the LC/MS/MS technique.

APPLICATIONS OF PELLETS:

1. Pellets with a controlled release for encapsulations.
2. Enteric coated pellets with delayed release or sustained release.
3. Multiparticulate oral sustained release delivery method that floats.

4. Using Natural Polysaccharides prepare, evaluate, and optimize Multiparticulate System for Colon Targeted Drug Delivery.
5. Pellets with a multi-unit erosion matrix.
6. Pellets for unique tableting purposes.
7. Pellets with an immediate release for sachets.
8. Multiparticulate colon targeted drug delivery system using a pH and bacteria combination approach.
9. Due to their huge surface area, pellets particularly for oral medicines solve the challenging taste masking problem while preserving a high degree of bioavailability. Antibiotics (Clarithromycin, Roxithromycin and Cephelexin) as well as bitter-tasting anti-inflammatory medications can now be manufactured in products with excellent patient compliance.
10. The compacted tablet dosage type requires that separate tablets be taken but the pellet dosage just requires that one capsule be taken.
11. Due to their good flow characteristics pellets can easily be used to fill capsules, allowing the manufacturer to alter the dosage without having to reformulate the product.

CONCLUSION:

Today pelletization represents an efficient pathway for novel drug delivery in the scope for different oral immediate or controlled delivery systems. Pelletization has a unique place in the pharmaceutical sector due to its straightforward design, great efficiency at manufacturing spherical pellets and quick processing. Since, due to the several disadvantages of traditional techniques for pelletization there is need of development of novel techniques which are efficient as well as cost effective.

REFERENCES:

1. Virendra K.D, Bhaskar C, Kar A. Development and evaluation of floating pulsatile multiparticulate drug delivery system using aceclofenac as a model drug. International journal of pharmacy & life sciences, 2012; 3(6): 1787-1796.
2. Gandhi B, Baheti J, Middha A. Development and in vitro evaluation of multiparticulate controlled drug delivery system. International Journal Of Pharmaceutical Innovations, 2012; 2(5): 11-18
3. Bipin R.G, Bhatu P.B. Ankit VK. Development and in vitro evaluation of multiparticulate system using novel coating material for controlled drug delivery system. International Journal of Pharmacy and Pharmaceutical Sciences, 2011; 3(3): 96-99.
4. D"Souza A, Sutar K.P, Sutar P.S. The use of chronotherapeutics in design of pulsatile delivery systems a review. Journal of Pharmaceutical And Scientific Innovation, 2012; 1(2): 50-55.
5. Jeevana J.B, Jyosna D. Multiparticulate drug delivery systems using natural polymers as release retardant materials. International Journal of Pharmacy and Pharmaceutical Sciences, 2010; 6(10): 61-65.
6. Asha P, Nilam B, Patel K.R. Colon Targeted Drug Delivery System: A Review System. Journal of Pharmaceutical Science and Bioscientific Research, 2011; 1(1): 37-49.
7. Vishal S, Shoaib A, Ramesh K, Mahesh K.K. Oral multiunit pellet extended release dosage form: A review. International Current Pharmaceutical Journal, 2013; 2(10): 177-184.
8. Parul B.P, Avinash S.D. Multiparticulate approach: an emerging trend in colon specific drug delivery for Chronotherapy. Journal of Applied Pharmaceutical Science, 2011; 1(5): 59-63.
9. Anantha N.R, Bairi A.G. A Review on Recent Advances in Oral Pulsatile Drug Delivery. Journal Of Advanced Pharmaceutical Sciences, 2011; 1(1): 132-145
10. Dey N.S, Majumdar. Multiparticulate Drug Delivery Systems for Controlled Release. Tropical Journal of Pharmaceutical Research, 2008; 7(3): 1067-1075.
11. Shailesh L.P, Mahesh. K.B. Controlled release approach to novel multiparticulate drug delivery system. International Journal of Pharmacy and Pharmaceutical Sciences, 2012; 4(3): 757-763.
12. Deepak S, Sanjay K.S, Manish J. A review on multiparticulate floating drug delivery system. International Journal of Pharmaceutical, Chemical and Biological Sciences, 2014; 4(1): 201-207.
13. Haritha V.V. Multiparticulate drug delivery system: pelletization. American Journal of PharmTech Research, 2012; 2(1): 81-87.
14. Jawahar N, Patel H.A. Multi Unit Particulates Systems (MUPS): A Novel Pellets for Oral Dosage Forms. Journal of Pharmaceutical Science & Research, 2012; 4(9): 1915-1923.
15. Veena M.C, Senthil Kumar S.K, Parthiban S. Pelletization technique in drug delivery system a review. International Journal of Pharmaceutical Development & Technology, 2013; 3(1): 13-22. 28

16. Anshuli S, Sandhya C. Multiparticulate drug delivery systems: pelletization through extrusion and spheronization. International Research Journal of Pharmacy, 2013; 4(2): 6-9.
17. Vaphare A.M, Banerjee S.K, Gadhave M.V. Pelletalization techniques: a review. Asian Journal of Pharmaceutical Research and Development, 2014; 2(3): 103-114.
18. Shivani M.U, Mukesh R.P. Recent advances in pellets and pelletization techniques for oral sustained release drug delivery. World Journal of Pharmaceutical Research, 2015; 4(3): 629-656.
19. Kundu S, Srinivasan G. A review on solid oral dosage form of antiepileptic drugs by pelletization techniques. International Journal of Pharmaceutical Innovations, 2013; 3(6): 19-32.
20. Kammili L, Senthil V, Varun R.L. Pelletization technology: a quick review. International Journal of Pharmaceutical Sciences and Research, 2011; 2(6): 1337-1355.
21. Anwar K, Rishabha M, Pramod K.S. Multi unit drug delivery system- A brief review of pelletization technique. International Journal of Pharmacy, 2014; 4(3): 234-237.
22. Pathik kumar J.M, Tanvee M.D. Multiple unit pellet system a new path for drug delivery. International Journal of Universal Pharmacy and Bio Sciences, 2013; 2(4): 401-415.
23. Anwar K, Rishabha M, Pramod K.S. Multi Unit Drug Delivery System a Brief Review of Pelletization Technique. World Applied Sciences Journal, 2014; 31(12): 2137-2140. .
24. Kumar V, Mishra S.K, Lather A, Singh R. Multiple unit dosage form pellet and pelletization techniques: an overview. International Journal of Research in Ayurveda & Pharmacy, 2011; 2(1): 121-125.
25. Deb R, Ahmed A.B. Pellets and pelletization techniques: a critical review. International Research Journal of Pharmacy, 2013; 4(4): 90-95.
26. Jagan M, Venkatesham A, Chandra Mohan E, Vasu K, Kiran K.J. Pelletization Techniques for Oral Drug Delivery. International Journal of Pharmaceutical Science and Drug Research, 2009; 1(2): 63-70.