Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Review Article

Pellets as Drug Delivery System

JAMADAR SARITA, SHIRSATHKRUSHNA, MAHAJAN HITENDRA*

R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur (MS) 425 405

ARTICLE DETAILS

Article history:
Received on 2 April 2019
Modified on 10 May 2019
Accepted on 14 May 2019

Keywords:
Pellets,
Mutiparticulate,
Spheronizer,
Extrusion.

ABSTRACT

Pellets are agglomerates of granules or core powders and blend of active pharmaceutical ingredients with pharmaceutical excipients. Pellets size ranges from size 0.5 to size 1.5 mm. The process of pellet formation known as pelletization. In relation to pharmaceuticals, pellets offer high degree of flexibility in design and development of oral dosage form. This review outlines theory of pellet formation, mechanism of drug release from multi-particulates, and factors affecting on multiparticulate system. Various pelletization techniques used for manufacturing of pellets includes agglomeration, direct pelletization, compression, extrusion–spheronization, layering technique, droplet formation, freeze pelletization, hot-melt extrusion technology (HME) and Pellet coating include fluidized bed processor. Also give idea about Characterization and application of pelletization techniques.

INTRODUCTION

Conventionally, pellets have been reported as agglomerates that are manufactured from various types of raw materials. Pellets are agglomerates of granules or core powders and blend of active pharmaceutical ingredients with pharmaceutical excipients. [1] Pellets size ranges from size0.5 to size 1.5mm. Pellets decreases local irritation of the mucosa cause due to different irritant drugs. A pellet helps to reduce patient to patient variability because only lesser amount of drug given in single pellet. Drug safety and effectiveness enhance by pelletized product. There is no issue of dose dumping seen in pelletized product. [2] Pellets classified into intended dose strengths without changing process or formulation parameters. Pellets are helpful for releasing incompatible bioactive agents at the same site or different site inside gastrointestinal tract. [3] Multiparticulates when taken orally they are release in gastrointestinal tract and they are less affected by gastric emptying time compare to single unit dosage form. Pellets are simply passing through pyloric sphincter because it's little size. As result of this in gastrointestinal transit time both intra and inter subject deviation falls down.

Author for Correspondence:
Email: hsmahajan@rediffmail.com

Also they properly distributed in gastrointestinal tract and increase absorption. Design and development of pellets have good flexibility in pharmaceutical dosage form. There is no problem occurs in packaging of pellets due to their good flow ability. So weight variation in tablet and capsule is avoided. Equal fill weight and Reproducible weight of capsules and tablets achieved in pelletized product. Identical spherical shape and less surface area-to-volume ratio produce by pellets. Because of this accurate film coating can be given to pellets. Various types of active agents can be manufactured and blended in pellets in single dosage forms. This helps to two or more active pharmaceuticals ingredient, which are chemically compatible or incompatible release at the targeted site in gastrointestinal tract.

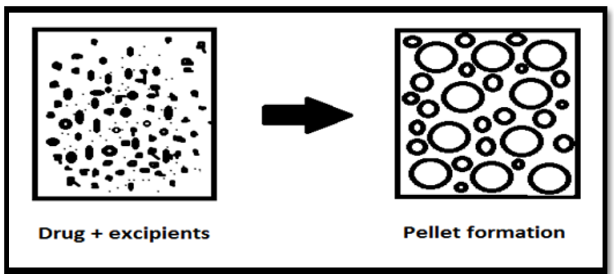

Figure 1: Pellets Formation

Pellets having different release rates of same drug can be given in single dosage forms. For pellet preparation different techniques are

available. Non-uniformity in the size of the pellets and less drug loading is some limitations of layering processes. Extrusion-spheronization, cryopelletization, freeze pelletization and hot melt extrusion techniques use in recent years for manufacturing spherical pellets. [4]

Historical Development

After 20th century various companies utilized pelletization processes to formulate particles of appropriate sizes and shapes. In early 1950s sustained release drugs for longer period of time developed so pharmaceutical industry developed interest in pelletization process.[5] In 1949 a most important innovation happened in pharmaceutical companies. SmithKline and French pharmaceutical scientist know the possible uses of candy seeds in sustained release formulation as well as begin the formulation of small drug particles filled in capsules. In 1964 SmithKline and French patented pelletization techniques which provided sustained release pellets available in size ranging from 0.25-2.0mm and commercially marumerizer or spheronizer was established. Japan developed new machine had capacity to produced more amounts of spherical pellets in less time. In USA marumerizer and variation of it consequently patented. Pharmaceutical process applications process for the developing of pellets were firstly produced in literature in the early 1970 and process has been topic of intensive research from more than four decades. In 1970s growth of controlled release technology takes place that have benefits over single unit dosage form. [1]

Pelletization

Pellets defined as spherical agglomerate ranging from size of 0.5 to 2.0 mm and having less intra agglomerate porosity i.e. 10% approx and this process of size enlargement know as pelletization. The pellets have both therapeutic as well as technical advantages. Technical advantages includes more strength, decrease friability, increase flow ability because equal spherical shape and size, large physical consistency of spherical shape, homogeneous packing properties, better quality for coating application and narrow particle size distribution also have many therapeutic advantages such as decrease gastric irritation, dose dumping inhibited and increase absorption of drug due to large gastrointestinal surface. The pellets compressed into tablets and can also fill into hard gelatin capsule. Compare to single unit dosage form in modified release pellets of powder filled capsule dosage form have uniform distribution of drug. From many years, Suspension layering, powder layering or Solution layering techniques used for manufacturing of pellets. But above processes have some limitations like less drug loading and unequal size of pellets obtained. Formulation of uniform size of pellets containing high drug loading with help of extrusion spheronization is target of many pharmaceutical scientist. Freeze pelletization, cryopelletization and hot melt extrusion techniques used in recent years for formulation of spherical pellets. [6] Granulation is size enlargement process having porosity approx 20 -50% porosity and produce agglomerates from 0.1 to 2.00mm in size whereas pelletization is a size enlargement process which having porosity approx 10% and produce agglomerates from 0.5 to 2.00mm. [7]

Advantages of Pellets

- Pelletizations have better flexibility in design and development of dosage form.
- Flow characteristics in formulation development enhance by pellets.
- Pellets flow freely and there is no problem occurs in packaging of pellets so reproducible and equal fill weight of capsule is obtained.
- Dose dumping is less seen in pellets.
- Accumulation of drug decreases by pellets this is beneficial for irritating drugs. [8]
- In gastrointestinal tract different release profiles at different sites can be achieved with help of pellets.
- Film coating avoid deterioration of drugs occur by moisture or oxidation.
- Pellets having less than 2-3 mm size so it quickly pass through pyloric sphincter.
- Pellets easily fill in capsules.
- Enhances patient compliance because pellets aid in reducing variation in whole gastrointestinal region. [9]
- The division of incompatible drugs is bitterly adjusted by pelletization.
- Differentiation in gastric emptying rate as well as intestinal transit time decrease by pellets.
- Taste masking difficulty is avoided in pelletization.
- Smaller particle size of pellets increase surface area of pellets this help in better distribution.
- Powder dusting is avoided in chemical industry. [10]

Disadvantages of Pellets

- Pellets fill in capsule so cost of product is increases.
- Film coating on pellets destroy at time of tableting of pellets.
- The pellets available in size ranges from 0.05 mm to 2 mm. [11]
- Very rigid pellets give problem to compressed pellets into tablets so they are encapsulated in hard gelatin capsules.
- Highly sophisticated and specialized equipment, required for pelletization so cost of manufacturing is increases.
- There is various process and formulation parameters maintain at time of manufacturing pellets. Therefore this is too complicated process. [3]

Desirable Properties of Pellets

Uncoated Pellets

- Pellets have smooth surface and uniform spherical shape.
- Pellets have size from 0.5 to 2.00mm.
- Good flowability.
- Pellets have more physical strength and integrity.
- Less friability and Better hardness.
- More bulk density.
- Coating properties is simple and superior.
- Packing of columns and beds is reproducible.

Coated Pellets

- All of the above properties maintain.
- Active ingredients quantity in final dosage form easily maintain within limits.
- Pellets have desired drug release properties. [12]

Theory of Pellet Formation and Growth

Stages of Pellet Growth

Sastry and Fuerstenau proposed the nucleation, layering, abrasion transfer, coalescence, crushing, onion skinning, snow balling and crushing steps which occurs in mechanism of pellet formation.

Nucleation

Nucleation is the starting phase of agglomeration. Loose and porous structure is created from nuclei or small size of agglomerates once the primary particles are wetted with aid of binding liquid droplet. In pendular state primary particles are bounded by liquid bridges. Coalescence happens in the primary particles with the Formed nuclei or wetted primary particles result in vanishing of fines. This is the characteristic of nucleation phase. Under the effect of the externally given mechanical forces consolidation experience in resultant nuclei and also obtained equate strength to stop additional breakdown by impact forces and will be result in growing into larger agglomerates. For improvement in the size of the formed nuclei transition phase is followed by nucleation. Layering and coalescence are transition region affecting development of growth mechanisms.

Coalescence

In this by random collision of well formed nuclei form Large-sized particles known as coalescence and on the nuclear surface little more moisture requires for mechanism. Although the number of nuclei is increasingly reduced the total mass of the system remains constant during this step. During coalescence total mass of system is constant but number of nuclei is slowly reduced. [13]

Layering

Successive deposition of materials on already formed nuclei explains layering process. The dry or moist material deposited over nuclei and slow growth rate happen on growing nuclei. Small amount of material is added at any specified time. As time passes uniform particle size increases even number of particles remain unchanged. Total mass increases in it.

Abrasion Transfer

This involves transfer of material from one particle to another without varying in directions. So there is no change observe in the total number or mass of the particles. As condition changes particles undergo continuous changes that lead to continuation in transfer of material.

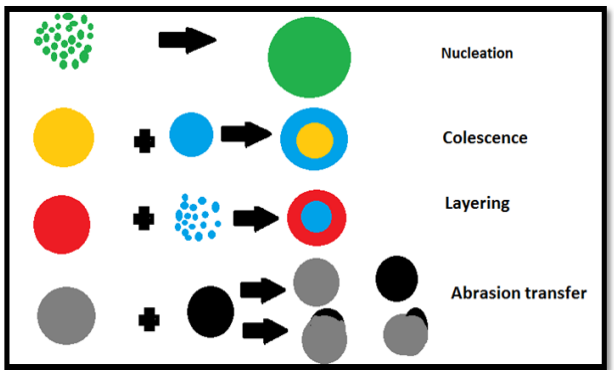

Figure 2: Pellet growth mechanism [8]

Size Reduction

Three size reduction mechanisms have indirect effect on the elementary growth mechanisms, that includes layering and also to some amount

coalescence. Due to attrition rupture and sudden breakage particles undergo size reduction. Particles coalesce to form larger size particles upon collision if particle posses adequate surface plasticity. [14]

Mechanism of Drug Release from Multi-Particulates

Mechanism of drug release from multiparticulates occurs by following ways:

Diffusion

In diffusion system into the inner of the particle water gets diffuse when it comes in contact with gastrointestinal tract. Across the release coat to the outside drug solution diffuses and dissolution of drug takes place. [15]

Diffusion controlled systems are classified into reservoir systems and matrix systems.

Reservoir Systems

It is also called as membrane-controlled drug delivery system. In this reservoir system the core having a drug should enclosed with and encapsulated in definite shape of rate controlling membrane having specific thickness. By membrane diffusion the core drug will dissociate and dissolve in its surrounding medium. The core of reservoir have spherical, cylindrical or disc like shape. Core is bounded to non-biodegradable polymer. The diffusion rate of drug release in blood stream controlled with compatibility and physicochemical properties. On reservoir thickness drug release rate depends. The core drug in reservoir system is independent on P^H. Parameters used in reservoir systems are pore former polymer for film coat, solubility and drug load. Ethyl cellulose (Surelease or Aquacoat), acrylic copolymers (EudragitRL30D, RS30D and NE30D) and water soluble polymer like HPMC and polyethylene glycol these polymers used for membrane in wurster coater.

Matrix Systems

In this system drug is equally distributed all over polymer. The drug release from polymer matrix is uniformity seen in drug release from matrix. Dose dumping not observed in matrix system. Drug dissolved up to or below saturation level of solubility in polymer in this system. Compared to reservoir system matrix system has lower permeability. The matrix system is conventional, bilayer or trilayer. Finely powdered drug is dissolved up to or below saturation solubility with pre polymer in matrix system. Then this mixture is transferred in mould. Barrier layer over the core not formed in this system. [16]

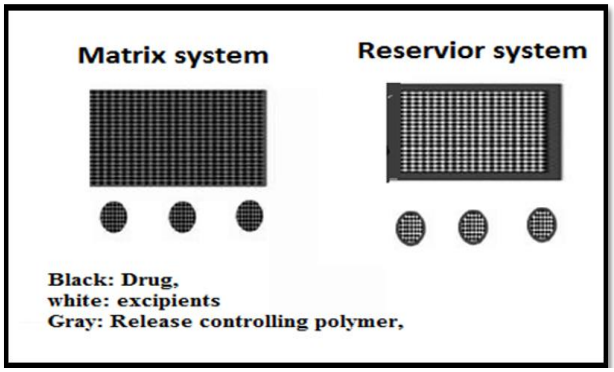

Figure 3: Schematic presentation of matrix system and reservoir system [17]

Erosion

Some coatings can be developed to erode gradually with time, results in releasing of drug occurs.

Osmosis

An osmotic pressure can be built up inside the inner side of the particle; this allows water to enter in system. Through the coating drug is release from system. [15]

Factors Affecting on Multiparticulate System

Physical Properties of Material

Pellets are a particular form of granulates identified by a very regular, less porosity, spherical shape, and smooth surface. Pellet size ranges from 0.2 to 2mm.Pellets classified into homogeneous and heterogeneous according to drug distribution inside pellets.

Type and Composition

The multiple unit compositions consist of enteric coated pellets as well as minimum one tablet excipients which have consequence on formulation.

Size of the Pellets

Both compaction characteristics as well as drug release through the compact pellet affected by size of pellets.

Shape of the Pellets

Various methods used to determine sphericity which has effect on flowability.

Porosity of the Pellets

The compaction property is affected by porosity of pellets. So this affects the polymer coat reliability in compression step.

Density of the Pellets
Density of pellets has effect on Gastric residence time.

Elasticity
Pellet composition related to elasticity. The strongness of pellet core depends on plasticity.

Coating
The quantity of polymer coating has impact on protecting the polymer film reliability in compression step. In common, a thicker coating can avoid damage compare to thinner one.

Cushioning Excipients
To protect the integrity of coated pellets in tablet preparation excipients with protective (cushioning) characteristic included. Hard tablets with less friability and constant drug release profiles observed when there is addition of 60-70% cushioning granules into multiparticulates system take place [18].

Moisture Content
Pellet growth affected by moisture content. Moisture in the wet mass carry cohesiveness to the powder carry by wet mass so it can bee spheronize as well as extracted to provide spherical shape. Agglomeration of pellets happened because of high moisture content. Spheronization is one of the successful method of pelletization techniques due to more amount of water in the surface of pellets and also low moisture content cause generation of fine with more difference in size distribution.

Rheological Properties
Flow ability depends on rheological condition of wet mass in extruder. Possible rheological state causes better flow ability to extrude the wet mass difference in rheology system. Improper and non uniform extrusion happens because of inappropriate rheology.

Solubility of Excipients and Drug in Granulating Fluid
Soluble drug get dissolved in granulating liquid. This enhances the amount of liquid phase which causes extra wetting of agglomeration of pellet sand which result in increase in wetting liquid that causes increasing plasticity but produce sticky mass.

Composition of Granulating Fluid
For granulating liquid, water or alcohol mixture, water, Ethyl Ether, Isopropyl alcohol and dilute acetic acid is used. Millili and Schwartz, said that a water present in at least of 5% of granulation liquid to form pellets containing the ophylline and Avicel pH (101). In various powders to liquid ratio other researchers used dilute acetic acid and water. For granulation step with aid of dilute acetic acid instead of demineralized water, mass fraction can be enhanced up to 100%.Hydroxy Propyl Methylcellulose gelatin, Poly vinyl pyrrilodine and Eudragit including aqueous polymer dispersion, is used for moistening liquid.

Speed of the Spheronizer
Hardness, accurate size, density and sphericity of pellets are affected by speed of the spheronizer. High speed result in more sphericity, smooth surface, less friability and increase crushing strength.

Drying Technique and Drying Temperature
Proper shape, size and flow of pellets are achieved by accurate drying technique and drying temperature. It must be reproducible and constant in all the batches. Difference in pellet's shape, size and flow cause to variation in physicochemical properties of final dosage form such as improper filling and variation in weight which affect the therapeutic effectiveness of the delivery system. Larger particle size distribution causes difference in the dose of drug delivery. Changes in shape changes compressibility as well as pellets flow ability.

Extrusion Screen
The superiority of the extrudate or pellets is significantly affected by the properties of the orifice of the screen. If orifice dimension increases it leads to increased mean pellet size. The more is orifice depth less with the existence of water at the extrudate surface, enhances the extrusion force, also had a negative impact on shape as well as granulometric distribution. [12]

Balling or Agglomeration or Agitation
Powders on addition of correct amount of liquid or when powder subjected to more temperature are produced spherical particles with tumbling action or continuous rolling. Spherical agglomeration classified into liquid- liquid and melt- induced agglomeration.

Liquid-Induced Agglomeration
In powder liquid is added during or before agitation step. The agglomerates or nuclei form when powder comes in contact with liquid phase. At first they are bound by liquid bridges which

are obtained from any additional dissolved material from the hardening binder. To other adjacent nuclei form collide and coalescence to form bigger nuclei or pellets. At this step coalescence is replaced by layering small particles adhere to very larger particle and size of latter increases until pelletization is completed.

Table 1: Different formulation aids used in the pelletization process

Sr. No.	Excipient	Function	Examples
1.	Filler[18]	To increase bulk property.	Lactose, cellulose, starch, phosphate salts, mannitol, maltose, maltodexin, sorbitol, sucrose
2.	Binder[17,18]	To bind powders and maintain integrity of pellet formulation.	Dextrin, dextrates, dextrose, cellulose derivatives, gelatin, gums, sucrose, ydroxypropyl methyl cellulose.(HPMC), Hydroxy propyl cellulose(HPC), Gelatin, microcrystalline cellulose(MC), polyvinylpyrrolidone(PVP), starch, sucrose
3.	Lubricants[17,18]	To decrease friction between die wall and material mix either during ejection phase or the compression process	Calcium stearate, polyethylene glycol (PEG), Magnesium stearate. Glycerin,
4.	Separating agent[17,18]	To promote separation of pellets into individual unit	Purified talc Kaolin, , silicon dioxide
5.	Disintegrant[17,18]	This help to break up the compacted mass of solid dosage form in fluid.	Polyvinylpyrrolidone phthalate (PVPP), agar, bentonite, carboxymethylcellulose, sodium alginates, starch, magnesium stearate, hydrogenated castor oil, Alginate, cross carmellose sodium. glycerylester, polyethylene, glycol, sodium stearyl fumarate, stearic acid,
6.	P^H adjuster[17]	To maintain microenvironment of drug molecules in pellets. It aid to protect acid labile compounds from acidic environment by enteric film coating.	Sodium carbonate
7.	Release modifiers[17]	These agents incorporate with drug and polymer to alter drug release kinetics.	Ethyl cellulose, carnauba wax, shellac, and carbomers.
8.	Surfactants[8,17]	To improve wettability and solubility also to increase dissolution rates to reduce surface tension	Polysorbate, sodium lauryl sulphate
9.	Spheronization enhancer[17,19]	To formulate spherical particle	Microcrystallinecellulose(MCC), Sodium carboxymethylcellulose(CMC)
10.	Glidants[17]	To improve flow properties during layering of pellets	talc
11.	Plasicizers[17,18]	To decrease tensile strength and glass transition temperature it helps to improve flexibility of polymers.	Dimethyl, diethyl and dibutyl phthalate, tributyl, triethyl, acetyl citrate, triacetin and castor oil
12.	Colourant[17,18]	To improve appearance and increase patient compliance	FD&C and D&C blue, green, orange, red, violet, yellow, E 100 to 180Titanium dioxide
13.	Flavouring agent[17,18]	It helps to improve flavor strength. These agents are important for pediatric geriatric and bitter tasted drugs.	Sweet -Berry, Vanilla. Sour - Citrus Fruits, liquorice, Root beer, Raspberry Salt - Butter scotch, Apple, Apricot, Vanilla, Peach Bitter- Wild Cherry, Walnut, Chocolate, Mint, Passion fruit.
14.	Granulating fluid[17]	It helps formation of wet mass and maintains moisture content.	Ethyl ether, dilute acetic acid, isopropyl alcohol
15.	Polymers[17]	Drug release from the oral dosage forms controlled by polymers.	Microcrystalline cellulose and hydroxyl propyl methyl cellulose. Eudragit RL 30D, RS 30D, NE 30D. Eudragit RS PO and RL PO. Methocel-E5 (HPMC) or AMB, Eudragit L 30D-55.

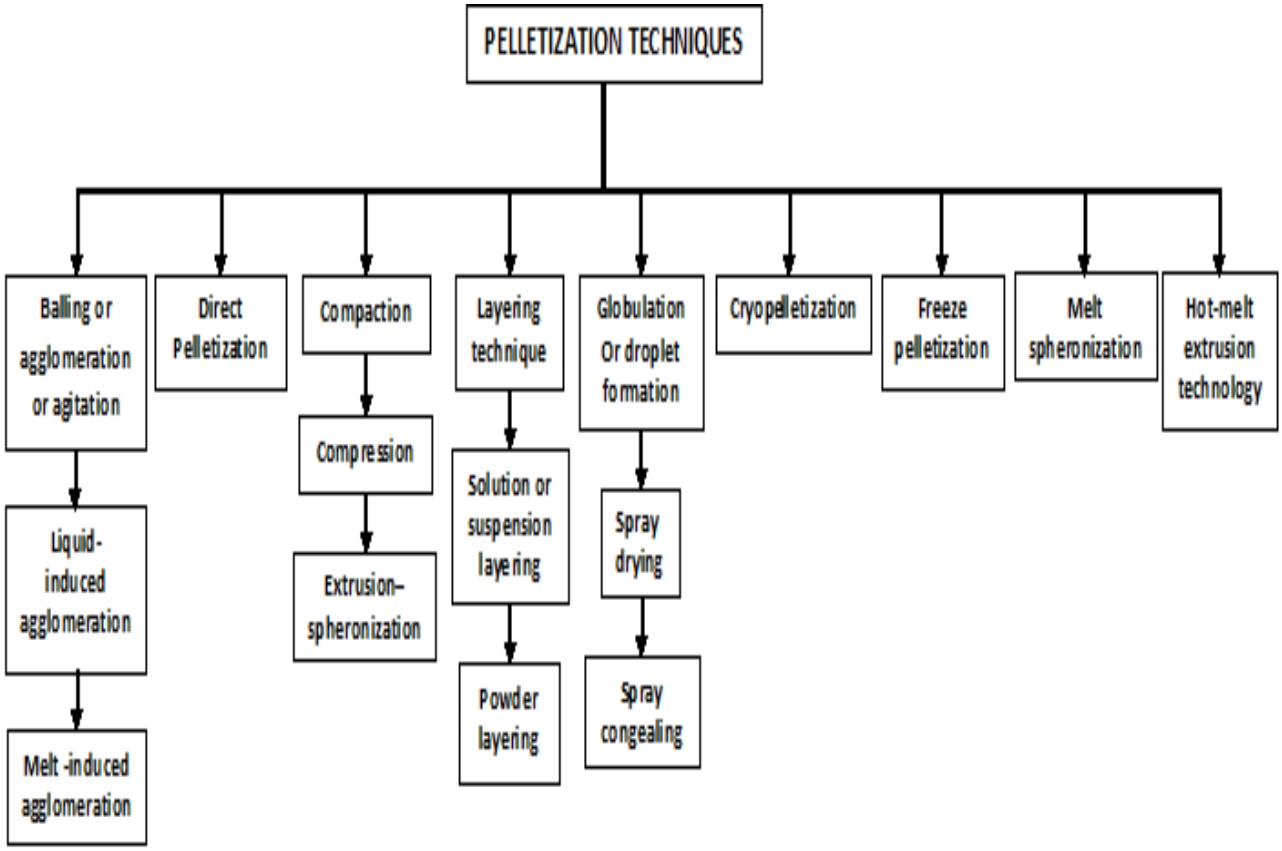

Figure 4: Pelletization Techniques

Balling or Agglomeration or Agitation

Powders on addition of correct amount of liquid or when powder subjected to more temperature are produced spherical particles with tumbling action or continuous rolling. Spherical agglomeration classified into liquid- liquid and melt- induced agglomeration.

Liquid-induced Agglomeration

In powder liquid is added during or before agitation step. The agglomerates or nuclei form when powder comes in contact with liquid phase. At first they are bound by liquid bridges which are obtained from any additional dissolved material from the hardening binder. To other adjacent nuclei form collide and coalescence to form bigger nuclei or pellets. At this step coalescence is replaced by layering small particles adhere to very larger particle and size of latter increases until pelletization is completed.

Melt -Induced Agglomeration

Melt induced agglomeration has similarity with liquid-induced agglomeration except that in melt-induced agglomeration material is melt. So congealed material without go through the formation of solvent-based liquid bridges form the pellets. Particles may go through both coalescence as well as nucleation at different speeds and produced different sizes of nuclei mixed with the bigger pellets. As an effect spherical agglomeration leads to form pellets with a large particle size distribution[20].

Direct Pelletization

In fluidized bed equipment and high shear mixers direct pelletization is mainly performed. In this process formation of homogeneous pellets takes place which have microscopically uniform structure and core cannot detected in it [12].

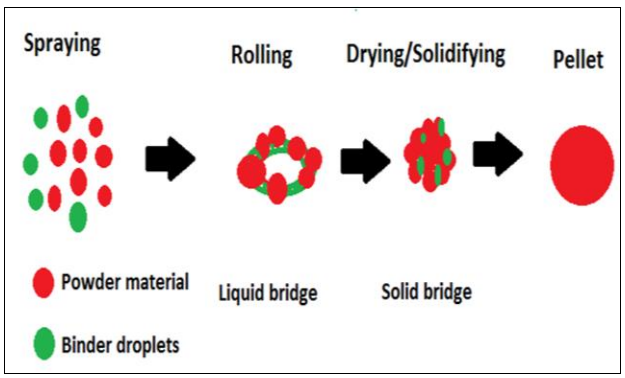

Figure 5: Principle of Direct pelletization technique[21]

Compaction

Drug particles or granules are formed by compaction technique which is type of pressure agglomeration with aid of mechanical force with or without preparation aids for the generation of pellets having well-defined sizes and shapes. The process can be divided into compression and extrusion.

Compression

Particles that are penetrated through wet granulation and dry blending rearrange themselves and formed closely packed mass. Particles are opposing each other with strong force at more pressure it results in plastic and elastic deformation generation. In extrusion–spheronization, initially with help of binding liquid dry powder mixture is agglomerated then it is further processed in the extruder to form high density extrudates. With aid of spheronizer in extrusion– spheronization technique, extrudates are finally converted to pellets[22].

Extrusion–Spheronization

The extrusion–spheronization technique is the most popular technique in the pharmaceutical field for pellet formation. Extrusion–spheronization process was initially reported by Conine Hadley and Reynolds, This technique involves four steps:

i. Preparation of wet mass (granulation)
ii. Convert wet mass into cylinders (extrusion)
iii. Breaking of extrudate and convert rounded particles into spherical particles (spheronization)
iv. At final step drying of spherical pellets occurs.

Galland et al. said that due to wetting process material is seen in a state in which water content connected porosity. In spheronization hydro-structural state maintains and shapes to pellet given. Textural characteristics to product provided due to drying operation.

Advantages of extrusion–spheronization over other techniques includes modification in physical characteristic of active ingredient and excipient take place, high bulk density, low hygroscopicity, high sphericity, having narrow particle size distribution, smooth surface, capacity to incorporate more levels of active components without forming excessively large particles and free from dust.

Steps and Equipment Used in Extrusion–Spheronization

Granulation

Preparation of plastic mass of material takes place in Granulation process. This step is used to perform mixing of powder blend and granulation liquid. A planetary mixer, sigma blade mixer or high shear mixer used in granulation step. In this step physical properties of wet masses and prediction of formation and quality of pellet take place. This has advantage in formulation development. Wet granulation has major role in extrusion-spheronization. Twin screw extruder allows wet granulation to run continuously while high shear mixture used in conventional batch process. Lee et al. investigated this process and compared this process with high shear mixer by considering granule properties.

Extrusion

In this formed plastic mass undergoes extrusion. In this pressure given to mass until it flows outside through orifice for production of extrudes. Depending on preparation method of extrusion, physical properties of material to be extruded and particles changed after extrusion process. Extrusion is performed with aid of extruders such as sieve, screw and roll basket and ram extruders

Spheronization

In this step cylindrical shaped particles i.e. extruded converted into equal length and then transformed into spherical shapes pellets. Due to plastic deformation particles undergo spherical shape. Extrudates initially broken to approximately equal length all three dimensions of agglomerates shape find out and nearly equal diameter spheres are formed. Both frictional and rotational forces concerned in spheronization process. On rotating plate extrudates are charged and converted into small segments by contact in friction plate. Collision between particles and wall occurs. In mechanically fluidized bed, friction plate produced mechanical energy produced by friction causes the extrudate material to deform slowly in spherical shape particle.

Drying

Drying is final step in extrusion- spheronization. In oven or fluidized bed pellets are dried at room temperature or at elevated temperature[22].

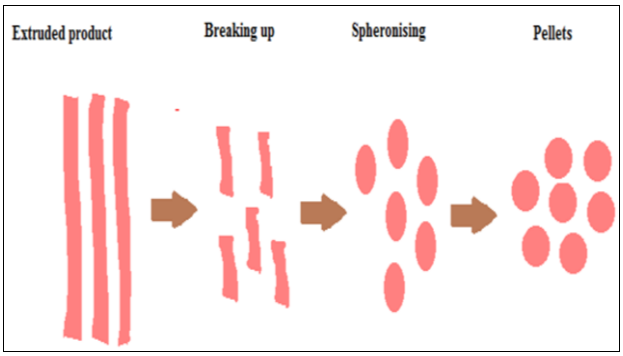

Figure 6: Principle of Extrusion and spheronization process [23]

Layering Technique

Layering technique involves powder layering and solution or suspension layering.

Solution or Suspension Layering

In solution or suspension layering powder feed material and other components are suspended or dissolved in suitable solvent. This prepared solution or suspension sprayed on the surface of core and spread equally as soon as it collides on its surface. Spraying is conducted with drying phase. This allow dissolved material to get crystallized so between core and coating layer of drug substance as well as consecutive layers of polymers and drug the formation of solid bridge happens. Drying method has impact on functional and structural characteristic of pellets. Due to increase pore diameter fluidized bed drying enhance dissolution also due to increase porosity of pellets lyophilized pellets increase dissolution[24].

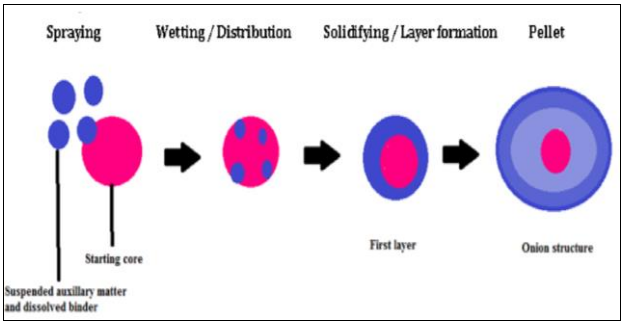

Figure 7: Principle of solution and suspension layering process [13]

Powder Layering

In pelletizer the seed for ex. Sugar spheres are charged on its surface. On pelletizer surface the powder feed material i.e. drug and excipient and binder liquid is sprayed tangentially. On the surface of seed powder is properly distributed. With aid of roll movement, it confirms spherical shape of pellets. It involves successive deposition of drug and other component. Also on the surface of starting core with aid of bridging liquid drug particles attached to starter core aid of binding liquid which spread on it. This resulted in liquid bridge formation. After this liquid bridge replaced by solid bridge which come from a binder in solvent or from any other material that has capacity to soluble in medium. It is needed to delivered powder in proper rate that should be in equilibrium with binder liquid application rates overall the process. Improper rate of powder leads to dust generation or over wetting which causes decrease yield and quality of product[24].

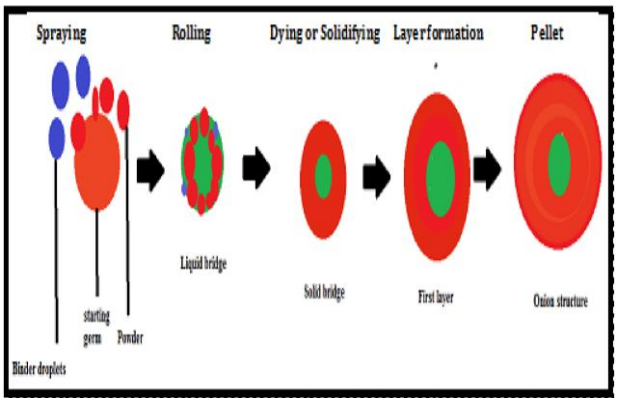

Figure 8: Principle of powder layering process[13]

Globulation or Droplet Formation

Spay drying and spray congealing process occurs in globolation or droplet formation. The droplet size in globulation or droplet formation is keep small which increase rate of evaporation or congealing and also to keep small particle size of formed pellets[23].

Spray Drying

In spray drying for formation of dry spherical particles suspension or solution form of drugs sprayed into hot air stream controlled release system is formed by this technique to improve bioavailability of less soluble drugs.

Spray Congealing

Inspay congealing drug is melted then it dissolved or dispersed in hot melt of waxes, fatty acids or gums. The formed dispersion is sprayed into air chamber. The air chamber temperature maintains at lower melting point compare to formulation components to obtained spherical congealed pellets. Both immediate as well as sustained release effect of pellets obtained spray congealing technique [10].

Cryopelletization

In cryopelletization for the preparation of pellets initially droplets of emulsion liquid formulation like emulsion, solution and suspension contact with liquid nitrogen at -160°c.Liquid nitrogen plays role as solidifying medium .The process permits freezing of material. Rapid heat transfer between liquid nitrogen and droplets for formulating a specific quantity depends on the temperature of suspension or solution and solid content. In conventional freeze dryer pellets are dried to remove organic solvents and water[25].

Freeze Pelletization

Freeze pelletization novel and simple technique for formulating spherical matrix pellets including active ingredients. In inert and immiscible column of liquid molten solid carrier and dispersed active ingredient as droplet is introduced quality of pellets and process cost offer more advantages of this technique over other techniques. Narrow size distribution and spherical pellets produced by these techniques. If pellets are solid at room temperature so drying is not necessary. Into column of liquid molten solid carriers as droplets are introduced in which molten solid is immiscible. Depending on density and liquid in column droplets can more in upward and downward direction carrier may be available in hydrophilic and hydrophobic in nature and melted at 5-10°c temperature more than melting point of carrier solids. According to density of molten solid carrier two types of equipments are used. Column temperature maintained in between 0 to -40°c with aid of cooling mixture i.e. dry ice as well as acetone. Active agent and other excipient are mixed with molten carrier for formation of solution or dispersion using needle or nozzles formed solution or dispersion introduced as droplets in the column of liquid and it dropped from particular height therefore droplets remain intact as they fall into liquid column. Depending on size of pellets size of needle gauze decided i.e. 16 to 31.Carrier which is solid at room temperature and has melting point less than 100c is suitable for freeze pelletization. Aim of this temperature is to avoid degradation of active moiety.

Freeze Pelletizer I

In these from top portion of column molten solid carrier is introduced. Comparatively density of liquid used in column is kept less than density of solid carrier. At bottom portion carrier get solidify. Hydrophilic carrier like polyvinyl alcohol, polyethylene glycol and low melting point sugars such as maltose and dextrose are used. Low density oil like vegetable oil silicone oil and mineral oil these are useful liquids for column in freeze pelletizer I.

Freeze Pelletizer II

In these from bottom portion of column molten solid carrier is introduced. Comparatively density of liquid used in column is kept more than density of solid carrier. At top portion carrier is solidify. Hydrophobic carriers of low density like glyceryl palmitostearate glyceryl monostearate and glyceryl behenate are used as solid carriers. Water, glycerin, ethyl alcohol, liquid polyethylene and glycol used. These are suitable high density hydrophilic liquids for column is used for freeze pelletizer I[4].

Melt Spheronization

Melt spheronization is technique in which for production of solid spheres pellets drug substance and excipients are converted into semi molten or molten state with help of suitable equipment. The different parts of equipment used in this process such as extruder cutters (known as pelletizers in the plastics industry) spheronizer and cutters. The drug substances and excipients such as waxes and polymers are blended at suitable temperature in such way melting of at least one or more formulation components. The extrudate material cut into equally cylindrical segments with aid of cutter. In jacked spheronizer segments are spheronized to formulate equal sized pellets. According to properties of formulation components pellets that have immediate release effect can be formulated in single step. Mono sized pellets prepared by melt spheronization[26].

Hot-Melt Extrusion Technology (HME)

This technique involves pumping raw materials by using rotating screw with increase temperature through die to form equal shape product. Mixing and agitation occur with rotating screw to form deaggregation of suspended particles in molten polymer. More uniform dispersion formed. It is evaluated that 40% new molecular entities have less bioavailability due to less aqueous solubility. Hot- melt extrusion helpful to increase bioavailability of low water soluble drug with preparation of molecular dispersion.

Advantages

Better stability at different P^H, no need of additional film coating because drug release is

diffusion controlled, degradation of many drugs avoided due to water or solvent not used.

Disadvantages

High melting point binders need high melting temperature, less melting point binders risks in softening or melting of binder, for extruder cleanness maintenance is complicated so good manufacturing issues i.e. (GMP) issue occur, suitable plasticizer amount and type requires because it has directly effect on stability and dissolution of product.

Process of Hot-Melt Extrusion

Process occurs in following steps:

1. Firstly plasticizing or melting of solid material then molten material shaping and solidification of material in various shapes.
2. Initially material feed into extruder plasticizing or melting solid material in which drug substance is dispersed into thermal carrier has low melting point wax or polymers(high to low molecular weight polymer selected) such as e.g. Vinyl polymers (polyvinylpyrrolidone-vinyl acetate, polyvinylpyrrolidone,); acrylates; polyethylene oxide; cellulose derivatives copovidone and polyethylene glycol.
3. Mechanism of drug release includes erosion (HPMC) and diffusion (carnauba wax and ethyl cellulose.)
4. Mass flow through die in extruder shape given to molten content and it converted to equal cylindrical segments.
5. At high temperature extrudes spheronize and this spherical extrudes deform by softening and helping to form uniform spheroids.
6. To get intended shape of spheroids it solidified which remove from die and downstream processing. To end of barrel endplate die connected determines the extruded product shape.

Factors Affecting Hot-Melt Extrusion Technique

Product Parameters

Nature and composition of extrudate material, glass transition temperature physical and chemical properties, tensile strength, melting point and glass transition temperature.

Process Parameters

Rate of Feed, load of motor, melt pressure, construction of the extruder die and extruder screw speed barrel temperature operating parameters.[17]

Coating of Pellets

Coating process involves spraying coating material on moving bed of pellets with aid of heating air for evaporation of solvent.

The important objectives of coating of pellets are as follows:

- It avoids inactivation of drugs in stomach.
- It increases patient compliance.
- It helps to prolong dosing interval.
- It enhances appearance of dosage form.

Film Coating

In this coating pellets are surrounded by thin layer of polymer it includes spraying a coating solution containing polymer solvent colorants and plasticizers. On the moving pellets coating solution sprayed followed by drying process. Drying helps for removal of solvent which leaving behind deposition of film coating material around pellets.

Various types of coating are as follows:

1. Immediate release
2. Modified release
3. Extended release
4. Enteric coating

Extended Release

In this type drug is dissolved for longer time to achieve slow and constant release of drug into bloodstream. Compared to immediate release formulation of drug less frequent intervals occur in extended release.

Enteric Release Coating

For oral medication this release is beneficial which prevent acid degradation of drug in stomach.

Pellets Coating Process

To modify drug release from pelletized drug delivery system coating provided to pellets[24].

For Pellets Coating Following Equipments Are Used

Conventional Pan System

The Standard Coating Pan

In standard coating pan angularly on stand circular coating pan mounted with help of motor. the pan is rotated on its horizontal axis. The hot air passed into pan and onto surface of bed. Then hot air is exhausted by ducts located through the front of pan. Coating material solution sprayed on the bed surface.

Perforated Coating Pan

Perforated pan coaters having high coating capacity and efficient drying occur in it. It performs both film and sugar coating processes automatically. Acela-Cota, Driacoater, Hi-Coater, and Glatt coater, these are four different types of coater available. In this with aid of spraying nozzles which located inside drum coating solution applied on surface of rotating bed of pellets[21].

The Fluidized Bed Coater (Processor)

The fluidised bed processor is mostly used equipment in which coating drying pelletizing and granulation process occurs. In this top spray coating bottom spray coating and Tangential spray coating (Rotor pellet coating) take place.

Top Spray Coating

Top spray coating is used for powder granulation. In the flow of heated air particles are fluidized which is introduced into product container through base plate. Binder solution is sprayed trough nozzle into fluid bed from top against air flow. Air volume is maintained at this stage. Particles travel in upward direction in the flow of air under controlled of drying process. It is suitable for taste masking as well as hot melt coating application.

Bottom Spray Coating

In this pellet suspension coating or sugar coating or film coating occurs to achieved controlled release action of active ingredients. From the bottom screen of container and coating column hot air flows. It will form the siphon age principle. Convection is generated through the strong force from bottom to top. The pellets fall down and then again sucked into the coating column. Bottom spray gun helped for pellets spray upward to achieve proper coating.

Tangential Spray Coating: (Rotter Pellet Coating)

Pellets sugar or film coating, powder coating or suspension coating perform by tangential spray coating. Firstly the Cores are positioned on turntables, between the turntables and granulation area in which hot air are blown upward. Core is roll onto turntable due to air at same moment on the rolling cores through the spray gun and pump coating solution sprayed. Drying and coating of cores, layer after layer until the similar action get the intended granule size or coating thickness. This all process occurs in tangential spray coating[27].

Parameters Consequences Fluidized Bed Coating Process

Feed Particle Dimension

Ideal particle size of pellets should be required for coating and fluidization. The improper fluidizing observe if particle size is very little or over large. Too small particle size of pellets causes twinning and agglomeration of pellets.

Coating Solution

In previous stage for preparation of coating solution organic solvents are used. At low temperature and low fluidization gas rates organic solvents allowed fast coating. Due to working environment and safety measures stringent regulation on industrial hygiene organic solvents use decreases.

Spray Gun Parameters

An ideal solution provided by atomization of the coating solution to the problem of introducing the solution to the bed this is helpful to solve the local wet quenching problems which may be due to large coating droplets which forms excessive wetting of particles. There is risk of defluidization observe because of wet quenching happens in a fluidized bed processor when bottom spray is used. Modification occurs in bottom spraying design to move particles from the spraying zone as early as possible. Different types of nozzles used for bottom spraying. Excessive spray drying and elutriate of the coating material occurs easily in top spraying. This may be recommended for enhancing risk of wet quenching linked with submerged spraying. The particles wet ability as well as coat drying changes with various coating materials. Nozzle diameter has effect on coating. If load in fluidized bed coater increases so there is need to increase diameter of nozzles. Bigger nozzle diameter used for large viscous solution.

Particle Circulation

Fluid bed coater had inner cylinder i.e. draft tube fitted in fluidized bed coater to expand the particle movements inside the bed. At the bottom center of distribution plate spray nozzle is loaded. The movement of coated particles is in equal directions of fluidizing gas. The congregation causes draft movement of particle which help to increase partical circulation but decrease all assimilation.

Temperature and Wetness Distribution

Mass as well as heat transfer occurs for the particles to be coated in fluidized bed coating

process. The wetness and temperature in the rest of bed in the spraying section there was an inverse proportion between the size of agglomerates and variations between the outlet and inlet wet bulb temperature.

Coating Thinners and Consistency

Coated particles used for controlled release action the quality of coating must be strictly maintained most advantageous operation condition required for particular seed and coating material. The ability to monitor consistency and thinness of coating within individual particle and between individual particles is crucial in evaluating the suitability of any process condition position.

Dewdrop Magnitude

To control in the application of polymeric film coats the crucial processing characteristic is required. This mean dewdrop magnitude the polymeric solution or dispersion must contact all surface equally and evaporate quickly to obtained accurate, reliable and thin film formation on the surface of substrate. The shearing action of pressurized air on an emerging column of polymer liquid results in dewdrop formation. Dewdrop sprayed onto tablet bed from the atomizing nozzle onto surface of substrate and in conical pattern into the fluidized air where they spread and then evaporate to their solid constituents. Some dewdrops contact the multiparticulates and dry film formation or complete coalescence occurs. Large droplets causes over wetting. This results in sticking of multiparticulates in pans or loss of fluidization in air suspension coater or agglomerates form. So there is need to control diameter of droplets for optimization of process. Dewdrop size of liquid spray determined by atomization air pressure delivered to nozzle spray.

Table 2: Characterization of pellets

Sr. No.	Evaluation parameters	Significance
1	Crushing strength[20]	To determine the strength or load required to break pellets.
2	Density of pellets[20]	It gives idea about filling and packaging characteristic during capsule manufacture and tablet compression.
3	Angle of repose[29]	To know flowability of pellets.
4	Hausner's ratio[29]	To know flowability of pellets.
5	Carr index[29]	To know flowability of pellets.
6	Moisture content[17]	To see where agglomeration or fines are formed.
7	Content uniformity[17]	To Determine the active ingredient in each dosage form.
8	Drug content[17]	To determine therapeutic effect of drug.
9	Scanning electron microscopy[17]	To study Surface morphology and cross section of pellets.
10	Specific surface area[20]	It is important in the absorption and the diffusion of the excipients and the active constituents. Also the drug release is influenced by the surface area.
11	Particle Size distribution[20]	Particle size has significant influence on the release kinetics and the compactivity.
12	Friability[6]	To study Pellets flake off during handling, shipping, storage coating process and other unit operations thereby resulting in formation of dust.
13	Hardness[16]	Hardness testing is necessary task for handling, shipping, storage and coating.
14	Stability study[29]	The physical properties of pellets as well as the *In vitro* release, profile of the drug was found to be a function of the different storage conditions.
15	Porosity[17]	To study drug release rate of pellets by affecting the capillary action of the dissolved drug.
16	Disintegration Time[6]	Disintegration apparatus is used to determine disintegration time; it is a very vital feature for immediate release pellets.
17	*In Vitro* Dissolution Studies[17]	To study the release behavior of different formulations in different dissolution media as well as to found a co-relation between in vitro release and in vivo absorption for the modified-release pellets.

Table 3: Application of pelletization techniques

Sr. No.	Drug	Material used	Application	Technique used
1	Diltiazem hydrochloride[30]	Ethyl cellulose(EC) and hydroxylpropyl methylcellulose phthalate(HPMCP)	To develop controlled release pellets	Fluidized bed processor
2	Lansoprazole[31]	Methacrylic acid co-polymer	To prepare delay release pellets	Fluidized bed processor
3	Duloxetine Hydrochloride[32]	Aqoat AS-LF, Eudragit L30D55 and HPMCP-HP55	To prepare delay release pellets	Fluidized bed processor
4	Potassium Chloride[33]	Hydroxyl propyl methyl cellulose. HPMC and Ethyl cellulose (EC)	To formulate Extended release pellets	Fluid bed granulator
5	Metformin hydrochloride[34]	Methacrylic acid copolymers (Eudragit_ L30D-55, Eudragit_ NE30D)	To prepare sustained-release drug-loaded pellets	Centrifugal granulator
6	Aceclofenac[35]	Ethyl cellulose N50 and hydroxy propyl methyl cellulose E5.	To formulate sustained-release drug-loaded pellets	Fluidized bed processor
7	Ketoprofen[36]	Ethyl cellulose(EC)	To achieve Colon specific drug delivery	Powder layering technique
8	Piroxicam[37]	Eudragit L30D-55	To minimize gastrointestinal adverse effects.	Powder layering technique

Spray Velocity

Spray velocity is very crucial and important processing factor in fluidized bed processor. In spray velocity the polymer solution or coating dispersion is sprayed on solid substrate. Aqueous film coating requires uniform application of polymeric dispersion to solid substrate and simultaneously well-controlled evaporation of water from substrate. To decide the drying ability of coating dispersion the air quantity temperature and dew position will consider. [28]

CONCLUSION

Now a day different pelletization techniques developed for manufacturing of pellets. Pelletization has scope for various oral immediate or controlled delivery system. Due to its simple design, fast processing, high efficacy and safety; it has found a special place in the Pharmaceutical industry. Compare to granulation process pelletization technique produces more spherical particles and has many advantages over it. Pellets helpful for avoidance of dose dumping and decrease gastric irritation. Pellets formulation given by oral route in the form of tablet and capsules. Hot-melt extrusion technique has provided a new, wider platform for producing spherical pellets of drugs which are unstable or have compatibility issues in existence of solvents also extrusion spheronization represents an efficient pathway for novel drug delivery system to formulate suitable dosage forms of drugs that will have more patient compliance.

REFERENCES

[1] Ahir AA, Mali SS, Hajare AA, Bhagwat DA, Patrekar PV. Pelletization technology: Methods and applications-a review. Research Journal of Pharmacy and Technology. 8(2):131.

[2] Bathool A, Vishakante GD, Khan MS, Gupta VK. Pelletization as a key tool for oral drug delivery: A review. Journal of Pharmacy Research. 4(10):3282-6.

[3] Srinivasarao K. SLJKaRNR. Pellets and pelletization techniques: a review International journal of research in pharmacy and chemistry [review]. 2017; 7(2):141-7.

[4] Kandukuri JM, Allenki V, Eaga CM, Keshetty V, Jannu KK. Pelletization techniques for oral drug delivery. Int J Pharm Sci Drug Res. 2009; 1(2):63-70.

[5] Hirjau M, Nicoara AC, Hirjau V, Lupuleasa D. Pelletization techniques used in pharmaceutical fields. Farma. 4(3):4.

[6] Rahman MA, Ahuja A, Baboota S, Bali V, Saigal N, Ali J. Recent advances in pelletization technique for oral drug delivery: a review. Current drug delivery. 2009; 6(1):122-9.

[7] Supriya P, Rajni B, Rana AC. Pelletization techniques: A literature review. International Research Journal of Pharmacy. 3(3):43-7.

[8] Lavanya K, Senthil V, Rathi V. Pelletization technology: a quick review. International Journal of Pharmaceutical Sciences and Research. 2(6):1337.
[9] KUMAR D CT. Advancement in the field of pelletization technique for novel drug delivery systems. Advance research in pharmaceutical and biologicals an international peer reviewed journal for pharmaceutical and alleed research. [review]. 2018; 2(2):911-9.
[10] Reeta Chandak KS. Pelletization technique in drug delivery system-a review. American journal of pharmtech research. [review]. 2014; 4(2):71-86.
[11] Rashmitha NM SC, Tamizh MT. Pellets and pelletization: review World journal of pharmacy and pharmaceutical sciences. [review]. 2018; 7(10):1570-80.
[12] Ramu S RG, Balaji M, Kondala KR. Multiple unit drug delivery system: Pelletization Techniques. American journal of advanced drug delivery. [review]. 2013; 1(1):11-21.
[13] Vaphare AM, Banerjee DS, Gadhave MV, Gaikwad DD. Pelletalization techniques: a review. Asian Journal of Pharmaceutical Research and Development.103-14.
[14] Jawahar N, Anilbhai PH. Multi unit particulates systems (MUPS): a novel pellets for oral dosage forms. Journal of Pharmaceutical Sciences and Research. 4(9):1915.
[15] Dey NS, Majumdar S, Rao MEB. Multiparticulate drug delivery systems for controlled release. Tropical Journal of Pharmaceutical Research. 2008; 7(3):1067-75.
[16] Chaudhari P, Sonawane R, Deore P. Pelletization techniques: Novel approach for drug delivery. The Pharma Innovation. 6(2, Part A):3.
[17] Bhairy SR, Habade BM, Shivram KG, Vidula RG, Yogita KG, Sagar KK. Pellets and pelletization as multiparticulate drug delivery systems (mpdds): A conventional and novel approach. International Journal of Institutional Pharmacy and Life Sciences. 5(4).
[18] Ozarde YS, Sarvi S, Polshettiwar SA, Kuchekar BS. Multiple-Unit-Pellet System (MUPS): A Novel Approach for Drug Delivery. Drug Invention Today. 4(12).
[19] Kumari MH, Samatha K, Balaji A, Shankar MSU. RECENT NOVEL ADVANDCEMENTS IN PELLET FORMULATION: A REVIEW. International Journal of Pharmaceutical Sciences and Research. 4(10):3803.
[20] Shelke T, Aher U, Patel E. Recently used technologies in Pellet Formulation-A Review. Pharma Tutor. 5(7):22-30.
[21] Sandeep D, Battu S. An overview on multiparticulate drug delivery system: Pellets.
[22] Muley S, Nandgude T, Poddar S. Extrusionâ€“spheronization a promising pelletization technique: In-depth review. Asian journal of pharmaceutical sciences. 11(6):684-99.
[23] Dalvi HD, Khutle N, Pawar P, Kunwarpuriya A. Review on pelletization: techniques, characterization and applications.
[24] Yadav N, Verma A. Pharmaceutical pellets: a versatile carrier for oral controlled delivery of drugs. Indian J Pharm Educ.50:S146-60.
[25] Vats T, Shah N, Shah S. Pelletization techniques: a review. Journal of Pharmaceutical Science and Bioscientific Research (JPSBR).5(3):247-8.
[26] Saini V, Bhatt JK, Ahuja N, Gupta VB. Emerging trend in pelletization techniques. Asian Journal of Chemistry. 2007; 19(7):5652.
[27] Ghorpade IP PV, Mahanavar SM. Pellets: as pharmaceutical dosage form. Journal of advanced drug delivery 2016; 3(3):1-6.
[28] Saini V. Fluidized bed processing for multiparticulates. J Chem. 2009; 2(2):447-50.
[29] Gupta AM, Shivhare UD, Suruse PB. Different Aspects of Pellets Formulation and their Evaluation. International Journal of Pharmaceutical and Phytopharmacological Research. 4(6):331-6.
[30] Prasad MB, Vidyadhara S, Sasidhar RLC, Balakrishna T, Trilochani P. Development and evaluation of diltiazem hydrochloride controlled-release pellets by fluid bed coating process. Journal of advanced pharmaceutical technology & research. 4(2):101.
[31] Petchimuthu S, Narayana N, Subashini U. Formulation and characterization of lansoprazole DR pellets by fluid bed coating technique. Int J Biol Pharm Res. 4:977-86.
[32] Kuang C, Sun Y, Li B, Fan R, Zhang J, Yao Y, et al. Preparation and evaluation of duloxetine hydrochloride enteric-coated pellets with different enteric polymers.

asian journal of pharmaceutical sciences.12(3):216-26.
[33] Kumar CP, Rao KM, Saravanan D, Padmavathy J, Kumar CP, Lakshmi IA. Formulation and evaluation of potassium chloride extended release capsules. J Pharm Res. 4:2529-32.
[34] Hu L-D, Liu Y, Tang X, Zhang Q. Preparation and in vitro/in vivo evaluation of sustained-release metformin hydrochloride pellets. European journal of pharmaceutics and biopharmaceutics. 2006;64(2):185-92.
[35] Ravella VN, Nadendla RR, Kesari NC. Design and evaluation of sustained release pellets of aceclofenac. Journal of Pharmacy Research. 6(5):525-31.
[36] Subhabrota M, Souvik R, Subhadeep C. Preparation and gamma scintigraphic evaluation of colon specific pellets of ketoprofen prepared by powder layering technology. Daru: journal of Faculty of Pharmacy, Tehran University of Medical Sciences. 19(1):47.
[37] Varshosaz J, Tavakoli N, Serri A. Preparation and in vitro characterization of piroxicam enteric coated pellets using powder layering technique. Pharmaceutical development and technology. 2009; 14(3):305-11.