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PELLETS AND PELLETIZATION AS MULTIPARTICULATE DRUG DELIVERY SYSTEMS (MPDDS): A CONVENTIONAL AND NOVEL APPROACH

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ABSTRACT

Pharmaceutical research and development are increasingly 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. Multiparticulate drug delivery systems (MPDDS) are suitable for conventional as well as novel drug delivery techniques. Pelletization is a novel drug delivery system which converts the fine powder into pellets. The present work mainly focuses on the all aspects that are related to the 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, freezepelletization, Hmto melt extrusion and melt spheronization along with traditional techniques.
INTRODUCTION TO MPDDS

With the advancement of the technologies in the pharmaceutical field, drug delivery systems have drawn an increasing interest over the last few decades. Nowadays, the emphasis of pharmaceutical galenic research is turned towards the development of more efficacious drug delivery systems with already existing molecule rather going for new drug discovery because of the inherent hurdles posed in drug discovery and development process. Pharmaceutical research and development started focusing on delivery systems which enhance desirable therapeutic objectives while minimizing side effects. [1, 2, 3] 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. [4] 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. [5] The purpose of designing multiparticulate dosage form is to develop a reliable formulation that has all the advantages of a single unit formulations and yet devoid of the danger of alteration in drug release profile and formulation behavior due to unit to unit variation, change in gastro luminal pH and enzyme population. [6]

TYPES OF MULTIPARICULATE SYSTEM

Matrix Coated Pellets
In matrix systems, drug solution or dispersion is granulated with excipients to form pellets or sprayed onto pellets in order to achieve extended drug release. The drug homogeneously distributed within the polymer is dissolved, dispersed or dissolved and dispersed. Drug-polymer interactions can occur and bring benefits in terms of mechanical properties such plasticizing effect. This system offers the advantages such as Easy manufacture, low cost, lower risk of dose dumping, improvement of aqueous drug solubility. The disadvantages such as fast initial release and incomplete release in a defined time. The latter could be avoided by coating sugar cores with different polymer which leads to drug in deep layers and counteracting for increased diffusion pathway. [7]

Reservoir Coated Systems
Such systems consist of a drug layered core surrounded by a polymer. The mechanism of controlling the drug release from reservoir type systems is often complex and depends on coating type, thickness, drug type and core type. Those mechanisms include: 1) Diffusion through the continuous polymer film surrounding the drug loaded core and later dissolution of drug outside the pellets. 2) Drug release can occur through water filled pores due to leaching of water soluble compounds into the release medium or due to cracks formed by high hydrostatic pressure generated inside these systems upon water uptake. 3) Drug release occurs as an osmotic active core is surrounded by semi-permeable membrane. [5] The major advantage is high drug load capacity and obtaining variable release profile by type of polymeric membrane. [7]
DESIGN OF MULTIPARTICULATE DRUG DELIVERY SYSTEM

The purpose of designing multiparticulate dosage forms is to develop a reliable formulation that has devoid of the danger of alteration in drug release profile and formulation behaviour due to unit to unit variation. Multiparticulate systems are formulated as:

Reservoir system with rupturable polymeric coating:-
In this system, the drug release is achieved by disintegration mechanism which is achieved by rupturing the coating by different mechanisms like swelling, disintegration, and effervescent excipients or by osmotic pressure. Example, the effervescent mixture incorporated into polymer & upon contact with aq. Fluid generation of CO2 causes the rupture of coat and releases the drug. Mechanical properties of coating layer, thickness of coating and hardness of core controls the drug release and lag time. Swelling agents like Cross-caramellose sodium (CCS), sodium starch glycollate (SSG), low substituted hydroxyl propyl cellulose (L-HPC) swells, uptake followed by drug release. Here, the composition of coat controls the lag time.\(^{[4,8,9]}\)

Reservoir systems with soluble or eroding polymer coatings:-
In this system, the polymer coat either solubilized or eroded in Aq. Fluid after specific lag period and causes burst release of drug. The thickness, pH sensitivity of polymer controls drug release and lag period. Due to burst release, to avoid irritation caused by drug, it is essential to have high ratio of drug solubility relative to the dosing amount. (Dissolution is the drug release mechanism).

a. Time Clock System:- the polymer coat consists of lipid substances as barrier with surfactants (spans). The erosion/emulsification occurs on contact with Aq. Nature after specific lag period then the core is available for dispersion.

b. Chronotropic System: - Here, the coating is swellable Hydrophilic polymers such as HPMC. Drug is released by swelling of polymer. The viscosity and thickness of polymer controls lag phase.\(^{[8,9]}\)

System with changed membrane permeability:-
The osmotic MPDDS which release the drug at fixed time interval is the example of this type of system. The design consist of drug core and water soluble osmotic agent (NaCl) enclosed in water permeable water insoluble polymer film. The film coating of each population of pellets differs from the coating of every other population of pellets in the dosage form in the rate at which water passes through to the core and the rate at which drug diffuses out of the core. The osmotic agent dissolves in the water, causing the pellet to swell and regulating the rate of diffusion of drug into the environment of use. It produces pulsatile blood concentration with time.\(^{[8]}\)
MECHANISM OF DRUG RELEASE FROM MULTI-PARTICULATES

Table 1 the Mechanism of Drug Release From Multiparticles \(^{10, 11, 12}\)

<table>
<thead>
<tr>
<th>Diffusion</th>
<th>Erosion</th>
<th>Osmosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.</td>
<td>Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle.</td>
<td>In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating.</td>
</tr>
</tbody>
</table>

PELLETS AS MPDDS

INTRODUCTION TO PELLETS
Historically, the word pellet has been used by a number of industries to describe a variety of agglomerates produced from diverse raw materials. Pellets are spherical, free-flowing granules with a narrow size distribution, typically varying between 500 and 1500 μm in size for pharmaceutical applications. \(^{13}\) Pellets Are Systematically Produced, Geometrically Defined Agglomerates of Bulk Drugs and Excipients with Binder Solution. They are formed as a result of a pelletization process which is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free-flowing, spherical or semi-spherical units. \(^{14, 15}\) Pellets as suitable systems for extended release formulations with respect to their spherical/semi-spherical shape, low surface area-volume ratios that provides ease of coating and reduction in the dosage regimen. \(^{16}\) The interest in pellets as dosage forms (filled into hard gelatin capsules or compressed into disintegrating tablets) has been increasing continuously. \(^{17}\) The pelletized products can improve the safety and efficacy of the active agent. These are formulated in the form of suspensions, capsules or disintegrating tablets, showing a number of advantages over the single-unit dosage system. Pellets offer a great flexibility in pharmaceutical solid dosage form design and development. They flow freely and pack easily without significant difficulties, resulting in uniform and reproducible fill weight of capsules and tablets. Successful film coating can be applied onto pellets due to their ideal spherical shape and a low surface area-to-volume ratio. Pellets composed of different drugs can be blended and formulated in a single dosage form. This approach facilitates the delivery of two or more drugs, chemically compatible or incompatible, at the same sites or different sites in the gastrointestinal tract. Even pellets with different release rates of the same drug can be supplied in a single dosage form. \(^{13}\)

NEED OF PELLETS / RATIONALE BEHIND DESIGNING THE MPDDS
There are many reasons for designing and delivering drug as a multiparticulate system e.g.

i. To facilitate disintegration in the stomach. Shows better reproducible pharmacokinetic behaviour than conventional (monolithic) formulations.

ii. After disintegration, the individual subunit particles pass rapidly through the g.i.t. If these subunits have diameter of less than 2 mm, they are able to leave the stomach continuously, even if the pylorus is closed. These results in lower intra and inter individual variability in plasma levels and bioavailability.

iii. Drug safety may also increased by using multiparticulate dosage forms. \(^{8, 18}\)
IDEAL PROPERTIES

Table 2 Ideal Properties for Pellets [19, 20, 21, 22, 23]

<table>
<thead>
<tr>
<th>For coated pellets</th>
<th>For uncoated pellets</th>
</tr>
</thead>
<tbody>
<tr>
<td>❖ Uniform spherical shape and smooth surface.</td>
<td>❖ Maintain all of the above properties.</td>
</tr>
<tr>
<td>❖ Optimum size, between 600 and 1000 m.</td>
<td>❖ Contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits.</td>
</tr>
<tr>
<td>❖ Improved flow characteristics.</td>
<td>❖ Have desired drug release characteristics.</td>
</tr>
<tr>
<td>❖ High physical strength and integrity.</td>
<td></td>
</tr>
<tr>
<td>❖ Good hardness and low friability.</td>
<td></td>
</tr>
<tr>
<td>❖ Low dust producing capacity</td>
<td></td>
</tr>
<tr>
<td>❖ High bulk density.</td>
<td></td>
</tr>
<tr>
<td>❖ Ease and superior properties for coating.</td>
<td></td>
</tr>
<tr>
<td>❖ Reproducible packing of beds and columns.</td>
<td></td>
</tr>
</tbody>
</table>

ADVANTAGES AND DISADVANTAGES OF MPDDS (PELLETS)

Table 3 Advantages and Disadvantages of MPDDS (Pellets) [8, 11, 16]

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Predictable, reproducible and short gastric residence time.</td>
<td>I. Low drug loading.</td>
</tr>
<tr>
<td>II. Less inter- and intra-subject variability.</td>
<td>II. Proportionally higher need for excipients.</td>
</tr>
<tr>
<td>III. Improve bioavailability.</td>
<td>III. Lack of manufacturing reproducibility and efficacy.</td>
</tr>
<tr>
<td>IV. Reduced adverse effects and improved tolerability.</td>
<td>IV. Large number of process variables.</td>
</tr>
<tr>
<td>V. Limited risk of local irritation &amp; modified release causes less dose dumping than reservoir.</td>
<td>V. Multiple formulation steps.</td>
</tr>
<tr>
<td>VI. No risk of dose dumping.</td>
<td>VI. Higher cost of production.</td>
</tr>
<tr>
<td>VII. Flexibility in design.</td>
<td>VII. Need of advanced technology.</td>
</tr>
<tr>
<td>VIII. Ease of combining pellets with different compositions or release patterns</td>
<td>VIII. Trained/skilled personal needed for manufacturing.</td>
</tr>
<tr>
<td>IX. Improve stability.</td>
<td></td>
</tr>
<tr>
<td>X. Improve patient comfort and compliance.</td>
<td></td>
</tr>
<tr>
<td>XI. Achieve a unique release pattern.</td>
<td></td>
</tr>
<tr>
<td>XII. Extend patent protection, globalize product, and overcome competition.</td>
<td></td>
</tr>
<tr>
<td>XIII. Better invivo-invitro release of drug</td>
<td></td>
</tr>
<tr>
<td>XIV. Homogeneous spreadability in GIT</td>
<td></td>
</tr>
<tr>
<td>XV. Usefull in case of difficulty in swallowing and dysphagia like in case of children and aged people.</td>
<td></td>
</tr>
</tbody>
</table>

PELLETIZATION

INTRODUCTION TO PELLETIZATION

Pelletization is an attractive and novel drug delivery system a technique which converts fine powder particles into pellets. These oral MPDDS offer biopharmaceutical advantages with respect to predictable and even distribution and transportation in the gastro-intestinal tract, ease of filling, better flow properties of spherical pellets, sustained, controlled or site-specific drug delivery, ease of coating and uniform packing. [24, 25] Pelletization can be defined as an
agglomeration (size-enlargement) process that converts fine powders or particles of bulk drugs and excipients into small, free-flowing, spherical or semi spherical units, referred to as pellets. Pellets range in size, typically, between 0.5 – 1.5 mm, though other sizes could be prepared. [26,27]

ADVANTAGES OF PELLETIZATION

- Pelletization produces spheroids with high loading capacity of active ingredient without producing extensively large particles.
- Pellets exhibit better roundness than the commercial nonpareil seeds and have excellent flow and packing properties by the pelletization technique.
- Particles less than 2-3 mm rapidly pass the pylorus regardless of the filling level of the stomach or the size and density of chyme. Also, GI irritations are limited spread as the particles spread in the intestine these sizes are achieved by pelletization. [25, 28, 29]

NEED / PURPOSE OF PELLETIZATION

- To improve flow, dispersion, solubility, stability and compaction.
- To have less variation in transit time through the GIT than single-unit dosage forms like tablets prepared by granulation and compression.
- To produce pellets of uniform size with high drug loading capacity.
- To prevent segregation and dust.
- Pellets can be compressed into tablets called ‘pelltabs’ and can also be filled into capsules. [25,29]

FACTORS AFFECTING PELLETIZATION

Moisture content:-moisture causes cohesiveness of powder and produce wet extrudate further spheronized to give pellets. High moisture contents lead to agglomeration of pellets during the process of spherization due to excess of water in the surface of pellets and low moisture content lead to generation of fines with large variation in size distribution. [22]

Rheological characteristics:-The Rheological condition of the wet mass determines the flow ability in extruder and further spherization operation. So, wet mass variation in rheology make improper and nonuniform extrusion. [22]

Solubility of excipients and Drug in granulating fluid:-A soluble drug get dissolve in a granulating liquid. Thus increasing the volume of liquid phase lead to over wetting of system of agglomeration of pellet sand increase in wetting liquid increases plasticity but induces sticky mass. [22]

Composition of Granulating Fluid: Besides water, alcohol, water / alcohol mixture, Ethyl Ether, Dilute Acetic Acid, Isopropyl alcohol is also used as a granulating liquid. A minimum of 5% of granulation liquid have to be water in order to produce pellets of good quality. [22]

Physical Properties of Starting Material:-the parameters such as content, composition, different grades of starting materials, type of filler and its particle size have the effect on the
pelletization process. The swelling property of material used in pelletization technique decides the release rate of the drug in pellets. [22]

**Speed of the Spheronizer:** The speed of the spheronizer affects the size, hardness, sphericity and density of pellets, high speed gives high sphericity, lower friability, smooth surface and higher crushing strength. [22]

**Drying technique and drying temperature:** Variation in pellet’s size, shape and flow will lead to difference in physicochemical properties of final dosage form like weight variation, improper filling etc, which will further affect the therapeutic efficiency of the delivery system. Wider particle size distribution may lead to variation in the dose of drug delivery so, proper drying is essential to obtain ideal pellets.

**Extrusion Screen:** The quality of the extrudate/ pellets is greatly influenced by the characteristics of the orifice of the screen. An increase in orifice dimension resulted in increased mean pellet size. The increase in orifice depth decreased with the presence of water at the extrudate surface, increasing the extrusion force, and then had a negative effect on granulometric distribution and on shape. [22, 30]

**THEORY AND PRINCIPLE OF PELLET FORMATION AND GROWTH**
The fundamental principle/mechanism of formation and growth of pellets are essential for selecting the pelletization procedure. Numbers of theories are available for the mechanism of growth and formation of pellets. Some of them are derived from research while others are postulated from visual observations. Pelletization process mainly involves 3 steps: Nucleation, Transition and Ball growth. But, based on experiments on the pelletization technique steps proposed are: 1) **Nucleation**, 2) **coalescence**, 3) **layering** & 4) **Abrasion transfer**. [31]

![Figure 2 Principle of Pellet Formation and Growth](image)

**Nucleation:** Initially the powder is wetted with solvent system for obtaining primitive particles together to form threephase air-water-liquid and bonding strength increased by reduction of particle size. Further the size, the rate and the extent of nuclear formation depends upon the size of the particles, the moisture content, the viscosity of the binding particles, the wettability of the substrate and the processing conditions, such as tumbling and drying rates. Nucleation is followed by a transition phase where the growth mechanisms affecting are coalescence and layering. [32, 41] The nucleation phase is characterized by the disappearance of fines as a consequence of coalescence between the wetted primary particles or the primary particles with the formed nuclei. The resultant nuclei would undergo
consolidation under the impact of the externally applied mechanical forces and acquire sufficient strength to resist further breakdown by impact forces and will be able to grow into bigger agglomerates. [22] The liquid is either added to the primary particles at once in a carefully controlled manner or sprayed slowly onto a mass of dry powder to produce moist nuclei. An important feature of nucleation is that both the mass and nature of the nuclei in the system changes as a function of time. [27]

Coalescence: the formation of large sized particles following random collision of well-formed nuclei is known as coalescence. To obtain proper collision of nuclei the slight excess of surface moisture is essential. If slight excess of moisture is absent it requires additional mechanical pressures to coalescence. This phase is characterized by the decrease number of nuclei but, no change in mass of system. [27, 32]

Layering: Layering is a slow growth mechanism and with the successive addition of fragments and fines on an already formed nuclei. In the layering step, the number of particles remains constant while the total mass of the system increases due to increasing particle size as a function of time. The fragments or fine particles can be formed by particle size reduction. The fines and the fragments produced through size reduction are taken up by larger pellets. Production of fines and subsequent coalescence and layering continues until the number of collisions declines rapidly, thereby leading to a reduction in the rate of growth of the pellets. At this point the third phase, the ball growth region, is reached. [32] The material deposited over the nuclei may be dry or moist and the growth rate is always slow, since a small amount of material is added to the growing nuclei at any given time. [27]

Abrasion transfer: It involves the transfer of materials from one granule formed to another without any preference in either direction. there is no change in the total number or mass of the particles. Particles undergo a continuous change in their size as long as the conditions that lead to the transfer of material exist. [32]

Size reduction: Well formed particles may undergo size reduction due to attrition, breakage and shatter. If the particles have sufficient surface plasticity, however, they may coalesce to form larger particles upon collision. [27]

TECHNIQUES AND EQUIPMENTS OF PELLETIZATION

Figure 3 Different Techniques of Pelletization
I. AGITATION
It is a pelletization process in which powders, on addition of an appropriate quantity of liquid or when subjected to high temperatures, are converted to spherical particles by a continuous rolling or tumbling action. [34]

A. BALLING/SPHERICAL AGGLOMERATION
The finely divided particules of powder converted to spherical shape by the addition of liquid prior or during the agitation stage by continuous rolling or tumbling action. If the liquid is used to form spherical shape called liquid induced agglomeration or subjecting it to high temperature called melt induced agglomeration.Round curvature pans, horizontal drum mixer and rotatory fluid – bed granulator can be used for the production of spherical pellets by balling.[19, 35]

i. Liquid-induced agglomeration
In this system, the agglomerates or nuclei formed by addition of liquid to powder before or during agitation and nuclei are bound together by liquid bridge and subsequently replaced by solid bridges formed by hardening of binder or any material dissolved in liquid medium. Further, larger nuclei/pellets are formed by colliding and coalescence steps.during the growth of pellet coalescence is replaced by layering whereby small particles adhere on much larger particles and increase the size of the latter until pelletization is completed.

ii. Melt-induced agglomeration
It is similar to liquid induced process. But, binding material is melt. The melted material undergoes nucleation and coalescence to form pellets with wide particle size distribution.[20, 30]

![Figure 4 Principle of Balling (Spherical Agglomeration)](image)

*Mechanism of pellet growth by spherical agglomeration:* The liquid added to powder or melt forms the agglomerates or nuclei which are bounded together by liquid or melt bridges which are subsequently replaced by solid bridges and later forms the pellets by hardening the binder or melt.[37]
Figure 5 Pellet Growth Mechanisms in Spherical Agglomeration [27]
A balling disc machine also known as pelletizing machine which is used for pelletizing of powder materials into balls/pellets of agglomerates. It is original and peculiar with largescale disc-pellet machine and designed on the basis of the largescale disc-pellet machine that is used in industries like iron and steel industry, chemical industry. [38, 39]

Figure 6 The Balling Disc Machine. (A) Front View, (B) Side View [39]

B. DIRECT PELLETIZATION
In this system, the uniform sized dense pellets are formed from the spherical agglomeration which is formed by subjecting the blended material and solvent (organic, any other) into centrifugal motion. [32, 40] The pellets are formed from agglomerates due to random collisions. This agglomeration is facilitated by sufficient surface moisture and/or significant mechanical pressure developed by centrifugal motion. [40]

Figure 7 Principle of Direct Pelletization [40]
This technology offers the advantages such as -01. Effective process (fast process, low usage of auxiliary materials.) 02. Product advantages (Compact, round pellets - ideal for automatic dosing and even coating and Pellet diameter also obtained between 0.2 mm and 1.2 mm.) [35] The main disadvantage of this technology is the coexistence of different growth mechanisms, which makes it difficult to control the pellets growth. For this reason, pellets for pharmaceutical purposes are rarely produced by balling. [40]
II. COMPACTION

In the compaction technology, the pellets of defined shape and size are formed by subjecting the blend of powder or granules are forced together under pressure. The interparticulate contact is increased by mechanical interblocking and the bonding forces like Vander-wall forces, electrostatic forces is applied to make adsorption layer effective. [41, 42]

A. COMPRESSION

It is one type of compaction technique in which pellets are produced by subjecting the material to the mechanical pressure. The formulation and process variables are similar to that of the tablet manufacturing. [32] In fact pellets produced compression is nothing but small tablets that are approximately spheroidal in shape. [43] The sustained release pellets of poly (lactic acid) with increasing bovine serum albumin (BSA) load and studied the invitro release pattern of theophylline from prepared pellets. They reported that release mechanism was driven by leaching through channels and not by polymer degradation. The release rate was found to be dependent on BSA loading and annealing. [20]

Mechanism of pellet growth by compression: In this system, the particles are pretreated by blending or wet granulation and drying. Then, they are subsequently subjected to mechanical pressure where the spheroidal shaped pellets grows and bonding between spheroids accurs by mechanical interblocking. [27]

B. EXTRUSION SPHERONIZATION

This technique is used for the purpose of formulating conventional, controlled or modified release, a consistant smooth surface is required with a narrow size distribution in order to ensure uniform coating and free flowing property. This technique can be used to achieve this and also to produce pellets/spheroids of uniform size with high drug loading capacity. Extrusion spheronization is a multiple process involing a pre-consolidation stage by extrusion followed by spheronization to produce uniform size spherical particles, called as spheroids, pellets, beads, or matrix pellets depending upon material as well as process used. Hence good extrudates will have to posses the desirable attributes to be broken down into regular fragments that can be rounded into pellets of a narrow size distribution. [44] Wet mass extrusion also called cold-mass extrusion has become the method of choice when one is desirous of having dense spherical pellets of uniform size and shape With high drug loading for controlled-release oral solid dosage forms with a minimum amount of excipients. [45]

Extrusion

Extrusion consists in applying pressure to a wet mass until it passes through the calibrated openings of a screen or die plate of the extruder and further shaped into small extrudate segments. [26] The wet mass prepared by mixing the liquid and powder material which are held together by capillary forces and solid bridges formed due to loss of moisture, mechanical interlocking and to some extent molecular forces. [42] As the mass passes through the extruder screen, the resulting extrudates eventually break under their own weight. Usually the extrudates have the same length. The extrudates must have enough plasticity in order to deform, but an excessive plasticity may lead to extrudates which stick to each other as they are collected and further processed in the spheroniser. The diameter of the segments and the final size of the spheroids depend on the diameter of the openings in the extruder screen. To obtain reproducible results the monitoring of parameters like feed rate, powder consumption, die temperature and Compression chamber pressure is essential. [26]
Spheronization
Spheronisation refers to the formation of spherical particles from the small rods produced by extrusion [26]. During spheronization process, the extrudates break into small cylinders with a length equal to their diameters. Two mechanisms are proposed for the formation of spheres:-

- These plastic cylinders are rounded due to frictional forces into cylinder with rounded, dumbbells and elliptical particles to eventually form perfect spheres.
- A twisting of the cylinder occurs and finally resulting into the breaking of the cylinder into two distinct parts having a round and a flat side. Due to the rotational and frictional forces involved, the edges of the flat sides fold together like a flower forming the edges cavity.

At the end of the spheronization process, the wet pellets must be dried to adjust pellet size, density, hardness, etc. [29]

Advantages And Disadvantages Of Spheronization

Advantages [28, 13, 46]

1. **Optimum Flow and Handling Characteristics:** The flow characteristics of spheres make them suitable for transportation by most systems found in the pharmaceutical industry, including vacuum transfer.

2. **More Reproducible Packing Into Small Containers:**
   a) The packing of small sphere into small containers, such as hard gelatin capsules, or larger packages is much more convenient than other dry forms such as powders or granules. b) Eliminate quality problems with variable dosage due to packaging problems with powder.

3. **Minimum Surface Area/Volume Ratio:** Spheres provide the lowest surface area to volume ratio and thus pharmaceutical compounds can be coated with a minimum of coating material important for effective release of some drugs.

4. **Optimum Shape for Coating and for Controlled Release:**
   a) Coating can provide controlled, targeted release at different locations within the body. b) Spheres are a dense material that can easily be coated with a minimum of coating material. Since, smooth spheres are ideal for coating. Hence, minimum coating material and coating time is required.

5. **Easy mixing of non-compatible products**
   Spherical particles are easily mixed.

6. **Elimination of Dust:**
   a) The elimination of dust removes the hazards and problems associated with material in this form. b) Contamination is reduced. c) The amount of fines and dust will be reduced during transport and handling.

7. **Improved Hardness and Friability:**
   a) Dependant upon adhesive forces and surface characteristics. b) Spheronization increases the hardness and reduces friability of granules.

8. **Improved Packing of Beds and Columns:**
   a) In some chemical processes porous beds or packed columns are used as chemicals reactors and catalysts. b) Spherical surfaces allow the reproduction of beds with always the same volume of void space. c) Modeling and calculations are easier when the products flow around symmetrical bodies.
Disadvantages
This process is more labor and time intensive than other commonly used granulation techniques. [47]

Stages Of Extrusion-Spheronization:-

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

2. **Wet Massing:** - This process of powder dispersion is done to produce a sufficient plastic mass for Extrusion. It is similar to the wet granulation method. The most commonly used granulator is planetary mixer or sigma blade mixer or high shear mixer and Horbat mixer.

3. **Extrusion:** - It is the method of applying the pressure to wet mass to pass/flow through the openings of the extruder to get rod shaped particles and bonding of wet mass obtained by solvent system. Extrudate should have enough plasticity to deform but not to adhere in spheronization operation. The granulation solvent serves as the binding agent to form the granules and as the lubricating during the extrusion operation.

4. **Spheronization:** - The instrument used is called Spheronizer where the extrudate is rotated at higher speed by friction plate that breaks the rod shaped particles in to smaller particles and rounded them to form spheres. [30, 41, 48, 49] The spheronization operation has been divided into 3 stages:-
   - **Breaking of cylindrical segments or extrudates**
     It has been attributed to interaction of the extrudate with the rotating plate, the stationary wall and the extrudate particles.
   - **Agglomeration of broken segments**
     Agglomeration occurs when small fragments produced during the breaking stage are picked up by larger particles during smoothing.
   - **Smoothing of particles.**
     The smoothing stage creates spherical pellets by generating rotational motion of each granule about its axis in constantly changing planes.

The friction plate is responsible for providing the energy necessary to produce pellets and for controlling the extent of pellet growth. [29]

![Figure 8 Principle of Spheronization operations](image)
5. **Drying:** The ideal pellets are obtained by proper drying either at room temperature or elevated temperature in a tray dryer or in a fluidized bed dryer. The freeze drying method retains the shape and size and the granules whereas the oven drying produces rough granules.

6. **Screening:** It is necessary to achieve the desired size distribution and for this purpose sieves are used. Based on the type of feed mechanism and to transfer the mass towards the die, variety of extruders is used. \[^{30, 41, 48, 49}\]

![Figure 9 Process of Extrusion-Spheronization \[^{35, 47}\]](image)

![Figure 10 Different transitions from extrudate to pellets \[^{36}\]](image)

**Factors Affecting Extrusion-Spheronization**

1. **Starting material**-
   - The nature of the starting material influences the size, hardness, and sphericity of the particles as well as the release rate of loaded drug.
   - **Binders:** If too much binder is added and the granules become too hard, it will be difficult to obtain good spheres.
   - **Lubricants:** If too much water is used as lubricant, sticking can occur on the friction plate and bowl wall. It can also happen that the granules will stick together, forming big lumps. If the extrudates are dry, a high amount of fine dust will be generated.
   - **Fillers:** Fillers like MCC, lactose regulate water content, rheological properties and plasticity of the pellets.
   - **pH modifiers:** Organic acids pH modifiers stabilize sensitive drug substances or modify the release characteristics, especially the solubility of the drug substance. \[^{45}\]
   - The use of similar products manufactured by different suppliers also showed changes in characteristics of the pellets produced.
2. **Extruders**
   According to Reynolds and Rowe an axial screw extruder produces a denser material than a radial screw extruder. The latter has a higher output but also produces but shows greater heat production during the processing. Pellet quality is dependent on the thickness of the screen and the diameter of the perforations. A thinner screen produces a rough and loosely bound extrudate, whereas a thicker screen forms smooth and well-bound extrudate because of the higher densification of the wet mass. Similarly, the diameter of the perforations determines the size of the pellets – a larger diameter in the perforations will produce pellets with a larger diameter under similar processing conditions.

3. **Extrusion speed**
   The output depends on the extrusion speed. The increasing speed causes at surface impairments such as roughness and shark-skinning which leads to pellets with lower quality because the extrudate will break up unevenly during the initial stages of the spheronization process, resulting in a number of fines and a wide particle size distribution.

4. **Extrusion temperature**
   The extrusion cycle during the operation may lead to rise in the temperature which could cause the granulating liquid to evaporate from the granules which causes difference in the quality of the extrudate right in the beginning of the batch itself. Extrusion temperature controls is especially taken into the consideration when processing thermolabile drug formulations.

5. **Spheronizer specifications**:
   - Pellet quality is also dependent on spheronizer load which affects the particle size distribution, bulk and tapped density of the final pellets.
   - *Disc speed*: The speed of spheronization plate should be kept constant during the whole process as Speed affects the size, hardness, sphericity and density of the pellet. High speed has been reported to give higher sphericity, lower friability, smooth surface and higher crushing strength. The speed of the plate was found to have a major influence on the overall dissolution rate which is linked to pellet size.
   - *Spheronizer drum charge volume*: the volume depend on machine size. The machine with 380mm has volume of 4 lit depending on density. Increased load causes increased hardness and smoothness of sphere.
   - *Disc Groove Geometry*: Both radial and cross hatched will work effectively. Radial disc had gentler and more controlled action. Radial not suitable for large diameter discs, generally, extrudates up to 0.8 mm in diameter are normally processed on a 2 mm pitch plate with a 3 mm pitch plate is used for extrudates up to 3 mm in diameter.
Disc Diameter: Loads from 0.5 to 25 kg can be compared. One plane critical stability (OPCS) can be expressed as a function of number of revolutions of the plate. Number of revolutions can be used to predict scale-up.

- The increase in the spheronerizer speed and a low spheronerizer load will result in wider particle size distribution with less yield of pellets, whereas it increases the extended spheronerization time at a higher spheronerizer load.
- It was also reported that an increasing spheronerizer load decreased the roundness and increased the hardness of pellets.\(^{29,32}\)

Figure 11 (A) Extrusion/spheronerisation flow chart with individual processing variables, (B) Lay out of Extrusion-Spheronerisation\(^{[7, 36, 50]}\)

EQUIPMENTS

EXTRUDERS:

Wet mass forced through the dies to produce small cylindrical uniform size particles. This shaping of wet mass into uniform size is known as “Extrusion” and long roads are known as “Extrudates”.\(^{[51]}\) Extruder is to develop sufficient pressure in the material so as to force the material through the die. The pressure necessary to force a material through the die depends on the geometry of the die, the flow properties of the material, and the flow rate. Basically, an extruder is a machine capable of developing pressure. In other words, an extruder is a pump.\(^{[45]}\)

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>TYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screw feed extruder</td>
<td>Axial / end plate, Radial and Dome</td>
</tr>
<tr>
<td>Gravity / Roll feed extruder</td>
<td>Roatry cylinder, Rotary Gear and Radial</td>
</tr>
<tr>
<td>Sieve and Basket feed extruder</td>
<td>-</td>
</tr>
<tr>
<td>Piston feed extruder</td>
<td>RAM</td>
</tr>
</tbody>
</table>

Screw Feed Extruder

It utilizes the screw to develop necessary pressure to force material to flow through uniform opening and produces uniform strands and extruded. It has three zones namely feed zone, transport and compression zone and extrusion zone. The feed zone is the area where the
material is first introduced into the extrusion device. It consists of hopper to channel the flow of material into the chamber where the screws are located. Material in the transport zone is moved by the auger like screw from the feed zone to the compression zone. In the compression zone air is forced out from between the loose agglomerates and from the interstitial voids as particles are compacted together. Some extruders may have vents to expell gases from equipment. [45]

![Figure 12 Generalized Screw Feed Extruder](image)

**Axial/Endplate Feed screw Extruders:** Axial extruders which have a die plate that is positioned axially, basically consists of a feeding zone, a compression zone, and an extrusion zone. The temperature of the product during extrusion is controlled by a jacket barrel. [36] i.e. Screen is placed at the end of screw. [51]

**Radial Feed screw Extruders:** In radial extruders, the transport zone is short, and the material is extruded radially through screens that are mounted around the horizontal axis of the screws. [36, 36, 51]

![Figure 13 (A) Axial/Endplate Feed screw Extruder, (B) Radial Feed screw Extruder](image)

**Gravity/Roll Feed Extruders**
In this design the product is gravity fed into two hollow, meshing, and gears. The die is formed by drilling holes between the gear teeth through to the hollow bore. As the gears
rotate each gear tooth enters the gap between the two opposite teeth producing a form of piston (ram type) action and pressurises the product through the die. Also known as ‘pellet mills’ to operate by feeding material between a roller and a perforated plate or a ring die, a method that forces moist formulation through the die. The basic designs can vary considerably and are summarized as follows:

**Rotary cylinder Extruder:** In the rotary cylinder extruder, one of the two counter rotating cylinders is hollow and perforated; whereas the other cylinder is solid and acts as a pressure roller both are moved in opposite direction. \(^{[30, 51]}\)

**Rotary gear Extruder:** In the rotary gear extruders there are two hollow counter rotating gear cylinders with counter board holes. The feed material is charged into top of chamber and pressed out the bottom through die plate. \(^{[30, 51]}\)

**Radial extruder:** A ring die rotates around one or more rollers installed inside the cylindrical die chamber, each of which rotate on its stationary axis. All rotating components turn in the same direction. Feed material is introduced onto the inside surface of the ring die and pressed outward by the rollers. The orientation of the perforated cylinder is horizontal, sometimes with a slight inclination to facilitate feeding. \(^{[45]}\)

**Figure 15 (A) Rotary cylinder Extruder**, **(B) Rotary gear Extruder**, **(C) Radial type Extruder.** \(^{[32]}\)

**Sieve And Basket Feed Extruder**
Sieve Extruders are constructed rather like the flour sifter used in baking. That is, they have a chamber that contains the material to be extruded and a plate or screen. A rotating or oscillating arm presses the damp material through a sieve or perforated screen to form short or long extrudates, depending on the moisture content. These devices generally give the least compaction of the various extrusion devices and therefore the number of attractive applications for this extrusion technique is rather limited.

Basket type extruders are similar to sieve extruders except that the sieve or screen is part of a vertical cylinder wall. The extrudate falls vertically from the sieve plate of a sieve type extruder, while in a “basket” extruder, the extrudate is formed in the horizontal plane as it is forced through the vertical holes. \(^{[29, 33, 45]}\)
Piston Feed Extruders/Ram Extruders

A piston riding inside a cylinder or channel is used to compress material and force it through an orifice on the forward stroke. Each return stroke allows material to fall into the chamber. The back pressure, due to friction in the die and from the compression of material against the walls, compresses the material, and a dense extrudate is formed. The important process variables are the length of the piston stroke, the frequency or period between strokes, the degrees to which the cavity is filled on the backstroke, flow characteristics of the material, and configuration of the channel. The product temperature increases very little during the extrusion step, probably because of a shorter compression zone and shorter depth of die openings. In addition, it allows the processing of thermolabile drug substances. Pressure is produced with a minimum of shear work and a minimum pressure must be generated before extrusion begins, (or can be maintained). Extrusion is continuous at this pressure until the Ram is nearly empty, at which point pressure has to rise because of complex flow patterns set-up as the piston face approaches the die plate. Ram extruders are preferentially used in the development phase, because they can also be used to measure the rheological properties of the formulations.

Figure 16 (A) Sieve Extruders, (B) Basket Extruder

Figure 17 RAM extruder

Figure 18 (A) Axial Piston (RAM) Extruder, (B) Radial Piston (RAM) Extruder
**Spheronizer:**
A spheronizer is a device consisting of a vertical hollow cylinder (bowl) with a horizontal rotating disk (friction plate) [45] which consist of a static cylinder and a rotating friction plate where extrudates will break in small cylinder with the length equal to their diameter. These cylinders rounded by friction.) [51] Extrudate is charged onto the rotating plate and broken into short segments by contact with the fraction plate, by collisions between particles, and by collisions with the wall. The spheronization of a product usually takes 2-10 min. A rotational speed of the friction plate in the range between 200 and 400 rpm would be satisfactory to obtain a highly spherical pellet [45] Two geometric patterns are generally used. A cross hatched pattern with grooved running at right angle to one another and a radial pattern with grooved running radially from the center of the disc. [28] Typically, the surface texture of the rotating frictional plates is made up of a cross-hatch pattern of square pyramidal studs with rectangular grooves. The plate can also be of a radial pattern, consisting of rectangular grooves radiating from the center of the plate. It has been reported that cross-hatch or radial textured rotating frictional plates did not affect spheroid quality unless the extrudates were of poor quality [52].

![Figure 19 (A) Schematic presentation of spheronizer & Geometry of spheronization plate: (B) Cross-hatch, (C) radial pattern](image)

**Pellet growth mechanism in spheronizer:** the feed of extrudate in spheronizer falls on frictional plate and cut into segments of length 1-1.2 times than diameter. The frictional plate throws inside the plate and centrifugal force converts into pieces of equal length relative to the diameter of the extrudate. [33] The frictional plate acts as a energy provider in the form of interparticulate friction for producing pellets and for controlling the extent of pellet growth mechanism. [44] The ongoing action of particles colliding with the wall and being thrown back to the inside of the plate creates a "rope-like" movement of product along the bowl wall. The continuous collision of the particles with the wall and with the friction plate gradually turns the cylindrical segments into spheres, provided that the granules are plastic enough to allow the deformation without being destroyed. [33]
Figure 20 (A) The movement of the product along the spheronizer chamber wall and (B) The whirling movement of the particles at the spheronizer chamber wall $^{[26]}$

Standard Features for Spheronizers

- Various designs of chequered plate starting from 1mm chequered size.
- Plate and shaft seals not in direct contact with the product
- Perfect cGMP-design: smooth covering, no external tubing and piping allowing easy cleaning
- Completely integrated full opening side discharge: perfect discharge of difficult products
- Through the wall installation: minimum space required in GMP area
- User-friendly operator-machine interaction via graphical operator panel 12” Industrial PC software with PROCESS+ range of software which helps interlinking all plant equipments to a single system.
- Flexibility (processes and products) for spheronization or pellet line / pelletization process $^{[46]}$

Rotary Processor
The rotary processor can be considered as a hybrid of a fluidized bed and a spheronizer. During RP, liquid addition, wet massing, agglomeration and spheronization would take place simultaneously. $^{[52, 53]}$ There are two basic designs, single and double chamber systems. The single chamber processor is comparatively simpler in design. However, for drying and coating to take place within a single chamber, the limited drying capacity of the processor extends the processing time considerably, especially with coating applications. Some of the single chamber processors have the motor housing separated from the processor itself. The double chamber design is more complicated but offers the flexibility of efficient pellet drying and coating. The rotary processor with a double chamber design consists of an inner metal
chamber housed inside a larger outer chamber. The frictional plate resides within the inner chamber, with a narrow gap between the frictional plate and inner chamber wall. A perforated metal ring encircles the circumferential area separating the two chambers. Fluidizing air may be introduced through the outer chamber via perforations on the metal ring. Drying of pellets after preparation may be effected by lifting the inner chamber pneumatically to present a gap for pellets to move to the outer circumferential area to be dried by the fluidizing air. The second chamber equipped the rotary processor with a highly efficient fluidized bed drying capacity. The frictional plate provides the centrifugal force which propels the pellets towards the wall of the processing chamber and kinetic force for material movement. The uniqueness of the rotary processor lies mainly with the frictional plate. Studs described as pyramidally shaped elevations or square studs with rounded edges positioned in a cross-hatch pattern on the surface of the frictional plate have been used in pellet production by rotary processing. A smooth plate is also best for avoiding material adhesion but it does not supply sufficient shear for effective spheronization. [54]

![Figure 22](A) Pyramidally shaped studs in cross-hatch pattern, (B) Its dimensions [53, 54]

![Figure 23](A) Schematic diagram of designs of rotary processors (A) single chamber; (B) double chamber. [53, 54]

III. LAYERING
Pelletization by layering involves the deposition of successive layers of drug entities from solution, suspension or dry powder on preformed nuclei, which may be crystals or granules of the same material or inert starter seeds. The initial materials required for the preparation of pellets by the layering process are the inert starter seeds over which the powdered drug(s) is
(are) layered and the possible coating applied. Non-pareils have been widely used as initial substrates in the preparation of pellets by the layering process. However, sucrose, the main component of non-pareils, has some well-known drawbacks like harmful effects on diabetics and potential carcinogenicity. Most recently, microcrystalline cellulose (MCC) has been tested as a substrate for drug layering. [13,42]

**A. SUSPENSION / SOLUTION LAYERING TECHNIQUE**

Solution/suspension layering involves the deposition of successive layers of solutions and/or suspensions of drug substances and binders on starter seeds, which may be inert materials or crystals/granules of the same drug. During processing, all the components of the formulation are first dissolved or suspended in an appropriate quantity of application medium to provide a formulation with the desired viscosity and is then sprayed onto the product bed. The sprayed droplets immediately impinge on the starter seeds and spread evenly on the surface, provided the drying conditions and fluid dynamics are favorable. This is followed by a drying phase that renders dissolved materials to precipitate and form solid bridges that would hold the formulation components together as successive layers on the starter seeds. The process continues until the desired quantity of drug substance and thus the target potency of the pellets are achieved. In this, the particle population remains same but, size and total mass of system increases with time. The high viscosity binders recommended for suspension layer to avoid settling of drug particles. For suspension layering process, the particle size of the API should be less than 10 - 50 μm. Consequently, conventional coating pans, fluid bed centrifugal granulators, and wurster coaters have been used successfully to manufacture pellets [22]

![Figure 24 Principle of solution and suspension layering](22, 42)

_Wurster coating process (bottom spray):_ Wurster equipment has cylindrical partition in the product chamber and orifice plate. Orifice plate allows the drying air to pass at the high velocity around the nozzle and through the partition. Once, the particles exit the partition they enter in to expansion chamber. Here, velocity of the air decreases than the entrainment velocity. Particles fall on the surrounding area of the partition known as down bed. Particles from the down bed transported to the gap between orifice plate and partition by suction. Partition height is the gap between orifice plate and partition, controls the rate at which particle enter in to spray zone. It is optimized for the different batch size as it is an important
Variable. Inaccessibility and clogging of nozzles is a major disadvantage. Hence, frequent cleaning is necessary.\[49,51\]

Solubility, concentration of binder, viscosity of solution/suspension, particle size are important parameters that affect the process. This process is used when drug load is low because production of high potency pellets from low solid content is not economically feasible.\[20\]

![Figure 25 Schematic Representation of Wurster Product Chamber and Process (A) Product chamber, (B) Partition, (C) Orifice plate, (D) Nozzle, (E) Expansion chamber.\[51\]](image)

**B. POWDER LAYERING TECHNIQUE**

In this, the successive layers of powder and excipients are added on starting seeds by the help of binding liquid. The small particles and nuclei adhere to each other by means of capillary forces developed in liquid medium. The process continues till the desired pellet size is obtained.\[13\] The major problem is formation of fines due to interparticulate and wall to particle friction at the end of process which can be avoided by spraying the application medium at the end of process. Care must be taken to control moisture level of final pellets.\[42,51\] It is extremely important to deliver the powder accurately at a predetermined rate throughout the process and in a manner that maintains equilibrium between the binder liquid addition rate and the powder addition rate. If the powder addition rate is high, dust generation may occur, and if the liquid addition rate is high, over wetting of the pellets may take place and neither the quality nor the yield of the product can be maximized.\[22\]

![Figure 26 Principle of powder layering\[35\]](image)
The most commonly used equipments for layering are the:- coating pans (standard or conventional ) and Fluidized bed granulators-bottom spray (wurster coating and continous fluid bed), top spray and Tangential spray (rotor pellet coating). [13, 55]

**COATING PANS (STANDARD OR CONVENTIONAL)**

The conventional coating pan is used as pelletizing equipment but, has significant limitation such as high labour cost, time consumption, and low yield. And also disadvantages like degree of mixing are poor, drying is not efficient and shortage of process control. [13, 44, 49] The formulation of pellets of Domperidone by powder layering on sugar cores in conventional coating pans and evaluated the prepared pellets for various in-vitro parameters. The results showed that the pan coating system is efficient for manufacturing highly stable instant release pellets. [20]

![Figure 27 Conventional coating pan: 1-inlet air, 2-inlet air filter and air heater, 3-coating pan, 4-compressed air (control pressure 5-6 bar, atomizing air pressure 1-2 bar), 5-pneumatic spray, 6-outlet air, 7-container with pneumatic stirrer, 8-peristaltic pump.]

**FLUIDIZED BED GRANULATORS / PROCESSOR**

Fluidized bed processor is equipment that can perform multiple functions like coating, drying, granulation and pelletizing. It has highly efficient drying system and uniform, continuous product coating achieved. It protects product against moisture, light, air, ideal for control release film coating, pellet granulation and hot melt coating. [13, 56] The fluid-bed granulation is performed following these steps:

- The preblending of the formulation powder, including the active ingredients, fillers, disintegrants, in a flow of air;
- The granulation of the mixture by spraying a suitable liquid binder onto the fluidized (suspended) powder bed;
- The drying of the granulated product to the desired moisture content. [26]

Three different spray patterns are used for pelletization:-

a) **Bottom Spray (Continuous Fluid Bed):** The product is continuously fed into one side of the machine and is transported onwards via the sieve bottom by means of the air flow. Depending on the application, the system is subdivided into pre-heating zones, spray zones and drying zones whereby spraying can take place from below in the form of a bottom spray. The dry, coated particles are continuously extracted. [27, 23] Some of the
advantages are: (Aqueous or organic, Polymer solutions or dispersions, Controlled release, Enteric coating, Coating of very fine particles, Active ingredient layering, protective coatings, color coatings) \(^{[15]}\)

b) **Top spray:** Particles are fluidized in the flow of heated air, which is introduced into the product container via a base plate. The binder solution is sprayed into the fluid bed from above against the air flow (counter current) by using nozzle. Drying takes place as the particles to move upwards in the air flow.\(^{[13]}\) Small droplets and a low viscosity of the spray medium ensure that the distribution is uniform.\(^{[27]}\) Depending on the application, the system is sub-divided into pre-heating zones, spray zones and drying zones. The dry, coated particles are continuously extracted.\(^{[27]}\)\(^{[23]}\) Advantages of top spray includes 1) Agglomeration or granulation processes (Reduction in the amount of fines, Improvement in the flow, Elimination of segregation, Homogenous distribution of all components, Controllable bulk density, Optimized solubility) 2) Coating process (Lipid coating, taste masking, Moisture & oxidation protection coatings, hotmelt coating, color coatings) \(^{[57]}\)

c) **Tangential spray (rotor pellet coating / centrifugal fluid bed granulator):** the basic operational principle includes centrifugal force, fluidization air velocity and gravitational force.\(^{[56]}\) In this process the cores are placed on the turntables and hot air is blown upward between the turntables and the granulation area. The passage of air causes the cores to roll on the turntables (spiral motion). At the same time, the coating solution is sprayed on the rolling cores through the pump and spray gun. The process involves simultaneous coating and drying of the cores, layer after layer, until the repeated actions achieve the desired coating thickness or granule size.\(^{[13]}\) the product is set in spiral motion by rotating base plate and spray nozzle is arranged tangentially to rotor disc.\(^{[27]}\) the degree of mixing depends on fluidization air volume, air temperature, air velocity, slit width, bed size, disc speed determines yield and quality of final pellets.\(^{[56]}\) Uses of tangential spray: 1) Granulation process: For improved dissolution behaviour, better compressibility, higher density, spherical morphology 2) Spheronization: Higher density, production of pellets, and higher content of active ingredients. 3) Layering: Powder layering, narrow particle size distribution 4) Coating: Film coating, enteric coating, delayed release and hot- melt coating, sugar coatings, modified release.\(^{[13, 57]}\)
Figure 28 Different Spray Patterns in Fluidized Bed Processor:
(A) Bottom Spray, (B) Top spray, (C) Tangential spray \[23\]

A GPCG (Glatt-Powder-Coater-Granulator) from Glatt are used for processes those are uniform, reproducible and gentle on the product using fluid bed techniques. Batch sizes from 5kg to 1.5t/batch. \[23\]

IV. GLOBULATION / DROPLET FORMATION

Spray Drying and Spray Congealing, also known as globulation process, involve atomization of hot melts, solutions, or suspensions to generate spherical particles or pellets. In globulation, atomization produces solid particles directly from the liquid phase through evaporation or cooling and subsequent solidification of hot melts, solution and suspension. The droplet size in both processes is kept small to maximize the rate of evaporation or congealing, and consequently the particle size of the pellets produced is usually very small. \[27, 28\]

Figure 29 Principle of Globulation \[36\]

A. SPRAY DRYING

The drug entities in solution or suspension are sprayed, with or without excipients, into a hot air stream to generate dry and highly spherical particles. As the atomized droplets come in contact with hot air, evaporation of the application medium is initiated. This drying process continues through a series of stages whereby the viscosity of the droplets constantly increases until finally almost the entire application medium is driven off and solid particles are formed. Generally, spray-dried pellets tend to be porous. \[28\]

Mechanism of pellet formation: During spray drying, the atomized droplets are contacted by a hot gas stream and evaporation of the liquid is initiated, which involves simultaneous heat-
and mass transfer and depends on the temperature, humidity, and transport properties of the air surrounding the droplet. As more and more liquid evaporates, surface saturation conditions are reached and formation of solid begins. These particles are initially held together by capillary forces developed by the liquid phase and are gradually replaced by solid bridges. This process continues till desired size is obtained. [27]

![Figure 30 Schematic Representation of Spray dryer][33]

This technique offers advantages like: 1) increase in solubility & dissolution of poorly soluble drug. Hence, increases bioavailability. 2) Produces homogeneous, approximately spherical, nearly uniform pellets. [44, 51] the design and operation of equipment has effects on particle size, size distribution, bulk density, porosity, moisture content, flowability and friability. [26]

**A. SPRAY CONGEALING / SPRAY CHILLING**

The transition of a melt from a soft or fluid state to a rigid or solid state by cooling is called congealing. [51] In this technique the drug is allowed to melt, suspend or dissolve in hot melt of gum, fatty acid, waxes and other solid then sprayed into air or steam chamber with temperature below the melting point of formulation components under appropriate processing conditions to obtain spherical congealed pellets. [19]

**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 bonds formed from the congealed melts. Due to the absence of solvent evaporation during most spray congealing processes, the particles are generally nonporous and strong and remain intact upon agitation. The physical forces coupled with the elementary growth mechanisms ultimately determine the strength and performance of pellets and should be taken into account during the design and development of pellet dosage forms. [27]

![Figure 31 Schematic Representation of Standard spray congealing][30]
A critical requirement in a spray congealing process is that the formulation components have well defined, sharp melting points or narrow melting zones. Because the process does not involve evaporation of solvents, the pellets produced are dense and non porous. The congealing process require higher ratio of coating agents to active material than does the spray drying, because only the molten coating agent constitutes the liquid phase. Depending upon physic-chemical property of the drug and other excipients, one can prepare both immediate and sustained release pellets.

V. CRYOPELLETIZATION

In cryopelletization the pellets can be produced by allowing droplets of liquid formulation such as solution, suspension or emulsion to come in contact with liquid nitrogen at -160°C in which liquid nitrogen used as solidifying medium. The procedure permits instantaneous and even freezing of the material being processed due to the rapid heat transfer that occurs between the droplets and the liquid nitrogen. The frozen pellets are transported into storage container at -60°C before drying and are finally dried into the freeze dryer. The pellets are dried in conventional freeze dryers to remove water or organic solvents. The equipment consists of a container equipped with perforated plate below which a reservoir of liquid nitrogen in which a conveyer belt with transport baffles is immersed. The variable speed of conveyer belt provides the required residence time required for freezing the pellets. Droplet formation is a critical step in cryopelletization and is influenced by formulation related variables, equipment design and the corresponding processing variables. Formulation related variables include viscosity, surface tension and solids content. Surface tension of the liquid formulation also influences droplet formation and size. Addition of a surfactant reduces the surface tension and produces smaller particle. When it is desirable to have pellets with diameter less than 2 mm, the liquid nitrogen should be stirred continuously to prevent agglomeration. This technology was first developed to lyophilize bacterial suspension in the nutrition industry and now a days it is used in the pharmaceutical industry to produce drug loaded pellets for immediate as well as controlled release formulations. Immediate release formulation typically consists of drugs, fillers (lactose and mannitol) and binders (gelatin and PVP) while crosslinked polymers of collagen derivatives are used in the sustained release formulation. Generally, 3-5 kg of liquid nitrogen is required for preparation of 1Kg pellets.

VI. FREEZE PELLETIZATION

In this technique a molten solid carrier along with a dispersed active ingredient is introduced as droplets into an inert and immiscible column of liquid. The technique involves less process variables and also offers several advantages over other pelletization methods, In terms of quality of pellets and process cost. The pellets produced by this technique are spherical in shape with narrow size distribution. Since the pellets are solid at room temperature, they do not require drying. Molten solid carriers are introduced as droplets into the column of liquid in which the molten solid is immiscible. These droplets can move either in upward or downward directions depending on their density with respect to the liquid in the column and solidify into spherical pellets. Carrier may be hydrophilic or hydrophobic in nature and are melted at a temperature 5-10°C higher than the melting point of the carrier solids.
Two types of equipments are used and the selection of equipment depends upon the density of the molten solid carrier. The column is 24 inches long and made of borosilicate glass. The column of both the apparatus is divided into two parts, initial portion from which the molten solid carrier is introduced and is maintained between 25-100°C, and the cooling portion in which droplets solidification occurs and is maintained between 0 to -40°C using cooling mixture of acetone and dry ice. The active constituent and other excipients are mixed with the molten carrier to form solution or dispersion. This solution or dispersion is introduced as droplets using needles or nozzles into the inlet column of liquid and dropped from a certain height, so that droplets remain intact as they fall into the liquid column. Size of needle gauge from 16-31 depending on the size of the pellets desired.

In case of freeze pelletizer I the molten solid carrier are introduced from the upper portion of the column because density of the solid carriers is more than the density of the liquid used in the column and the carriers solidify in the bottom portion, while in case of freeze pelletizer II the molten solid carrier is introduced from the bottom of the column because density of the solid carrier is low as compared to the liquid used in the column and the carrier solidify at the top. Suitable carrier for freeze pelletization are those, which are solid at room temperature and have melting point below 100°C in order to minimize degradation of the active constituent. For freeze pelletizer I, hydrophilic carrier such as polyvinyl alcohol, polyethylene glycol and low melting point sugars (dextrose, maltose) are used. Suitable liquids for column are low density oil such as mineral oil, vegetable oil, and silicone oil. For freeze pelletizer II, hydrophobic carriers of low density such as glycercyl palmitostearate, glycercyl behenate and glycercyl monostearate are used as solid carriers. Suitable liquids for column are high density hydrophilic liquids such as liquid polyethylene glycol, ethyl alcohol, glycerine and water. 

VII. HOT-MELT EXTRUSION TECHNOLOGY (HME)

It is process of pumping raw materials with a rotating screw under elevated temperature through a die into a product of uniform shape. Rotating screw impose mixing and agitation result in the de-aggregation of suspended particles in the molten polymer resulting in the more uniform dispersion. Hot melt-extrusion is initially used in the plastic industry, slowly gaining popularity in the pharmaceutical industry for the production of pellets. It has been estimated that as many as 40% of all new molecular entities have poor bioavailability because of low aqueous solubility. HME has been used to improve the
bioavailability of drug substances especially those having low water solubility by formation of molecular dispersions. HME requires a pharmaceutical grade polymer that can be used at relatively low temperature. All components using in the HME process should be thermally stable during the short duration of heating process. [51, 60]

**Advantages**

- Neither solvent nor water used in this process prevents degradation of many drugs. Fewer processing steps needed thus time consuming drying steps eliminated. Uniform dispersion of fine particle occurs. It is simple and efficient.
- Good stability at varying pH and moisture levels, do not require additional film coating since the drug release is diffusion controlled. Safe application in humans due to their non-swellable and water insoluble nature [13]
- It helps to mask the bitter taste of the active ingredient. Poorly compatible materials can be incorporated into tablets produced by cutting an extruded rod. [48]

**Disadvantages**

- Lower-melting-point binder risks situations where melting or softening of the binder. Higher-melting-point binders require high melting temperatures [13]
- Type and amount of plasticizer may affect the dissolution and stability of the product.
- Cleaning is difficult and the material requirements for extruder often conflict with good manufacturing practices (GMP) issues. [61]

**Process Proceeds in 4 Steps**

Melting or plasticizing a solid material, shaping the molten material and solidification of the material into the desired shape. [32]

1. Feeding into extruder and melting or plasticizing the solid material in which drug is dispersed in a thermal carrier usually a low melting point wax or polymers (starting from high molecular weight to low molecular weight polymers) eg. Vinyl polymers (polyvinylpyrrolidone, polyvinylpyrrolidone-vinyl acetate); copovidone; polyethylene oxide; polyethylene glycol; acrylates; cellulose derivatives. Drug released mechanisms are diffusion (ethyl cellulose, carnauba wax) and erosion (HPMC).
2. Conveying of mass, flow through the die and shaping of molten content into uniform cylindrical segments by extruder.
3. Spheronization of extrudes at high temperature to deform by softening and assist uniform spheroids.
4. Solidifying spheroids to get the desired shape spheroids, exit from the die and downstream processing. The endplate die connected to the end of barrel determines the shape of extruded products.

The factors that influence hot-melt extrusion and spheronization: (a) Process Parameters: barrel temperature, feed rate, screw speed, motor load, melt pressure, design of the extruder die and operating parameters of the extruder (b) Product Parameters: nature and composition of extrudate material, melting point, physical and chemical properties, tensile strength, glass transition temprature. [58]
Equipment
A hot melt extrusion line consists of a material feed hopper, extruder inside a heated barrel, having three different sections, and spheronizer. The feed hopper holds the material and continuously feeds it into the extruder, which has a heated barrel containing the rotating screw. The extrudate is then cut into uniform cylindrical segments, which are spheronized to generate uniform sized pellets. The temperature maintained in the spheronizer should be high enough to soften the extrudate partially and facilitate its deformation and eventual spheroid formation. [40]

Figure 33 Schematic Representation of a hot melt extrusion system [62]
Most pharmaceutical extrusion utilizes „screw extrusion” rather than ram extrusion because it gives better control of temperature profiles and product homogeneity. Screw extruder consists of 3 different parts:
- Conveying system for material transport and mixing,
- Dye system for extrudates formation and
- Downstream auxiliary equipment for cooling, cutting and collecting the extrudates product.

Basically, there are 2 types of screw extruder: Single screw and Twin screw. The single screw utilizes 2 screw usually arranged side by side. In Twin-Screws extruder, screws can rotate in the same or opposite direction. In typical extrusion process screw dimensions are in 20 to 40:1 (L/D) range or longer. Residence time of screw is 5 second to 10 minute depending upon the L/D ratio, type of extruder, screw design & how it operates. Screw is typically divided in to 3 sections along the length of barrel: Feeding, Melting or Compression and Metering. [61]

Figure 34 Heating barrels and Co-rotating screws for Hot-Melt Extruder [58]
Table 5 Distinguishing Characters of Single and Twin Screw Extruder [63]

<table>
<thead>
<tr>
<th>Single screw extruder</th>
<th>Twin screw extruder</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Used in simple profile extrusion and coextrusion</td>
<td>● Used in compounding profile and reactive Extrusion</td>
</tr>
<tr>
<td>● Modular design of screw and barrel is rarely used, less flexibility</td>
<td>● Often used with modular design of screw and barrel, great flexibility</td>
</tr>
<tr>
<td>● Prediction of extruder performance less difficult than for TSE</td>
<td>● Prediction of extruder performance is often difficult</td>
</tr>
<tr>
<td>● Fair feeding, slippery additives tend to cause problems</td>
<td>● Good feeding, can handle pellets, powder, Liquids</td>
</tr>
<tr>
<td>● Fair melting, continuous solid melting Mechanism</td>
<td>● Good melting, dispersed solids melting Mechanism</td>
</tr>
<tr>
<td>● Good distributive mixing with effective mixing elements</td>
<td>● Good distributive mixing with effective mixing elements</td>
</tr>
<tr>
<td>● Good dispersive mixing with effective mixing elements</td>
<td>● Good dispersive mixing with effective mixing elements</td>
</tr>
<tr>
<td>● Fair degassing</td>
<td>● Good degassing</td>
</tr>
<tr>
<td>● Not self-wiping, barrel is wiped but screw root and flight flanks are not</td>
<td>● Intermeshing can have completely selfwiping Characteristics</td>
</tr>
<tr>
<td>● Relatively inexpensive</td>
<td>● Modular is very expensive</td>
</tr>
<tr>
<td>● Usually run between 10-150 rpm; high screw speeds possible but not often used</td>
<td>● Co-rotating can run at very high screw speed, up to 1400 rpm</td>
</tr>
</tbody>
</table>

VIII. MELT SPHERONIZATION

Melt Spheronization is a process whereby a drug substance and excipients are converted into a molten or semi molten state and subsequently shaped using appropriate equipment to provide solid spheres or pellets. The drug substance is first blended with the appropriate pharmaceutical excipients, such as polymers and waxes, and extruded at a predetermined temperature. The extrusion temperature must be high enough to melt at least one or more of the formulation components. The extrudate is cut into uniform cylindrical segments with a cutter. The segments are spheronized in a jacketed Spheronizer to generate uniformly sized pellets. [28] The process requires several pieces of equipment such as blenders, extruders, cutters (known as pelletizers in the plastics industry), and spheronizer. [42] The process is similar to wet granulation, except that the binder is in molten state and hence do not require water or other solvent to liquify it. Due to the randomness of the interparticulate collisions that occurs during the process, the particle size distribution of the pellets tends to be wide as is commonly observed with balling. In fact the process is considered a variation of the balling process. [43]

FORMULATION AIDS

Active Pharmaceutical Ingredient: The different drugs can be used to develop immediate release, sustained release pellets with diversified applications in different areas. Pellets can be formulated with the drugs that can be delivery even subcutaneously and intramuscularly depending on the size variations where the size range is maintained below 600 microns and
are called as micro pellets. Pellets technology is widely used to delivery GIT drugs at a specific site to release drug in a controlled manner.\[32\]

**Fillers:** These are water soluble or insoluble substances that are incorporated into pellet formulations mainly to add bulk. They can range from 1-99% and selection is done on the basis of physicochemical and pharmacological inretness. \[2\] Generally microcrystalline cellulose is used for this purpose. Avicel PH 101, Glyceryl mono stearate, Starch RX1500, spray dried lactose are also used. \[32\]

**Binder (agglomerating inducer/bridging agents):** These are adhesive materials that can be incorporated into pellet formulations to bind powders and maintain integrity on pellet formation. The mechanism of binding involves formation of liquid bridges that holds initially and later liquid evaporates and crystallizes out and forms solid bridges. The binders are commonly used in the range of 2-10%w/w or v/v. Gelatin, HPC, PVP, sucrose, starch are commonly used. \[32\]

**Granulating fluid:** It helps in formation of wet mass and maintains moisture content. It is necessary to add accurate amount of granulating fluid because excess of fluid causes agglomeration of pellets whereas less amount causes generation of fines during pelletization. Besides the use of aqueous forms as a granulation liquid, use of alcoholic or hydroalcoholic systems, ethyl ether, dilute acetic acid, isopropyl alcohol has also been reported. Addition of binders provides more cohesiveness. \[32\]

**Spheronizing Enhancer:** they improve the production of spherical pellets, mainly during spheronization and balling processes. They not only impart plasticity onto the formulation, but also impart binding properties that are essential for pellet strength and integrity. \[32\]

**Plasticizer:** Plasticizers improve the flexibility of polymers by reducing the tensile strength and glass transition temperature of the material. Sometimes drugs and other excipients are employed as plasticizers. Reported that non-traditional plasticizers including methyl paraben and drugs such as ibuprofen, Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, Citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer excipients. \[32\]

**Lubricants:** they are incorporated to reduce the coefficient of friction between individual particles or between the particles and the surface of the processing equipment. \[43\] They also play a significant role in smooth discharge of the pellets from the Spheronizer. Examples of lubricants widely used in pellet processing are calcium stearate, glycerin, PEG, Magnesium stearate. \[32\]

**Separating Agents:** Separating agents are materials which are adsorbed on the surface and promote the separation of pellets into individual units during a pelletization process, which are incorporated initially in the formulation or externally during processing to prevent pellets attracting one another due to surface charge development during the process. Commonly purified talc is used. \[32\]

**Surfactants:** the initial formation and subsequent growth of the pellets depends on liquid bridges that hold the primary particles together. Therefore it is important that the liquid (water in most cases) wet the particles effectively. That is by lowering the surface tension of
binding liquid, surfactants tend to weaken the liquid bridges and make the forming pellets friable. Polysorbate, sodium lauryl sulphate are commonly used. [43]

**pH adjusters:** The pH adjusters are substances that are incorporated in pellet formulations which influence the microenvironment of drug molecules. Generally acid-labile drugs are protected from the pH conditions of the GIT by giving an enteric coating. Buffer systems may also be added to the core formulation to maintain the stability of core in a favorable range. Therefore, specific buffer systems or dual buffer systems are incorporated in pellet formulations to adjust the solubility of drugs to fit a particular process. Sodium carbonate is commonly used. [32]

**Release modifiers:** incorporation of these agents along with drug and polymer alters the drug release kinetics. Generally, water soluble low molecular weight excipients, surfactants and disintegrants are incorporated in formulations to enhance the drug release kinetics, while water insoluble polymers, hydrophobic substances, inorganic salts, and hydrophilic polymers that swell and/or form gels are incorporated in pellets that retard release kinetics. Generally used polymers are ethyl cellulose, carnauba wax, shellac, and carbomers. [32]

**Disintegrants:** these are the substances which in the presence of liquid, promote the disruption of solid dosage form, tablets, pellets, granules, capsules plugs or any other agglomerated materials to regenerate the primary particles that were originally compacted or agglomerated to produce the dosage form. [43]

**Glidants:** Flow characteristics are important in powder layering because the process require a well controlled powder feed rate to balance the simultaneous application of binder solution, it is imperative that the powder does not adhere to the sides of the hopper and form bridges or rat holes. Commonly purified talc is used. [43]

**Flavoring agent:** these are important in case of pediatric, geriatric and bitter tasted drugs (to mask taste) Flavoring agents can be selected from synthetic flavor oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers. Flavors can be used alone or in the combination. Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are examples of flavor oils while vanilla, cocoa, coffee, chocolate and citrus are fruity flavors. Apple, raspberry, cherry, pineapple are few examples of fruit essence type. The amount of flavor needed to mask the taste depends on the type and strength of the flavor. Preferably up to 10%w/w flavors are added in the formulations. Cooling agents like monomethyl succinate, menthol can be added to improve the flavor strength and to enhance the mouth-feel effect of the product. Other cooling agents’ likeWS3, WS23 and Utracoll II can also be used in conjunction with flavors. [32]

<table>
<thead>
<tr>
<th>Taste sensation</th>
<th>Recommended flavor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salt</td>
<td>Butter scotch, Apple, Apricot, Vanilla, Peach</td>
</tr>
<tr>
<td>Bitter</td>
<td>Wild Cherry, Walnut, Chocolate, Mint, Passion fruit</td>
</tr>
<tr>
<td>Sweet</td>
<td>Berry, Vanilla.</td>
</tr>
<tr>
<td>Sour</td>
<td>Citrus Fruits, liquorice, Root beer, Raspberry</td>
</tr>
</tbody>
</table>

**Sweetening agent:** natural sweetners like glucose, dextrose, fructose, maltose, liquid glucose. But, these are not usefull in case of diabetic and diet concious patients. Therefore, synthetic
sweeteners like saccharin, aspartamate are used but are carcinogenic. Rebiana which is a herbal sweetener, derived from plant Stevia rebaudiana is also used. Polyhydric alcohols such as sorbitol, mannitol, isomalt and maltitol can be used in combination as they additionally provide good mouth-feel and cooling sensation.\[^{32}\]

**Coloring agents:** Coloring agents are generally used in order to improve the appearance and make it more patient compliance. Pigments such as Titanium dioxide or FD&C approved coloring agents are used either in the dry form or mixed with the granulating fluid during the formulation.\[^{32}\]

**Table 7 Showing Different Polymers Used In the Pelletization Process** \[^{32}\]

<table>
<thead>
<tr>
<th>Polymer used in pelletization</th>
<th>Formulation</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbopol 974P,NF, Resin.</td>
<td>Beads containing Weakly basic drugs.</td>
<td>Slower release of the salts of weakly basic drugs.</td>
</tr>
<tr>
<td>Crosscarmelllose sodium or sodium starch glycolate.</td>
<td>Super-disintegrants in avicel pellets.</td>
<td>Increase dissolution rate, increase the pellet micropore volume.</td>
</tr>
<tr>
<td>Eudragit RS PO and RL PO.</td>
<td>Polymer (with combination) based pellets.</td>
<td>Better characterization like elastic modulus of the pellets, surface characteristics, sphericity.</td>
</tr>
<tr>
<td>Eudragit RL 30D, RS 30D, NE 30D.</td>
<td>A multiple- unit floating drug delivery system.</td>
<td>Prolong the gastric residence time and to increase the overall bioavailability of the dosage form.</td>
</tr>
<tr>
<td>Methocel-E5 (HPMC) or AMB, Eudragit L 30D-55.</td>
<td>Enteric coated pellets.</td>
<td>Improved film formation and polymer coalescence.</td>
</tr>
<tr>
<td>Microcrystalline cellulose, Ac-Di-Sol.</td>
<td>Floating pellets with bacterial antagonist.</td>
<td>Improving floating property.</td>
</tr>
<tr>
<td>Microcrystalline cellulose and hydroxypropyl methyl cellulose.</td>
<td>Pellets with water insoluble drugs in self-emulsified form.</td>
<td>Controlling the drug release from the oral dosage forms.</td>
</tr>
<tr>
<td>Pectins or alginates.</td>
<td>Polysaccharide gel coated pellets.</td>
<td>Oral administration of theophylline in the coated pellets.</td>
</tr>
</tbody>
</table>

**CHARACTERIZATION AND EVALUATION OF PELLETS**

**1. Bulk density and tapped density** \[^{21, 32, 64}\]

The prescribed quantity of formulation is transferred to measuring cylinder and the volume of cylinder is measured. Tapped density is calculated using following formula.

\[
\text{Bulk density} = \frac{\text{weight of sample in g}}{\text{volume occupied by the sample in Ml}}
\]

A given quantity of the formulation is transferred to the measuring cylinder and it is tapped mechanically either manually or mechanical device till a constant volume is obtained.

\[
\text{Tapped density} = \frac{\text{Wt. of sample in g}}{\text{Tapped volume in mL}}
\]

It is determined simply by USP density apparatus. The bulk density of pellets can be measured by using an automated tapper, while the true density of pellets can be
determined by an air-comparison pycnometer or by solvent displacement method. Bulk density is indicates the packing properties of pellets or spherical seeds which provide higher bulk densities due to small intraparticle porosities. True density indicates the extent of densification or compactness of pellets.

2. **Carr’s compressibility index** \([12, 64]\)
Compressibility index (C.I.) or Carr's index value of micro particles was computed according to the following equation:

\[
\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100
\]

The value given below 15% indicates a powder with usually give rise to good flow characteristics, whereas above 25% indicate poor flow ability.

3. **Hausner ratio** \([12]\)
Hausner's ratio of micro particles was determined by comparing the tapped density to the bulk density using the equation:

\[
\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}
\]

4. **Angle of Repose** \([12, 64]\)
The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane. The fixed funnel and free standing cone methods employ a funnel that is secured with its tip at a given height, \(h\), which was kept 2 cm above graph paper that is placed on a flat horizontal surface. With \(r\) being the radius, of base of conical pile, angle of repose can be determined by following equation:

\[
\theta = \tan^{-1} \left(\frac{h}{r}\right)
\]

Where, \(\theta\) is the angle of repose, \(h\) is the height and \(r\) is the radius.

5. **Moisture content** \([12]\)
Moisture content is determined by means of Karl Fisher titration.

6. **Content uniformity** \([12]\)
Content uniformity (assay) is performed for each batch as per the procedure given in the official pharmacopoeia.

7. **Drug content** \([65]\)
Drug containing core as well as final functional coated pellets were evaluated for drug content. Drug content was determined using calibration curve.

8. **Surface morphology** \([32]\)
Scanning electron microscopy is used to examine the surface morphology and cross section of pellets. The sampling pellets are mounted onto the aluminum stub, sputter-coated with a thin layer of Platinum using sputter coater (Polaron, UK) under Argon atmosphere, and then examined using SEM. The use of optical microscopy to examine the microstructure of pellet surface.
9. Sphericity & shape analysis
The shape factor estimates the amount by which the projected image of particles deviate from a circle and it is calculated by means of the projected area of the pellets and its circumference. For acceptable quality of pellets the roundness index/shape factor should be between 1 and 1.2. For perfectly circular projected image, the shape factor should be 1 while a value of 0.6 describes a particle of good sphericity. Visual inspection of pellets by microscope and stereomicroscope is another method to determine shape of pellets. [30] Spherical shape (sphericity) is determined by taking optimum size pellets, stained with dye solution in a petri dish and dried on a hot air oven. Each pellet is recorded for two dimensional image i.e., length and width using camera lucida fixed to an optical microscope and circulatory factor(s) was calculated using the equation.

\[
S = \frac{P^2}{12.56 \times A}
\]

Where, \(A\) is the area (cm\(^2\)), \(P\) is the perimeter (cm) of circular tracing. [49]

At least 50 pellets from each batch are randomly selected for shape analysis. The pellets were mounted on a light microscope fitted to a camera lucida and the images of the pellets were drawn manually on a graph paper. The area of the images \((A)\) the maximum and the minimum radius are calculated from which the various shape factors are calculated from which the shape factors are calculated as per the following formulae-

\[
\text{Aspect ration} = \frac{d_{\text{max}}}{d_{\text{min}}}
\]

Where, \(d_{\text{max}}\) and \(d_{\text{min}}\) are maximum diameter and minimum diameter of pellets respectively. [37]

10. Specific surface area
Surface area of pellets is directly related with size and shape of the pellets. Specific surface area of pellets is determined by gas adsorption technique.

- **Mathematical calculations:** A spherical pellet, which is smooth and dense, has minimum surface area per unit volume and can be characterized by its diameter. Since surface area is equal to \(\pi r^2\). True density measurements can also be used to determine the specific surface area.

- **Gas adsorption technique:**
  In this method the volume of nitrogen that is absorbed by the substrate contained in an evacuated glass bulb is measured at different pressures, and the results are plotted as \(P/V\) (p0-p) versus p/p0 to generate a linear plot where \(V\) is the volume of gas in cm\(^3\) adsorbed per gram of substrate at pressure p and p0 is the saturation vapour pressure of liquefied nitrogen at the temperature of the experiment. The slope and intercept of the plot yield the values b and Vm. The specific surface (sw) of the pellets is then obtained by using the following BET equation: [22]

\[
SW = 4.35 \times Vm
\]

11. Pellet surface roughness
The surface roughness measurements were carried out on the same samples of pellets as those used to measure the diameter. Samples were mounted on a non-reflective
black plate, which was placed on an air-bearing table and the surface roughness measured with a laser profilometer. The light spot diameter of the sensor was 1 mm and the sensor aperture angle was 53°. Measurements were performed in 3D at a frequency of 100 points and a measuring depth of ±0.5 mm. The area scan was carried out across the 2.00 mm x-transverse, with a resolution of 1000 points/mm and the 0.20 mm y-transverse, with a resolution of 200 points/mm. The roughness descriptors, \( R_a \) (rugosity), \( R_q \) (root mean square deviation of the asperity height distribution), and \( R_{tm} \) (average peak-to-valley ratio) were assessed. The results are the arithmetic mean and standard deviation of five replicates of the above procedure. \[^{32}\]

12. Particle Size distribution:
The use of Vernier calipers to determine the size of pellets. \[^{32}\]

- **Sieving method:** The prepared pellets were estimated by sieving method. Sieving method directly gives weight distribution. Sieves were arranged in a nest with the coarsest at the top. A sample (5 gm) of the dried pellets was placed on the top sieve and subjected to mechanical agitation. The sieve set was fixed and shaken for a certain period of time (10 minutes). The pellets retained on each sieve were weighed. Frequently, the pellets were assigned the mesh number of the screen through which it passed or on which it was retained. It was expressed in terms of Arithmetic mean of the two sieves.

\[
\text{Mean particle size} = \frac{\sum Xi Fi}{\sum Fi}
\]

Where, \( \sum Xi Fi \) = Weight size; \( \sum Fi \) = Percent weight retained. \[^{21, 32}\]

9. **Friability** \[^{33}\]
Friability is a measure of strength to withstand attrition during processing, transport and storage. A friability of less than 0.08% is generally accepted for tablets, but for pellets this value could be higher due to the higher surface area/unit and subsequent involvement of frictional force.

**Table 8 Overview of Friability Testing Methods for Pellets**

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erweka Friabilator, Roche</td>
<td>Rotating drum like Friability testing apparatus</td>
</tr>
<tr>
<td>Turbula</td>
<td>Turbula blender (closed test system)</td>
</tr>
<tr>
<td>Born Friabimat</td>
<td>Horizontal shaker (closed system)</td>
</tr>
<tr>
<td>Laboratory coating apparatus</td>
<td>Fluid bed device (open system)</td>
</tr>
</tbody>
</table>

13. **Hardness**
Hardness of pellets can be determined using Kahl pellet-hardness tester but might not be accurate.

- **Tensile Strength:** It is determined by using tensile apparatus with a 5 kg load cell. The radius of pellets is recorded and these pellets were strained continuously until failure occurs. Further load is recorded. The tensile strength is calculated by applying the value for the failure load (\( F \)) and the radius of the pellets (\( R \)). Formula \( \sigma = \frac{0.4F}{\pi R^2} \). \[^{32, 49}\]
- **Cushing strength**: The crushing strength (the load needed to break the pellets) and elastic modulus of 15 pellets (850–1000mm size fraction) were determined using a Material Testing Machine. The speed of the upper mobile platen fitted with a 1 kN load cell was set at 1 mm/min. Elastic modulus and force–displacement graphs were obtained by a computer system attached to the apparatus. \[^{32,55}\]

14. **Porosity**

The porosity of the pellets influences the release of drugs from the pellets by affecting the capillary action of the dissolved drug. The porosity of the pellets can be measured quantitatively by mercury porosimetry. The porosity of the pellets can also be determined qualitatively by SEM with image analysis and quantitatively by using optical microscopy rarely. Pore radius is given by Washburn equation;

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

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

Thus, determination of the porosity of pellets by mercury porosimetry is a very well-established method showing reproducible results. \[^{32,49}\]

15. **Wettability**

Pellet is placed on clean glass slide. A 15μl drop of distilled water is placed carefully with the help of micro-syringe on the pellet. Photographic impressions of the water drop in contact with the pellet are recorded in the static stage. \[^{37}\]

16. **Floating behaviour**

Appropriate quantity of the floating micro particulate was placed in 100 ml of the simulated gastric fluid (SGF, pH 2.0), the mixture was stirred with a magnetic stirrer. The layer of buoyant micro particulate was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in a desiccator until constant weight was achieved. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

\[
\text{Buoyancy (\%) = } \frac{W_f}{W_f + W_s}
\]

Where, \(W_f\) and \(W_s\) are the weights of the floating and settled micro particles \[^{12,18}\]

17. **Disintegration time**: - it is important in case of immediate release pellets. The reciprocating cylinder method (USP APP3) with certain diameter and length with sieve of 710mm mesh size at the top and bottom of tube is used. \[^{32}\]

18. **Dissolution test**

The release rate of floating multiparticulate was determined in a United States Pharmacopoeia (USP) XXIII basket type dissolution apparatus. A weighed amount of floating multiparticulate equivalent to 50 mg drug was filled into a hard gelatine capsule (No.0) and placed in the basket of dissolution rate apparatus. The dissolution
fluid was maintained at 37 ± 1° at a rotation speed of 100 rpm. Perfect sink conditions prevailed during the drug release study. 5ml samples were withdrawn at each 30 min interval, passed through a 0.25 μm membrane filter (Millipore), and analyzed using LC/MS/MS method to determine the concentration present in the dissolution medium.

SOME RESEARCH EVIDENCE INDICATING FORMULATIONS OF PELLETS AS MPDDS

<table>
<thead>
<tr>
<th>Author</th>
<th>Method</th>
<th>API</th>
<th>Inference</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suresh G. Sudke et al 2013</td>
<td>extrusion-spheronization</td>
<td>fenoverine</td>
<td>The study shows that the formulation of high quality of pellets. The release rate is controlled by coating material like Cow ghee and carnauba wax.</td>
<td>[66]</td>
</tr>
<tr>
<td>Prabhakar reddy veerareddy et al 2014</td>
<td>Fluid bed processor</td>
<td>Tolterodine tartrate</td>
<td>An optimized formulation was obtained and releasing the drug around 90% within 5 hours. It has similar parameters to that of marketed product.</td>
<td>[64]</td>
</tr>
<tr>
<td>Alamdari et al 2013</td>
<td>Solution layering</td>
<td>Tramadol hydrochloride</td>
<td>The eudragit polymer forms sustained release pellets with decreasing of time intervals which decreases doses and drug toxicity.</td>
<td>[67]</td>
</tr>
<tr>
<td>Senthilkumar et al 2012</td>
<td>suspension layering in FBD</td>
<td>Rabeprazole Sodium</td>
<td>Enteric coating by Eudragit L 30D 55 shows drug release same as marketed products even after 3 months evaluated by accelerated stability studies.</td>
<td>[68]</td>
</tr>
<tr>
<td>Srinath reddy et al 2013</td>
<td>Powder layering in fluid bed coater</td>
<td>Ketoprofen</td>
<td>Drug Release from the optimized formulation is better than the marketed extended release tablet even after the stability studies.</td>
<td>[21]</td>
</tr>
<tr>
<td>Suresh G. Sudke et al 2013</td>
<td>Hot melt extrusion-spheronization</td>
<td>Aspirin</td>
<td>The hot-melt coating technique can be an efficient, eco-friendly and economical tool for formulating enteric coated pellets.</td>
<td>[69]</td>
</tr>
</tbody>
</table>

APPLICATIONS OF PELLETS

1. Controlled release pellets for encapsulations.
3. Floating multiparticulate oral sustained release drug delivery system.
5. Multi-unit erosion matrix pellets.
6. Pellets for special tableting applications.
7. Immediate release pellets for sachets.
9. **Taste masking**: The pelletization technique solves difficult taste masking problem while maintaining a high degree of bioavailability due to their high surface area, especially for oral products. Many products, such as antibiotics (clarithromycin, roxithromycin and cephelexin) and antiinflammatory drugs with a bitter taste, can now be formulated in products with high patient compliance.

10. **Chemically Incompatible Product**: In the compressed tablet dosage form separate tablets would have to be administered, but the pellets can be administered in a single capsule.

11. **Varying dosage without reformulation**: Pellets have excellent flow properties, due to this, they can be conveniently used for filling capsules and the manufacturer can vary the dosage by varying the capsule size without reformulating the product. [33, 70, 71, 27, 72, 55]

**MARKETED TECHNOLOGIES** [42, 73]

<table>
<thead>
<tr>
<th>Technology</th>
<th>Proprietary Name</th>
<th>Drug</th>
<th>Indication</th>
<th>Design parameters</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>CODAS®</td>
<td>Verelan® PM XL</td>
<td>Verapamil HCl</td>
<td>Hypertension</td>
<td>Nonenteric release controlling Polymer (combination of water soluble and insoluble polymers) applied to drug loaded beads.</td>
<td>Lag-time–4–5 h. Early morning peak plasma concentrations following bed time dosing. Rate of release is independent of pH, posture and food and gastrointestinal motility.</td>
</tr>
<tr>
<td>DIFFUCAPS®</td>
<td>Innopran® XL</td>
<td>Verapamil HCl, Propanolol HCl</td>
<td>Hypertension</td>
<td>Drug was layered on sugar bead, followed by a controlled release and delayed release Coatings.</td>
<td>Lag time–4–5 h Cmax–12–14 h after dosing trough levels after 24–27 h of dosing. The rate of release is independent of pH, posture and food and gastrointestinal motility.</td>
</tr>
<tr>
<td>PULSYS™</td>
<td>Moxatag™ tablet</td>
<td>Amoxicillin</td>
<td>Infection</td>
<td>Consisting of three components: one immediate release and two delayed release (by soluble And insoluble coatings)</td>
<td>More efficient killing of bacteria exposed to antibiotics in front-loaded, sequential bursts Reduces duration of therapy</td>
</tr>
<tr>
<td>IPDAS® Technology</td>
<td>Naprelan®. Naproxen</td>
<td>Inflammation</td>
<td></td>
<td>high density multiparticulate tablet technology,</td>
<td>fast onset of action and reduced gastric irritancy.</td>
</tr>
</tbody>
</table>

Some other technologies are Eurand MINITABS, Macrocap®, InnoHerb, SODAS® Technology (Spheroidal Oral Drug Absorption System), Orbexa® [74]
CONCLUSION
Today pelletization represents an efficient pathway for novel drug delivery in the scope for different oral immediate or controlled delivery systems. Because of its simple design, high efficiency of producing spherical pellets and fast processing, pelletization has found a special position in pharmaceutical industry. Since, due to the several disadvantages of traditional techniques for pelletization there is a need of development of novel techniques which are efficient as well as cost effective.

REFERENCES


