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An Overview on Pelletization Techniques

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A B S T R A C T

Technologies related to pelletization are currently gaining a lot of attention because they provide a practical means of creating innovative drug delivery systems. It is better than the conventional dose form in several aspects. The process of pelletization aids in the production of 0.5–1.5 mm spherical beads or pellets that can be coated later on to create modified release dosage forms.It results in an improvement in the fine powder's physical and chemical properties as well as its flow ability, appearance, and mixing qualities, preventing the production of excessive dust and minimising segregation. The goal of this study is to provide a comprehensive and varied set of pelletization techniques, such as powder stacking, suspension/solution layering, cryopelletization, extrusion and spheronization, etc.

Keywords: extrusion, pelletization, cryopelletization, spheronization.

1. INTRODUCTION:

Historically, a number of industries have used the term "pellet" to refer to a wide range of agglomerates made from various basic materials. Pellets are defined as agglomerates of fine powders or granules of bulk medicines and excipients in the pharmaceutical business. They are mainly meant to be administered orally and are composed of small, freely flowing, spherical or semi-spherical solid units, usually ranging in size from 0.5 mm to 1.5 mm. The active agent's safety and effectiveness may be enhanced by the pelletized products. These multi-unit dosages have several benefits over the single-unit administration method and are typically made as suspensions, capsules, or dissolving tablets.

In comparison to single-unit systems, multiple-unit systems release numerous particles into the gastrointestinal tract upon oral administration, requiring less stomach emptying. They can readily pass through the pyloric sphincter due to their small size. This decreases the variance in gastrointestinal transit time both within and between subjects. Because of their small size, they may also be dispersed widely throughout the gastrointestinal tract, which enhances absorption and lessens the potential irritation that single-unit systems may have on the mucosal lining, particularly if they are trapped at one location for an extended length of time .When designing and developing solid pharmaceutical dosage forms, pellets provide a great deal of freedom. Their unhindered flow and easy packing lead to a consistent and repeatable fill weight in capsules and tablets.

2.REASONS FOR PELLETIZATION:

For a number of reasons, the pharmaceutical industry has grown quite interested in pelletization.

- The product's defined shape and weight improve its appearance;
- The free-flowing properties of the pellets improve their handling qualities;
- The hardness and friability of the pellets improve their handling properties;
- The controlled release application of the pellets is made possible by their ideal low surface area-to-volume ratio, which creates an ideal shape for the application of film coatings. The prevention of segregation of co-agglomerated components improves the uniformity of the content;
- The prevention of dust formation improves process safety.

3.ADVANTAGES:

1. Uniformity of dose.
2. Improved safety and efficacy of the product.
3. Reduces the accumulation of drugs(irritant to GI mucosa).

4. Pellets disperse freely in the GIT and hence greater absorption of the active drug occurs and also reduce peak plasma level fluctuations.
5. When formulated as modified release preparation, pellets are less susceptible to dose dumping thus lowering the risk of side effects.
6. Improved appearance of the product.
7. Improved flow properties and ease resulting in uniform and reproducible fill weight of tablets and capsules.
8. Reduce inter and intra patient variability.
9. Pelletization can be used for taste masking of unpalatable drugs.

4.DISADVANTAGES:

1. The production of pellets is quite an expensive process due to the requirement of highly specialized equipment and trained personnel.
2. The control of production process is difficult.
3. Pellets are rigid and so cannot be pressed into tablets. Hence they are filled into capsules.

5.PELLETIZATION:

The agglomeration process known as "pelletization" turns medication and additive powders into small, spherical, freely flowing particles known as "pellets." The methods are divided into categories according to various methods of production, equipment type. .. Centrifugal granulation, a recently popular and widely accepted method of pelletization, involves the creation, drying, and coating of pellets in a single pot (a closed system). In this process, yield is high compared to other techniques. The other techniques are direct pelletization, solution/suspension layering, extrusion/ spheronization and powder layering.Other rarely used pelletization processes has limited application and less industrial applications are melt spheronization, cryopelletization, congealing/drying and spherical agglomeration. .. Drugs are added to the pellets in powder form using powder layering technique, which also involves continuous binder spraying. The process variables include pellet speed, atomization air pressure, powder addition rate, and binder spray rate. Various Pelletization methods are explained in **Fig.1**

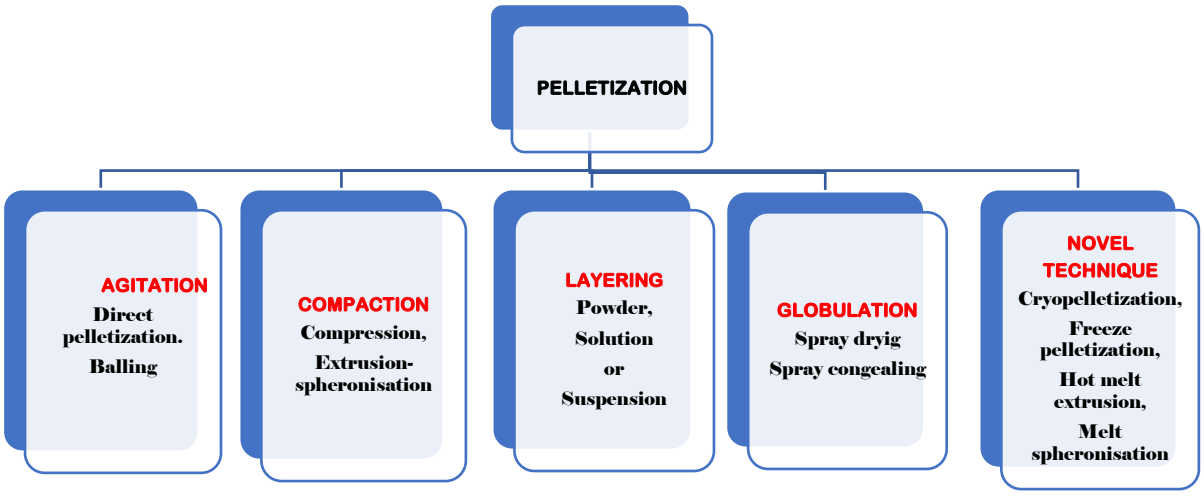

Fig:1 : DIFFERENT PELLETIZATION TECHNIQUES

6.FACTORS AFFECTING PELLETIZATION TECHNIQUE :

6.1.Moisture Content : It is one of the most important parameters in the pelletization process for pellet growth.The wet mass's moisture helps the powder to become cohesive so that the wet mass can be removed and spheronize to take on a spherical shape. Because there is an excess of water on the particle surface during the process of spheronization, one method of pelletization, high moisture contents cause the pellets to clump together, while low moisture contents cause the formation of fines with a wide range in size distribution.

6.2.Solubility of excipients and Drug in granulating fluid : A granulating liquid dissolves a soluble medication.Consequently, increasing the liquid phase volume causes the system that aggregates the pellet sand to become overly moist. This promotes plasticity but creates sticky mass.

6.3.Composition of Granulating Fluid : As a granulating liquid, ethyl ether, diluted acetic acid, isopropyl alcohol, and water/alcohol mixture are also utilised. Researchers such as Millili and Schwartz state that in order to make pellets containing theophylline and Avicel pH (101), at least 5% of the granulation liquid must be water. Researchers found that by substituting diluted acetic acid for demineralized water in the granulation step, mass fraction

can be improved by up to 100%. The researchers utilised water and acetic acid in varying ratios of powder to liquid. The moistening liquid is an aqueous polymer dispersion that contains Eudragit, Hydroxy Propyl Methylcellulose (HPMC), Poly vinyl pyrrolidine (PVP), and Gelatin.

6.5.Physical Properties of Starting Material: Pelletization is influenced by formulation variables such as filler type, constituent particle size, and starting material type and content. Pellet quality is influenced by both composition and grade variations within the same product. The drug's release rate in pellets is determined by the material's swelling characteristic when utilised in the pelletization process.

6.6.Drying technique and drying temperature: Achieving the right pellet size, shape, and flow is crucial, and it needs to be repeatable and constant throughout all batches. Changes in the size, shape, and flow of the pellet will result in variations in the physicochemical features of the finished dosage form, such as uneven filling, weight variation, etc., which will further reduce the delivery system's therapeutic efficacy. A wider range of particle sizes could result in different medication delivery doses. Changes in shape have the potential to affect flow and compressibility.

7.AGITATION : Agitation is the process of adding the necessary liquid while continuously rolling or tumbling the finely separated particles into spheroidal particles. The liquid can be introduced either at the start of the procedure or while it is being stirred. Pellets can be made by the balling process in pans, discs, drums, or mixers. It is the earliest and least effective method of producing pellets.

7.1.Balling: Either applying a high temperature or adding the necessary volume of liquid to the powder will accomplish the goal. There are two types of spherical agglomeration: melt-induced agglomerations and liquid-induced agglomerations. devices such as rotary fluid-bed granulators, inclined dish pelletizers, tumbling blenders, and traditional horizontal drum pelletizers. The industries that deal with iron ore and fertiliser frequently employ this technology. Particle size, the degree of liquid saturation, the liquid phase's viscosity, and the powder's solubility are some of the formulation variables that affect the rate and extent of agglomeration development.

7.2.Direct Pelletization :Powders, upon incorporation of a suitable amount of moistening liquid or when heated to elevated temperatures, may be directly transformed into spherical aggregates by a continuous rolling or tumbling action in a direct pelletization.

8.COMPACTION:

Agglomeration of drug particles or granules takes place in presence of pressure which gives out well-defined shape and size of pellet.

8.1.Compression: Blend of active ingredients and number of excipients are compressed with the aid of pressure to give out defined shape and size of the pellet.

8.2. Extrusion–Spheronization: #### To create spheroids with consistent sizes, the pharmaceutical sector frequently uses the extrusion-spheronization technique. Extrusion spheronization's primary goal is to create uniformly sized pellets or spheroids with a high drug loading capacity. The multistep process of extrusion-spheronization includes wet granulation, dry mixing, extrusion, spheronization, drying, and screening. The medication and excipients are first mixed dry in appropriate mixers, and then the powder is wet granulated to create a plastic mass that is easy to extrude. To create cylindrical extrudates, the wet mass is extruded via cylindrical dies or perforated screens that have circular holes that are usually between 0.5 and 2.0 mm in diameter. These can be treated one more time to create cylindrical granules by cutting and drying. The extruded strands are moved into a spheronizer, where centrifugal force causes them to instantly break into short cylindrical rods upon coming into contact with the rotating friction plate. The rods are then propelled forth and up the processing chamber's stationary wall. The particles eventually return to the friction plate due to gravity, and the cycle is repeated until the required sphericity is attained. To modify the wet pellets' size, density, hardness, and other properties, they must be dried at room temperature or at a higher temperature after the spheronization process is complete. Air-assisted spheronizers, ram extruders, screw-fed extruders, gravity-fed extruders, fluid bed dryers, microwave ovens, and high shear mixers, drive circulation broiler are utilized for differing shapes. Schematic representation of pellets course of activity are portrayed in **Fig.2**

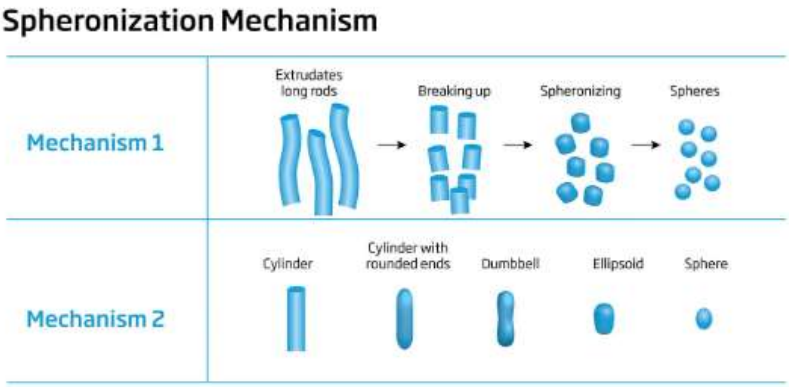

Fig.2: SCHEMATIC REPRESENTATION OF DIFFERENT PELLETS FORMATION STAGES DURING SPHERONIZATION

9.LAYERING:

Pellet formation by layering involves the deposition of successive layers of drug molecules from dry powder or granules, suspension, a solution of drug particles.

9.1.Powder Layering: With the aid of a binding agent, successive layers of dry drug powder, excipient powder, or both are placed on prepared nuclei or cores in the process known as powder drug layering. Powder stacking typically requires specialised equipment because the binding liquid and dry powder are applied simultaneously. The product container must have solid walls without any holes in order to prevent powder from leaking beneath the product chamber before the powder is gathered by the wet mass of pellets being layered on top of it. This is the main equipment need for a powderlayering process. A finely ground powder and a binding solution are simultaneously and gradually introduced to a bed of starting seeds during the powder layering process. Initially, liquid bridges from the sprayed liquid are used to bind the drug particles to the starting seeds and then to the pellets that are forming. Eventually, solid bridges made from a binder in the application medium or from any component that is soluble in liquid—including the drug—will take the place of these liquid bridges. The drug and binder solution are layered one after the other until the required pellet size is achieved. Throughout the procedure, it is crucial to precisely administer the powder at a predetermined rate in a way that keeps the powder addition rate and the binder liquid addition rate in balance. Dust creation might result from a high powder addition rate, and overwetting of the pellets could happen from a high liquid addition rate, which would not maximise the product's quality or yield. A coating pan, tangential spray, or centrifugal fluid bed granulator can all be used for powder layering. The steps in the powder layering technique are listed in **fig 3**

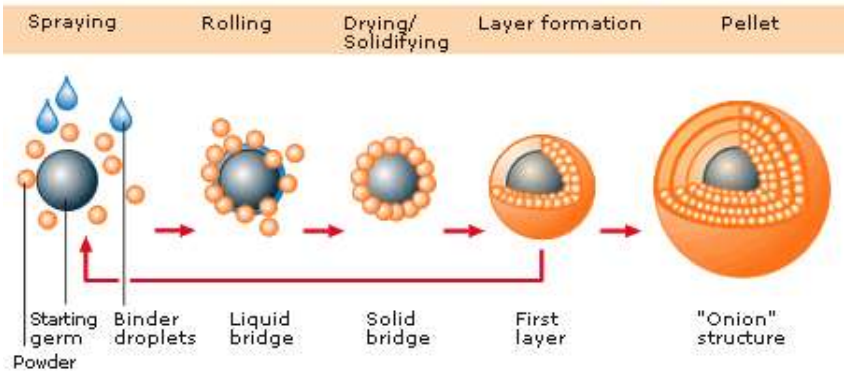

Fig.3: STEPS INVOLVED IN POWDER LAYERING PROCESS

9.2.Solution/Suspension layering: Applying successive layers of pharmacological chemicals and/or suspensions along with binders to starting seeds—which could be inert materials or drug crystals—is known as solution/suspension layering. Before spraying over the product bed, all of the formulation's constituents must be dissolved or suspended in the appropriate volume of application medium in order to produce a formulation with the necessary viscosity. The sprayed droplets instantaneously impinge on the initial seeds and spread uniformly across the surface if the fluid dynamics and drying conditions are suitable. Solid bridges made of precipitating dissolved elements during the drying step hold the subsequent layers of the formulation components on the starting seeds together.

In a perfect world, there would be no new nuclei and the particle population would remain unchanged; in reality, though, as time goes on, the pellet sizes enlarge and the total mass of the system rises. The medication's particle size has a significant role in suspension layering. If the drug particles are large in size, more binder may be needed to ensure that they adhere to the pellet surfaces. To stop any drug particles from settling, it is recommended to use high viscosity binders and to shake the suspensions when adding the medications. If the tube has an overly large diameter, using very large particles could jam the spray cannon or cause them to get blocked in the tubing. The API particle size for the suspension stacking procedure should be less than 10–50 µm. Since the same parameters that govern coating operations also, in theory, govern solution or suspension layers, the same processing equipment is largely required for both applications.

Consequently, wurster coaters, fluid bed centrifugal granulators, and conventional coating pans can all be used to successfully manufacture pellets. The steps in the solution/suspension layering procedure are outlined in **Fig.4**

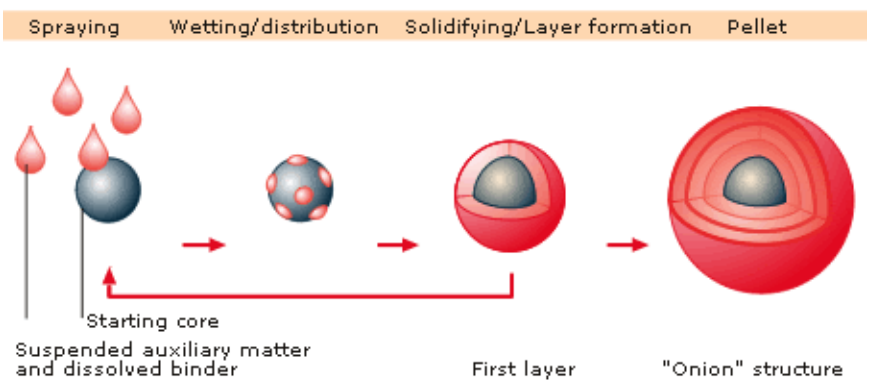

Fig.4 :STEPS INVOLVED IN SOLUTION/ SUSPENSION LAYERING PROCESS

10.GLOBULATION:

This technique, which also known by the name "droplet formation," has two steps: spray drying and spray congealing. In order to create pellet particles, it atomizes hot melts, suspensions, or solutions.

10.1.Spray drying and Spray congealing: This method produces dry spheroids by spraying drug components or solution into a heated stream of air, with or without excipients. The application medium evaporates when atomized droplets come into contact with hot air. This drying process is carried out in a number of steps where the droplet's viscosity steadily rises until the application medium is completely evaporated and solid particles are eventually produced. The powder particles that have been spray-dried are uniformly sized and homogeneous.Particle size, distribution, bulk density, porosity, moisture content, flow ability, and friability of the final pellet can all be enhanced by the design and operation of the spray drier. With or withoutexcipients, drug ingredients or solutions are sprayed into a heated stream of air.
In order to produce spherical congealed pellets under the right processing conditions, spray congealing is the process of allowing a drug to melt, disperse, or dissolve in hot melts of gums, waxes, or fatty acids and then spraying into an air chamber where the temperature is kept below the melting point of the formulation components.

11.NOVEL TECHNIQUES:

11.1.Cryopelletization: Fluid nitrogen is utilized as the settling medium within the cryopelletization handle, which turns fluid detailing beads into strong, circular particles or pellets. After that, water and natural solvents are extricated from these pellets by means of lyophilization or solidify drying. The temperature and strong concentration of the fluid detailing manage how much fluid nitrogen is used generally. The pharmaceutical industry currently uses this strategy to make drug-loaded pellets for both prompt and controlled discharge formulations. Originally, it was created to lyophilize bacterial arrangement within the sustenance division. Drugs, fillers (lactose and mannitol), and covers (gelatin and PVP) are as a rule found in quick discharge details, while crosslinked polymers of collagen subsidiaries are utilised in supported discharge details. The device comprises of a punctured plate that's plunged into a fluid nitrogen supply with a transport belt that varies in speed and a transport perplex. The transport belt's variable speed can be modified to supply the pellets the essential home time to solidify. The solidified pellets are moved into a holder for capacity at -60°C, where they are cleared out to dry in a solidify drier. The foremost imperative stage in this handle is bead arrangement, which is decided by variables connected to detailing, counting surface pressure, thickness, strong substance, hardware plan, and process factors.

11.2.Freeze pelletization: The freeze pelletization procedure is a novel way to make spherical matrix pellets with active ingredients. Using this technique, droplets of a molten solid carrier and a dispersed active component are added to an inert and immiscible liquid column. These droplets can go either upward or downward before forming into spherical pellets, depending on how dense they are in comparison to the liquid in the column. This technology offers substantial advantages over conventional pelletization procedures in terms of pellet quality and process cost, in addition to having fewer process variables. The product of this method is spherical pellets with a narrow size distribution. The pellets are solid at room temperature, so there's no need to dry them.

11.3.Hot melt extrusion & spheronization: There are many advantages to this solvent-free technique, particularly for drugs that show instability due to water left over from processing and storage. Therefore, no extra film coating is needed to ensure controlled release. Rather, formulations comprising water-insoluble polymers, such as ethylcellulose or carnauba waxes, can facilitate release by the following mechanisms: (a) diffusion; and (b) both erosion and diffusion for formulations containing water-soluble polymers, such as hydroxypropyl cellulose. This technology is used to make pellets as well as specific rate release dose forms including tablets, capsules, transdermal implants, etc. A hot melt extrusion line consists of a spheronizer, an extruder with three distinct sections in the heating barrel, and a feed hopper.

12.CHARACTERIZATION OF PELLETS

12.1Rheological characteristics: The Rheological condition of the wet mass determines the flow ability in extruder optimum Rheological condition leads to good flow ability in order to extrude the wet mass variation in rheology make improper and non uniform extrusion.

12.2.Particle size distribution: The distribution of particle sizes ought to be as limited as feasible. This will guarantee the least amount of variance in coating thickness and make the blending process easier if it's necessary to blend different kinds of pellets. Particle size distribution is most commonly measured by sieve analysis using a sieve shaker. The direct way for figuring out the distribution of particle sizes is microscopy. Pellet diameter is measured using optical microscopy and scanning electron microscopy. In 2004, Patappee W. reported using vernier callipers to measure particle sizes.

12.3.Surface area: Surface area, Size, shape, porosity, and surface roughness are the primary attributes of pellets that determine their surface area. The surface area of pellets can be measured using three different techniques. Since the surface area is equal to πd2, it can be computed from the particle size distribution by measuring or utilising the mean diameter. The contributions of surface area resulting from other morphologic features, such as porosity, surface roughness, and pellet shape, are not taken into consideration in this computation. Therefore, surface area may be directly calculated using two methods: gas adsorption and air permeability. Pharmaceutical companies frequently employ air permeability techniques to measure specific surfaces, particularly to regulate batch-to-batch changes. The main obstruction preventing a fluid, such air, from passing through the surface area of the substance is a plug made of compacted material. The BET method, also referred to as the gas adsorption method, was created by Brunauer, Emmett, and Teller in 1937. Using this method, the amount of nitrogen absorbed by the substrate inside an evacuated glass bulb is measured at various pressures. The results are plotted as P/V (p0-p) versus p/p0 to create a linear plot, where p0 is the saturation vapour pressure of liquefied nitrogen at the experiment's temperature and V is the volume of gas in cm3 adsorbed per gramme of substrate at pressure p. The values of b and Vm are obtained from the plot's slope and intercept.

12.4. Porosity: By altering the dissolved drug's capillary action, pellet porosity affects how quickly pharmaceuticals are released from the pellets. Mercury porosimetry provides a quantitative measurement of the pellets' porosity, while scanning electron microscopy (SEM) provides a qualitative assessment. Along with images, optical and scanning electron microscopy can also be used to quantitatively assess the porosity of pellets.

12.5. Density : Changes in the formulation and/or method can impact the density of pellets, which in turn can impact other elements or processes including coating, mixing, and capsule filling. A machine that tappers pellets automatically can determine their bulk density. The degree of densification or compactness of a substance is indicated by its true density.

12.6.FTIR studies: Fourier transform infrared spectroscopy, or FTIR spectroscopic analysis, is used to analyse pure drugs and pellet grains by the use of a KBr pellet procedure on an FTIR spectrometer. After mixing the medication with KBr, spectra are obtained. The FTIR spectra of medication formulations and pure drug are compared. The FTIR 8400-S, Shimadzu, Japan model instrument can be used to study the disappearance or shifting of peaks in any of the spectra.

12.7. Hardness and Friability: Determining the hardness and friability of pellets is essential since they must endure handling, transportation, storage, and additional processing like coating. Relative harness values are provided by devices like the Kaul pellet hardness tester, and the friability of pellets is ascertained by combining glass beads of a specific diameter with an Erkewa type tablet friabilator or turbula mixer for a predetermined amount of time to produce abrasion. Another method for determining friability is to use a fluidized bed with a Wurster insert and an air stream.

13.EVALUATION OF PELLETS:

13.1. Percentage yield :

The percentage yield determination process is used to determine if the preparation method selected for pellet creation is effective or not, as well as to assess the significance of the method in terms of safety and efficacy with minimal effort and maximum benefit. Thus, during the pelletization process, the amount of polymers, binding agents, anti-frictional agents, starch paste, active medicinal ingredients, and other process parameters are the key factors that determine the pellet yield.

The formula for calculation of % yield of a pellet is written below:

% yield= weight of pellets/Weight of drug+weight of polymers×100

13.2. Loose surface crystal study (LSC) :

A total amount of 200 mg of pellets are suspended in a beaker containing 100 ml of phosphate buffer (pH 7.4). The amount of drug present in the solution can be analyzed by spectrophotometrically at 265 nm.

13.3. Determination of drug content : A UV/Visible spectrophotometer can be used to measure the medication content of pellets after they have been ground into a powder. Additionally, the finely crushed pellet sample equal to 100 mg of DPP is transferred to a 100 ml volumetric flask and diluted with a 100 ml solvent specifically made for those pellet particles. The absorbance value is then noted at an appropriate wavelength. Initially, a background scan must be completed before placing the sample, and the drug content in the pellet is calculated using a calibration curve.

13.4. Surface Morphology: The surface morphology of produced pellets and the cross-section pattern of pellets can be determined using the scanning electron microscopy approach. Researchers used a non-contracting laser profile metre to analyse the surface roughness of the particle. Additionally, the surface microstructure of spheroidal particles can be ascertained through the use of an optical microscope.

CONCLUSION:

Due to its unique characteristics in both conventional and innovative drug delivery systems, as well as the ability to manufacture incompatible pharmaceuticals by bypassing the granulation process, pelletization technology has emerged as a major player in the pharmaceutical sector in the current landscape. Many techniques can be employed to create pellets, but the "Extrusion Spheronization" technique is the most popular due to its quick working procedure, simple design, and high production efficiency of uniformly shaped pellets.

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