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Review Article

Development of Multi Unit Pellet System (MUPS) in Capsule

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ABSTRACT

Capsules are the single unit dosage forms that are used for the immediate release of the drug into the systemic circulation. Now a day's capsules are modified to deliver the drug as controlled, modified, delayed release dosage form. Most commonly used controlled release form of capsules is filled by mini tablets, mini capsules, pellets, powders, liquids and semi solids. There are two types of capsules they are soft and hard gelatin capsules, soft are used for the filling semisolids and liquids and hard are used for the filling pellets, tablets, capsules and powders. MUPS (Multi-Unit Pellet System) are the multi particulate pellet formulation that can be administered as tablet or capsules these after administration get disintegrated and covert into their sub unit so they show the combine advantage of tablets and capsules. MUPS are prepared by the pelletization technique that is formation of agglomerates among particles that convert the fine particles into the free flowing spherical or semi spherical units. The size of pellets ranges from the 0.5 to 1.5 mm. The most commonly used pelletization techniques are balling, globulation, drug layering and compaction. Fluid bed processor is the most preferred pelletization technique for the MUPS. These are mostly used for the controlled delivery of the drug and for increase the bio availability and to decrease the local irritation of some drug.

Keywords: Pellets; Fluid bed processor; Multi unit particulate system; Capsules

INTRODUCTION

Pelletization started in 20th century but pharmaceutical industry started in using since 1950 due to the gained demand of sustained release formulation. These pellets are either compressed as tablets or encapsulated into capsules. Pellets are defined as the tiny agglomerates of spherical or non-spherical units upon administration converted into their subunits of narrow size range that is 0.5-1.5 mm [1-3]. They are gaining attention due their development as sustained or controlled release formulation. These are converted into the controlled or modified by coating the respective polymer layer. Pellets get degraded during the manufacturing of tablets due to the mechanical stress so it is mostly preferred to encapsulate the pellets into capsules [4].

Ideal properties:

1. Quantity of drug should be maximum to obtain the desired efficiency and size of pellets.

2. It should be spherical in shape and smooth in texture.

3. Size of particles should range between 0.5 to 1.5 mm

Advantages:

- It improves the safety and efficacy of the active ingredients.
- Improve the appearance of the product.
- Easy transport and decrease the handling hazards.
- It is used to mask the taste.
- Improves the flow property by increasing the filling rate of capsules.
- It shows uniform content.
- It can also be used for the separation of the incompatibility between the active ingredients and the excipients.
- Pellets reduce the intra and inter subject variability.

Disadvantages:

- Pellets are rigid.
- They are expensive.

MULTI-UNIT PELLET TECHNOLOGY

Pellitization

Pelletization is agglomeration process that converts the fine material into the free flowing spherical or non-spherical units referred as pellets. Pellets are the multiple small discrete units that exhibit its desired characteristics. Pelletization and granulation is

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interchangeable word with difference of size range. Pelletization and granulation techniques are used to develop pellets and granules respectively pellet size ranges 0.5 to 1.5 and granules size 1.0 to 2.0 mm and 20 to 50% porosity [5-8].

Pelletization techniques

Extrusion-spheronization: It is developed in 1960's for the purpose of developing controlled release and modified release of dosage form to ensure uniform size distribution, free flowing property, and uniform coating, high drug loading capacity [9-13]. It is a multi-step process where the material undergoes extrusion followed by spheronization to produce uniform size spherical particles called spheroids or pellets or beads depending on the material and the process used. It involves;

• Dry mixing: It involve the mixing of dry material to get homogenous dry powder

• Wet massing: Dry mass is mixed with the liquid mixture to form the plastic mass this is done mostly by the planetary mixer.

• Extrusion stage: Extrusion stage is production of cylindrical segments of uniform diameter from the wet mass. The major contributing factors to be considered are final particle size of pellets and diameter. The diameter is controlled by the extrudate screen diameter. In extrusion the plastic and brittle extrudates are produced from the moisture powder mass which is broken by moderate shear force into fragment. They should possess the enough plasticity to deform but excessive plasticity may lead to the sticking of particles during the process and collecting. Extrudation parameters to be controlled are feed rate, powder, die temperature, and compression chamber pressure.

• Spheronization stage: Nakahara first introduced this technique in 1964. This technique involves 3 stages.

1. Breaking of cylinder or extrudate.

2. Agglomeration of broken particles.

3. Smoothing of particles.

Breaking occurs due to the interaction between the extrudate with rotating grooved plate wall or other extrudate particles. Spherical particles are created by the rotational motion of each particle in its own axis and changing plane. These fragments are rounded into pellets under stress for remodeling

Drying of spheroids: To attain the desired moisture content drying is done at room temperature or elevated temperature in tray drier or fluid bed dryer.

Screening: screening is done to achieve the desired narrow size distribution.

Extruders: Extruders are the 3 different types.

They are:

• Screw feed extruder: these contain screws that rotate in horizontal axis that transfer material horizontally. Axial have axillary placed die plate contain feeding zone, extruder zone.

• Gravity fed extruders: Gravity consist of rotary cylinder and gear extruder. In this the gear extruder contains two counter rotating cylinders, and rotary cylinder contains one or two counter rotating cylinders.

• Piston feed extruders: piston extruder is also called as ram extruder which contain piston which displaces and force the material through die at end. In development phase it is also used for the measurement of the rheological properties of formulation.

Cryopelletization: The Cryopelletization technique is obtained from the Lyophilization of viscous bacterial suspension. It can be used to produce pellets or spherical particles by converting the liquid medium into the solid spherical particles by using liquid nitrogen as fixing medium. This allows instant freezing of the liquid medium or processes material that cause rapid heat transfer between the droplets and liquid nitrogen. The pellets are dried by the conventional freeze dryers to remove water or organic solvents. Equipment contains perforated plate, reservoir and conveyer belt with transport baffles storage container. The liquid material is sprayed from the top and it passes through the perforated plate and then it gets contacted with the liquid nitrogen and get freezed. These frozen pellets are stored in -600°C.

Freeze pelletization: This technique involves less process variables and also, they possess high or desired quality of pellets. It involves the dispersion of active ingredients into the molten solid carrier mass and this mixture is introduced as droplets into an inert and immiscible column. In this there is no need of drying process and the pellets formed will possess narrow size distribution. In this the material will undergo down and upward movement depending on the density of the material. The solid carriers used should contain the melting point less than 100 where the degradation of active ingredients is minimized. There are two types of equipment's.

1. Molted solid carriers are introduced from the upper portion of column because of density of solids is more than the liquid used in column. And the hydrophilic polymers used are polyvinyl alcohol, poly ethylene glycol, and low melting point sugars like dextrose and maltose. Liquids used are mineral oil, vegetable oil and silicone oil.

2. Molted solid mass is introduced from the bottom because the density of solids is less than the liquid used in column and hydrophobic carriers of low density are liquid poly ethylene glycol, ethyl alcohol, glycerin and water.

For sustained release containing mixture of hydrophilic and hydrophobic solids where they are immiscible in both hydrophilic and hydrophobic molten solids so cooling liquid column are used.

Globulation: It involves two processes they are spray drying and spray congealing. Pellets are produced by the atomization 5 of the solution, suspension, and hot melts. The pellets size is small to maximize the rate of evaporation or congealing. Used mostly to improve the dissolution rate, so it increases the bioavailability of poor soluble drugs. The coating solution is atomized into hot air where the particles or pellets are formed it is done in series till the desired solid particles are formed. In congealing the active ingredient is dispersed in the hot melts of gums, waxes and spray into chamber where the temperature is below the melting point of formulation components. These both are used for immediate release and controlled release formulation.

Compression: It is a type of compaction techniques in which the mixture or blend of active ingredient and excipients are compacted to prepare pellets.

Balling: In balling the pellets are formed by the continuous tumbling or rolling motion. It is done by the addition of liquid medium.

CPS (Complex Prefect Spheres) pelletization: This technique

was invented by the glatt gm blt in binzen, Germany in the year 2000. In this they produce micro pellets and matrix type pellet by using direct pelletization technique and advanced fluid bed rotor. The modified bed rotor containing conical shaped rotating disc and additional devices for direct movement of particles. It is a type of drug layering on the inert core and also dry powder by the liquid that is in different forms like solution suspension and emulsion which exhibit drug layer quality. The solvent used for the dissolution or dispersion of active ingredient may be organic or inorganic or aqueous solvent. The end point of the pelletization is identified by the CPS rotor. Desired density of pellets can be achieved by rolling movement of particles, different forces like centrifugal force and speed of rotating disc. In this process the particle size ranges 0.1 to 1.5 mm, smooth surface, drug loading 0.1%-90%, low attrition and friability, high density, low porosity, dust free surfaces, particle size distribution >90% between 0.7-0.9 mm.

Pro-cell technique: It is a spouted type of continues agglomeration technique where the particles are fluidized in process spouted bed by vertical air flow process. The air entering the processing chamber is done through the side not through the bottom plate or inlet distribution plate as in the conventional fluid bed processor. The shape of the fluid bed processor is broader at the top and become narrow it may result in sharp decrease of fluidized velocity of process air. Due to this effect, it shows controlled flow pattern and circulation of particulate in chamber. It is a direct granulation and pelletization process. In this technique as such in other techniques inert beads are not used. The formation of pellets or granules is occurred by spray solidification and agglomeration. It is used in the manufacturing of the spherical pellets with high density and low porosity resulting in matrix type granules or micro pellets with the size ranges 0.05-1.5 mm. it is a type of hot melt granulation process where there is no need of evaporation of organic or water solvents and there is no use of excipients where the d rug loading is up to 100% it is achieved due to the design of process chamber and its processing characteristics.

Drug layering: the layering is one of the controlled pelletization techniques. This process involves the drug deposition from the solution, suspension, emulsion and hot melt containing the active ingredients and other excipients. It forms the solid bridges between the core and the drug particles and among the successive layers of drug substance and polymer. This is continued until the desired layer of drug is attained. If the coating mixture is in the suspension form then the particles size is the major parameter to be considered. The first equipment used commercially for manufacturing of pellets is conventional coating pan but it has limitations as the pelletization equipment that is degree of mixing is very poor and drying is not efficient. other equipment used are the tangential spray granulator, centrifugal fluid bed granulator.

1. Powder layering: In this technique the inert core material is coated with the mixture of binder and then are subjected to rotating pan where the powder Particles are coated on to it. In this technique the liquid bridges between the solvent and the powder material are form the solid bridges.

2. Solution or suspension layer: the drug substance and the other excipients are dissolved or dispersed into the solvent mixture and sprayed onto the inert core slid material. The major difference in solution and the suspension is the solid material is dissolved I the solution and dispersed in the suspension. the major parameter considered in suspension is the particles size. The material sprayed on core get solidified and form solid bridges between the inert core and spray coated particles.

Pellet coating process: pellet coating is done to modify the release of drug from pelletized drug delivery system.

The equipment used are;

- Standard coating pan
- Perforated coating pan
- Fluidized bed coater

Standard coating pan contain circular metal pan mounted angularly and the pan is rotated its own horizontal axis by using motor, then hot air is directed into the bed for the drying of material on the bed surface and the air is exhausted from the dust in front of pan.

Perforated pan is most effective with high coating capacity. It is used for both sugar and film coating of materials. They are 4 types

1. Accela-cota.
2. Hi-coater
3. Dria coater
4. Glatt coater.

In all 4 types coating is done by spraying the solution through nozzle positioned inside drum onto the bed of pellets. Fluid bed coating is mostly preferred for the drug to attain the gastric resistance and controlled release formulations. It is not only used for coating and also for the drying, pelletization in same equipment commonly used for film coating of pellets.

Fluid bed coating for layering of pellets: Influenced by quoting, the particles are fluidized and the coating mixture is prayed and right. It provides even product coating due to small droplet size and low viscosity. Glad offers batch fluid systems. They are

- Top spray.
- Bottom spray
- Tangential spray

- The top spray is used for coating of pellets with enteric coating. The particles are fluidized with the flow of heated air, which is introduced through base plate into the product container and the liquid continuously sprayed onto the particles against the air flow. Concurrently, through nozzles. Drying is also takes place simultaneously. It shows uniform distribution depending on applications they are divided into pre heating zone, spray zone, drying zone. Continuous feed is suitable for protective and color coating of Material.

- The bottom spray is of two types wruster Bottom spray and continuous fluid bed bottom spray

1. In Wruster Bottom spray. It is suitable for coating of controlled release formulations. In wruster with the low use of coating substances complete seal is occurred. Spray nozzles displays spray concurrent to the Fed rate. Drying also occurs due to the movement of particles up and down into the wruster base plate. Particles of different size also evenly coated.

2. Continuous fluid bed bottom spray is suitable for protective coating and color coating of substances. Depending on application they add divided into pre heating zone, spray zone drying zone.

- Tangential Is used for coating of high solid content. The product

is in spiral motion by rotating base plate. The spray nozzle is in tangential to the rotating disc. In this rotor method, thick film is formed.

Advantages:

• This shows uniform coating of Particles

• Continuous product coating can be seen to unit operation coating and drying occurs in same machine.

• GPCG (Glatt powder coater granulator) provide an optimum ratio of air volume flow to quantity of product used.

Capsules and its technology: Capsules are the single unit solid dosage form made up of gelatin mixture. Capsules shell are used as the immediate release dosage form where recent advances it is converted or modified into the sustained or controlled release formulation by encapsulation of mini tablets, mini capsules, powder that possess the sustained release profile, liquids, semi solids and pellets. These can be attained by the sustained release coating by the polymer.

Sustained release capsules: These formulations are developed to rectify the problem faced by frequent dosing of dosage form. This is overcome by the sustained release formulation by coating mixture of active ingredient and the adhesive on to the inert core material called as pellets or particles and then they are coated with the delay release polymer for protective action and then they are filled into the capsules.

Hard gelatin capsule is used for pellet filling it is manufactured by dipping method there include different steps are dipping, rotation, drying, stripping, trimming and joining (Table 1).

Table 1: ADME Properties.

Capsule size	Volume in (ml)
5	0.13
4	0.2
3	0.27
2	0.37
1	0.48
0	0.67
0	0.95
0	1.36

FILLING TECHNIQUES

There are different types of filling techniques and different steps. Steps involved are;

• **Rectification**

Empty capsules are oriented so that all the capsules are in same direction. They are mostly aligned as body end downwards.

• **Separation of capsules**

The rectified capsules are delivered as the cap first into the inner upper portion of split filling ring. Vacuum is applied from below pulls the body down into the bottom portion split filling ring.

• **Filling:** There are two types of filling direct filling and indirect filling.

➢ Direct filling is done manually they are punch method and feton method.

➢ Indirect method involves auger filling, vibratory filling and piston.

➢ The auger filling contains rotating auger and the mass flow hopper where the powder or pellets are present. The number of pellets loaded depends on auger speed and time of capsules body spent underneath the hopper outlet.

➢ Piston lightly compresses the individual dose of powders into plugs and ejected the plug into the empty capsules.

➢ In vibratory filling there is a perforated resin plate is positioned and connected to vibrator. Powder blend is fluidized due to vibration of plate and powder flow into body through the holes of resin plate.

• **Sealing:** sealing is a technique of joining the cap and body of capsule. It is done by colored band of gelatin through a heat welding process that fuses the capsule to the body through the double wall thickness at their junction.

This technique is known as the weld's gelatin seal.

FACTORS INFLUENCING PELLETIZATION

• Moisture content: moisture content plays a major role in the quality of pellets. If the pellets are drying heavily then it may lead to production of high amount of fine and if the water content is more than it leads to the agglomeration of the particles.

• Rheology: variation in rheology may lead to non-uniformity and improper extrusion. Rheology is used to determine the flow property of pellets.

• Size: size of pellet affects the drug release profile of dosage form.

• Shape: sphericity play a major role in flow property of the pellets or powder material.

• Porosity: It affects the polymer coat integrity and another key factor effecting the flow, content uniformity.

• Density: It is important if it is used to reach prolonged gastric residence.

• Elasticity: It is related to pellet composition. Pellet core should be strong with some degree of plasticity.

• Composition of granulating fluid: pellets are manufactured by wet granulation technique where the composition of the fluid is the major parameter. Aqueous and binary mixture of solvent are used as a granulating solvent. Millili et.al used alcohol as solvent but it does not yield successful pellets, while using 90%of ethanol effective pellets are formed. By using water, it forms sticking material. Morkhade researched on different solvent like Poly ethylene glycol, poloxamers, glycerol, sodium lauryl sulfate, glycerol, polysorbate 80, tri ethyl citrate in combination with water. Among them PEG 400 found effective.

• Spheronizer speed rate: It affect hardness, density, size, high speed of spheronizer yield high sphericity, lower friability, smooth surface.

• Drying temperature: The drying influence the flow, size, shape.

CHARACTERISTICS

Particle size

Size of pellets is important parameter where it influences the release kinetics of dosage form. It is measured by using sieve Shaker. In recent wiwattapatapee 2004 reported particle size of pellets using

vernier calipers.

Shape

The shape of pellets should be spherical which affects the flow property, Content uniformity, weight, uniformity of dosage form. The shape of pellets can be mounted by light microscope fitted to camera lucida an image is drawn manually on graph. Shape factor is used to estimate the deviations of projected image from the circle and calculated by pellet projected area. The shape factor should be between one and two. Visual inspection of pellets by microscope and stereo microscope is another method for determining the shape of pellets.

Morphology

SEM is used to determine the surface morphology and cross section of pellets.

Surface area

Surface area of pellet plays a major role in drug release where it also related to size and shape of pellets. It is determined by gas adsorption technique.

Hardness and friability

Hardness is an important factor where the pellet lack of hardness produces dust by the flaking of during the handling, storage, processing, shipping, lack of mechanical strength also effects the pellets in tablet compression. It may be due to variation in formulation process or raw materials. Hardness tested by Erweka and also Kahl pellet hardness tester but it is not accurate. friability can be determined by fluid bed with Wuster insert by using steam of air.

Tensile strength

The tensile strength is defined as a maximum load that a material can with stand without the fracture of particles. It can be measured by tensile strength apparatus with a load of 5 kg cell. The pellets are strained till failure and the value is recorded and calculated.

Cushing strength

Cushing strength is the strength used to break the pellets. It is tested or determined using material testing machine.

Porosity

The porosity can be measured by the Mercury porosimeter and also qualitatively by SEM with image analysis and quantitatively by optical microscope. It effects on the release of drug from pellets by effect on capillary action of dissolved drug.

Dissolution

Dissolution is the major factor to be considered. It is performed to identify the correlation between the in vitro and in vivo of Modified release pellet formulation. It is determined as a quality control parameter for pellet. It is affected by the hardness composition size polymer end binder used. Solubility of pellets is identified by USP and IP apparatus (Table 2).

Table 2: Types of dissolution apparatus.

Types	USP	IP
1	Basket apparatus	Paddle apparatus
2	Paddle apparatus	Basket apparatus
3	Reciprocating cylinder	
4	Flow through cell	
5	Paddle over disc	
6	Rotating cylinder	
7	Reciprocating disc	

Dissolution apparatus 3 (reciprocating cylinder) is used to study the dissolution profile of pellets with delayed release. It is carried out by using 0.1 N HCL for 2 hrs followed by PH 6.8 phosphate buffer USP for 45 min. The phosphate buffer is prepared by using combination of required amount of HCL with tribasic sodium phosphate. The reciprocating cylinder moved between rows and switched from one medium to another during the study. The sample are collected with duration of 5 min and pass through the 0.22 µm Millipore filter and analyzed by UV-Visible spectrometer (Table 3).

Table 3: Dissolution profile of pellets.

Parameters	Dissolution test conditions	Reciprocating disc	Reciprocating disc
Dissolution medium	0.1 N HCL and pH 6.8 phosphate buffer	Reciprocating disc	Reciprocating disc
Temperature	37 +/-0.5°C	Reciprocating disc	Reciprocating disc
Volume in ml	150/200/250	Reciprocating disc	Reciprocating disc
Reciprocating speed	5/15/2025	Reciprocating disc	Reciprocating disc
Sample holder	Reciprocating cylinder 40	Reciprocating disc	Reciprocating disc
Volume of sample with draw	5 ml	Reciprocating disc	Reciprocating disc
Test duration	2 hrs in 0.1 N HCl followed by 45 min in pH 6.8 phosphate buffer.	Reciprocating disc	Reciprocating disc

APPLICATION

Taste masking: pellets are used for taste masking of some Drugs like anti-inflammatory and antibiotics. There are various types of taste masking techniques, like coating with insoluble polymers or soluble polymers, addition of flavors, sweeteners, complexation, use of insoluble products. It causes the lowering of bioavailability of Oral product. Pelletization techniques is used to solve problems which are involved in taste masking techniques, by increasing the bioavailability and also by taste masking due to their high surface area.

Immediate release

The drug in pellet form led to increasing the surface area. As compared to traditional compressed tablets or capsules. The effect that reducing in disintegration time.

Sustained release

The sustained release pellet shows immediate release of drag to maintain the therapeutic response Followed by gradual release of drug to maintain the therapeutic response by the smooth absorption of drug through the stomach, into the intestine, at steady rate which maintains the plasma Level.

Delayed release

The delete release formulations may be affected by the environmental

conditions like the gastric pH, enzyme and pressure. Acid resistance of pellets; A gastro resistance study was performed using apparatus 2 of USP at 100 rpm in simulated gastric fluid at 37 degrees for two hours. The test was run in gastric fluid for two hours at the end of the pellet are removed from the vessel, Media was discarded. The pellets were crushed and powdered equivalent to 40 MG of drug was transferred to volumetric flask. Required amount of 0.1 N NaoH added mixed filtered. The filtrate was suitably diluted with pH 6.8 phosphate buffers and analyzed by U spectrometer.

Chemical incompatibility

The incompatibility of drug lead to toxic problems so it can be rectified or minimized by the pellet formation.

DISCUSSION AND CONCLUSION

The capsules at the solid to sage forms made up of gelatin by dipping method filled by using different equipment's like Auger filling, vibratory and piston filling methods. The capsule is modified for the sustained release formulations in which the capsule is filled with pellets, tablets, capsules, semi solids or liquids. In MUPS are the solid dosage form which can be compressed into tablet or encapsulated into capsules. Pellets are multi-unit dosage form where it contains a core sphere on which the drug is coated as a sustained release and on it delayed release coat is coated which used to maintain the plasma drug levels. Different pellet techniques, was used for manufacturing of MUPS like compaction, balling, extrusion spheronization, layering like solution, layering, suspension layering and powder layering and they are evaluated for particle size, shape, surface area, dissolution of dosage form.

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