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Review Article

# Multiple Unit Drug Delivery System: Pelletization Techniques

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## ABSTRACT

The present study aims at discussing the potential advantages of multiple unit dosage forms (pellets etc.) over the single unit dosage forms (tablets). Pelletization is a novel drug delivery system; a technique which converts fine powder particles into pellets. Review deals with the pellet and its various types of pelletization techniques like spheronization and extrusion, pelletization by layering, pelletiztion by solution layering &direct pelletization.The advantages, disadvantages & various applications of above mentioned techniques.spheronization and extrusion pelletization by layering are most widely used techniques.The study also deals with factors and evaluation of pellets.

**Keywords**: Pellets**,** Multiple unit dosage form, Spheronization, Extrusion, & Modified release

## INTRODUCTION

Oral modified drug delivery systems can be classified in to two broad groups Single Unit dosage forms &multiple unit dosage forms. Multiple unit dosage forms (MUDFs), such as granules, pellets, or mini tablets. The concept of MUDFs was initially introduced in 1950s. The production of MUDFs is a common strategy to control the release of drug as Shown by the reproducibility of the release profiles when compared to the ones obtained with SUDFs.The development of mini matrices is a promising area in pharmaceutical research concerned with a high control over the release rate of the drug combined with a high flexibility on the adjustment of both the dose and the release of drugs and has attracted some attention in the 1990s. Like other MUDFs, several mini tablets can either be filled in to hard capsules or compacted in to bigger tablets. Then after disintegration, they release these sub-units as multiple dosage forms. There has been increasing interest in the development of

MUDF'S incorporated into tablets instead of hard gelatin capsules in order to overcome the higher production costs of capsules. In contrast to Monolithic dosage forms multiple unit dosage forms offer several advantages.

## Pellets

Pellet has been used to describe a variety of systematically produced, geometrically defined agglomerate obtained from diverse starting materials utilizing different processing conditions. They contain multiples of free-flowing, spherical or semi-spherical solid units which are smaller in size (0.5 mm to 1.5 mm), and are intended mostly for oral administration[1,3]. The small sterile masses which are obtained from the compression of implants or sterile cylinders are termed as pellets in pharmacy[4,5]

Regardless of which manufacturing process is used, pellets have to meet the following requirements:[6,7]

- Spherical shape and smooth surface is considered as desired characteristics for uniform film coating.
- The particle size of pellets should be in range of 600-1000µm.
- The quantity of the active ingredient in pellets should be maximum in order to maintain size of pellet.

For the past two decades, pellets made their use promising for are ideal characteristics.[8] Due to free-flowing character of Pellets they are packed easily without any difficulties and hence flexibility in design and development a uniform solid dosage form. (Uniform weight of capsules and tablets) [9-10.] The spherical shape and a low surface area-to-volume ratio of pellets made uniform film coating.[11] two or more drugs can be formulated in a single dosage form, chemically compatible or incompatible, at the same sites or different sites in the gastrointestinal tract different release rates of the same drug can be supplied in a single dosage form.[12]

Multiple-unit dosage forms are showing a number of advantages over the single-unit dosage system like suspensions, capsules or disintegrating tablets.[13] With pellets, the above mentioned goals can be obtained through the application of coating materials (mainly different polymers), providing the desired function, or through the formulation of matrix pellets to provide the desired effect.[14]

## Therapeutic Advantages of Multiple Units over Single Units

When taken orally, multiple unit dosage forms

- Disperse freely in the gastro intestinal tract.
- Maximize drug absorption, reduce peak plasma fluctuations, minimize local irritation of the mucosa by certain irritant drugs and minimize potential side effects without appreciably lowering drug bioavailability.
- Offer reduced variation in gastric emptying rate and transit time which is less dependent on the state of nutrition.
- Provides less risk of dose dumping.
- Reduces localized concentration of irritative drugs.
- Improves safety and efficacy of a drug.
- Reduce inter and intra patient variability.
- More suitable for fabrication of formulations with acid-sensitive drugs. (e.g.Erythromycin)(Digeenis GA 1994).

## 1. Desirable Properties of Pellets

### Uncoated pellets

- Uniform spherical shape and smooth surface.
- Optimum size, between 600 and 1000µm.
- Improved flow characteristics.
- High physical strength and integrity.
- Good hardness and low friability.

- High bulk density.
- Ease and superior properties for coating.
- Reproducible packing of beds and columns.

Coated pellets

- Maintain all of the above properties.
- Contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits.
- Have desired drug release characteristics.

2. Advantages of Pellets

- The smooth surface and the uniform size of the pellets allow uniform coating not only for each pellet but also from batch to batch. Coating of pellets can be done with different drugs to enable a controlled release rate.
- In case of immediate release products, larger surface area of pellets enables better distribution.
- Chemically incompatible products can be formed into pellets and delivered in a single dose by encapsulating them.
- The beads or granules of different thickness of coatings are blended in the desired proportions to give the desired effect.
- The thickness of the coat on the pellets dictates the rate at which the drug or contents are released from the coated particles.
- By selecting the proper formulation, processing conditions and processing equipment, it is possible to attain smooth surfaced and uniform pellets.
- Improved appearance of the product and the core is pharmaceutically elegant.
- They offer high degree of flexibility in the design and development of oral dosage form like suspension, tablet and capsule.
- Recently, coated pellets are compressed to rapidly disintegrating tablets. For this purpose small pellets with the mean diameters below 0.5 mm are most suitable. Such pellets can be produced by direct pelletization methods.

3. Disadvantages of Pellets

- The manufacturing of multiple unit dosage forms is more complicated and more expensive.
- The filling into gelatin capsules is difficult to accomplish, especially in the case where different subunits are involved.

**Factor Affecting Pelletization Technique**

1. Moisture Content

It is one of the critical parameter for pellet growth in pelletization technique .Moisture in the wet mass bring cohesiveness to the powder so that the wet mass can be extracted and spheronize to give spherical shape. High moisture contents lead to agglomeration of pellets during the process of spheronization which is one of the technique of pelletization 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.[11]

2. Rheological 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.[15]

3. 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.[12]

4. Composition of Granulating Fluid

Besides water, alcohol,water / alcohol mixture, Ethyl Ether, Dilute Acetic Acid,

Isopropyl alcohol is also used as a granulating liquid. According to researcher like Millili and Schwartz, a minimum of 5 % of granulation liquid have to be water in order to produce pellets be water in order to produce pellets containing Avicel pH (101) and theophylline.[16] Some researchers used water and dilute acetic acid in different powder to liquid ratio and concluded that mass fraction can be increased up to 100% by using dilute acetic acid for granulation step in place of demineralized water.[29] Aqueous polymer dispersion containing Eudragit,Hydroxy Propyl Methylcellulose (HPMC), Poly vinyl pyrrilodine (PVP) and Gelatin is used in the moistening liquid.

### 5. Physical Properties of Starting Material

Formulation variable such as type and content of starting material, type of filler and particle size of constituent have the effect on the pelletization process. Quality of pellets depends not only composition but also on different grades of the same product.[30] The swelling property of material used in pelletization technique decides the release rate of the drug in pellets.

### 6. 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.[31]

### 7. Drying technique and drying temperature

It is important to get proper size, shape and flow of pellets and it must be reproducible and consistent in all the batches. 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. Variation in shape may lead to variation in flow and compressibility.

### 8. 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.[20]

## PELLETIZATION TECHNIQUES

Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free-flowing, spherical or semi-spherical units, referred to as pellets. The type of coating technique strongly affects the film microstructure and thus affects the release mechanism and rate from pellets coated with polymer blends. There are several manufacturing techniques for production of spherical pellets.[21]

### Agitation

### Balling

Finely divided particles are converted upon the addition of appropriate quantities of liquid, to spherical particles by a continuous rolling or tumbling motion. Pans, discs, drums, or mixers may be used to produce pellets by the balling.

### Compaction

### Compression

Mixtures or blends of active ingredients and excipients are compacted under pressure to generate pellets of defined shape and size.

### Extrusion – Spheronization

It is a multistep process invented by Nakahara, in 1964. Extrusion spheronization follows mainly five steps that is mixing or blending, extrusion, spheronization, coating and finally drying, which can be explained/described as

- Dry mixing of ingredient to achieve homogenous powder dispersion.
- Wet massing to produce a sufficient plastic mass.
- Extrusion to form rod shaped particles of uniform diameter.
- Spheronization to round off these rod shaped particles into spherical particles with narrow size distribution.
- Drying to achieve desired final moisture content.
- And screening to obtain desired size of spheres/pellets.

It involves dry mixing of the active compound with excipients, granulation of wetted mass, extrusion of the mass, transfer of the mass to spheronizer to produce spherical shape, drying of the wetted mass in a dryer, and at the end screening to obtain required particle size.

### Layering

In this process, drug is layered onto seed materials (generally, a coarse material or nonpareil) in powder, solution or suspension form and leads to heterogeneous pellets, which consist of an inner core region and an outer shell region of a different composition. This process is classified into three categories namely direct pelletization, solution or suspension layering and powder layering.

#### I. Direct Pelletization

A process that leads to formation of homogeneous pellets which have microscopically uniform structure and no core can be detected. Direct pelletization is mainly performed in high shear mixers and fluidized bed equipment.[22]

#### II. Powder Layering

Powder layering involves the deposition of successive layers of dry powder of drug or excipients or both, on preformed nuclei or cores with the help of a binding liquid. Equipment used is tangential spray/centrifugal/rotary fluidized bed granulator.[14]

Some of the disadvantages are:

- Low amount of drug loading which is not suitable for high-dose drugs.
- Final composition of pellets can vary if spray loss occurs.

#### III. Solution/Suspension Layering

- In the case of Solution/Suspension layering, growth of pellets involve deposition of successive layers of solution and/or suspension of drug substance and binders on existing nuclei, which may be inert seed, crystal or granule. The drug particles are dissolved or suspended in the binding liquid, with or without the binder. Droplets of the binding liquid spread on the surface of the nuclei. During drying, liquid evaporates and the dissolved substances crystallize out and capillary forces which are formed draw the particles towards each other and towards the inert seed, forming solid bridges. In suspension layering, particles have low solubility and are bonded by solid bridges formed from the hardening binder i.e., that higher concentration of binder might be necessary.
- In this process fines are produced as a result of attrition or spray drying, especially when the process is not optimized.
- The efficiency of the process and the quality of pellets produced are in part related to the type of the equipment used.
- As a starter seeds usually sugar spheres consisting of a sugar-starch mixture or

recently microcrystalline cellulose pellets and the pure drug crystals are used.

- The most common configuration used is Wurster, bottom spray coater.
- This technology is applied to produce enteric coated Esomeprazole pellets for improving the stability in acidic media, due to the enhancement of the polymer film formation on the surface of the pellet. On the other hand enteric coating assures immediate release in alkali media at the site of the action.

### Globulation

Globulation or droplet includes spray drying and spray congealing.

### Spray Drying

Drug entities in solution or in suspension form are sprayed, with or without excipients, into a hot air stream to generate dry and highly spherical particles. It is generally employed to improve the dissolution rates and hence, bioavailability of poorly soluble drugs.

### Spray Congealing

A process in which a drug is allowed to melt, disperse, or dissolve in hot melts of gums, waxes, fatty acids, etc., and is sprayed into an air chamber where the temperature is below the melting points of the formulation components, to provide spherical congealed pellets under appropriate processing conditions.

## EVALUATION OF PELLETS

### 1. Size Distribution

The sizing of pellets is necessary because it has significant influence on the release kinetics.[24] Particle size distribution, means ferret diameter, geometric mean diameter, means particle width and length, is the parameters by which size of pellets can be determined. In most of the cases particle size determination is carried out by simplesieve analysis using sieve shaker[24] reported the use of vernier calipers to determine the size of pellets.

### 2. Pellets Shape

Sphericity of the pellets is the most important characteristics and various methods have been used to determine it. 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.[25] 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.[26] One plane critical stability, which an angle at which a plane has to be tilted before a particle begins to roll, is one of the important methods used for determining shape.[5] The angle of repose is an indirect indication of the circularity of pellets and is calculated by the ratio of double the pile height and pile radius by fixed funnel method measured after a certain amount of pellets are allowed to fall from a given height through a specific orifice.

### 3. Surface Morphology

Scanning electron microscopy is used to examine the surface morphology and cross section of pellets. Sood et al. in 2004 reported the use of optical microscopy to examine the microstructure of pellet surface.[27] Some researcher analyzed surface roughness of pellets by applying a non contracting laser profile meter.[28]

### 4. Specific Surface Area

Surface area of pellets is directly related with size and shape of the pellets. Knowledge

of the surface area is desirable especially if film coating is considered. Knowledge about the surface area is important even in case of uncoated pellets, since drug release isinfluenced bythesurface area.[23] Specific surface area of pellets is determined by gas adsorption technique.[28]

### 5. Friability

The mechanical properties of pellets are important for processing. Pellets flake off during handling and coating process resulting in formation of dust. In the case of subsequent coating it is desirable to have pellets with low friability. Friability of pellets are determined by using Erkewa type tablet friabiliator[24]or turbula mixer for a fixed period of time combined with glass beads of certain diameter in order to generate abrasion. Friability can also be determined using fluidized bed with Wurster insert by using stream of air.[17]

## CONCLUSION

Today pelletization represents an efficient pathway for novel drug deliveryin 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 inpharmaceutical industry and especially in case of production of multiparticulate oral controlled release dosage forms ascompared to granulation. Pelletization technique produces more spherical pellets and offers more advantages than granulation process. In addition, hot-melt extrusion method has provided a new, wider platform to produce spherical pellets of drugs which are not stable or have compatibility problemsin presence of solvents.

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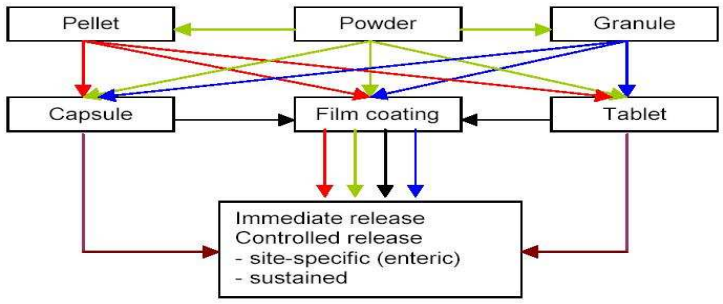


Figure.1. Relationship of Pharmaceutical Delayed Release Solid Oral Dosage Forms

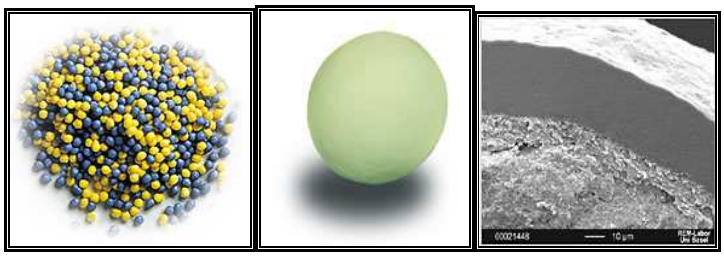

Figure.2. (a) Pellets, (b) Perfect pellet, (c) Coated pellet.

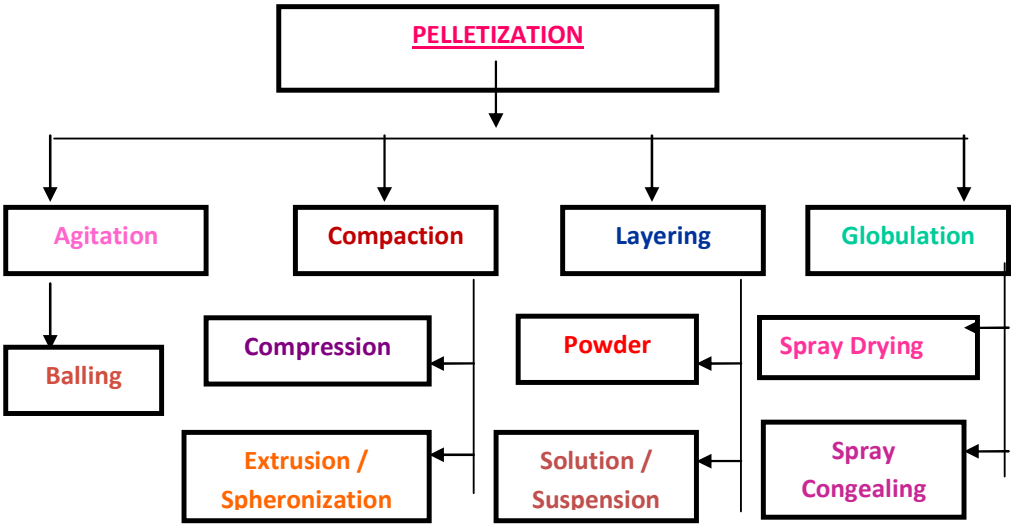


Figure.3. Different Pelletization Techniques.

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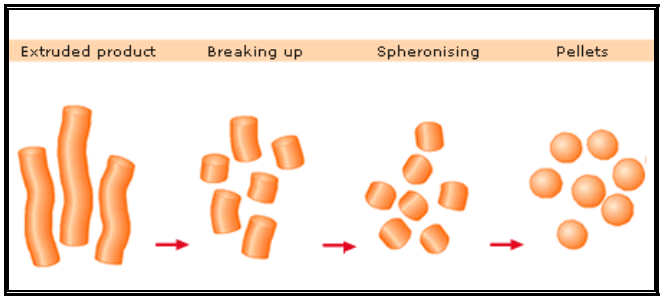


Figure.4. Principle of Extrusion – Spheronization process

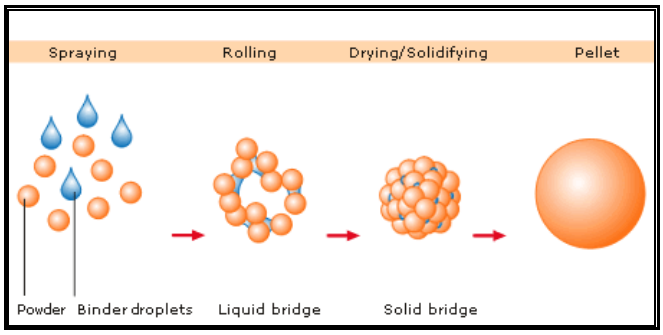


Figure.5. Principle of direct pelletizing process.

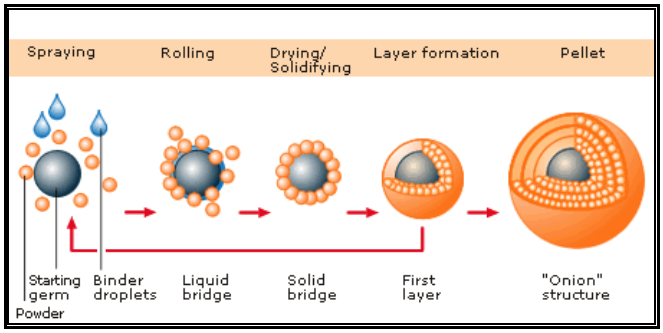


Figure.6. Principle of Powder Layering Process.

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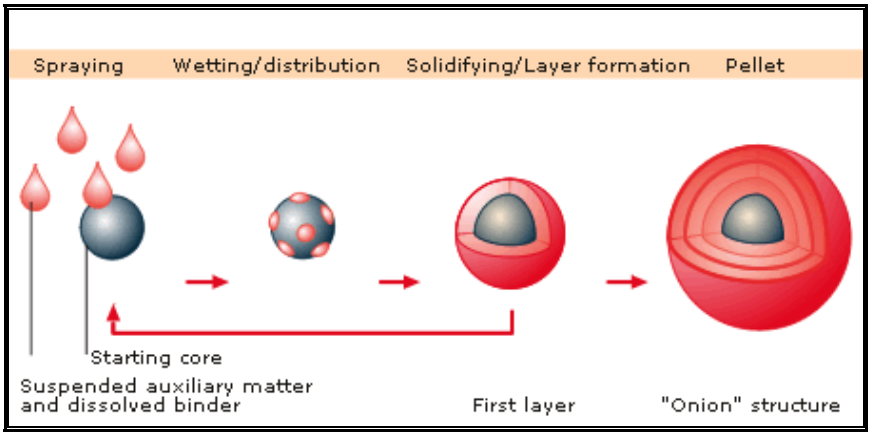


Figure.7. Principle of Solution and Suspension Layering Process.