EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 2
Issue: 5
537-546
Year: 2015

A REVIEW: MICROPELLETS AN APPROACH TOWARDS NOVEL DRUG DELIVERY

Swati Chaudhary*, Ashutosh Badola, Sweta Baluni, Monika Bhatt, Somya Sah

Division of Pharmaceutical Sciences, S.G.R.R.I.T.S, Patel Nagar Dehradun-248001, Uttrakhand, India

Article Received on 19/08/2015 **Article Revised on 11/09/2015** **Article Accepted on 02/10/2015**

***Correspondence for Author**
Swati Chaudhary
Division of Pharmaceutical Sciences, S.G.R.R.I.T.S, Patel Nagar Dehradun-248001, Uttrakhand, India

ABSTRACT

Pharmaceutical pellets are isometric aggregates with smooth surfaces and narrow particle size distribution. Nowadays, the mean pellet size ranges from 300 μm to 3 mm. besides the shape, they also have low porosity and high mechanical stability. due to the roundness and closed shape of the particles, the flowability of pellets is excellent. Micropellets show a number of additional favourable properties. The most important of which is the larger specific surface area, which results in faster dissolution rates. Micropellets can be used in a number of dosage forms that may be beneficial for certain patient groups. Micropellets and regular pellets are usually processed into tablets or filled into capsules. Further investigations are underway to use micropellets as solid drops in a 'sprinkle capsule' or in a 'dose sipping technology' (dst). These application forms are especially suitable for patients who have problems swallowing drug products and therefore refuse to take medicine at all (e.g. paediatric or elderly patients).[6]

KEYWORDS: Micropellets, Pharmaceutical pellets.

INTRODUCTION

Traditionally, the word "Pellet" has been used to describe a variety of systematically produced, geometrically defined agglomerates obtained from diverse starting materials utilizing different processing conditions. Pellets are agglomerates of fine powders or granules of bulk drugs and excipients with binder solution. These pellets are usually of size range 0.5-1.5 mm and in some applications may be as large as 3.0 mm. Recently pellets as a vehicle for a drug delivery at a controlled rate, has received significant attention. Pellets

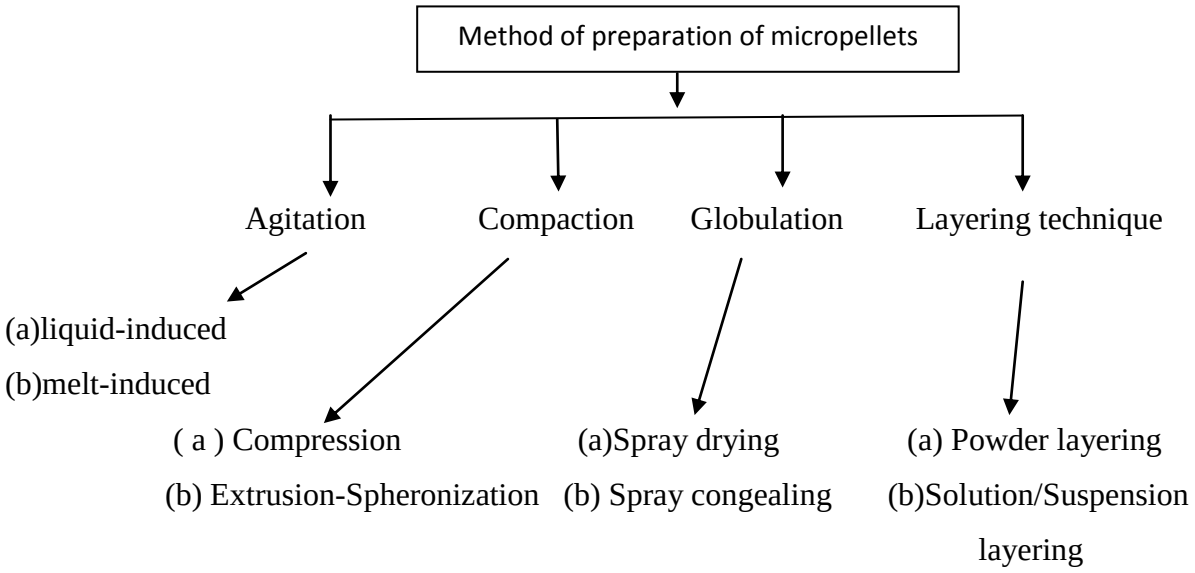
disperse freely in the gastrointestinal tract, so they invariably maximize the drug absorption, reduce peak plasma fluctuation and minimize potential side effects without appreciably lowering drug bioavailability.[6]

(a) Ideal properties of the pellets

- Spherical shape and smooth surface.
- The particle size of pellets should be in the range of 1-1000µm.
- The quantity of the active ingredient in pellets should be maximized in order to maintain the size of pellets.[2]

(b) Advantages

- The appearance of the product which is having fine pharmaceutical elegance.
- Pelletization offers flexibility into the dosage form design and development.
- Pellets improve the flow properties in formulation development.
- They flow freely and are easy to pack without significant difficulties (resulting in uniform and reproducible fill weight of capsules).
- Pellets are less susceptible to dose dumping.
- Accumulation of drugs is reduced in case of pellets, which is proved to be advantageous in the case of irritating drugs.
- It improves safety and efficacy of a drug.
- Pelletization is a convenient way to manage the separation of incompatible drugs.
- Pellets offer reduced variation in the gastric emptying rate and intestinal transit time.
- Pellets disperse freely in G.I.T. and invariably maximize drug absorption and also reduce peak plasma fluctuation
- Pelletization solves the problem of taste masking.
- The coating material may be colored with a dye material so that the beads of different coating thickness will be darker in colour and distinguishable from those having fewer coats.
- In case of immediate Release Products larger surface area of pellets enables better distribution.
- Chemically incompatible products can be formed into pellets & delivered in a single dose by encapsulating them.[8]



1. Agitation- Spherical agglomeration, or balling, 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. Over the years, spherical agglomeration has been carried out in horizontal drum pelletizers, inclined dish pelletizers, and tumbling blenders; more recent technologies use rotary fluid-bed granulators and high-shear mixers.

Spherical agglomeration can be divided into two categories- liquid-induced agglomerations and melt-induced agglomerations.[1]

- **Liquid-induced agglomeration**

In this process, before or during the agitation step, liquid is added to the powder. As powders come in contact with a liquid phase, they form agglomerates or nuclei, which initially are bound together by liquid bridges subsequently replaced by solid bridges, derived from the hardening binder or any other dissolved material within the liquid phase (Figure 1). The nuclei formed collide with other adjacent nuclei and coalesce to form larger nuclei or pellets .

- **Melt-induced agglomeration**

This process is similar to liquid-induced processes except that the binding material is a melt. Therefore the pellets are formed with the help of congealed material without formation of solvent-based liquid bridges.

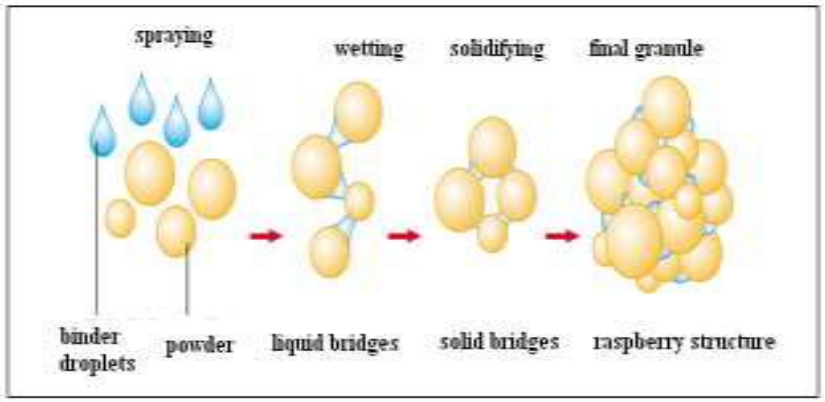


Figure 1: Mechanism of agglomeration or granulation

2. Compaction- It is a general pelletization process which produces denser pellets. Compaction technique can be subdivided into compression and extrusionspheronization.

- **Compression**

In this technique, particles that are prepared through dry blending or wet granulation followed by drying, rearrange themselves to form a closely packed mass. During this phase, the original particles retain most of their properties.

- **Extrusion-Spheronization**

It is most popular in pharmaceutical industries for the manufacturing of pellets. Reynolds (1970) and Conine and Hadley (1970) first reported this process and involves four steps (Figure 2).

(1) Granulation- Preparation of the wet mass using binding solution or hot melt wax.

(2) Extrusion- shaping the wet mass into cylinders using different types of extruders.

(3) Spheronization- breaking up the extrudate and rounding of the particles into spheres in spheronizer.

(4) Drying- drying of the pellets at room temperature or at an elevated temperature in the fluidized-bed drier, in an oven, in a forced circulation oven or in a microwave oven.

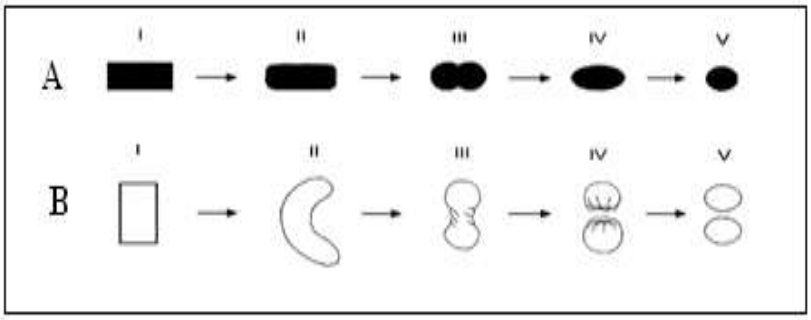


Figure 2: Pellet-forming mechanism (A): (i) cylinder (ii) cylinder with rounded edges (iii) dumb-bell (iv) ellipse (v) sphere (B): (i) cylinder (ii) rope (iii)dumb-bell (iv) sphere with a cavity outside (v) spheres.

3. Globulation- Spray drying and spray congealing, known as globulation processes, involve atomization of hot melts, solutions, or suspensions to generate spherical particles or pellets.

- **Spray drying**

During spray drying, drug entities in solution or suspension are sprayed, with or without excipients, into a hot air stream to generate dry and highly spherical particles (Figure 3). 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.

- **Spray congealing**

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

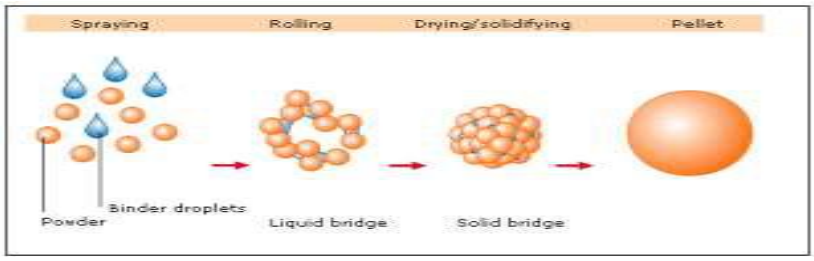


Figure 3: Mechanism of spray drying

4. Layering technique- Layering results in heterogeneous pellets with a core and a shell. For this process, seed or starting core material is required. Often, sugar spheres, nonpareils or spheres made from microcrystalline cellulose are used as core material.[1]

- **Powder layering**

During powder layering, a binding solution and a finely milled powder are added simultaneously to a bed of starter seeds at a controlled rate. In the initial stages, the drug particles are bound to the starter seeds and subsequently to the forming pellets with the help of liquid bridges originated from the sprayed liquid (Figure 4). Today fluidized bed equipment is used in order to ensure rapid drying. The core particles (seeds) are fluidized in a warm or hot air stream. A binding liquid is sprayed and simultaneously add the drug substance as a powder. The particles stick to the wetted surface of the seed material and form a layer together with the binder after drying.

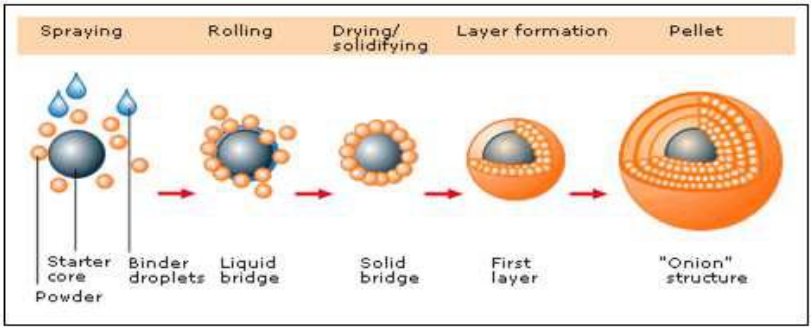


Figure 4: mechanism of powder layering technique.

- **Solution/ Suspension layering**

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. The process continues until the desired quantity of drug substance and thus the target potency of the pellets are achieved (Figure 5).[1]

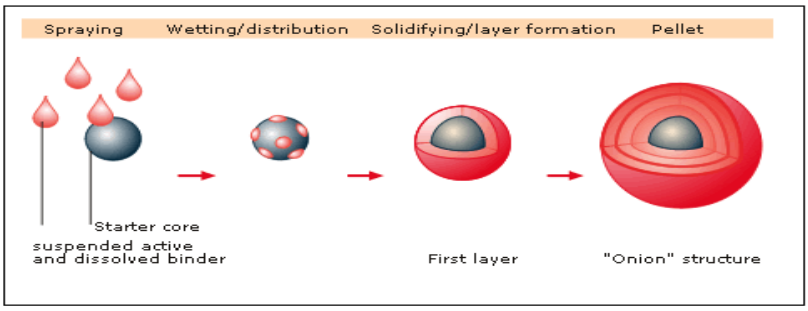


Figure 5: Mechanism of solution/ suspension layering technique.

- **Design/ Approches of pellets**
- **Mucoadhesive polymer-coated pellets**

Mucoadhesive pellets can be prepared by layering technique using mucoadhesive polymers like Hydroxy methyl cellulose (HPMC), sodium alginate (Na-Alg), HPMC/Carbopol, and sodium Carboxyl methyl cellulose (Na- CMC) etc. This result in increase in gastric residence time and hence improve bioavailability of the drug.[1]

- **Time-Controlled Explosion based Rupturable coating System**

This is a multiparticulate system in which drug is coated on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer. Upon ingress of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. The release is independent of environmental factors like pH and drug solubility.

- **Osmotic-Based Rupturable Coating Systems Permeability Controlled System**

This system is based on a combination of osmotic and swelling effects. The core containing the drug, a low bulk density solid and/or liquid lipid material (e.g., mineral oil) and a disintegrant is prepared. This core is then coated with swellable polymer like cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of coating. In another system each pellet has a core that contains the therapeutic drug and a water-soluble osmotic agent. Water-permeable, water-insoluble polymer film encloses each core. A hydrophobic, waterinsoluble agent that alters permeability (e.g., a fatty acid, wax, or a salt of fatty acid) is incorporated into the polymer film. The osmotic agents dissolve in the water causing the pellets to swell, thereby regulating the rate of drug diffusion. This system was used for the delivery of antihypertensive drug, diltiazem. The coating materials reported include different types of poly (acrylate-methacrylate) co-polymers and magnesium stearate, which reduces water permeability of the membrane, thus allowing for use of thinner films. Using ethyl cellulose as a coating material, it was possible to affect lag time of enteric polymer to achieve rupturing after a predetermined time.[1]

- **Pulsatile Delivery by Change in Membrane Permeability**

The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter-ions in the medium. Several delivery

systems based on this ion exchange have been developed. In one such attempt cores were prepared using theophylline as model drug and sodium acetate. These pellets were coated using Eudragit RS30D (10% to 40% weight gain) in four different layer thicknesses. It was found that even a small amount of sodium acetate in the pellet core had a dramatic effect on the drug permeability of the Eudragit film. After the lag time,interaction between the acetate and polymer increases the permeability of the coating so significantly that the entire active dose is liberated within a few minutes. The lag time increases with increasing thickness of the coat, but the release of the drug was found to be independent of this thickness and depended on the amount of salt present in the system.

❖ **Evaluation Parameters**

- **Appearance-** The pellets were visually observed for physical appearance of pellets.[4]
- **Drug loading-** Drug loading of the pellets is calculated by amount of the drug in the sample/total weight × 100.[3]
- **Amount of the drug present-** It was calculated by weight of pellets after drying ×amount of drug taken/ total weight.[3]
- **Particle size-** Particle size distribution of micro pellets was determined by optical microscopy using calibrated ocular eye piece. Fifty micro pellets were evaluated and the experiment was performed. Geometric mean diameter was then calculated using the equation.[4]

$$Xg=10 X [(niXlogXi)/N]$$

where, Xg is geometric mean diameter, ni is number of particles in the range,
Xi is the midpoint of range,
N is total number of particles analyzed.

- **Angle of repose-** The dried micropellets were allowed to fall freely through a funnel fixed at 1 cm on a horizontal surface and the angle of repose (θ) was measured.

$$\theta = \tan^{-1}h/r.$$

Where, h is the height of the heap, r is the radius.

- **Drug content-** 200mg pellets were weighed and powdered, a quantity of powder equivalent to 20 mg of each formulation was transferred to a 25 ml volumetric flask and 15 ml solvent is added. The drug is extracted in solvent by vigorously shaking the Stoppard flask for 15 minutes. Then the volume is adjusted to the mark with suitable solvent and the liquid

is filtered. The drug content was determined by measuring the absorbance at appropriate wavelength after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated.

- **Scanning electron microscopy**

Morphological examination of the surface and internal structure of the dried pellets was performed by using a scanning electron microscope (SEM). Micro pellets before dissolution only subjected to SEM study since, after dissolution the pellets become swollen palpable mass. Photographs were taken within the range of 50-500 magnification.

- **Density**

Weigh the empty, dry pycnometer as (W1), fill the pycnometer with distilled water up to its neck and measure the weight as (W2.) then fill the pycnometer with the formulation and measure the weight as (W3) then calculate the density of the liquid formulation by using the formula[3].

Density of water = W2-W1/ Volume

Density of sample=W3-W2/W2-W1×Density of water

- **FT-IR Analysis**

Fourier Transform Infrared Analysis (FT-IR) measurements of pure drug, carrier and drug loaded Micro pellet formulations were obtained using a Perkin- Elmer system 200 FT-IR spectrophotometer. The pellets were prepared on KBr-press under hydraulic pressure of 150kg/cm2; the spectra were scanned over the wave number range of 3600 to 400 cm-1 at the ambient temperature.[3]

- **Stability studies**

Micro pellet formulations are subjected to stability studies under ambient temperature at 37°C±2°C for 3 months.

- **In vitro drug release**

An accurately weighed sample (50 mg) of pellet formulation was taken in 900 ml of appropriate buffer, maintained at a temperature of 37°C ± 0.5°C and stirred at a speed of 50 or 100 rpm using USP dissolution apparatus type I (Basket) . At different time intervals, a 5 ml of the sample was withdrawn and the same volume was replaced with an equal amount of plain dissolution medium. The collected samples were filtered and analyzed at appropriate

wavelength , using a UV spectrophotometer against the medium buffer as a blank. The data obtained from *in vitro* drug release were fitted with various kinetic equations like Zero order, Higuchi, Korsmeyer-Pappas and Hixson Crowell equation.[5]

- **Drug entrapment efficiency (DEE)**

Pellets (500mg) were dissolved in 50 ml buffer for overnight in 100 ml volume flask. 1ml of solution was withdrawn and diluted to 10 ml and analyzed at appropriate wavelength to calculate the drug content. It was calculated by actual drug content/ practical content × 100.

- **Stability studies**

Micro pellet formulations were subjected to stability studies under ambient temperature at 37°C±2°C for 3 months.

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