

# Multiparticulates Drug Delivery Systems: A Review

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## ABSTRACT

Pharmaceutical research and development are increasingly focusing on delivery systems which enhance desirable therapeutic objectives while minimising side effects. Recent trends indicate that multiparticulate drug delivery systems are especially suitable for achieving controlled and delayed release oral formulations with low risk of dose dumping. These oral multiparticulate drug delivery systems offer biopharmaceutical advantages with respect to predictable and even distribution and transportation in the gastro-intestinal tract. Pelletization is novel drug delivery system that converts fine powder particles into pellets and it is useful in order to develop a site-specific drug delivery system. There are different techniques in the preparation of pellets. Consequently, multiparticulate drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations, thus extending the frontier of future pharmaceutical development.

**Keywords:** Pelletization, Multiparticulate drug delivery system, Novel drug delivery system, Pellets.

## INTRODUCTION

### Multiparticulate Drug Delivery Systems (MDDS)

The concept of multiple unit dosage form was initially introduced in the early 1950's. These forms play a major role in the design of solid dosage form processes because of their unique properties and the flexibility found in their manufacture. These forms can be defined as oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. Together, these characteristics units provide the overall desired controlled release of the dose. These multiple units are also referred to as pellets, spherical granules or spheroids. 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. Pellets or spherical granules are produced by agglomerating fine powders with a binder solution. These pellets usually range in size from 0.5-1.5mm and in applications may be as large as 3mm.

Multiparticulate drug delivery systems (MDDS), mostly used for oral route, consist of multiplicity of small discrete units that exhibit different characteristics. It is based on subunits such as granules, beads, microspheres, pellets, spheroids and Minitab. These subunits show various advantages over monolithic devices (non-divided forms). In MDDS, drug substances are divided into number of subunits, typically consist of

thousands of spherical particles having diameter of about 0.05-2.00 mm. To administer or to recommend total dose these subunits are compressed into a tablets or filled into a sachets or encapsulated<sup>1</sup>. The formulation of multicomponent MDDS is also possible because it shows different mechanism of action, provides additive/synergistic effect, and reduces the doses of individual agents and limited side effects. Though it is costlier than monotherapies in short term, it reduces treatment failure rate, lower case fatality ratios and reduction in development of resistance for development of new products in long term therapy<sup>2</sup>. Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free-flowing, spherical or semi-spherical solid units and are intended usually for oral administration.

### ADVANTAGES OF MULTIPARTICULATES (PELLETS)

The use of pellets as a vehicle for drug delivery at controlled rate has recently received significant attention. Pellets can be prepared by many methods, the drug-layering technique is most widely used today. Multiparticulates provide various advantages<sup>3</sup> as given below,

1. Avoidance of the dose dumping
2. Gastric emptying is faster.
3. Performance is less dependent on nutritional state as multiparticulates are

sufficiently small and can be evacuated through pylorus during digestive phase.

4. Shows improved reproducibility of transit time and high degree of dispersion in digestive tract.
5. Better distributed and less likely to cause local irritation.
6. Improved stability, patient comfort and compliance.
7. Achieve unique release pattern.
8. Extend patent protection, globalize product and overcome competition.

Now days, emphasis is being given on the development of MDDS in preference to single unit system because of their potential benefits<sup>4</sup> like

1. Increased Bioavailability
2. Reduced risk of local irritation
3. Decreased risk of systemic toxicity
4. Predictable gastric emptying

#### Drawbacks of Multiparticulates (Pellets)

1. Low drug loading
2. Proportionally higher need for excipients
3. Lack of manufacturing reproducibility and efficacy
4. Large number of process variables
5. Multiple formulation steps
6. Higher cost of production
7. Need of advanced technology
8. Trained/skilled personal needed for manufacturing

#### Rationale for Pellets<sup>4-7</sup>

Pellets are of great interest to the pharmaceutical industry for a variety of reasons. Pelletized products not only offer flexibility in dosage form design and development, but are also utilized to improve safety and efficacy of bioactive agents. However, the single most important factor responsible for the proliferation of pelletized products is the popularity of controlled release technology in the delivery of drugs. When pellets containing the active ingredient are administered in the form of suspensions, capsules, or disintegrating tablets.

#### Techniques of Pelletization

Depending on the type of equipment and process selected, pellet formation and growth may occur in number of ways. Nevertheless, the underlying phenomena describes the systematic formation of pellets during the various pelletization process can be explained in terms of the bonding forces and the elementary growth mechanisms. Given the enormous advantages of multiparticulate systems over single-unit oral dosage forms, extensive research has focused recently on refining and optimizing existing pelletization techniques as well as on the development of novel manufacturing approaches that use innovative formulations and processing equipment. The most commonly used and intensely investigated pelletization processes are powder layering, solution/suspension layering, and extrusion-spheronization<sup>8,9</sup> and are shown in Figure.

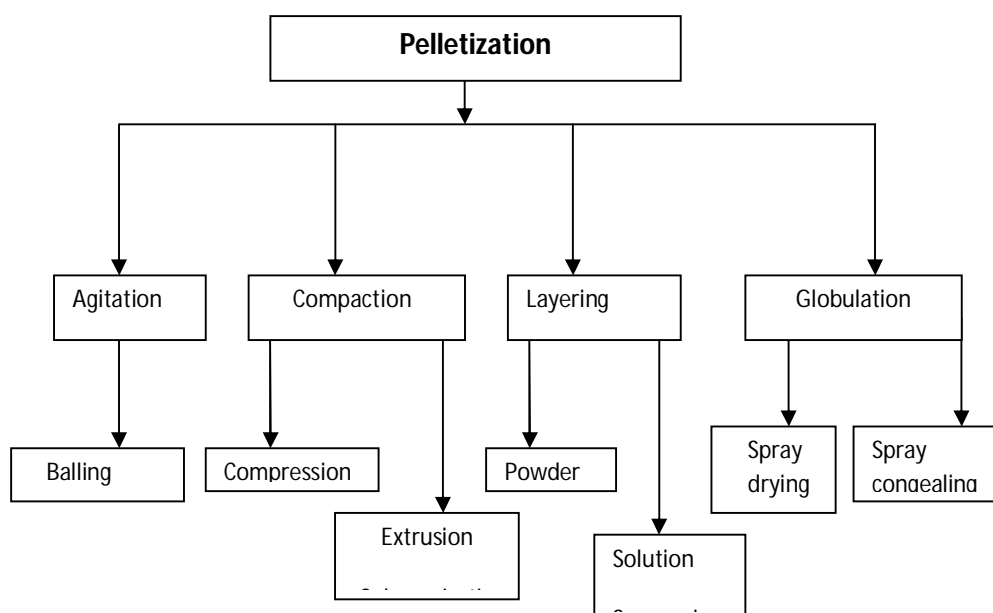


Fig.1: Different techniques of Pelletization

### A. Balling

Balling or Spherical agglomeration is a Pelletization process in which powders, upon addition of an appropriate quantity of liquid, are converted to spherical particles by a continuous rolling or tumbling action. The liquid may be added prior to or during the agitation stage. Over the years balling has been carried out in horizontal drum. Pelletizers, inclined dish pelletizers, and tumbling blenders; a more recent technology uses rotary fluid-bed granulators

### B. Drug layering

Pelletization by layering involves the deposition of successive layers of drug entities from solution, suspension or dry powder on preformed nuclei, which may be crystals or granules of the same material or inert starter seeds. The initial materials required for the preparation of pellets by the layering process are the inert starter seeds over which the powdered drug(s) is (are) layered and the possible coating applied.

Non-pareils have been widely used as initial substrates in the preparation of pellets by the layering process. However, sucrose, the main

component of non-pareils, has some well-known drawbacks like harmful effects on diabetics and potential carcinogenicity. Most recently, microcrystalline cellulose (MCC) has been tested as a substrate for drug layering.

### C. Powder Layering<sup>10</sup>

In powder layering liquid saturation is low and irrespective of the solubility of the drug in the binding liquid, complete dissolution does not occur. Typically, a binder solution is first sprayed onto the nuclei, followed by the addition of powder. The most nuclei tumble in the rotating pan of disc, pick up powder particles, and form layers of small particles that adhere to each other and the nuclei by means of capillary forces developed in the liquid phase. As additional bonding, liquid is sprayed, layering of more powder on the nuclei continues until the desired pellet sizes are obtained. On drying, the binder and other dissolved substance crystallize out and the liquid bridges are partially replaced by solid bridges. On spraying with binder, fines may pick up moisture and enter a nucleate on phase. Figure 2 shows the principal of powder layering.

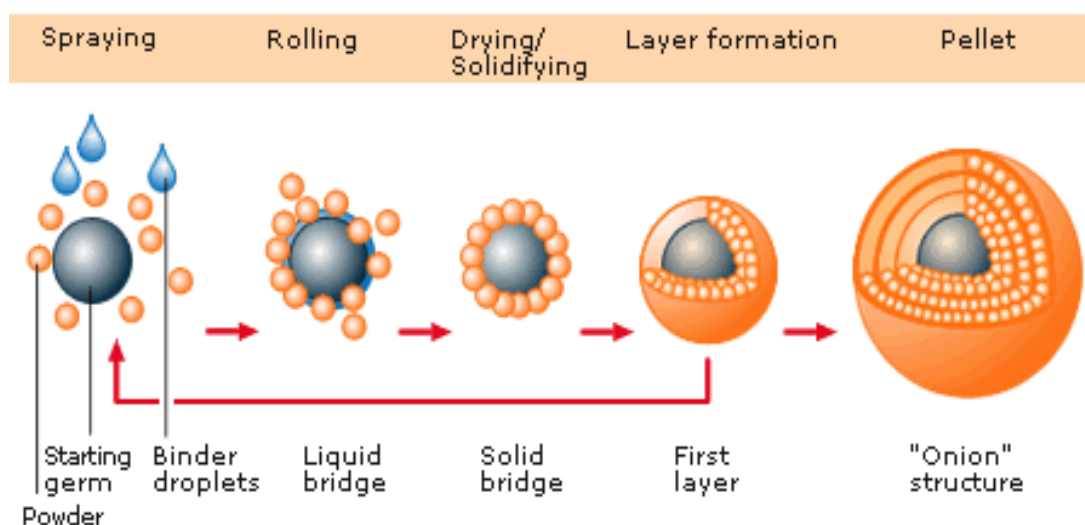


Fig. 2: Principle of Powder layering

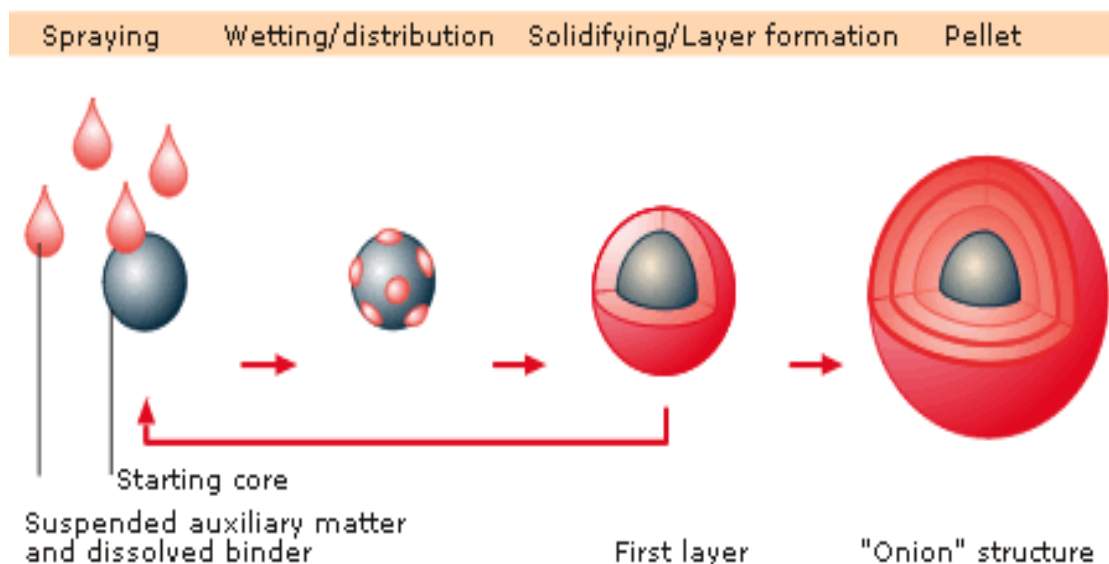
### D. Solution and Suspension Layering<sup>11</sup>

Principle of the suspension and solution layering process: Solution and suspension layering involve the deposition of successive layers of solutions and suspensions of drug substances, respectively, on starter seeds that may be inert materials or crystals or granules of the same drug. In principle, the factors that control coating processes apply directly to solution or suspension layering. During solution or suspension layering, all the

components of the formulation are dissolved or suspended in the application medium and hence determine the solids contents and the viscosity of the liquid sprayed. As the solution or suspension is sprayed onto the product bed, the droplets impinge on the starter seeds or cores and spread evenly on the surface, provided that the drying conditions and fluid dynamics are favorable. This is followed by the drying phase which allows dissolved materials to crystallize and form

solid bridges between the core and initial layer of the drug substance as well as among the successive layers of drug substance. The process continues until the desired layers of drug and hence the target potency of the pellets are achieved. The rate of particle growth is rather slow due to

the incremental addition of the dissolved or suspended drug. In this process, though the particle population remains the same, the size of the pellets increases as a function of time and, as a result, the total mass of the system increases. Figure 3 shows the principal of solution or suspension layering.



**Fig. 3: Principle of solution / suspension layering**

#### E. Spray Drying and Spray Congealing

Spray drying and spray congealing, known as globulation processes, involve atomization of hot melts, solutions, or suspensions to generate spherical particles or pellets. During spray drying, drug entities in solution or suspension is sprayed, with or without excipients, into a hot air stream to generate dry and highly spherical particles. As the atomized droplets come in contact with hot air, evaporation of the application medium is initiated. This drying process continues through a series of stages where 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.

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 under appropriate processing conditions spherical congealed pellets.

#### F. Compaction

Compaction is a form of pressure agglomeration in which drug particles or

granules are forced together with or without formulation aids by a mechanical force to generate pellets of well-defined shapes and sizes. Compaction, as a general Pelletization process can be subdivided into compression and extrusion. Recently, however, melt Pelletization has been used frequently in making compaction pellets using a different type of equipment, e.g. a high-shear mixer. Other Pelletization methods, such as globulation, balling and compression are also used in the development of pharmaceutical pellets although in a limited scale.

#### G. Compression

During first stage of compression, particles that are pretreated through dry blending or wet granulation followed by drying, rearrange themselves to form a closely packed mass. At higher pressures, the particles are forced against each other even more and undergo elastic and plastic deformation, thereby increasing interparticle contact. Because particles approach each other closely enough, short range bonding forces like Van der Waals forces, electrostatic forces, and sorption layers become effective.

#### H. Extrusion<sup>12</sup>

Extrusion is another form of pressure

agglomeration is not, by itself, a single pellet process. It is one of the three unit operations that constitute the bulk of the extrusion/spheronization process. During wet granulation, dry powder mixture is agglomerated with help of a binding liquid. The agglomerated are held together mainly by capillary forces. The granulation is then fed into the extruder to produce high-density extrudates. These extrudates are bonded together by capillary forces, solid bridges formed due to loss of moisture, mechanical interlocking, and, to some extent, molecular forces. These extrudates are finally converted to pellets on spheronization.

### I. Spheronization<sup>12</sup>

Spheronization is not a relatively new technique. The early trade name was Marumerizer, which means "round maker." Spheronization typically begins with damp extruded particles, granules from one of the extruders and the extruded, cylindrically shaped particles are broken into uniform lengths almost instantaneously and are gradually transformed into spherical shapes.

### J. Melt Spheronization

Melt spheronization is a process whereby a drug substance and excipients are converted into a molten or semi molten state and subsequently shaped using appropriate equipment to provide solid spheres or pellets. The process requires several pieces of equipment such as blenders, extruders, cutters (known as pelletizers in the plastics industry), and spheronizer.

### K. Cryopelletization<sup>12</sup>

Cryopelletization is a process whereby droplets of a liquid formulation are converted into solid spherical particles or pellets by using liquid nitrogen as the fixing medium.

### L. Preparation of pellets using Fluid Bed Coating Process<sup>13-17</sup>

With fluid bed coating, particles are fluidized and the coating fluid sprayed on and dried. Small droplets and a low viscosity of the spray medium ensure an even product coating.

Glatt offers Batch Fluid Bed Systems in different batch sizes with:

1. Top Spray Coating
2. Bottom Spray Coating (Wurster Coating)
3. Tangential Spray Coating (Rotor Pellet Coating).

### Marketed Technologies<sup>3, 18-20</sup>

Presently marketed multiparticulate drug delivery systems are listed in Table 1. In 1998, Elan Drug Technologies got FDA approval for their chronotherapeutic technology, CODAS<sup>®</sup> as multiparticulate pH dependent system, for delivery of Verapamil HCl (Verelan<sup>®</sup> PM) in form of extended release capsule. This was followed by the FDA approval of DIFFUCAPS<sup>®</sup>, a multiparticulate technology by Reliant Pharmaceuticals LLC, for chronotherapeutic delivery of a combination of two drugs, Verapamil HCl and Propranolol HCl, as an extended release tablet (Innopran<sup>®</sup>). But the biggest breakthrough in multiparticulate technology was achieved when MiddleBrook<sup>™</sup> Pharmaceuticals, Inc. (earlier known as Advancis Pharmaceutical) got the green signal from FDA in 2008 for its proprietary, once-a-day pulsatile delivery technology called PULSYS<sup>™</sup>, which enables the delivery of antibiotic amoxicillin in regular concomitant pulses. MiddleBrook<sup>™</sup> is developing a broad portfolio of drugs based on the novel biological finding that bacteria exposed to antibiotics in front-loaded, sequential bursts, or pulses, are killed more efficiently and effectively than those exposed to standard antibiotic treatment regimens. When an immediate release antibiotic is administered, bacteria respond to it by going into a dormant stage, while the administration of a pulsatile system in such a case is more effective because the regular release of increased pulses of antibiotic does not let the defense system of the bacteria to go into a dormant stage. By examining the resistance patterns of microorganisms and applying its improved technologies, MiddleBrook<sup>™</sup> has redefined microbial infection treatment significantly improving drug efficacy, shortening length of therapy, and reducing the emergence of antibiotic resistance.

**Table 1: Marketed technologies of Multiparticulates drug delivery**

Technology	Proprietary name	Drug	Indication	Design parameters	Advantages
<b>CODAS®</b>	Verelan® PM XL release capsule	Verapamil HCl	Hypertension	Nonenteric release-controlling polymer (combination of water soluble and insoluble polymers) applied to drug loaded beads.	Lag-time-4-5 h. Early morning peak plasma concentrations following bed time dosing. Rate of release is independent of pH, posture and food and gastrointestinal motility.
<b>DIFFUCAPS®</b>	Innopran® XL tablet	Verapamil HCl, Propranolol HCl	Hypertension	Drug was layered on sugar bead, followed by a controlled release and delayed release coatings.	Lag time-4-5 h Cmax-12-14 h after dosing trough levels after 24-27 h of dosing. The rate of release is independent of pH, posture and food and gastrointestinal motility
<b>PULSYS™</b>	Moxatag™ tablet	Amoxicillin	Infection	Consisting of three components: one immediate release and two delayed-release (by soluble and insoluble coatings)	More efficient killing of bacteria exposed to antibiotics in front-loaded, sequential bursts Reduces duration of therapy

## CONCLUSION

The recent market for novel drug delivery system has continued to grow at an impressive rate. Today's drug delivery technologies enable the incorporation of drug molecules into a new delivery system, thus providing numerous therapeutic and commercial advantages. Pelletization lays the scope for different oral immediate or controlled delivery system. Due to its simple design, greater flexibility, efficiency of producing spherical pellets and fast processing; it has found a special place in the Pharmaceutical industry.

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