

## Pharmaceutical Pellets: Industrial applications & Innovative perspective

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### Introduction

Small, free flowing spherical units, ranging in size, prepared by an agglomeration of fine powders or granules excipients, are called as Pellets.

Pellets ensure improved flow properties and flexibility in formulation development and manufacture. If the pellet surface is smoother it allows thin or thick coat of the polymer on the surface of the pellets. The thickness of the coat determines the rate at which the drug is released from the coated pellets. The coating material may be colored with a dye materials so that the beads of different coating thickness will be darker in color and distinguishable from those having fewer coating. It is widely used for frequently administered drugs having a half-life of 0.5-2 hr. The excellent reproducibility and homogeneity of the particle size and the round shape and smooth surface of the particles makes micro-pellets with sizes smaller than 200 µm a perfect match for powder injections.

In addition, the very high drug substance load level of the micro pellets promotes lower injection volumes, thus increasing patient acceptance. Many drug substances, e.g. narcoleptics, peptides, hormones, therapeutic proteins; vaccines etc. in need of slow release formulations are product candidates for this technology. Micro pellets have thus opened a new dimension in parenteral depot technologies. Drug substance particles can either be coated with biodegradable polymers or embedded in a polymer matrix. Using these approaches, release profiles ranging from days to months and even pulsed release can be obtained at wish.

The release rate of drugs from the polymer coat can be modified using various concentration of plasticizer and influence of pH. Even if they are useful

as drugs, the necessity of frequent injection makes them inconvenient and often causes pain and trouble to patients.

### 1) Chemically incompatible products

At times such ingredients are required to be delivered in a single dose. In the compressed tablet dosage form separate tablets would have to be administered, but the pellets can be administered in a single capsule.

### 2) Varying dosage with out reformulation

Pellets have excellent flow properties, due to this, they can be conveniently used for filling capsules and the manufacturer can vary the dosage by varying the capsule size with out reformulating the product.

### Rationale for Pelletization

Pellets are of great interest to the pharmaceutical industry for a variety of reasons and these products not only offers flexibility in dosage form design and development, but also utilized to improve the 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 the pellets containing active ingredient are administered in-vivo in the form of suspensions, capsules, or disintegrating tablets, they offer significant therapeutic advantages over single unit dosage forms, since pellets disperse freely in the GIT, they invariably maximize drug absorption, reduce peak plasma fluctuations and minimize potential side effects without appreciably lowering drug bioavailability.

In case of oral products micro pellets solve difficult taste-masking problems

while maintaining a high degree of bioavailability due to smaller in size (10 - 600 µm) furthermore, because of the special design of the manufacturing process; dust fractions which could cause taste problems are absent in micro pellets. Pellets also reduce variations in gastric emptying rate and overall transit time, thus, intra- and inter subject variability of plasma profiles, which are common with single unit regimens, are minimized.

Another advantage of pellets over single-unit dosage forms is that high local concentrations of bioactive agents, which may inherently be irritative or anesthetic, can be avoided<sup>11</sup>. When formulated as modified release dosage forms, pellets are less susceptible to dose dumping than the reservoir-type single unit formulations.

Micro pellets technology delivers almost perfectly spherical particles exhibiting a very narrow particle size distribution and excellent flow properties and these are characterized by a smooth surface free of dust and thus provide optimal conditions for subsequent film coating. Controlled release pellets are manufactured either to deliver the bioactive agent at a specific site within the GIT or to sustain the action of drugs over an extended period of time. While these results have been traditionally achieved through the application of a functional coating material, at times the core pellets themselves have been modified to provide the desired effect. This further enhances the role of pellets in oral dosage form development.

Pellets also provide the pharmaceutical scientist with tremendous flexibility during the development of oral dosage forms. Pellets composed of different drug entities can be blended and formulated in a single dosage form. This approach has numerous advantages. It allows the combined delivery of two or

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more bioactive agents; they may or may not be chemically compatible, at the same site or at different sites within the GIT. It also permits the combination of pellets of different release rates of the same drug in a single dosage form. In addition, pellets have an enough surface area-to-volume ratio and provide an ideal shape for the application of film coatings. As pellets flow and pack freely, it is not difficult to obtain uniform and reproducible fill weights in capsules, provided that the size and densities are favorable. Pellets can also be made attractive due to the various shades of color that can easily be imparted to them during manufacturing process. As the application of pellets in the development of oral dosage forms increases, so does our understanding of the basic principles governing pellet formation and growth. Critical process and formation variables are being systematically evaluated and characterized. Consequently, general processing conditions are being adapted to fit to specific manufacturing needs. Due to their unique properties and flexibility of manufacturing involved, pellets are expected to continue to play a major role in the fabrication of solid dosage forms. Many generic companies have already shown an interest in micro-pellets for the development of superior line extensions of existing products that suffer from taste-masking problems. The antibiotic market also provides a target for this technology and a blockbuster macrolide antibiotic was recently introduced into the market as micro pellet formulation.

An even more exciting area of application is the use of micro pellets for subcutaneous and intramuscular administration. The excellent reproducibility and homogeneity of the particle size and the round shape and smooth surface of the particles make micro pellets with sizes smaller than 200  $\mu\text{m}$  a perfect match for powder injectors. Micro pellets have a tremendous potential as depot formulations. In sterile dosage form technology only suspensions of (lipophilic) drug particles and micro particles using biodegradable polymers are used as depot principles. Micro pellets that use parenteral acceptable polymers ensure that the entire slow release strategies normally used for solid dosage forms can now be made available for sterile products. Drug substance particles can either be coated with biodegradable polymers or embedded in a polymer matrix. Using these approaches, release profiles ranging from days to months and even pulsed release can be obtained at wish. The full impact of systematically agglomerated spherical units or pellets in oral dosage form design and performance was not

realized until the early 1950s, when attempts were made to develop extended release products. Since then, the manufacture of pellets has been the subject of intensive research, in terms of both innovative formulations and processing equipment. Traditionally, the word "pellet" had been used to describe a variety of systematically produced, geometrically defined agglomerates obtained from diverse starting materials utilizing different processing conditions. 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. New Micro pellet Technology has opened new avenues in Pharmaceutical Development and Production

#### **Advantages**

1. No Multiparticulates Drug Interactions - Physical & Chemical
2. Ease of dose divisibility & compliance.
3. Enhanced efficacy of drugs. Larger surface area of pellets enables better distribution.
4. Improved flow properties and flexibility in formulation development & manufacture.

Solid spherical pellets represent an area of considerable interest as drug delivery systems. Multi-particulate pellet systems are utilized as both immediate and modified release dosage forms; therefore, the ability to describe drug release from such systems is of importance.

#### **Innovative approaches in pellets delivery system**

Pellets are always advantageous than tablets or capsules for predefining any desired release profiles. In this line there is always flexibility for the formulation scientist to modulate the release profiles based on pharmacokinetic data. Some of the latest innovative trends in pellets dosage forms are summarized herewith:

**1) Self emulsifying pellets formulation:** -Nowadays, an increasing number of drugs are characterized by being poorly water soluble and highly lipophilic, resulting in a low and highly variable oral bioavailability. Due to this fact, many drug candidates fail to reach the market, although they exhibit potential pharmacodynamic activity. On the other hand, to achieve the desired plasma level, marketed poorly water soluble drugs are administered in higher doses than actually needed, leading to the rise of toxicity problems. Therefore, suitable formulation approaches need to be developed to improve solubility and bioavailability of poorly soluble drugs.

Usually Strategies such as micronization, co-solubilisation, inclusion complexation, use of Nano-suspensions, micellar solubilisation by surfactants, drug dispersion in carriers, and lipid-based formulations are presently employed to tackle the formulation challenges of poorly soluble drugs in order to improve the oral bioavailability. Lipid formulations are a diverse group of formulations with a wide variety of properties and usually consist of mixture of excipients, ranging from triglyceride oils through mixed glycerides, lipophilic surfactants, hydrophilic surfactants and co solvents. Lipid-based formulations can decrease the intrinsic limitations of slow and incomplete dissolution of poorly water soluble drugs by facilitating the formation of

Solubilized phases from which absorption takes place. The achievement of such phases will not essentially take place from the formulation itself, but alternatively from taking the advantage of the intraluminal processing to which lipids are subjected. The extent of drug absorption from lipid

Vehicles are significantly affected by the dispersability of the administered lipid and drug. On the other hand, because of the inherent physical instability, the large volume of the two phase emulsion, and the poor precision of dose, the use of conventional emulsions is problematic. A formulation approach for avoiding such restrictive problems is the use of self-emulsifying drug delivery systems.

Usage of pellets in self emulsifying systems: Due to the fact that pellets disperse freely in the gastro-intestinal tract, drug absorption is maximized with a subsequent reduction in peak plasma fluctuations and hence minimizing potential side effects without lowering drug bioavailability. Pellets also reduce variations in gastric emptying rates and overall transit time and therefore a reduction of intra- and intersubject variability of plasma profiles is achieved. In addition, pellets reduce the problem of high local concentration of drugs and thus avoiding irritation that may be caused by certain active constituents. It is therefore very attractive to combine the advantages of self-emulsifying delivery systems with pellets.

A general brief manufacturing methodology of preparation of such pellets system can be as follows:-

- a) Melting of glyceryl mono-stearate and a suitable surfactant been usually chosen for emulsification, at its melting temperature

- b) Dissolving the model drug in above melt
- c) Addition of water to the molten lipid blend until a creamy mass is produced.
- d) Cooling to room temperature.
- e) Addition of the cooled creamy base with microcrystalline cellulose and mixing in a kneader for required time
- f) Further addition of water until a mass suitable for extrusion is obtained.
- g) Subjecting the extrudes into spheronizer to form uniform spherical pellets.
- h) To dry the above pellets in a suitable dryer and encapsulate in capsule shells

**2) Biphasic/Dual release profiles pellets (i.e. loading dose of immediate release + maintenance dose of extended release)**

In certain conditions (migraine and sleeping disorders), drug treatment may be advantageous to be delivered in a bi-phasic manner rather than a single phase extended release preparation. In the first phase of drug release, the immediate release dose fraction (also called "loading-dose") reaches a therapeutic drug level in the blood plasma quickly after administration, while the second extended release phase (called the "maintenance-dose")

provides the dose fraction, required to maintain an effective therapeutic level for a prolonged period. Examples of such systems can be found as bilayer tablets, drug layered matrices, or combinations of immediate, and extended release multiparticulates. Formulating or deciding the release profiles in each dosage forms like bilayered tablets is always very tedious to arrive to a definite & desired combination of dissolution profiles due to the bilayer and more formulation variables involved in tablets dosage form.

In such dosage forms, a capsule contains immediate release pellets and mixed uniformly with extended release pellets and encapsulated. If there the desired dissolution profiles need to be changed then it becomes very easy to the formulator to play with the proportion of dual release pellets by just changing the fill weights. This approach of pellets provides better flexibility to govern the desired combination of drug release profiles.

**3) Nano-particulate active(s) in a pellets system:** There are several drugs which are practically insoluble in water and therefore there solubility becomes the rate limiting site in absorption and bioavailability. Owing to such problems it may be required to

even micronize the active ingredient to nanometer range so that there is considerable increase in surface area and solubility also increases on same hand. But there is always a challenge to formulate the active ingredients which are in nanometer range into a suitable dosage form like tablets or capsules. Due to the cohesive/sticky, static charge generation on the particle surface the processing becomes difficult because the manufacturing losses can come more. On the same hand if the molecule exhibits high intra subject variability and non-reproducible absorption profiles then there would be a need to formulate such actives in pellets dosage form.

**4) Multiple unit pellets system (dual action):** Those drugs which are highly unstable in gastric conditions and on the same hand also have target specific deliveries specifically to colon (as in case of colon related disorders).The enteric coated drug-pellets are blended with sustained release matrix granules and compressed into tablets in order to impart sustained release action in colon.

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