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MULTIPARTICULATE DRUG DELIVERY SYSTEM: PELLETIZATION

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ABSTRACT

Pelletization is a novel drug delivery system; a technique which converts fine powder particles into pellets. These oral multiparticulate drug-delivery systems offer biopharmaceutical advantages with respect to predictable and even distribution and transportation in the gastro-intestinal tract. It has many advantages compared to single-unit dosage forms for ease of filling, better flow properties of spherical pellets, sustained, controlled or site-specific drug delivery, even distribution in the GI tract, less GI irritation, good bioavailability, ease of coating and uniform packing. Pelletization is easier and simple technique compared to granulation in order to develop a site-specific drug delivery system. There are different techniques in the preparation of pellets for a drug which includes hot-melt extrusion, extrusion spheronization, spray drying, spray congealing, roto granulation and drug layering. This article is divided into introduction containing the definition of Pelletization and its need, second part includes the preparation of pellets and the two most widely used methods; extrusion-spheronization and hot-melt techniques, third part includes advantages, problems faced during pelletization and the final part consists of the importance of pelletization over granulation. This multiparticulate drug delivery system can be used in formulations requiring immediate as well as prolonged release. Hence they can be formulated for chewable and disintegrating tablets[1].

Key words: Pelletization, Multiparticulate drug delivery system, Novel drug delivery system, Pellets, Granulation.

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INTRODUCTION

Multiparticulate drug delivery systems are the most extensively used dosage than unit dosage forms for their improved bioavailability because of increased surface area, reduced inter-subject variation, good distribution and transportation and reduced chances of dose dumping. One such multiparticulate drug delivery system is the Pelletization[2].

Pelletization is an agglomeration process which converts fine powders or granules of bulk drugs or excipients into small, free-flowing, spherical or semi-spherical units called as pellets. The size of pellets is from 0.5 – 1.5 mm.

Need for pelletization[3]:

- To improve flow, dispersion, solubility, stability and compaction.
- To have less variation in transit time through the GIT than single-unit dosage forms like tablets prepared by granulation and compression.
- To produce pellets of uniform size with high drug loading capacity.
- To prevent segregation and dust.
- Pellets can be compressed into tablets called 'pelltabs' and can also be filled into capsules.

PREPARATION OF PELLETS[4]:

One of the important steps in the preparation of pellets is the use of granulation fluid. An appropriate amount and type of granulating fluid is required to prepare the wet mass for Pelletization. The granulating fluid provides rheological properties to the formulation for the extrusion through the extrusion screen and for the transformation into spherical pellets in the spheronizer. Moisture content will yield fines and excess moisture will lead to agglomeration; thus water content of the formulation before and after extrusion and spheronization is important for pellet quality. Pellet size, flow rate, friability index, pellet bulk and tapped density vary with the amount of water added in the formulations which are the essential to determine pellets.

Some of the methods used for the preparation of pellets are[5]:

- **Extrusion-spheronization[6]:** Pellets are produced from mixtures of solids and liquids by the involvement of forming and shaping forces. It involves four main steps:

1) Preparation of wet mass called granulation,
2) Shaping the wet mass into cylinders called extrusion,
3) Breaking up the extrudate and rounding of the particles into spheres called spheronization and

4) Drying of pellets.

Hot-melt extrusion[7]: A novel method used in preparing matrix pellets for controlled release drug delivery system to overcome the disadvantages associated with wet granulation is called as a hot-melt extrusion method where a thermal agent softens or gets melted during the process to obtain matrix pellets. Its advantages are:

1. It is a simple, efficient and continuous process with fewer processing stages,
2. It does not require drying for long duration since it does not involve water or solvent
3. The absence of water prevents drug degradation,
4. It reduces the loss of coating material during coating process.

Advantages of Pelletization[8]:

1) Can be used for patients having difficulty in swallowing and dysphagia, children and geriatrics.
2) Different drugs can be blended and formulated in single unit dosage form thus facilitating delivery of 2 or more chemically compatible or incompatible drugs at the same or different site in GIT.
3) Reduces variations in gastric emptying rates and overall transit times.
4) Pellets with different release mechanisms can be mixed to give a new modified release profile.
5) Have excellent flow and packaging properties.
6) When formulated as modified release dosage form, pellets are less susceptible to dose dumping.
7) Have greater absorption since they disperse freely in GIT.
8) Produces spheroids with high loading capacity of active ingredient without producing extensively large particles.
9) GI irritation are limited spread as the particles spread in the intestine since particles less than 2-3 mm pass pylorus rather than filling level of the stomach.
10) Reduce peak plasma fluctuations and minimize potential side effects without lowering drug bioavailability.

Problems Faced During Pelletization[9]:

The size, shape and flow of pellets must be consistent in all batches, since variation in these factors will lead to difference in physiochemical properties of final dosage form; further

affecting the therapeutic efficiency of the delivery system. Variation in size leads to variation in dose and variation in shape leads to variation in flow and compressibility.

Other factors causing problems are: type of excipient used, solubility of excipients and drug in granulating fluid, type of extruder used, type and diameter of the spheronizer plate time, load and speed of spheronization, and drying technique and drying temperature.

Pelletization V/S Granulation[10]:

1) Pelletization produces spheroids with high loading API than granules as it require excipients.
2) Pelletization is simple, requires less equipments and fast processing than granulation.
3) Coating of pellets is easier than coating granules due to their spherical shape and low surface area to volume ratio.
4) Pelletization gives better results in formulation of sustained release and controlled release delivery system than granulation.
5) Pelletization gives high throughput with low wastage unlike in granulation.
6) Pellets are easier to produce of uniform shape, size, good flow properties, reproducibility in packing, high strength, low friability and smooth surface with high drug loading capacity which is not possible with granulation.

NOVEL APPROACH TO PELLETIZATION[11]:

This novel approach of pelletization is used in manufacturing tablets using flat die press. Many drugs such as paracetamol, furosemide, hydrochlorothiazide and theophylline can be formed into pellets using k-carrageenan. All these pellets of drugs containing API and excipients have high yield due to pelletization and a narrow size distribution and also high dose of the formulation can also be implemented such as in the case of furosemide. On dissolution these produced formulations of tablets showed fast drug release with low standard deviation thus providing good batch uniformity. Thus pelletization of such drugs using flat die press makes a challenging and successful combination[12].

Another use of pelletization is in the Formulation of Polycarbophil calcium antacids using pelletization. The new approach will combine the new formulation of antacids using Polycarbophil calcium as the active pharmaceutical ingredient and formulate an antacid by pelletization and making a chewable or a disintegrating tablet. This would reduce the diarrhoea and constipation problems of the hydroxides and also provide a complete and prolonged effect of antacid property.

The formulation of floating tablets[13] did not prove to be useful as the floating antacids did not reach the entire site of action and also made digestion is difficult is the patient is lying on the left side[14]. Second problem observed is the incapability of antacids to produce a prolong effect[15]. For this two-layered tablet were formulated but these were not capable of being distributed over large parts of the gastric wall. Third problem is the use of aluminium in the formulation may cause constipation and use of magnesium which is a laxative may cause diarrhoea[16].

This formulation of antacid was implemented by using pelletization. However these pellets can be used to produce enteric-coated tablets by using eudragit[17] or can be made into tablets or capsules by adding excipients such as disintegration auxillaries, plasticizers, fillers, and sweeteners can be added to modify or replace; to require the specific dosage form[18].

Pelletization process is used while formulating this antacid due to the many advantages in the GI tract which are useful for providing antacid properties[19]. Also Polyethylene glycol (PEG) can be used as it provides good adhesion to the gastric mucosa and also prolongs gastric release; also polymers[20] can be used which have good swelling properties and increase the pH. Hence provide prolonged action and adhesion, get distributed to a larger area and also don't affect during antacid action.

Thus Pelletization is one of the novel methods used in formulation of antacids which can provide prolonged action and also reduce the side-effects.

CONCLUSION:

Pelletization lays the scope for different oral immediate or controlled delivery system. Due to its simple design, efficiency of producing spherical pellets and fast processing; it has found a special place in the Pharmaceutical industry and moreover its use in production of multiparticulate oral controlled release dosage forms overtaking granulation[21].

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