



A NOVEL APPROACH OF ENTERIC COATED PELLETS FOR IMMEDIATE RELEASE BY USING EXTRUSION-SPHERONIZATION TECHNIQUE

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ABSTRACT

In the present study, an attempt was made to prepare immediate-release enteric-coated pellets of a NSAID class of drug, a poorly soluble nonsteroidal anti-inflammatory drug that has a gastrointestinal intolerance as its serious side effect. Formulation of enteric-coated pellets with improved solubility of drug could address both of these problems. To achieve these goals, pellets were prepared by extrusion-spheronization method using pelletizing agents that can contribute to the faster disintegration and thereby improve the solubility of the drug. Different disintegrants like α -cyclodextrin, cross carmellose sodium, sodium starch glycolate, Prosolve, crospovidone were tried in order to further improve disintegration time. The pellets were characterized for drug content, particle size distribution, flow properties, infrared spectroscopy, surface morphology, disintegration rate, and dissolution profile. The Formulation was Coated with an enteric-coated polymer which does not dissolve at gastric pH but dissolves at intestinal pH, releasing the drug immediately in dissolution medium. The improvement was substantial when it was compared with solubility of pure drug under the same conditions. Here in this review article these topics are discussed briefly.

Keywords: NSAID class of Drug, enteric-coating, Immediate release, Super disintegrant, pellets, Extrusion-Spheronization technique

INTRODUCTION

Pellets are small free flowing, spherical particulate, manufactured by the agglomeration of fine powder or granules. In recent years, there has been a growing interest in the field of pelletization to produce spherical pellets which can be changed into several dosages forms like tablet and capsule or can be administered as such. Pelletization involves size enlargement process and if the final agglomerates are spherical in shape in the size range of 0.5-2.0 mm, they are called pellets.

⁽¹⁾ Pellets have numerous therapeutic as well as technical advantages such as enhanced drug absorption due to involvement of large GI surface in absorption process, less gastric irritation by limiting localized buildup and dose dumping, good flow ability due to uniform size and shape, high tensile strength, low friability, narrow particle size distribution, and uniform packing characteristics.⁽²⁾

The pelletized products can improve the safety and efficacy of the active agent. The pellets are directly filled into capsule and can also be compressed into tablets. The compression of pellets into tablets is much more ideal than enclosing them in a hard gelatin capsule.⁽³⁾ In multiple unit

systems, the total drug dose is divided over many units. Failure of a few units may not be as consequential as failure of a single-unit system. Manufacturing of pellets using layering process such as solution layering, suspension layering or powder layering and extrusion-spheronization process have been used over the years. These processes have major limitation such as use of granulating liquid which causes stability problems during processing and storage. In recent years hot melt extrusion and freeze pelletization have been used to produce spherical pellets without the use of water. ⁽⁴⁾ The word pellet is used to describe a variety of systematically product geometrically defined agglomerates obtained from diverse starting material. In the pharmaceutical industry, pellets can be defined as agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free-flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and are intended usually for oral administration. It consist of small discrete unit and exhibit some derived characteristics produced by agglomeration of fine powder with binder solution normally the size of the pellets varies from 0.5 – 1.5 mm for oral dosage form. ⁽¹⁾

An innovative use of pellet in pharmaceutical field are given as....

- Improve aesthetic appearance of products.
- Achieve control release rate of drugs when coated with polymers.
- Improve flow properties and flexibility in formulation development and manufacturing.
- It has less variance in transient time through the gastro intestinal tract (GIT) than a single unit dosage form like tablet.

Application of spherical crystallization in Pharmaceuticals^(3,5)

- For increasing solubility and dissolution rate of poorly soluble drug.
- For masking bitter taste of drug.
- Improve flow ability and compressibility.
- Reduces cost of production

Advantages of Pelletization Technique⁽⁶⁾

- When formulated as modified release dosage forms, pellets are less susceptible to dose dumping than reservoir type single unit formulations.
- Pellets are recommended for patients with difficulty in swallowing and dysphasia like in case of children and aged people.
- Pelletization reduces intra and inters subject variability of plasma profiles by reducing variations in gastric emptying rates and overall transit times.
- Pelletization produces spheroids with high loading capacity of active ingredient without producing extensively large particles.
- Pellets exhibit better roundness.
- Pellets composed of different drugs can be blended and formulated in single unit dosage form that facilitates delivery of two or more chemically compatible or incompatible drugs at the same or different site in GI tract.
- Incompatible drugs processed separately and mixed later, or pellets with different release mechanisms can be mixed to give a new modified release profile.
- Pellets reduce peak plasma fluctuations and minimize potential side effects without appreciably lowering the drug bioavailability.

Suitable properties of the drugs to be formulated in pellets

Pelletization Techniques ⁽²⁾

SerialNo.	Natureoftheproperties	
1	Physicochemical properties	Drugshavinglowmolecularweight Drugswithgoodwatersolubility pHindependent Withnon-aqueoussolubility Unionized(atleast0.1-5%)inGItract VeryweakbasespKa<5.0 VeryweakacidspKa>8.0(PentobarbitalpKa=8.1) UnionizedatallpH ModeratelyweakacidspKa2.5-5 Moderatelyweakbases
2	Pharmacokinetic properties	Shorthalf-life WellabsorbedfromallregionsofGItract
3	Pharmacodynamic property	Therapeuticrangeofbloodconcentration- wideenough

- Powder layering technique
- Suspension/Solution Layering technique
- **Extrusion - Spheronization**
- Cryopelletization
- Hot Melt Extrusion
- Freeze Pelletization

Powder Layering Technique⁽²⁾

This is the process in which consecutive layers of dry powder of the drug or/and excipients are deposited on preformed core. First, a binding solution is prepared having a suitable binder. The prepared binding solution is sprayed over the inert core of microcrystalline cellulose or sugar to prepare a sticky core with the ability to bind the drug powder over it. The drug, which is to be layered over prepared core, is grinded or micronized, if required, to prepared fine powder and then the finally divided powder is sprinkled over the inert spherical core in controlled manner to achieve uniform sized circular pellets. Conventional coating pan is usually used for this purpose but it has few drawbacks like poor mixing and poor drying. The substrate particles are fluidized and suspended by heated and conditioned air. One or several nozzles atomize and spray the drug powder onto the substrate.

Suspension/Solution Layering technique⁽²⁾

In this process, successive layering of solution/suspension of ingredient including binder on starter seeds is done. Starter seeds are usually of inert material or may be of the same drug. In

this method, solution or suspension of active ingredients along with other excipients is prepared. This solution/suspension is sprayed over the core material. Fluid-bed apparatus, traditionally a Wurster column (Wurster HS, Glatt). In the Wurster column, the substrate particles are fluidized and suspended by heated and conditioned air. One or several nozzles atomize and spray the drug dispersion onto the substrate. The heated and conditioned air then evaporates the liquid carrier, leaving the drug deposited on the substrate. Drying process is very important as it crystallizes the dissolved material that link the core with consecutive layers of the drug or other polymers. This process is continued until the required drug or polymers layer is achieved. It is also an effective technique but there are few drawbacks of this and one of them is difficulty in achieving evenness in the drug distribution and uniformity in the size of the pellets.

Extrusion-Spheronization⁽⁷⁾

Shaping the wet mass into cylinders called extrusion. Breaking up the extrudate and rounding of the particles into spheres called spheronization.

The extrusion-spheronization technique is the most popular method of producing pellets. This process was first reported by Reynolds and by Conine and Hadley and involves four steps: (i) preparation of the wet mass (granulation); (ii) shaping the wet mass into cylinders (extrusion); (iii) breaking up the extrudate and rounding of the particles into spheres (spheronization); (iv) drying of the pellets.

According to Galland et al., wetting operation brings the material to a state in which porosity is linked to water content. The extrusion operation densifies the material to saturation point while spheronization is only a shaping process which maintains hydro-textural state. The drying operation finalizes the textural characteristics of the product by densifying the medium through induced shrinkage.

Advantages of extrusion-spheronization over other techniques includes: ability to incorporate higher levels of active components without producing excessively larger particles; two or more active agents can be easily combined in any ratio in the same unit; physical characteristics of the active ingredients and excipients can be modified; and particles having high bulk density, low hygroscopicity, high sphericity, dust free, narrow particle size distribution and smoother surface can be produced.

Cryopelletization⁽²⁾

It is a unique process as it requires a fixing medium. Usually liquid nitrogen is used as fixing medium which is applied on the droplets of liquid formulation to convert them into solid pellets. This technique is similar to the one which is used for the lyophilization of viscous bacterial suspension. Liquid nitrogen prepares pellets at the temperature of 160 which causes vigorous transformation of heat between drugs loaded droplets and fixing medium. Amount of solid and temperature of the solution or suspension describe how much nitrogen should be used in this process. Apparatus for this process consists of a perforated plate, a conveyor belt which acts as a reservoir, transport baffles storage container. Droplets are generated through perforated plates and freeze when exposed to liquid nitrogen and finally extracted out from the medium and stored at -160 .

It is a unique method for the preparation which is an expensive one and required expertise for the preparation of pellets by using this technique.

Hot Melt Extrusion⁽²⁾

Hot-melt extrusion is one of the most extensively used techniques in different industries like plastic, rubber and food industry. Nowadays, this technique is succeeded in gaining entry into the

pharmaceutical industry. In pharmaceutical industry, this technique is valuable in formulating different dosage forms including pellets, granules and transdermal drug delivery systems. In this method, drugs and other excipients are mixed evenly and then melted on a temperature which is high enough to convert the ingredients in molten state. Usually a spheronizer is used to convert the pellets into spherical form.

It is a very effective and used full method for pelletization but heat labile drugs and excipients cannot be fabricated as pellets.

Freeze Pelletization⁽²⁾

It is a simple but new technique for the preparation of pellets. In this technique drug carrier is used in molten form. Active ingredient is dispersed in the molten carrier that is added dropwise in the column of immiscible liquid. These droplets can move in both directions either upwards or downwards depending upon the densities of the material. Drug carrier can be hydrophilic or hydrophobic and melted at the temperature 5 to 10 greater than its melting point. Liquid column is divided into two parts. One part with temperature range of 25 to 100 and send portion with 0 to 40°C, used for the solidification of melted material. In order to maintain this temperature cooling mixture of acetone and dry ice is used.

Depending upon the nature of the carrier, two types of apparatus are available for pelletization that are Freeze Pelletizer I and Freeze Pelletizer II.

In Freeze Pelletizer I, water soluble material and low melting point materials are used for example: polyethylene glycol (PEG), polyvinyl alcohol (PVA), dextrose and maltose etc. are used. Low density liquids are used for column such as mineral oil, vegetable oil and silicon oil. In Freeze Pelletizer II, hydrophobic carriers are used such as glyceryl palmitostearate, glyceryl behenate and glyceryl monostearate. In column, high density hydrophilic liquids like ethyl alcohol, glycerin, polyethylene glycol and water are used.

Examples of Drugs Marketed as Pellets

No	Drug	Manufacturer	Product	Therapeuticclass
1	Omeprazolemagnesium	AstraZeneca	LosecMUPS	Antiulcer
2	Esomeprazolemagnesium	AstraZeneca	Esomeprazole	Antiulcer
3	Metoprololtartrate	AstraZeneca	ToprolXL	Antihypertensive
4	Lansoprazole	Takeda	PrevacidsoluTab	Antiulcer
5	Theophylline	Key	Theodur	Antiasthmatic

CONCLUSIONS

The study has revealed that it is possible to overcome the problem of gastric damage during the use of NSAID class of Drugs, avoiding the exposure of the drug to the ulcerprone area of the GI tract, by enteric coating of the pellets. It can also be concluded from the study that, in the same formulation, solubility of the drug can also be improved by formulating fast-disintegrating pellets, making the drug available in the intestine for rapid absorption, by using -carrageenan as a pelletizing aid and sodium starch glycolate as a disintegrant by extrusion–spheronization technique.

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