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Review

Extrusion–spheronization a promising pelletization technique: In-depth review

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ABSTRACT

This review article deals with various aspects of the extrusion–spheronization technique. The first part includes different steps in the production process of pellets such as granulation, extrusion, spheronization, and drying. In the second part, the parameters which can influence the quality of pellets including formulation (moisture content, granulating liquid, excipients, and drugs), equipment (mixer, extruder, friction plate, and extrusion screen) and process (extrusion speed, extrusion temperature, spheronizer load, spheronization time, spheronization speed, and drying method) are discussed. In the final part, methods available for characterization (particle size distribution, surface area, shape and sphericity, porosity, density, hardness and friability, flow properties, disintegration, and dissolution) of the pellets are explained.

1. Introduction

Multiparticulate dosage forms are gaining much favor over single-unit dosage forms because of their potential benefits like predictable gastric emptying, no risk of dose dumping, flexible release patterns, and increased bioavailability with less inter and intra-subject variability [1]. Pellets are one of the most popular multi-particulate dosage forms. 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 range in size, typically, between 0.5 mm and 1.5 mm [2]. Pellets as a drug delivery system offer not only therapeutic advantages, such as less irritation of the gastro-intestinal tract and a lowered risk of side effects due to dose dumping, but also technological advantages, for example, better flow properties, less friable dosage form, narrow particle size distribution, ease of coating and uniform packing. The reproducibility of the drug blood levels is an additional advantage to the use of a pellet formulation. Pellets are commonly filled into hard gelatin capsules but can also be compressed to tablets. The commercially available pellet formulations are mainly coated with a polymer film in order to obtain a controlled release effect. The thickness and composition of the film influence the release pattern; so by mixing different types of coated pellets, the desired release profile can be obtained [3].

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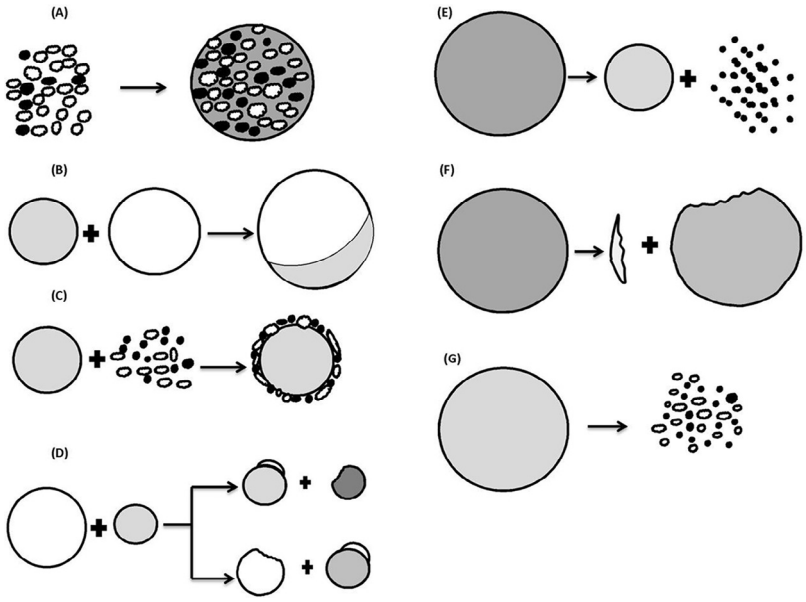

Fig. 1 – Formation and growth mechanism of pellet (A) nucleation, (B) coalescence, (C) layering and (D) abrasion transfer and mechanism of size reduction (E) attrition, (F) breakage and (G) shatter.

1.1. *Formation and growth mechanism of pellets [4]*

In order to select and optimize any pelletization process, it is essential to understand the fundamental mechanisms of pellet formation and growth. Nucleation, coalescence, layering, abrasion transfer and size reduction are the events that lead to the formation and growth of pellets. In nucleation, primary particles are drawn together to form three-phase air–water–solid nuclei (Fig. 1A). The collision of well-formed nuclei to form larger size particles is known as coalescence (Fig. 1B). Successive addition of material on already formed nuclei is layering (Fig. 1C). Transfer of material from one particle to another without any preference in either direction is abrasion transfer (Fig. 1D). There are three size reduction mechanisms which have an indirect effect on the growth mechanism, particularly layering and to some extent coalescence. Well-formed particles may undergo size reduction due to attrition (Fig. 1E), breakage (Fig. 1F) and shatter (Fig. 1G).

1.2. *Pelletization techniques*

Depending on the type of equipment and processes selected, pellet formation and growth may occur in a number of ways (Fig. 2). Here are phenomena that describe the systematic formation of pellets during the various pelletization processes.

1.2.1. *Agitation*

In agitation, finely divided particles are converted to spherical particles, upon the addition of appropriate quantities of liquid, by a continuous rolling or tumbling motion. The liquid may be added prior to or during the agitation stage. Pans, discs, drums, or mixers may be used to produce pellets by the balling process [5].

1.2.2. *Compaction [4,6]*

A 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 shape and sizes. In compression, particles that are pretreated through dry blending or wet granulation followed by drying rearrange themselves to form a closely packed mass. At higher pressure, the particles are forced against each other and undergo elastic and plastic deformation. In extrusion–spheronization, first the dry powder mix is agglomerated with the help of a binding liquid. Then it is processed in the extruder to produce high-density extrudates. These extrudates are finally converted to pellets on spheronizer.

1.2.3. *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 material. In powder layering, a binder solution is first sprayed onto the nuclei, followed by the addition of powder. The moist nuclei tumble in the rotating pan or 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 binding liquid is sprayed, layering of more powder on the nuclei continues until the desired pellet sizes are obtained. In solution/suspension layering, the drug particles are dissolved or suspended in the binding liquid. The liquid is then sprayed on preformed nuclei and spread out on nuclei followed by drying. Spreading depends on the droplet wetting characteristics, the wettability of the material, and droplet dynamics [4].

Kovacevic et al. have compared powder, solution and suspension layering for the preparation of enteric coated pellets and reported that suspension layering proved to be superior to other techniques both in drug loading and enteric layering phase [7].

1.2.4. *Globulation*

Globulation is a process where liquid materials like melt, solution, or suspension are atomized to generate spherical