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Research paper

Spheronization of solid lipid extrudates: Elucidation of spheroid formation mechanism

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ABSTRACT

To explain the rounding mechanism of extrudates by spheronization method, two main concepts are found in literature: one proposed by Rowe (1985) and one proposed by Baert et al. (1993). These concepts are based on wet extrusion-spheronization method using microcrystalline cellulose as mains excipient. However, there are no concepts for the spheronization mechanism of extrudates based on solid lipids as spheronization aid. Therefore, the aim of this study is to systematically investigate the mechanism of pellet formation of lipid based extrudates by lipid spheronization method. Different lipid based extrudate formulations were spheronized and particle size distribution and shape of the pellets, at each minute of the process, were characterized. Additionally, visual investigations of the morphological alterations were performed by optical and scanning electron microscopy. Two main material temperature phases were identified as presenting important influence on the pellet formation during the process: (1) a "brittle phase", where the extrudates are broken into smaller particles and (2) a "plastic phase", where the material starts to partially melt, allowing the particles to deform. By the same token, different morphological stages, from cylindrical rods to sphere-shaped passing through a dumbbell-shaped particle, were observed and showed to be highly dependent on temperature and process time. Moreover, a new particle shape, defined as "two-spheres", was recognized and a sequential material overlapping (covering) phenomenon was identified. This particular dislocation of material, from the edges to the central region of the particles (increasing their mean diameter), was recognized at longer process times and led to the formation of a smooth surface and the final spherical shape. At the end, a new concept of pellet formation from lipid extrudates is presented considering the observed changes in the morphology and particle size of the pellets during the spheronization process.

1. Introduction

In the pharmaceutical area, pellets can be defined as small, free-flowing, spherical-shaped particles produced by agglomeration of fine powders of active pharmaceutical ingredients (APIs) and excipients using specific processing equipment's [1]. There are several methods that could be used to produce pellets. One of the most commonly employed is extrusion followed by spheronization (ES). Regarding the spheronization step, the starting material (usually rod-shaped extrudates or irregular granules) is subsequently rounded into spherical-shaped particles by a spheronizer. The working parts of this equipment consist of a bowl having fixed sidewalls with a rapidly rotating bottom plate or disk (usually called friction plate). The rounding of extrudates into spheres or pellets is mainly dependent on frictional forces, which are generated by particle-particle and particle-equipment interactions. For this reason, the friction plate is generally manufactured with a structured surface that increases the generated forces as particles move across its surface [2]. Plain disks are also available, but they showed to be less efficient [3].

In literature, there are two main concepts that describe the mechanisms of pellet formation of wet-extruded masses by spheronization method: one proposed in 1985 by Rowe [4] and a posterior, proposed in 1993, by Baert, et al. [5]. A graphical representation of these two main concepts are depicted in Fig. 1. The first model (Fig. 1A) describes a transition from cylindrical-shaped into spherical-shaped particles due to an initial breakage of longer extrudates followed by a plastic (or viscoplastic) deformation. This deformation is promoted by collisions of the particles with other particles, with the friction plate, and with the equipment internal walls. Initially, the edges of the rods are broken and rounded. Subsequently, a "dumbbell-shaped" particle is generated.

Abbreviations: API, Active pharmaceutical ingredient; AR, Aspect ratio; TT, Targeted material temperature; ES, Extrusion-spheronization; HCl, Hydrochloride; LES, Lipid extrusion-spheronization; LP, Lipid pellet; MCC, Microcrystalline cellulose; SEM, Scanning electron microscopy; WES, Wet extrusion-spheronization

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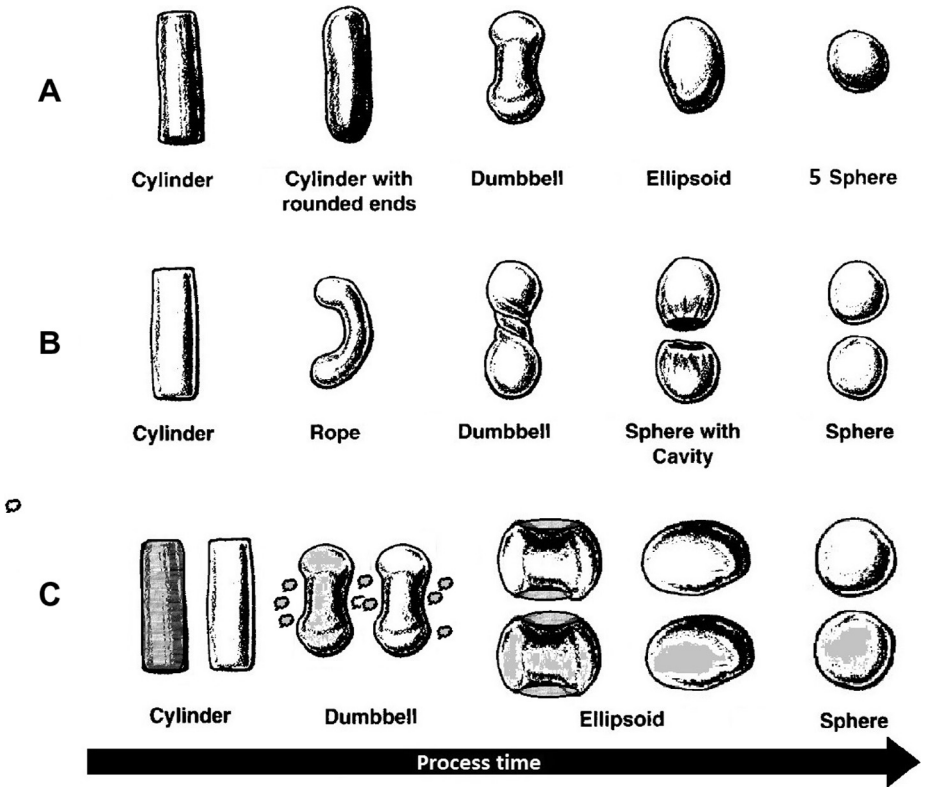

Fig. 1. Graphic representation of the main proposed models to describe the mechanism of spheronization: (A) mechanism according to Rowe [4], (B) to Baert et al. [5], and (C) combined deformation and agglomeration mechanism (figure adapted from Erkoboni [2] and Koester and Thommes [7]).

Continuing the process, a spherical pellet is achieved at the end of the spheronization. The model proposed by Baert, et al. [5] (Fig. 1B) describes a similar mechanism. However, in this mechanism, the transition from the initial cylindrical-shaped particle includes a second breakage phase where a twisted "dumbbell-shaped" particle breaks into nearly spherical particles. At the end, a formation of two small spheres is achieved [2].

Recently, a new complementary concept for these mechanisms was proposed by Liew, et al. [6], called "mass transfer mechanism". This mechanism includes a random attrition and adhesion of fine particles at the pellet surface during the spheronization process with further coalescence and material change between with other pellets. This concept was further improved by Koester and Thommes [7], since agglomeration of fine particles at specific regions of the pellets was observed. The fines presented a tendency to agglomerate mainly in the central band around the pellet, implementing the transformation from "dumbbell-shaped" particles into spherical pellets (Fig. 1C).

Regarding the extrudates and aiming the production of good quality pellets, the formulation to be spheronized requires certain rheological properties. The material should present adequate surface plasticity under stress, allowing morphological remodeling. Besides, it should possess sufficient cohesiveness to remain as an entity during the frictional stresses generated by the spheronization step [8]. In other words, the extruded mass should present adequate relationship between brittleness and plasticity [2]. These properties are usually provided by addition of pelletization aids in the formulation. Usually, microcrystalline cellulose (MCC) or, in exceptional cases, *k*-carragenan are employed since they showed adequate properties to obtain spherical pellets by wet extrusion-spheronization (WES). In these cases, water is added to improve the plasticity of the formulation. However, WES present some disadvantages such as the use of solvents (more specifically water), which must be evaporated from the extrudated mass and the use of a drying step (presence of high temperatures). These requirements may cause degradation of the API.

Recently, solvent-free cold extrusion-spheronization (or simply lipid extrusion-spheronization; LES), was introduced as a methodology to obtain pharmaceutical lipid based pellets that employs powdered solid lipids as extrusion and/or spheronization aids [9–11]. Regarding the lipid spheronization process, it is performed using the same piece of equipment and under similar conditions compared to the traditional spheronization (wet spheronization). However, an additional thermomechanical treatment of the material is required during the process, since the rounding of the extrudates requires a certain plasticity of the mass. This plasticity of the material is achieved by heating it during the spheronization process using a heat source. Moreover, this specific condition is reached by raising the material temperature to a suitable temperature, which was reported as approximately 10 °C below the melting temperature range of the employed solid lipids. At this temperature, the lipids contained in the formulation partly melts (or are "softened") and the mass becomes moldable or deformable. The material temperature can be raised by increased friction forces generated by collisions among the particles and the friction plate or by heating the spheronizer wall generally using a double jacket wall [12]. However, this process presents some limitations at high process temperatures: strong agglomeration of material was observed, especially for formulations based on high fractions of lipid binders [10,11]. Recently a new spheronization approach was successfully introduced employing an external source of heating (an infrared thermal light). This approach enabled, for the first time, a successful spheronization of different formulations based on high fractions of lipids allowing the achievement of longer process times [13].

There are several studies regarding the understanding of the spheronization mechanism of extrudates, but, these studies are mainly focused on the investigation of WES, which uses liquid solvents as plasticizer and, commonly, MCC as extrusion-spheronization aid [4–7,14–17]. There are only few reports in recent literature regarding investigations of the spheronization process of solid lipid based extrudates. These studies are focused on formulation investigations and optimization of process parameters, but not on understanding nor modelling the pellet formation mechanism behind the rounding process [9–11,13]. Thus, there is a lack of fundamental understanding of the mechanism of pellet formation by spheronization using lipid based