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Research Paper

Spheronization of solid lipid extrudates: A novel approach on controlling critical process parameters

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ABSTRACT

Solid lipids are non-toxic excipients, which are known to potentially enhance delivery and bioavailability of poorly water-soluble drugs and moreover to mask unpleasant tasting drugs. Multiple unit matrix dosage forms based on solid lipids, such as lipid pellets, can be obtained by solvent-free cold extrusion and spheronization. This method presents advantages in the processing of sensitive substances, such as low process temperatures, the absence of solvents and a drying step. However, the material temperature during the spheronization showed to be critical so far. The process leads to increased material temperatures, causing particle agglomeration and discontinuity of the spheronization. In the present study, extrudates of 0.5 mm in diameter containing metformin hydrochloride, and either semisynthetic hard fat (Witocan® 42/44) or different ternary mixtures based on hard fat, glyceryl trimyristate, and glyceryl distearate, were spheronized. By applying common process parameters, particle agglomeration or material stickiness on equipment walls was observed in preliminary experiments after 2–6 min, depending on the lipid composition. Therefore, an innovative instrumental setup to control the spheronization process was developed utilizing an infrared light source, which was positioned over the particle bed. The new approach enabled a spheronization process that reached the desired spheronization temperature after 2–3 min and neither particle agglomeration nor material adherence occurred even after longer process times. The different formulations, even those based on high amount of solid lipids, were successfully spheronized over 15 min, resulting in small diameter lipid pellets with smooth surface and aspect ratios below 1.3.

1. Introduction

Various methods can be applied to produce pharmaceutical pellets, such as layering, direct pelletization, high shear or fluid-bed granulation. The most traditional pelletization process is the wet extrusion/spheronization, mostly using microcrystalline cellulose (MCC) as pelletization aid. However, the use of powdered solid lipids as excipients has recently gained interest in the pharmaceutical development. These excipients have been used in the food industry for many years, especially due to their safety profile. Furthermore, they have already successfully been used to enhance drug delivery and bioavailability of poorly soluble drugs [1] or as taste masking agents for bitter drugs [2–4].

Solid lipid extrusion by either twin-screw or ram extruder followed by spheronization is a relatively new manufacturing method for lipid pellets [5–7]. During the extrusion process, material plasticity is achieved by a thermomechanical treatment of the lipid binders, without melting the bulk part of the lipid, by applying temperatures below their melting ranges [8]. As the applied temperatures are normally close to ambient temperature, solid lipid extrusion is applicable for temperature sensitive drugs. In order to achieve a "softening" of the particle surface, the pelletization step of the lipid extrudates is also performed under specific thermomechanical conditions, resulting in deformation of the particles prior to adequate sphericity [6]. However, the spheronized mass should provide a certain brittleness at low temperatures, permitting the extrudate to break into short segments. On the other hand, the mass should also dispose a certain plasticity at intermediate temperatures, which is required to form rounded pellets. Some solid lipids with low or intermediate melting ranges, such as Witocan® 42/44 (a semi-synthetic powdered hard fat), glyceryl trimyristate or glyceryl distearate, provide these temperature-dependent mechanical characteristics. They are brittle at room temperature and softened within a broad temperature range, in which they are plastically deformable without sticking properties [6].

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Breitkreutz et al. developed sodium benzoate coated lipid pellets, using solvent-free cold extrusion followed by spheronization [5]. With the aim to produce a slowly releasing, taste-masked multiparticulate dosage form, they investigated pellets containing 10–25% of solid lipids (stearic acid, glyceryl distearate and hard fat). During the spheronization, uncontrolled agglomeration of the particles was observed after 5 min, especially when the material temperature reached 39 °C. Due to these short spheronization times, ideal spherically shaped pellets were not obtained. In 2009, Krause et al. applied the same spheronization method to sodium benzoate extrudates based on 20% of hard fat or a binary, ternary and quaternary mixture of solid lipids [7]. Parameters such as the friction plate speed and spheronizer jacket temperature were also evaluated. It was observed that material agglomeration temperatures closer by 8 °C to the melting point of the binder were inadequate for the production of suitable shaped pellets. Equipment jacket temperature of 33 °C, friction plate speed of 1500 rpm and process time of 15 min were defined as more suitable for the spheronization of lipid extrudates based on 20% of hard fat. However, depending on the lipid binders used, these parameters were still not sufficient to obtain adequate spherical pellets due to material agglomeration.

The impact of the equipment jacket temperature on the spheronization process was assessed by Reitz and Kleinebudde in 2009 [6]. In their work, the spheronization of lipid based extrudates, containing theophylline and 45% of binary mixtures of glyceryl trimyristate and hard fat in different proportions, was evaluated. They observed that the variation on the lipid binders' proportion, especially the increase of hard fat content in the extrudate, strongly influenced the spheronization process time. Due to agglomeration, the spheronization process of some compositions needed to be stopped after 5–9 min, especially at material temperatures around 39 °C [5]. However, spheronization times of 15 min were required to obtain pellets with adequate spherical shape.

So far, previous works dealing with the spheronization of solid lipid extrudates could not completely solve the problem of material agglomeration or adherence at the spheronizer walls. Appropriately shaped pellets obtained from extrudates based on higher lipid amounts could so far not be obtained due to extremely fast material agglomeration. Prior works indicate that the material temperature is the most critical factor of the solid lipid spheronization step and a successful control would be of great benefit. Thus, the purpose of this study was to investigate a new spheronization approach that avoids particle agglomeration and material stickiness at the equipment walls by controlling the material temperature during the spheronization process.

2. Materials and methods

2.1. Materials

Metformin hydrochloride (Wanbury, Maharashtra, India), semi-synthetic powdered hard fat (melting range: 42–44 °C) (Witocan® 42/44, Cremer Oleo, Witten, Germany) – in the present work referred as "hard fat" – glyceryl distearate powder (melting range: 53–57 °C) (Precirol® ATO 5, Gattefossé, Weil am Rhein, Germany) and glyceryl trimyristate powder (melting range: 55–58 °C) (Dynasan® 114, Cremer Oleo, Witten, Germany) were used. Each material was sieved through a 300 μm sieve before usage.

2.2. Methods

2.2.1. Solid lipid extrusion

Different mixtures of powdered lipids were blended with metformin hydrochloride (Table 1) in a laboratory scale blender at 25 rpm for 15 min (LM40, Bohle, Ennigerloh, Germany). The extrusion step was performed on a co-rotating twin-screw extruder (Mikro 27GL-28D, Leistritz, Nuremberg, Germany). The blend was transferred into a dosing device (KT20K-Tron Soder, Lenzhard, Switzerland) that fed the powder into the barrel of the twin-screw extruder gravimetrically. The feed rate was adjusted to 40 g min^{-1} and the screw speed to 50 rpm. The extruder was equipped with an axial screen plate with 91 dies of 0.5 mm diameter and 1.35 mm length each. The barrel temperature of the extrusion process was set to 25 °C and the temperature of the last barrel to 33 °C.

2.2.2. Spheronization

Batches of 300 g extrudate were transferred into a spheronizer (RM 300, Schlüter, Neustadt, Germany). The device was equipped with a cross-hatched rotor plate of 300 mm diameter. The lipid extrudates were spheronized for 15 min at 1500 rpm. The spheronizer jacket was adjusted to a pre-defined temperature. The material temperature was measured contact-free using the infrared thermometer LaserSight® (Optris, Berlin, Germany). During the temperature measurements, the thermometer was adjusted at the upper shell of the spheronizer. The spot size with a constant diameter of 16 mm was aimed to the surface of the rotating particles in the spheronizer bed at a distance of approximately 17 cm. The temperature measurements were recorded using the software Connect v.2.0.5 (Optris, Berlin, Germany). The pellets were sieved and the fraction between 250 μm and 1000 μm was used for further evaluation.

2.2.3. Particle size and shape

The particle size distribution was determined using a Camsizer® XT (Retsch Technology, Haan, Germany). The particle size distribution diameters (d_{10}, d_{50}, d_{90}), and aspect ratio (AR) [9] were determined for each batch of pellets. The distribution of the particle size was also characterized by the "10% interval" fraction according to Thommes and Kleinebudde [10]. The parameter is based on a dimensionless diameter (d), and contains the fraction of pellets within the 0.9–1.1 particle size distribution interval ($d \pm 10\%$). The dimensionless particle size was calculated from the following equation:

$$d = d_F / d_{F50}$$

where d_F the mean Feret diameter, and d_{F50} the median of all mean Feret diameters. The size distribution is characterized as good, if the fraction of the 10% interval exceeds 50%, and as excellent, if it exceeds 75%.

2.2.4. Scanning electron microscopy (SEM)

The surface morphology was evaluated using a G2 PRO Desktop scanning electron microscope (Phenom-World, Eindhoven, the Netherlands).

3. Results and discussion

3.1. Extrudate formulations

Spheronization experiments were performed using lipid based extrudates containing metformin hydrochloride as model drug. The API was chosen due to its high water solubility, high drug load requirement in oral solid dosage forms, and due to its known strong bitter taste. The applied solid lipid binders hard fat, glyceryl distearate and glyceryl trimyristate were chosen according to previous works, which assigned this mixture to have improved properties for the spheronization process compared to formulations based on pure hard fat as binder [6,7]. However, with the aim to evaluate the influence of the spheronization process itself,