Production and Characterization of Rapidly Dissolving Cryopellets

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ABSTRACT: The procedure described in this study provides a platform technology for rapidly dissolving, single-dosed cryopellets. The different steps during cryopellet production were investigated, covering droplet generation, droplet freezing in liquid nitrogen (LN_2) as well as cryopellet properties. With the setup developed, uniform droplets between 4 and 14 μL were produced. The freezing behavior was similar to approaches reported in the literature. A weight loss reported for droplets frozen in LN_2 could not be confirmed. Mechanical stability as observed with texture analysis as well as dissolution time increased with increasing solid content. All cryopellets immediately disintegrated when in contact with the dissolution medium. The dissolution times of amorphous sucrose and trehalose-based cryopellets at different solid content levels were comparable. Crystalline mannitol cryopellets showed in general a higher dissolution time. The formation of δ-mannitol potentially makes the cryopellets suitable as an intermediate product for tableting.

Keywords: lyophilization; solid dosage form; excipients; mechanical properties; physical characterization; dissolution

INTRODUCTION

Cryopelletization is a special application based on freeze-drying similar to spray freeze-drying (SFD).[1] During a cryopelletization or SFD process, the solution is not frozen in vials within the freeze dryer but dropped or sprayed into a cryogen,[2,3] resulting in spherical particles because of the inverse Leidenfrost effect.[4,5] Different cryogenics are reported in the literature including isopentane[6] and propane,[7] but the most commonly used cryogen used is liquid nitrogen (LN_2)[6] because it is chemically inert, needs no recycling, is not flammable, and has a low boiling point (77 K). As the freezing step cannot be so precisely controlled as in a standard freeze-drying procedure, its detailed characterization is crucial. Diverse approaches to the freezing of droplets of various size and shape are available in the literature.[3,6,8–10] These studies often refer to droplets with a diameter of only a few micrometers produced by spraying and assume parts of the freezing process are negligible, for example, time for phase change.[6] This may be correct for small droplets, but the latent heat-connected constant temperature region must be considered when dealing with larger droplets as it may reach several seconds.[10] In this work, the approach made by Eguchi et al.[10] is therefore selected to calculate the different steps of the freezing/cooling process because the droplet volume investigated is comparable to the droplet volume in their study.

Approaches to cryopelletization include the procedure described by Knoch.[1] as well as recent studies describing the formation of cryopellets in order to generate sustained-release pellets.[1,11,12] Compared with these approaches, this study will focus on the production of rapidly dissolving cryopellets. A rapidly dissolving cryopelletized product could be used as a single dosage form as well as a bulk product. It is therefore more flexible than a classical freeze-dried product considering special needs and applications that require low thermal stress or rapid dissolution. These include multiparticulate dosage system with modified release[1] or single-dosage reagents for diagnostic use that require rapid result generation, for example, coagulation diagnostics. Three well-established freeze-drying bulking agents were therefore investigated: mannitol as a crystalline bulking agent, as well as sucrose and trehalose as amorphous bulking agents. The aim of this study is the characterization of the developed setup as well as the establishment of a platform technology for rapidly dissolving cryopellets. A novel aspect of this work is the mechanical characterization of the cryopellets produced. This topic has not been investigated before, although cryopellets could serve as an intermediate product or single-dosed product that both must be resistant to mechanical stress during handling. The description of the mechanism of cryopellet deformation will therefore provide more insight into the production of stable cryopellets.

MATERIALS AND METHODS

D-Mannitol, sucrose, and trehalose dihydrate were purchased from Sigma–Aldrich GmbH (Steinheim, Germany).

Differential Scanning Calorimetry

A Mettler Toledo DSC822e was used to investigate thermal transitions of excipients as well as cryopelletized products. All samples were weighted into 40 μL aluminum pans using an AT261 DeltaRange balance (Mettler Toledo, Gießen, Germany) and sealed in a glove box (r.H. ~0.1%; room temperature). Heating and cooling rate was set to 10 K/min. Between heating and cooling steps, an isothermal equilibration step was performed for 5 minutes.

X-ray Powder Diffraction

The samples were analyzed using a Philips X'pert model X-ray diffraction (XRD) with Cu Kα radiation at 40 kV/40 mA. For all samples, temperature control was set to 25.0°C. Powdered samples were filled into an aluminum sample holder and gently compressed with a cover glass generating a flat surface. All

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scans were measured in the range $2\theta = 0.5°-40°$ with a step size of 0.02°/1 s per step.

Mechanical Properties

The mechanical properties of the cryopellets were analyzed using a TA-XT2i Texture analyzer (Stable Micro Systems, Godalming, UK) equipped with a 5-mm (diameter) tip. All pellets were analyzed using single-particle compression tests. Data were collected with the exponent software as force versus distance or time. Single cryopellets were placed below the tip and were compressed against the flat surface. Two settings were developed to characterize the cryopellets:

1. Detection of the breaking point after elastic deformation (yield point) (Method I)

TA tip settings: speed = 0.01 mm/s; distance = 0.1 mm

Using this method, the initial break, that is, maximum force value causing mechanical failure of the interior structure after the elastic region, was detectable.

2. Detection of the breaking point of the overall structure (Method II)

TA tip settings: speed = 0.10 mm/s; distance = 1.0 mm.

This method was used to identify the breaking point of the whole pellet structure, which is connected with an optical loss of spherical shape, that is, cracking. During the compression of a pellet between two flat surfaces, the contact area changes constantly. The radius of the contact area depending on the level of compression ($r_{k,el}$) was therefore used to calculate the maximum in the ellipsoid pressure distribution during elastic deformation of a spherical particle (p_{max}).[13] With $r_{k,el}$ depending on radius (r), tip speed (v), and the time (t):

$$p_{max} = \frac{3F}{2\pi r_{k,el}^2} \tag{1}$$

$$r_{k,el} = \sqrt{r^2 - (r - vt/2)^2} \tag{2}$$

This equation is based on an equal deformation of a spherical particle compressed between two surfaces that exhibit the same strain at both contact areas. The energy necessary to cause a break of the overall structure (W_{break}) was determined using the Exponent 6 software (Stable Micro Systems, Godalming, UK) calculating the area under the force–displacement curve. The yield point was also determined by the Exponent 6 software represented by the slope change after the elastic region.

Friability

Friability (Fr) was calculated using the mass of the sample before (m_1) and after analysis (m_2):

$$\mathrm{Fr} = \frac{m_1 - m_2}{m_1} \times 100\% \tag{3}$$

The device used to analyze friability of the cryopellets was similar to the one used for friability testing of uncoated tablets in European Pharmacopeia section 2.9.1., but with a purpose-adjusted fall height of 5 cm. After production, the pellets are normally filled in glass vials with a height of 4 cm. A drop of 5 cm will therefore assure that the pellets remain undamaged during filling and transport. The device was covered with an aluminum layer to inhibit electrostatic charges. A sample consisting of 20 pellets was analyzed with 20 rpm over 30 min.

Dissolution Time

As there is no standard dissolution procedure for freeze-dried products, a technique was developed based on an application in coagulation diagnostics. Cryopellets were dropped into an Eppendorf cup (1 mL, PP) containing 300 µL HEPES buffer (isotonic, pH 7.4 at 25.0°C) and were dissolved without stirring. The dissolution time was defined as the time necessary to dissolve the cryopellet completely, that is, no visible residues detectable, which was detected visually.

Residual Moisture Determination (Karl–Fischer Coulometry)

A Karl–Fischer device with electronic dead stop method (831 KF Coulometer and 832 KF Thermoprep (Oven); Methrom, Filderstadt, Germany) was used to determine residual moisture content. Hydranal® Coulomat AG Oven served as a reagent. About 80 mg were used for an expected moisture content of about 1% (m/m). The temperature of the oven was set to 130°C. Lyophilized samples were sealed in a glove box at approximately 0.1% relative humidity (controlled with testo 605-H1 "mini humidity stick" dew point hygrometer).

Scanning Electron Microscopy

Interior structure, surface structure, and particle shape of the cryopellets were examined with an Amray 1810T Scanning Electron Microscope (SEM) at 20 kV. For preparation, the cryopellets were placed on aluminum sample stubs (Model G301; Plano GmbH, Wetzlar, Germany) using a self-adhesive film and were sputtered with gold for 1.5 min at 20 mA/5 kV (Hummer JR Technics, Munich, Germany).

Droplet Temperature Measurement–Freezing Time Determination

A technique was developed to measure the droplet temperature during freezing in LN_2. A T-type thermocouple (TC) (Omega Engineering, Stamford, Connecticut) connected to an OM-SQ2010 datalogger (Omega Engineering; recording 10 data points per second) was used for temperature reading (Omegalog® software) during the freezing process. It was introduced through a 0.5–10-µL Eppendorf pipette tip. A droplet was attached to the thermocouple placing its end at the center of the droplet. This construction was dipped into LN_2 contained in an isolated steel cylinder so that the droplet was completely covered with LN_2. This experiment was carried out using double-distilled, filtered (0.2 µm membrane filter) water with no solute addition. The freezing time determined was compared with the model from Eguchi et al.[10] that was developed for rain droplets. This approach separates the three different steps of the freezing process and defines the overall time as[10]:

$$t_{total} = t_1 + t_2 + t_3 \tag{4}$$

In this equation the sum of t_1 and t_2 describe the cooling and the freezing of the droplet and the total time describes

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