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Review

Pharmaceutical spray freeze drying

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ABSTRACT

Pharmaceutical spray-freeze drying (SFD) includes a heterogeneous set of technologies with primary applications in apparent solubility enhancement, pulmonary drug delivery, intradermal ballistic administration and delivery of vaccines to the nasal mucosa. The methods comprise of three steps: droplet generation, freezing and sublimation drying, which can be matched to the requirements given by the dosage form and route of administration. The objectives, various methods and physicochemical and pharmacological outcomes have been reviewed with a scope including related fields of science and technology.

Contents

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1. Why to spray-freeze-dry medicinal products

Since its introduction by Werly and Baumann, (1964), "spray-freeze drying" (SFD) has attracted much interest in various areas of research, though for the fulfillment of different objectives. The process has been widely used in pharmaceutical research, as well as food science and technology (Ishwarya et al., 2015).

In this review, we aim to provide an overview about the potentials of SFD for the development of pharmaceutical products. We will discuss the main steps involved within the production process (i.e., spraying, freezing and drying) and introduce, describe, and evaluate different available technical approaches related to each step. The findings of the reviewed papers are then discussed in terms of physical and therapeutic characteristics and are subsequently evaluated in regard with the intended pharmaceutical application.

Different approaches have been developed to enable the delivery of biologicals to the body. In addition to the well-known routes of administrations, less conventional pathways such as the pulmonary and nasal routes and delivery to the epidermis by needle-free injection have been investigated. The prime goal of exploring such administration pathways is to develop alternatives to parenteral injection (Schiffter et al., 2010; Klingler et al., 2009; Bi et al., 2008) and to enhance the drug targeting potential (Roa et al., 2011; Gao et al., 2011).

As an approach facilitating the development of dosage forms for alternative delivery pathways, SFD is preferred over classical spray-drying (SD) or freeze-drying (FD) for various reasons. First, using SFD methods can enhance the apparent solubility of poorly water-soluble drugs, which is a common problem with newly developed active pharmaceutical ingredients (API) (Vu et al., 2013). Additionally, due to an ultra-fast freezing process, the drug is embedded amorphously in the excipient thereby minimising the possibility of phase separation between drug and excipients and therefore leading to a molecular distribution of the drug in the excipient material.

Within the context of delivering biologicals as sustained release injectables, some research groups have used SFD for preprocessing the protein/peptide ingredient prior to encapsulation in poly (lactic-*co*-glycolic acid) (PLGA) microspheres. Others have used the process to enable the pulmonary, nasal, and needle-free epidermal drug delivery (e.g., non-invasive vaccination). Biologicals are usually freeze-dried in vials to enhance storage stability, but when aiming for the latter applications, a development of a flowable powder is mandatory. SFD offers the possibility to produce such powders with controlled particle-size distributions, and is hence more favorable than classic FD. On the other hand, SFD is preferable over SD due to the possibility of processing thermosensitive ingredients (Cheow et al., 2011) and the improvement of the reconstitution characteristics of polymeric nanoparticles (Ali and Lamprecht, 2014). Furthermore, SFD is economically preferable over the conventional FD in vials. Lyophilisation of spray-frozen products is more favorable than that of parenteral formulations in vials both in terms of time and energy consumption (Bosshammer, 2014; Claussen et al., 2007). Moreover, SFD allows the production of a flowable bulk ware. This leads to an enormous increase in flexibility of a production site, as the dosage in vials can be adjusted very easily. Table 1 presents an overview of different applications of SFD techniques.

2. How to spray freeze dry medicinal products

The term "spray-freeze drying" (SFD) refers to processes with the following three steps in common:

- Dispersion of bulk liquid solutions into droplets,
- Droplet freezing, and
- Sublimation drying of the frozen material, which may comprise particles or a film that can be subsequently pulverised.

Obviously, some aspects of SFD are closely related to SD and lyophilisation operations, which are widely employed in both pharmaceutical and food industries, but the intricate interactions between rheological and surface phenomena with the transfer of matter and energy and fast transitions from the liquid to the solid and from the solid to the gaseous phase generate opportunities for new products with unique features but also new challenges, particularly with respect to current good manufacturing practices (GMP) and process analytical technologies. Similar combinations of spray-congealing and drying operations have been in use for some time in the production of uniform spherical particles for fertilizers, detergents and explosives, where the process is known as "prilling".

In contrast to SD, where the size and shape of particles emerge upon drying, the size and essential features of the internal structure of lyophilised spherules originate from the freezing step, and with qualifications this holds also for the surface morphology. When droplets are frozen in flight, the particle size is nearly equal to that of the droplet. The surface of dried particles is spherical, usually covered with a smooth shell, which may be partially or completely missing, so that the irregular honeycomb of the internal structure becomes visible. Due to the high specific surface area, the maximal diffusion path length of solvent molecules is