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Active freeze drying for production of nanocrystal-based powder: A pilot study

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ABSTRACT

Active Freeze Drying allows for producing lyophilised powders by progressive agitation of frozen blocks undergoing sublimation. One potential application of this process is the formulation design of unstable nanosuspensions for oral drug delivery, as here shown for nanocrystal-based ketoconazole powder. With this technique, a critical vapour flow needs to be achieved in order to obtain reasonable process yields (> 78%). The size distribution of powder particles (median size between 21 and 44 µm) was affected by the nanocrystal concentration and the drug-to-stabilizer ratio. This was assumed to be related to the mechanical strength of the solid network from which the powder particles break off. The adjustments of the drug-to-stabilizer ratio and the freezing procedure proved to play a major role in improving powder redispersibility. However, differences in powder redispersibility did not translate into significant changes in *in-vitro* dissolution rates. Active Freeze Drying has confirmed to be a promising tool to efficiently produce redispersible nanocrystal powders.

1. Introduction

In recent years, drug discovery strategies in the pharmaceutical industry have led to an increasing number of poorly water-soluble drug candidates under development (Lipinski, 2002). Subsequently, oral bioavailability of many of them is often limited by the dissolution rate in the gastrointestinal tract (Butler and Dressman, 2010). A universal formulation approach to enhance bioavailability of these compounds is nanosizing or nanomilling of the respective drug crystals. The simultaneous increase in surface area generally results in faster dissolution rates based on the Noyes-Whitney equation (Kesisoglou et al., 2007; Shegokar and Müller, 2010). Such a formulation strategy is particularly attractive due to the versatility and the ease of use of the main production method by wet bead milling. This technology, from which several products are currently available on the market, enables the development of nanocrystal formulations from early phases to large-scale manufacture (Junghanns and Müller, 2008; Kesisoglou and Mitra, 2012; Moschwitzer, 2013; Müller and Keck, 2012).

Drug nanocrystals are typically produced in an aqueous dispersion medium, hence forming nanosuspensions. However, physical (e.g. aggregation and Ostwald ripening) and chemical (e.g. hydrolysis) stability issues are frequently encountered upon long term storage in this suspended state (Wang et al., 2013; Wu et al., 2011). To overcome them, nanosuspensions are usually converted into powders, subsequently processed into solid dosage forms (e.g. hard capsule filling or tableting). Different unit operations based on water evaporation like spray dying and coating/granulation in fluidized bed (Bhakay et al., 2013; Bose et al., 2012; Chaubal and Popescu, 2008; Kayaert et al., 2011; Knieke et al., 2015; Kumar et al., 2014; Sun et al., 2015) can be used to achieve this transformation step. In contrast to these methods, freeze-drying is more suitable for products sensitive to temperature or to high residual moisture content. However, this process is money- and time-consuming and the resulting product in the form of a cake still needs to be milled to obtain a powder.

As any form of drying, freeze-drying generates various stresses (related to the freezing and heating conditions) that can cause nanocrystals aggregation (Wang et al., 2005). Consequently, the presence of such aggregates is likely to slow down the dissolution rate of the dried product (Van Eerdenbrugh et al., 2008). Accordingly, powder redispersibility and the following dissolution performance can play a decisive role and need to be optimised for each drug formulation and process design.

In the present study, the performance of a new stirred freeze-drying process called “active freeze drying” (AFD) is evaluated for the first

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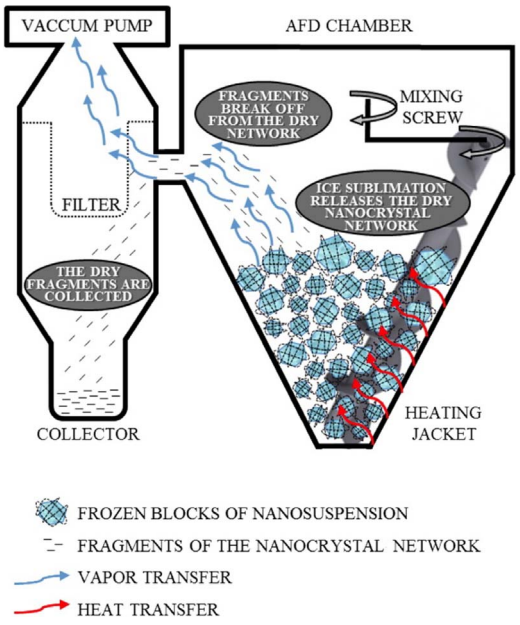

Fig. 1. Schematic representation of the sublimation of a frozen nanosuspension during active freeze drying.

time. Recently developed by Hosokawa Micron BV, this system allows to convert a solution or suspension directly into the form of a fine powder. In contrast to other approaches based on spray-freeze drying (Ali and Lamprecht, 2014; Niwa and Danjo, 2013), powder particles are prepared in one processing step. The product is first frozen dynamically in the conical chamber of the apparatus, equipped with a mixing screw and a controlled heating/cooling jacket (Fig. 1). Freezing is performed through a Vacuum Induced Surface Freezing technique (VISF), and mixing leads to formation of individualized frozen blocks. Thereafter, the ice crystals contained in these blocks are progressively sublimated starting from the outer layers, towards the inner ones. However, the dry layer created around each frozen core does not remain intact. Due to the mixing stress, fragments constantly break off from this dry layer and migrate out of the chamber up to a collector driven by vapour flow which is regulated by heat supply. This parameter must be controlled to collect the powder particles while preserving the structure of the dry layer undamaged. Indeed, excessive heat supply leading to collapse of the outer layer prevents its fragmentation. Constant removal of the dried fraction also minimizes the development of a resistance to vapour transfer. At the same time, mixing enlarges the sublimating surface and supports an effective heat transfer throughout the product. Therefore, in addition to a minimal processing aspect (i.e. the direct production of a powder), this technology also aims to achieve shorter drying time compared to a bulk freeze-drying process on trays.

Here, the suitability of the AFD technology for production of nanocrystal-based powder was investigated using ketoconazole as a poorly water-soluble model drug. By the means of a design of experiments (DoE), emphasis was first placed on the identification of the critical process parameters affecting the size of the powder fragments generated, the redispersibility of nanocrystals as well as the process performance. Based on the results of this DoE, additional tests were then performed by adjusting the stabilizers composition in the formulation and the freezing process to improve powder redispersibility. Finally, dissolution tests were run, comparing optimised versus non-optimised formulations.

2. Materials and methods

2.1. Materials

Ketoconazole, provided by Aarti Drugs Ltd. (Mumbai, India), was used as a poorly water-soluble model drug. Hydroxypropyl cellulose SSL grade (HPC-SSL) was kindly donated by Nisso (Tokyo, Japan). D-α-tocopherol polyethylene glycol 100 succinate (TPGS) was purchased from Antares Health Products Inc. (St Charles, Illinois, USA). All the nanosuspensions were produced in purified water.

2.2. Production of the nanosuspensions

Ketoconazole nanosuspensions were prepared using wet bead milling. Briefly, raw ketoconazole (20% w/w) was dispersed in an aqueous solution containing stabilizers (HPC-SSL 5% w/w, TPGS 1% w/w) under mechanical stirring. Then nano-grinding was performed in a Delta Vita 300 mL (Netzsch, Selb, Germany) filled up to 80% v/v (volume of the grinding beads relative to the volume of the milling chamber) with 0.3 mm yttrium-stabilized zirconium oxide beads (Silibeads ZY-S, Warmensteinach, Germany). Milling, operated in a recirculation mode with a stirrer-tip-speed set at 10.21 m/s (3000 rpm), allowed the production of nanosuspensions (Dv90 < 1μm) in one hour. To constitute the 2 levels of the DoE, one batch of nanosuspension concentrated at 20% w/w in drug crystals was simply water diluted at 10% w/w. In the following optimisation step, extra TPGS was included before each additional test in a nanosuspension concentrated at 20% w/w to reach a ketoconazole/HPC-SSL/TPGS 20/5/3 mass ratio.

2.3. Active freeze drying of the nanosuspensions

2.3.1. Freezing methods

A 1L AFD apparatus (Hosokawa, Doetinchem, Netherlands) connected to a Leyvac LV140C vacuum pump (Leybold GmbH, Cologne, Germany) was used to elaborate the powdered products containing nanocrystals, starting from 500 g of nanosuspension for each test. Prior to freezing, the nanosuspension was cooled below −1 °C by setting the jacket at −3.5 °C. Two distinct VISF methods were then employed as part of the DoE, intended to induce either a slow or a fast freezing rate.

2.3.1.1. The slow freezing method. The pressure inside the chamber was gently lowered until ice nucleation is induced (to about 25 mbar) and was then kept constant for 30 min (Fig. 2). The jacket temperature was raised to 0 °C as soon as the nanosuspension began to freeze to avoid the formation of a “hard ice layer” on the jacket that hampers the screw rotation and heat transfer during the sublimation phase. Close to the end of this step, the whole nanosuspension was solidified in single frozen blocks and concomitantly, the product temperature started to decrease. In order to further promote the product solidification, the pressure was then reduced up to maximal depressurization

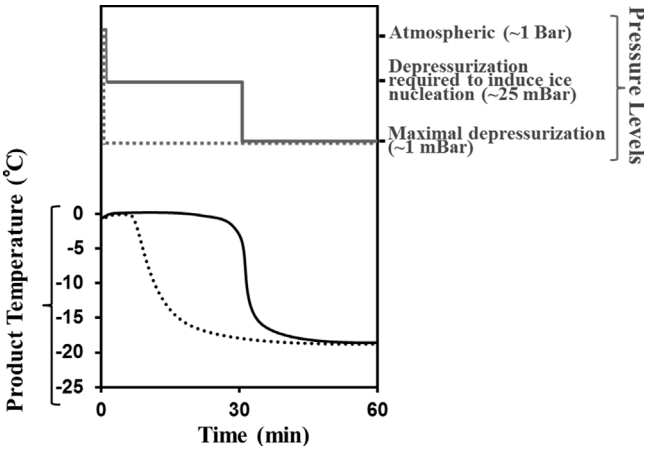

Fig. 2. Representation of the product temperature and pressure levels over the freezing step as a function of the freezing methods (full line: slow freezing method; dotted line: fast freezing method).