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Modelling the primary drying step for the determination of the optimal dynamic heating pad temperature in a continuous pharmaceutical freeze-drying process for unit doses

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ABSTRACT

In the pharmaceutical industry, traditional freeze-drying of unit doses is a batch-wise process associated with many disadvantages. To overcome these disadvantages and to guarantee a uniform product quality and high process efficiency, a continuous freeze-drying process is developed and evaluated. The main differences between the proposed continuous freeze-drying process and traditional freeze-drying can be found firstly in the freezing step during which the vials are rotated around their longitudinal axis (spin freezing), and secondly in the drying step during which the energy for sublimation and desorption is provided through the vial wall by conduction via an electrical heating pad. To obtain a more efficient drying process, the energy transfer has to be optimised without exceeding the product and process limits (e.g. cake collapse, choked flow). Therefore, a mechanistic model describing primary drying during continuous lyophilisation of unit doses based on conduction via heating pads was developed allowing the prediction of the optimal dynamic power input and temperature output of the electric heating pads. The model was verified by experimentally testing the optimal dynamic primary drying conditions calculated for a model formulation. The primary drying endpoint of the model formulation was determined via in-line NIR spectroscopy. This endpoint was then compared with the predicted model based endpoint. The mean ratio between the experimental and model based predicted drying time for six verification runs was 1.05 ± 0.07, indicating a good accordance between the model and the experimental data.

1. Introduction

In 2016, 50% of the by the FDA's Center for Drug Evaluation and Research (CDER) approved novel drugs were biopharmaceuticals (FDA, 2016). Many biopharmaceuticals are unstable in aqueous solution (Chi et al., 2003). The fact that approximately 50% of the approved biopharmaceutical drug products on the list of the Food and Drug Administration (FDA) and European Medicines Agency (EMA) are freeze-dried (lyophilised), indicates that freeze-drying is the preferred technology to stabilize these products (Costantino and Pikal, 2004).

Lyophilisation is a low temperature drying process, based on the principles of mass and heat transfer, employed to convert solutions of (heat) labile materials into solids having sufficient stability for distribution and storage (De Meyer et al., 2015).

Traditional freeze-drying is performed in three consecutive steps: freezing, primary drying and secondary drying (Wang, 2000; Pikal et al., 1983; Rey and May, 2010; Jennings, 1999). After aseptic filling of the formulation into the vials, they are positioned on the shelves of the freeze-dryer. During the freezing step, the temperature of the shelves is decreased to approximately −40 °C and most of the water in the formulation crystallizes into ice, thus concentrating the solutes which are in between the ice crystals (freeze-concentration). These solutes can

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Nomenclature

ΔH_s	latent heat of ice sublimation (2838 J/g)
Δl	increase in dry product layer per time step t (m)
Δt	time step to calculate l (h)
$\dot{m}_{sub}$	sublimation rate (kg/h)
α	parameter describing K_v in function of P_c
β	parameter describing K_v in function of P_c
γ	adiabatic constant for triatomic gas (–)
ϕ	volume fraction of ice (–)
ρ_{ice}	density of ice (kg/m^3)
A_p	product area available for sublimation (m^2)
A_{Rp}	constant describing R_p in function of l (1/s)
B_{Rp}	constant describing R_p in function of l (1/m)
c	speed of sound for an ideal gas (m/s)
$d_{v,o}$	diameter of the vial opening (m)
h_f	height of the spin frozen product (m)
K_v	heat transfer coefficient (J/m^2 s K)
M	molecular weight of water (0.018015 kg/mol)
P_c	chamber pressure (Pa)
P_{sub}	power required for ice sublimation (W)
$P_{w,c}$	partial water vapour pressure in the drying chamber (Pa)
$P_{w,i}$	vapour pressure at the sublimation front (Pa)
R	gas constant (8.3144621 J/(mol K))
R_p	dry product mass transfer resistance (m/s)
$R_{p,0}$	constant describing R_p in function of l (m/s)
$r_{p,i}$	radius from the centre of the vial to the border of the spin frozen layer (m)
$r_{v,i}$	inner radius of the glass vial (m)
T_c	collapse temperature (K)
T_{eu}	eutectic temperature (K)
T_g'	glass transition temperature of the maximum freeze-concentrated formulation (K)
T_h	heating pad temperature (K)
T_i	product temperature at sublimation front (K)
T_p	product temperature (K)
T_{wv}	temperature of water vapour (K)
V	filling volume (m^3)
V_{max}	maximum volume of sublimed gas
$v_{sound,safe}$	safe velocity of sound (m/s)
$\dot{m}_{max}$	maximum sublimation rate (kg/s)

crystallize at the eutectic temperature (T_{eu}). If no crystallization occurs, the solutes concentrate until a glass is formed at the glass transition temperature of the maximally freeze-concentrated amorphous matrix (T_g') (Kasper and Friess, 2011). During primary drying, a vacuum, in general between 10 and 30 Pa, is introduced. Subsequently the temperature of the shelves is increased to supply the energy for sublimation. It is of utter importance to keep the product temperature at the sublimation front (T_i) below the collapse temperature (T_c) for an amorphous product or T_{eu} in case of a crystalline product during the entire primary drying process. The final step of the freeze-drying process is secondary drying where most of the unfrozen water is removed by desorption under deep vacuum and at an increased shelf temperature (Pikal, 2002).

Freeze-drying, as it is performed these days in the pharmaceutical industry, is a batch-wise process (Sarragua et al., 2010). Despite the increased importance of freeze-drying, indicated by the higher number of biopharmaceuticals, it is still an expensive and time-consuming process exhibiting several disadvantages such as the uncontrolled freezing step and uneven heat transfer in the freeze-drying chamber. The disadvantages of batch-wise freeze-drying have been extensively described in a previous paper from the authors (Kasper and Friess, 2011; Kauppinen et al., 2013; De Meyer et al., 2015). To overcome these disadvantages and to guarantee a uniform product quality, a continuous freeze-drying process has been developed.

The continuous freeze-drying process introduces two major differences compared to conventional batch freeze-drying. Firstly the freezing step, during which the vials are spun around their longitudinal axis, creating a thin frozen product layer at the vial wall (spin freezing) (Fig. 1). The solution is solidified by a flow of cold, sterile gas. The thinner product layer and larger surface area of the spin frozen product significantly contributes improving the efficiency of the freeze-drying process. The second major difference occurs in the drying step where energy is homogeneously supplied towards the vial wall either by conduction (e.g. electric heating pad) or radiation (e.g. infra-red heater) (De Meyer et al., 2015; Corver, 2013; Van Bockstal et al., 2017; Van Bockstal, 2017).

In the case of conductive drying, the energy can be provided by an electric heating pad which is wrapped around the vial creating a close contact between the vial and the heating pad for a homogeneous energy transfer (Fig. 2).

The continuous freeze-drying process is extensively described in previous work (De Meyer et al., 2015; Van Bockstal et al., 2017; Van Bockstal, 2017).

The most critical parameter during the primary drying step is T_i. To achieve an efficient freeze-drying process, T_i should be as high as possible during the primary drying step without exceeding T_c or T_{eu} for amorphous or crystalline materials, respectively. T_c is in general a few degrees higher than T_g' since the molecular motion at T_g' is sufficiently low to prevent viscous flow due to the high viscosity (Kasper and Friess, 2011). During secondary drying, the product temperature (T_p) should not exceed the glass transition temperature (T_g) to avoid cake collapse. Collapse is a loss of product structure, causing a poor cake appearance and possibly impeding the reconstitution of the dried product (Koganti et al., 2011; Jennings, 1999). If using constant freeze-drying settings (chamber pressure and energy input for drying), T_i would not be constant during the sublimation process because it depends on several parameters which continuously change during the process, e.g. the dried product mass transfer resistance (R_p) (Mortier et al., 2016). When the sublimation front is moving, a dried product layer is formed, leaving behind a network of pores which create a water vapour removal resistance (Konstantinidis et al., 2011). The continuous increase of the dried product layer (l) during sublimation also leads to a continuous increase in R_p. As a result, T_i at the sublimation interface will increase when a constant energy input and freeze-dryer chamber pressure is maintained for the whole drying trajectory.

However, in order to perform sublimation as efficient as possible, it

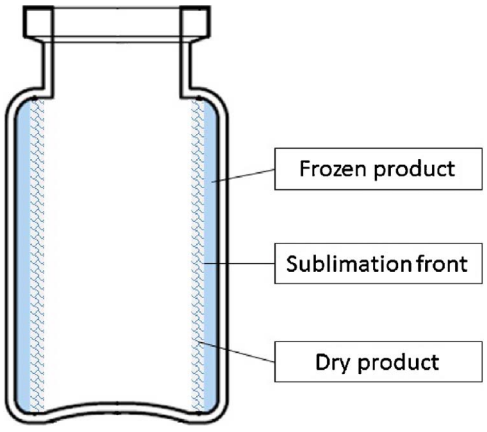

Fig. 1. schematic illustration of a spin frozen vial during the drying process.