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Research paper

Determination of the dried product resistance variability and its influence on the product temperature in pharmaceutical freeze-drying

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ABSTRACT

During the primary drying step of the freeze-drying process, mass transfer resistance strongly affects the product temperature, and consequently the final product quality. The main objective of this study was to evaluate the variability of the mass transfer resistance resulting from the dried product layer (R_p) in a manufacturing batch of vials, and its potential effect on the product temperature, from data obtained in a pilot scale freeze-dryer. Sublimation experiments were run at −25 °C and 10 Pa using two different freezing protocols: with spontaneous or controlled ice nucleation. Five repetitions of each condition were performed. Global (pressure rise test) and local (gravimetric) methods were applied as complementary approaches to estimate R_p. The global method allowed to assess variability of the evolution of R_p with the dried layer thickness between different experiments whereas the local method informed about R_p variability at a fixed time within the vial batch. A product temperature variability of approximately ± 4.4 °C was defined for a product dried layer thickness of 5 mm. The present approach can be used to estimate the risk of failure of the process due to mass transfer variability when designing freeze-drying cycle.

1. Introduction

Freeze-drying is a gentle-drying process which consists of the dehydration of the frozen product under-vacuum by sublimation followed by desorption. This process is currently the method of choice in the pharmaceutical industry for the preservation of heat sensitive products (such as vaccines, proteins or micro-organisms) [1–3]. Several quality attributes of these products, *e.g.,* the visual aspect of the dried cake, the reconstitution time and the moisture content, are governed by the product temperature profile during the sublimation step [4–6]. If the temperature of the sublimation interface exceeds a critical value, *i.e.,* collapse temperature, the product may experience abrupt loss of quality resulting from the collapse of its dried porous structure [4–6].

The thermal history of the product cannot be directly controlled but it is determined by the heat and mass transfer occurring during the process. Mathematical models derived from theoretical considerations of these phenomena are extensively used to predict the product temperature, for process design and scale-up [7–13]. Freeze-drying models involve the determination of heat and mass transfer parameters, such as the vial heat transfer coefficient K_V and the mass transfer resistance due to the dried layer of the product R_p [7,10,12,13]. The accurate evaluation of these model parameters and their variability is of paramount importance for a reliable prediction of the product temperature within the vials batch and between different freeze-dryers.

The vial heat transfer coefficient K_V is specific for the container, and depends on the chamber pressure and on the dimensions of the vial bottom geometry. It is usually determined by the gravimetric method [12,14–16], which allows to have a detailed picture of the variability of this parameter among the vials on the shelf. In contrast, the product resistance R_p highly depends on the formulation and on the freezing protocol. Its value continuously increases with the increase of the dried layer thickness.

In literature, several methods were proposed to measure the evolution of the product resistance along with the changes in the dried layer thickness by estimating the mass flow rate value, such as the microbalance [17,18], the Pressure Rise Test (PRT) [19–21], the Tunable Diode Laser Absorption Spectroscopy (TDLAS) [22]. Product resistance can also be estimated from the product temperature profile recorded by thermal sensors during the process by using mathematical models and soft sensors (or software sensors) [23,24]. Some of these techniques, such as the PRT and the TDLAS, provide a global value of the product resistance in the vial batch, from the measurement of the

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Nomenclature

A	cross sectional area (m^2)
df	degrees of freedom
ΔH	latent heat of sublimation ($J\,kg^{-1}$)
K_V	vial heat transfer coefficient ($W\,m^{-2}\,K^{-1}$)
l	layer thickness (m)
$\Delta m(t_{sub})$	sublimed mass at time t_{sub} (kg)
$\dot{m}$	mass flow rate ($kg\,s^{-1}$)
PleaseCheck	molecular weight of water ($kg\,kmol^{-1}$)
N_V	number of vials
P	pressure (Pa)
$\dot{Q}$	heat flow rate (W)
R_g	ideal gas constant ($J\,K^{-1}\,kmol^{-1}$)
R_p	product resistance ($Pa\,m^2\,s\,kg^{-1}$)
SD	standard deviation
SE	standard error
t_{sub}	sublimation time (s)
T	temperature (K)
V	volume (m^3)

Greek

λ	thermal conductivity ($W\,m^{-1}\,K^{-1}$)
ρ	density of ice ($kg\,m^{-3}$)

Subscripts

0,1	index of parameters in Eq. (6)
B	bottom
C	chamber
d	dried
f	frozen
i	interface
S	shelf
v	vapour
V	vial

global mass flow rate. Other methods allow to determine product resistance evolution in one vial (such as the microbalance) or in a limited number of vials (for example the use of thermocouples). Thus, the determination of the variability of the product resistance within a manufacturing batch of vials remains particularly challenging.

The product resistance value and variability are directly influenced by the freezing step. Some authors have shown a direct correlation between nucleation temperature, ice crystal size, and mass transfer during sublimation [20,25,26]. It was reported that high values of nucleation temperature generate few and large ice crystals, which upon sublimation leave larger pores and smaller specific surface area than low values of nucleation temperature. The dimension of the pores dramatically influences the resistance of the product due to the dried layer, and thus the sublimation rate [25,27]. Furthermore, the stochastic nature of nucleation temperature leads to different kinetics of sublimation within a same vial batch [20,28,29], resulting in potentially high vial to vial variability that would make it difficult to achieve homogeneous product quality.

In the present work, the product resistance R_p in a manufacturing batch of vials was estimated from data obtained at pilot scale. Sublimation experiments were performed using a 5% sucrose solution at 10 Pa and −25 °C in a pilot scale freeze-dryer. Two different freezing protocols were used, *i.e.,* the nucleation of ice crystals was either spontaneous or controlled using a nucleating agent. Five repetitions of each condition were carried out, in order to evaluate the product resistance variability between different pilot scale batches. Two additional cycles with partially stoppered vials were carried out, to study the effect of the presence of the stopper on the mass transfer resistance. Two experimental methods were used for the determination of the product resistance: (1) a global/batch one, namely the pressure rise test (PRT), to evaluate the average evolution of the product resistance with the dried layer thickness in single batches, and (2) a local/single vial one, namely the gravimetric method, to evaluate the variability of the mass loss between single vials at a given dried layer thickness. The use of the global method can provide an estimation of the product resistance variability in a large batch of vials (manufacturing scale), by considering repetitions of cycles performed at pilot scale, whereas the use of the local vial method can provide an estimation of the product resistance variability within a small batch of vials (pilot scale). Finally, the effect of R_p variability on the product quality was quantified by calculating the product temperature distribution and by assessing the risk of failure (potential percentage of collapsed vials) during the sublimation step.

2. Materials and methods

2.1. Materials

Siliconized 3 mL tubing vials (Müller + Müller, Holzminden, Germany) filled with a 5% w/w aqueous sucrose solution were used throughout this study.

The experiments were carried out using a pilot scale freeze-dryer (REVO model, Millrock Technology, Kingston, NY, United States). This device included three temperature controlled shelves and a condenser connected to the drying chamber by a butterfly valve. The drying chamber had a volume of 0.12 m^3. Two pressure gauges, a capacitance manometer (MKS) and a thermal conductivity gauge (Pirani) were used to monitor the pressure in the chamber. In order to monitor the product temperature during the cycles, 7 type-T thermocouples were placed in the bottom center of selected vials (Fig. 1).

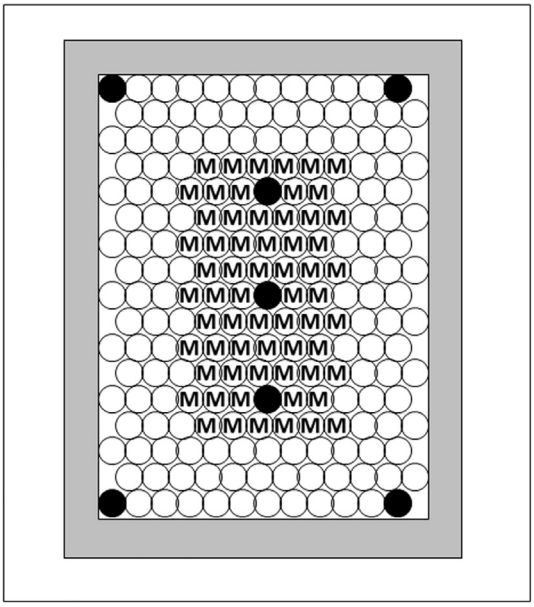

Fig. 1. Arrangement of the vials on the shelf. Symbols: black circle, vials in which the thermocouples are located; letter 'M', gravimetrically-analyzed vials. All vials were filled with 1.8 mL of the selected product.