Smart thermocouples for in-line lyophilization monitoring

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SMART THERMOCOUPLES FOR IN-LINE LYOPHILIZATION MONITORING

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Abstract

The paper describes design, development and characterization of a measuring system for in-line temperature monitoring during freeze-drying of pharmaceutical chemicals. T-type thermocouples with sub-micrometric thickness deposited via plasma-coated with SiO_x film and embedded into the vial walls have been realised as prototypes and successfully tested. The measuring system does not alter the vial shape and its thermal conductivity and does not react with the lyophilized product thus avoiding any interference with the lyophilization process.

Keywords: *Thin film thermocouples, freeze-drying, temperature monitoring*

1. Introduction

Freeze-drying of pharmaceutical products is a process which can last several days, so it is important to optimize it for reducing freezing time and cost. In principle, it is possible to predict the amount of heat which is required by the sublimation to reduce the sublimation time by means of predictive modelling (Velardi *et al.* 2008). However, the model parameters uncertainties can easily lead to a not negligible uncertainty of the freeze-drying process and, consequently, to the risk of overheating the lyophilized product. Indirect measurements e.g. based on the manometric pressure measurement (Barresi *et al.* 2009, Fissore *et al.* 2011) are often employed and even if they proved to be suitable for monitoring the average batch behaviour, they do not consider the nonuniformity of the batch and the effect of the radiating energy from the freeze-drier walls. The insertion of either RTD sensors or bulk thermocouples, even if of very small size, can significantly modify the structure of the final cake and, generally, the monitored vial dries much faster than the rest of the batch. It is therefore important to develop a non-invasive in-line monitoring system able to measure the product temperature during the entire freeze-drying without altering the lyophilization process inside vials, so that they can be considered representative of the entire batch behaviour. The proposed solution is based on an array of thin film T-type thermocouples directly deposited on the vial walls and coated by a SiO_x thin film to make them passive, that can measure the product temperature without altering thermal distribution and shape of the drying front, and without modifying the cake structure during the freezing step (Grassini *et al.* 2013).

2. Material and method

The thermocouples have a thickness of 160 nm and are based on the couple copper/copper-nickel (constantan, Cu55Ni45), with a thermoelectric power is of 16.9 μV/◦C. The TC strips are deposited by DC plasma sputtering on the vial walls and coated with a protective SiO_x thin film (200 nm) deposited by PECVD (Plasma Enhanced Chemical Vapor) (Angelini et al. 2006).

3. Results and discussion

Fig. 1 shows, as an example, the response of the thin film TC during a freeze-drying process of a sucrose solution, which lasted 3 days, in comparison with a conventional TC. The process is composed of 5 h waiting time, 18 h freezing with shelf temperature at −50°C, 65 h of drying with chamber pressure at about 10 Pa, shelf temperature at −20 °C, and condenser temperature at −70 ◦C, and finally 10h with shelf temperature at +20 ◦C for the secondary drying.

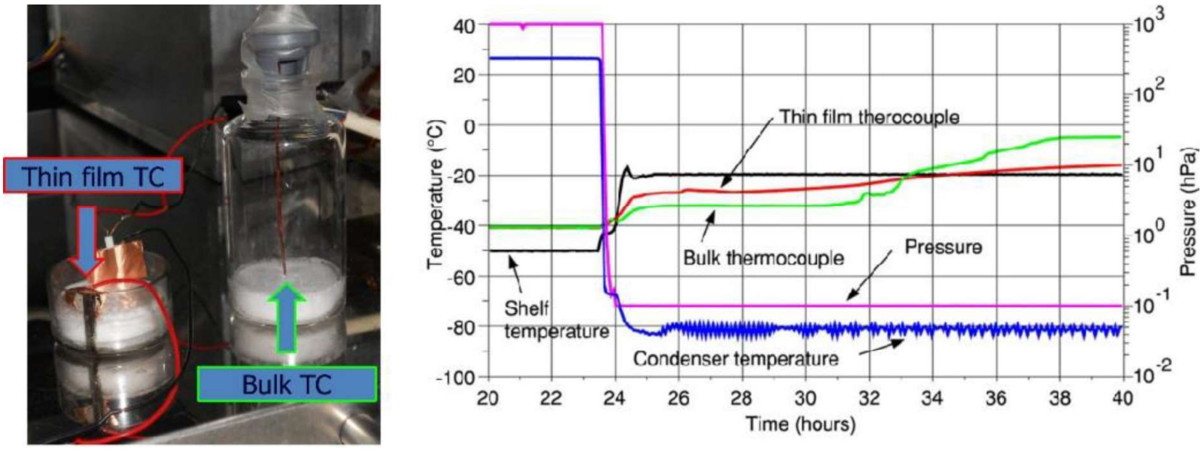

Fig. 1 Thin film TC and bulk TC (left); example of temperature trends measured during lyophilization of a sucrose solution (right)

The figure shows that the bulk thermocouple acts as a nucleation point, starting the ice generation at about −5 ◦C, while the nanometric thermocouple does not show this effect so that the icing starts later, at about −10 ◦C, and resulting in a different structure of the frozen cake. The difference is even larger during the drying phase which is an endothermic process. In this phase the cake goes to a temperature lower than the surrounding and the bulk thermocouple, which is not in close contact with the vial bottom and has a remarkable thermal conductivity, measures a temperature which is lower than the one present on the bottom where the shelf heats the vial and which is measured by the sputtered thermocouple.

4. Conclusions

The use of nanometric TC coated with a thin film of SiO_x is an effective alternative to traditional temperature measurement system and can be used to in-line monitor the freeze-drying process without altering the drying itself.

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