# Infrared Thermography for Monitoring of Freeze-Drying Processes: Instrumental Developments and Preliminary Results

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**ABSTRACT:** Coupling an infrared (IR) camera to a freeze dryer for on-line monitoring of freeze-drying cycles is described for the first time. Normally, product temperature is measured using a few invasive Pt-100 probes, resulting in poor spatial resolution. To overcome this, an IR camera was placed on a process-scale freeze dryer. Imaging took place every 120 s through a Germanium window comprising 30,000 measurement points obtained contact-free from −40°C to 25°C. Results are presented for an empty system, bulk drying of cheese slurry, and drying of 1 mL human serum in 150 vials. During freezing of the empty system, differences of more than 5°C were measured on the shelf. Adding a tray to the empty system, a difference of more than 8°C was observed. These temperature differences probably cause different ice structures affecting the drying speed during sublimation. A temperature difference of maximum 13°C was observed in bulk mode during sublimation. When drying in vials, differences of more than 10°C were observed. Gradually, the large temperature differences disappeared during secondary drying and products were transformed into uniformly dry cakes. The experimental data show that the IR camera is a highly versatile on-line monitoring tool for different kinds of freeze-drying processes. © 2014 The Authors. *Journal of Pharmaceutical Sciences* published by Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:2088–2097, 2014

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## INTRODUCTION

Freeze-drying is an excellent way of drying thermally sensitive materials and preserving thermally labile compounds. It is extensively used in the pharmaceutical and biotechnology industry to produce active pharmaceutical ingredients (e.g., small molecules and proteins), which then can be conveniently distributed and stored. Freeze-drying is also used in other sectors, for instance, in food industry (instant coffee), bacteriology (strain conservation), or chemical synthesis. Moreover, freeze-drying is a versatile means for processing of reference materials (RMs) for various application fields (e.g., clinical chemistry, food, and environment). Such RMs and especially certified RMs (CRMs) are important tools enabling laboratories all over the world to deliver accurate measurement results of demonstrated reliability.[1–3]

Considering the major efforts required for planning, processing, characterizing, and certifying a RM, the production of large and stable batches is preferred, so that the CRM is available for several years after production. To achieve the desired long-term stability of biological materials, removal of water is essential. Freeze-dried materials can be kept for many years for most matrix/analyte combinations, provided that they are stored at an appropriate storage temperature. Obviously, similar requirements apply for many pharmaceutical products with respect to stability and therefore freeze dryers are also widely used in pharmaceutical industry.

A freeze-drying cycle normally consists of the following three steps:

1. Freezing of the water present in the matrix at ambient pressure.
2. Sublimation or primary drying, whereby the water is evaporating from the solid ice in the material and captured on the condenser under vacuum.
3. Secondary drying where most of the remaining water is removed under hard vacuum and temperatures above 0°C.

During freezing, it is of interest to produce as large ice crystals as possible in the matrix.[4,5] Large crystals contribute to the formation of larger pores in the material to be dried, which results in a higher flux of water vapor from the material during primary drying. However, high freezing rates result in smaller ice crystals and smaller pores.[6] Hence, different ice crystal structures result in different flux of water vapor.

During sublimation, the chamber pressure is normally around 0.2 mbar (for the equipment used in this study) and the water vapor that leaves the ice is captured on the ice

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condenser placed under the freeze-drying chamber. When the sublimation step is approaching the end, the pressure is further reduced in the chamber to about 0.005 mbar, and the secondary drying is started. At the same time, the shelf temperature is further increased on the shelves so that most of the last free water can be removed from the matrix. Monitoring of product temperature is achieved through point measurements using Pt-100 probes directly placed in the material. Some brands of freeze dryers also have so-called Lyo sensors that measure the resistivity in the material that is undergoing drying.

The spatial resolution is severely limited when using probes and moreover the probes are invasive, that is, in direct contact with the material. It is therefore difficult to judge how well the probes are characterizing the temperature of all the material that is loaded on a tray and if there are large differences between different areas on the tray. For applications involving drying in ampoules or vials, only a few units can be monitored when probes are used. In addition, when considering the limited sample amounts filled in vials (1 mL serum resulted in 80 mg dry mass in this study), the mass of the Pt100 probe itself of 160 mg adds additional mass to the monitored sample. This could potentially distort the measurement in comparison with vials that are not monitored with the probes. Measurements employing multiple probes systematically placed in the materials have been used to assess the spatial differences in temperature. Still, this approach is invasive, difficult, and unpractical and has inferior spatial resolution in comparison with a thermogram from an infrared (IR) camera.

A thorough literature search has not resulted in any findings of previous reports describing the combination of an IR camera with a freeze dryer. A US patent identifies IR imaging as a potential tool for monitoring of freeze-drying processes but it is suggested to place the IR camera inside the freeze-drying chamber.[7] Another report was found where a normal camera was suggested to be placed inside a freeze dryer.[8]

Other means of monitoring freeze-drying processes have been based on Raman spectroscopy and near-IR spectrometry.[9] There is also a commercially available system for monitoring of the water flux to the condenser using very small inductively coupled plasma atomic emission spectrometer. This so-called Lyo track system can effectively display the flux of water to the condenser during the primary and secondary drying as a function of time.[10] Finally, a thesis by Schneid contains a very comprehensive overview dealing with process analytical technologies for monitoring of freeze-drying processes.[11] However, none of these reported systems is actually monitoring the spatial temperature distribution on materials or between vials placed inside the freeze dryer.

In this paper, the technical details of the new coupling are presented alongside with results from a run of an empty system, one run of a system loaded with slurry made of cheese spiked with a bacterial protein toxin, and a run monitoring 136 vials of human serum during the whole freeze-drying cycle.

## MATERIALS AND METHODS

An IR camera (VarioCAM; Jenoptik; InfraTec GmbH, Dresden, Germany) was mounted vertically on the chamber-roof of a freeze dryer (Epsilon 2-100D; Martin Christ, Osterode, Germany) where a hole of 70 mm diameter had been made in the

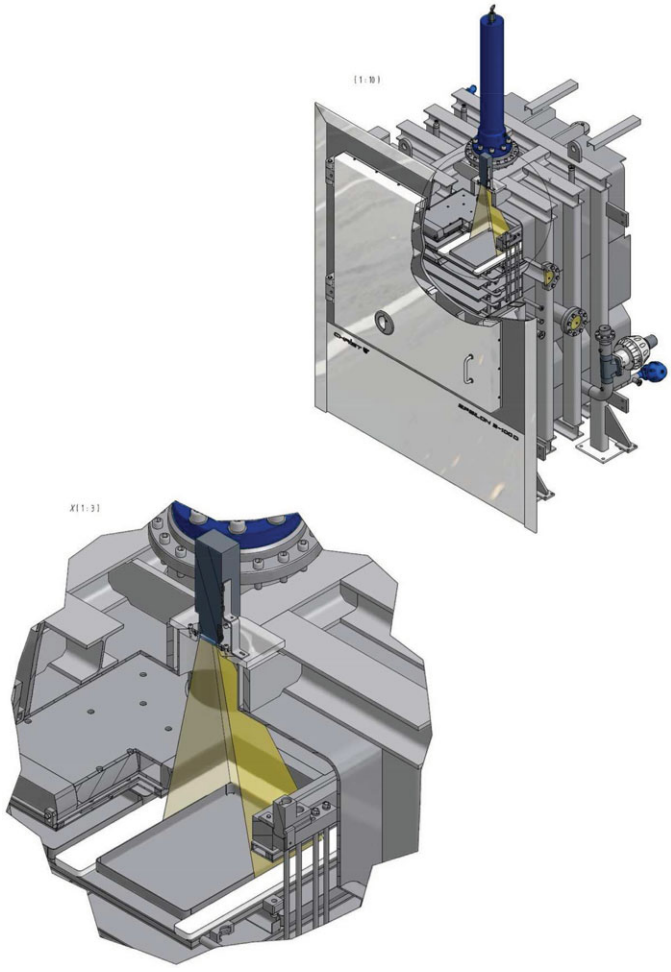

**Figure 1.** Integration of IR camera in freeze dryer. Top right shows the freeze-drying chamber in full and four shelves. Bottom left shows a magnification of area of interest with IR camera, viewing area, tray, and white holder for good alignment of the tray with the optics of the IR camera. During the operation of the freeze-drying programs, this holder had been removed.

roof of the freeze-drying chamber. Inside the chamber, a cut had been made in the radiation shield to allow a free view of the top shelf as can be seen in Figure 1. The IR camera recorded images of the material on the test tray with a high spatial and thermal resolution ($\sim 2 \times 2$ mm$^2$) and (50 mK). Obviously, only the top shelf was possible to monitor with the current system.

Because the drying chamber is subjected to low pressures during operation, the opening was closed with a suitable window having sufficient IR transmission. Therefore, an 8-mm thick window made of Germanium of 10 cm diameter, which had been optically brightened and treated with a special coating, was placed over the opening. The Germanium window was resting on an O-ring and held in place by a steel ring that was fixed with eight screws. The Germanium window allows 80% transmission in the wavelength interval of interest (7.5–14 μm). The IR camera was equipped with a precision wide-angle lens with 64° flare angle. The lens was resting directly on the Germanium window and the camera itself was fixed to the freeze dryer with a z-shaped holder made from stainless steel. The resulting image was matching the size of a standard freeze-drying tray of 30 $\times$40 cm$^2$ placed on the top shelf. The