Summary

Infrared thermography for freeze-drying applications: from ice crystal size prediction to primary drying process monitoring and design space determination

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Freeze drying processes are crucial to the pharmaceutical industry because they can produce shelf-stable high-quality heat-sensitive medicines. Freeze-dried products make up 16% of the top-selling 100 pharmaceuticals and ensuring product quality is of most importance. In fact, the 2004 FDA Guidance for Industry states that product quality needs to be achieved by design and not by testing after production. Hence, optimal cycle design and thorough process monitoring are pivotal for high-quality drug manufacturing through freeze-drying processes.

Most temperature monitoring tools currently in use are invasive ones, i.e., they are in direct contact with the product. With a sensor in direct contact with the product, the product phase change dynamics is affected. During freezing, the first step of a freeze-drying process, the presence of the sensor will drive ice nucleation to happen earlier. If this happens, freezing will occur at a higher temperature for that particular vial, resulting in larger ice crystals than in other vials. This way, their monitoring may not represent well the batch. Additionally, thermocouples are destructive to the monitored sample as they are invasive sensors and sterility concerns arise. Within this scenario, non-invasive temperature monitoring tools become essential.

IR-based sensors can measure product temperature in a non-invasive way without presenting the drawbacks of commonly used tools. Of course, as a novel technology, they present their own drawbacks such as the field of view, low penetration and the need to pre-establish the object's emissivity prior to IR monitoring. Nonetheless, preliminary studies using IR thermography to monitor freeze-drying processes have shown encouraging results, and further studies regarding its application became imperative.

In this present research work, the application of infrared thermography to monitor freeze-drying batches is investigated. The prototype used in this research is placed inside the drying chamber on the same shelf as the monitored vials. This positioning allows monitoring the whole product's axial temperature profile. However, this placement inside the chamber makes it necessary first to evaluate if the sensor's presence can have an effect on batch dynamics. Hence, the starting point of the research was to evaluate this by performing tests with and without the IR camera inside the drying chamber. Thermocouple-based temperature profiles from each batch were compared. It was found that the sensor's case can have a slight shielding effect when a long freezing duration is used or a slight irradiating effect if a short freezing duration is used. This effect is strictly related to the temperature of the camera case after freezing and was ruled as not relevant. Once the sensor's effect was deemed minimal, its accuracy had to be verified. Hence, IR-based thermal profiles were confronted with TC-based ones from the same batch. Different batch and vial sizes were

tested, and the IR temperature measurements were always in good agreement with those of the thermocouples within their accuracy range ± 1 K.

Following the process steps in order, applying IR monitoring to the freezing step brought great insights into the freezing phenomena in vials. Since ice nucleation and crystal growth are exothermic phenomena, special attention was given to maxima temperature points and any evidence of heat release. IR thermography allowed the observation of the heat of nucleation affecting neighbouring vials. Additionally, tracking the axial T_{max} after nucleation could be an experimental inference of the freezing front temperature and position for vials being cooled in direct contact with the shelf. The correlation between larger temperature gradients during nucleation and freezing resulting in larger variability on the resulting cake pore sizes was confirmed in this study. Additionally, the *in-line* application of the IR-based freezing front data coupled to different mathematical models to estimate the resulting pore sizes was successfully validated using vacuum induced surfaced freezing (VISF). Three different freezing models were used, an empiric, a mechanistic and a supersaturation one. The first two, were not very well suited to predict the resulting pore sizes for the cake edges using the experimental data. The last was the more suited for the *in-line* application with IR-based experimental data.

Moving on to primary drying, batch representativity of IR-thermography had to be investigated. A series of tests with up to 157 vials were performed comparing thermocouple temperature measurements to IR-based ones. A hexagonal array was used to improve batch representativeness, and an assumption was made based on the observed results. The front-row vials that are more shielded in this array were regarded as representative of central vials, while the more exposed ones were regarded as representative of edge vials. This assumption worked well to represent the batch better. Additionally, since sublimation is an endothermic process, tracking the axial T_{min} during primary drying allowed the inference of the sublimation front temperature and position for vials being heated in direct contact with the shelf. This data yielded a more accurate estimation of the primary drying end-time and, thus, a new non-gravimetric K_v estimation method. Based on this, a new and more straightforward design space calculation protocol was developed and proved successful.

In sum, IR temperature monitoring applied to freeze-drying batches offers unique advantages for process assessment and design. IR-monitoring is a promising non-invasive tool to monitor freeze-drying processes.