Integrated heat flux measurements as a non invasive monitoring technique for freeze drying

Ilona Konrad[1,2], Victoria Pauli[1,2], Wolfgang Friess[2], Andrea Hawe[1], Gerhard Winter[2], Angelika Freitag[1]

[1]Coriolis Pharma Research GmbH, D-82152 Martinsried, Germany
[2]Ludwig-Maximilians-University, D-81377 Munich, Germany
Department of Pharmacy; Pharmaceutical Technology and Biopharmaceutics

Corresponding author: e-mail: ilona.konrad@coriolis-pharma.com, Phone +49-89-5 42 44 98 206, Fax +49-89-5 42 44 98 22

Purpose

Freeze drying is a well established technique to improve the stability of biopharmaceuticals, specifically proteins, if a liquid formulation is not sufficiently stable. Freeze drying is a complex process, where the product temperature (T_p) during primary drying is a highly critical parameter, because a loss of product quality can occur if T_p exceeds the glass transition temperature (T_g) or the collapse temperature (T_c) resp.. Thus, monitoring of this critical parameter in combination with a good process and product understanding is of utmost importance. A common method for temperature monitoring is the usage of thermocouples, which are placed in some product containers of a batch. A major drawback of thermocouples is their contact with the product, the difficult handling to assure their optimal and reproducible positioning in the vial center close to the bottom and their limitation in usage in aseptic manufacturing. The aim of this study was to evaluate heat flux measurements using LyoPAT™ (Accuflux™ and FreezeBooster™) as a new, non invasive monitoring technique during freeze drying. The heat flux sensor is mounted on the shelf and analyzes the heat transfer from shelf to product.

Methods

Accuflux™ sensors varying in size (4 x1.4 cm vs 3.6 x 3 cm) and mounting (scaffolding for evenly standing containers vs no scaffolding) were tested regarding repeatability, linearity, and robustness. The impact of the freezing protocol (controlled nucleation (Millrock FreezeBooster™) at -5°C and random ramp freezing 1°C/min), shelf loading (partially vs fully loaded), total solid content (3 ml of 5 to 50% sucrose in 10R vials) and vial filling volume (1 ml, 3 ml, and 5 ml of a 5 % sucrose solution in a 10R vial) on the heat flux and vial heat transfer coeffients (K_v) were tested. In addition, the accuracy of the K_v determination and the calculated T_p was investigated. Therefore, Accuflux™ data was compared to thermocouple readings. Data evaluation was performed with Origin®.

Results

The measurements of the heat flux between shelf and vials were repeatable and robust for both tested Accuflux™ sensors, with a better robustness for the larger, evenly mounted sensor. As expected, an increasing solid content of the formulation led to a decrease in heat flux from the shelf to the vial and a longer primary drying time due to the higher product resistance, while K_v remained constant. In contrast, an increase in filling volume did not affect the heat flux and K_v. However, drying times were obviously prolonged with increasing filling volume. During freezing Accuflux™ detected nucleation events of the containers, which were in direct contact with the heat flux sensor. Further, the heat flux sensor determined the end of primary drying non-invasively in accordance with the thermocouple readings. In comparison with comparative pressure measurement, Accuflux™ detected the end of primary drying earlier, as it cannot observe the whole batch containing some vials which run behind. T_p calculated via LyoPAT™ was correlated well with the thermocouple measurements.

Conclusion

In this study, it was shown that integrated heat flux measurement is a reliable new technique to monitor T_p during primary drying. Furthermore, Accuflux™ in combination with LyoPAT™ detected nucleation events and determined the end of primary drying comparable to thermocouples. In addition, Accuflux™ measures non-invasively and does not require exact positioning as it is the case for thermocouples. For better batch representation, sensors in different spots of the shelf and of larger size should be used.