**Improving the calibration of freeze drying models by model-based design of experiments**

Riccardo De-Luca1, Gabriele Bano1, Emanuele Tomba2, Fabrizio Bezzo1, Massimiliano Barolo1\*

*1 CAPE-Lab - Computer-Aided Process Engineering Laboratory, Department of Industrial Engineering, University of Padova, via Marzolo 9, 35131 Padova PD (Italy)*

*2* ***GSK,*** *via Fiorentina 1, 53100 Siena SI (Italy)*

\**Corresponding author: max.barolo@unipd.it*

**Highlights**

* A lab-scale freeze-drying model is calibrated/validated
* MBDoE is proposed to design the best protocol for model re-calibration for new products
* The optimal recipe for model re-calibration lasts 10 h
* The proposed approach avoids the occurrence of critical operating conditions

**1. Introduction**

Over the last decades, freeze-drying (lyophilization) process has been extensively used in pharmaceutical manufacturing for the development of heat-sensitive protein-based therapeutic drugs/vaccines. Lyophilization consists in removing a solvent from a frozen solution by sublimation [1], and its characteristic low pressures/temperatures are suitable to guarantee both product stability and easy reconstitution of the dried product before use. Freeze drying is a time consuming process that is carried out through three main steps: freezing, primary drying and secondary drying. Primary drying is the most energy intensive (~36% of the total exergy input [2]) and time consuming step (up to 48h long, corresponding to over 50% of the typical total duration of a drying cycle [3]). Therefore, one way to increase process performance, guarantee product quality and run safe operations is to develop a reliable model to describe the primary drying phase for future optimization. However, once the primary drying model is calibrated for a specific product, new experimental runs are required to identify the model parameters (i.e., model re-calibration is needed) if new formulates are to be processed. In this study, model-based design of experiments (MBDoE) techniques are proposed in order to reduce the time needed for model re-calibration.

**2. Methods**

In primary drying, the frozen product is processed in vials placed over shelves in a high-vacuum drying chamber linked to a condenser that removes the water vapor generated by ice sublimation. The vials dynamics during the primary-drying phase has been described using a modified version of Fissore *et al*. [4] model. Namely, the original model has been augmented with a dynamic energy balance that takes into account radiation phenomena. The model has been calibrated (and validated) through industrial experimental runs conducted in a VirTis Genesis 25 EL freeze dryer at different chamber pressures and shelf temperatures, using non siliconized vials filled with 0.6 mL of a 5% w/w sucrose solution. The measured variables are: *(i)* the vial bottom temperature (*T*B) for the central zone of the shelves in the freeze-dryer chamber; *(ii)* the chamber pressure obtained using both a Pirani gauge and a capacitance manometer. After validation, the model has been used to optimally design the model identification experiment that is needed when a new formulate needs to be processed in the same freeze-dryer. The MBDoE activity [5] consists on identifying the design vector (initial conditions on measured variables, dynamic profiles of manipulated variables, experiment duration) that maximizes the information related to the mass transfer parameters to be identified.

**3. Results and discussion**

The optimal experiment designed by MBDoE uses the shelf temperature (*T*shelf) and chamber pressure (*P*c) as manipulated inputs. A piecewise linear profile is designed for the former input, and a piecewise constant for the latter. The maximum experiment length is set to 10 h. As shown in Figure 1a, the optimal profile for the shelf temperature shows an initial ramp lasting ~45 min, to which a stationary phase follows for almost the rest of the experiment; conversely, the optimal chamber pressure profile shows a double pulse about halfway the experiment. As shown in Figure 1b, the final part of the experiment is characterized by short time intervals where the manipulated inputs are slightly adjusted to avoid reaching the formulate collapse temperature (~240 K). By carrying out an experiment according to this schedule, it would be possible to identify all model parameters in a statistically meaningful way.

 

**Figure 1.** *Time profiles of* *(a) shelf temperature (blue solid line) and chamber pressure (red dashed line) in the optimally designed experiment; (b) resulting profile of the bottom temperature.*

**4. Conclusions**

The application of MBDoE techniques showed that one single, optimally designed experiment can be enough to allow a statistically meaningful identification of the mass transfer parameters, while maintaining a reasonable length of the experiment.

**References**

1. M. J. Pikal, M. L. Roy, S. Shah, J. Pharm. Sci. 73(9) (1984) 1224–1237.
2. Y. Liu, Y. Zhao, X. Feng, Appl. Therm. Eng. 28 (2008) 675–690.
3. M. Bjelošević, K. B. Seljak, U. Trstenjak, M. Logar, B. Brus, Eur. J. Pharm. Sci. 122 (2018) 292-302.
4. D. Fissore, R. Pisano, A. A. Barresi, in: F. Jameel et al (Eds.), Quality by design for Biopharmaceutical Drug Product Development, AAPS Advances in the Pharmaceutical Sciences Series 18 (2015), pp. 565-593.
5. G. Franceschini, S. Macchietto, Chem. Eng. J. 63 (2008) 4846-4872