Model-based optimization of the primary drying step during freeze-drying

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Since large molecules are considered the key driver for growth of the pharmaceutical industry, the focus is shifting from small molecules to biopharmaceuticals. The list of approved biopharmaceutical drug products from the Food and Drug Administration (FDA) and European Medicines Agency (EMA) consists of approximately 50% freeze-dried products (Constantino and Pikal, 2004). Therefore, freeze-drying is the preferred way to stabilise biopharmaceutical drug products which are unstable in aqueous solution. However, freeze-drying requires a lot of energy and has a long processing time, making it a costly process (Burns, 2009; Gieseler, 2012). The largest fraction of freeze-dried biopharmaceutical products are therapeutic protein formulations and vaccines (Pikal, 2002).

Conventional pharmaceutical freeze-drying (lyophilisation) is a batch process that consists of three consecutive steps: freezing, primary drying (ice sublimation) and secondary drying (desorption of unfrozen water). During the primary drying step the temperature at the sublimation front is critical, and should not exceed a critical value (dependent on the freeze-dried product) to prevent cake collapse. In this project, the focus is on the modelling of the primary drying step. The purpose of the model is to use it to support future optimisation of the process parameters during operation of the freeze-dryer in a dynamic way. During primary drying only two process parameters are adaptable, i.e. the shelf temperature and the chamber pressure. In conventional pharmaceutical manufacturing, both process parameters are fixed, resulting in a conservative cycle. However, by dynamically updating both variables (i.e. resulting in a time variant Design Space), a substantial decrease in processing time can be obtained.

The modelling approach can benefit from incorporating model parameter uncertainty to prevent that the critical temperature at the sublimation front is exceeded. Once the time variant Design Space is created for a certain set-up (i.e. a combination of a specific product and a piece of freeze-drying equipment), the values for both process variables can be fed to the equipment and a significant decrease in processing time can be obtained. As a result, the cost of processing will also be decreasing. Moreover, end product quality is guaranteed.

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