A MODEL PREDICTIVE CONTROL STRATEGY OF THE DYNAMIC PRIMARY DRYING SETTINGS FOR A BATCH FREEZE DRYING PROCESS

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INTRODUCTION

Nowadays, the standard way of operating a batch lyophilisator is a protocol-driven method. All freeze-drying phases (i.e. freezing, annealing, primary and secondary drying) are programmed sequentially at fixed time points and within the phase all critical process parameters (CPP) are kept constant or varied in a linear way between two setpoints. This way of managing is not the most optimal and efficient way (i.e. process time, quality) to run the process. The primary drying phase is by far the most time-consuming step, a significant time reduction has a large impact on the total process length. A model predictive control methodology also including uncertainty analysis could help fastening the primary drying phase herewith ensuring a controlled risk of failure of the CPPs. An essential CPP is the sublimation interface temperature (T_i) that needs to be kept under the collapse temperature, especially during unexpected disturbances, to prevent the loss of product structure (which is an important CQA).

MATERIAL AND METHODS

At first, the timings of the local controls, i.e. the chamber pressure (P_c) and shelf temperature (T_s) loop, were analysed and the dead time and time constants were determined. Next, a model predictive control with uncertainty analysis of the primary drying phase was developed using Labview and Matlab software (Mortier et al., 2016). Before the process, the uncertainty range of the model parameters (i.e. product resistance (Rp), heat transfer coefficient (Kv), P_c, T_s) were based on historic data. At the start of primary drying, the most optimal dynamic trajectory of P_c and T_s was calculated to maximize sublimation and keep the T_i under control. During operation, T_i was measured at regular intervals using a pressure rise test and verified against its prediction whereof the model uncertainty level was determined. Subsequently, the uncertainty ranges of the recorded CPPs were adjusted incorporating its measurement errors. Finally, the most optimal dynamical set of P_c and T_s, incorporating the model uncertainty, was calculated and implemented for the prediction horizon. The end-point of primary drying was detected by the convergence of the Pirani and capacitance pressure measurements hereafter secondary drying was initiated automatically.

RESULTS

The lyophilisation process was shortened significantly due to a reduction in the primary drying time, from 19.5 h with a traditional protocol-driven operating principle (P_c: 10 pa and T_s:-20°C) to 9h for a dynamic trajectory with a 1% risk of failure acceptance (Mortier et al., 2016). The automatic transition to the secondary drying phase reduced the process time even further since no primary drying safety margin was required. Furthermore, no signs of substandard quality (i.e. melt-back or collapse) were identified when a deliberate disturbance was introduced due to the periodic update of the model parameters and uncertainty levels.

CONCLUSION

A model predictive control strategy was successfully applied on a dynamic primary freeze-drying process with incorporation of uncertainty analysis. Based on a receding horizon principle, the uncertainty analysis was updated regularly utilizing the recorded CPPs and the dynamic prediction of P_c and T_s were applied for the prediction horizon.

Mortier, S. T. F. C., Van Bockstal, P. J., Corver, J., Nopens, I., Gernaey, K. V., & De Beer, T. (2016). Uncertainty analysis as essential [illegible] *European Journal of* [illegible]