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Model-based tools for cycle optimization and scale-up

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freeze-drying of unit doses). Thomas De Beer is also director of Ghent University's Center of Excellence in Sustainable Pharmaceutical Engineering (CESPE) which is founded in 2016. In 2018, Thomas De Beer became co-founder and CTO of the Ghent University spin-off company RheaVita which provides a continuous freeze-drying technology for the pharmaceutical market.

KYUYA NAKAGAWA

Kyuya Nakagawa is an Associate Professor at the Department of Chemical Engineering, Kyoto University. He received his PhD from the Department of Chemical Engineering, Kyoto University in 2003. Now he specializes in the areas of food drying, freezing, freeze-drying, and microencapsulation. He has published over 100 scientific articles, and these articles have ever been cited more than 1500 times. He is interested in the development of sophisticated-practical processing technologies that allows to design desirable qualities in bio-based products to give various functionalities. He is now motivated to apply QbD approach for food freeze-drying, where numbers of qualities must be realiezed in a cost-effective processing. He recognizes that physicochemical phenomena during freezing and drying are of great tool to design functional products.

ANTONELLO BARRESI

Antonello Barresi is currently full professor of Transport phenomena at Politecnico di Torino, in charge of the course of Process development and design. Currently Italian national delegate in the WP on Drying of the European Federation of Chemical Engineering. His main research interests in drying include: drying and freeze drying of pharmaceuticals and enzymes, modelling and optimization of freeze-drying processes, control of industrial freeze-dryers. Most recent research is focused on process transfer, scale-up and cycle development, and new approaches for process development and quality control in freeze-drying of pharmaceutical and food products. Author of more than 250 papers (of which

List of Abstracts for Invited Lectures

Model-based tools for cycle development and scale-up

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Abstract

This contribution discusses how recently developed model-based tools for monitoring and closed-loop control of freeze-drying process can be useful employed for automatic cycle development. Alternatively, they can be used to obtain the parameters needed for off-line optimization and calculation of design space.

Introduction

Tools developed for automatic control can be used for process optimization, process intensification and cycle transfer. In fact, they allow both the determination in-line of base cycles and of reliable heat and mass transfer parameters which can then be used for scale-up and cycle development using off-line approaches.
Different monitoring and control strategies will be considered and commented, showing examples of cycle development.

Automatic cycle development and scale up

An apparatus equipped with an automatic closed-loop control, like LyoDriver, can be used to develop in a few steps (or even with a single run) a close-to-optimal cycle; only the maximum allowable product temperature must be specified, and in additions constrains on the maximum shelf temperature, and on the number and type of steps can be fixed. Examples will be shown of cycles developed for different formulations and for different freezing condition, with controlled and uncontrolled nucleation, to show that differences in the sequence of shelf temperature set points reflects the different thermal characteristics of the excipients and the different matrix structures.
If the industrial apparatus is also equipped with monitoring and control tools, these can also be employed to adapt and transfer the cycle for it, overcoming the well/known scale up issues. It would be sufficient to launch a cycle imposing the proper restrictions on the product temperature.

Off-line cycle optimization and process transfer

The same tools can be adopted also to recover in-line the process parameters, to develop off-line optimization strategies or design spaces; safety margins can be handled in both cases, but in a different way, The design space can be obtained in-line also using a soft sensor, and generally speaking the design space approach can be used to handle the effect of the freezing protocol and of batch non-uniformity.
Alternatively, the same parameters obtained can be used to simulate the drying behavior using a mathematical model of the process; an example will be shown.

Selection of optimal pressure

Most of the methods developed find the optimal shelf temperature sequence for a given pressure, which can be identified by an off-line optimization procedure. Some examples will show how the result depends on the control logic adopted (comparing feedback and model-based controllers).
If LyoDriver is used for cycle development, pressure should be manually adjusted by the user as soon

as there is evidence to suggest that sublimation is rate-controlled by mass transfer. However, this strategy requires that the pressure dependence of the heat transfer coefficient is known at priori, but unfortunately these data are not always available and are both equipment- and container-specific. In case the pressure dependence of the heat transfer coefficient is known, which means that the equipment-vial system has been fully characterized, the manipulation of both shelf temperature and pressure using a MPC (Model Predictive Control) algorithm gives the highest rate of sublimation and hence the shortest drying time.

Optimisation of secondary drying

Coupling the measurement of the desorption rate, obtained by means of the PRT or other devices, with a mathematical model of the process, it is possible to obtain a soft-sensor that estimates in line the desorption constant and the residual amount of solvent in the product at the end of primary drying.

The parameter estimated can be used to obtain the design space also for secondary drying, but the soft sensor can also be integrated inside a control loop which determines the optimal heating strategy for the secondary drying step. In fact, the maximum allowed product temperature of the lyophilized product increases with a decrease in the residual moisture; if this relationship is known, the cycle can be optimized increasing progressively the shelf temperature as far as secondary drying goes on and the residual moisture decreases.