Model based process engineering: Recent advances in freeze-drying

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Model based process engineering: Recent advances in freeze-drying

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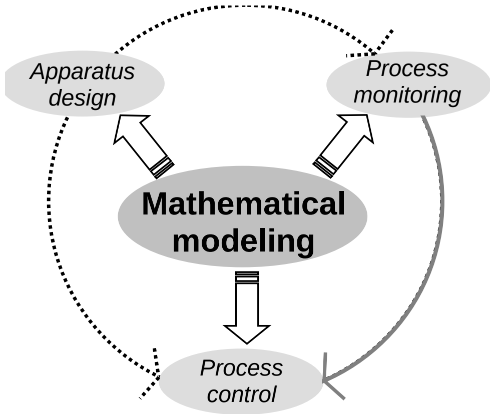
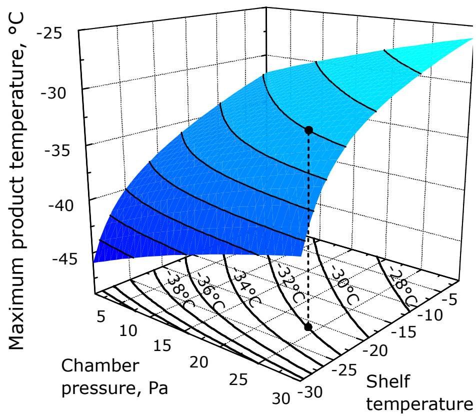
Freeze-drying is a process widely used to recover pharmaceuticals from aqueous solutions. Although regarded as a soft dehydration process, due to the low operating temperature, total or partial inactivation of the product is not unusual. A model based approach can be very effective to improve quality and reduce variance of the product, to optimize and develop freeze-drying cycles, to monitor and even to control them, to improve equipment design.

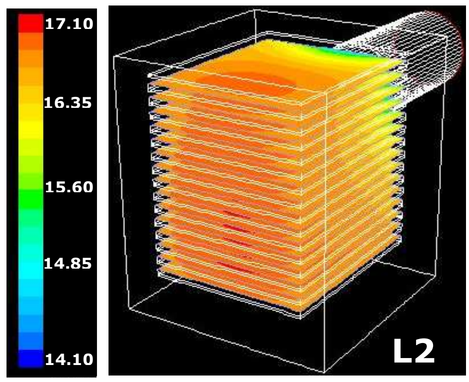


Quality by design can be obtained by building, and validating, the design space, i.e. a multidimensional space that encompasses combinations of product design and processing variables that guarantee product quality. A mathematical model of the process can be used to build the design space both for the primary and the secondary drying step; the uncertainty of the various parameters can also be taken into account. Process modeling can be used also for troubleshooting, i.e. for estimating the consequences of process failures (e.g. uncontrolled pressure rise in the drying chamber) on product quality.



Poor process control is a consequence of the impossibility of measuring in-line the variables of interest, i.e. the temperature and the residual water content of the product; model based approaches allow to develop soft sensors and other non invasive monitoring tools. Future perspectives concerning improvement in the performance of monitoring systems and the possibility of using more sophisticated control systems, like Model Predictive Control or software that can take into account batch heterogeneity, will be discussed. Finally, product quality can be built in-line, by using a suitable control algorithm that looks for the best values of shelf temperature and, eventually, of chamber pressure, according to a specified target (e.g. maximization of the drying rate).

Cycle development in pilot units can be obtained *in-line*, by using some tools to monitor the process, and then manipulating the operating variables in order to achieve the desired goals, or can be designed *off-line*, by using mathematical models to build the Design Space. Process transfer or scale-up can be made easy and robust either using a specific software tool after a process identification step, or using a monitoring and control system, if available in the large scale equipment.



Contours plot of the absolute pressure over the plates in q large scale apparatus.

Finally equipment design can affect product quality and batch heterogeneity during operation (mainly during primary drying), through pressure gradients in the drying chamber and temperature gradients over the various shelves, beside the well known effect of radiation. The use of Computational Fluid Dynamics can be very effective to improve the design not only of the drying chamber, but also that of the condenser, and for a selection of duct size and valves that assure the required performances.