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Overcoming common scale-up issues

Antonello Barresi

The same recipe obtained in laboratory-scale equipment cannot, without modifications, generally be used to freeze-dry the product in a pilot-scale or industrial-scale freeze-dryer. This is because scale up does not guarantee that you will obtain the same dynamics of product temperature and ice content (i.e., the same primary drying length). Product temperature can often exceed the limit value, and/or the length of the process can be different.

Two of the main sources of the problem relate to the freezing and primary drying steps. The level of undercooling and, thus, nucleation can be different in the two apparatus, and heating conditions may also vary. In a laboratory freeze-dryer, heat is mainly supplied by radiation, and the large transparent window of a freeze dryer has a big influence. In these conditions, there is a small influence and relationship between shelf temperature and process evolution. This aspect is often overlooked, even if it can be evidenced quite easily. On several occasions I have seen presented data where the product temperature was higher than the shelf temperature, while the speaker was explaining the several trials conducted to improve the quality of the cake! As the process is endothermic, product temperature can be higher than shelf and fluid temperature only if heat is supplied by radiation.

The list of variables that have to be considered is quite long, but is summarised below:

- environmental conditions in the manufacturing area, which can affect nucleation as explained above
- shelf surface temperature distribution
- contribution by radiating heat
- chamber pressure
- heating and cooling rates.

Up until now, the influence of pressure distribution over the shelves has been generally neglected, but is important in the case of small clearances (to increase the loading) and high sublimation rates. Finally, because of the strong effect the chamber pressure has on the process, pressure control must be similar and effective—higher impedance of the dryer can cause chocked flow conditions and, thus, uncontrolled and higher pressure in the chamber. Obviously, human errors such as using different types of pressure sensor, like a capacitance manometer and a Pirani gauge, with the same pressure set point, must be avoided.

Controlling variance

The vials in the chamber of the freeze-dryer can exhibit different dynamics, resulting in intra-shelf variance and inter-shelve variance, which generally may be even larger. The causes, however, may differ. Even in a freeze-dryer that guarantees uniform operating conditions, the cake structure can be different because ice nucleation is a stochastic event that may result in ice crystals of differing size in a different resistance to mass transfer, and finally in different drying kinetics and a different temperature profile. This phenomenon can be very pronounced in some cases, with freezing occurring over a long time interval and, thus, with very different vial supercooling, which can be reduced only by utilising a device that controls nucleation.

Many factors contribute to significantly different heat transfer rates in the vials of a batch, such as the shape of the bottom of the vial, which affects the heat transfer from the fluid in the shelves to the product, the contact between the vials, and the radiation from the chamber walls and the chamber door.

Another significant cause of inter-vial variance is the fluid dynamics of the sublimating vapour inside the lyophilisation chamber. This effect can be efficiently achieved by using computational fluid dynamics, which evidences the influence of some geometrical parameters of the drying chamber (clearance between the shelves and position of the duct between the chamber and the condenser). The pressure gradients inside the chamber are important because the product temperature depends on the pressure (i.e., the higher the vapour pressure, the higher the product temperature) and, thus, represent a source of batch unevenness. Of course, irregular positioning of the stoppers can also be a cause of variance, affecting the total resistance to vapour flow and product temperature.

Estimating variance is necessary to select a proper safety factor for the shelf temperature set point in order to avoid collapse or scorch in some vials that experience higher temperatures—to avoid collapse in vials that have a higher residual moisture content due to slower drying (or melting in case of residual ice), as a consequence of earlier transition to the secondary drying step. The apparently strange phenomenon for which, in some productions, collapsed products are observed in vials in different positions in the batch, without an apparent reason, can be simply attributed to the casual combination of different effects (cake resistance, gap at the vial bottom, temperature gradients on the shelf) in case the recipe has very low safety margins.

Different sublimation rates over the shelf can be easily measured by stopping a freeze-drying cycle and weighing a sufficient number of

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vials. From these results, it is then possible to evaluate, for example, the distribution of the heat transfer coefficients and the its average value and variance.

It is also possible to predict the behaviour of single vials in a batch, evaluating the effect of hydrodynamics, radiation and shelf temperature gradients. A dual-scale model is required for this purpose because it couples a 3D-model, describing the fluid dynamics in the chamber, and a second mathematical model, either mono- or bi-dimensional, describing the drying of the product in the vials. Different mathematical approaches are possible, as described in the literature (1–4).

Scale up and predictive modelling

Up until now, much attention has focused on the scale up of the drying recipe. A survey of literature shows that scaling up a freeze-drying recipe is an open problem (5–11). The PAT Guidance for Industry released by the FDA in 2004 emphasises the need for a deep understanding of biotech processes to improve manufacturing efficiency, with the goal of building product quality into the process.

A first proposed approach to the problem was to design a robust recipe (or a robust design space) that could be used in both the lab-scale and pilot-scale freeze-dryer under the hypothesis that the two pieces of equipment are equivalent. In this case, no scale-up is actually carried out because the same recipe is used in different freeze dryers. The recipe that is used can be excessively conservative, and the procedure is based on a trial and error approach because it is hard to establish if the recipe is robust enough.

Recently, predictive modelling has been examined as a potential method of aiding scale up.

Predictive modelling

Predictive modelling can strongly improve lyophilisation processes in several ways. My research team has recently published several papers demonstrating that predictive modelling is not only possible, but reliable and effective, and has developed dedicated software for major multinational companies to solve specific requests.

The first point to evidence is that modelling can be very useful, but only if the proper model is selected and developed, taking into account the allowed complexity and parameters that must be determined. Literature is rich with very detailed and accurate models, but a detailed model is not always a good model. The level of detail must be chosen according to the final use; for example, a model for predictive control will be different to a model for off-line optimisation. It must be stressed that the quality of the prediction generally depends more on the uncertainty connected with the parameters used, than on the complexity (and the dimension) of the model. The good engineering rule is that the model must be the simplest one that gives the requested accuracy.

The second point is that modelling should supply the requested answer, and not just a lot of (perhaps interesting) data. To explain this concept, I will take the example of scale up. Recently a few papers were published that showed the use of modelling to address the scale up problem. In these cases, the model was used to supply predictions that helped obtain the final recipe, but a lot of simulation work was required (together with experimental trials) because no direct answer was obtained. The straightforward approach, in my opinion, is to solve the "inverse problem": calculate the sequence of set points that enable you to obtain the required temperature history of the product.

The subject is very wide, so I will limit myself to evidence from the field where predictive modelling has already been used with success, in particular for the development of sensors, for equipment design and optimisation, and for in-line and off-line process optimisation. In some cases, commercial products are already

available or will become available soon.

Sensor development

Predictive modelling can be used to develop software sensors. These sensors combine a model with physical measurements to estimate variables that cannot be measured directly. This is particularly interesting in freeze-drying because the main quantities of interest (residual amount of ice, residual moisture in secondary drying) cannot be measured directly. One example of this technology is "smart vials" where a temperature measurement of the product, or even of the vial wall, can be transformed into an estimation of interface temperature, residual ice or heat transfer coefficient. Another tool enables the residual moisture in secondary drying to be estimated, without the need to extract any sample, and to carry out preliminary experiments.

Tools for parameter identification are also available. As with methods based on the pressure rise test (this is carried out by closing the duct from the chamber to the condenser for a few seconds), using improved methods based on process modeling extends the range of operation and improves accuracy, especially for evaluating the parameters necessary for process control and optimisation.

Equipment design and optimisation

Equipment design can affect product quality and batch heterogeneity during operation (mainly during primary drying), through radiation, as well as through pressure gradients in the drying chamber and temperature gradients over the various shelves. The use of Computational Fluid Dynamics can be very effective, especially if dual-scale modelling approaches are adopted. When applied to the drying chamber, this approach can allow the variance of the batch to be estimated, and thus suggest the necessary modification of the design to reduce variance below a set value, or to estimate the influence of loading

(and also of the clearance between shelves) to pressure drops. This can evaluate whether this affects product uniformity. Modelling can be used not only to improve the design of the drying chamber, but also that of the condenser and the selection of duct size and valves, which ensure the required performance. It is also possible to predict chocked flow conditions and, thus, the conductance of the apparatus.

Process optimisation and control

Model-based tools enable the freeze-drying of a pharmaceutical formulation in a specific freeze-dryer to be optimised, thus minimising the duration of the process, as well as maintaining product temperature below a limit value to preserve product quality. This can be done either off-line, using the design space concept, or in-line, using a predictive control algorithm.

In fact, if a preliminary investigation determines model parameters (cake resistance and an effective heat transfer coefficient), it is possible to optimise the recipe off-line using a mathematical model of the process to build the design space of the formulation. With this approach, it is also possible to build a design space for each group of vials, to take into account batch heterogeneity, thus identifying the optimal operating conditions for the whole batch. Modification of the cake resistance during drying can also be taken into account.

A predictive control system based on a simplified model can enable the development of an optimal freeze-drying cycle in a single run. For this purpose, it is necessary for sensors, such as those mentioned above, to supply both the status of the system and the value of the parameters of interest. A system of this type, which we have called LyoDriver at the Politecnico di Torino, has already been developed and tested. PTE

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More on lyophilisation scale up, predictive modelling and controlling variance is available at: www.pharmtech.com/barresi

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