Applicazione del Quality by Design nella produzione dei medicinali Milano, 27 Aprile 2015

> Uso della modellazione matematica e del QbD nella produzione di medicinali liofilizzati

Roberto Pisano, PhD



DiSAT

Dipartimento di Scienza Applicata e Tecnologia Politecnico di Torino e-mail: roberto.pisano@polito.it

Outline of this presentation





Freeze-drying modelling

- General modelling principles
- The rationale for modelling freeze-drying



Model-based methods for rapid cycle development

- Unidirectional models for cycle development
- Methodologies used to characterise heat and mass transfer in freeze-drying apparatus
- Design space vs. in-line control



Model-based tools for process transfer and scaleup



Conclusions

Freeze-drying process

Freeze-drying is a process where water (or another solvent) is removed from a frozen solution by sublimation.

The process consists of three steps:

- Freezing
- Primary drying
- Secondary drying

The process is suitable for those products that can be damaged by drying processes at higher temperatures.

The freeze-dried products can be stored for long time and can be easily reconstituted.



Freeze-drying process

During the operation, product temperature has to be maintained below a maximum value, in order to avoid the collapse of the cake structure (or melting).



Besides, the sublimation flux has to be maintained below a limit value corresponding to the occurrence of sonic flow in the duct connecting the drying chamber to the condenser.

Modelling and Process Efficiency

The **lyophilisation** process is known to be time consuming and expensive and is often **the rate-limiting process**.

In order to make the lyophilisation process more efficient, formulations and **drying conditions should be optimised**. At this purpose, models can give a valuable contribution.

Theoretical models can predict the behavior of a system under a set of conditions and this information is useful to guide the design of a cycle.



General modelling principles

How to choose the best model?

You cannot choose the best model, because there is not one, but you can choose a useful model.



The best material model of a cat is another, or preferably the same, cat. Norbert Wiener

How to make a useful model?

The level of detail depends on the final use and on the existing knowledge of the process.



A theory has only the alternative of being right or wrong. A model has a third possibility: it may be right, but irrelevant.

Manfred Eigen

General modelling principles

How to choose the best model?

You cannot choose the best model, because there is not one, but you can choose a useful model.



The best material model of a cat is another, or preferably the same, cat. Norbert Wiener

How to make a useful model?

The level of detail depends on the final use and on the existing knowledge of the process.

Approximate mechanisms to a satisfactory degree.









General modelling principles

ICH-Endorsed Guide for ICH Q8/Q9/Q10 Implementation

The level of oversight should be commensurate with the level of risk associated with the use of the specific model. An important factor to consider is the model contribution in assuring the quality of the product.

- Low-Impact Models which are used to support product and/or process development.
- Medium-Impact Models which can be used to insure that the quality of the product is respected, but are not the sole indicators of product quality.

High-Impact Models which predictions are a significant indicator of

the final quality of the product.



The rationale for freeze-drying modelling

In freeze-drying, models can be used to ...

- Improve understanding of the process,
- Train plant operators,
- Find the optimal design of the equipment,
- Support process troubleshooting,
- Develop a cycle,
- Transfer and scale up a cycle from laboratory to industrial apparatus.

Modelling & Freeze-dryer design

Theoretical models (from first principles) provide physical insight into process behaviour and are applicable over wide ranges of conditions. That allows engineers to design and operate pharmaceutical plants more efficiently.

For example, we used CFD to better understand the role of vapour fluid dynamics in the batch heterogeneity.



Pressure contour plot in (S) laboratory and (L) industrial equipment.

Modelling & Freeze-dryer design

Theoretical models (from first principles) provide physical insight into process behaviour and are applicable over wide ranges of conditions. That allows engineers to design and operate pharmaceutical plants more efficiently.

For example, we used CFD to study the role of vapour fluid dynamics in the batch heterogeneity.



Two-scale model: 3D model for fluid dynamics of vapour and an unidirectional model for the product being dried.

Modelling & Process troubleshooting

A lumped parameter model of the equipment can be used to predict the product behaviour when inputs are changed. That prediction can be used to, e.g., establish whether or not product quality is preserved after a given disturbance on process conditions.



The plant has been decomposed into four subsystems:

- Drying chamber,
- Condenser chamber,
- Duct,
- Product being dried.

The dynamics of each subsystem has been described by lumped parameter models.

Modelling & Process troubleshooting



>>>

Cycle carried out at (black) T_f -15 °C, P_c =10 Pa and when (blue) the temperature of the heat transfer fluid is increased from -15 °C to -5 °C for 5 h

Modelling & Cycle development



During cycle development, scientists aim to find a combination of temperature, pressure, and time that satisfies specific product quality attributes.

The optimal combination is typically found through an extended experimental campaign based on trial and error.

Mathematical modelling allows scientists to make better decisions during experimentation, enhance scientific understanding and predict the behaviour of a process under a set of conditions. Models are thus an effective tool to obtain product **quality by design** and also to **reduce processing cost**.

Modelling & Cycle development



Various process variables affect the efficiency of the freeze-drying process.

The temperature of the product is one of these key variables because ...

- Ice sublimation is faster at higher temperature,
- Drying at temperatures above the collapse temperature produces product damage.

Several models have been proposed to describe the product dynamics but, as they have the same practical implications, we should choose the simplest one.

Unidirectional model for primary drying



Determination of model parameters

The heat transfer coefficient (K_v)

An effective coefficient can be used to account for all the mechanisms involved in the heat transfer between the product and the heating shelf.



Distribution of the heat transfer coefficient within a batch of vials as measured by the gravimetric procedure

Off-line methods for cycle development

Design Space



P_c, Pa

Modelling & Cycle scale-up

A cycle obtained with laboratory equipment cannot be used (without any modifications) in large scale apparatus, because of variations in:

- equipment characteristics,
- heat transfer conditions,
- freezing conditions,
- etc...



The reasonable man adapts himself to the world; the unreasonable one persists in trying to adapt the world to himself. Therefore, all progress depends on the unreasonable man.

George Bernard Shaw

Modelling & Cycle scale-up

The solutions so far proposed are not always simple and effective, because the relationship between critical quality attributes and manufacturing process are not known. In this scenario, mathematical modelling is a powerful tool as models:

- Predict the evolution of the product state, for a given cycle, in different freeze-dryers,
- Require few experiments to determine the model parameters and equipment characteristics.

Modelling & Cycle scale-up

For a given cycle (T_{shelf} and P_c vs. time), if the parameters of the model (K_v and R_p) are known for both laboratory and industrial equipment, the same mathematical model used to develop the cycle can still be used to predict the product dynamics in both freeze-dryers.

$$T_{B} = T_{fluid} - \frac{1}{K_{v}} \left(\frac{1}{K_{v}} + \frac{L_{frozen}}{k_{frozen}} \right)^{-1} \left(T_{fluid} - T_{i} \right)$$



K_v characterises the heat transfer in the industrial freeze-dryer

 $L_{\rm frozen}$, $T_{\rm i}$ and $T_{\rm B}$ are known at lab-scale freeze-dryer



Mathematical modeling



time, h

Conclusions





Dipartimento di Scienza Applicata e Tecnologia Antonello Barresi Marco Bazzano Luigi Capozzi Davide Fissore Sabrina Grassini Daniele Marchisio Roberto Pisano Tereza Zelenkova

Dipartimento di Elettronica e Telecomunicazioni Simone Corbellini Marco Parvis Alberto Vallan