Wireless Temperature Measurement in Lyo Process Development, Validation and Production

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ABSTRACT

This article shows a new conceptual design to the development and modern validation of lyo cycles applying process control by determination of product temperature (T_P) in critical positions („hot" and „cold" spots) with wireless temperature measurement (TEMPRIS®). The approach was implemented into the Common Technical Document (CTD) regulatory submission and successfully approved. Currently, WTM is applied during the manufacturing of the market drug product as a key element of the continuous process verification (CPV).
The lyo process development based on the analysis of the critical formulation temperature, critical attributes and related critical process parameters, especially by product temperature measurement is shown in this article. Furthermore, the process validation, respectively process performance qualification (PPQ) strategy based on product temperature measurement is briefly described. Key elements of the respective regulatory strategy in CTD Module 3 sections 3.2.P.2 (Pharmaceutical Development) and 3.2.P.3 (Manufacturing and Process Validation) are presented. In addition, the current status of application of the T_P concept during ongoing production is given.

ZUSAMMENFASSUNG

Einsatz kabelloser Temperaturmessung in Entwicklung, Prozessvalidierung und Routineproduktion von Gefriertrocknungsprozessen
Dieser Beitrag zeigt ein prinzipielles neues Konzept für die Entwicklung und moderne Validierungsstrategie von Gefriertrocknungszyklen durch die Bestimmung der Produkttemperatur (TP) an den kritischen Positionen (hot und cold spots) mittels kabelloser Temperaturmessung (Tempris®) auf. Dieser Ansatz wurde bereits in einem Zulassungsverfahren eingesetzt und das Produkt erfolgreich zugelassen. Derzeit wird die kabellose Temperaturmessung bei der Herstellung jeder Marktcharge als Schlüsselelement für die laufende Prozessüberprüfung angewendet.In diesem Beitrag wird die Gefriertrocknungsentwicklung basierend auf der Analyse der kritischen Formulierungstemperatur, den kritischen Produkteigenschaften und den damit verwandten Prozesseigenschaften durch Anwendung der Produkttemperaturmessung dargelegt. Im Folgenden wird die Prozessvalidierung bzw. die Durchführungsstrategie der Prozessqualifikation, basierend auf der Produkttemperaturmessung, kurz beschrieben. Die entscheidenden Parameter für die Zulassungsstrategie im Modul 3, Abschnitt 3.2.P.2 (Pharmazeutische Entwicklung) und 3.2.P.3 (Herstellung der Prozessvalidierung) werden dargestellt. Darüber hinaus wird der Nutzen der Temperaturmessung für die laufende Produktion gezeigt.

KEY WORDS

- Critical Formulation Temperature (CFT)
- Product Temperature (T_P)
- Critical Product Parameter (CPP)
- Wireless Temperature Measurement (WTM)
- Process Performance Qualification (PPQ)
- Continuous Process Verification (CPV)

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1. Introduction

It is known that the product temperature (T_P) is of utmost importance in freeze drying as

- T_P is a critical product parameter, which determines the important critical product quality attributes (see table 1) such as physical appearance, residual moisture, storage stability, reconstitution time, etc.

Table 1

Analysis of critical quality attributes (CQAs) of lyo products and their relationship to the formulation and the lyo process; given in italics: CQA driven by formulation and lyo Process

Critical Quality Attributes	Comment
Appearance (of lyo cake)	• Formulation: appearance dependent on the selection of excipients, that either form a bulky, crystalline appearance or as in the case of, e.g., Sucrose or Trehalose result in a dry powder cake predominantly amorphous. • Lyo process: In case the critical formulation temperature (CFT) was exceeded, either melt-back or collapse will be observed.
Reconstitution time profile	• Formulation: reconstitution time dependent on the quantity and formulation type • Lyo process: In case the CFT was exceeded, either melt-back or collapse will be observed which will affect the reconstitution time to deviate from the established range. Either it will take longer or no complete reconstitution will be observed.
Clarity/Color of solution	• Clarity and color of the solution depend on the constituents. A solution not clear or different in color is an indication that the product temperature during the lyophilization was exceeded.
Identity/*Assay/Purity*	• In case melt-back or collapse occurred, assay and purity may be significantly affected.
Water content	• The residual moisture typically remaining is a function of the selected excipients, a robust lyo process controlled by T_P will yield in comparable residual moisture over different positions, i.e., the hot and cold positions in the lyophilizer will generate residual moisture values within a small range.
Sterility	• is a function of the aseptic process.
Endotoxins	• is dependent on the raw materials used.
Subvisible and visible particles	• Typically dependent on the environment and the aseptic conditions. If the CFT is exceeded, there might be also generation of particles in case the matrix is destroyed. Thus, the cake does not dissolve completely.
Container closure integrity (no leaks)	• Governed by the primary packaging components quality and the process technology to stopper and crimp.

- T_P cannot be controlled directly, but is influenced by shelf temperature, chamber pressure, product resistance and various other factors such as super cooling, environment, etc.
- T_P must not exceed the critical formulation temperature (CFT), i.e. the collapse temperature T_C or eutectic temperature T_E during primary drying to avoid collapse and melt-back (see figure 1).

It is shown how a modern lyo cycle controlled by product temperature determination applying wireless temperature measurement (WTM) in the critical positions („hot“ and „cold“ spots) of the freeze dryer was used for the regulatory submission in the Common Technical Document (CTD).

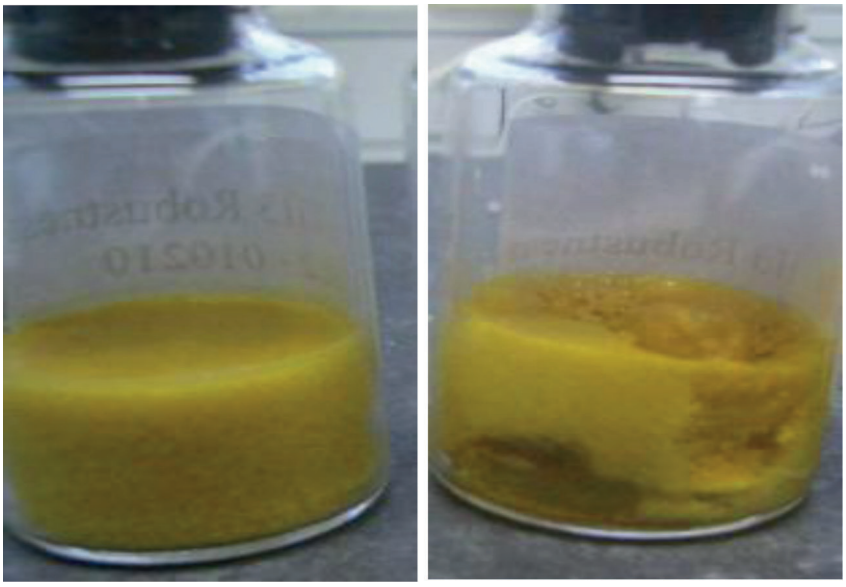

Figure 1: Elegant crystalline matrix cake appearance (left). Upon exceeding the critical formulation temperature (right): a not acceptable melt-back (Source: All figures were made by the author/Explicat Pharma).

In a previous article [1] the performance qualification as the basis and first step in the design of modern lyo cycles was explained. This article is used as a reference regarding this first step and process robustness testing [2].

The present article demonstrates how WTM may be used to justify a T_P-driven lyo cycle when used within critical positions (“hot” and “cold” spots).

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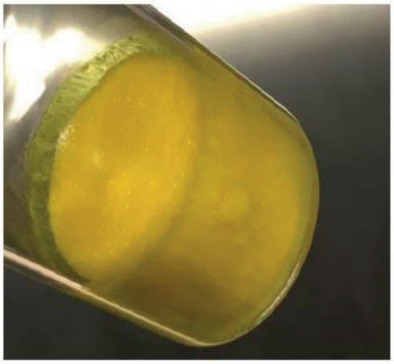

Figure 2: Elegant amorphous matrix cake appearance.

In order to define the T_P during the lyo cycle, it is essential to understand the relationship of the formulation and the CQAs (Table 1) as well as the CFT.

Product examples of cake appearances are given in fig. 1 (crystalline matrix) and fig. 2 (amorphous matrix).

The CFT determines the T_P in freeze drying. What determines the CFT? The CFT is depending on the predominant physical state of the matrix determined with X-Ray Powder Diffraction (figures 3 and 4). This drives the design of the lyo cycle. For details please refer to [3].

2. Lyo cycle development applying WTM

The application of WTM during development was previously published in [4] and also discussed in [1].

3. Applying WTM in critical positions during process validation or process performance qualification

Wireless temperature sensors can be aseptically placed and exactly positioned, thus making them a reliable tool to determine T_P in selected "hot" and "cold" spots (critical positions) to monitor and record T_P over time for the defined lyo cycle.

Sensor 2 is on shelf 1 in the relative coldest position (center position), Sensor 13 is on shelf 5 in the relative hottest position (close to the door). For example, at time point 41:40 Sensor 2 is at –17.6 °C and Sensor 13 is at –3.1 °C.

The lyo cycle in fig. 5 represents the optimized adapted lyo cycle based on lyo process robustness testing and taking into account the performance of the selected industrial lyophilizer.

The T_P over time illustrates that good homogeneity over positions could be achieved. This led to a product meeting all pre-defined critical quality attributes. The vi-

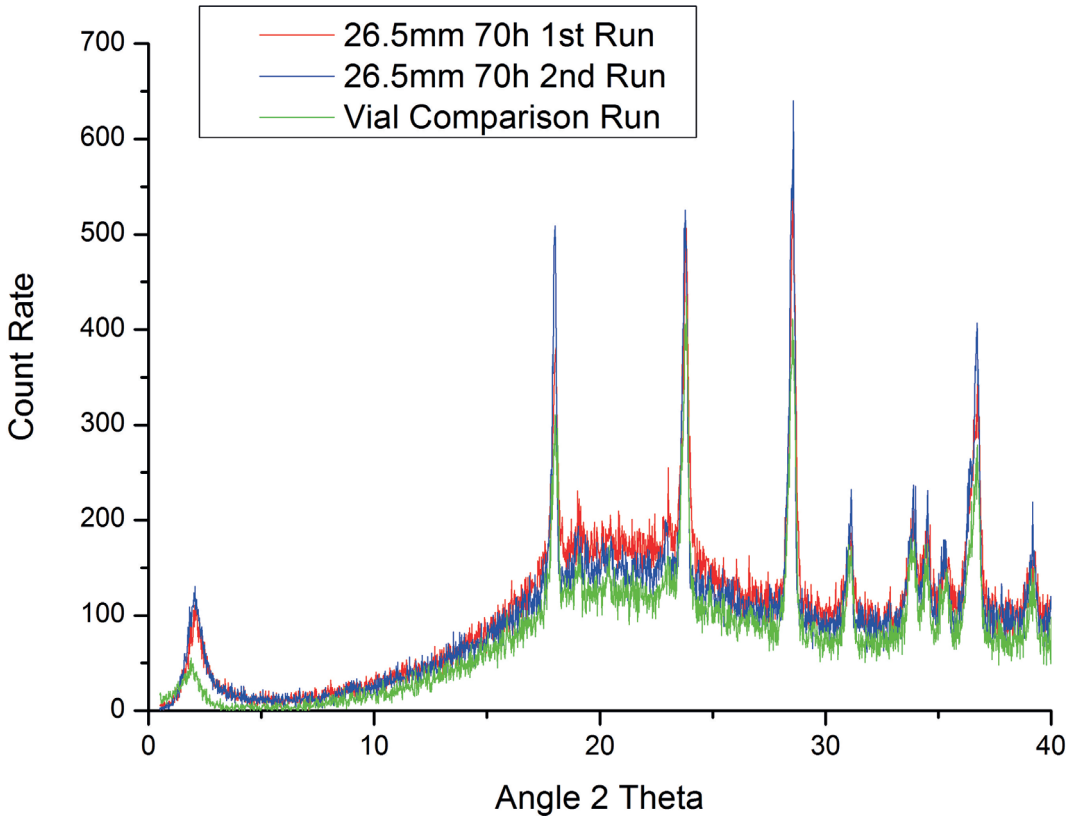

Figure 3: X-Ray Powder Diffraction example of a predominant crystalline matrix – the primary phase of lyo cycle driven by eutectic temperature T_{eut}.

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sual inspection results were 0 % defect attributable to appearance, the residual moisture with approx. 0.4 % determined by Karl Fischer over positions was very uniform.

4. The regulatory CTD

The PPQ strategy was accepted by the regulatory authority within Module 3 Process Validation, the lyo cycle was presented in Module 3.2. P.3.5.

A general lyo cycle was presented driven by T_P and chamber pressure control criteria to avoid variations in case of lyo cycle equipment transfer and to allow for partial loadings, e.g., in case of defects.

Some example text:

"Key in freezing step is to reach temperatures < $T_{g'}$ and achieve complete freezing, nucleation and crystallization of the bulking excipient and Ostwald ripening to obtain uniformly frozen vials amongst positions by annealing to achieve homogeneity within batch over shelves and within batches.

The detailed lyo cycle that was subject of process validation/PPQ including the details of the industrial lyophilizer used is an exemplary cycle meeting the criteria defined in the general lyo cycle.

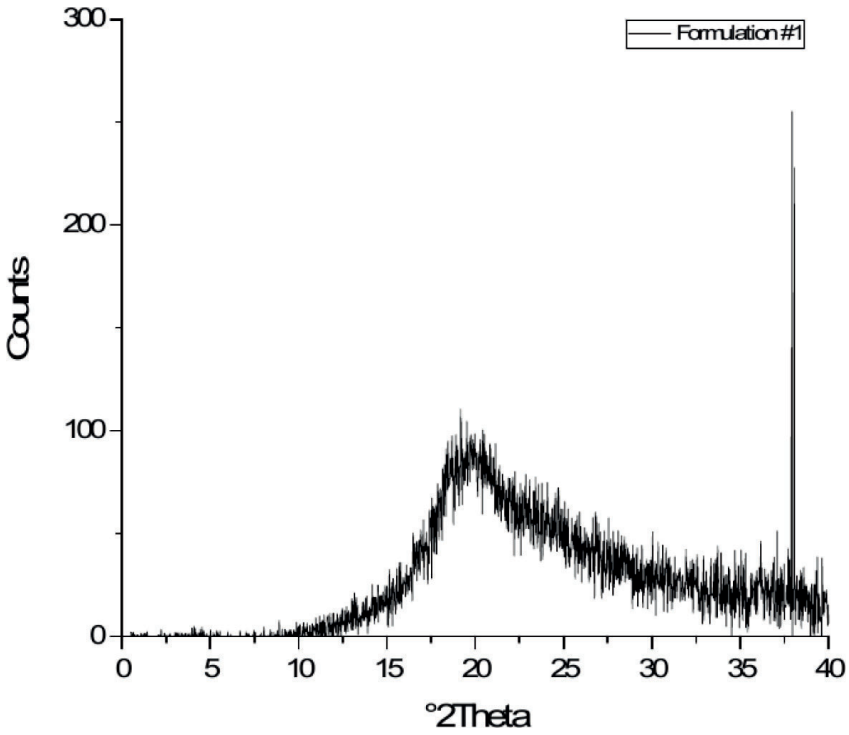

Figure 4: X-Ray Powder Diffraction example of an amorphous matrix – glass transition temperature $T_{g'}$, respectively collapse temperature /T_c.

Also by applying the T_P control concept (a real PAT tool) alternative loadings of the freeze dryer are possible as the general lyo cycle is adaptable. This might be needed for cases of technical defects occurring.

As long as the boundary conditions are kept, i.e. the T_P characteristics (over time), the product quality attributes will be similar."

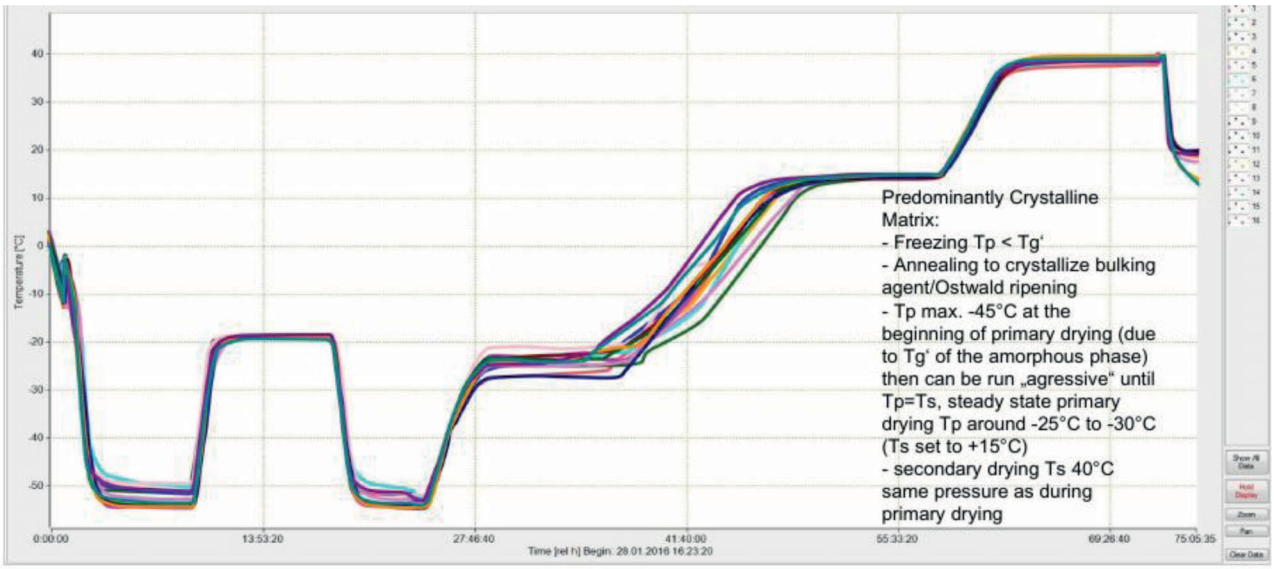

Figure 5: T_P over time; graph of a process performance qualification (PPQ) batch (18 shelves, production freeze drying with 30 sqm) – 16 sensors placed in critical positions.

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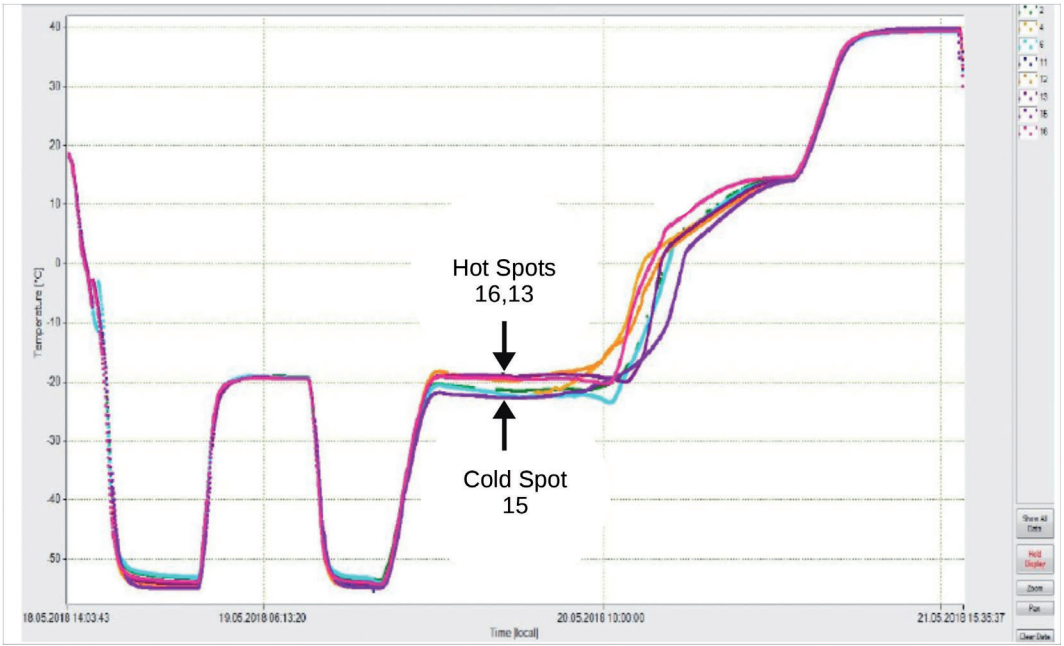

Figure 6: 8 sensors, positioned in previously identified hot and cold positions. Critical positions were confirmed, data of a production batch for market supply.

In summary, the outcome of the regulatory procedure regarding the lyo cycle was:

- T_P (over time) as process control accepted
- Partial loadings are possible and the lyo cycle can be adapted accordingly.
- Adaptations are possible without need of a change or variation procedure.

5. Current use of WTM in GMP production for market, as element of the CPV of the product

The product was approved and is being manufactured for market supplies. The lyo cycle is an element of the continuous process verification (CPV) of the product.

- T_P is used as process control.
- The lyo cycle is evaluated after each run. The WTM sensors to determine T_p are positioned into the previously identified critical positions. These are hot and cold positions defined over the shelves (fig. 6).
- Data are collected and a meta-analysis is carried out.
- It will also allow for scientific interpretation of data in case of deviations (e.g., delays with loading, loss of power) on basis of the development data (lyo robustness – lyo design space).

6. Conclusion

The determination and use of the T_P as process control within production as the most critical process parameter allows to control the temperature over time and therefore will yield a product that constantly meets its predefined critical quality attributes.

These data can be used as basis for CPV and subsequently for the product quality review (PQR).

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