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Lyophilization Process Optimization Within Strict Boundaries of Commercial Manufacturing

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PURPOSE

An established commercial product sensitive to oxygen and moisture had to be transferred to a new lyophilizer with the option to load on pre-cooled shelves. However, when introducing use of pre-cooled shelves (-45°C) to minimize oxidation, a less stable product was obtained. This poster describes how process optimization can be performed under the strict limitations of commercial manufacturing: all testing had to be done using a limited amount of API in a maximum of 3 predefined slots at the commercial site and the new lyophilization cycle should not be longer than the current. In addition, changes which might result in regulatory variations were out of scope.

METHOD(S)

Drug product characterization

Characterization of thermal events, which might be critical for cake structure and hence for drying properties, was performed using DSC analysis and freeze-drying microscopy (FDM).
For FDM 0.15ml sample was dispensed in a glass cell. The sample was placed in an Infinivar Microscope coupled to a Sony CCD color camera. Cooling was performed at -0.5°C/min to -50°C. Upon completion of freezing the chamber was evacuated to initiate sublimation. Subsequently, heating was performed at +0.5°C/min.
For DSC analysis a DSC Discovery250 (TA Instruments) was used. Aliquots of 4-6mg were filled into aluminum pans and loaded into the DSC apparatus. Subsequently, the freezing phase was mimicked and thermal events were recorded. Loading of a pan in a pre-cooled system at -45°C was not possible. Instead, freezing was performed as fast as possible.

Process optimization

The program had to be transferred from the old lyophilizer (capacity ca. 7500 vials) to the new lyophilizer (capacity ca. 18500 vials). Loading of vials on pre-cooled shelves was introduced. The test runs were performed using the top, middle and bottom shelves, all fully loaded. Thermocouples were placed on the 3 shelves. Headspace moisture (Lighthouse Instruments) mapping was performed for the new lyophilizer to identify critical spots. The new program was also tested with a fully loaded lyophilizer to confirm the suitability of the program for a fully loaded lyophilizer.

RESULT(S)

Drug Product Characterization

FDM:
During FDM ice nucleation was reported to start around -7.2°C. Formation of hazy white patches began around -15°C and formation of tiny white masses started around -20.2°C. This continued till -30°C where a secondary solidification step occurred; dense white circular areas with thin linear dendritic branches were formed. The sample was completely solidified at -37°C. With respect to mass, the main component of the drug product is NaCl (API 3mg, NaCl 30mg, other 1mg). The phase diagram of NaCl indicates that the solidification at -20°C is due to the formation of NaCl.dihydrate and the 2nd solidification due to the formation of NaCl crystals.
DSC:
The formation of $NaCl.2H_2O$ was also confirmed by DSC analysis where an endotherm with onset at -23°C was detected during heating (Fig. 1). This thermogram was found for both the samples frozen at normal rate (1A) as well as the rapid frozen samples (1B). The exotherm at -38°C (likely formation of NaCl) was not seen in thermogram 1B. This might be due to part of the exotherm not being measured or this crystallization is indeed not happening and is causing the instability of the drug product. Therefore, it was decided to design a freezing phase where both exotherms would occur. This was obtained with loading at -10°C followed by normal freezing rate to -45°C (1C). Due to a different thermal history, the exotherm appeared at -45°C instead of -38°C.

Process Optimization

The Headspace moisture (HSM) analysis showed that it is important to analyze all vials on the same day, to be able to compare. Therefore, analysis was performed on closed, capped vials all 4 days after manufacturing. Although there was a large variation seen in HSM of vials within 1 group (e.g. for shelf 4: max SD within 1 group was 0.68, minimum 0.13) it can be clearly seen that the HSM of the vials increases from top to bottom (Figure 2). This was not an issue but indicated that drying might be least efficient on the bottom shelf and that thermocouples needed to be placed at the top and bottom shelves in the corners at the right-hand side. Based on the DCS data, it was decided to perform loading at -10°C. To be sure that the -45°C thermal event occurred in the vials at all locations, it was decided to lower the freezing temperature to -55°C. Thermocouples in pucks and vials were used to determine the end of each phase. TC data of the final batch are depicted in Figure 3. The product of the test run with the fully loaded lyophilizer was analyzed by the QC lab and fulfilled the specifications.

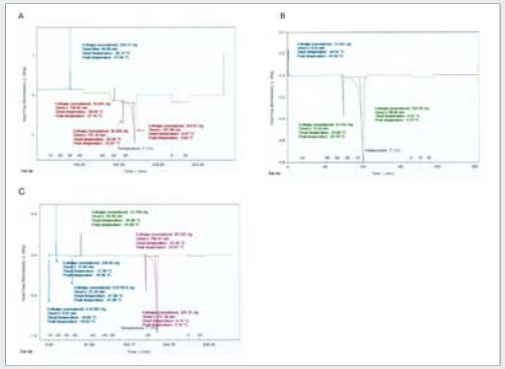

Figure 1: DSC thermograms of freezing phase: old program (A), rapid freezing to -45°C (B), rapid cooling to -10°C followed by normal freezing to -45°C (C).

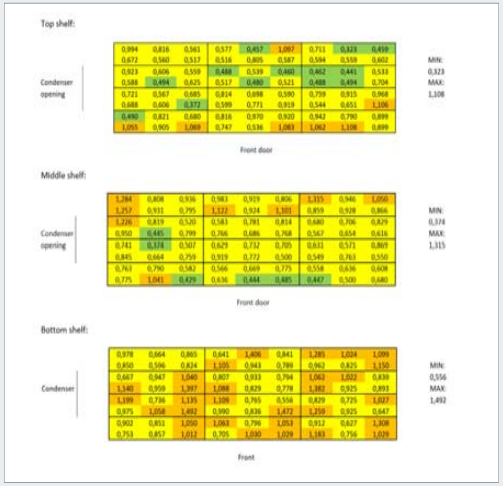

Figure 2: Mean headspace moisture (mbar) of drug product in new lyophilizer (12 trays per shelf, 6 groups per tray, value is mean HSM of 6 vials per group)

CONCLUSION

This study shows an example of how a lyophilization process can be optimized within the, sometimes very limited, boundaries of commercial manufacturing.

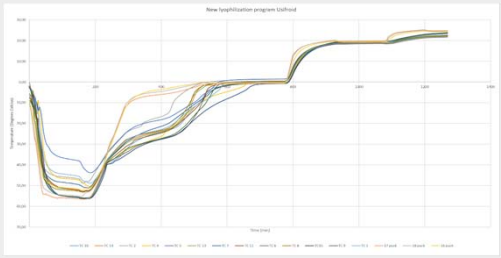

Figure 3: Thermocouple data optimized program

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