Coupling of Lyophilization Process and Product Attributes: Lyophilization Cycle Design

The estimation of product attributes such as T_g' and/or T_c is essential for successful lyophilization process development. As a general rule, lyophilization cycles should be designed such that the product temperature (T_p) during primary drying remains below the critical temperature. A temperature excursion above the critical temperature during drying could lead to a loss of physical structure of the lyophilized material, high residual moisture content, poor reconstitution times, and compromised long-term stability for the pharmaceutical product. For some formulations, in particular, high-concentration protein formulations, it is possible to lyophilize above the critical temperature (as measured using currently available instrumentation) with no impact on long-term stability [4, 5].

Following the International Conference on Harmonization Q8 R2 guidance and quality-by-design (QbD) approach, generation of a design space for primary drying using heat and mass transfer principles has been discussed in a number of publications [6–9]. Traditionally, three commercial batches at set point lyophilization conditions of time, temperature, and chamber pressure are used to qualify a drug product. However, in the event of a deviation from the set point, extensive investigation, root cause analysis, and additional studies are usually performed to assess the product quality impact. Using the QbD approach for lyophilization, such deviations in the set point conditions can be tolerated, as long as they remain within the design space, justifying completion of the lyophilization process with no impact on product quality. A general scheme of lyophilization cycle development using design space approach is shown in Fig. 2.

During the lyophilization process, T_p of a formulation contained in a vial is a function of heat ($\dot{Q}$) and mass transfer ($\dot{M}$) [10]. The effective $\dot{Q}$ and $\dot{M}$ is controlled by various parameters such as formulation composition, fill volume, vial design, shelf temperature, chamber pressure, design of chamber including shelves, vapor tube (if applicable), and condenser, and design of nitrogen bleed valve and vacuum pump capacity.

The critical temperature of a formulation is most commonly determined using modulated differential scanning calorimetry (mDSC) and freeze-drying microscopy (FDM). As the name implies, mDSC is a calorimetric method wherein thermodynamic (melting point and T_e) and kinetic parameters (T_g') associated with the freezing process are determined. A number of other methods have been used in the literature to characterize the freezing stage such as differential thermal analysis (DTA), thermo electric analysis (TEA), dynamic mechanical thermal analysis (DMA), thermo mechanical analysis (TMA), dielectric analysis (DEA), and thermally stimulated current spectrometry (TSC). Despite the advantages and disadvantages associated with each of these methods, mDSC has remained the method of choice for monitoring thermal transitions and estimation of critical temperature.

Light transmission FDM (LT-FDM) is used to determine the collapse temperature of a formulation. Here, a thin film of a small volume of liquid (1–2 µl) placed on a temperature-controlled stage is freeze-dried. The physical changes in the frozen film during the drying process are visually observed using a microscope as a