Impact of Controlled Nucleation on Primary Drying Time

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Abstract

The first phase in a freeze drying process is freezing the sample to initiate formation of ice which subsequently sublimes under the low pressure applied during primary drying. Freeze drying can be achieved by several procedures, e.g. putting the sample into a freezer, immersing it in LN2 or cooling it directly on the shelves of a freeze dryer. Before nucleation (i.e. the initial formation of ice crystals) starts, the sample has usually super-cooled to a greater or lesser extent. Super-cooling means that a solution is held at a temperature below its thermodynamic freezing point without nucleation occurring. The degree of super-cooling is defined as the temperature difference between the equilibrium freezing point and the temperature at which ice crystals start to form. Nucleation is a random process and the nucleation temperature (and time) may vary in a wide range, compromising batch homogeneity. The degree of super-cooling determines the ice crystal size and therefore the pore structure and pore size distribution (e.g. greater super-cooling results in smaller ice crystals and vice versa). Ice crystal size directly impacts primary drying rate and hence the time required for the primary drying phase in a freeze drying process.

Methodology

The key difference of the freezing step for the overall freeze drying process has been known for a long time and several approaches have been applied to control nucleation, e.g. ice-fog, inducing freezing of the solutions from the surface by applying vacuum, or ultra-sound. The drawback of many of the techniques is that they are only suitable in lab scale. Praxair, Inc. recently introduced a method for controlling nucleation which enables instantaneous and homogeneous nucleation of all product containers equally well for both lab and production scale freeze drying: ControLyo™ Nucleation On-Demand Technology (picture 1).

The purpose of this study was to determine the impact of controlling nucleation on the length of the primary drying phase, utilizing an FT Lyostar 3 equipped with the Praxair technology.

Objectives

The criticality of the freezing step for overall freeze drying process has been known for a long time and several approaches have been applied to control nucleation, e.g. ice-fog, inducing freezing of the solutions from the surface by applying vacuum, or ultra-sound. The drawback of many of the techniques is that they are only suitable in lab scale. Praxair, Inc. recently introduced a method for controlling nucleation which enables instantaneous and homogeneous nucleation of all product containers equally well for both lab and production scale freeze drying: ControLyo™ Nucleation On-Demand Technology (picture 1).

The purpose of this study was to determine the impact of controlling nucleation on the length of the primary drying phase, utilizing an FT Lyostar 3 equipped with the Praxair technology.

Material

Two 5% (w/w) sucrose solutions were prepared by dissolving sucrose (Fisher Chemical) in deionized water (Labchem Inc.). Prior to filling of 10 mL vials, the solution was filtered through a 0.22 µm filter (Millipore Inc.).

Methods

One Lyostar™ 3 shelf was loaded per run with 164 (run #1) and 166 (run #2) product containing vials, respectively. The outer one to two rows were vials with empty 10 mL vials. Type T thermocouples (TCs) were placed inside and/or outside of center and edge vials (picture 2). Odd numbers represent TCs attached outside whereas TCs with even numbers were inside the vial.

In run #1, no control of nucleation was used and the vials were allowed to randomly nucleate during a 0.5°C/min. ramp to -45°C. In run #2, nucleation was controlled and the vials were all nucleated at -3°C using the Praxair technology. In both cases, after equilibration, the cycle was advanced through primary drying and the end point was determined by Capacitance Manometer/Pirani differential.

Results

Figure 1 shows the difference in nucleation behavior when applying ControLyo™ technology compared to a standard freezing protocol without nucleation control. In controlled nucleation, all vials nucleate at the same time and at the pre-defined nucleation temperature (figure 1a), resulting in uniform temperature profiles of all TCs. In contrast, in the standard freezing protocol (figure 1b), the first vials nucleate at super-cools -7.4°C (TC05), and the vials with the highest degree of super-cooling (TC09) nucleate at -17.4°C, 27 minutes later than the first vial. With nucleation control, all vials nucleated at -3°C.

The drawback of many of the techniques is that they are only suitable in lab scale. Praxair, Inc. recently introduced a method for controlling nucleation which enables instantaneous and homogeneous nucleation of all product containers equally well for both lab and production scale freeze drying: ControLyo™ Nucleation On-Demand Technology, for the first time nucleation can be controlled during a freeze drying process both in laboratory and production scale. The reduction in primary drying, and the vial to vial uniformity, by applying ControLyo™ Nucleation On-Demand Technology compared to a standard freezing protocol was 24%. Pictures 3a and 3b show the lyophilized products. Both conditions result in acceptable cakes with the vials from run #3a (without controlled nucleation) showing slight shrinkage. This may be caused by locally high product temperatures due to the slower removal of water through smaller pores. Reconstitution time was <1 min for both products (data not shown).

Conclusions

With ControLyo™ Nucleation On-Demand Technology, for the first time nucleation can be controlled during a freeze drying process both in laboratory and production scale. The reduction in primary drying, and the vial to vial uniformity, by controlling nucleation, offer the potential for significant improvements in process time/costs and product quality.