APPLICABILITY OF MANOMETRIC TEMPERATURE MEASUREMENT (MTM) AND SMART™ FREEZE DRYER TECHNOLOGY TO DEVELOPMENT OF AN OPTIMIZED FREEZE DRYING CYCLE: PRELIMINARY INVESTIGATION OF TWO AMORPHOUS SYSTEMS

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INTRODUCTION

Rational development of a freeze drying cycle for a given product is often a trial and error approach and as a result time consuming, even for highly skilled personnel. To avoid a lack of quality and/or elegance of the final product, it is mandatory during the process that the product temperature (T_p) does not exceed a “critical” temperature, which usually refers to the collapse temperature (T_c), product pressure (P), heat transfer coefficient of the container (K), product resistance to vapor flow (R_P), etc. [1]. Manometric temperature measurement (MTM) is a technique to determine the product temperature during primary drying by rapid closure of a separation valve in between the drying chamber and ice condenser. The subsequent chamber pressure rise during this period was used in a “fit” to the MTM equation using the commercial software package MicroCal Origin and utilizing the Levenberg-Marquardt method. This analysis yields product temperature and the mass transfer resistance of the dried product [2]. Thus, the shelf temperature required to achieve a given target product temperature can be calculated from product temperature and dried layer resistance by steady state heat and mass transfer theory.

The purpose of this study is to evaluate the new Smart™ Freeze-Dry Technology, which combines MTM and freeze dryer control algorithms to automatically optimize the freeze drying process during a single experiment, with regard to repeatability and limits in applicability for pure sucrose and trehalose solutions.

MATERIALS & METHODS

SMART™ Settings & Freeze Drying Procedure:
Different numbers (N) of 5cc (A_p: 2.91cm²), 10cc (3.80cm²) or 20cc (5.74cm²) tubing vials (West Pharmaceuticals) were filled with either solutions of sucrose (50-200mg/ml) or trehalose (75mg/ml). A fill volume of 1cm³ or 3cm³ (fill weight: 1.04g and 3.04g, respectively) was used during all experiments. The middle shelf was completely loaded with 5cc tubing vials containing product vials as well as empty vials which were used as radiation shields (except at a full product load on the shelf). Aluminium foil was used to reduce radiant heat transfer from the front door. All necessary product parameters were then put into the Smart Cycle software followed by an upload of an initial shelf temperature and chamber pressure [1]. The software automatically readjusts these initial settings after the first MTM measurement in primary drying (60 min intervals) to further optimize the cycle.

Freeze Dry Microscopy (FDM):
Collapse temperature values (T_c) were determined by using a Zeiss microscope and a LINKHAN Freezing Stage (PDCS 196), including freezing, vacuum and graphoe graphic data. A 2D of sample solution were pipetted onto the microscope slide and fixed on a thermal element within the freezing stage. The system was then cooled down to -40°C (cooling rate: 15°C/min) and equilibrated for 10min. After pulling a vacuum (<100mHg), the temperature of the sample was increased with 5°C/min to a temperature 2-3°C beyond the expected T_c value, followed by a rate of 19°C/min throughout the point of T_c [4].

Chamber Volume Determination:
Since the chamber volume (V) is an integral part of the MTM equation, it was necessary to obtain this value for the Lyostat II™ freeze dryer. The exact volume of 5 vials (10cc, grey terr-butyl stoppers) was determined from the weight difference of the empty vials + stoppers after they were completely filled with water (25°C). Empty vials were then placed onto the middle shelf of the freeze dryer, followed by reduction of the distance to the upper shelf and thus pinching the vials off between two shelves. After evacuation of the chamber (~30mHg) and closure of the MTM valve, the stoppers were allowed to pop-out of the vial neck, resulting in a pressure increase in the chamber. The chamber volume was then recalculated, using the ideal gas law.

RESULTS & DISCUSSION

Freeze Dry Microscopy (FDM):
The most critical variable which needs to be determined before each run is the collapse temperature, T_c of the formulation. Onset and full collapse for trehalose as well as sucrose was found to approximately the MTM algorithm is found to be 107.48 ± 1.099 (mean ± sd) of 10 samples (n=10) for a typical Lyostat II™ freeze dryer.

Minimum Number of Vials:
A minimum ice sublimation area (A_{sub}) was recently reported to be necessary for accurate product temperature measurements in a FTS Durastop™ freeze dryer [4]. MTM analysis of pressure rise data using 308 (A_{sub}: 896cm²), 150 (A_{sub}: 437cm²), 100 (A_{sub}: 293cm²), 75 (A_{sub}: 218cm²), and 50 (A_{sub}: 146cm²) vials (5cc, 75mg/ml trehalose, 10cc solution) showed that the MTM equation with 5°C/min to a temperature 2-3°C beyond the expected T_c value, followed by a rate of 19°C/min throughout the point of T_c [4].

Evaluation of the Chamber Volume:
The volume (drying chamber + part of the duct) relevant to conduct the pressure rise experiments was determined by evaluating the volume of the duct for each chamber size.

Collapse temperature prediction by MTM, owing to water vapor absorption of the dried layer (Fig. 6, 7).

CONCLUSIONS

The Smart™ Freeze Dryer technology requires initial input parameters from the user. The precision of these input variables has a crucial impact on (a) the MTM curve fit quality (P, A_p, and R_P values) and (b) process design. Category (a) refers to the total number of product vials and the determination of the vial inner surface area, A_p, to refer to the collapse temperature, T_c, of the formulation. A minimum product surface area (218cm²) at the beginning of a Smart™ cycle is required to reduce temperature deviations between Smart™ calculations and thermocouple readings. These deviations are also investigated at high solid contents. The Smart™ Freeze Dryer technology is a reliable tool for a user to have the system automatically self-optimize a given freeze drying run.

REFERENCES