

SMART™ FREEZE DRYER TECHNOLOGY: IMPACT OF WATER RE-ADSORPTION OF POLYVINYLPIRROLIDONE (PVP) ON MANOMETRIC TEMPERATURE MEASUREMENTS (MTM) DURING PRIMARY DRYING



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INTRODUCTION

Polymers play a vital role in rational formulation design in freeze drying and have been used to stabilize proteins during freeze-thawing and freeze drying [1]. A commonly used polymer, Polyvinylpyrrolidone (PVP) was found recently to increase both the freeze-thawing and freeze drying recovery of LDH in a concentration-dependent manner [2]. PVP may also reduce the tendency of moisture-induced crystallization of lyophilized sucrose [3] and may increase the glass transition temperature (T_g) as part of the formulation due to its high T_g temperature (180°C) [4]. However, considering the structure of PVP the polymer may act as a strong proton acceptor (through either the O or N atoms of the pyrrole ring) which was investigated for indomethacin [5]. Thus, the removal of water molecules from the polymer or PVP containing formulations may be restricted to some degree during primary and / or secondary drying. The application of manometric temperature measurements (MTM) in freeze drying process design and control (the concept of the Smart™ Freeze Dryer) is dependent upon validity and accuracy of the MTM measurement. MTM was demonstrated to yield accurate product temperature and dry layer resistance data until at least 2/3 of primary drying [6]. However, serious errors for product temperatures and mass transfer rates were reported for high concentrated (>20%) solutes of small molecules (glycine and mannitol) owing to water re-sorption [7]. The goal of this study is (1) to study a potential water re-adsorption phenomenon of the sample polymer polyvinylpyrrolidone during MTM measurements, (2) to delineate the impact of polymer concentration on MTM accuracy and (3) to scrutinize the performance of the Smart™ Cycle and the resulting product quality.

MATERIALS & METHODS

Freeze Drying:

Freeze drying was performed with a FTS Lyostar II freeze dryer with installed Smart™ Freeze Dryer software (FTS Systems, NY). 5ml solution (fill depth: 0.87cm) of PVP at different solid contents (10-100 mg/ml, by weight) was filled into 20cc vials (West Pharmaceuticals, inner area: 5.74cm²) with a total number of 112 product vials. Product vials were surrounded by one row of empty (dummy) vials to cut heat transfer from the chamber wall, aluminum foil was used inside the chamber to cut the radiation from the door. Sample vials were loaded on the middle shelf of the freeze dryer.

The freeze drying cycles were:

(1) freezing: 1°C/min to 5°C, hold for 30min; 1°C/min to -5°C, hold for 30min; 1°C/min to -40°C, hold for 60min.

(2) primary drying conditions were generated according to Smart™ Cycle optimization, i.e. based on the reported collapse temperature (T_c) of PVP (-24°C) in the literature [8]. With a safety margin of 3°C, the temperature of the product (T_p) was controlled at a target temperature (T^*) of -27°C by adjusting the shelf temperature (T_s) automatically during the primary drying phase (between 10°C and 20°C). Adjustments of T_s were based on MTM measurements and therefore the results for P_{ice} and R_p from the curve fit.

(3) Secondary drying was performed at a ramp of 0.5°C/min to 40°C and hold for 4h.

Manometric Temperature Measurement (MTM):

MTM measurements were performed in 60min intervals during 1°drying, pressure data were collected at a rate of 10 points/sec. MTM analysis was performed automatically by the Smart™ Freeze Dryer as well as manually by the developer software Microcal Origin. All equations to calculate mass and heat transfer were used according to [6].

Thermocouple Placement:

Thermocouples (Copper-Constantan, FDPS 20, FTS Systems, NY) were calibrated (CL25, Omega) and product temperatures measured in the center of each batch, avoiding atypical vials (edge vial effect). All sensors were placed in the center of the vial touching the vial bottom. Data were then compared with product temperature (temperature at the vial bottom) data obtained by MTM measurements.

RESULTS & DISCUSSION

Product Temperature by MTM

For a 1% PVP solution and 10°C shelf temperature a 2°C lower product temperature (T_b by MTM compared to thermocouple data) was calculated from the vapor pressure of ice (P_{ice}) obtained from MTM and the non-linear regression analysis [6]. This value was consistent until about 2/3 of primary drying was completed. An increase in PVP concentration to 3% or 5% and a 10°C shelf temperature resulted in the same temperature bias in the initial phase of primary drying (Fig. 1). However, an elevation of the shelf temperature to 20°C to maintain product temperature at the sublimation interface within the predefined target temperature (-27°C) for solid contents > 3% led to an increase in the temperature bias (> 4°C). The temperature difference became even more divert throughout the rest of 1° drying at higher solid content and could thus be related to concentration of the polymer. Product temperatures determined by thermocouples were well below T_c for low solid content (≤ 30 mg/ml), close to T_c for 50mg/ml (Fig. 1), and beyond T_c for 100mg/ml solutions. However, no apparent collapse was found in the product at the end of secondary drying, even for products with high solid content. Note that thermocouple data do not represent the product temperature at the sublimation interface.

MTM vs. Gravimetric Mass Flux Calculation

Gravimetric evaluation of the total water removed after 1° drying using selected vials in the center of the batch revealed that the MTM method under predicted mass balance of about 30%. The mass transfer rate calculated from MTM data was 0.28 g/hr/vial and was significantly lower than calculated from thermocouple data (0.51 g/hr/vial) which, in turn, agreed with the gravimetric result. This low mass transfer rate might be accredited to either a low P_{ice} value or a high R_p value obtained from the MTM fit (Fig. 2).

Impact of Water Re-Sorption on MTM

The fitting of the pressure rise data to the MTM equation resulted in an almost perfect agreement between the raw data and the theoretical fit, even for a higher solid content (Fig. 2). However, theoretical modeling of the P_{ice} and R_p value, based on the thermocouple reading at the point of an MTM measurement and the (valid) assumption of a temperature gradient in the product of 1°C revealed that the low dm/dt value is rather based on a low P_{ice} than a high R_p value (Fig. 2). The bias between P_{ice} values obtained by non-linear regression analysis and theoretical P_{ice} calculations increased significantly with increasing total solid content. Some of the water molecules generated by sublimation might be absorbed by the partially dried layer [7, 8], resulting in a P_{ice} value determined by MTM which is lower than the actual vapor pressure of ice.

Modification of MTM Equation

The MTM equation published recently [6] was modified in term #3 (linear term) to compensate for re-sorption effects of PVP (Eq. 1). Application of this model led to a good agreement of T_b (MTM) and thermocouple data until 2/3 of 1° drying (Fig. 3), even for higher concentrations. However, this model was limited in its applicability to PVP.

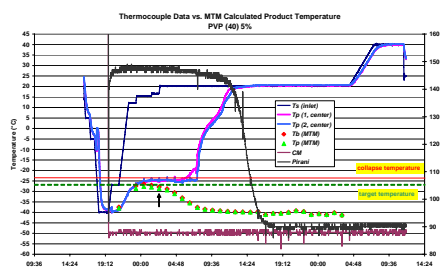


Fig. 1: Pressure and temperature (thermocouple data and calculated temperatures by MTM) profile for 5% (w/w) PVP. Note: At 5% (w/w) product temperature did not exceed T_c within the initial 2/3 of primary drying time.

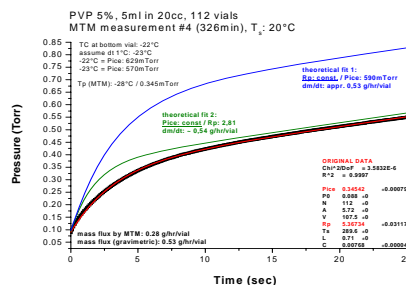


Fig. 2:

$$P(t) = P_{ice} - (P_{ice} - P_{ice}) \cdot \exp\left[-\frac{3.461 \cdot N \cdot A \cdot T_s}{V \cdot (R_p + \dot{R})} \cdot (x + t)\right] + 0.0465 \cdot P_{ice} \cdot \left[\frac{24.7 \cdot L_{ice} \cdot (P_{ice} - P_{ice}) \cdot (R_p + \dot{R})}{1 - 0.0102 \cdot L_{ice}} - 0.01012 \cdot L_{ice} \cdot (T_s - T_b)\right]$$

$$T = \frac{-6144.96}{\ln(P_{ice}) - 24.01849} \quad L_{ice} = \frac{V}{A \cdot 0.918}$$

Eq. 1: Modified MTM equation to account for water resorption of PVP. All parameters are given in reference [6].

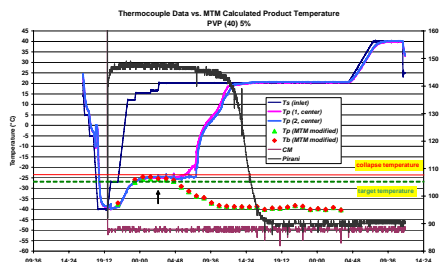


Fig. 3: Pressure and temperature profile for the 5% (w/w) PVP run, but calculated from the modified model. T_b calculated by MTM match with avg. thermocouple temperature data until about 2/3 of 1° drying.

CONCLUSIONS

- PVP was found to have a distinct tendency to re-sorb water during MTM measurements which affected in particular the prediction of the vapor pressure of ice. As a result, MTM yielded inaccurate results for dm/dt or T_b calculations, especially at concentrations $\geq 5\%$.
- The current version of the MTM equation was modified to account for the water re-sorption effect and its application led to better agreement between T_b (MTM) and thermocouple data.

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