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 can also enhance the physical stability of freeze-dried products and may increase the glass-transition temperature (Tg) as part of the formulation due to its high Tg temperature (180°C) [4]. However, considering the structuring of PVP the polymer may act as a strong proton acceptor (through either the O or N atoms of the pyrrol 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 primary and/or secondary drying process. The application of manometric temperature 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 temperature and mass transfer rates were reported for high concentrated (>20%) solutes of small molecules (glycine and mannitol) [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 Lyostat™ freeze dryer with installed Smart™ Freeze Dryer software (FTS Systems, NY). 5 ml 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 (Tc) of PVP (-24°C) in the literature [8].

RESULTS & DISCUSSION

Product Temperature by MTM

For a 1% PVP solution and 10°C shelf temperature a 2°C lower product temperature (Tp) by comparison to thermocouple data) was calculated from the vapor pressure of ice (Pice) 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 revealed that the low dm/dt value is 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 attributed to either a low Pice value or a high Rp value obtained from the MTM fit (Fig. 2).

Impact of Water Re-Sorption on MTM

The setting 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 Pice and Rp value, based on the thermocouple reading at the point of an MTM measurement and the (valid) assumption of theoretical fit revealed that the low dm/dt value is rather based on a low Pice value than a high Rp value (Fig. 2). The bias between Pice values obtained by non-linear regression analysis and theoretical Pice 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 Pice 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 Tp (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.

CONCLUSIONS

PV was found to have a distinct tendency to re-sorb 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 Tp calculations, especially at concentrations >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 Tp (MTM) and thermocouple data.

REFERENCES