INTRODUCTION

The secondary drying step of a lyophilization cycle is characterized by removal of water from the product by desorption after all ice has been removed during primary drying [1]. Secondary drying conditions determine the residual moisture (RM) in lyophilized products which is a critical parameter for long-term stability and is influenced by product formulation and processing. The secondary drying temperature (Tcond) is a critical parameter for primary drying and is determined by the driving force for mass transfer of water vapor concentration and flow rates and to develop a non-invasive secondary drying endpoint monitor. This method could be used to control residual moisture content during lyophilization and enable drying control to achieve intermediate RM targets.

MATERIALS & METHODS

Experiments were performed using a laboratory scale freeze dryer, FTS Lyostar II, equipped with a LyoPuls, a microscopic mass flow sensor (Physical Sciences Inc.) in the freeze dryer chamber. A Pirani sensor optically measured water vapor concentrations and gas flow velocities which were used to determine the water sublimation rate (g/s) [3]. The residual moisture content of amorphous lyophilisates at the end of primary drying is generally between 3% and 6% (w/w) of the cake, equivalent to less than 1% of the original amount of water in the solution [1]. Since the mass flow accuracy provided by TDLAS is approximately 5%, it was not possible to use integrated mass flux measurements as an indication for the amount of water left in the product. Instead the correlation between mass flow rate and moisture content at different shelf temperatures (10°C, 0°C) was determined by sampling vials during a secondary drying step and determining their residual moisture content by Karl Fischer analysis. This way, a single mass flow measurement at a given shelf temperature would be sufficient to estimate the moisture content of a homogenous batch of product vials and allow integration of the mass of water removed from this point without sampling.

RESULTS & DISCUSSION

Application of the sample equilibrium method following primary drying resulted in narrow distribution of RM component (example: 8%±0.5%) independent of vial position in the lyophilizer. Therefore, integrated mass fluxes were used as a comparison tool for Karl Fischer moisture data. Since the mass flow rate was calculated from a fitting equation (Fig. 4), it was necessary to fit the decreasing mass flow rate to a model function that allowed integration during the sampling period. The original mass flux recorded by TDLAS and average mass flux calculated with averaged gas flow velocity between the sampling point are displayed in Fig. 5. Additionally, the mass flux rate calculated from a fitting equation (L. order, Origin) and the corresponding RM content calculated from Karl Fischer measurements are shown. The curve profiles are in good agreement for all curves. The plot shows that the mass flux at constant product temperature decreased much more rapidly than the corresponding residual moisture content. Also, mass flux rate at constant temperature initially decreased linearly during secondary drying and then reached a plateau at moisture contents specific for the shelf temperature and turned off the vacuum pump. It is possible to improve mass flow rate accuracy by recalculation using average velocity data between sampling points. Mass flux data at the sampling times and the corresponding moisture content were plotted and the curve pattern was analyzed. Additionally, moisture contents were calculated from integrated TDLAS mass flux data using the first Karl Fischer sample as an anchorpoint.

CONCLUSIONS

An equilibrium method was developed resulting in homogeneous residual moisture contents independent of vial position in a freeze-dryer. The relationship between RM contents and mass flow rate at different product temperatures was successfully studied and correlated. Integration of TDLAS mass flux measurements for the prediction of residual moisture content during secondary drying was found reliable for freeze-drying runs with low drying heterogeneity. The results suggest that TDLAS might be a valuable tool for predicting intermediate moisture endpoints of moisture sensitive biopharmaceuticals.

REFERENCES


ACKNOWLEDGEMENTS

This project has been funded in whole or in part with federal funds from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services, under Contract HHSN26120062201C.

Fig. 1: Setup of the TDLAS sensor in the freeze dryer duct

Fig. 2: Sample thief door installed in the Lyostar I Lyo freeze dryer

Fig. 3: Optimized RM Equilibration Method

Fig. 4: Representative Secondary Drying Experiment

Fig. 5: Mass flow rate and Karl Fischer residual moisture during secondary drying at 10°C

Fig. 6: Mass flow rate versus RM content at 0°C

Fig. 7: Comparison of Karl Fischer RM measurements and integrated TDLAS mass flux rates

Fig. 8: Mass flux versus Residual Moisture at 10°C and 0°C, linear part

APPLICATION OF TUNABLE DIODE LASER ABSORPTION SPECTROSCOPY (TDLAS) AS A RESIDUAL MOISTURE MONITOR FOR THE SECONDARY DRYING STAGE OF FREEZE DRYING

S. Schröder 1, H. Gieseler 1, W. Kessler 3, M. J. Pikal 2

1 Department of Pharmaceutics + Friedrich-Alexander University + Erlangen (Germany)
2 School of Pharmacy + Department of Pharmaceutical Sciences + University of Connecticut + Storrs (USA)
3 Physical Sciences Inc + Andover (USA)

AAPS Annual Meeting • November 11 - November 15, 2007 • San Diego, CA