

Prediction of the Collapse of Freeze-Dried Lactose Solution using Through Vial Impedance Spectroscopy (TVIS)

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SUMMARY

The aim of this work is to evaluate the application of TVIS system for the prediction of micro-collapse during a freeze-drying cycle. The electrical impedance of a 5%w/v lactose solution contained within a modified glass freeze-drying vial was measured over the frequency range of 10 Hz to 1 MHz during the entire freeze-drying process. A significant decrease in C''_{PEAK} at the point of micro-collapse (as confirmed by SEM) highlights the potential for using TVIS for monitoring microscopic changes in the product resistance to vapour flow associated with the phenomenon of micro-collapse. This study also demonstrated a good correlation between TVIS data ($\log F_{PEAK}$) and temperature of the frozen solution during the annealing stage of the cycle. By using a temperature calibration from the annealing stage it was possible to predict the onset of collapse and thereby demonstrate the potential for TVIS to be used as a process control tool that would allow the cycle to be driven at the highest achievable temperature whilst avoiding collapse.

INTRODUCTION

During the primary drying stage of a freeze-drying cycle, an increase in product temperature above the glass transition temperature of the freeze concentrated solution, T_g' , may cause the collapse of a freeze-dried cake (at a temperature known as the collapse temperature, T_c) with the possible rejection of the entire production batch. Consequently, the product is usually dried at a low temperature but at the spend of a more prolonged drying time. To achieve a cost-efficient cycle, with acceptable product quality, then the process should be designed with due consideration to this critical temperature.

Collapse temperatures for different formulations are usually determined off-line, within a freeze-drying microscope (FDM) although the more recent development of optical coherence tomography based freeze drying microscopy (OCT-FDM) has been used to monitor the collapse process during a more representative process of freeze-drying within a conventional glass vial, Mujat (2012). The disadvantage however is that OCT-FDM does not lend itself to its integration within a conventional freeze-dryer, inside which a large number of vials are

packed within hexagonal arrays. In this study, a novel non-invasive approach to the measurement of electrical impedance (with the electrodes external to the glass vial) has been investigated with the purpose of trying to define a technique, which is predictive of micro-collapse. This approach, known as through vial impedance spectroscopy (TVIS) has been shown previously to be sensitive to the collapse event itself, through dramatic changes in the electrical capacitance of a solution-filled freeze-drying vial, Smith (2014).

MATERIALS AND METHODS

A 5%w/v solution of D-lactose monohydrate (Sigma® Life Science, UK) was prepared in ultrapure water. 3.1 g aliquots of this solution (corresponds to a fill factor (Φ) of 0.7, where the fill factor is defined as the relative height of the solution volume to the height of the electrodes from the base of the vial) were transferred to a cluster of nineteen 10 mL clear type I tubular glass vials and to two TVIS vials. A TVIS vial is a type I tubular glass vial with two copper foil electrodes (19×10 mm) attached to the external sidewall. Impedance spectra of the TVIS vials were acquired across the frequency range 10 Hz

to 1MHz every 2 minutes, throughout the entire freeze-drying process. One of the plain vials close to the TVIS vials had a type-K thermocouple placed at the bottom centre of the vial, to provide a representative temperature for the TVIS vial during the relatively steady state conditions of the annealing stage (i.e. when the solution is not experiencing any changes in state). A full load of vials was then placed on a single shelf of a Virtis Advantage Plus benchtop Freeze-dryer, with the cluster of solution-filled vials at the centre of an array of empty vials, and a freeze drying protocol with an annealing step used to dry the solution. Scanning electron microscopy (SEM) images of the freeze-dried cake were acquired at a 500x magnification.

RESULTS AND DISCUSSION

The parameters derived from the analysis of the peak in the imaginary part of the capacitance spectrum (not shown) which are the peak amplitude (C''_{PEAK}) and peak frequency (F_{PEAK}), can be used along with a thermocouple measurement of product temperature to assess the collapse event. The correlation between $\text{Log } F_{PEAK}$ from the TVIS vial and the thermocouple temperature in a neighbouring vial (data not shown) provides an opportunity to calibrate the TVIS response to give a predictive temperature known as $T-F_{PEAK}$. The premise for the prediction of the collapse event is the assumption that the calibration for the product temperature in the TVIS vial (as determined during the re-heating phase of the annealing stage) holds true during the primary drying stage, when the height of the ice layer in contact with the glass wall decreases progressively due to sublimation.

At 5.5 h into primary drying there is a significant increase in the rate of change of C''_{PEAK} which corresponds to an increase in drying rate as shown in Fig. 1. This suggests there is a microscopic change in cake structure, due to micro-collapse, which results in an increase the pore size distribution in the freeze-dried matrix thereby decreasing the product resistance and consequently improving vapour flux. This suggestion is confirmed by cake morphology images of the middle layer by SEM as shown in Fig. 1(b). The predicted temperature at this point in time is equal to the collapse temperature ($-32\text{ }^{\circ}\text{C}$).

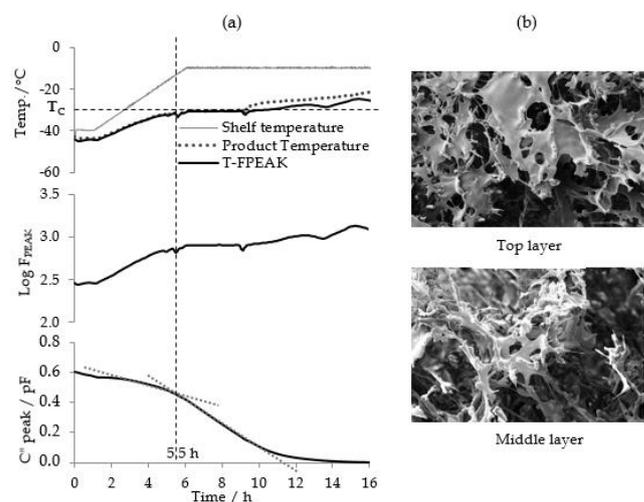


Fig. 1. (a) The temperature and TVIS parameter profile of 5% w/v lactose solution during the primary drying stage (b) SEM of top and middle layer of lactose cake at the end of the cycle.

CONCLUSIONS

The study has demonstrated that the features of the imaginary capacitance spectrum (i.e. F_{PEAK} and C''_{PEAK}) can be used to follow various process parameters throughout the freezing and primary drying stages of the cycle. A dramatic increase in drying rate coincided with the onset of micro-collapse, as evidenced by SEM (as the end of the cycle). More importantly was the observation that the temperature predicted from the TVIS measurement ($T-F_{PEAK}$) was equal to collapse temperature ($-32\text{ }^{\circ}\text{C}$) as determined by freeze-drying microscopy. This suggests the potential application for TVIS in driving process efficiencies by operating the dryer under conditions that maximise the product temperature while avoiding product failure, through collapse.

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