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

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Introduction

- Collapse is referred as the loss of the pore structure of freeze-dried cake whereas "**Micro-collapse**" is an intact cake with increasing pore in dried layer and can promote drying.

- **Dry product resistance (R_P)** is one of critical variables having a great impact on primary drying process.
- R_P is defined as the resistance to mass flow of water vapour from the product through the pores structure in the dried layer and can be expressed by:

$$\frac{dm}{dt} = A_p \frac{\Delta P}{R_P}$$

where $\frac{dm}{dt}$ is the drying rate (g/h/vial), A_p is the internal cross-sectional area of the vial, ΔP is the pressure difference between pressure of ice at sublimation interface and chamber pressure and R_P is the area normalized resistance of the dried product.

- An increase in product temperature during primary drying stage above the **Collapse Temperature (Tc)** may cause the collapse of a freeze-dried cake with the possible rejection of the entire production batch
- Collapse temperature could be determined by
  - A freeze-drying microscope (FDM)
  - An optical coherence tomography based freeze drying microscopy (OCT-FDM), Mujat (2012)
- However, these current techniques have some limitations
  - FDM ➡ Off-line measurement, Not always provide the information of micro-collapse, Varshney (2015)
  - OCT-FDM ➡ Single vial technique
- **Through vial impedance spectroscopy (TVIS)**,a novel non-invasive techniques has been shown previously to be sensitive to the collapse event itself, through dramatic changes in the electrical capacitance of a solution filled in freeze-drying vial, Smith (2014).

Aim

- To evaluate the application of TVIS system for the prediction of micro-collapse during a freeze-drying cycle.

Materials and Methods

- The electrical impedance of a 5%w/v lactose solution contained within modified glass freeze-drying vial (TVIS vial, Fig.1A) was measured over the frequency range of 10 Hz to 1 MHz by using TVIS system during a freeze-drying process.
- A full load of vials with TVIS vial at the center (Fig.1B) was then placed on a single shelf of a Virtis Advantage Plus benchtop Freeze-dryer.
- A freeze drying protocol with an annealing step is performed to dry the solution. A critical feature of the drying cycle is the inclusion of a ramp in the shelf temperature during primary drying that will force the product through its collapse event.
- Scanning electron microscopy (SEM) images of the freeze-dried cake were acquired at a 500x magnification.

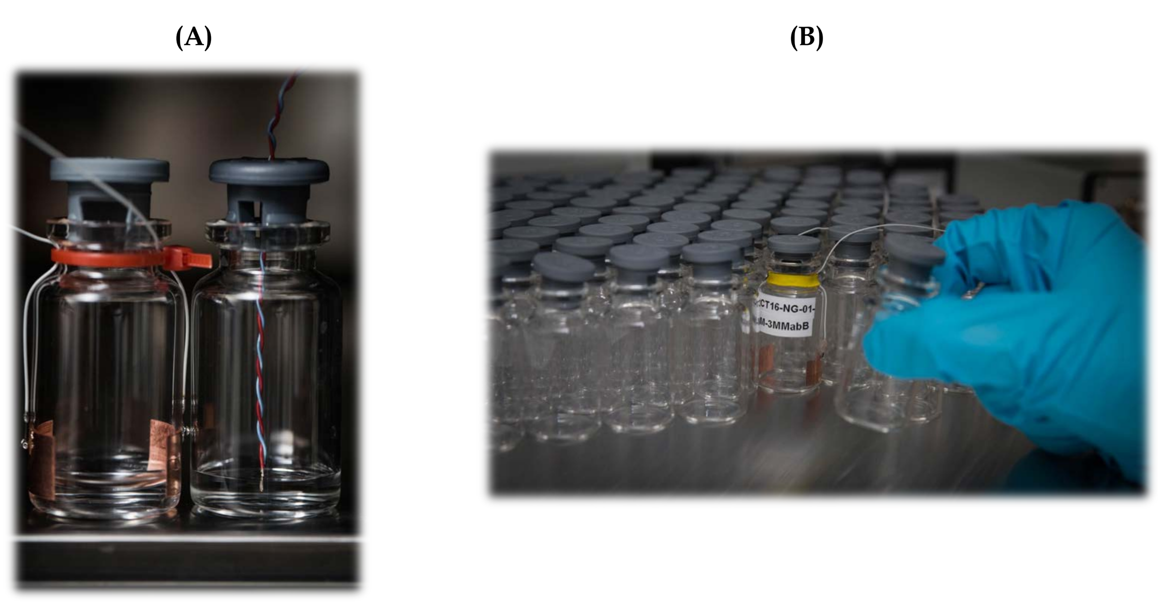

Fig. 1. *(A) TVIS vial (left) and a neighboring vial with thermocouple (right), (B) The cluster of vials with TVIS vial at center*

Results and Discussions

- The correlation between **LogF_{PEAK}** from TVIS vial and the thermocouple temperature in a neighboring vial of the re-heating part of annealing step (Fig.2A) provides a predictive product temperature at primary drying process defined as **T-FPEAK** (Fig.2B).
- The decrease in C''_{PEAK} parameter corresponding to the amount of ice bounded within electrode region can be used to estimate drying rate. However, this parameter also depends on temperature. As the temperature is increased, C''_{PEAK} value increases (Fig.2C). Therefore, the temperature compensation for this parameter defined as normalized C''_{PEAK} ($\hat{C}''_{PEAK}$) is required (Fig.2D) by using the **temperature correction factor (∅)** which is calculated from the re-heating phase of the annealing stage and C''_{PEAK} at starting temperature of primary drying as the reference value.
- C''_{PEAK} can be normalized by the following equation:

$$\hat{C}''_{PEAK} = \frac{C''_{PEAK}(T_t)}{\emptyset}$$

where $C''_{PEAK}(T_t)$ is C''_{PEAK} at time (t) and temperature (T) during primary drying and ∅ is the temperature correction factor from C''_{PEAK} calibration of re-heating step

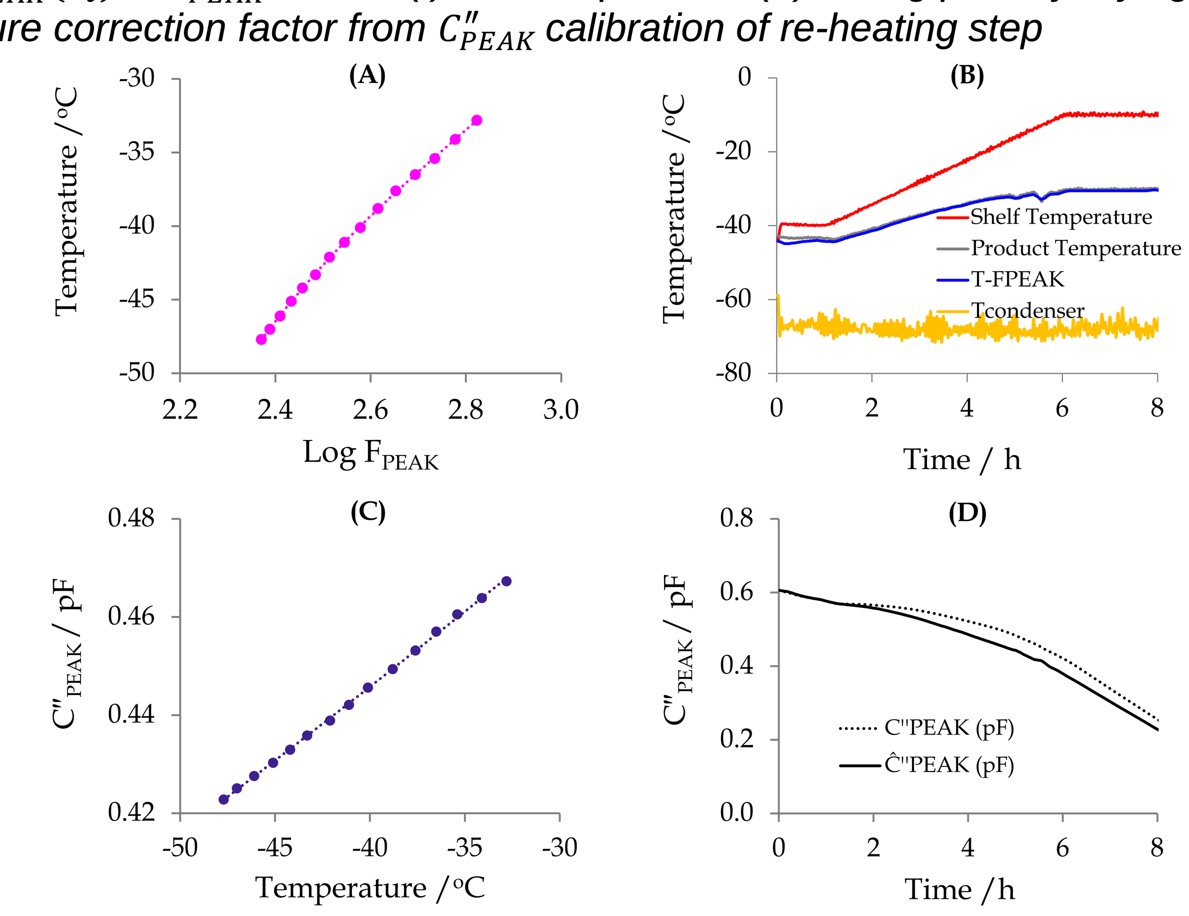

Fig. 2. *The temperature and TVIS parameters profile of 5%w/v lactose solution during the primary drying stage. (A) Temperature calibration from re-heating step, (B) a predictive temperature during primary drying, (C) C''_{PEAK} calibration from re-heating step and (D) Temperature-compensated C''_{PEAK} ($\hat{C}''_{PEAK}$)*

- At 4.8 hour into primary drying there is a significant increase in the rate of change of $\hat{C}''_{PEAK}$ which corresponds to an dramatic increase in drying rate as shown in Fig.3B. 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 (Fig.3C) and consequently improving vapour flux. The predicted temperature at this point in time is equal to the collapse temperature of − 32 °C (Fig.3A).
- This suggestion is confirmed by cake morphology images by SEM as shown in Fig.3E. At dried layer thickness of 0.27 cm corresponding to 4.8 hour of primary drying Fig.3D, a micro-collapse layer has developed which can be demonstrated by SEM as larger pores in middle layer.

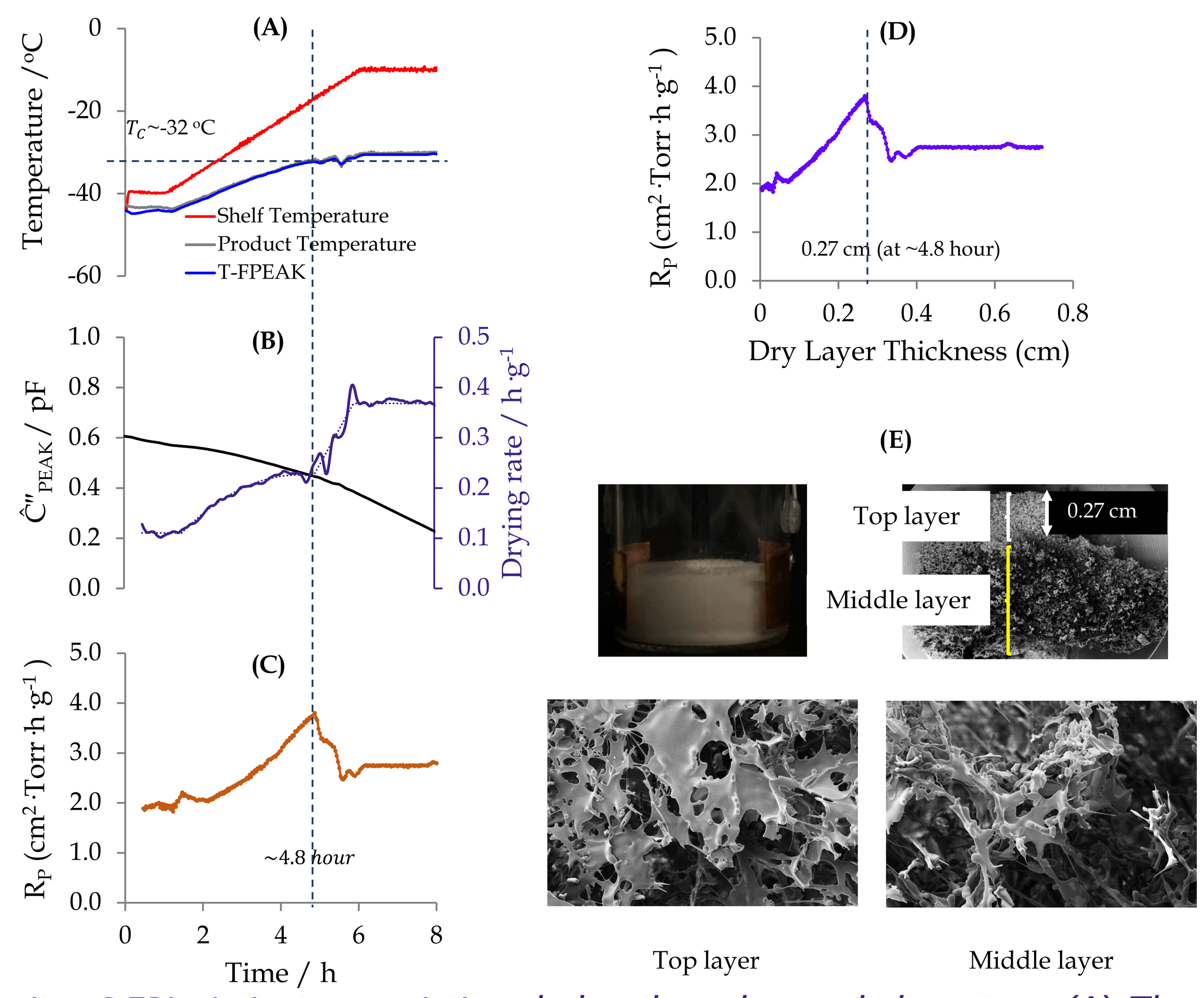

Fig. 3. *Results of 5%w/v lactose solution during the primary drying stage (A) The temperature (T-FPEAK) profile, (B) $\hat{C}''_{PEAK}$ parameters and drying rate over drying period, (C) Product resistance (Rp) as a function of drying time, (D) Product resistance (Rp) as a function of dry layer thickness and (E) SEM of top and middle layer of lactose cake at the end of the cycle.*

Conclusions

- 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 within cake during primary drying step.
- This study demonstrates a prospective use of TVIS as a process control tool that would allow the cycle to be driven at the highest achievable temperature whilst avoiding collapse.

References

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Through Vial Impedance Spectroscopy