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:
  \[
  \frac{dm}{dt} = A \frac{\Delta P}{R_p}
  \]
  where $\frac{dm}{dt}$ is the drying rate (g/vial/h), $A$ is the internal cross-sectional area of the vial, $\Delta P$ 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), Mual (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 freeze drying protocol with an annealing step is performed to dry the solution. A
- 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 Log$F_{PEAK}$ 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 $C_{FPAK}$ 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, $C_{FPAK}$ value increases (Fig.2C).
- Therefore, the temperature compensation for this parameter defined as normalized $C_{FPAK}$ ($C''_{FPAK}$) is required (Fig.2D) by using the temperature correction factor ($\delta$) which is calculated from the re-heating phase of the annealing stage and $C_{FPAK}$ at starting temperature of primary drying as the reference value.
- $C_{FPAK}$ can be normalized by the following equation:
  \[
  C''_{FPAK} = C_{FPAK}(T) \delta
  \]
  where $C_{FPAK}(T)$ is $C_{FPAK}$ at time (t) and temperature (T) during primary drying and $\delta$ is the temperature correction factor from $C''_{FPAK}$ 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) $C''_{FPAK}$ calibration from re-heating step and (D) Temperature-compensated $C''_{FPAK}$ ($C''_{FPAK}$) at 4.8 hour into primary drying there is a significant increase in the rate of change of $C''_{FPAK}$ 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.

Conclusions

- A significant decrease in $C''_{FPAK}$ 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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