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:

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

where $\frac{dm}{dt}$ is the drying rate (g/h/vial), $A_P$ 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 $h_o$ is the area normalized resistance of the dried product.

• An increase in product temperature during primary drying stage above the Collapse Temperature ($T_C$) 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)
  - 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 drying step.

• Scanning electron microscopy (SEM) images of the freeze-dried cake were acquired at 500x magnification.

Results and Discussions

• The correlation between $\log(T_P)$ 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 $T_T$-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 $C_{PEAK}$ ($C_{PEAK}^{″}$) is required (Fig.2D) by using the temperature correction factor ($\delta$) which is calculated from the re-heating phase of the annealing stage and $C_{PEAK}$ at starting temperature of primary drying as the reference value.

• $C_{PEAK}$ can be normalized by the following equation:

$$C_{PEAK}^{″} = \frac{C_{PEAK}(T)}{C_{PEAK}(T_o)}$$

where $C_{PEAK}(T_o)$ is $C_{PEAK}$ at time ($t$) and temperature ($T$) during primary drying and $\delta$ 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 product temperature during primary drying, (C) $C_{PEAK}^{″}$ calibration from re-heating step and (D) Temperature-compensated $C_{PEAK}^{″}$ ($C_{PEAK}^{″}$).

• At 4.8 hour into primary drying there is a significant increase in the rate of change of $C_{PEAK}^{″}$ 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 ($T_T$-FPEAK) profile, (B) $C_{PEAK}^{″}$ parameters and drying rate over drying period, (C) Product resistance ($R_P$) as a function of drying time, (D) Product resistance ($R_P$) 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

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

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