Application of Impedance Based Technology to Investigate the Collapse of Freeze-dried Sugar-salt Solutions

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INTRODUCTION

During primary drying, an increase in product temperature above the glass transition temperature of a freeze-concentrated solution (T_g') may provide a more efficient freeze drying process. However, it is essential to control the product temperature below its collapse temperature (T_C) to avoid a loss of cake structure leading to a decrease in sublimation rate. Moreover, a collapsed cake typically has a high moisture content which may then impact product quality in terms of the appearance and stability critical quality attributes.

Recently, an impedance based technique known as **Through Vial Impedance Spectroscopy (TVIS)** has been shown to be sensitive to the collapse event through the changes in the electrical capacitance of the sample filled in TVIS vial (Smith, et al. 2014). In this study, the impact of microcollapse on the primary drying process of sugar-salts preparations is observed using TVIS technology.

AIMS

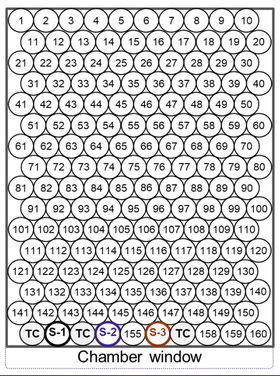
To evaluate the applicability of TVIS system for the impact of collapse on the sublimation rate during a freeze-drying cycle

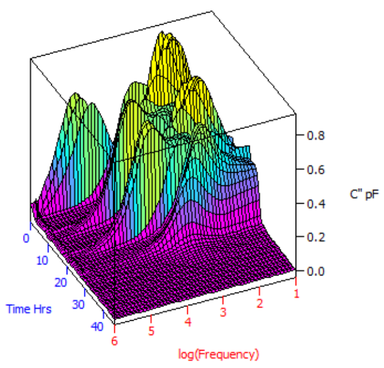
MATERIALS AND METHODS

Instrument / Sensor	Measurement / Process
TVIS	Electrical capacitance of TVIS vial containing sample measured every 2 min during freeze drying process
Thermocouple	Thermocouple temperature in nearest neighbour vial provides predictive temperature of TVIS vial (calibration)
VirTis Advantage Plus Freeze-dryer (lab scale)	Freeze drying with a reheating (temperature calibration) step and ramping during primary to to force the product through collapse
Differential scanning calorimetry (DSC)	Critical product temperature (T_g')
Digital camera	Photographic image for observation of visual collapse event

Sample preparations

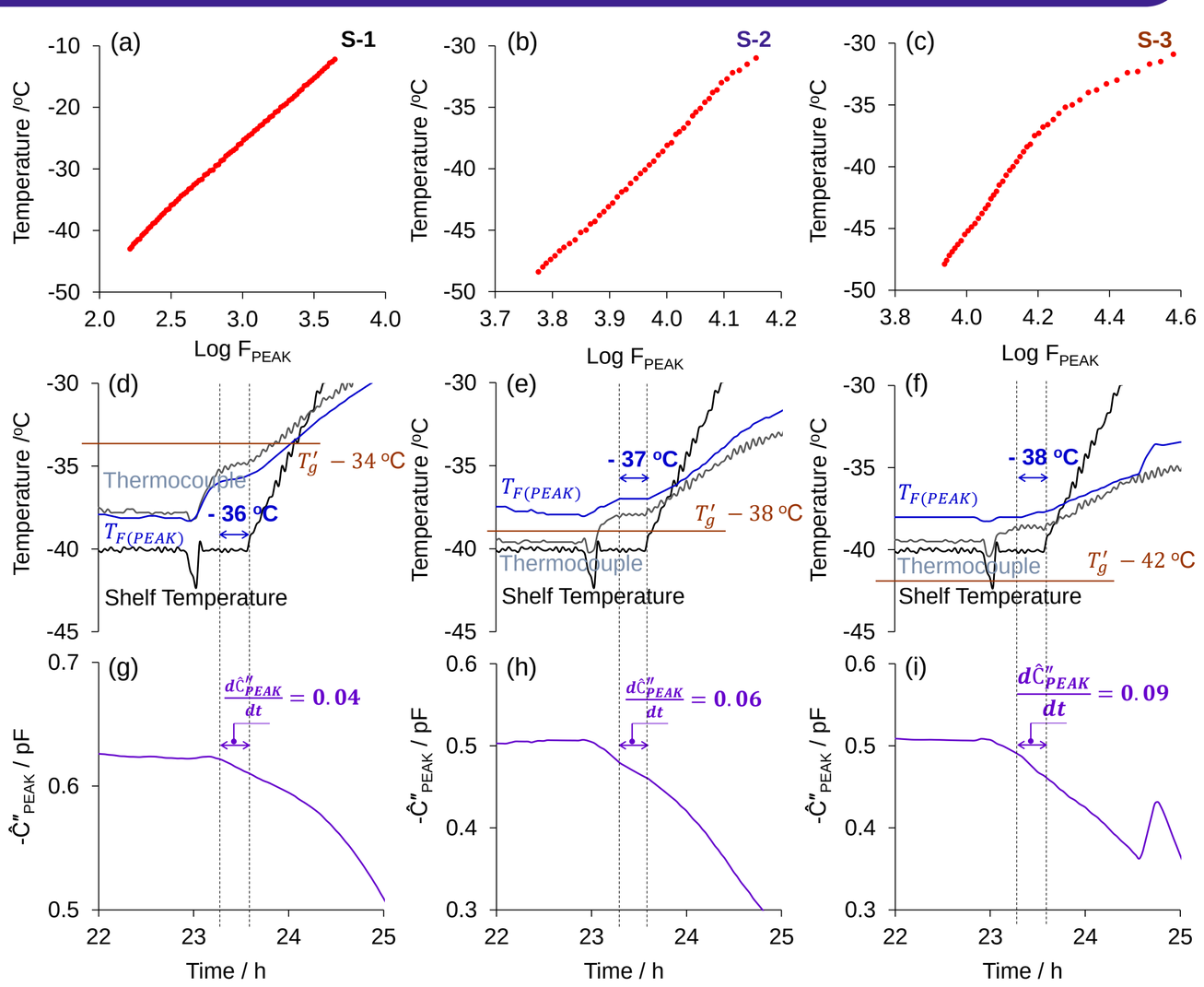
Sample	Sucrose (%)	NaCl (%)
S-1	5.00	0.00
S-2	5.00	0.26
S-3	5.00	0.55





RESULTS AND DISCUSSION

- The correlation between $\boldsymbol{Log\ F_{PEAK}}$ and temperature of neighboring TC containing vial, during re-heating step (Fig.1a-c), predicts the in-vial temperature ($\boldsymbol{T_{F(PEAK)}}$) during primary drying (Fig.1d-f)
- Predicted temperature from the TVIS measurement system ($T_{F(PEAK)}$) before the temperature was ramped (23.3-23.6 hour) were -36, -37 and -38 °C respectively for the solutions of 5% sucrose with 0%, 0.26% and 0.55% NaCl (Fig.1d-f). However, only pure sucrose had a product temperature lower than its respective T_g' (-34 °C from DSC) as shown in Fig.1d
- Higher surrogate drying rates (i.e. the rate of change in the $\hat{C}''_{PEAK}$ value which is proportional to the amount of ice) of 0.06 and 0.09 pF/h were found in sample with 0.26 and 0.55% NaCl (Fig.1h-i) as compared with the formulation without NaCl (0.04 pF/h) in Fig.1g .
- This finding suggests an alteration in microstructure that was not seen in the photographic evidence, which could promote mass flux due to an increase in pore size (microcollapse) (Milton, et al. 1997).



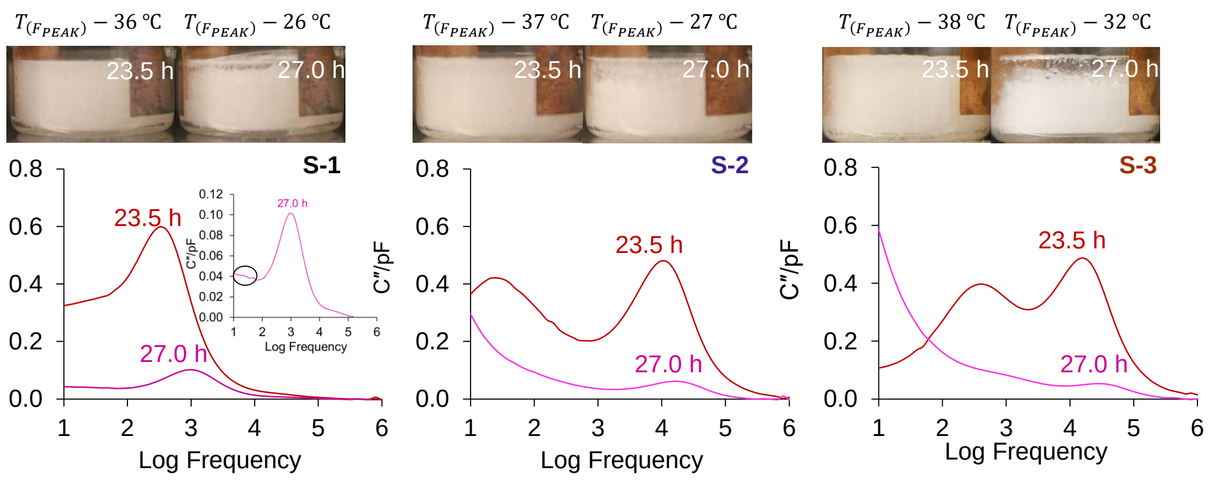


Fig.2 Image and imaginary capacitance of three sugar-salt solutions demonstrating the progression of collapse over drying period; without the loss of macroscopic structure at 23.5 hour and macro-collapse at 27.0 hour

Fig.1 TVIS parameters of three sugar-salt solutions during freeze drying; (a-c) temperature calibration from re-heating step, (d-f) a predicted temperature during primary drying, (g-i) surrogate drying rate calculated from temperature-compensated C''_{PEAK} ($\hat{C}''_{PEAK}$)

- Later in the cycle when the temperature was ramped (after 26 hour), a significant change in a capacitance spectrum, at low frequency range in particular, appeared to relate to the loss in macroscopic structure or macro-collapse as confirmed by the photographic images (Fig.2)

CONCLUSIONS

TVIS is a promising tool that would allow to the design the efficient process whilst avoiding collapse.

REFERENCES

Smith, G., Arshad, M.S., Nazari, K., Polygalov, E., Ermolina, I., Taylor, J., Page, T., 2014. Through-vial impedance spectroscopy: a new in-line process analytical technology for freeze drying. Pharm Technol, 38.

Milton, N., Pikal, M.J., Roy, M.L., Nail, S.L., 1997. Evaluation of manometric temperature measurement as a method of monitoring product temperature during lyophilization. PDA J Pharm Sci Technol, 51, 7-16

TVIS Through Vial Impedance Spectroscopy