Application of through vial impedance spectroscopy to different container

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INTRODUCTION

In the past few years, a new process analytical technology [through vial Impedance spectroscopy (TVIS)] has been developed for monitoring the lyophilisation process[1,2]. The majority of work to date has used a standard 10 ml glass vial with TVIS electrodes attached to the outside. This study compares the response from a standard vial with a container with a smaller diameter, i.e. 2.5 ml glass ampoule. This study aims to demonstrate the potential for transferring the TVIS technology from one container size to another. In addition, we will demonstrate a methodology for non-invasive prediction of ice nucleation temperature by calibrating the TVIS response against thermocouple measurements of temperature in a nearest neighbour vial.

MATERIALS AND METHODS

Materials/Instruments

- Freeze dryer - Virtis® Advantage Plus
- 10 ml glass vial (Schott, VC010-20C) (1 x TVIS and 1 x thermocouple)
- 2.5 ml glass ampoule (Schott, 1555839) (1 x TVIS and 2 x thermocouple)
- Thermocouple (TC) Type T
- Double distilled water (filling factor ϕ = 0.7, Equation 1)

$$Fill\ Factor\ (\Phi) = \frac{The\ height\ of\ sample\ fill\ within\ electrode\ region}{The\ height\ of\ eletrode}\quad Equation\ 1$$

Table 1: Showing Fill factor calculation using equation 1

Type of container	Up to lower edge (g) A	Up to upper edge (g) B	Φ = 1 (g) C	Φ = 0.7 (g) D	Filling weight (g) (A+D)
10 ml vial	0.56	4.60	4.04	2.828	3.39
2.5 ml ampoule	0.22	1.29	1.07	0.75	0.97

- LyoView™ analytical software provides estimates for the peak frequency (F_{PEAK}) and the peak amplitude (C''_{PEAK}) for the dielectric relaxation of ice, as shown in the imaginary capacitance spectrum

Digital camera

- Photographic images every 2 min, synchronised with LyoDEA™ measurements, provides visual confirmation of the ice nucleation event.

Freezing protocol

Table 2: Showing freezing parameter set-up on freeze dryer

Step	Start Temperature (°C)	End Temperature (°C)	Time (min) Ramp	Time (min) Hold	Cumulative (Time min)	Cumulative (Time h)
Equilibrium	RT	20	10	-	10	0.17
	20	20	-	10	20	0.33
Freezing	20	–20	80	-	100	1.67
	–20	–20	-	120	220	3.67

Prediction of ice nucleation temperature

1. Plot TC temperature in the adjacent container vs log F_{PEAK} during the cooling period prior the ice nucleation (Fig. 1).
2. Fit 2nd order polynomial to generate a quadratic equation
3. Identify the onset of nucleation point from log F_{PEAK} and C''_{PEAK} profile.
4. Substitute log F_{PEAK} value at nucleation into the quadratic equation to predict the ice nucleation temperature (T_n)

RESULTS

- Log F_{PEAK} value at the onset of nucleation (Fig. 2) and the nucleation temperature of the TVIS vial estimated from the quadratic fitting functions (Fig. 1) are given Table 3.

Table 3: Nucleation onset temperature predicted at given Log F_{PEAK}

	10 ml vial T_n(TVIS)>T_n(TC)	2.5 ml ampoule T_n(TVIS)<T_n(TC)	2.5 ml ampoule T_n(TVIS)>T_n(TC)
Log F_{PEAK}	3.647	3.859	3.902
Predicted T_n (°C) (Y-axis)	○ -16.2	□ -9.3	△ - 12.6

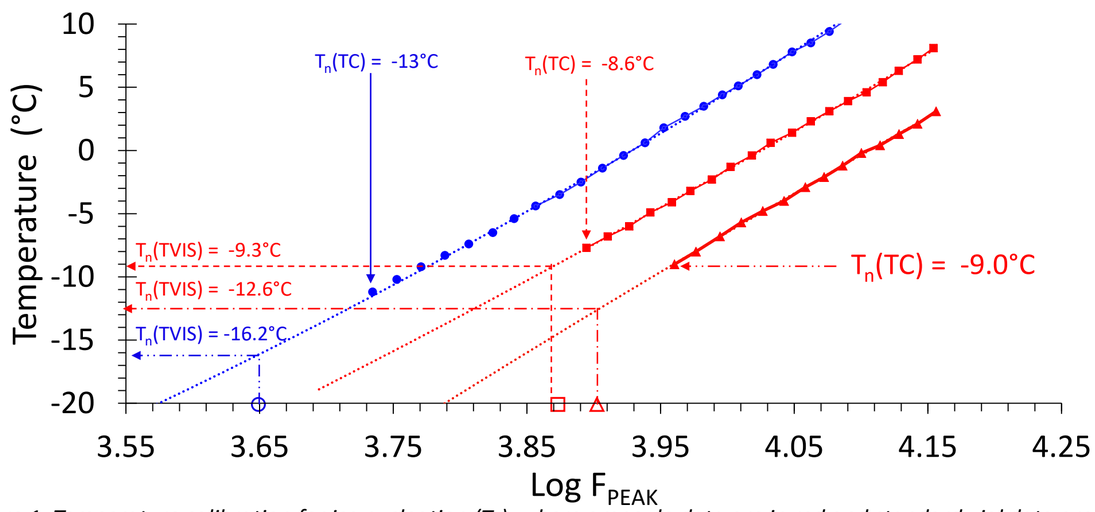

Figure 1: Temperature calibration for ice nucleation (T_n), where ampoule data are in red and standard vial data are in blue. Dotted line form the value of F_{PEAK} on the x-axes represent peak frequency before ice nucleation on TVIS container and from extrapolation from the curve to the left we demonstrate the predicted value of T_n.

Key: ▲ 2.5 ml ampoule T_n(TVIS)<T_n(TC) ■ 2.5 ml ampoule T_n(TVIS)>T_n(TC) ● 10 ml vial T_n(TVIS)<T_n(TC) △ F_{PEAK} of 2.5 ml ampoule T_n(TVIS)<T_n(TC) □ F_{PEAK} of 2.5 ml ampoule T_n(TVIS)>T_n(TC) ○ F_{PEAK} of 10 ml vial T_n(TVIS)<T_n(TC)

- Images (figure 2) qualifies the inflection (spike)in log F_{PEAK}, and C''_{PEAK} is due to ice formation. The calibration at the liquid state and the value of log F_{PEAK} before the inflection determines the temperature at nucleation. We have two nucleation temperate for the ampoule (-9.3°C and -12.6°C), and they are higher than the vial (-16.2°C).

TVIS parameters and nucleation onset time

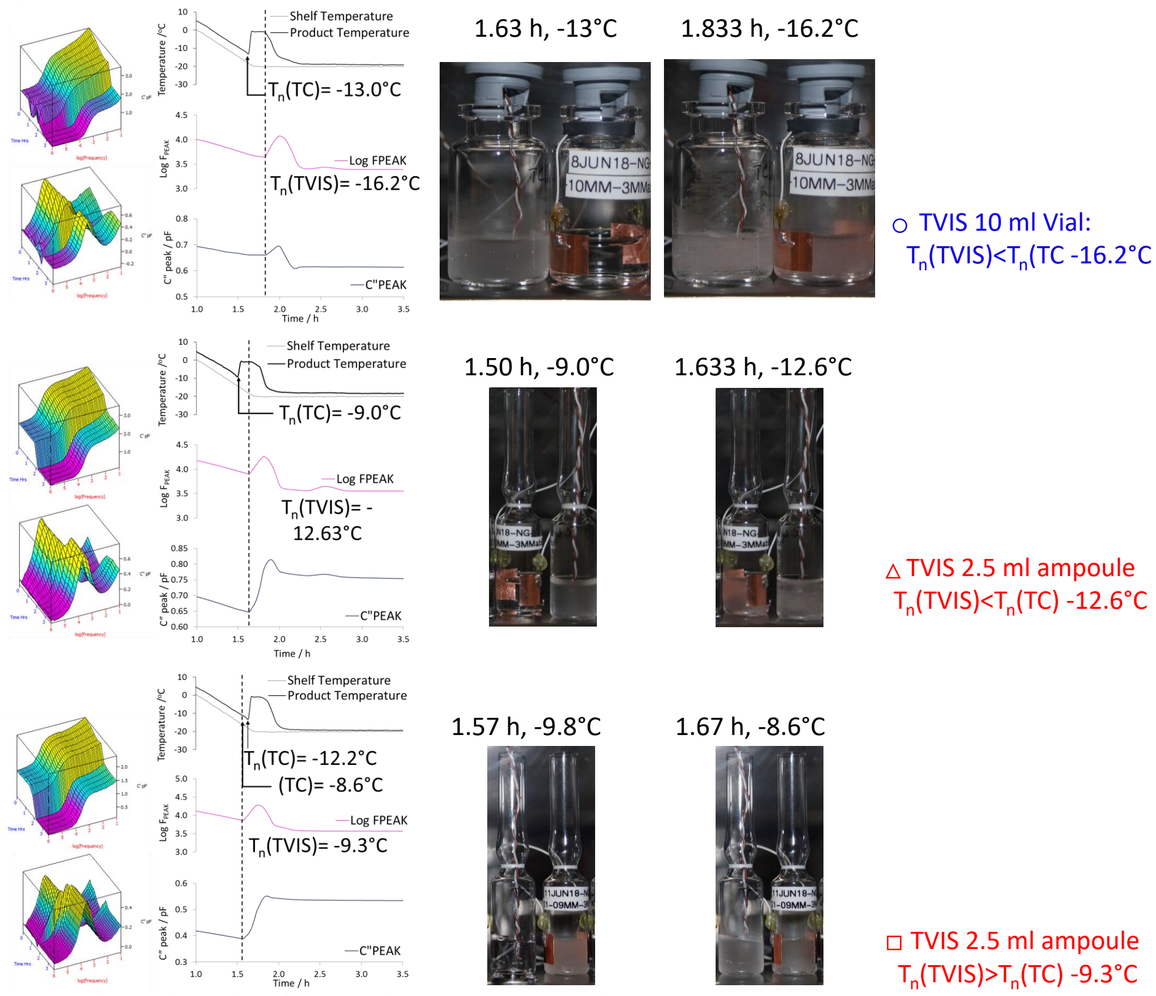

Figure 2: TVIS data and visual confirmation demonstrating ice nucleation

A limited number of measurement/repeats but the data seem to show that the vial nucleates (3-6°C) later than the ampoule. Given that nucleation is a stochastic event, based on probabilities and the probability of nucleation increases with a decrease in temperature because nucleation sites are more stable. The reason why ampoule nucleate before the vial because of the greater number (increase probability) of available nucleation sites per unit volume.

CONCLUSION

From the freezing study, it is evident that the TVIS approach is transferable from one size of the container to another.

REFERENCES

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