Through-Vial Impedance Spectroscopy (TVIS): A New Approach to Characterizing Phase Transition of Sugar-Salt Solutions

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INTRODUCTION

The development of a robust freeze-drying product and processes necessitates an understanding of the in-vial characteristics during processing especially freezing stage. The majority of techniques up to date for determining ice nucleation are restricted to the off-line instrument. Through-vial impedance spectroscopy (TVIS) is a relatively new technique which could explore the different facets of the in-situ material behaviour under freezing process (i.e. ice nucleation to solidification end points); however, the TVIS applications for the determination ice nucleation process have been recently restricted to the low-conductivity solutions such as pure water [1].

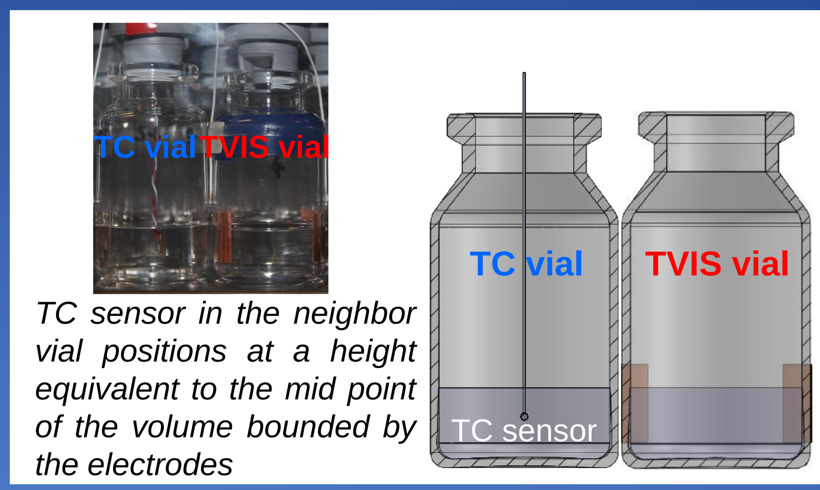
AIM

In this study, other features of TVIS system were explored to develop a new approach for determining nucleation process of conductive samples.

EQUIPMENT

Instrument / Sensor	Measurement / Process
TVIS	Electrical capacitance of TVIS vial containing sample measured every 2 min during freezing
Thermocouple	Thermocouple temperature in the nearest neighbour vial provides predictive temperature of TVIS vial (calibration)
VirTis Advantage Plus Freeze-dryer	Freezing from +20 to −45 °C at 0.5 °C·min-1
Digital camera	Photographic image for observation of ice nucleation event

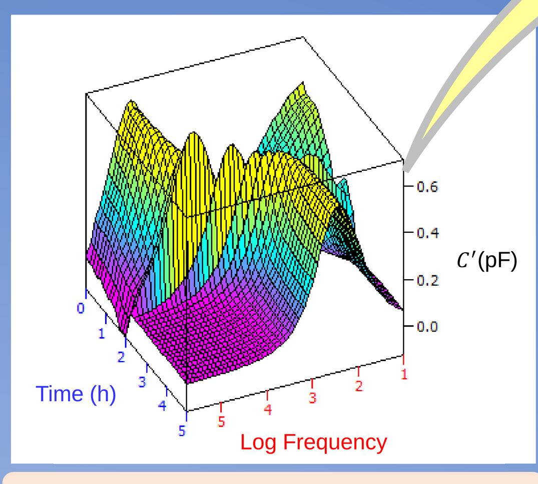
MATERIALS & METHODS



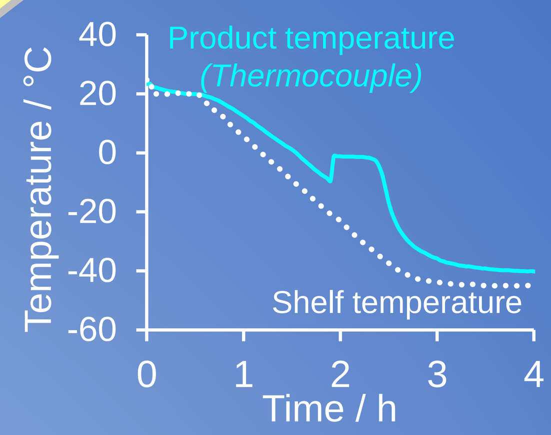
TC sensor in the neighbor vial positions at a height equivalent to the mid point of the volume bounded by the electrodes

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

1. In-vial measurement

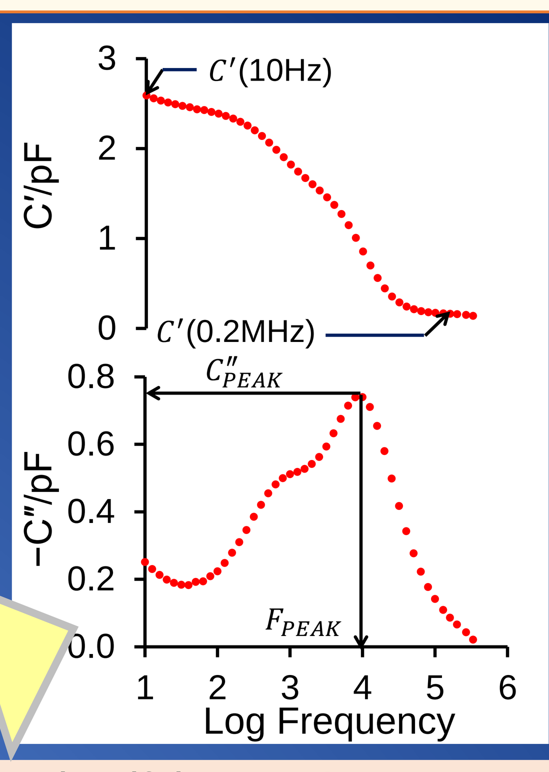


2. 3D-plot of TVIS spectra



3. Freezing sample

4. Monitoring nucleation event



5. Identifying TVIS parameters using **LyoView** software

RESULTS & DISCUSSIONS

- Inflections in the time profiles of TVIS parameters [C''_{PEAK}, F_{PEAK} and C'(10Hz)] corresponded with the onset of ice nucleation of 5% sucrose (as confirmed by images) as demonstrated in **Fig 1b – 1e.**
- However, samples having the higher conductivity (5% sucrose with either 0.26% or 0.55% NaCl), the relaxation process before frozen could not be detected by TVIS system (**Fig 1i – 1j** and **Fig 1p – 1q**, for 0.26% and 0.55% NaCl respectively). This could be exemplified by the spectrum of liquid state of sugar-salts solution (**Fig 1n** & **Fig 1u**) and pure sugar (**Fig 1g**). Hence, only real part capacitance at 10 Hz was used to indicate the onset of ice formation in a high conductive solution (**Fig 1k** & **1r**).

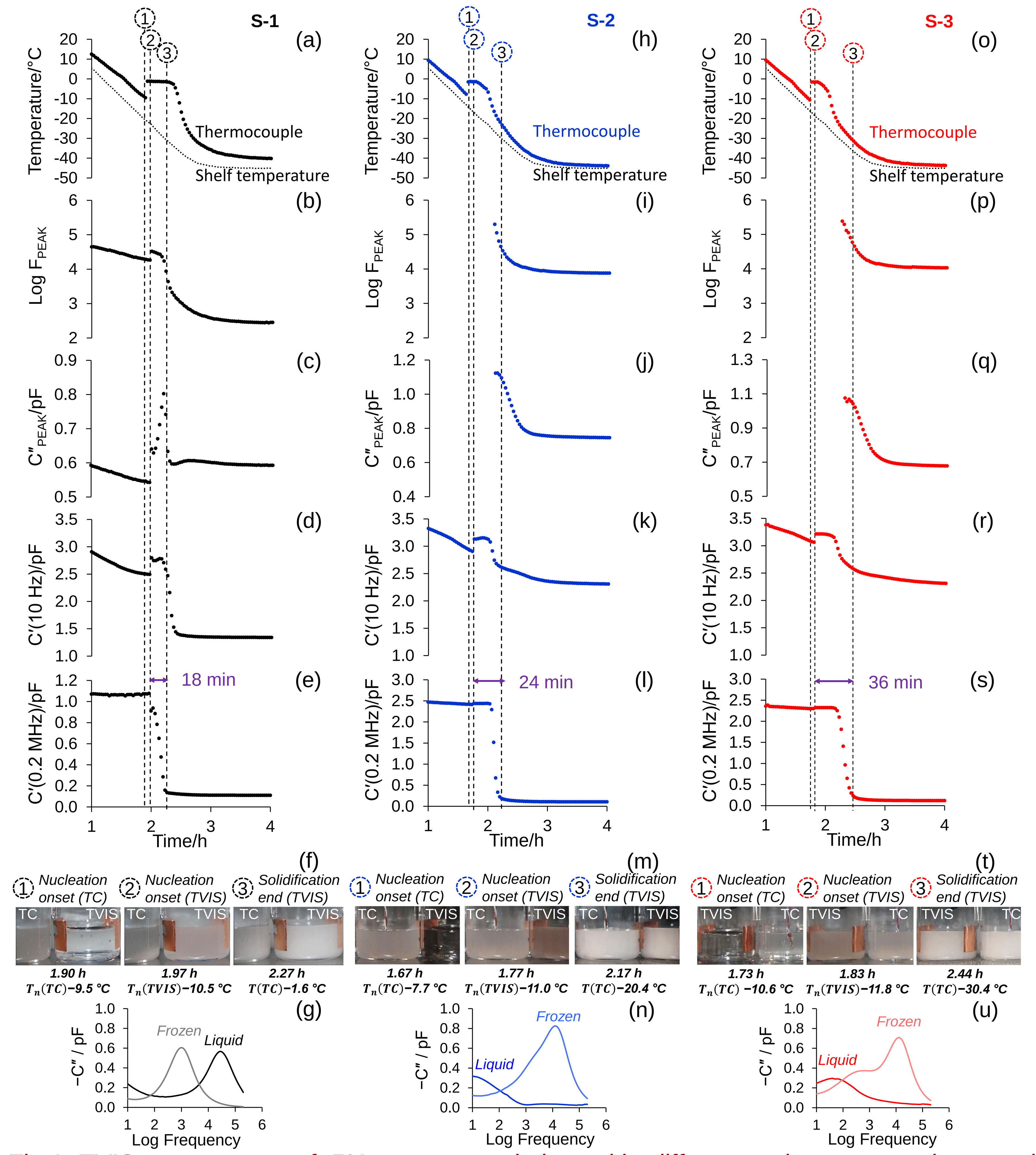


Fig.1 TVIS parameters of 5% sucrose solution with different salt concentrations and images during freezing; (a-g) 0% NaCl, (h-n) 0.26% NaCl, (o-u) 0.55% NaCl

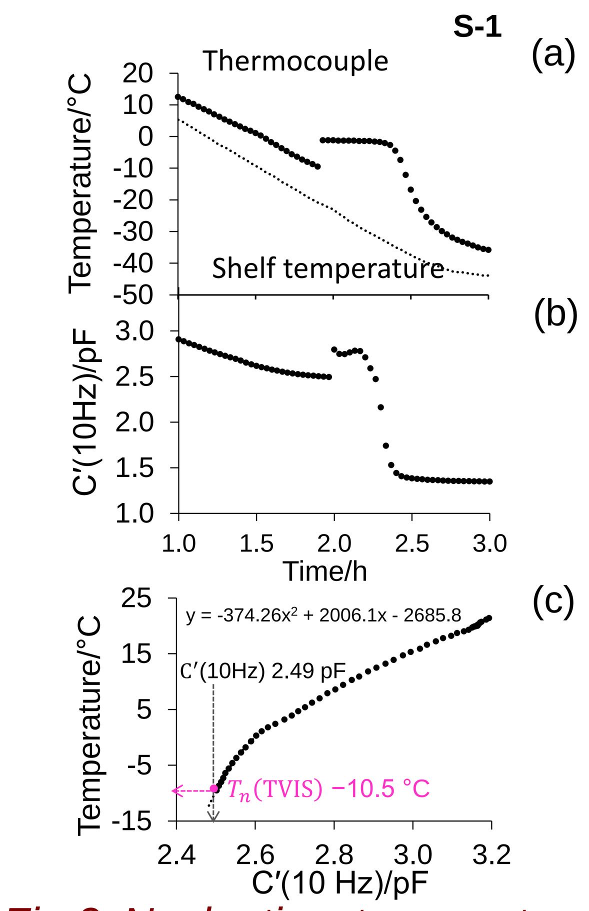


Fig.2 Nucleation temperature of 5% sucrose predicted by TVIS C'(10Hz) [$\mathbf{T_n(TVIS)}$]

- TVIS vial generally nucleate later than TC vial due to the impact of thermocouple probe. In this case, the nucleation temperature can be predicted by fitting a curve to the plot of temperature from neighboring vial (TC vial) against TVIS parameter [i.e. C'(10Hz)] as demonstrated in **Fig 2c**, which are −10.5, −11.0 and −11.8 °C respectively for the solutions of 5% sucrose with 0, 0.26 and 0.55% NaCl (**Fig 3**)

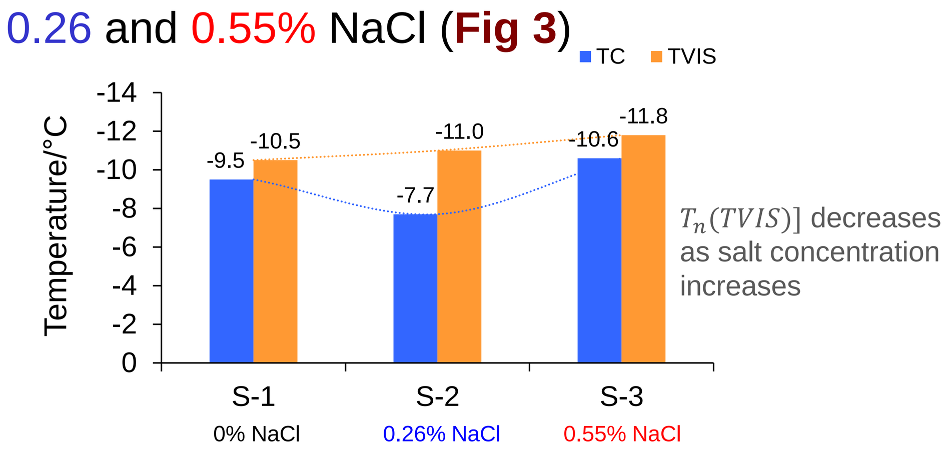


Fig.3 Nucleation temperature of sugar-salt solutions predicted by TVIS parameter $C'(10Hz)$

- At 200 kHz or 0.2MHz (which is well above the ice relaxation frequency of 1 kHz), the capacitance of ice has almost no temperature dependence and so any changes in C'(0.2MHz) either with time or temperature, can be associated with the completion of ice formation on freezing (**Fig 4b**). Here, the end point of solidification for 5% sucrose with 0, 0.26 and 0.55% NaCl were 2.27, 2.17 and 2.43 h, respectively.
- By using the time different between nucleation point (**Fig 4a**) and solidification end point (**Fig 4b**), ice forming duration was obtained. The results were reported in **Fig 5**, and also demonstrated a twofold increase in the solidification time as salt concentration increases from 0 to 0.55 %.

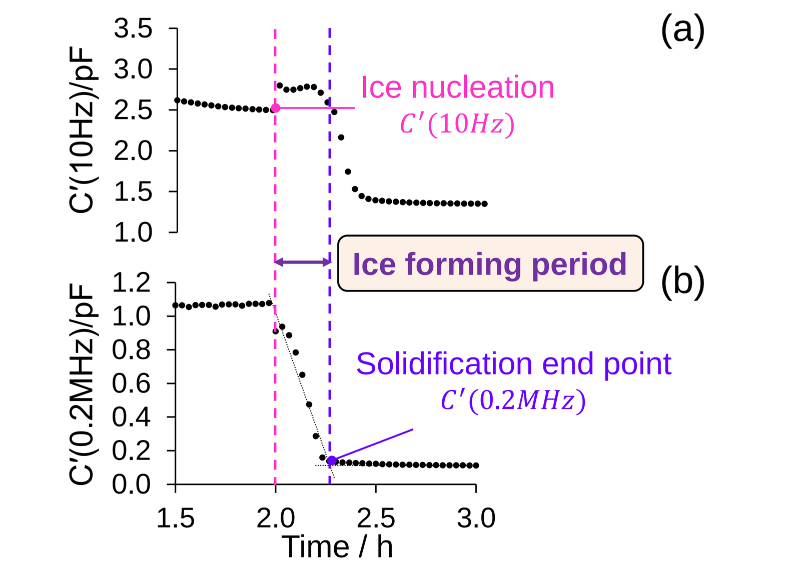


Fig.4 Determination of nucleation period of 5% sucrose by TVIS

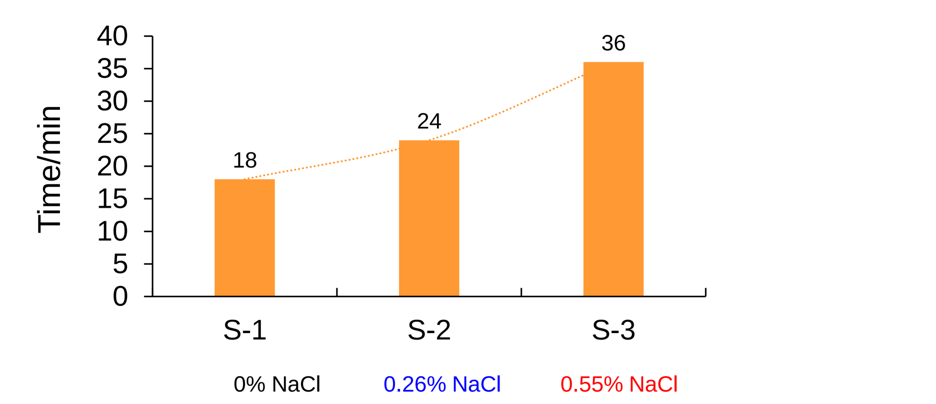


Fig.5 Time required for complete solidification of sugar-salt solutions estimated by real part capacitance at 10Hz and 0.2MHz by TVIS

CONCLUSION

TVIS creates new opportunities to detect phase change during freezing process including the nucleation onset and the solidification end point.

REFERENCE

[1] G. Smith, E. Polygalov, M.S. Arshad, T. Page, J. Taylor, I. Ermolina, An impedance-based process analytical technology for monitoring the lyophilisation process, Int. J. Pharm. 449 (2013) 72-83.

TVIS Through Vial Impedance Spectroscopy

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