Electrical Impedance Methods for Developing a Lyophilization Cycle

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ISLFD

ISLFD 2019 – 9th International Symposium on Lyophilization of Pharmaceuticals
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Overview

- Critical parameters in freezing

- On-line impedance spectroscopy (TVIS)
- Dielectric loss / dielectric relaxation processes (liquid to frozen)
- Dielectric loss or dielectric permittivity analysis?
- Dielectric permittivity spectrum: What frequency?

- In-vial determination of ……
  - Ice solidification rate
  - Ice nucleation temperature (T_n)
  - Eutectic melting (T_{eu}) or glass transition temperature (T_g')

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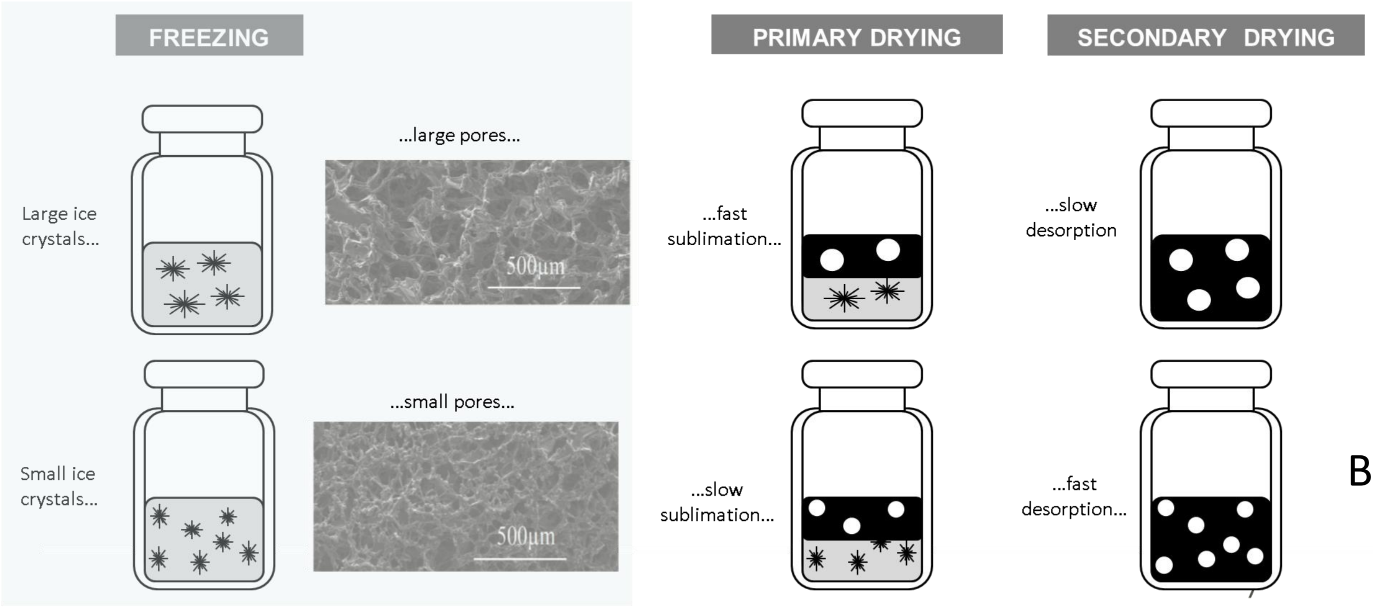
Critical Parameters

- Ice crystal structure (defined by freezing process and formulation)
  - Dry layer resistance impacting primary drying rate
  - Surface area of dry later impacting secondary drying rate



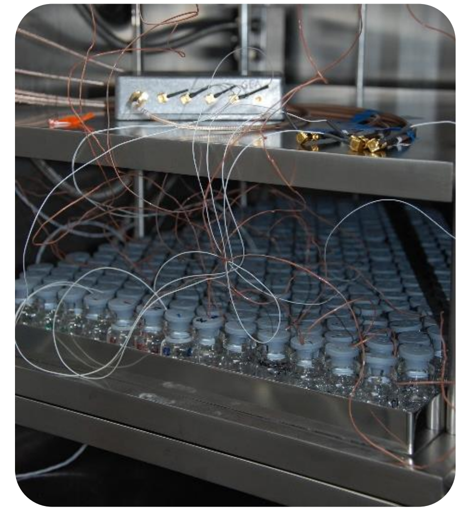
B Scutella

  - High temperature nucleation and slow cooling favours larger crystals
  - Low temperature nucleation and fast cooling favours smaller crystals

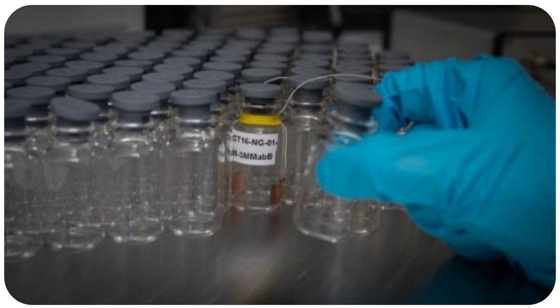
Through Vial Impedance Spectroscopy

Single Vial PAT

Multichannel



Non- perturbing to packing of vials



Thin flexible cables (0.5 - 2 m)

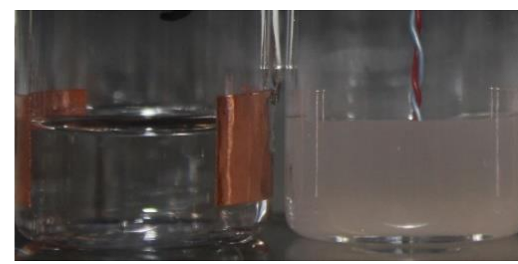
- Stoppering unaffected

Temperature calibration

- using nearest neighbour vial(s)

Low thermal mass of electrodes

- no interference with heat transfer & drying rates



Non-sample invasive

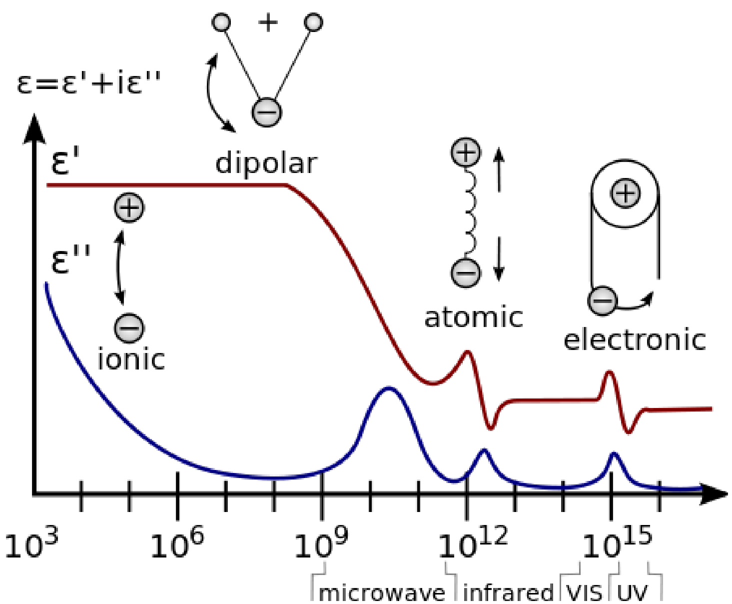
- no impact on ice nucleation

Through Vial Impedance Spectroscopy (TVIS)

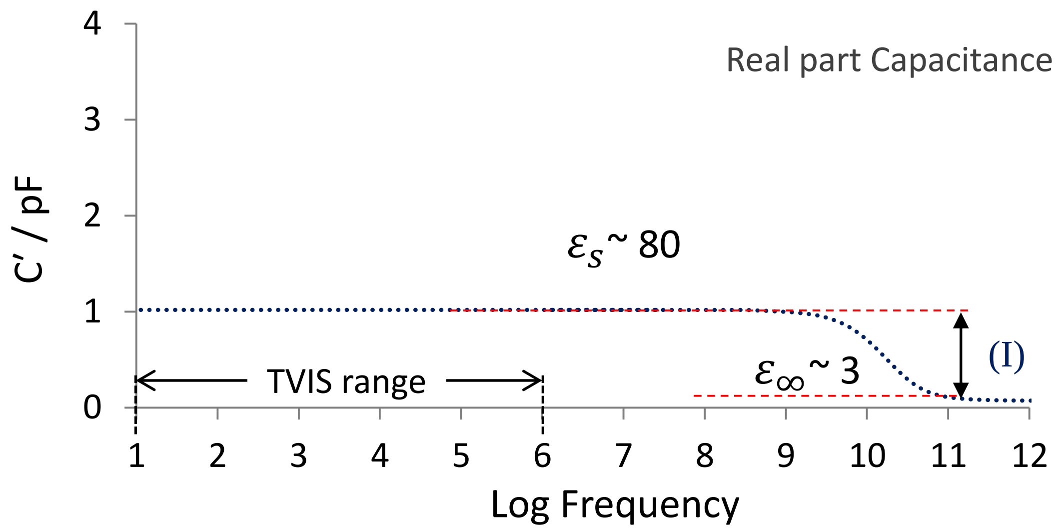
Dielectric Loss/Relaxation Mechanisms

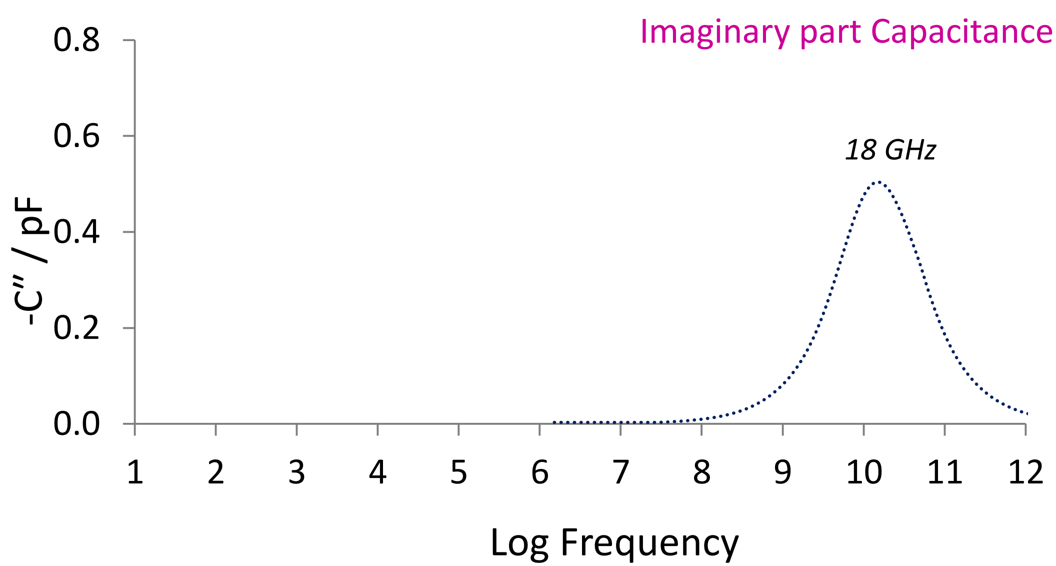
Dielectric Loss Mechanisms

I. The polarization of the water dipole in liquid water at 20 ˚C, with a dielectric loss peak frequency of ~ 18 GHz



https://en.wikipedia.org/wiki/Permittivity





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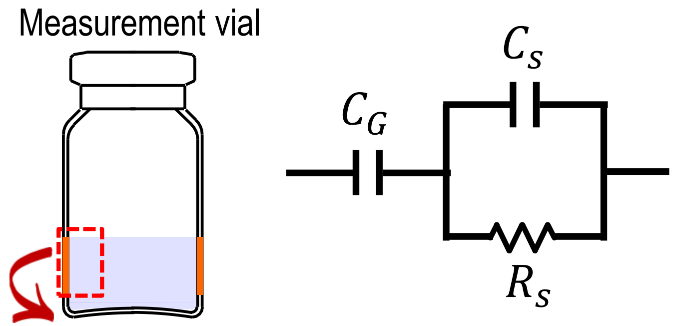
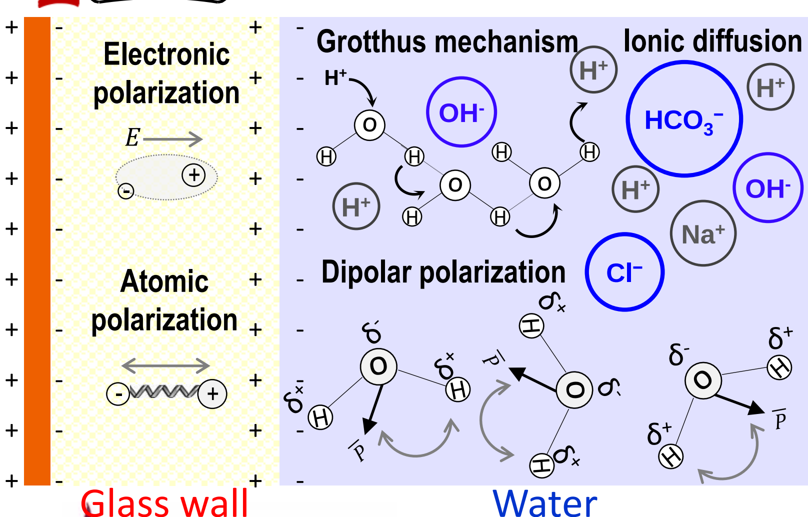
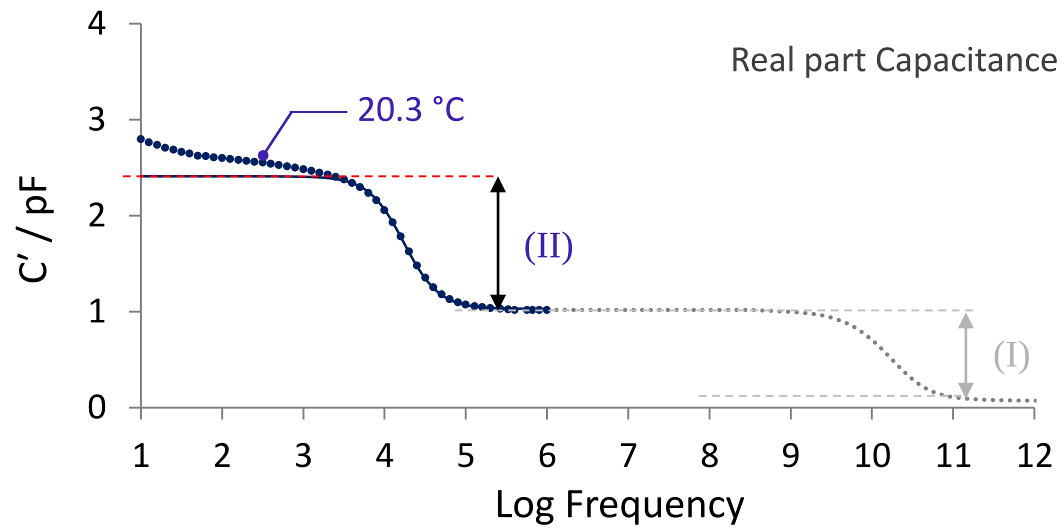
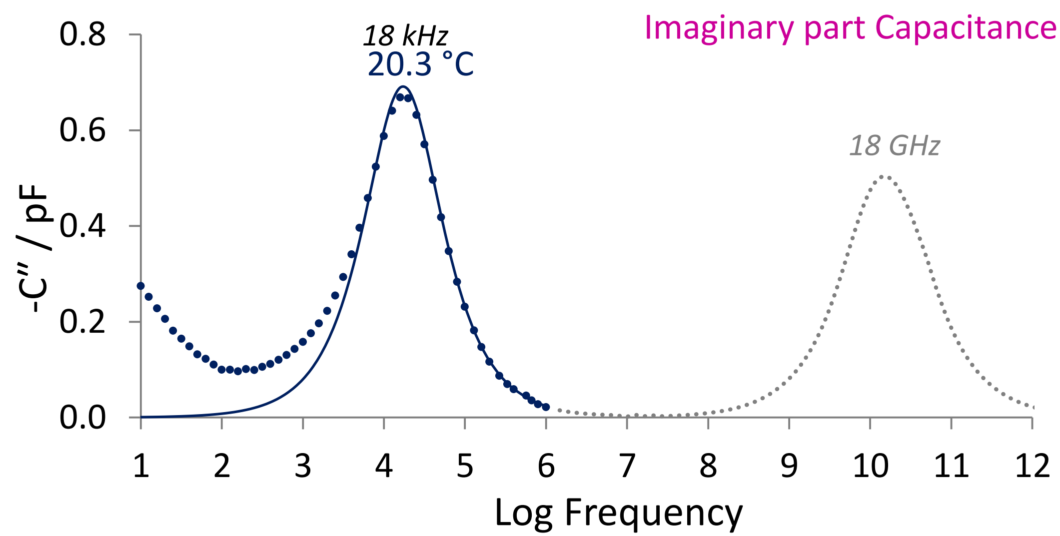
Dielectric Loss Mechanisms

II. Maxwell-Wagner (MW) polarization of the glass wall of the TVIS vial at +20 ˚C, with a dielectric loss peak frequency of 17.8 kHz









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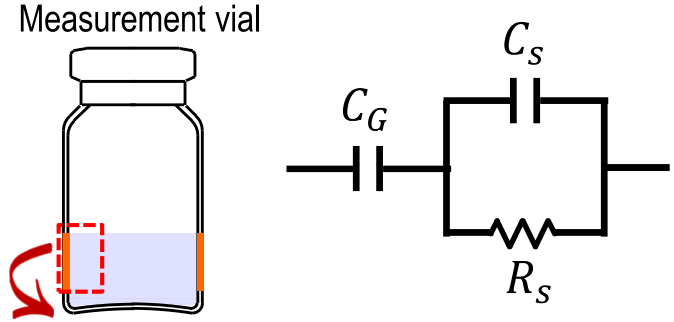

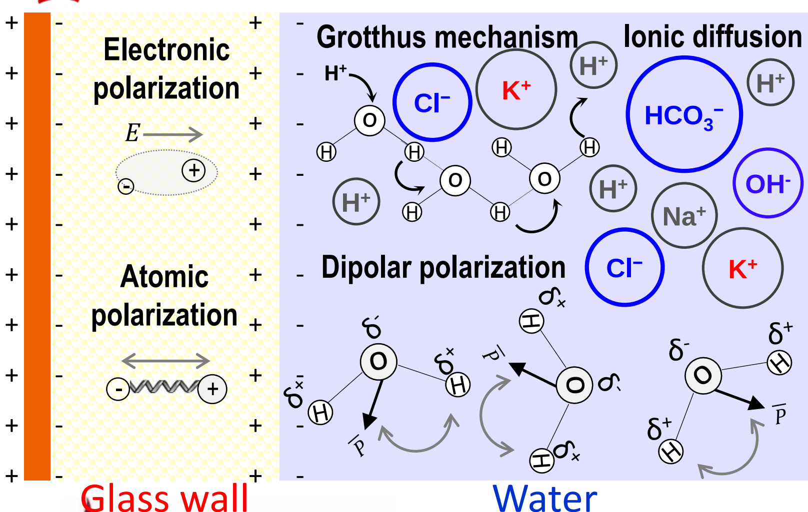

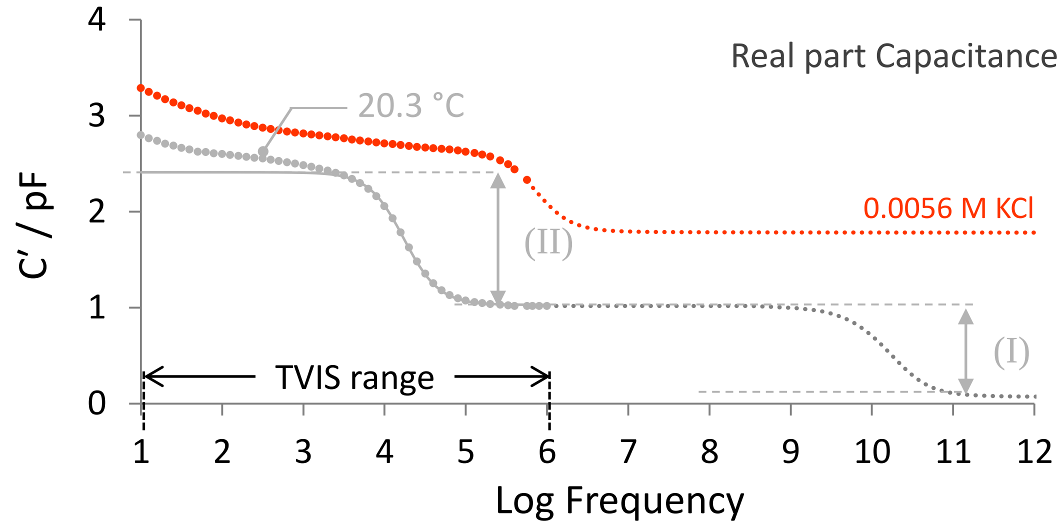

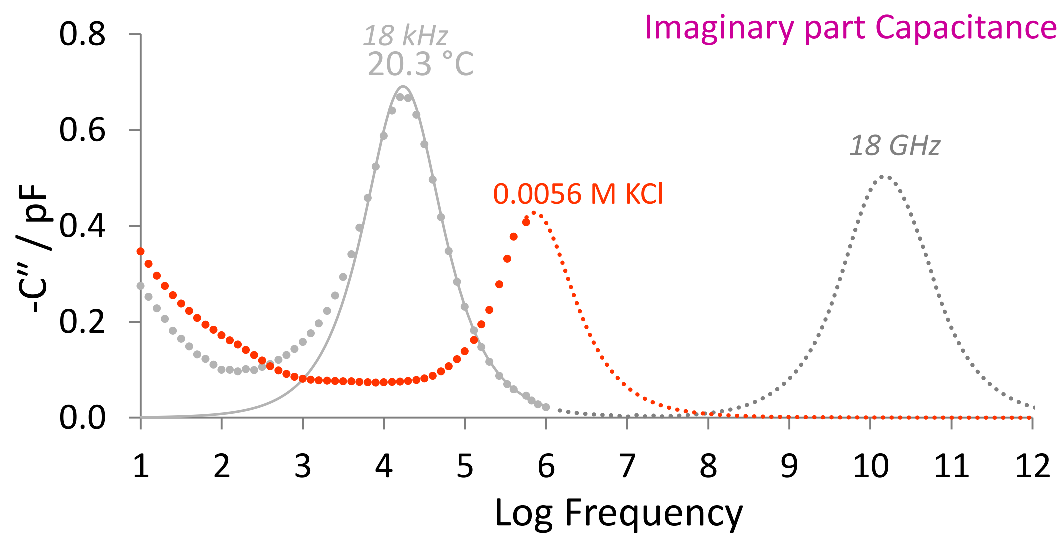

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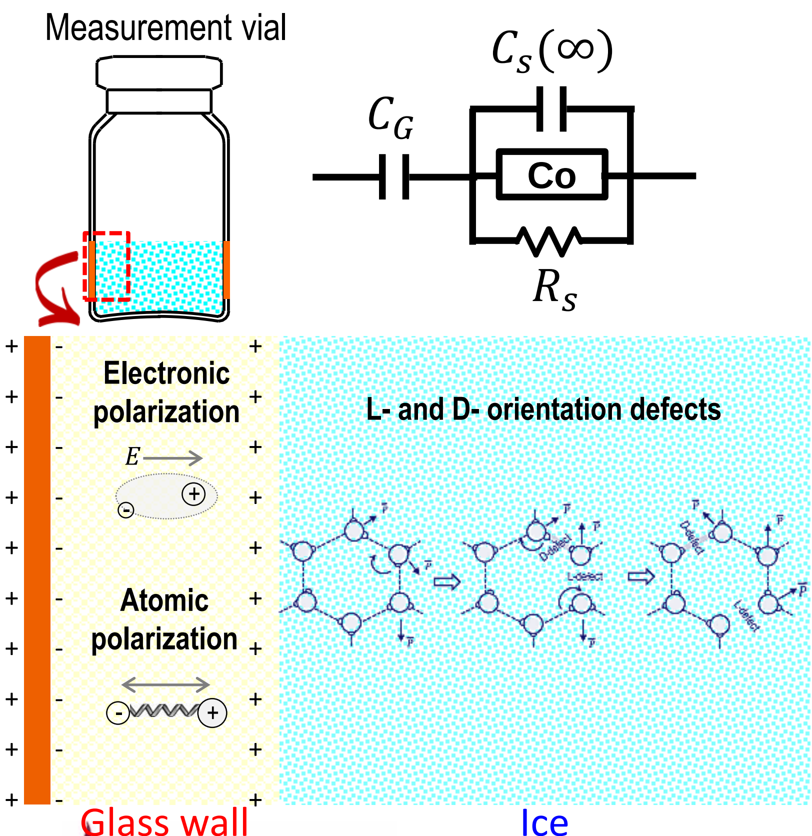
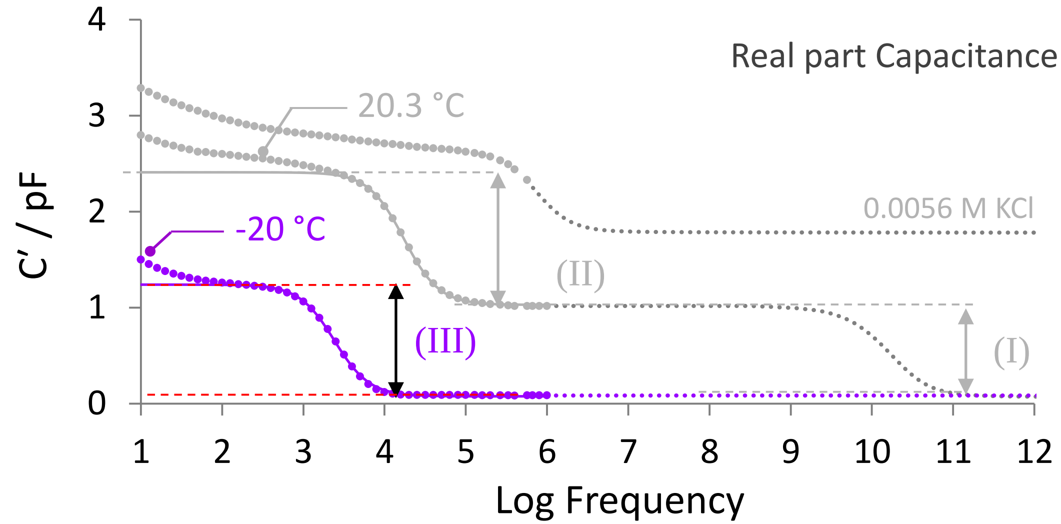
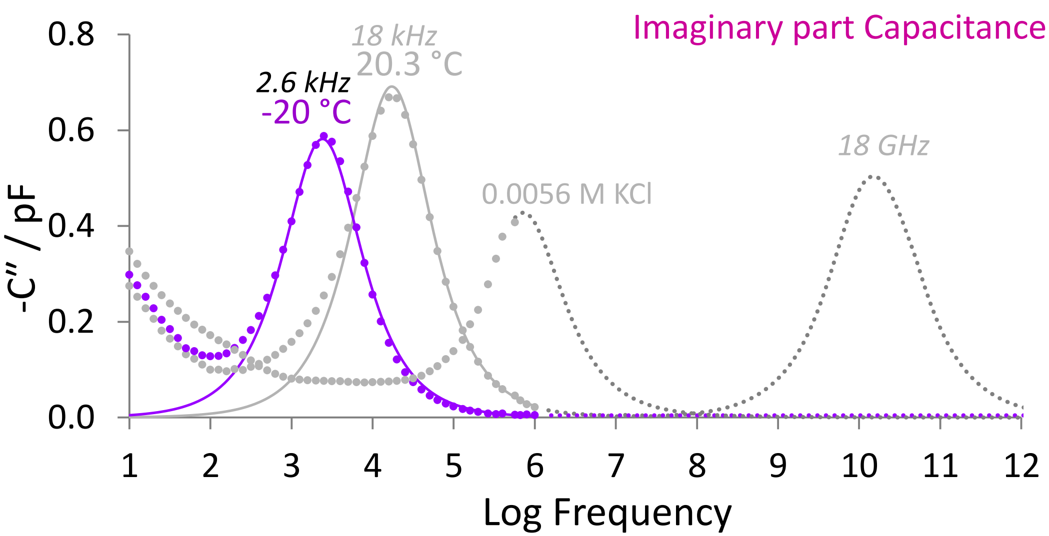
Dielectric Loss Mechanisms

III. The dielectric polarization of ice at −20 ˚C, with a dielectric loss peak frequencies of 2.57 kHz







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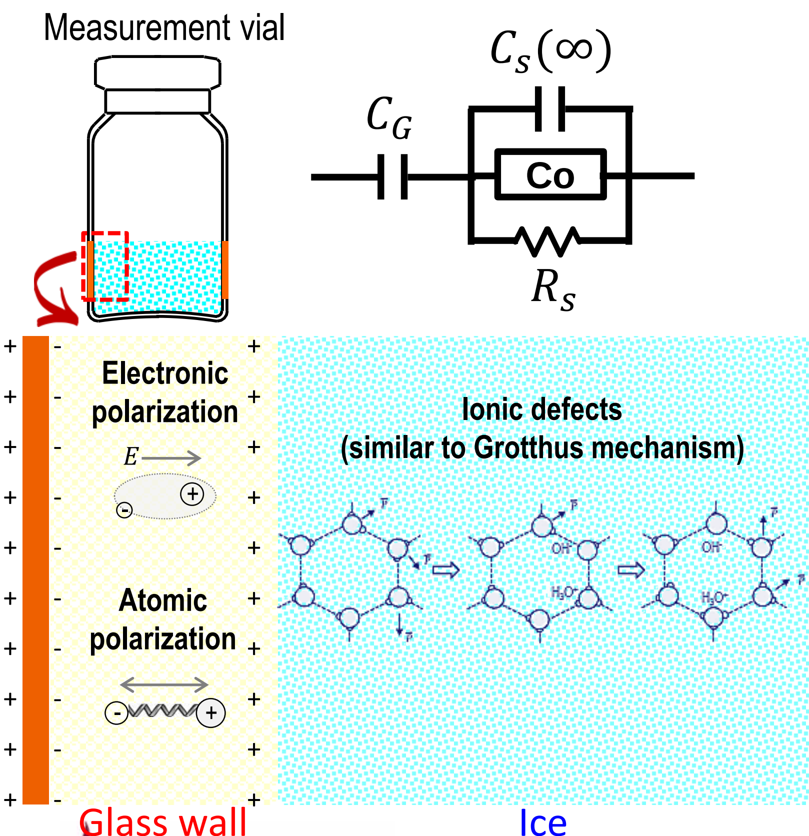
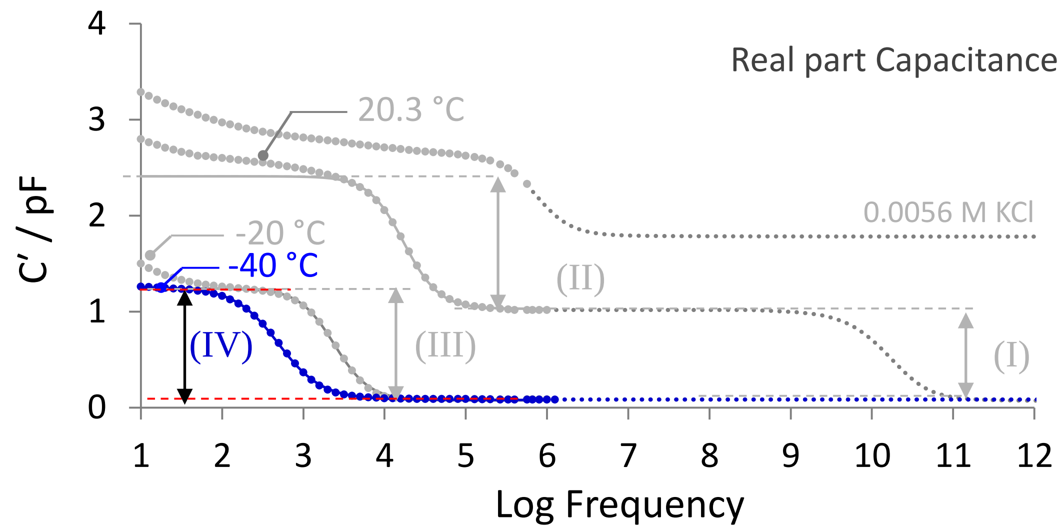
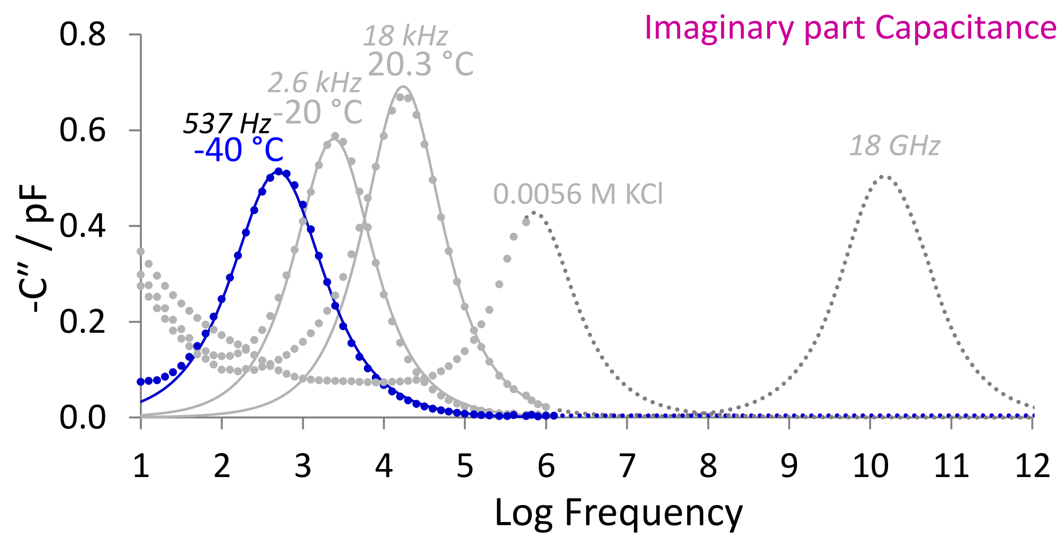
Dielectric Loss Mechanisms

IV. The dielectric polarization of ice at −40 ˚C with a dielectric loss peak frequencies of 537 Hz.







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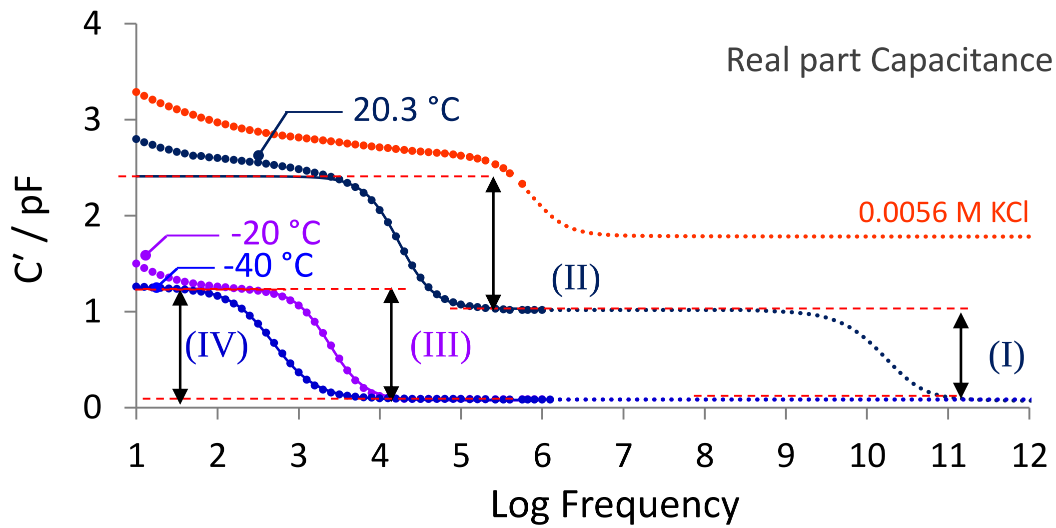
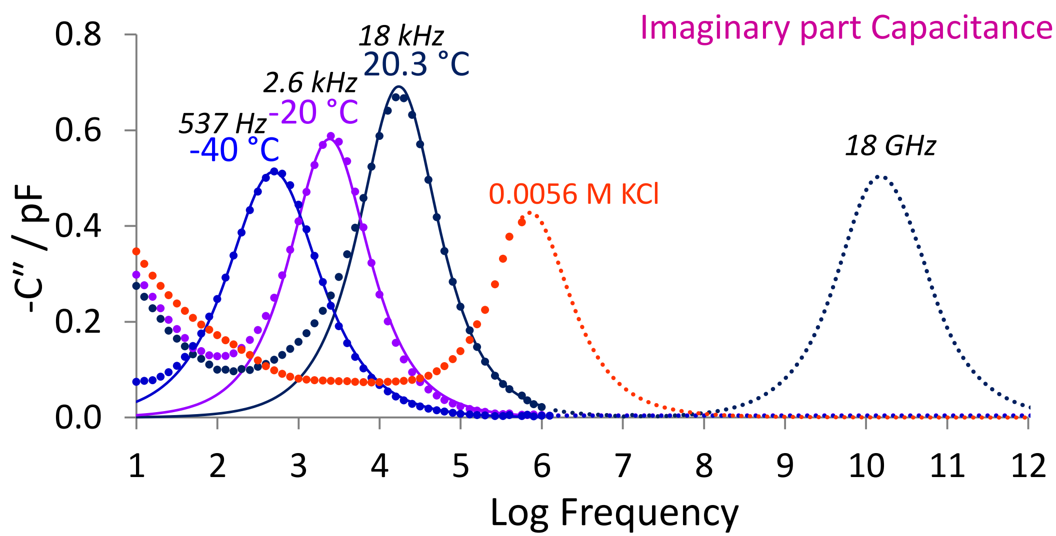
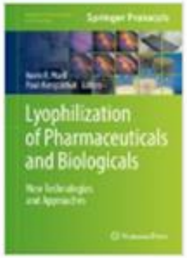
IV. The dielectric polarization of ice at −40 ˚C with a dielectric loss peak frequencies of 537 Hz.





Further Reading



Lyophilization of Pharmaceuticals and Biologicals pp 241-290 | Cite as

Through Vial Impedance Spectroscopy (TVIS): A Novel Approach to Process Understanding for Freeze-Drying Cycle Development

Authors | Authors and affiliations

Geoff Smith, Evgeny Polygalov

- Introduction to TVIS theory
- Description of the measurement principles
- Dielectric loss and relaxations mechanisms (liquid and frozen states)

Through Vial Impedance Spectroscopy (TVIS)

Dielectric loss or dielectric permittivity analysis?

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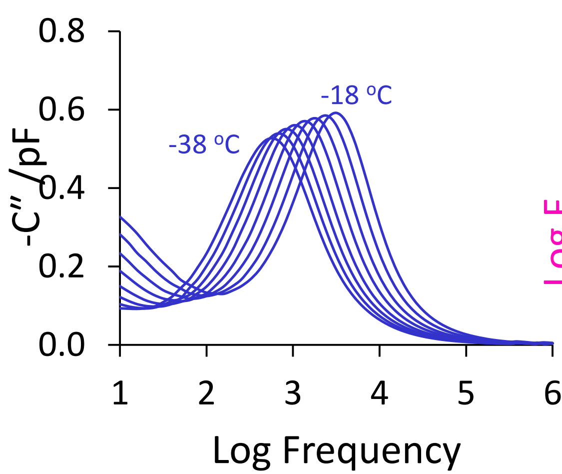
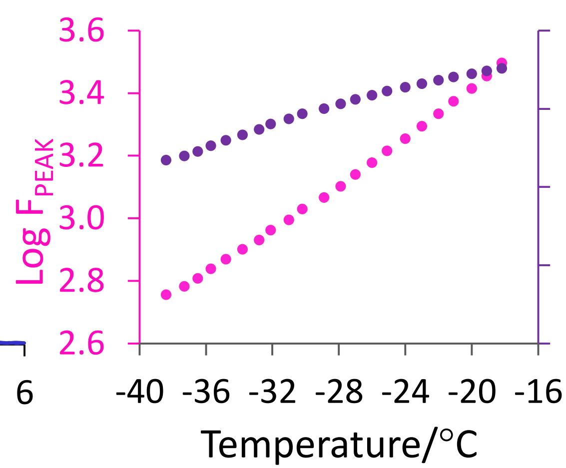
Applications for the dielectric loss spectrum

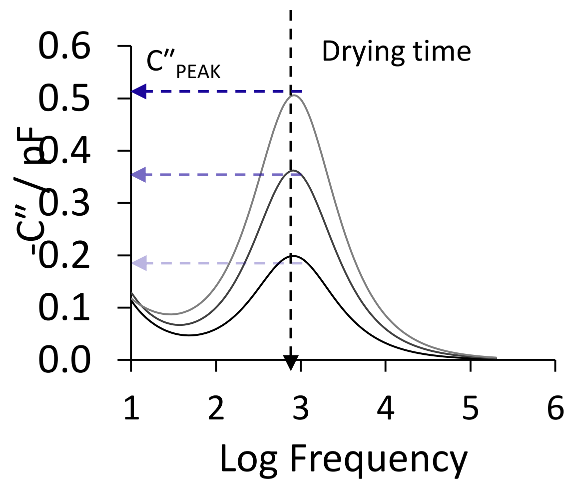
F_{PEAK} temperature calibration for **predicting temperature** of the product in primary drying

Temperature compensation for C''_{PEAK} prior to determination of drying rate

drying rate from $\frac{dC''_{PEAK}}{dt}$







These concepts were used in our recent paper :

Smith, G., Jeeraruangrattana, Y., Ermolina, I. (2018). The application of dual-electrode through vial impedance spectroscopy for the determination of **ice interface temperatures**, **primary drying rate** and **vial heat transfer coefficient** in lyophilization process development. European Journal of Pharmaceutics and Biopharmaceutics.

Applications for dielectric permittivity spectrum

- C'(~ 100 kHz) is highly sensitive to low ice volumes
- To date we have been using that for the determination **end point** of primary drying. # See Conference Poster 11 (Bhaskar et al)
- More recently we have started using the dielectric permittivity spectrum for
  - Ice nucleation temperatures
  - Ice crystallization end-point
  - Glass transition temperature………………” The focus for the rest of the presentation”

https://doi.org/10.21253/DMU.9771695

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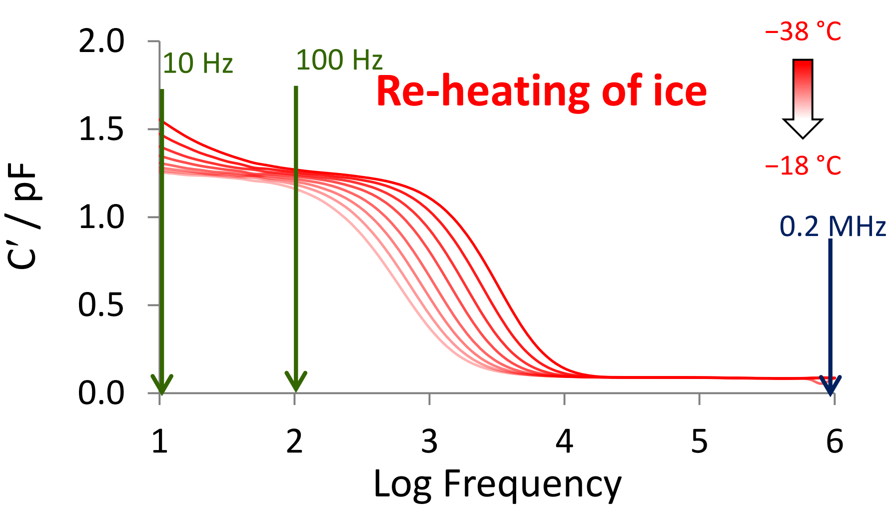
Dielectric Permittivity Spectrum: What ?

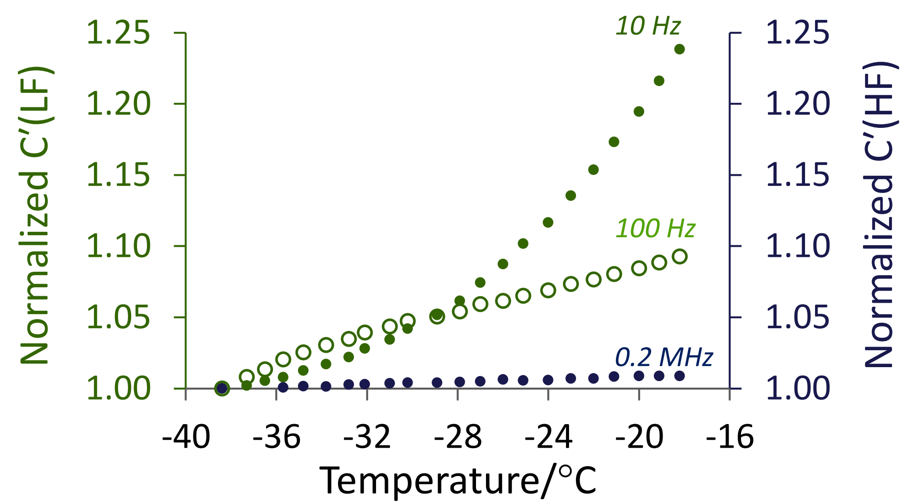
Through Vial Impedance Spectroscopy (TVIS)

Dielectric Permittivity Spectrum: What frequency?

Applications for dielectric permittivity spectrum

- Temperature sensitivity of the real part capacitance (dielectric storage or dielectric permittivity) of the TVIS vial (containing ice) depends on the measurement frequency
- The low frequency capacitance is <u>strongly</u> temperature dependent
- The high frequency capacitance is <u>weakly</u> temperature dependent





Significance: *Optimization of ice crystal structures with larger interconnected crystals increases the porosity of the dry layer, which is the layer that is restricting the diffusion of water vapour from the ice interface*

TVIS Applications

Ice solidification rate

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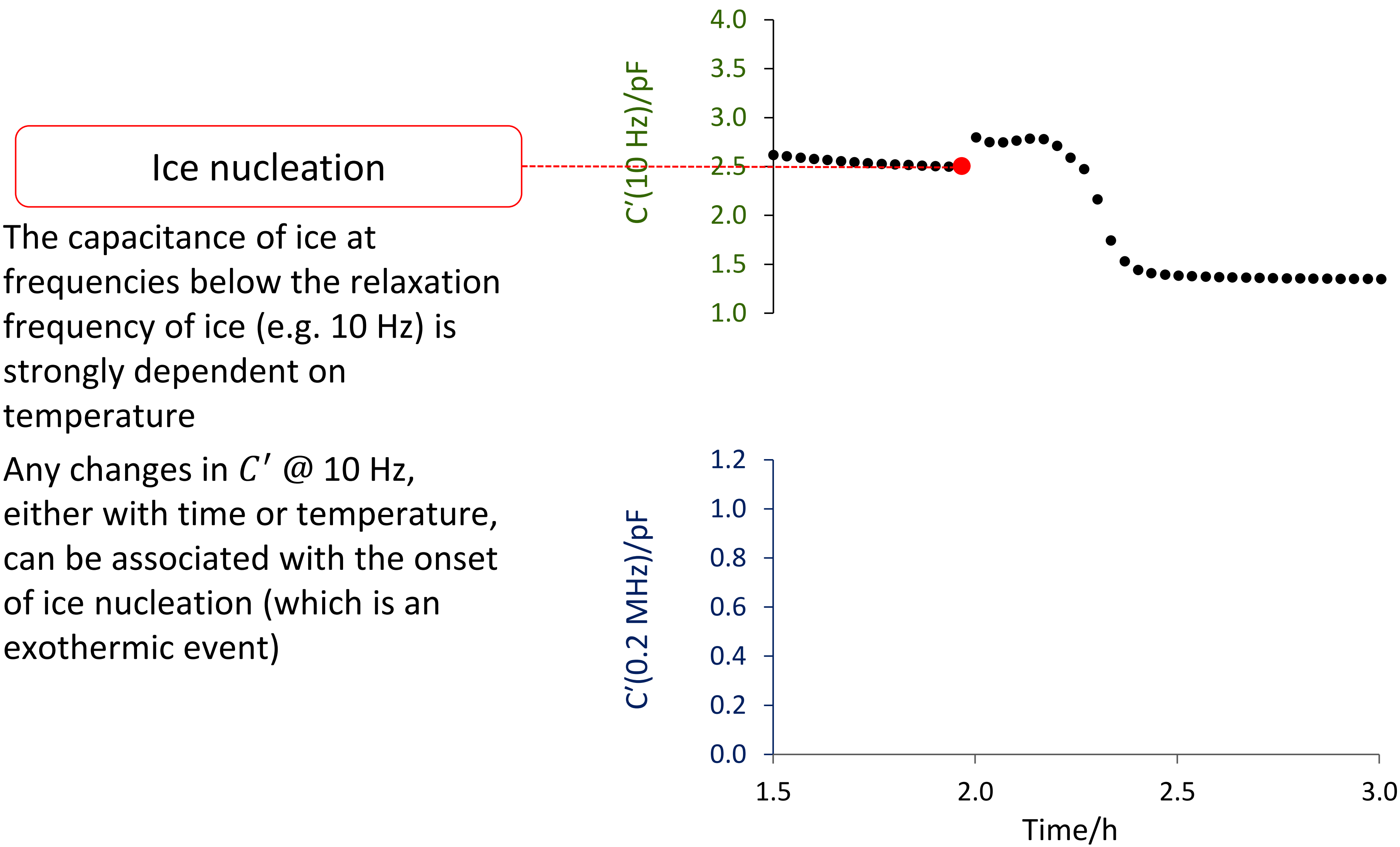
Nucleation onset

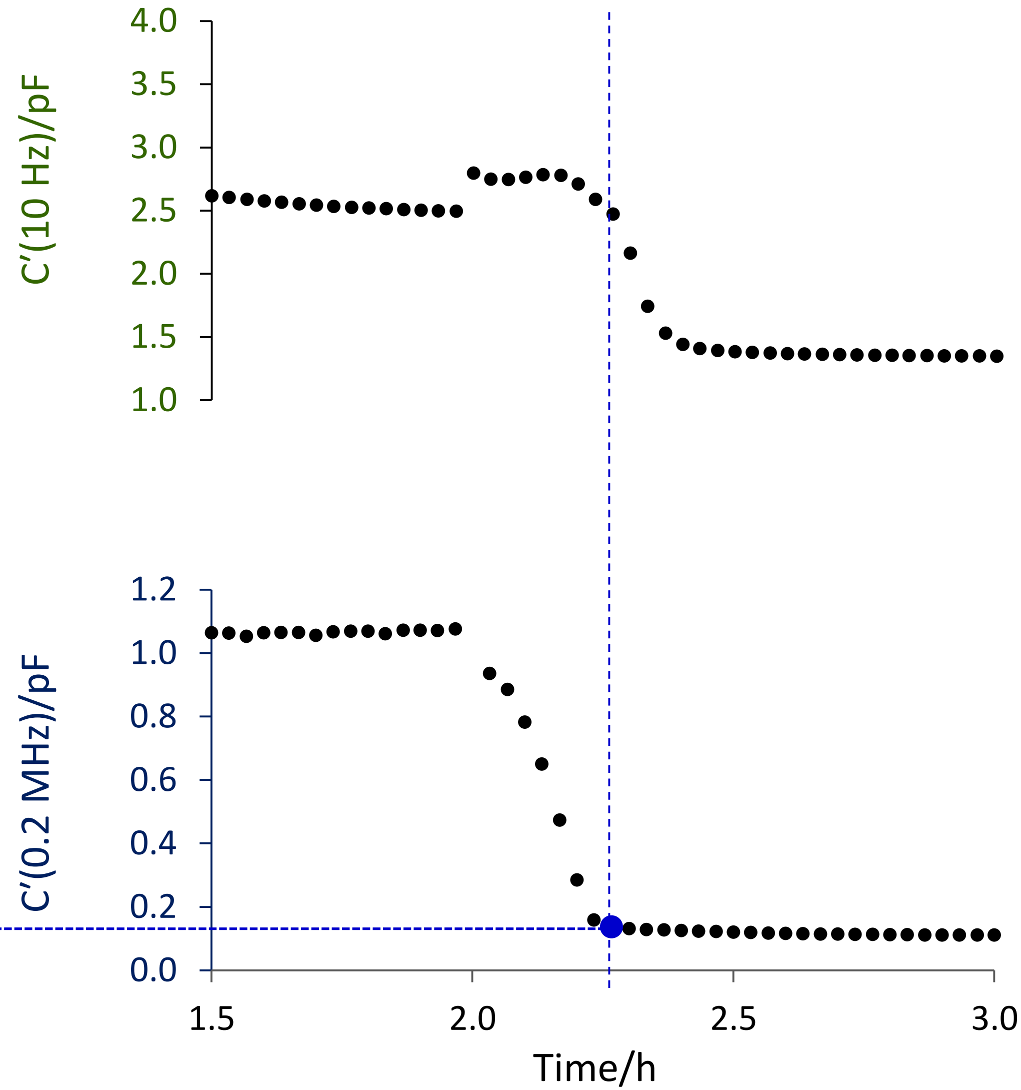
- The capacitance of ice at frequencies below the relaxation frequency of ice (e.g. 10 Hz) is strongly dependent on temperature
- Any changes in C' @ 10 Hz, either with time or temperature, can be associated with the onset of ice nucleation (which is an exothermic event)



Ice formation end point

- The capacitance of ice has almost no temperature dependence at frequencies above the relaxation frequency of ice (~1 kHz) such as C'(0.2 MHz).
- Any changes in C' (0.2 MHz) either with time or temperature, can be associated with the completion of ice formation on freezing

Ice solidification end-point

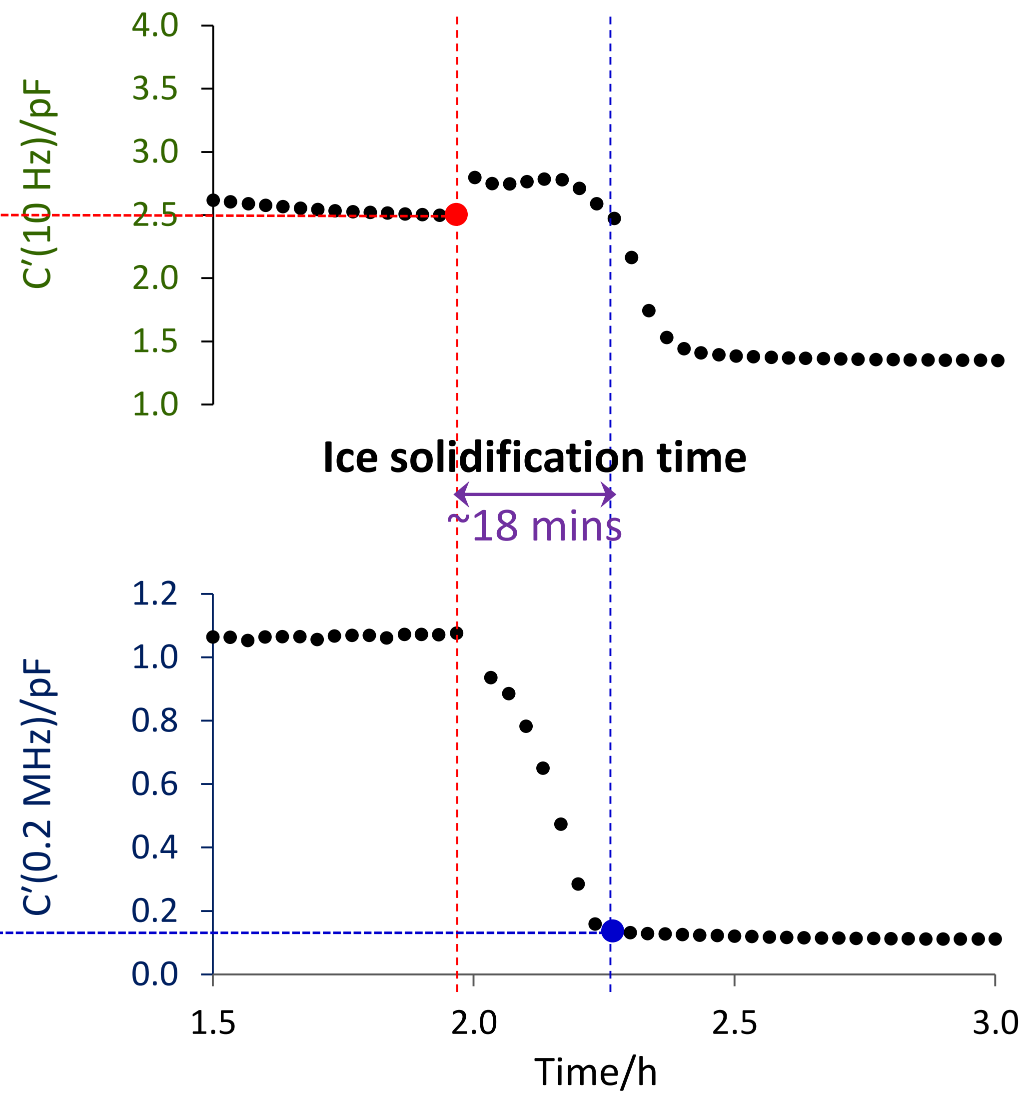


Ice crystallization period

Ice nucleation

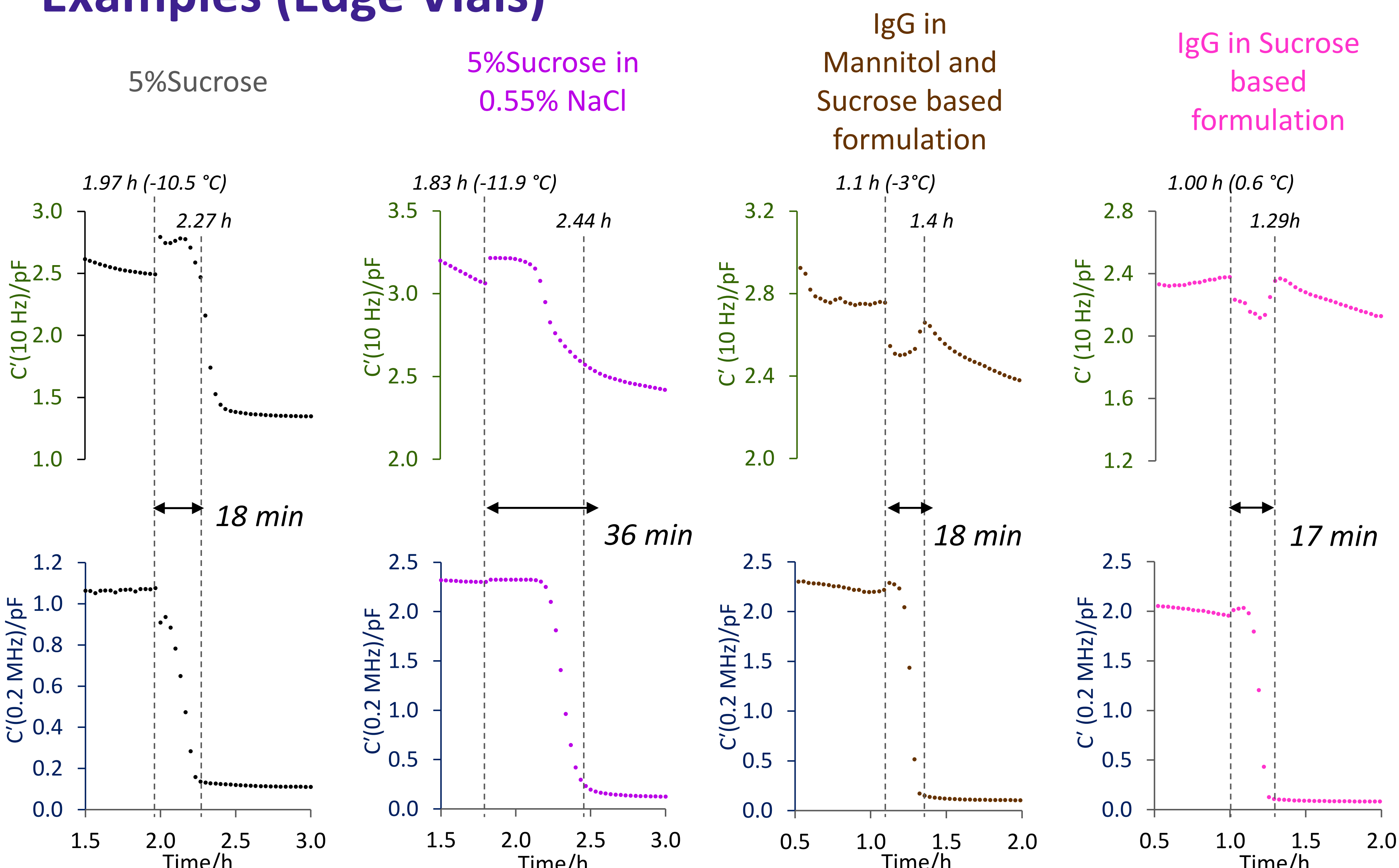
- The difference between these two times if the ice solidification time
- Knowing the height of the product in the vial one can then estimate an average solidification rate

Solidification end point



$$Average\ solidification\ rate\ (R_{av}) = \frac{Ice\ height\ (L)}{solidification\ time\ \Delta t}$$

Examples (Edge Vials)



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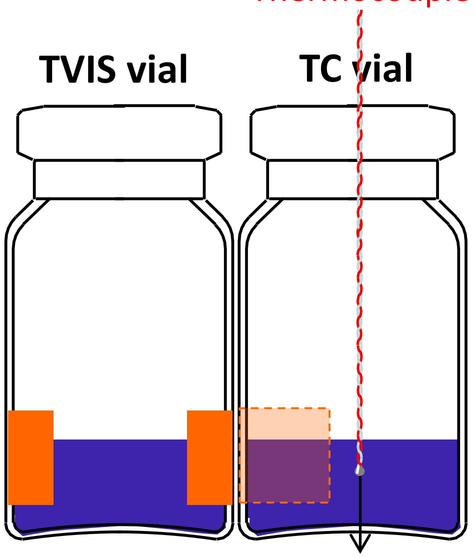
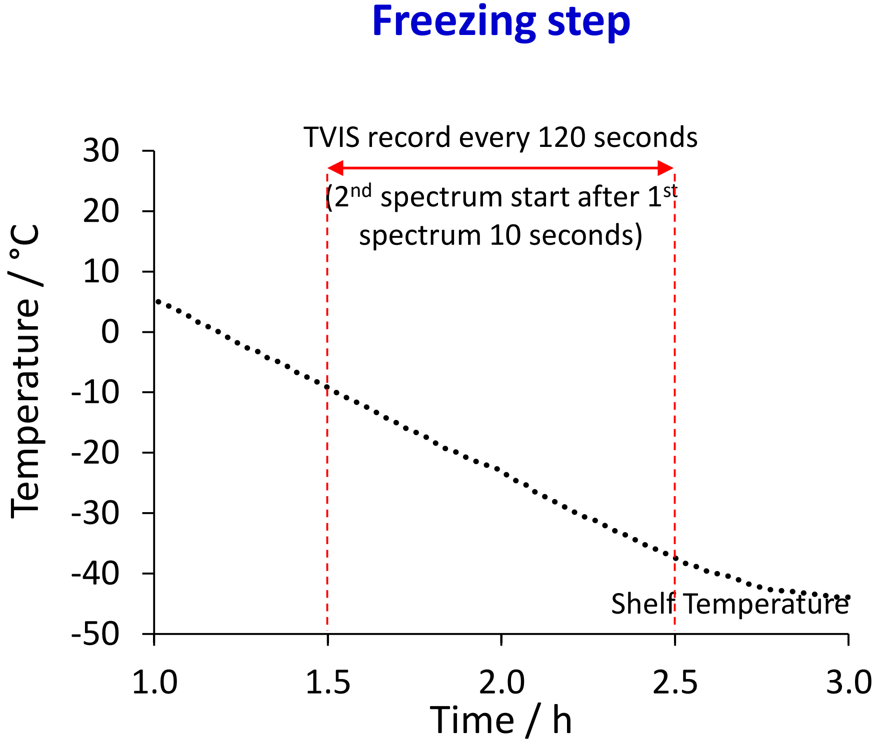
TVIS Applications

Determination of Ice Nucleation Temperature (T_n)

Ice Nucleation Temperature



Thermocouple position



Freezing from 20 °C to -45 °C with 0.5 °C/min

Ice Nucleation Temperature

- In case the TVIS vial nucleates before TC vial, the nucleation temperature in the TVIS vial can be inferred directly from TC temperatures in the nearest neighbor vials

Thermocouple

Shelf Temperature

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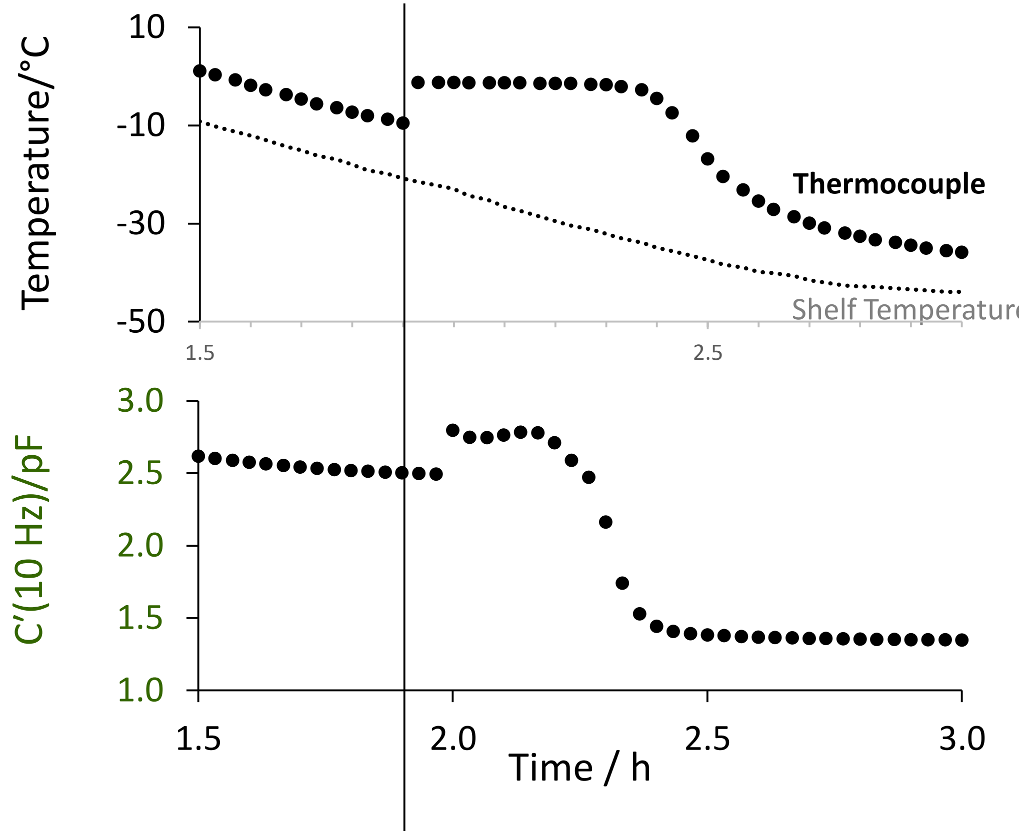
Ice Nucleation Temperature

- In case the TVIS vial nucleates before TC vial, the nucleation temperature in the TVIS vial can be inferred directly from TC temperatures in the nearest neighbor vials
- However, if TVIS vial nucleates later than TC vial,



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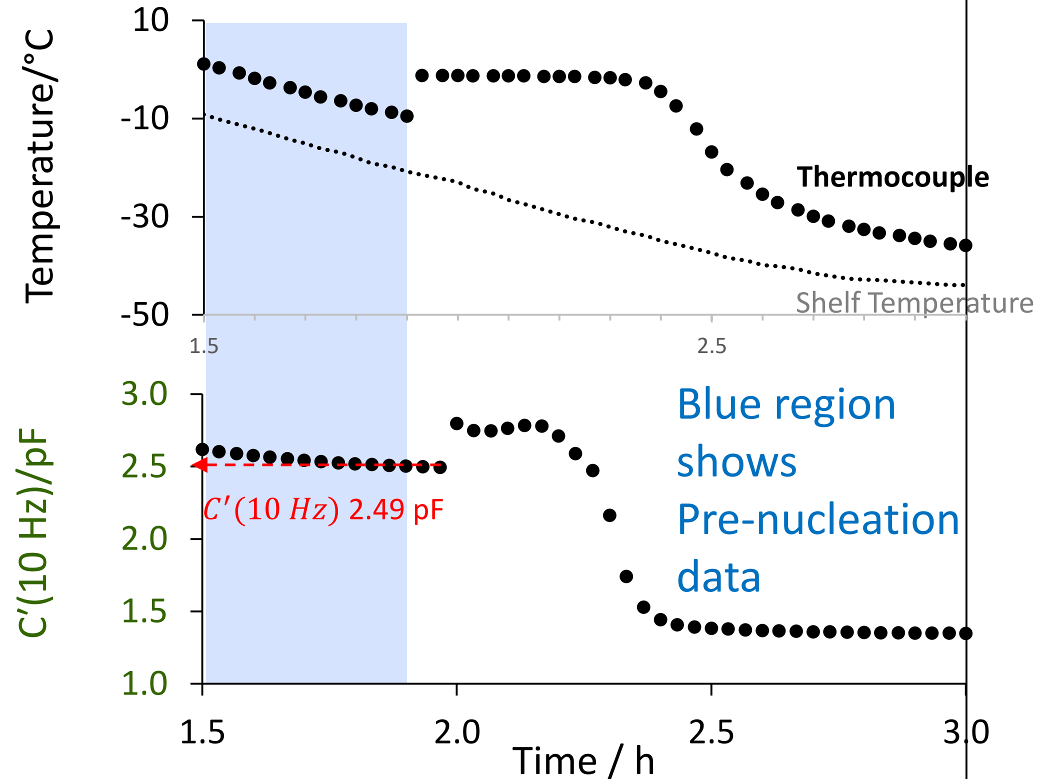
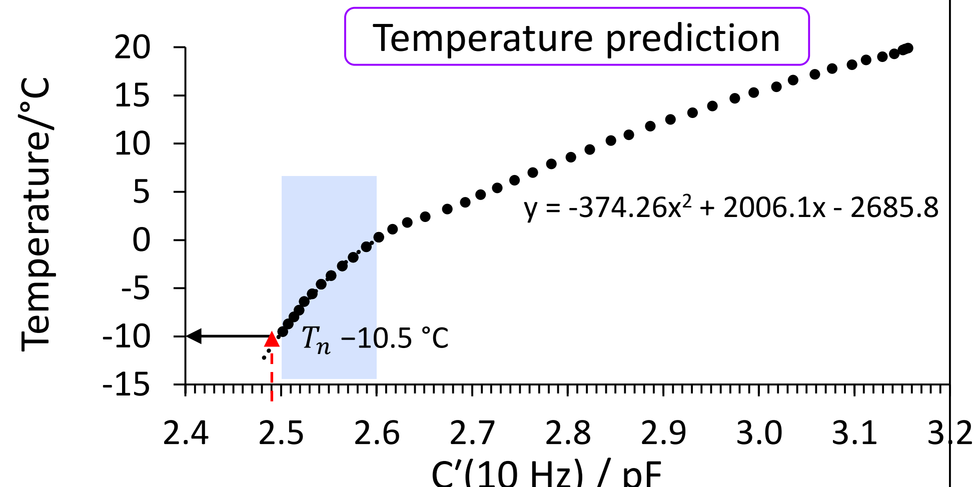
Ice Nucleation Temperature

- In case the TVIS vial nucleates before TC vial, the nucleation temperature in the TVIS vial can be inferred directly from TC temperatures in the nearest neighbor vials
- However, if TVIS vial nucleates later than TC vial, the nucleation temperature can be predicted by fitting a curve to the plot of the average temperature from thermocouple vials against TVIS parameter (i.e. $C'(10\ Hz)$)
- The ice nucleation temperature of sample (5 %w/v sucrose) was found to be -10.5 C in the case of this particular TVIS vial (other vials will differ owing to the stochastic nature of ice formation.





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Conclusions : Ice formation stage

- Ice nucleation onset (t_n)
  - determined at low frequency (e.g. 100 Hz)
- Ice solidification end point (t_s)
  - determined at high frequency (e.g. 100 kHz)
- Ice solidification time (Δt) is the difference between t_s and t_n
- Average ice growth rate determined by

$$Average\ solidification\ rate\ (R_{av}) = \frac{Ice\ height\ (L)}{solidification\ time\ \Delta t}$$

- Nucleation temperature (T_n)
  - determined from extrapolation of pre-nucleation data

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New Book

Chapter 5 Through Vial Impedance Spectroscopy (TVIS) A New Method for Determining the Ice Nucleation Temperature and the Solidification End point

CRC Press
Taylor & Francis Group

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Freeze Drying of Pharmaceutical Products

1st Edition

Davide Fissore, Roberto Pisano, Antonello Barresi

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£118.00

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ISBN 9780367076801 - CAT# K405807
Series: Advances in Drying Science and Technology

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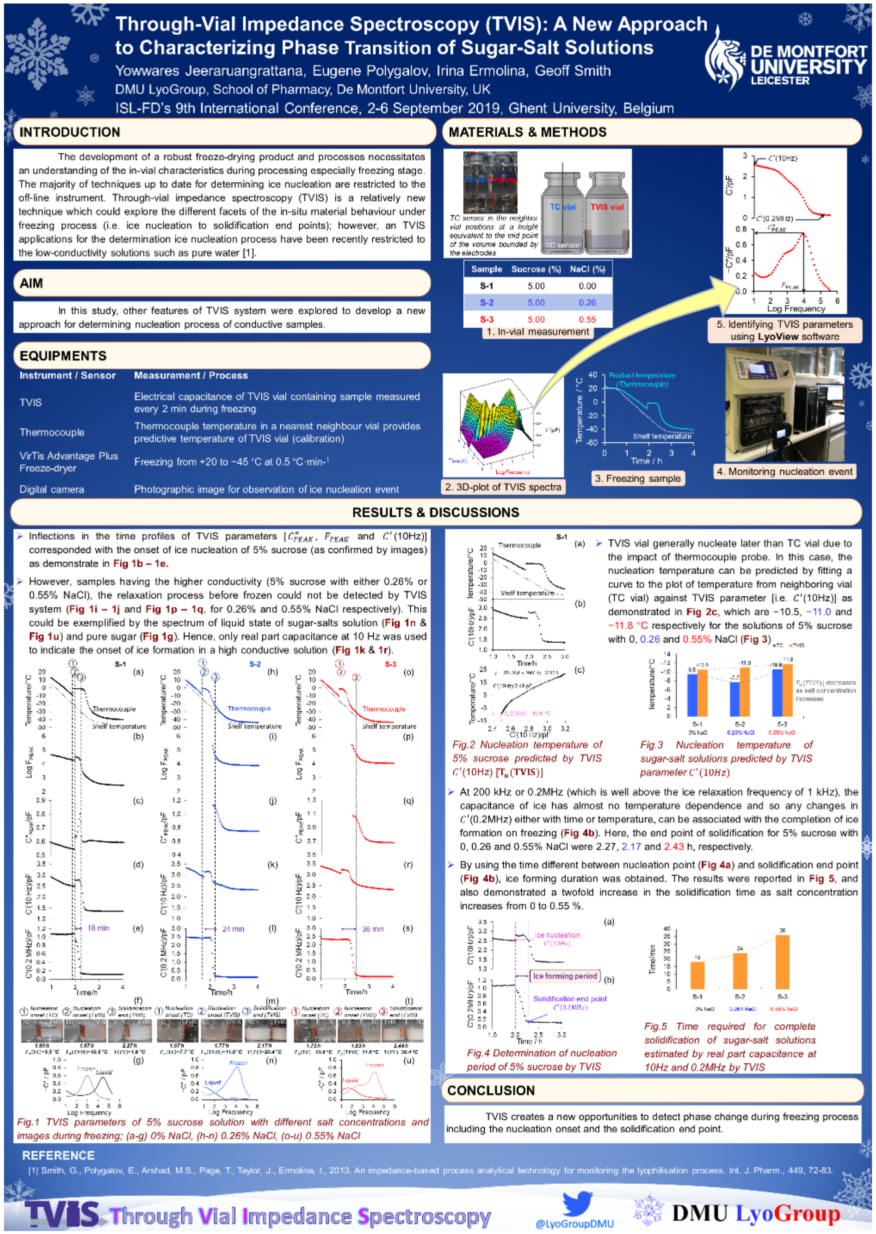

Jeeraruangrattana et al
Poster 10

ice formation time and nucleation temperature for Sucrose + NaCl solutions

https://doi.org/10.21253/DMU.9771512

Significance: T_g' or T_{eu} underpins/defines the collapse temperature which in turn defines the highest permissible product temperature during primary drying and therefore impacts the maximal achievable drying rate

TVIS Applications

Determination of in-vial

Eutectic melting (T_{eu}) or

Glass Transition temperature (T_g')

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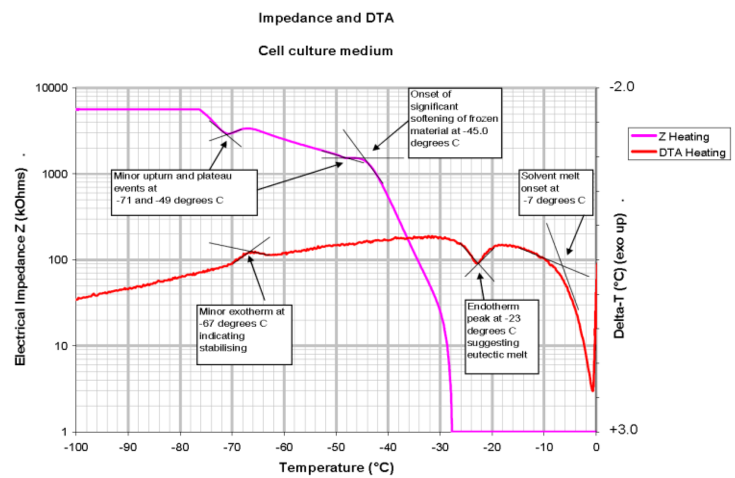
PAT for critical temperature determination T_m, T_e, T_g

- Collapse temperature (defined by formulation and related to T_{eu}, T_g)
  - Maximal permissible temperature avoiding structural changes to the product

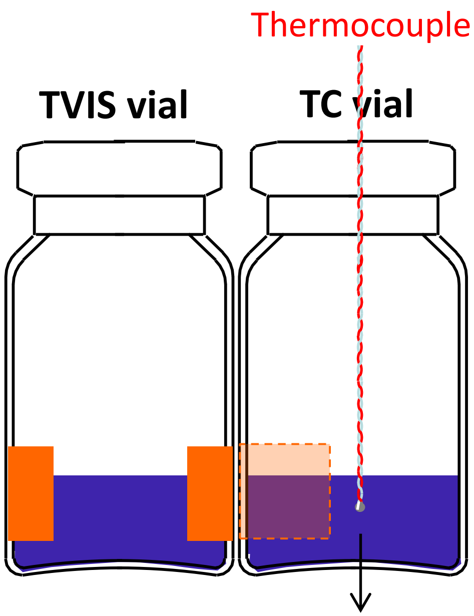
Lyotherm – integrated electrical Impedance (Zsinϕ) and DTA

designed to measure glass transition (Tg'), eutectic (Teu) and melting (Tm) temperatures relevant to freeze-drying fc



Ward & Matejtschuk , 2010 *in Freeze Drying/ Lyophilization of Pharmaceutical & Biological Products* 3rd ed. Rey,L & May JC eds, Informa Press, New York

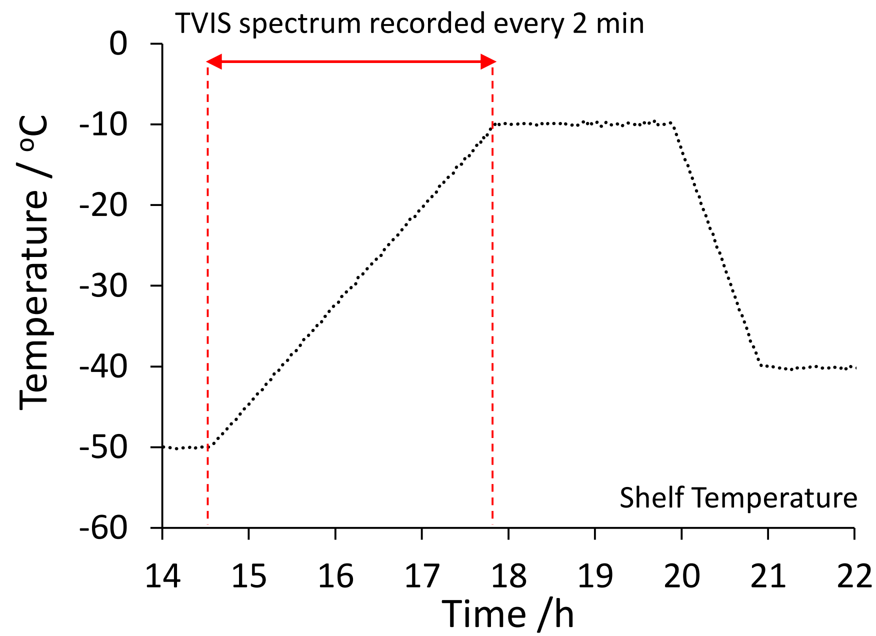
Glass Transition Temperature



TC at the middle of solution bounded within electrode region (defined as **Temperature node**)

Thermocouple position

Re-heating of pre-frozen solution

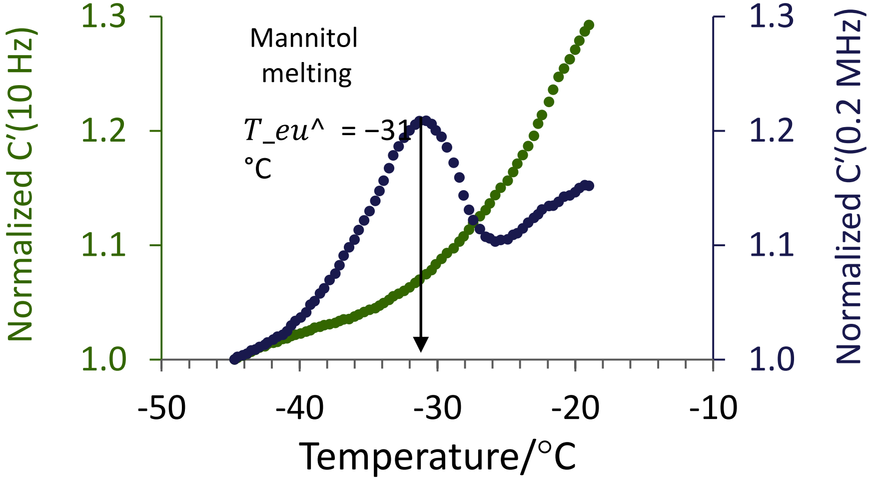


Ramp from -50 °C to -10 °C at 0.2 /min

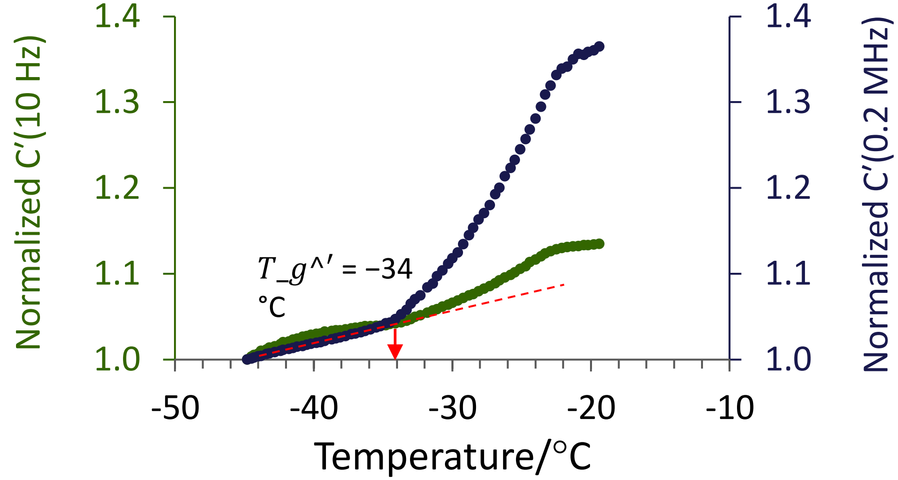
IgG formulations : melt back vs glass transition

NIBSC
Confidence in Biological Medicines

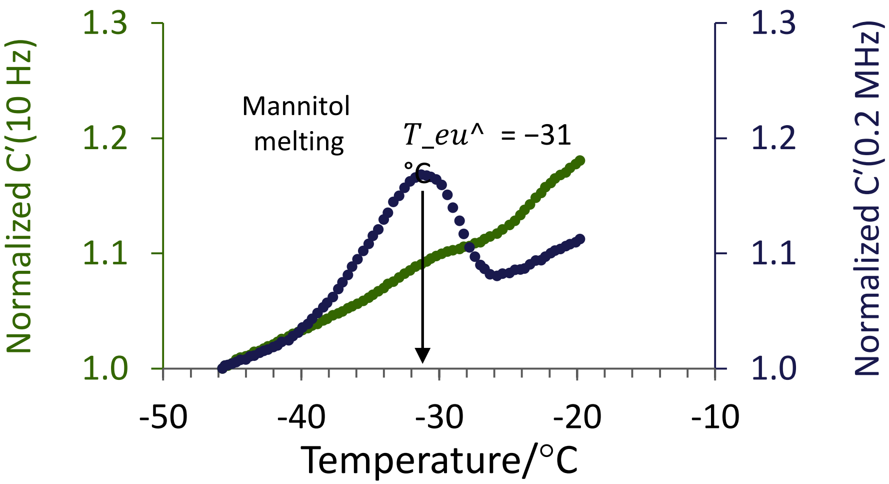
Mannitol+Sucrose based formulation at Edge



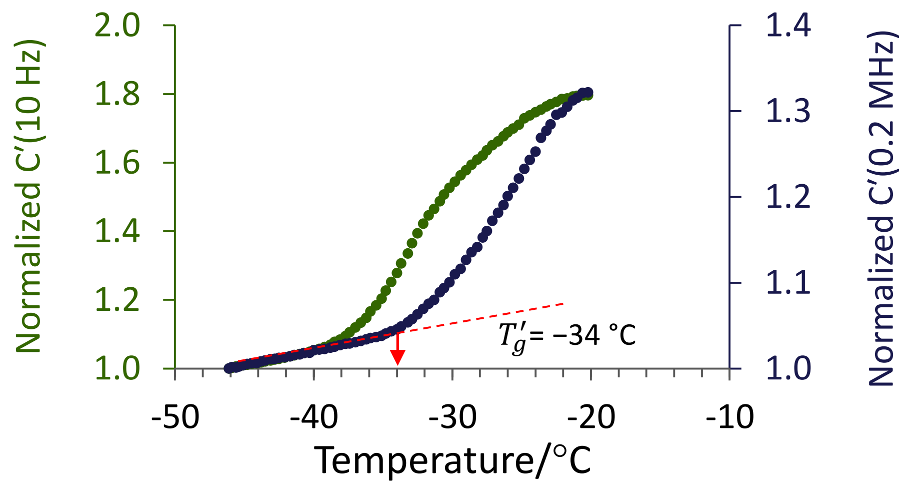
Sucrose based formulation at Edge



Mannitol+Sucrose based formulation at Core



Sucrose based formulation at Core



Conclusions concerning real part capacitance spectrum

- Low frequency dielectric properties of ice
  - Pronounced temperature dependency
  - Determination of the onset of ice formation
  - (and time point when excess thermal energy has dissipated from the system – use in defining start of annealing phase)
- High frequency dielectric properties of ice
  - Negligible temperature dependency
  - Determination of end point of ice crystallization
  - Mono-tonic changes with product temperature reflect changes in viscosity.
  - Discontinuity with product temperature reflect phase changes in the unfrozen fraction. Exploit in a study of the glass transition and/or eutectic melt of the unfrozen fraction.
- Onset and end point of ice crystallization gives rate of ice formation (dm/dt)
- Pre-nucleation data (MW relaxation) predicts the nucleation temperature (T_n)
- dm/dt and T_n (+ soln visc.) control the size distribution of ice crystals and R_p.

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Longinus et al # Poster 18

Mannitol crystallization & melt back

Through Vial Impedance Spectroscopy (TVIS) determination of ice nucleation, growth and crystallization of mannitol during lyophilisation

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International Society for Lyophilisation and Freeze-Drying (ISL-FD) 9th International Conference, Ghent, Belgium 2-6th sept 2019

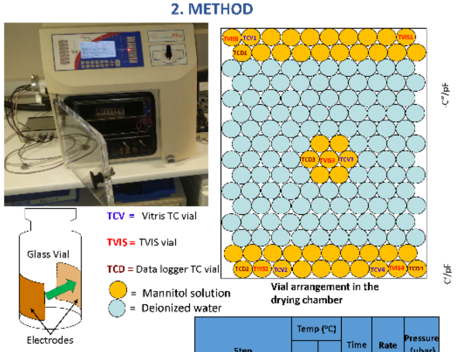
Longinus Ogugua, Geoff Smith, Ahmet Orun, Muyiwa Oyinlola

1. INTRODUCTION

- Mannitol improves mechanical strength of lyophilised product cake and thereby presents with elegant cake structure.
- Primary drying of mannitol-containing formulation must be performed below its critical temperature to avoid melt-back which would result to increase in primary drying time.
- Previous study (Kett et al. 2003) performed offline using DSC, CSM, and XRD showed mannitol crystallizes and melts at -30 °C.
- Online study during actual freeze-drying process may be required to ascertain this behavior in a continuous freeze drying condition.
- TVIS measures material charges across a vial rather than within the vial. It may be used to perform both invasive and online measurement of aqueous frozen mannitol.

AIM: To demonstrate the use of TVIS for online study of thermal transition events including ice growth, crystallization and melting-back of mannitol in aqueous solution during lyophilization process

2. METHOD



- Fill factor, Ø 0.7 used equivalent to 3.5g of solution
- Virtis Advantage Plus Benchtop Freeze dryer
- 5%w/v of 98% D(+)-Mannitol
- TVIS Multi-channel Sciospec

Step	Temp (°C) Start	Temp (°C) End	Time (min)	Rate (°C/min)	Pressure (µbar)
Equilibrium phase	20	20	30		
Freezing ramp	20	-45	120	0.1	
Freezing hold	-40	-45	120	-	
Re-heating ramp	-40	-10	100	0.2	
Re-heating hold	-20	-10	120	-	
Re-cooling ramp	-20	-45	40	0.2	
Re-cooling hold	-40	-45	120	-	
Primary drying equil.	-40	-40	30	-	400
Primary drying ramp	-40	-25	30	0.5	400
Primary drying hold	-25	-25	2500	-	400
Secondary drying ramp	-25	20	225	0.2	400
Secondary drying hold	20	20	480	-	400

Fig.1 Freeze drying instrument and methodology

3. RESULTS

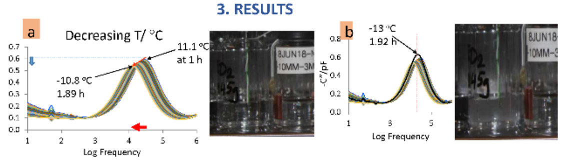


Fig.2 a) demonstrates C''_{PEAK} response to decreasing temperature with time by moving in two directions at a time: 1) lower frequencies (red arrow), and 2) downwards, reducing peak height (blue arrow). b) shows the event at the onset of ice growth depicted by sudden spike of C''_{PEAK} at 1.92 h when product temperature was -13 °C as determined by the temperature calibration of the F_{PEAK}. Evident pictures of the physical process shows that the peak upward spike was accompanied by a change of solution in vials to a cloudy ice matrix from clear solution 3 minutes before the solidification onset.

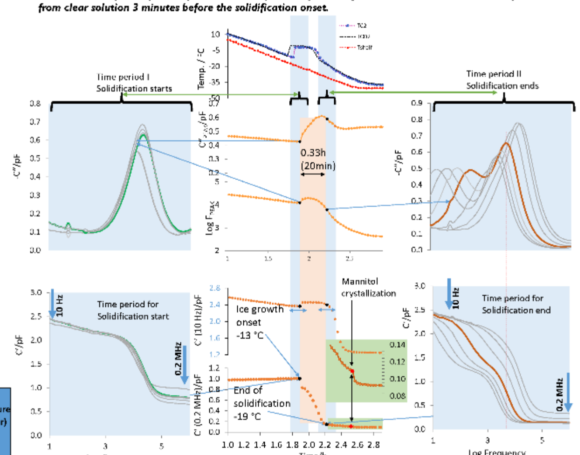


Fig.3 Log F_{PEAK} and C''_{PEAK} with respect to time depict the events that happened 6 min before and after ice growth onset and during the solidification end point. Spectra around the two major events in the freezing process could assist for more understanding of the happenings during freezing process. In addition, capacitance spectra at lower frequency (10 Hz) and higher frequency (0.2 MHz) show the temperature dependence in the lower frequencies.

- Real part capacitance shows response due to ice solidification from its onset to the end of the solidification period
- Lower frequencies are temperature dependent
- Unfrozen concentrate continued to respond to electric current (see fig.3 gradient from 2.2h-2.52h) until mannitol crystallised at 2.52 h

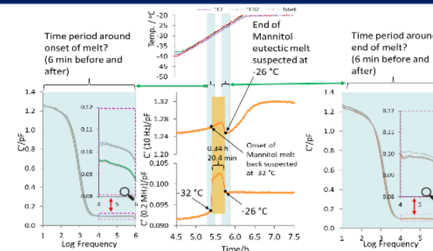


Fig.4 Capacitance and temperature spectrum for mannitol melt during re-heating period

- Fig.3 shows crystallization of mannitol. The black dotted line in fig.3 at 2.52 h sits on the point of crystallization where system experience exotherm. Temperature at this point was -32 °C.
- The change in gradient with time/ temperature after the end of solidification and before crystallization point supports the idea of TVIS response to events due to unfrozen fraction.
- Mannitol crystallization set in at 2.52 h evidenced by a step down in capacitance just 40 min from ice formation onset as shown in fig.3.
- Fig.4 shows TVIS response to the phase behavior of mannitol during re-heating process.
- Melting onset was detected in high frequency at -32 °C, but both the low and high frequencies agreed to the melt-back endpoint at -26 °C.
- Dielectric property of the TVIS vial and contents at 10 Hz is temp. dependent, the frequency is good for demonstrating the changes in temperature during freezing.
- But the dielectric properties at 0.2 MHz are dominated by the properties of the solution and insensitive to ice temperatures, hence good for determining the end of ice formation.
- Duration between the onset of ice growth and the solidification end-point is 20 min while the ice growth onset temperature is -13 °C.

4. CONCLUSIONS

- TVIS has demonstrated ability as an efficient non-invasive and real time PAT tool for determination of ice growth, crystallization and melting back of mannitol in aqueous solution during lyophilization.

5. SIGNIFICANCE

- In process development, freezing characteristics of materials are important as it impact process outcome
- Prediction of freeze drying parameters at the early stage of the process can inform decision making for production
- This investigation employed TVIS system to confirm thermal transformation events of mannitol in sub-ambient condition

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- National Institute for Biological Standards and Control
  - Paul Matejtschuk (IgG TVIS data)

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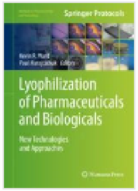

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Through Vial Impedance Spectroscopy (TVIS): A Novel Approach to Process Understanding for Freeze-Drying Cycle Development

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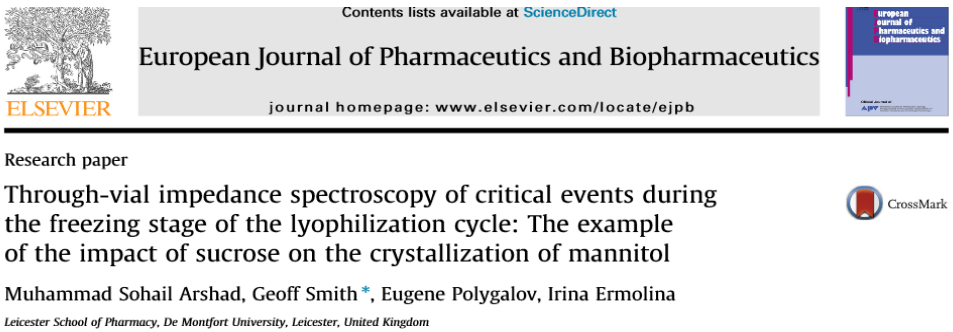
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Research paper

Through-vial impedance spectroscopy of critical events during the freezing stage of the lyophilization cycle: The example of the impact of sucrose on the crystallization of mannitol

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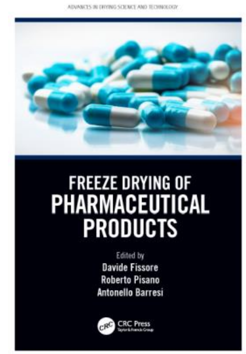

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