Novel impedance-spectroscopy process analytical technology for freeze drying process development

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Analytical challenges and solutions for medicines manufacturing towards Industry 4.0 event
KTN meeting at CPI, Darlington, 26 February 2020 13:55 – 14:15

Knowledge Transfer Network
Medicines Manufacturing
Challenge Community

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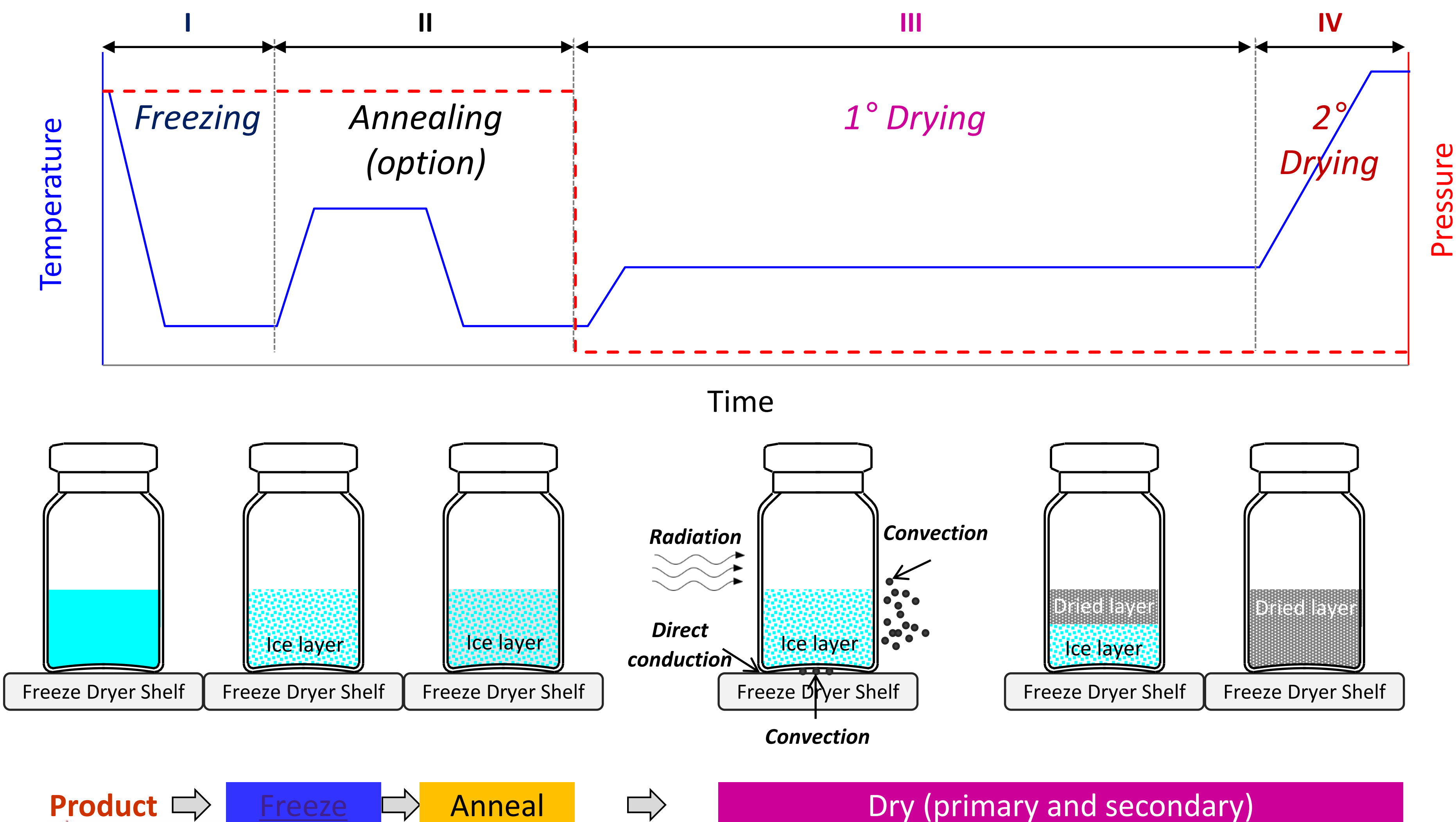
Global Sales of Top 10 Lyophilized Drug Products

The prevalence of stability challenges for complex APIs and biologics has resulted in more pharmaceutical and biotech manufacturers turning to lyophilization resulting in 13.5% annual growth in freeze-drying over the last five years.

Product Name	API	Indication	Owner	Estimated 2018 Product Sales
Herceptin IV	Trastuzumab	Cancer	Genentech	$7.2B
Keytruda	Pembrolizumab	Cancer	Merck and Co.	$7.2B
Remicade	Infliximab	Rheumatoid Arthritis, Crohn's Disease	Janssen Biotech	$6.4B
Botox	Daxibotulinumtoxin A	Various	Allergan	$3.6B
Carimune NF	Immunoglobulin	Immunodeficiency	CSL Behring	$3.3B
Xolair	Omalizumab	Asthma	Genentech	$3B
Orencia	Abatacept	Rheumatoid Arthritis	Bristol-Myers Squibb	$2.9B
Cosentyx	Secukinumab	Plaque Psoriasis	Novartis AG	$2.8B
Avonex	Interferon beta-1a	Relapsing MS	Biogen	$2.4B
Velcade	Bortezomib	Cancer	Takeda	$2.3B

https://lubrizolcdmo.com/blog/lyophilization-of-pharmaceuticals-an-overview/

Freeze-drying



Presentation Brief

1. Analytical techniques for medicines manufacturing
2. How the techniques used are being or can be applied in actual real-life processes
3. Where the measurement strategies replace/bring efficiencies in the control strategy for medicines above traditional testing strategies

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- Impedance spectroscopy
  - Z-FDM : Suitable for small scale formulation development

  - TVIS : Scale-able to process development

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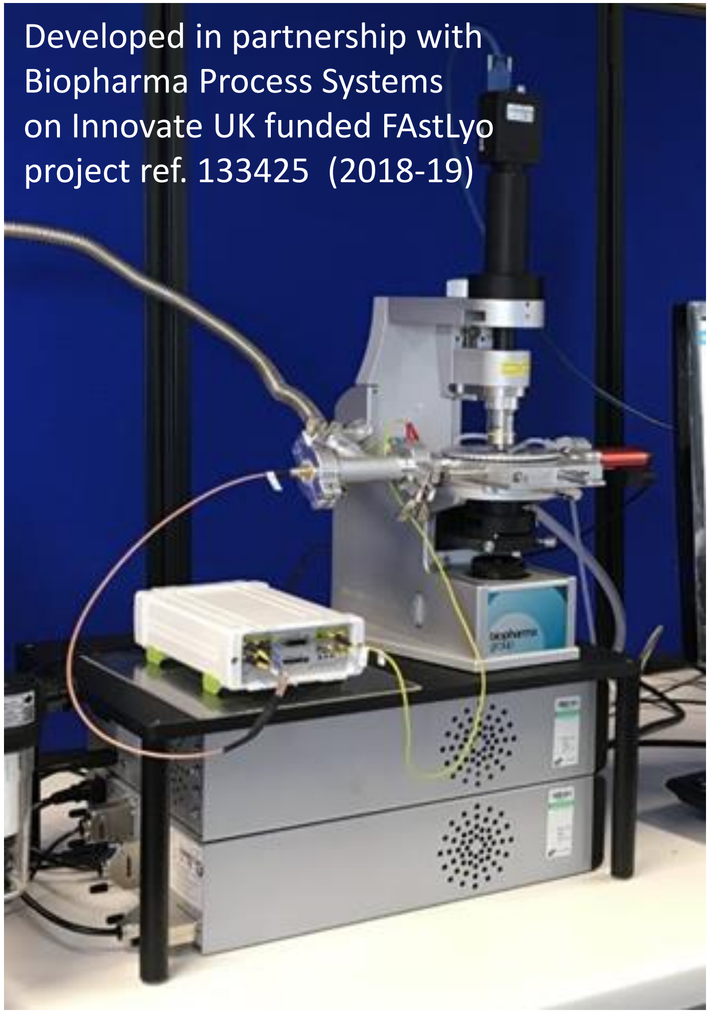

Application : objective assessment of thermal processes (crystallization, glass transition, collapse temperature) for **formulation Development**

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Application : In-vial assessment of multiple process parameters for **process development and scale up**

TVIS (Through-Vial Impedance Spectroscopy) was developed in partnership with GEA Pharma Systems on Innovate UK funded LyoDEA project (2010-13)

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Traditional testing – Formulation Dev.

- Relies on separate technologies, i.e.
  - Freeze-drying microscope for T_c
  - DSC for T_g and T_{eu}
- Disadvantages
  - Multiple techniques
    - FDM is subjective
  - One sample at a time
  - Not saleable to High-through-put

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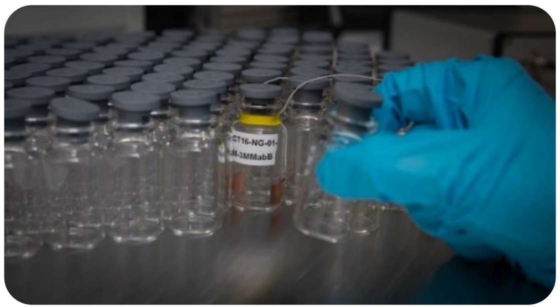
Traditional testing – Process Dev.

- Indirect estimates of critical temperatures based on calculations that have assumptions.
- Many tools provide ‘batch average’ information
  - does not provide the resolution needed to understand the process variations across batch of vials.

Through Vial Impedance Spectroscopy

Single Vial PAT

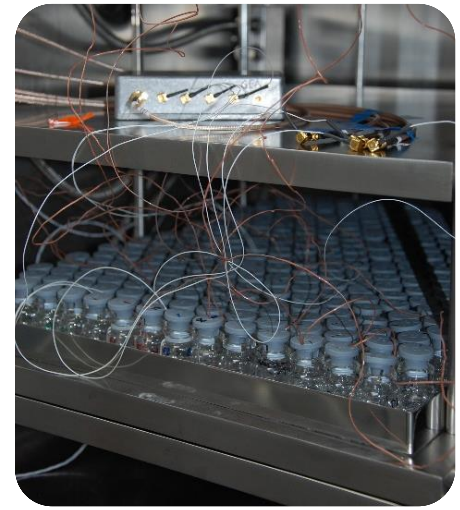
Non- perturbing to packing of vials



Thin flexible cables (0.5 - 2 m)

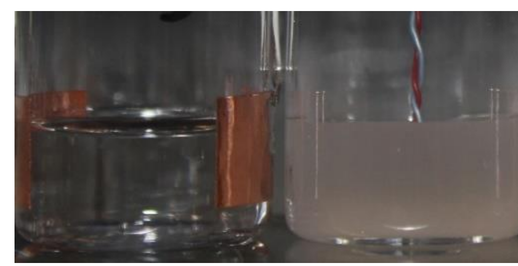
- Stoppering unaffected

Multichannel



Temperature calibration

- using nearest neighbour vial(s)



Non-sample invasive

- no impact on ice nucleation

Low thermal mass of electrodes

- no interference with heat transfer & drying rates

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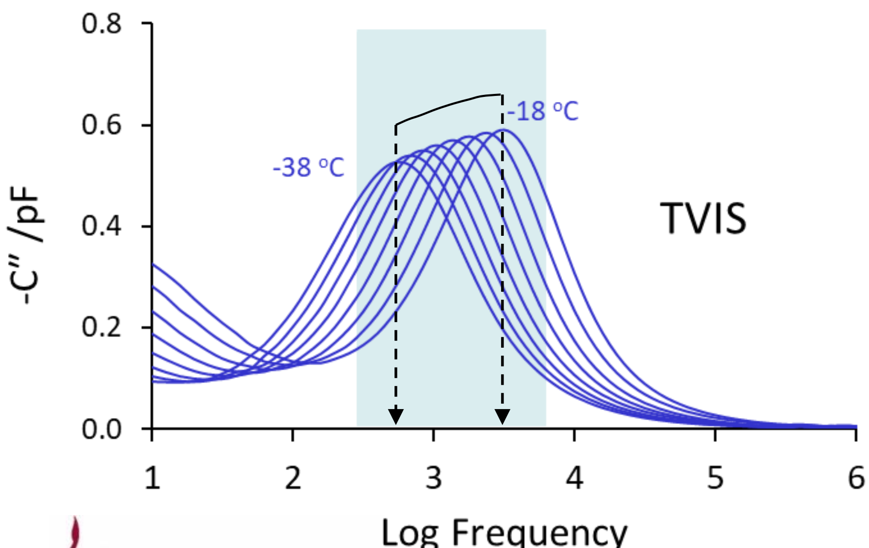
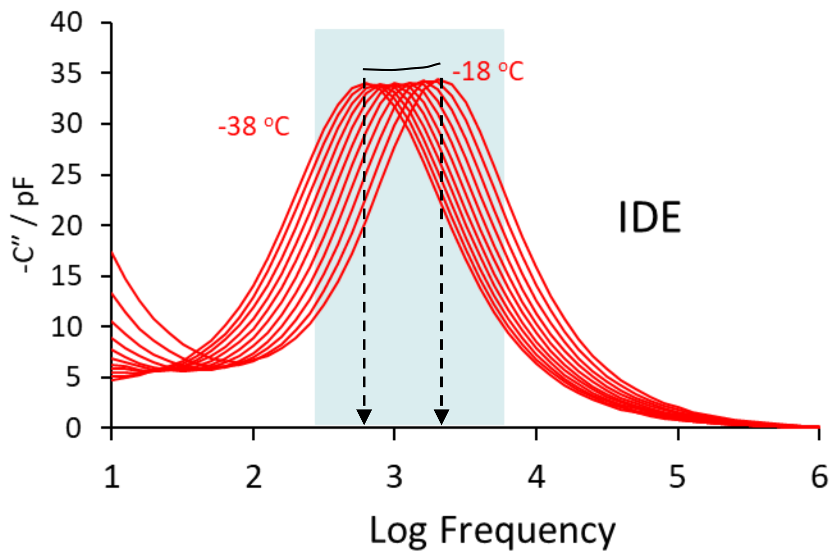
Dielectric relaxation of ice

5 mL water in
10 mL glass TVIS vial
(1 pair of 10/19 mm height/width electrodes)

2 μL water over IDE
(90 pairs of gold interdigitated electrodes)





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Freezing step

Nucleation onset

Solidification end point

Solidification period

Nucleation temperature

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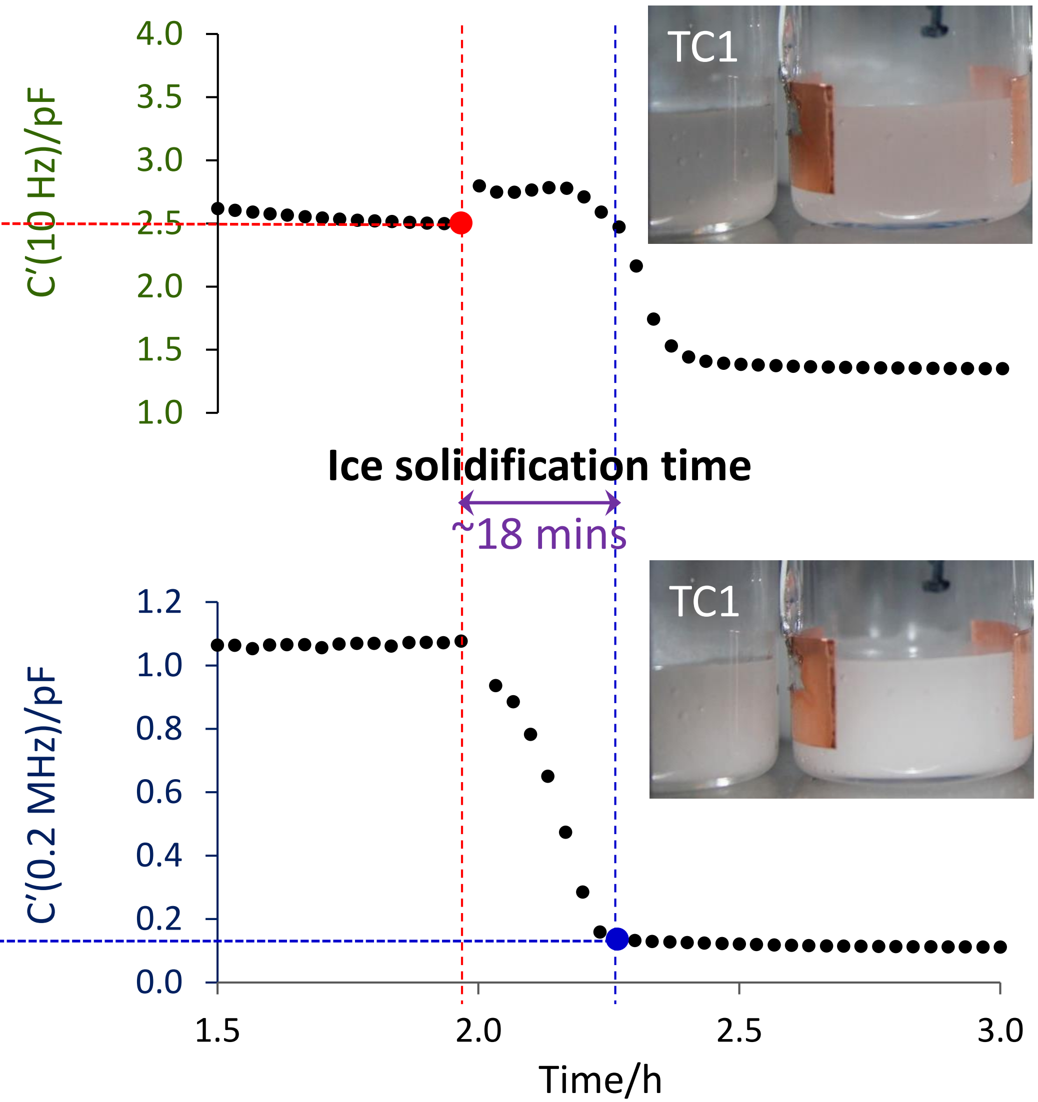
BACK to outline

Solidification 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



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

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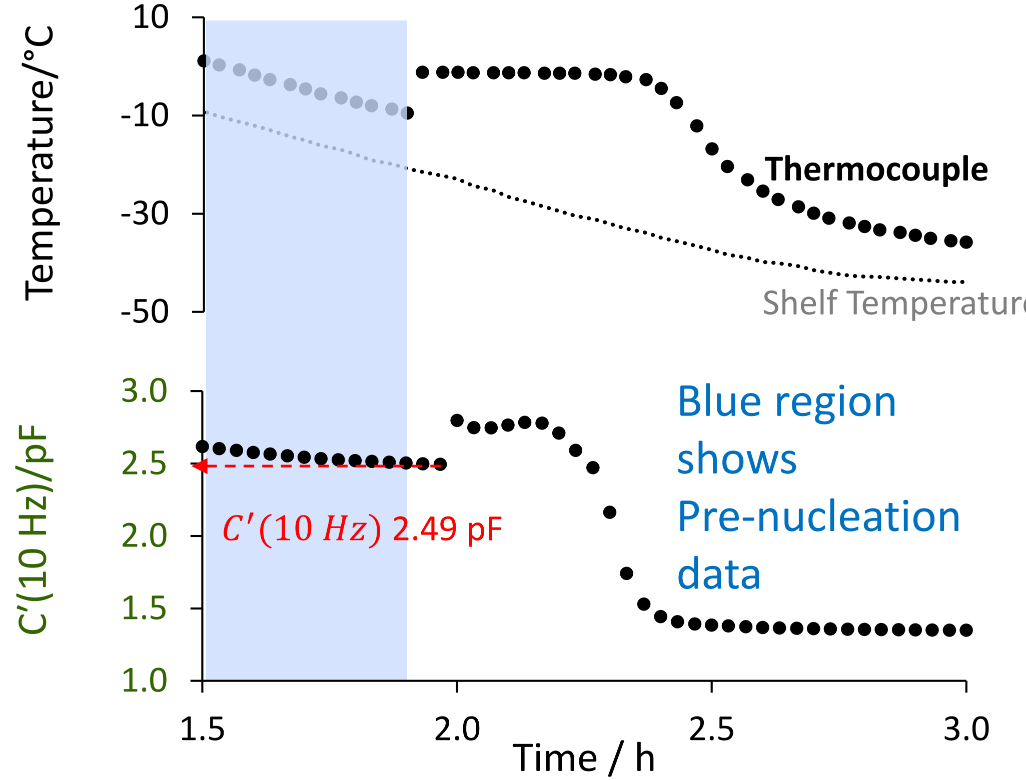
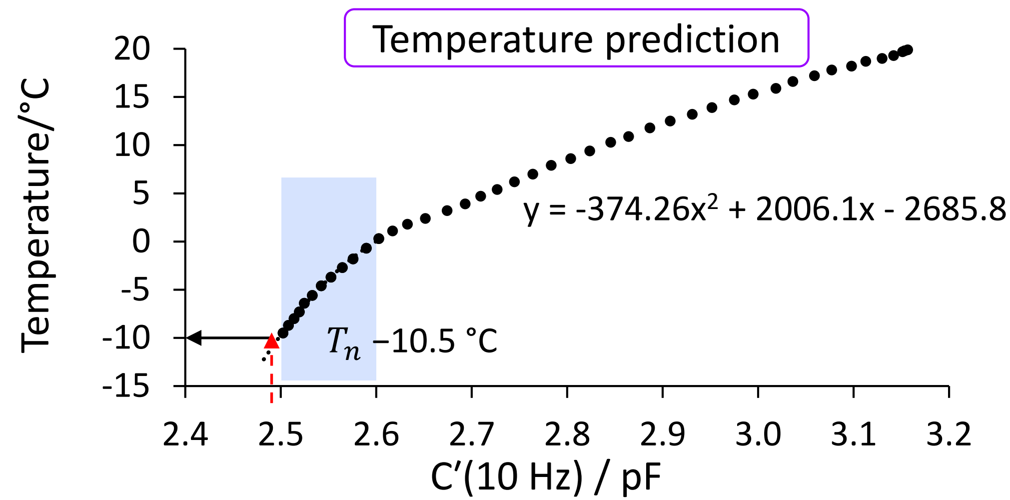
Nucleation Temperature

- 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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BACK to Freezing

Annealing

- Structural modification
- Glass transition
- Crystallization
- Completion of annealing

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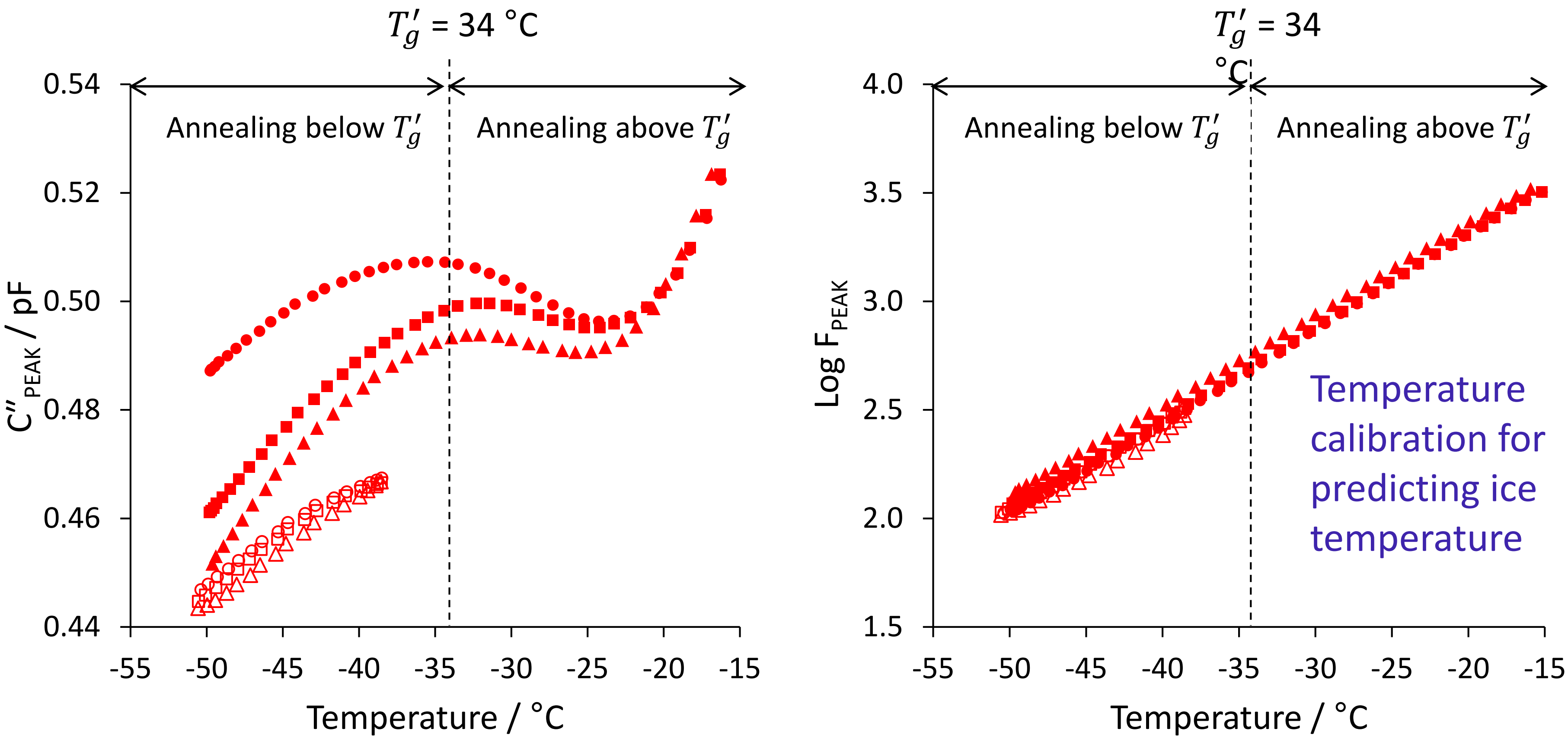
BACK to outline

Structural Modification

5% Sucrose solution



Closed symbols demonstrated the data when the sample was heated above its glass transition of freeze concentration (T_g' = -34°C) whereas the product which annealed below transformation points of -35 °C were represented by *open symbols*. Circle, square and triangle are 1st, 2nd and 3rd re-heating accordingly

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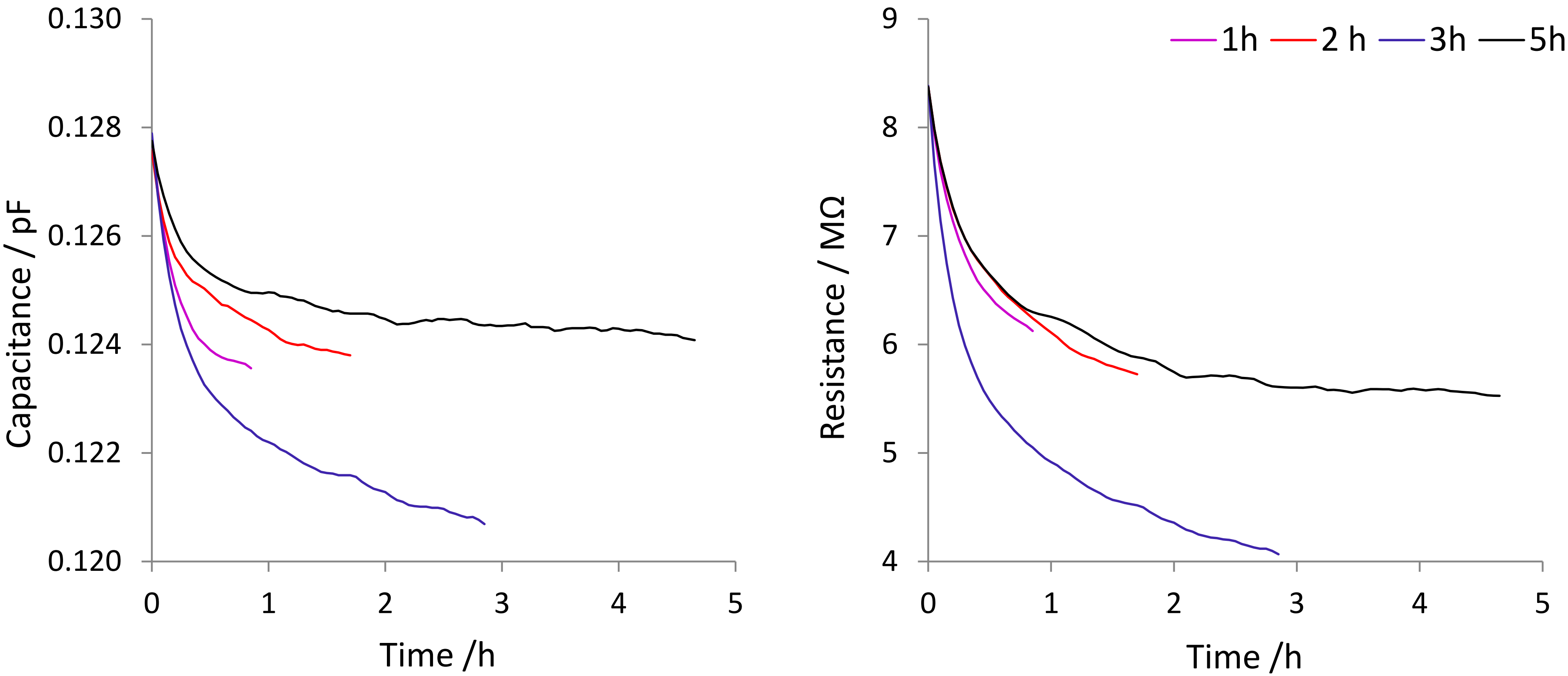
BACK to Annealing

Investigations of annealing times

10% Maltodextrin



- The capacitance of the formulation changes minimally while the resistance changes significantly and plateaus at 3-4 h
- After 3h annealing hold time, both the capacitance and drying time changes insignificantly

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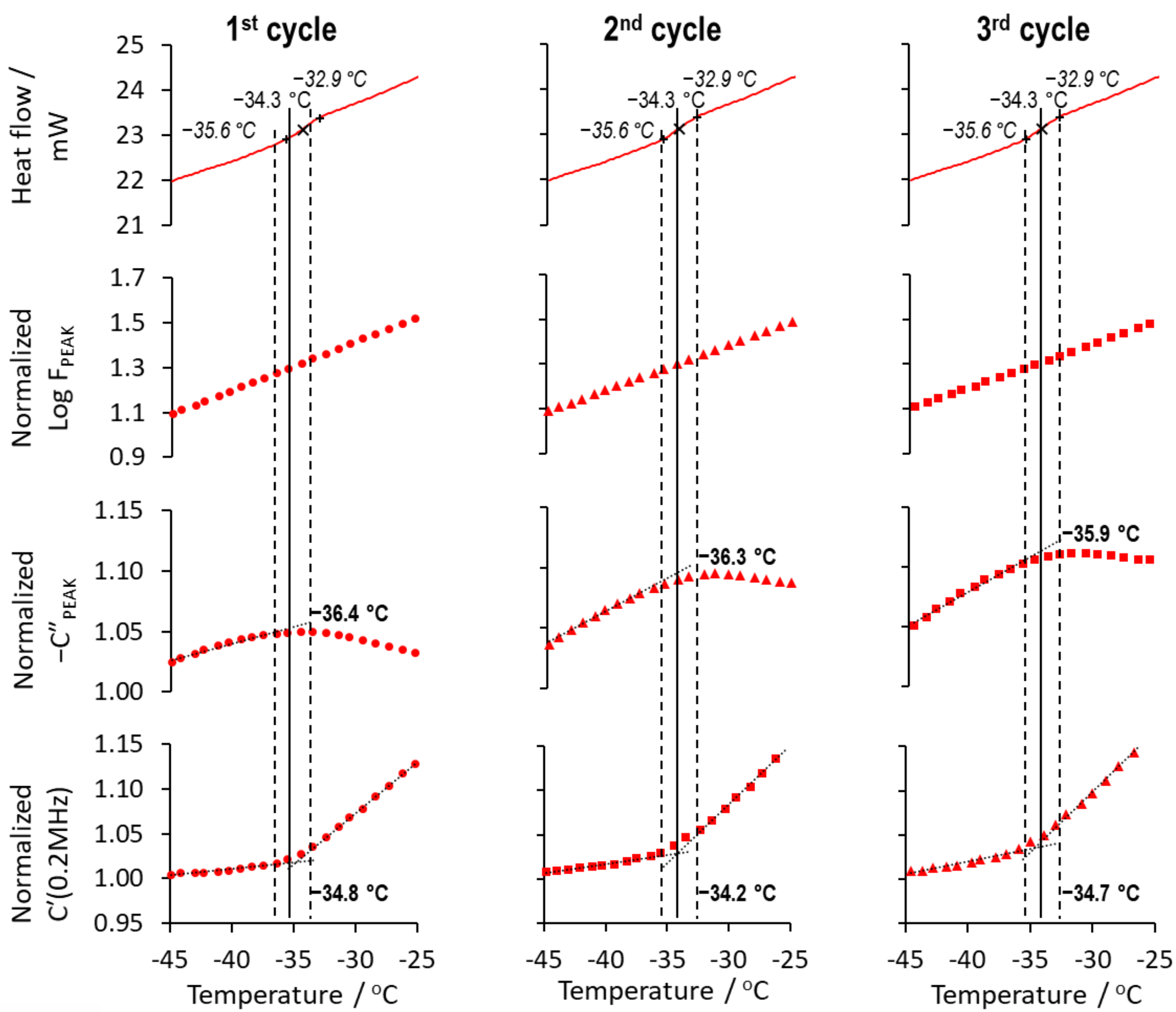
BACK to Annealing

Glass transition 5% Sucrose solution



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BACK to Annealing

Freezing and annealing of mannitol-sucrose

Freezing man-suc solution

Crystallization in man-suc formulations

Re-crystallization events

Change in crystal structures

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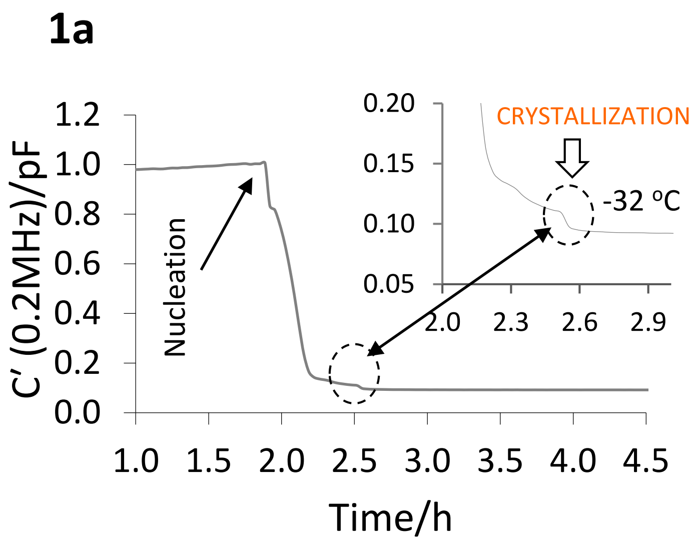
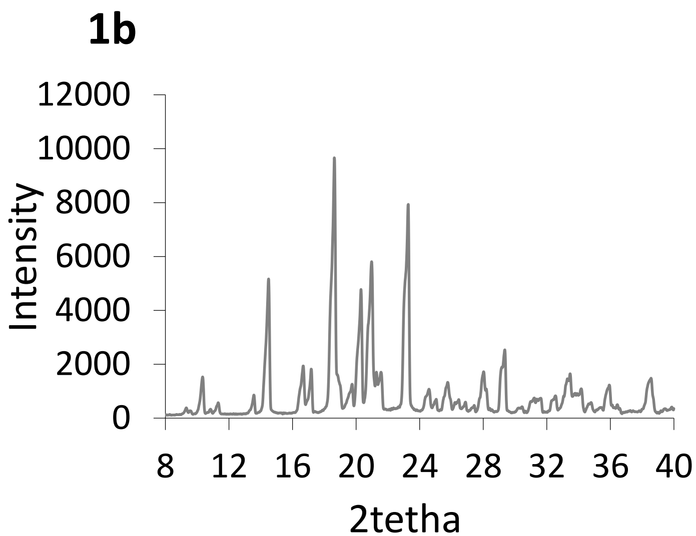
Crystallization events at freezing step for 5% mannitol

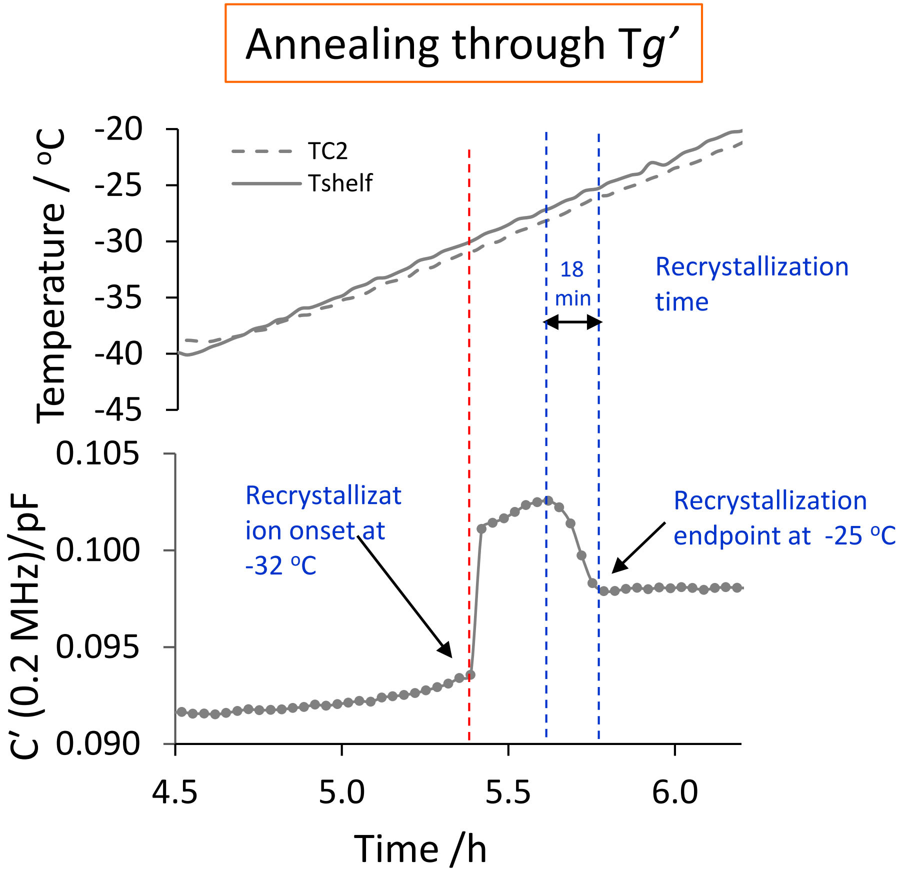




TVIS and XRD results for solution of 5% mannitol showing crystallization detected by TVIS

BACK to Drying

Re-crystallization on annealing step for 5% mannitol



On annealing to −20 °C $C'(0.2MHz)$ shows mannitol recrystallization with onset at – 32 °C end point at – 25 °C

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Primary drying

- Product temperature
- Sublimation rate
- K_v
- Primary drying endpoint
- R_p
- Collapse event

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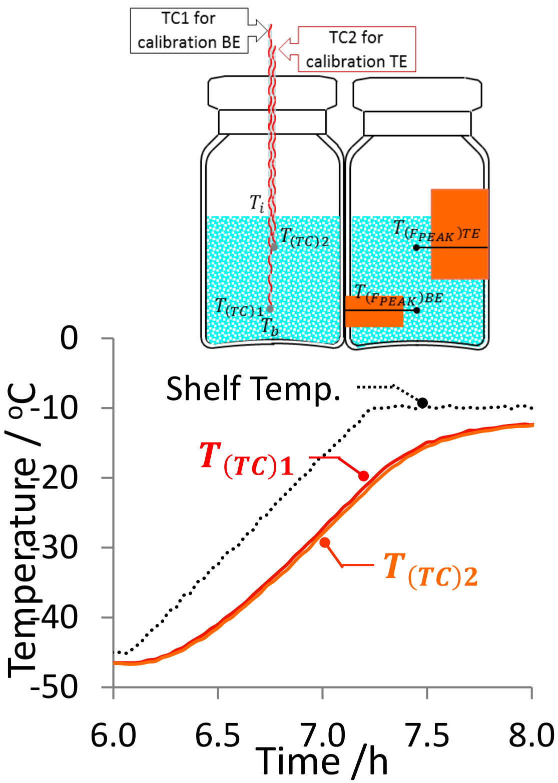
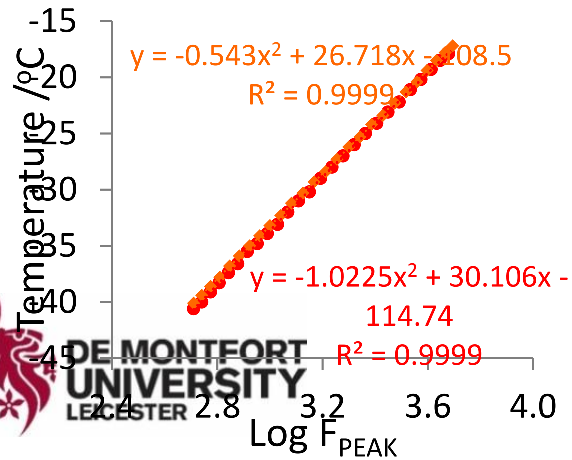
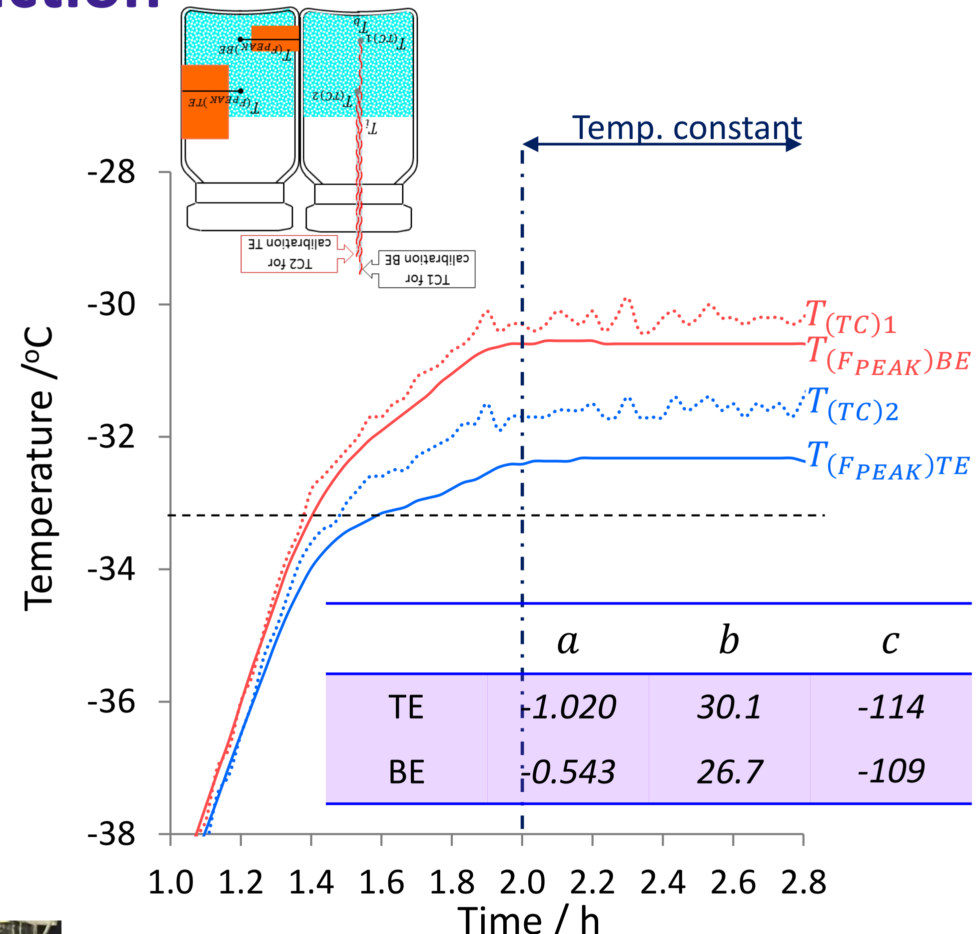
Product temperature prediction





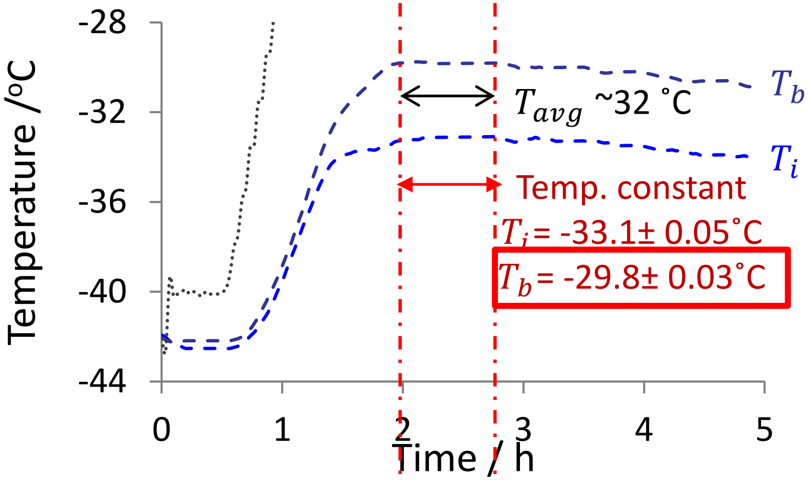


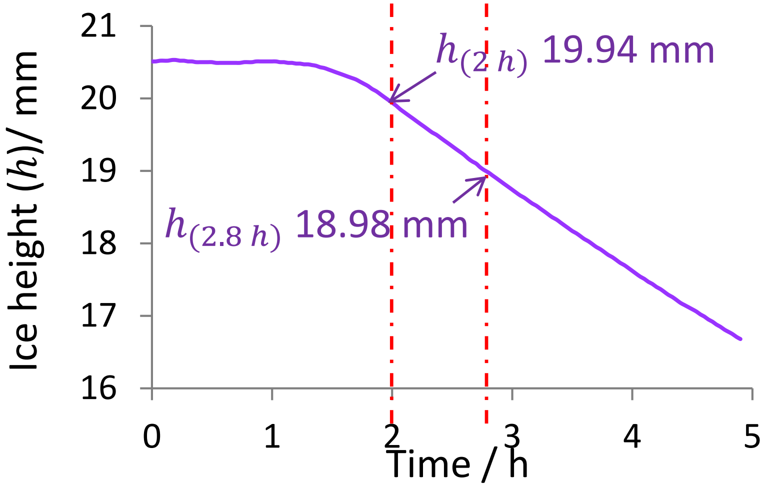
	a	*b*	*c*
TE	*-1.020*	*30.1*	*-114*
BE	*-0.543*	*26.7*	*-109*

The product temperature predicted by TVIS can demonstrate the temperature gradient across ice cylinder height

BACK to Drying

Drying Rate Estimation Pure ice





- Drying rate during the steady state

$$\boxed{Drying\ rate\ (\frac{\Delta m}{\Delta t}) = \rho_i \cdot A \cdot \frac{h_{(t1)} - h_{(t2)}}{t_2 - t_1}}$$

Ice density (ρ_i) at -32˚C = 0.920 g·cm^{-3}
(Calculated ice temperature between T_i & T_b)
Internal vial diameter (VC010-20C) = 2.21 cm
Cross-section area (A) = 3.80 cm^2
Ice height at 2 h ($h_{(2\ h)}$) = 19.94 mm
Ice height at 2.8 h ($h_{(2.8\ h)}$) = 18.98 mm

TVIS parameters used for determination:
$\frac{\Delta m}{\Delta t}$ = 0.42 g·h^{-1}
T_b= -29.8˚C

$$Drying\ rate\ = 0.920\ g \cdot cm^{-3} \times 3.80\ cm^2 \times \frac{(19.94 - 18.98) \times 10^{-1} cm}{(2.8 - 2.0)\ h}$$

$$\boxed{= \mathbf{0.42\ g \cdot h^{-1}}}$$

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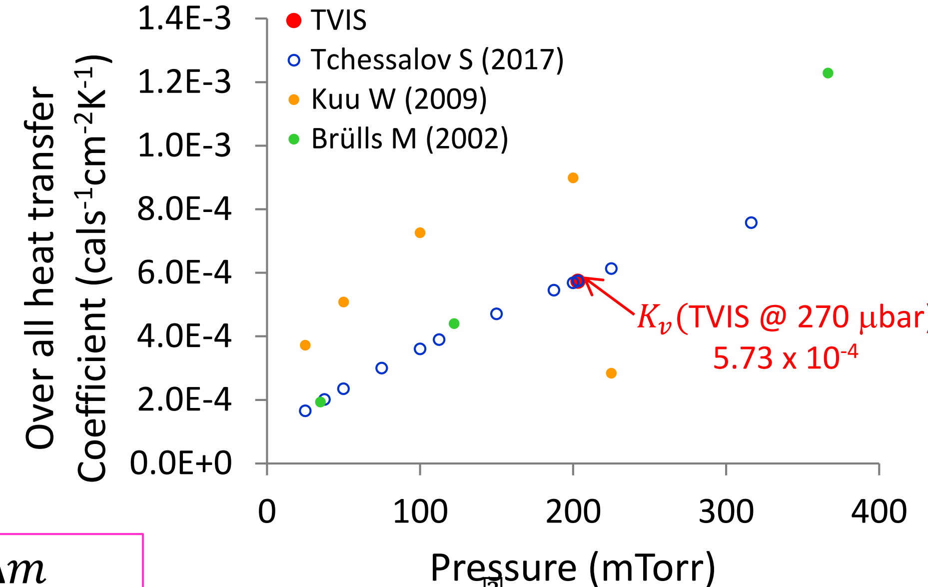
Heat Transfer Coefficient (K_v)Determination

Pure ice

Parameters	TVIS
Drying rate at steady state (g/h) (2-2.8 h into primary drying)	0.42
Shelf Temperature, T_s (K)	273.3
Vial's base Temperature, T_b(K)	243.3



$$L\frac{\Delta m}{\Delta t} = A_e K_v (T_s - T_b) \Rightarrow \boxed{K_v = \frac{L\frac{\Delta m}{\Delta t}}{A_e(T_s - T_b)}}$$

L is the latent heat of sublimation of ice (2844 J·g^{-1} or 679.7 cal ·g^{-1}) and A_e is external cross-sectional area of the base of the TVIS vial (4.62 cm^2)

$$K_v(270\quad bar) = \frac{L\frac{\Delta m}{\Delta t}}{A_e(T_s - T_b)}$$

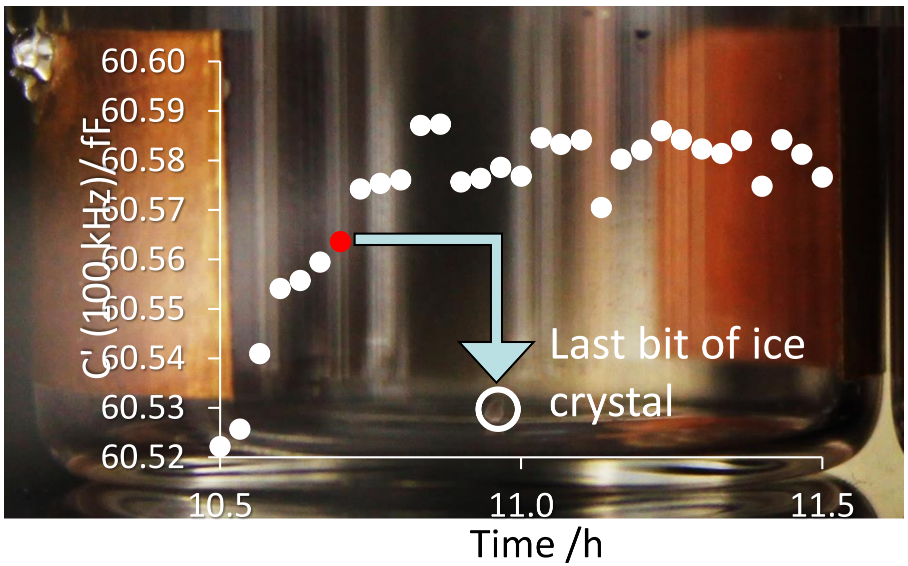
$$= \frac{679.7\ cal \cdot g^{-1} \times 0.42\ g \cdot h^{-1}}{4.62\ cm^2 \times (273.3 - 243.3)K}$$

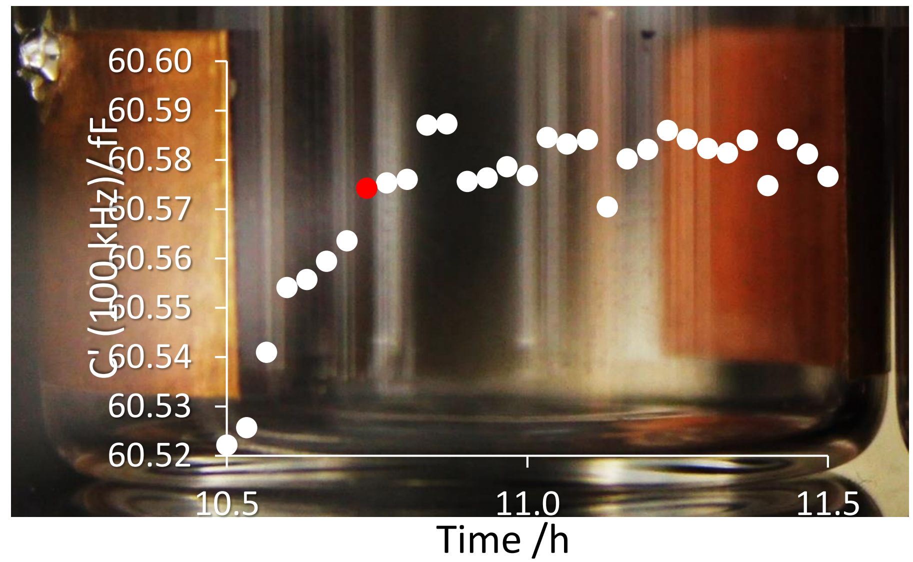
$$= 2.06\ cal \cdot h^{-1} \cdot cm^{-2} \cdot K^{-1}$$

$$= 5.73 \times 10^{-4} cal \cdot s^{-1} \cdot cm^{-2} \cdot K^{-1}$$

$$\boxed{K_v(270\ \mu bar) = 5.73 \times 10^{-4} cal \cdot s^{-1} \cdot cm^{-2} \cdot K^{-1}}$$

Primary Drying Endpoint
Pure ice





- End point determine by high frequency real part capacitance (i.e. 100 kHz for ice)
- Endpoint where C' (100 kHz) reaches plateau

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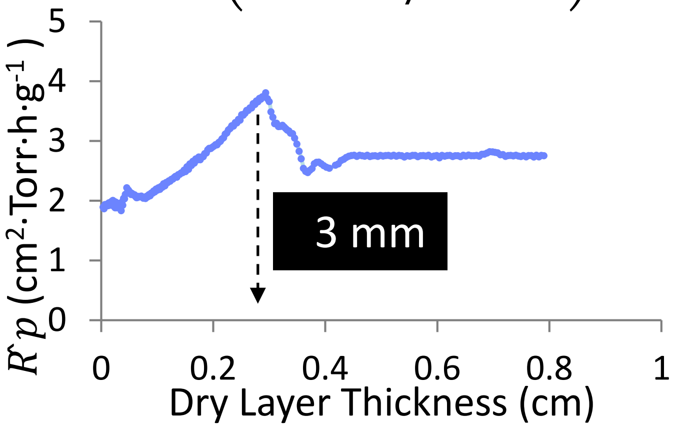
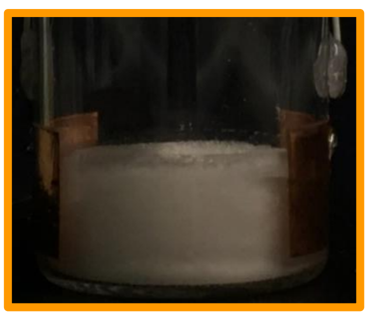
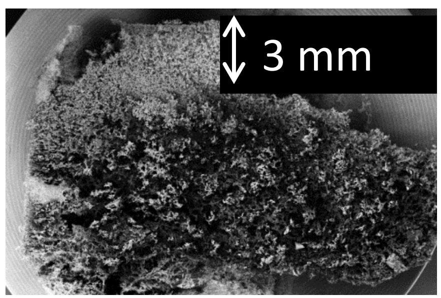
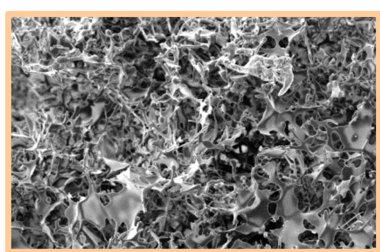
Dried product resistance (R_p) 5% Lactose

$$\hat{R}p = \left(\frac{P_{ICE} - P_{CHAMBER}}{dm/dt}\right) \cdot A_P$$

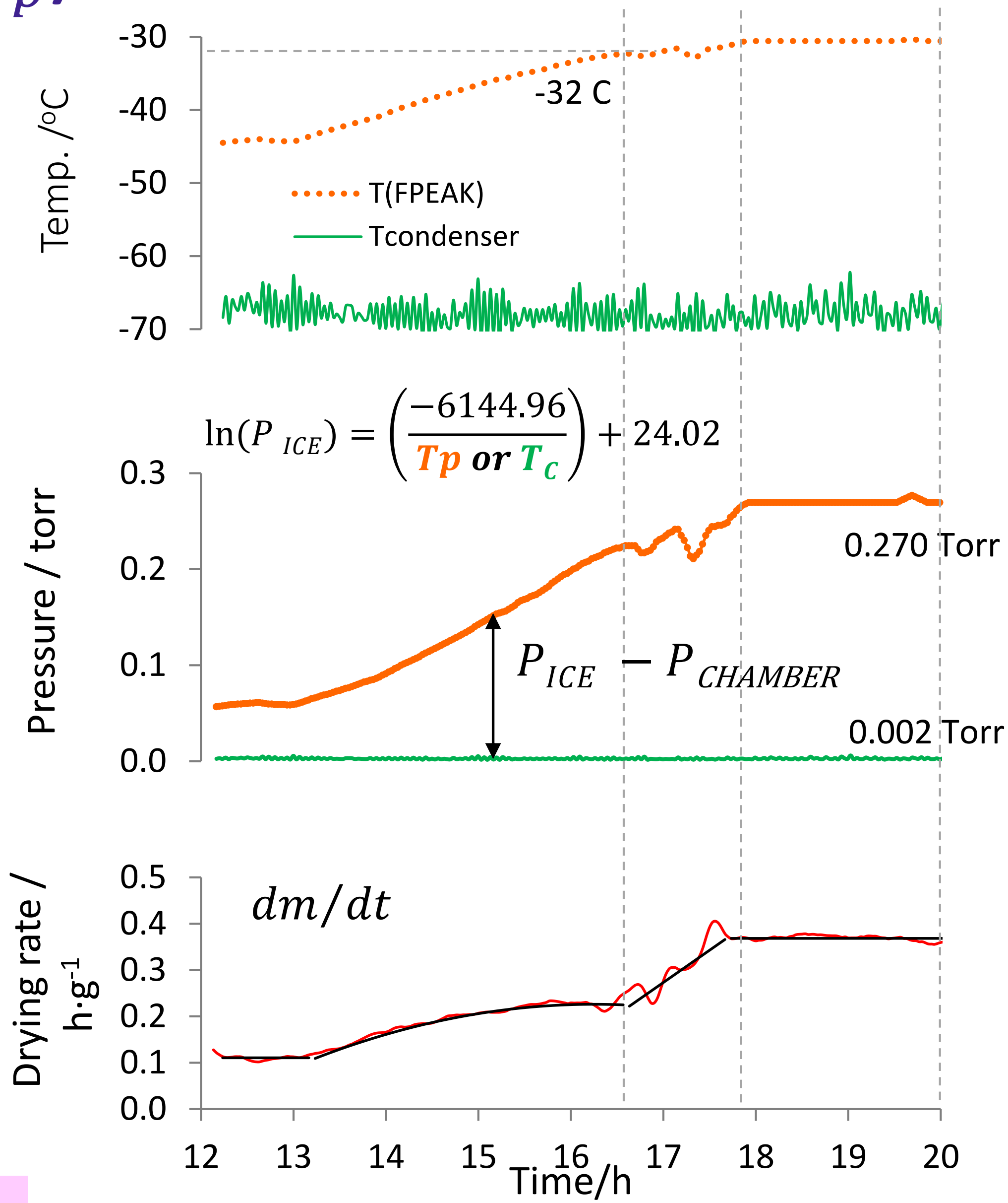








Middle layer micro-collapse



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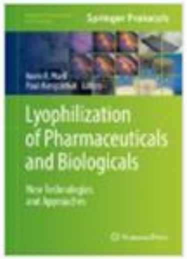
Further Reading



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)

Further Reading

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

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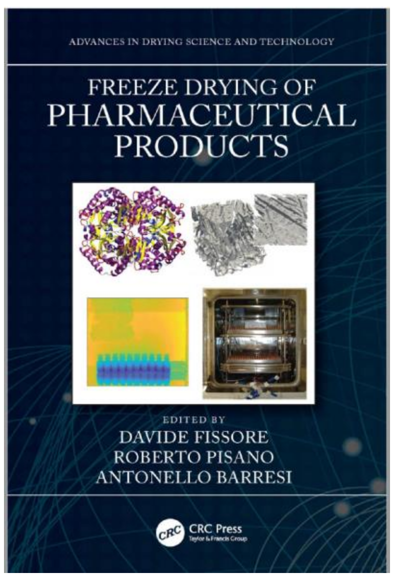

Freeze Drying of Pharmaceutical Products

1st Edition

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