Non-invasive impedance spectroscopy for single-vial PAT in biopharmaceutical freeze-drying

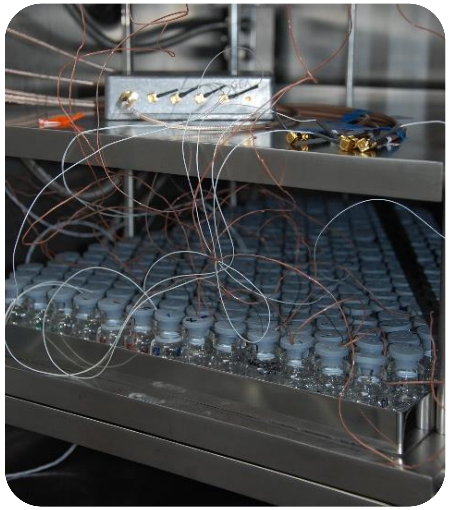
Prof. Geoff Smith

In collaboration with NIBSC

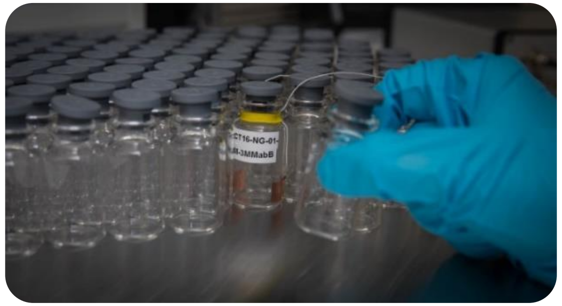
Through Vial Impedance Spectroscopy

Single Vial PAT

Multichannel



Non- perturbing to packing of vials



Thin flexible cables (0.5 - 2 m)

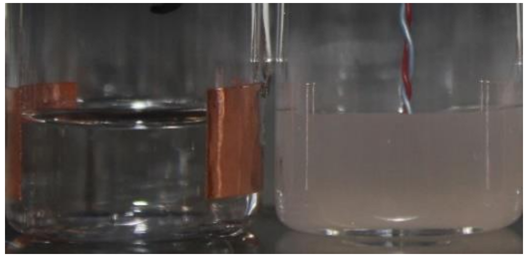
- Stoppering unaffected

Temperature calibration

- using nearest neighbour vial(s)

Low thermal mass of electrodes

- no interference with heat transfer & drying rates



Non-sample invasive

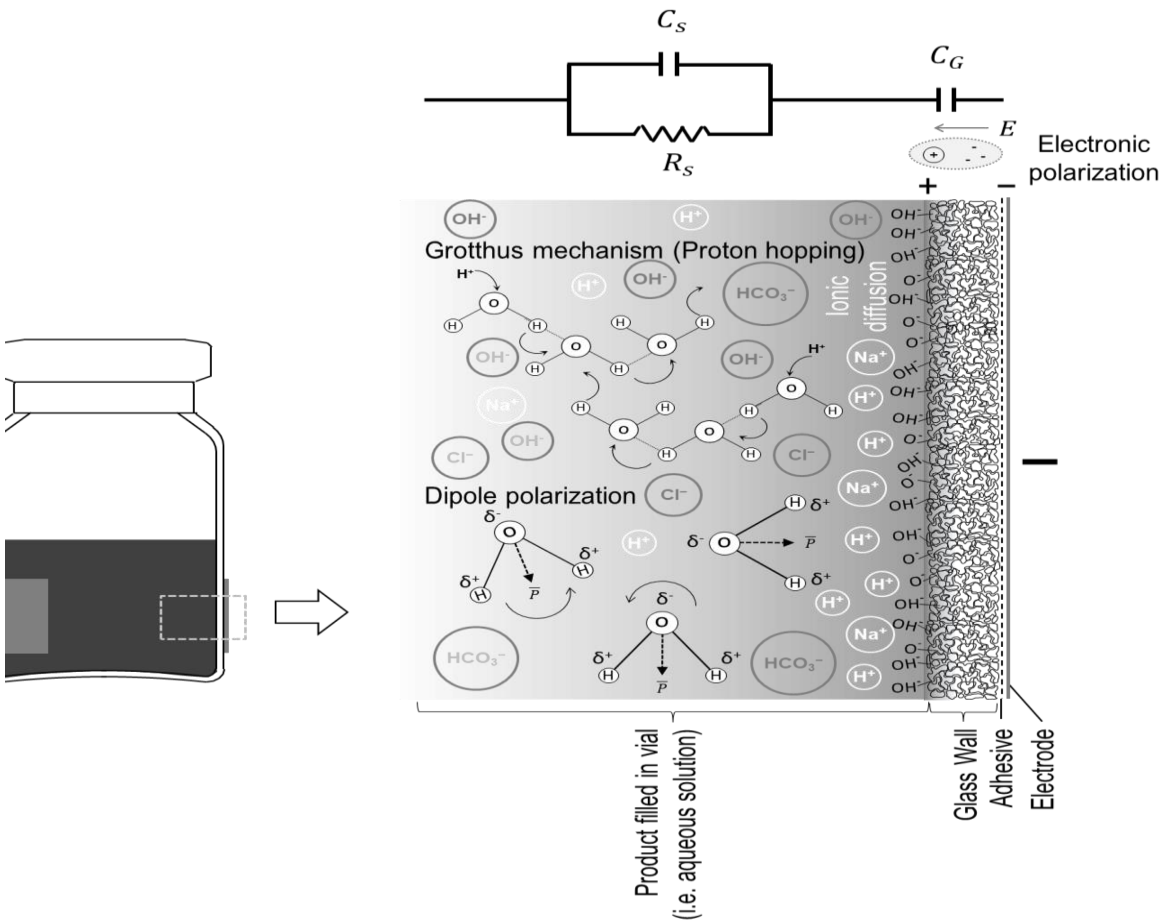
- no impact on ice nucleation

Junction box

TVIS theory

Electrical impedance and material attributes

Liquid state (Maxwell-Wagner)



Features

Relaxation frequency

- Strongly dependent on the conductivity of the solution
- Hence dependent on temperature

Dielectric permittivity

- Constant across the TVIS specrum

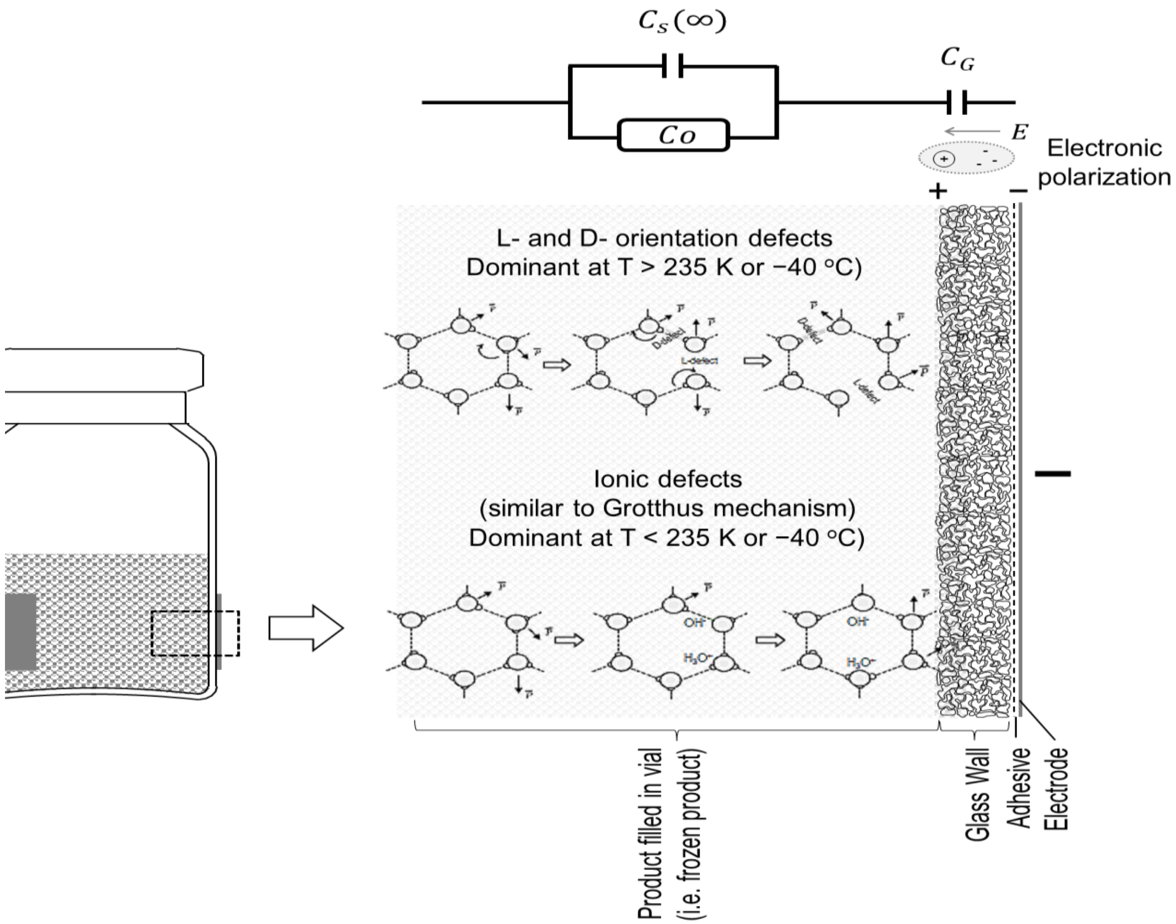
Electrical impedance and material attributes

Features

Relaxation frequency

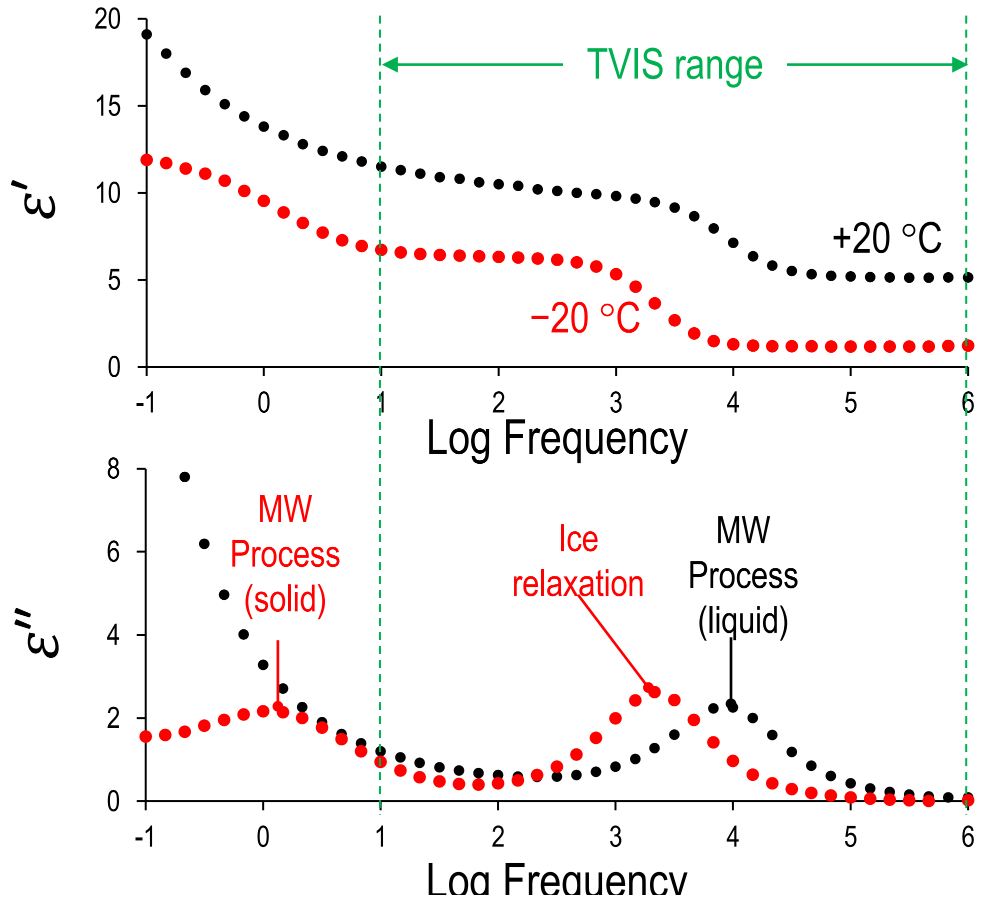
- Solid state (frozen) MW process shifts to low frequency
- The dielectric relaxation of ice appears
- Dielectric permittivity
  - ~ 100 at low frequency
  - ~ 3 at high frequency

Frozen state (dielectric relaxation)



Electrical impedance and material attributes

Maxwell-Wagner & ice relaxation



TVIS vial on cradle

To be placed in the cryostat

of Novocontrol BDS

Overview

TVIS temperature calibration	→ Temperature prediction in primary drying
Phase behaviour of the solid/solute fraction	→ Glass transitions and devitrification
Characterization of critical process parameters	→ Primary-drying end-point

CASE STUDY 1

TVIS temperature calibration

Method 1 : Triangulation

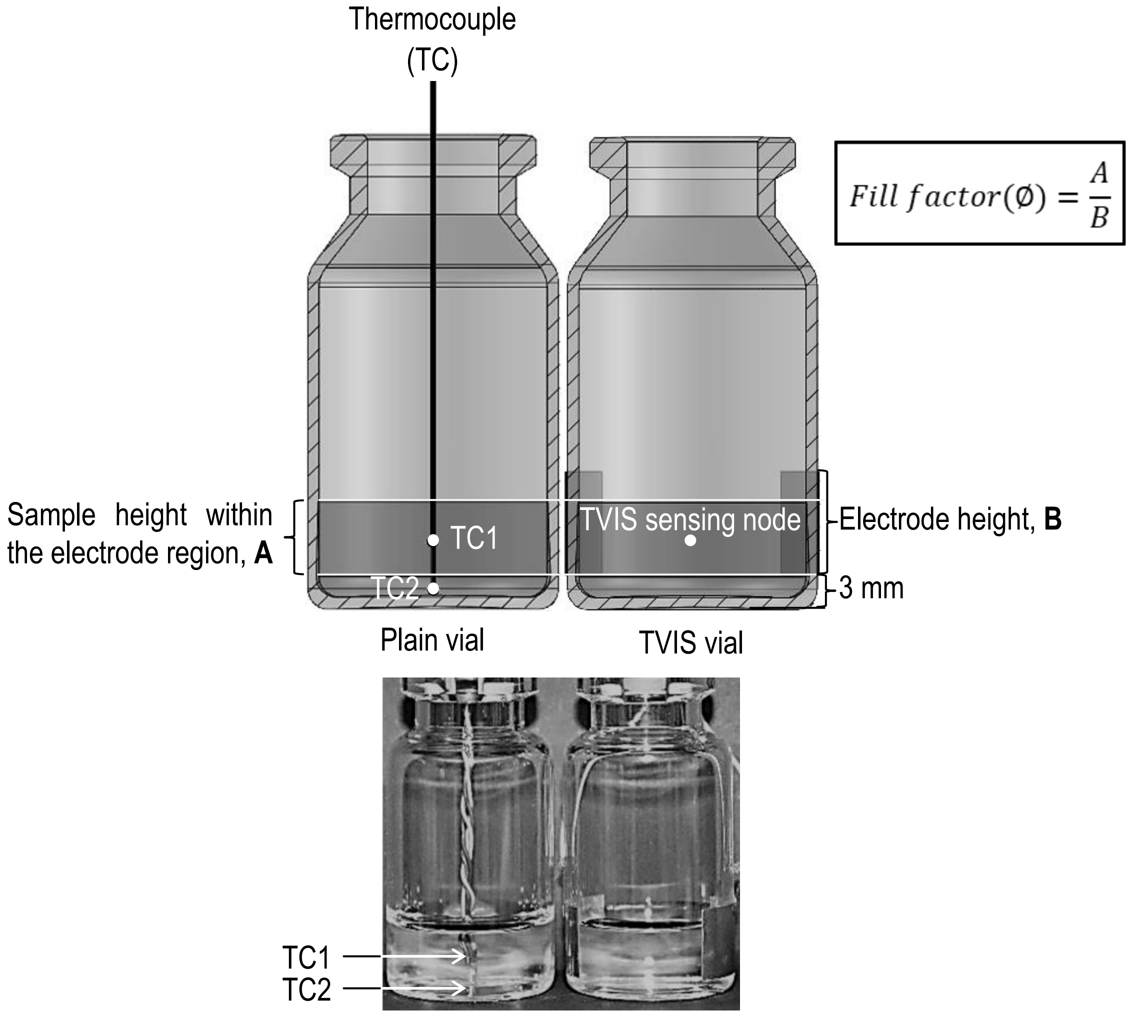
Mehod 2 : Tempris®

1. Triangulation method

TC in nearest neighbour vial

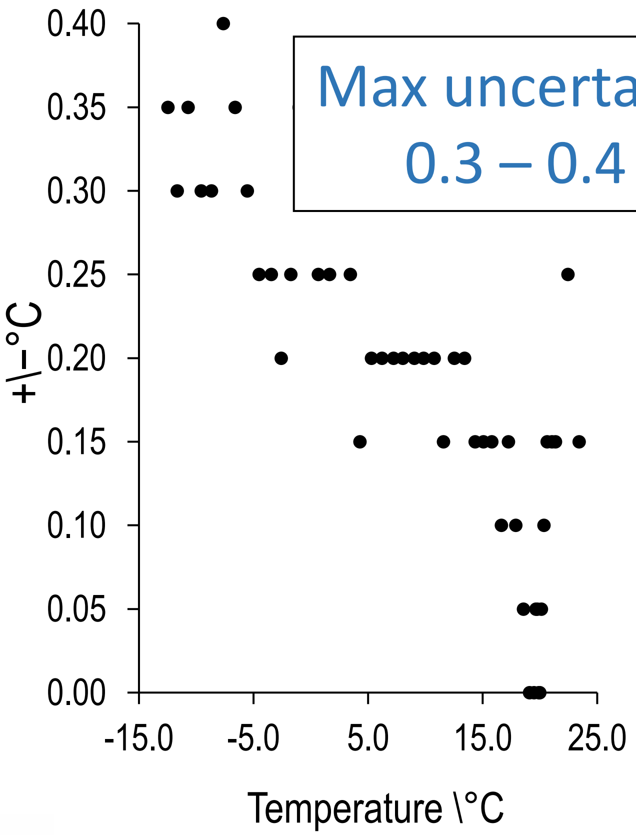
Placing a thermocouple at the TVIS sensing node allows for the calibration of the temperature inside the TVIS vial to a precision of +/- 0.4 C

(see next two slides)



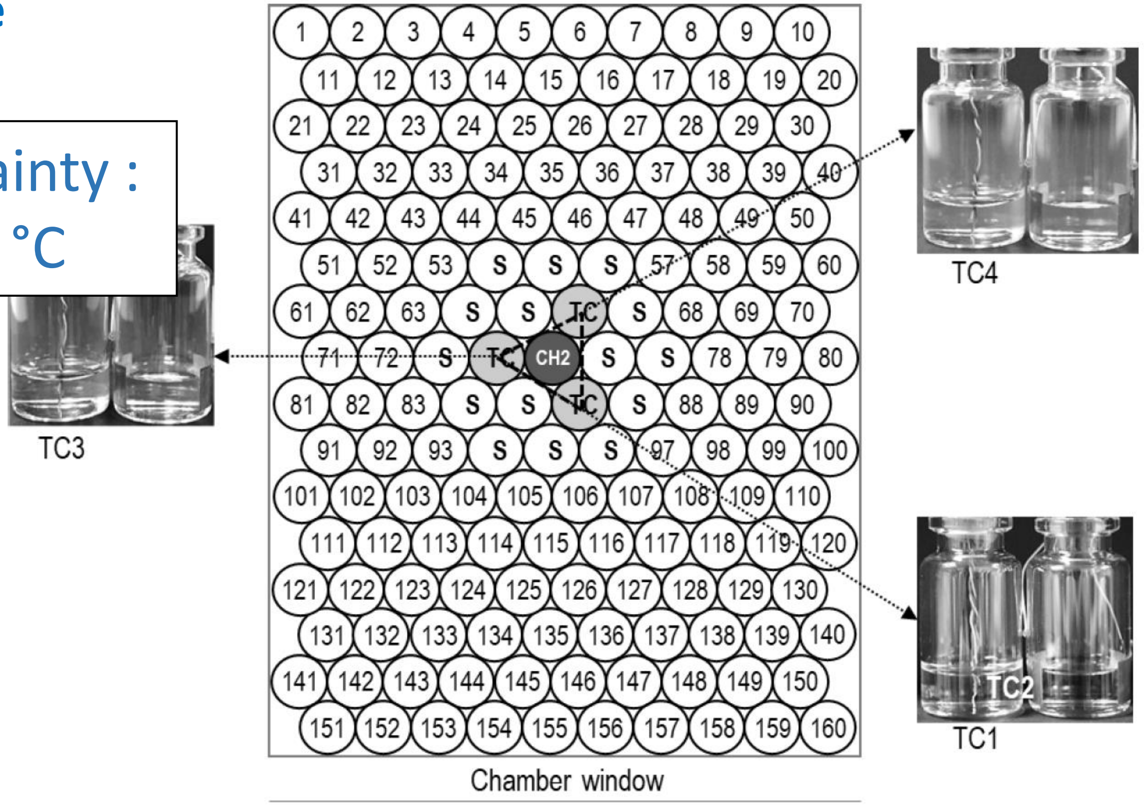
1. Triangulation method

Temperature uncertainty during freezing phase



Max uncertainty : 0.3 – 0.4 °C

TC in nearest 3 neighbour vials



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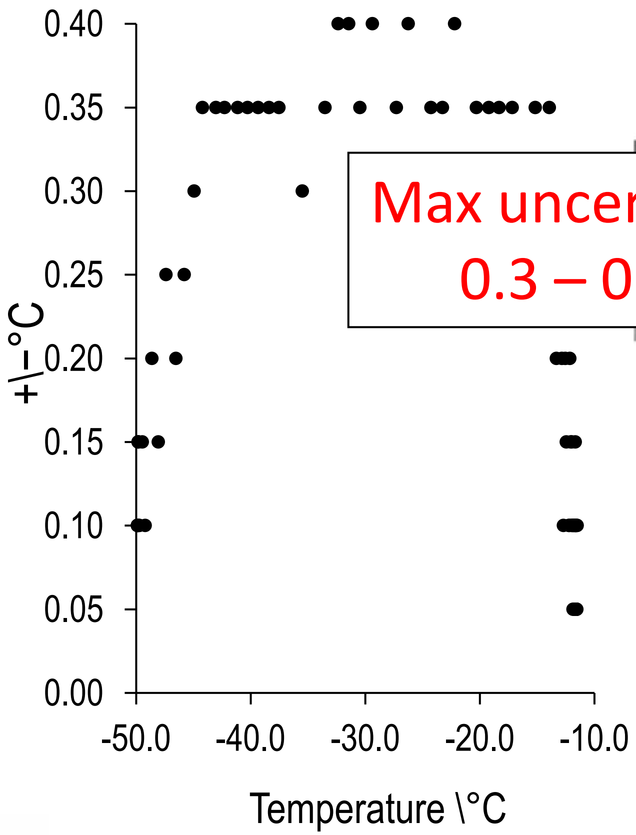
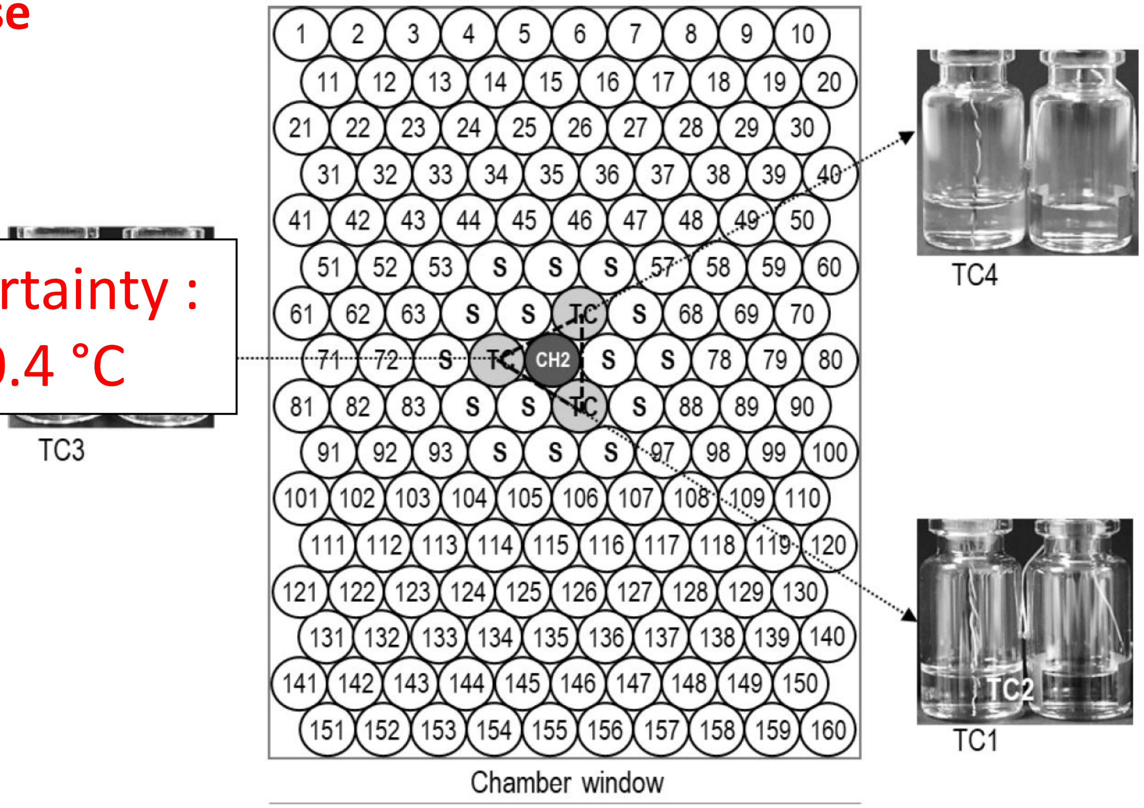
Temperature calibration for the TVIS vial:
1. Triangulation method

Temperature uncertainty during re-heating phase

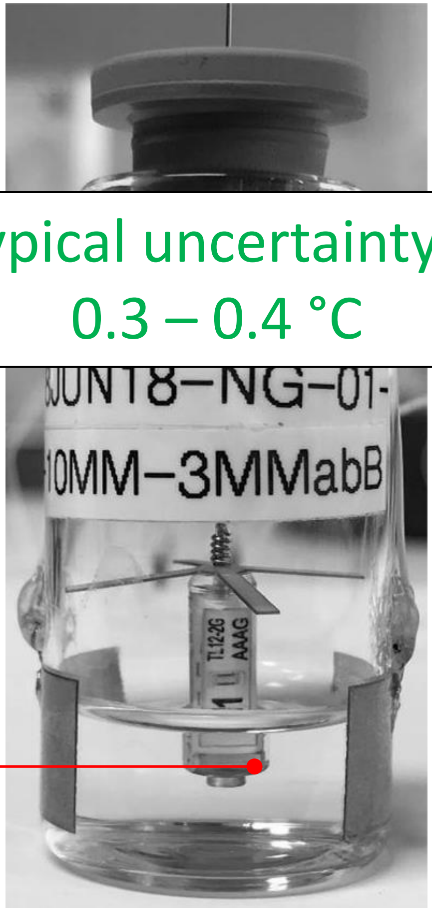


Max uncertainty :
0.3 – 0.4 °C

TC in nearest 3 neighbour vials

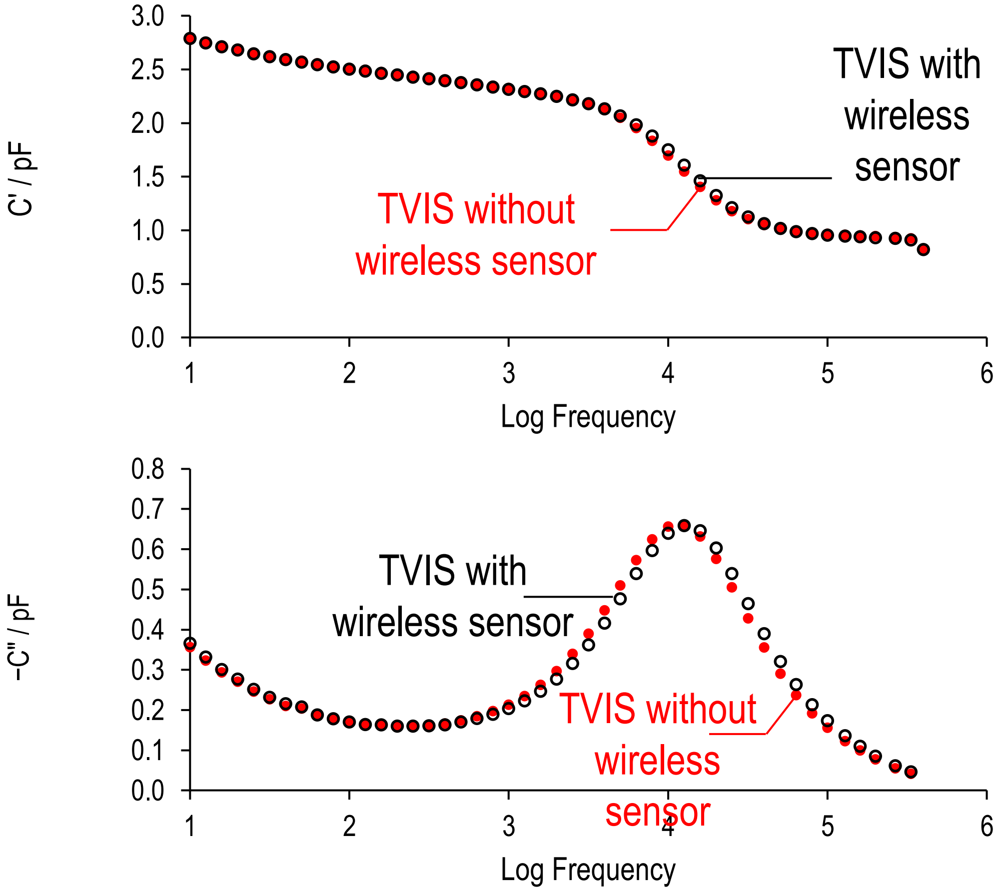


Temperature calibration for the TVIS vial:
2. Tempris® method



Typical uncertainty :
0.3 – 0.4 °C

TVIS spectra



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tempris® sensor technology

CASE STUDY 2

Phase behaviour of the solid/solute fraction

The behaviour predicted by DSC is not always evident in-vial!!

0%; 1% and 15% IgG

1% Sucrose, 4% Mannitol, 20 mM Histidine, 0.01% Tween 20

Conventional Method : mDSC

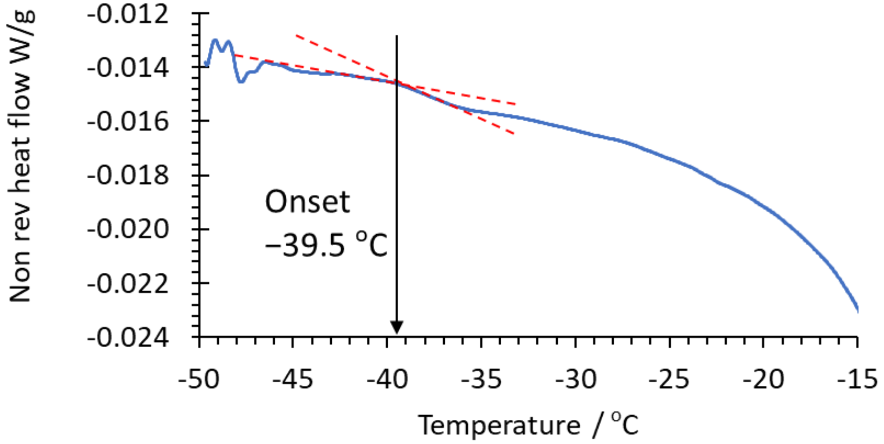
Sample	Amount (mg)
1% IgG	51.2
15% IgG	77.3
Excipients	82.3

DSC Q2000 V24.11 Build 124
(TA Instruments)

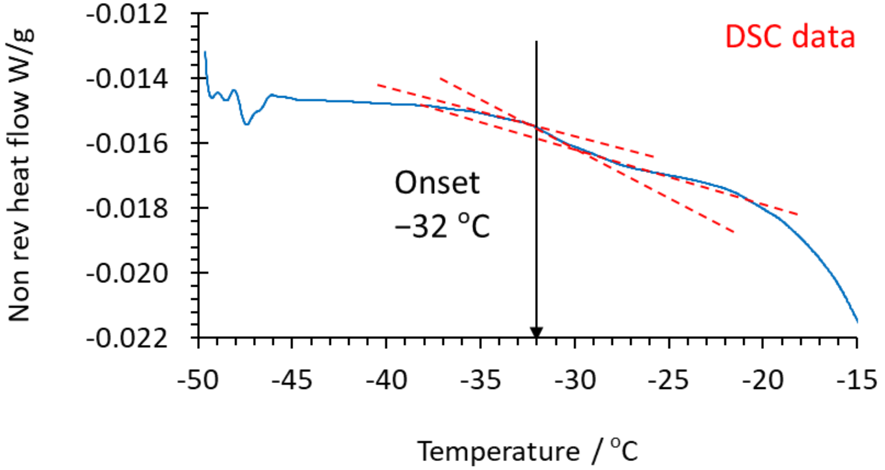
Step	Description
1	Isothermal for 2 min
2	Ramp 10 °C/min to -50 °C (mark end of cycle 1, data storage off)
3	Isothermal for 5 min
4	Ramp 1.5 °C/min to -15 °C
5	Isothermal for 10 min
6	Ramp 1.5 °C/min to -50 °C (data storage on, sampling interval 1 s/pt, modulate ± 0.23 °C every 60 s)
7	Isothermal for 8 min (data storage on, sampling interval 1 s/pt)
8	Ramp 1.5 °C/min to 25 °C (mark end of cycle 2)

mDSC Thermograms

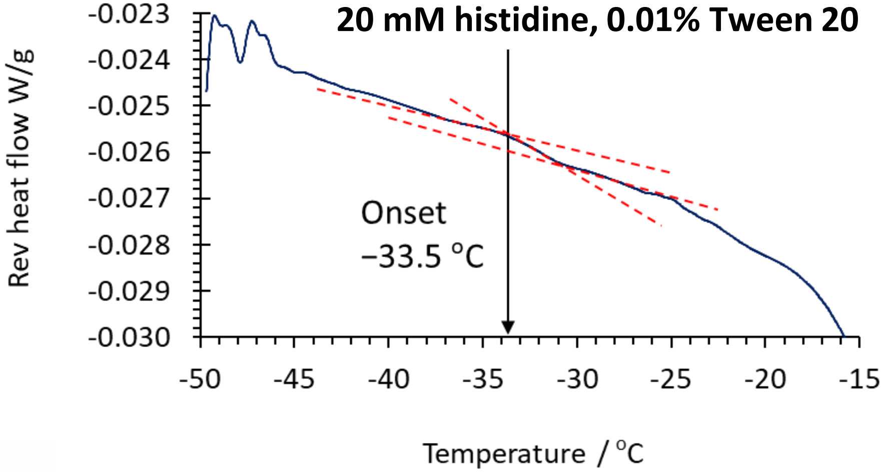
0% IgG
1% sucrose, 4% mannitol
20 mM histidine, 0.01% Tween 20



1% IgG
1% sucrose, 4% mannitol
20 mM histidine, 0.01% Tween 20



15% IgG
1% sucrose, 4% mannitol
20 mM histidine, 0.01% Tween 20



Sample	T_g onset (°C)		
	Heat flow	Non reverse heat flow	Reverse heat flow
0% IgG	−39.5	−39.5	
1% IgG	−31.9	−32.1	
15% IgG			−33.5

5 Channel TVIS System connected to Telstar LyoBeta (National Institute for Biological Standards and Control)

Impedance spectrometer

Pass through

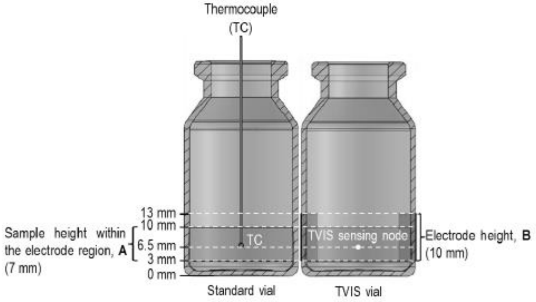
Junction box

Vial array

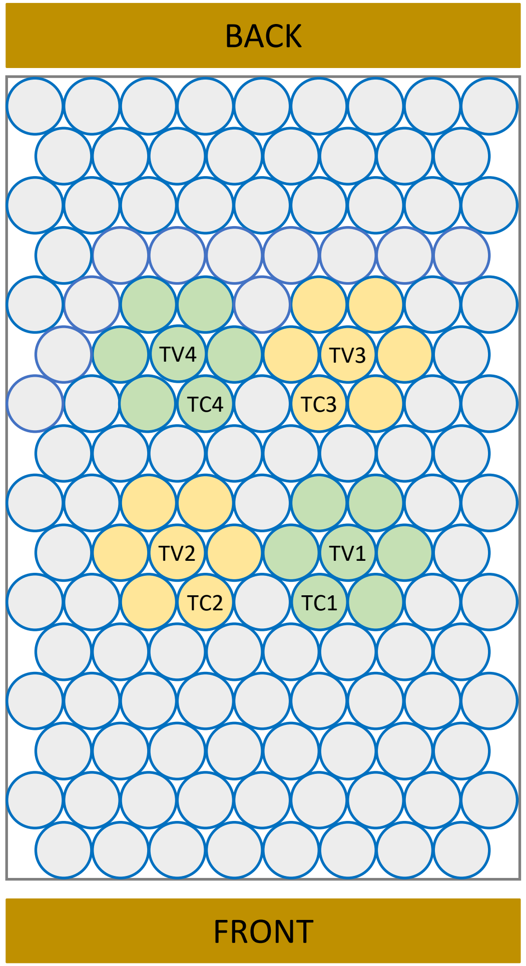
Telstar LyoBeta Pilot Freeze Dryer

Particulars	Details
Standard TVIS vial,	5 mL Type 1 Tubular Glass Vial from Schott, Hungary, VC005-20C
Electrode material	Copper Adhesive Tape 1181 3M
Electrode dimension	10 mm high and 19 mm wide
Position of the electrode from vial base	3 mm
Sample	Water for Irrigation IgG in 2 formulations
Weight	3 g (Fill factor 0.9)

Loading the freeze-dryer



TCx TVx



0% IgG

1% Sucrose, 4% Mannitol, 20 mM Histidine, 0.01% Tween 20

- Standard-unmodified vial

1% IgG

1% Sucrose, 4% Mannitol 20 mM Histidine, 0.01% Tween 20

TV2 - TVIS-modified vial connected to CH2

TC2 - Standard-unmodified vial with TC2

TV3 - TVIS-modified vial connected to CH3

TC3 - Standard-unmodified vial with TC3

- Standard-unmodified vial

15% IgG

1% Sucrose, 4% Mannitol, 20 mM Histidine, 0.01% Tween 20

TV1 - TVIS-modified vial connected to CH1

TC1 - Standard-unmodified vial with TC1

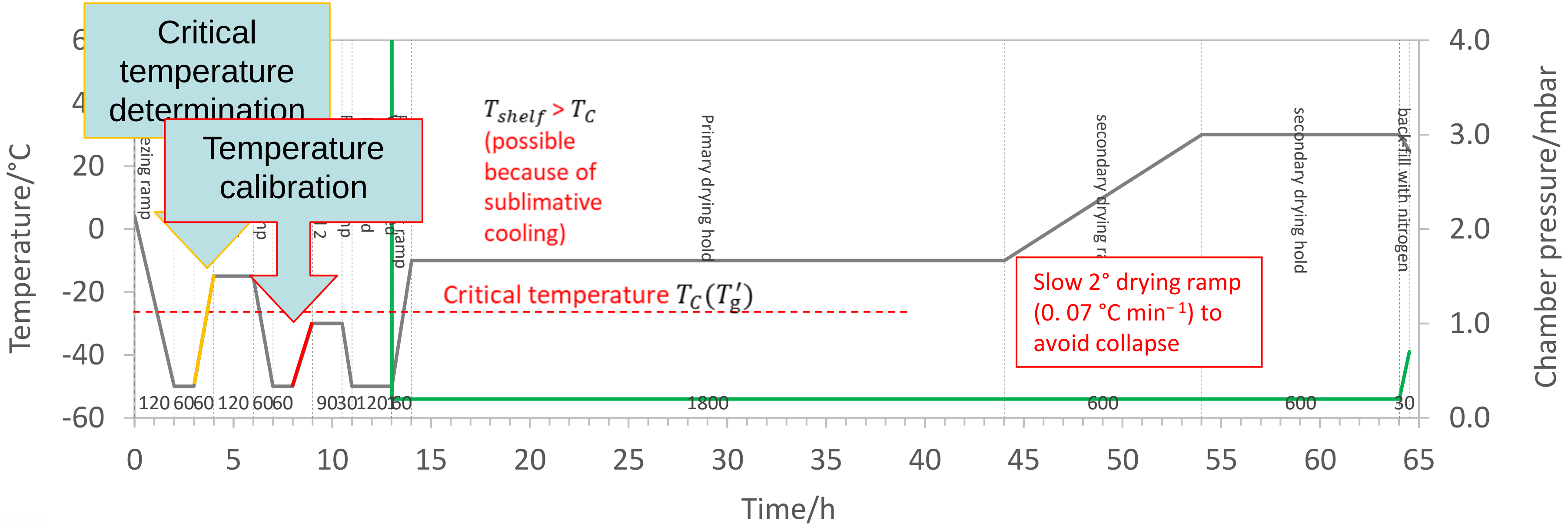
TV4 - TVIS-modified vial connected to CH4

TC4 - Standard-unmodified vial with TC4

- Standard-unmodified vial

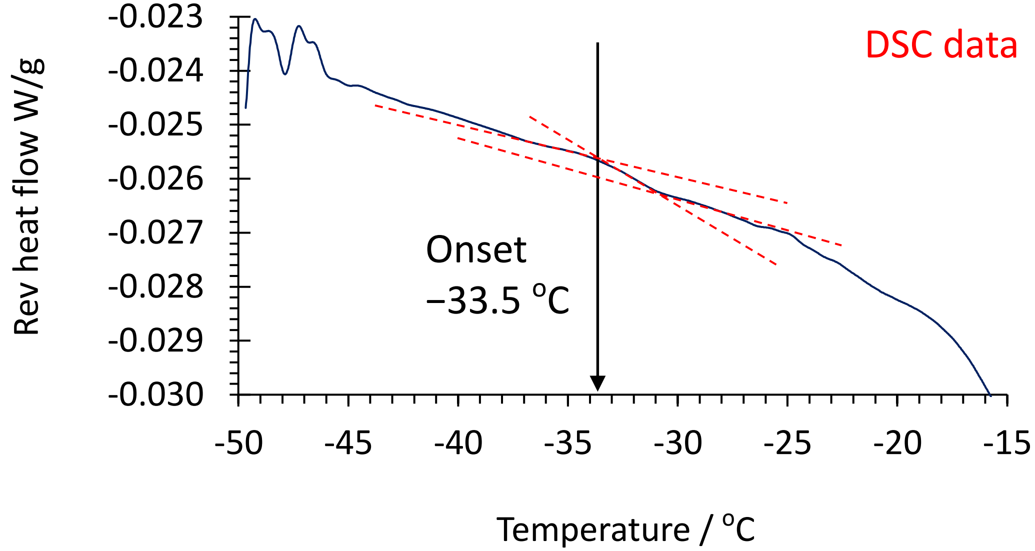
Freeze drying cycle

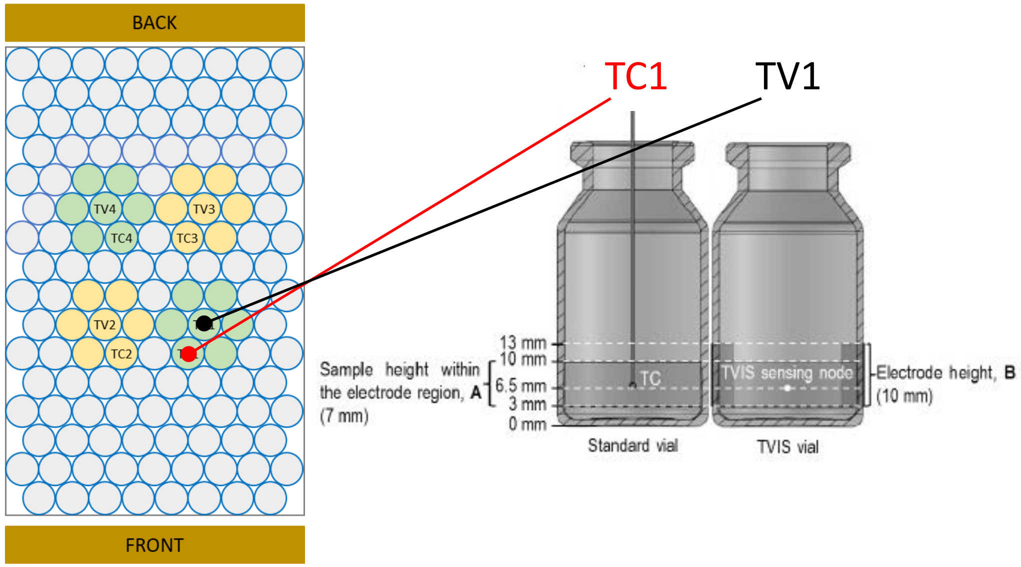
Step	Temperature (°C)	Ramp (°C/min)	Time (min)	Cumulative Time (h)	(mbar/min)	Set pressure (mbar)	Notes
Equilibrium phase	4		30	0		1000	Equilibrate
Freezing ramp	-50	-0.45	120	2		1000	Freeze to below maximal solidification point (determined by FDM/thermal m
Freezing hold	-50		60	3		1000	Soak to equilibrate whole batch at frozen state
Re-heating ramp	-15	0.58	60	4		1000	Warm to annealing temperature (temperature will need to be determined e
Annealing hold 1	-15		120	6		1000	Annealing (time will need to be determined empirically)
Re-cooling ramp	-50	-0.58	60	7		1000	Re-freeze to be below maximal solidification point
Re-cooling hold	-50		60	8		1000	Soak to equilibrate whole batch at frozen state
Re-heating ramp	-30	0.33	60	9		1000	Second warming
Annealing hold 2	-30		90	11		1000	Second annealing
Re-cooling ramp	-50	-0.67	30	11		1000	Re-freezing
Re-cooling hold	-50		120	13		1000	Soak to equilibrate whole batch at frozen state
Vacuum applied	-50	0.00	1	13	999.6	0.2	Apply vacuum
Primary drying ramp	-10	0.67	60	14		0.2	Ramp to primary drying temp (determined by thermal method/FDM)
Primary drying hold	-10		1800	44		0.2	Primary dry
secondary drying	30	0.07	600	54		0.2	Slow ramp to secondary drying conditions
secondary drying	30		600	64.02		0.2	Secondary drying to achieve ambient temperature stability
back-fill with	25		30	64.52		0.7	Back fill to inert atmosphere and partial vacuum, then stopper in dryer

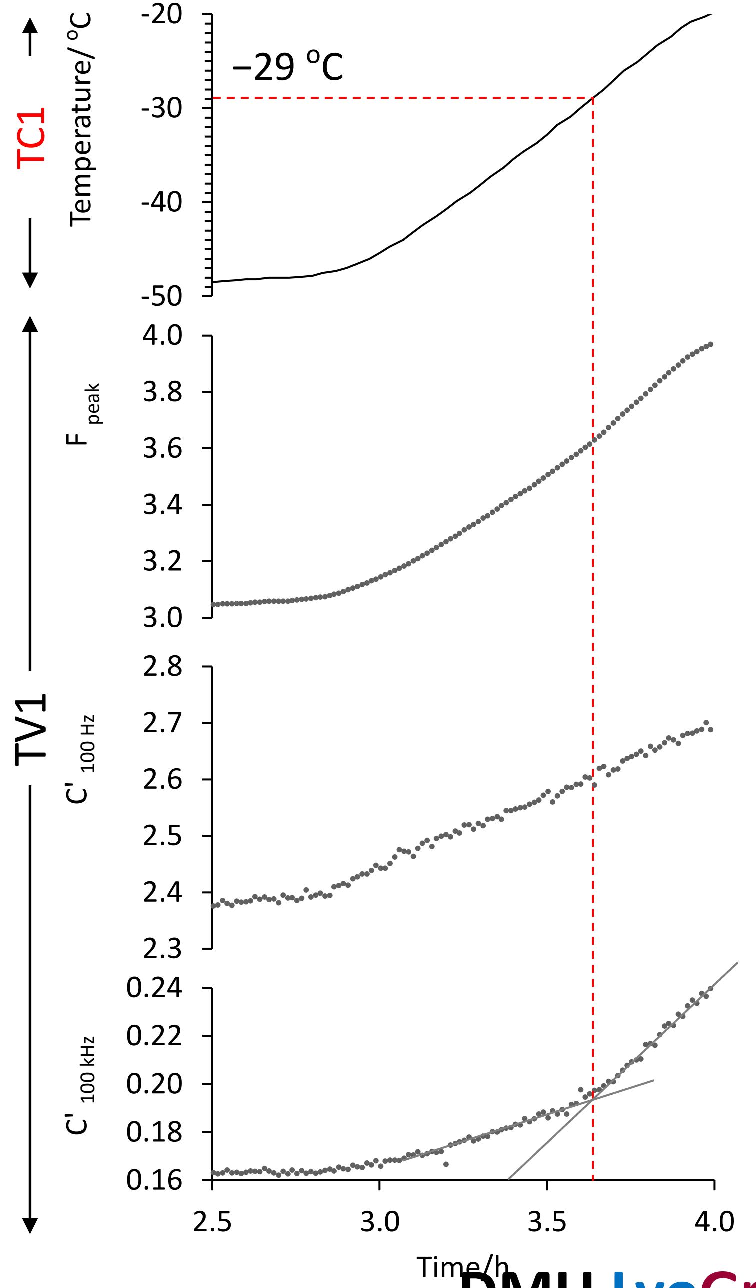


Anneal temperature and time and critical $T_C(T'_g)$ need to be determined empirically .Condenser temperature (not shown) should be 10-20°C below minimum shelf T,e.g. −70 °C

Re-heating of 15% IgG, 1% sucrose, 4% mannitol, 20 mM histidine, 0.01% Tween 20







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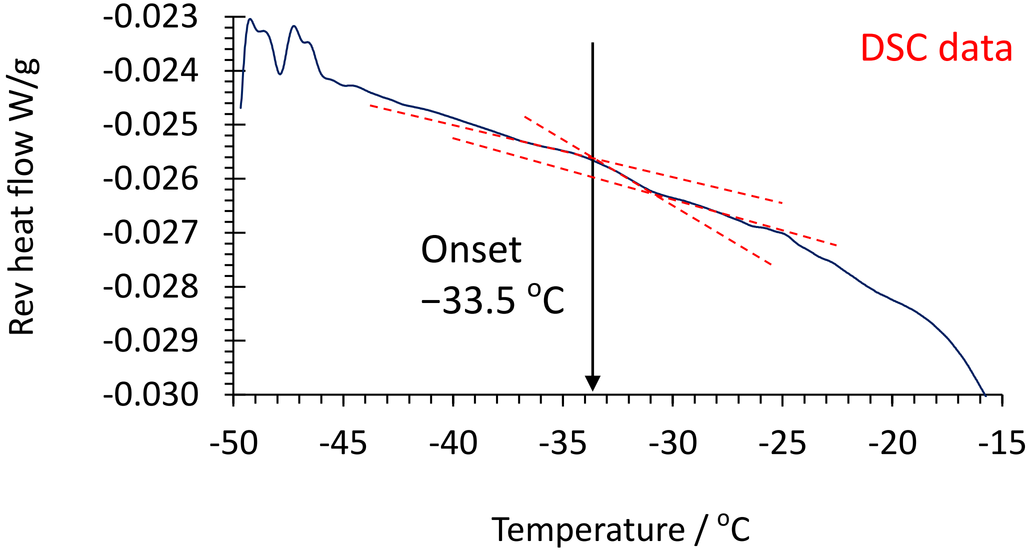

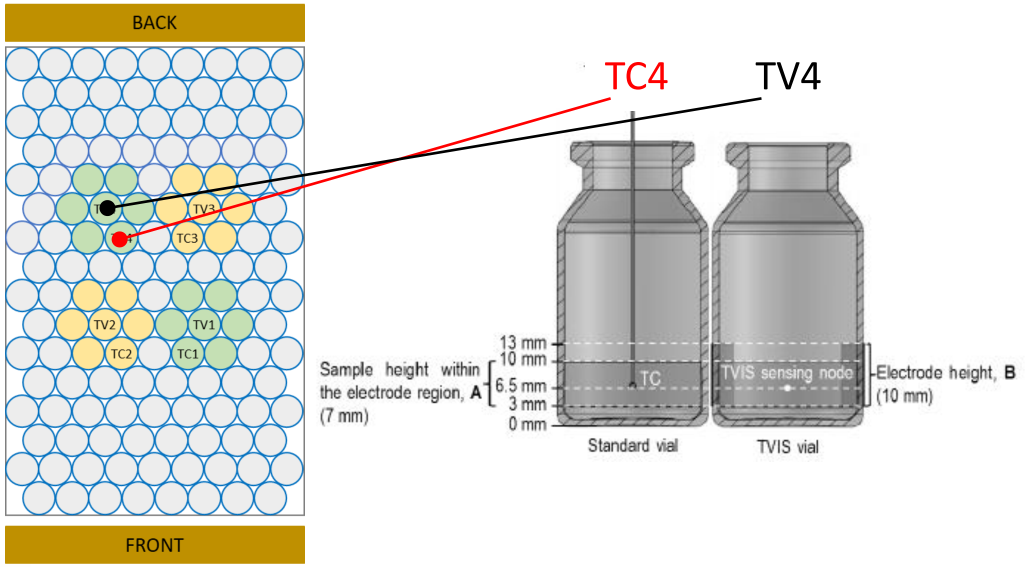

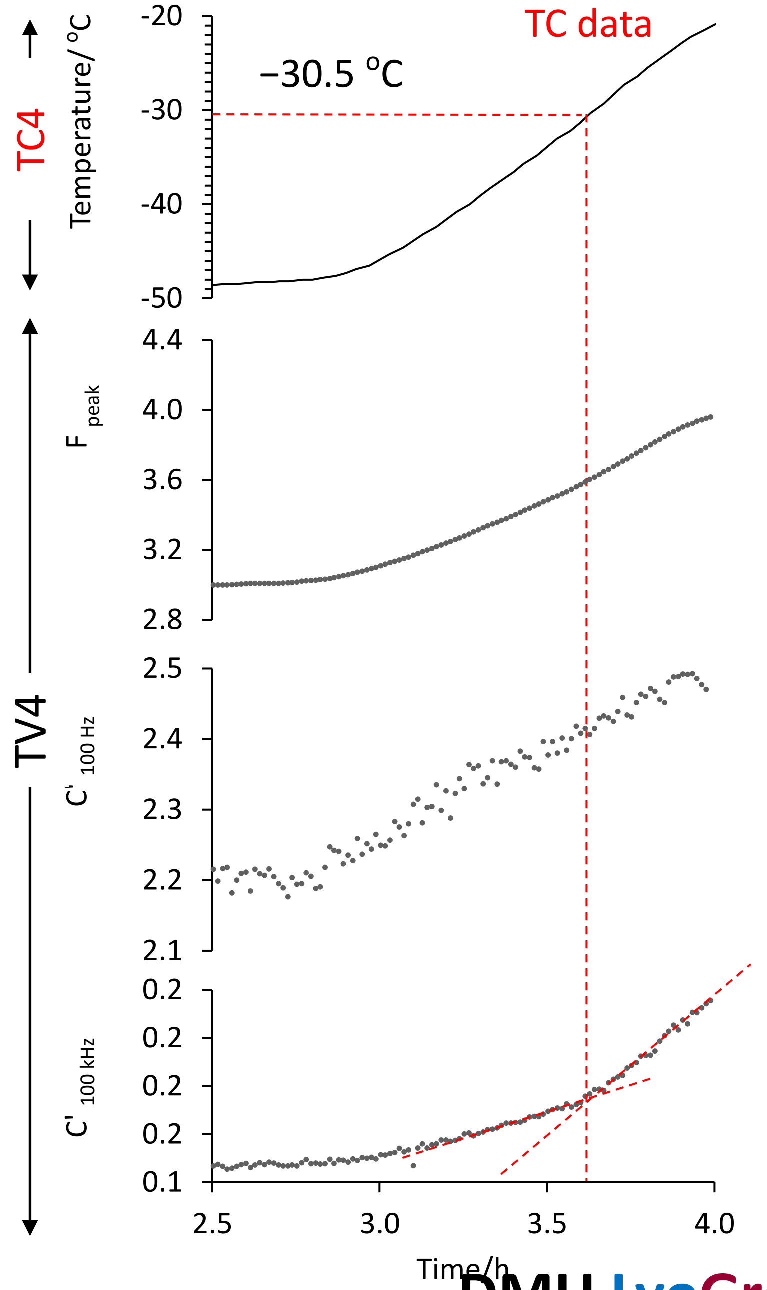

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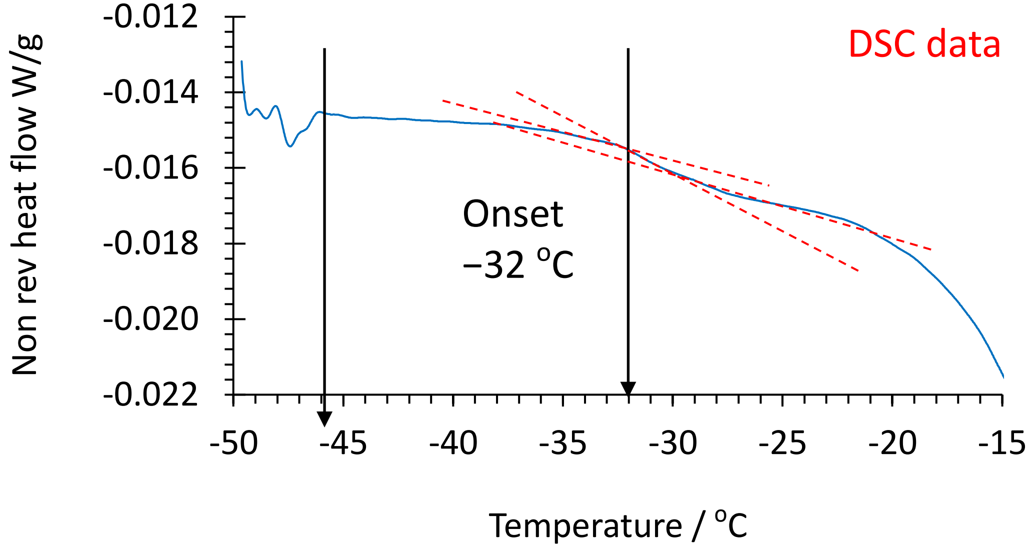
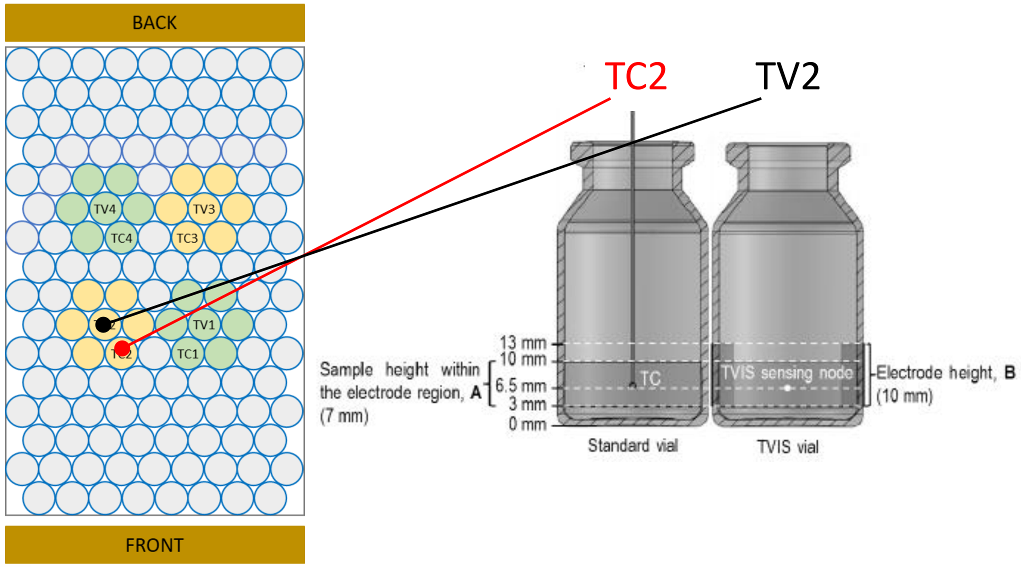
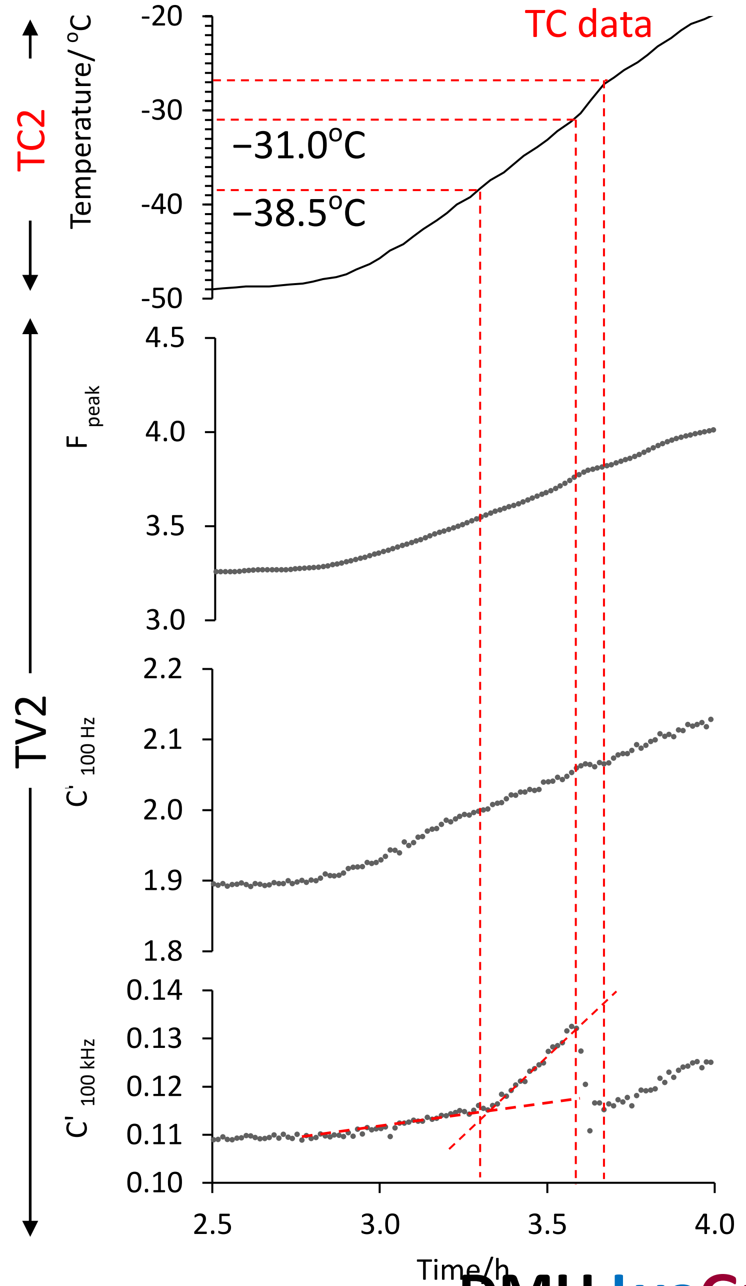
NIBSC
Confidence in Biological Medicines

DMU LyoGroup

Re-heating of 1% IgG, 1% sucrose, 4% mannitol, 20 mM histidine, 0.01% Tween 20







DMU LyoGroup

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NIBSC Confidence in Biological Medicines

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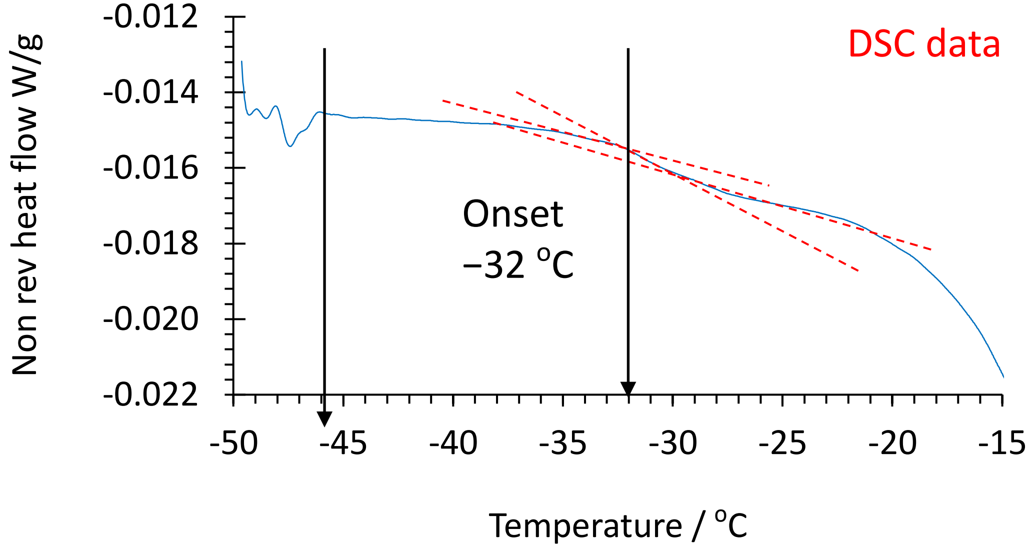
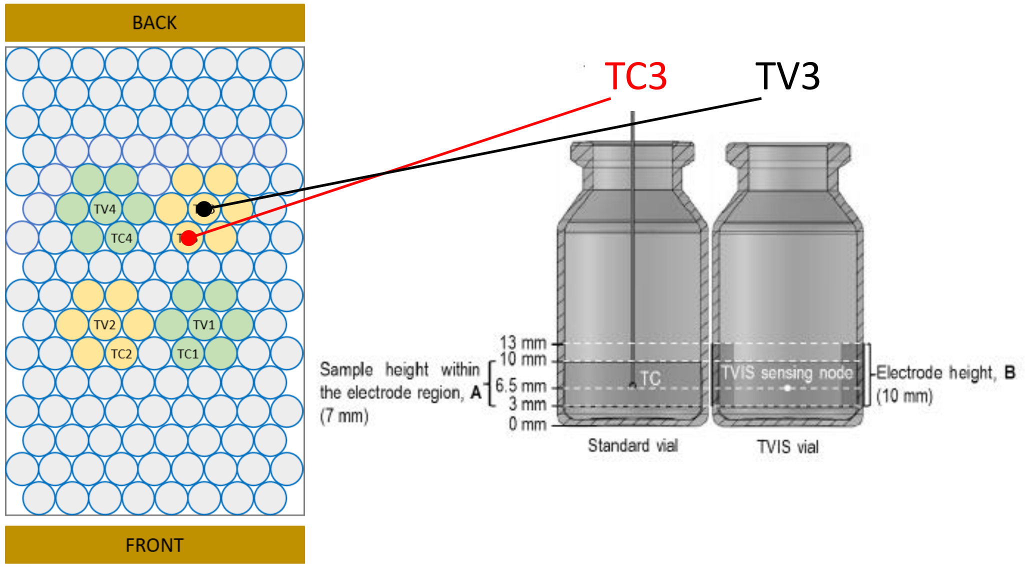
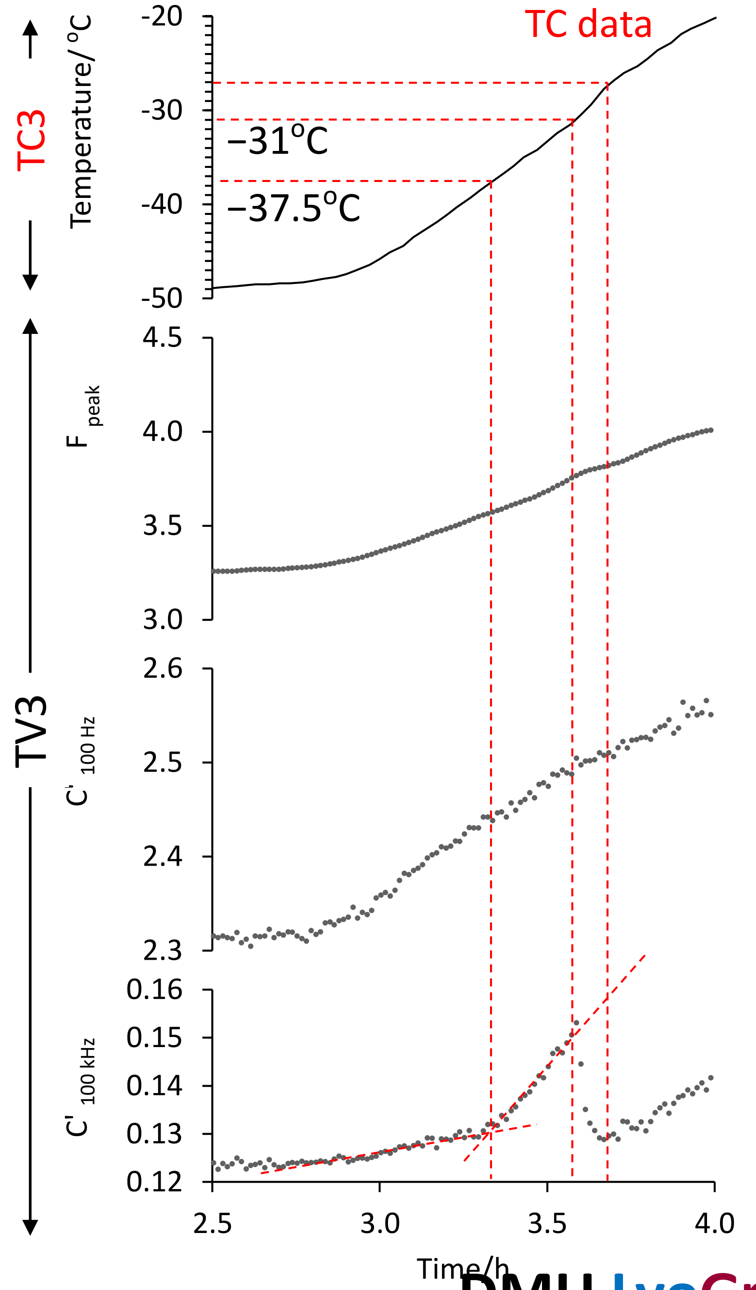


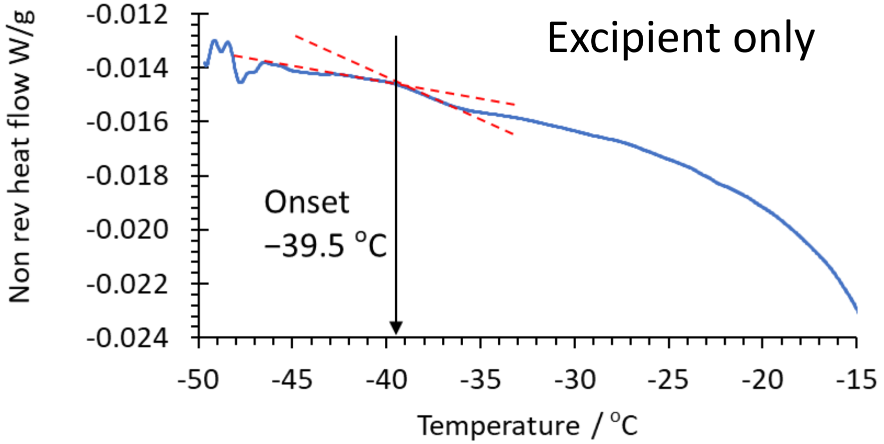


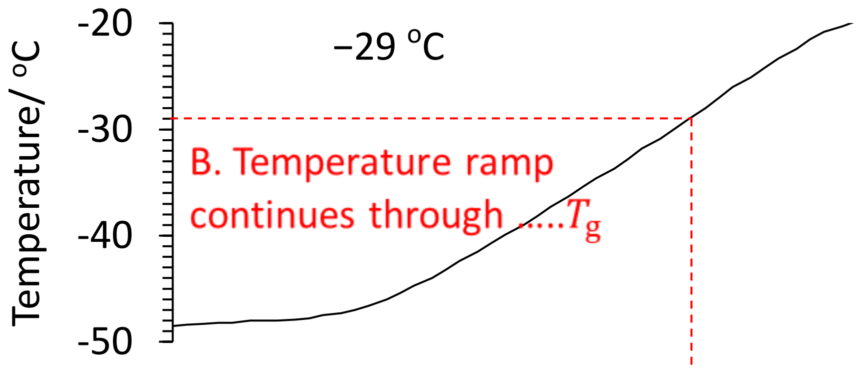


What does this mean?

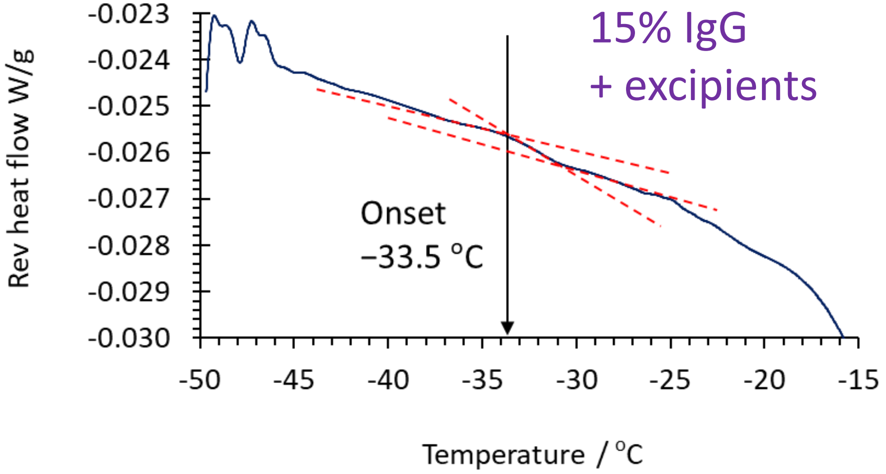
15% IgG, 1% sucrose, 4% mannitol, 20 mM histidine, 0.01% Tween 20

TC1

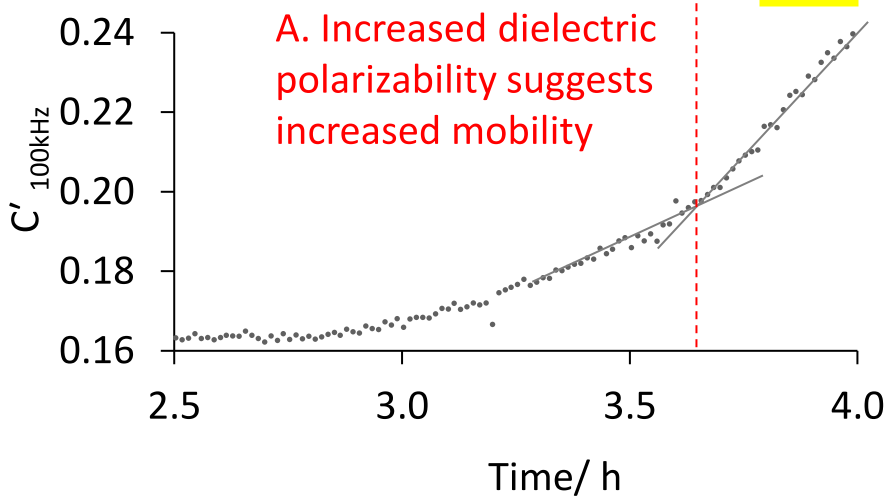




A with B suggests a glass transition

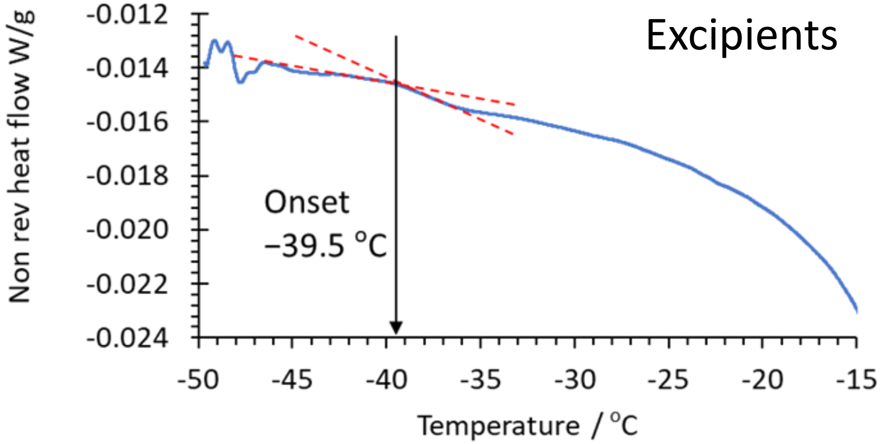


TV1

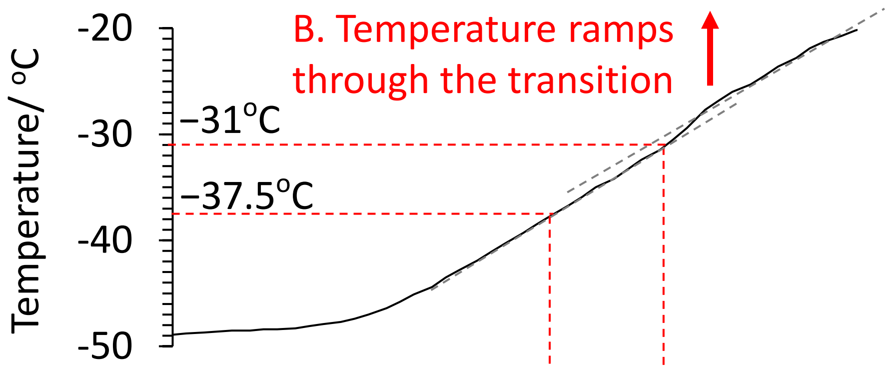


What does this mean?

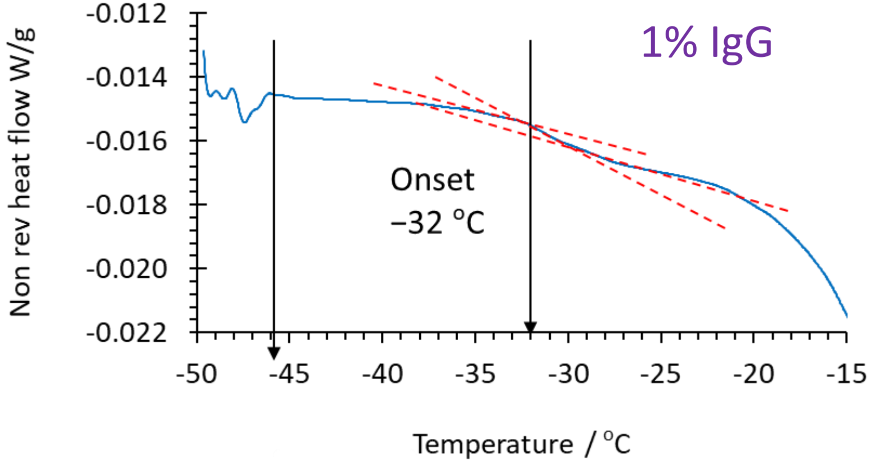
1% IgG, 1% sucrose, 4% mannitol, 20 mM histidine, 0.01% Tween 20



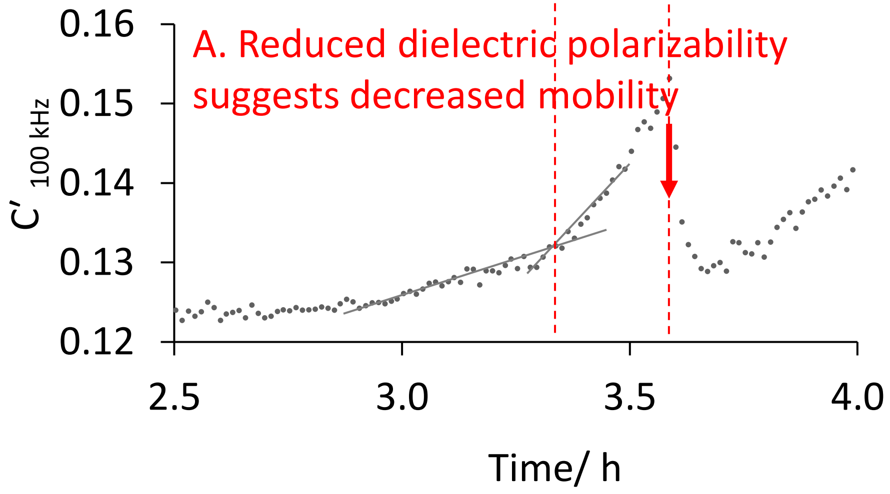
TC3



A with B suggests crystallization (i.e. devitrification)



TV3



Summary: "unexpected" phase behaviour at low IgG

CPP	0% IgG	15% IgG		1% IgG	
DSC T_g (Onset) (^oC)	−39.5	−33.5		−32	
TVIS data		TV1	TV4	TV2	TV3
devitrification (^oC)	N/A	-	-	−31	−31
glass transition (^oC)	N/A	−29	−30.5	−38.5	−37.5

CPP: critical process parameter

De-vitrification

The process of devitrification is not observed by the mDSC method

Devitrification occurs in-vial for the low concentration of IgG (1%)

Devitrification is suppressed by the higher concentration of IgG (15%)

Glass transition

The glass transition of the excipient only formulation by mDSC is **similar to** the in-vial response of 1% IgG

(excipient only studies by TVIS were not undertaken)

CASE STUDY 4

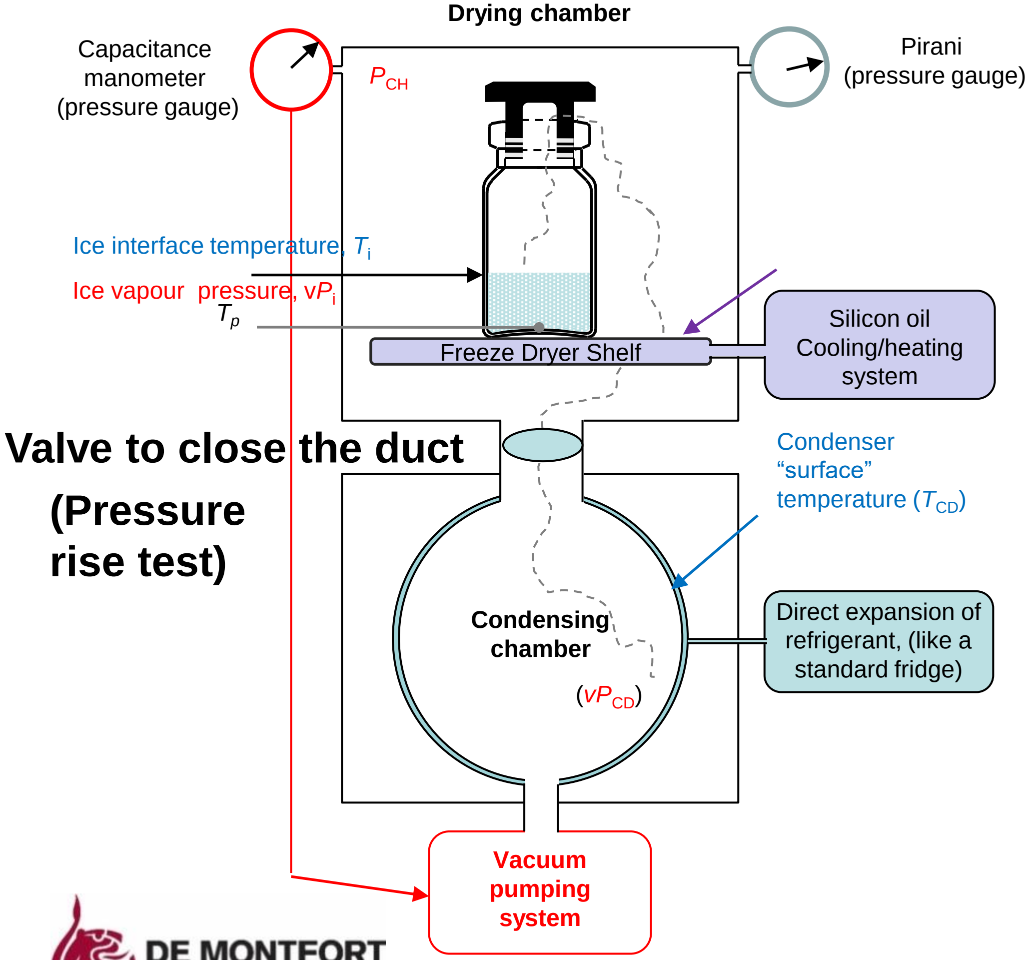
Primary drying end point

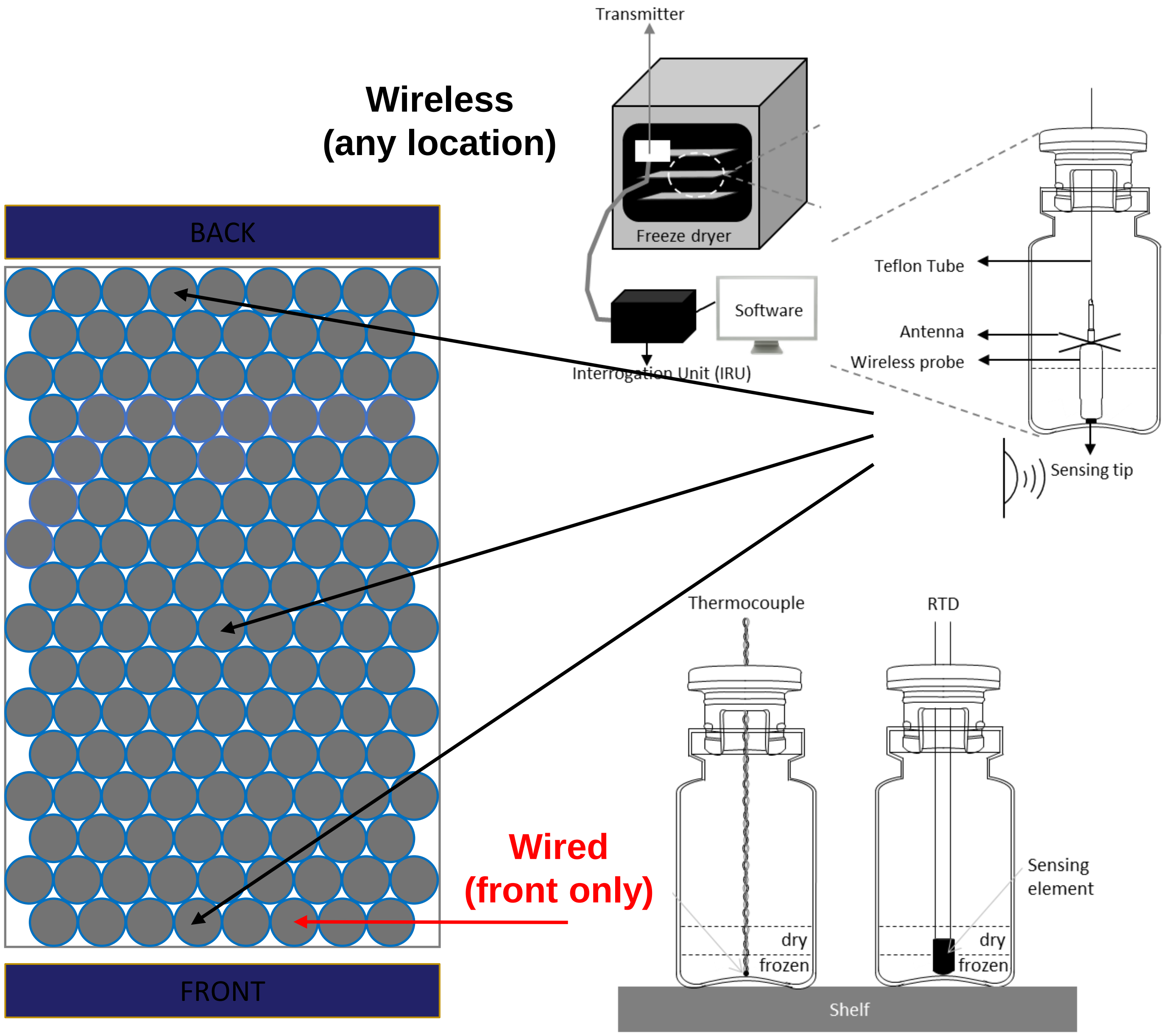
Separation between sublimation (primary drying) and diffusive desorption (secondary drying)

0%; 1% and 15% IgG

1% Sucrose, 4% Mannitol, 20 mM Histidine, 0.01% Tween 20

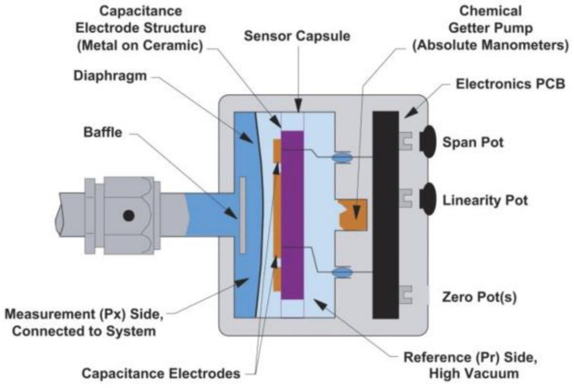
Comparative pressure measurement





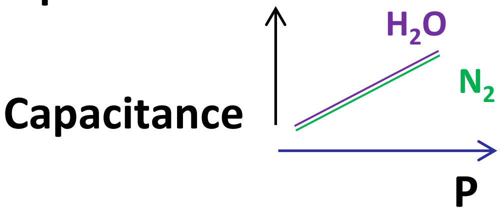
Comparative pressure measurement (CPM)

Capacitance manometer

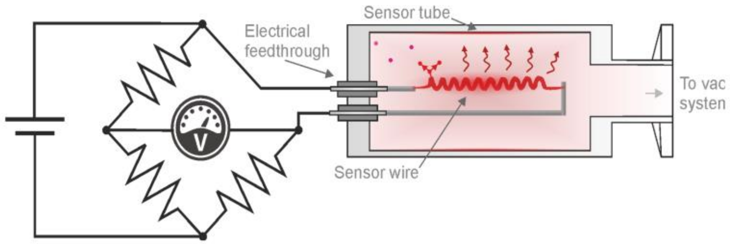


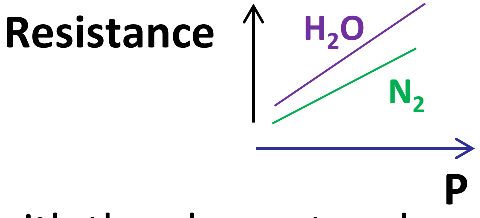
Pressure changes position of a diagraph with alters the electrical capacitance of the system

Sensitive to total pressure



Pirani gauge





Gas molecules collide with the element and removes heat changing the resistance

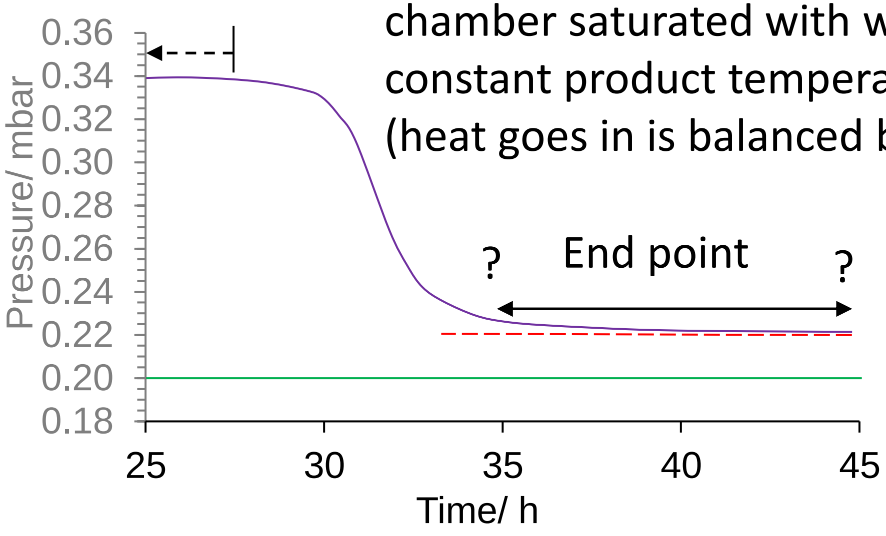
Sensitive to type of gas,

e.g., N_2, H_20

Comparative pressure measurement (CPM)

Pirani

Capacitance manometer



Steady state:
chamber saturated with water vapour
constant product temperature :
(heat goes in is balanced by heat going out)

- Comparative pressure measurement (CPM):
  - Capacitance manometer responds to absolute gas pressure
  - Pirani response to water vapour is ~ 1.6 x that of the capacitance manometer
  - Therefore, Pirani output is higher than the CM while water vapour is being generated
- When drying is complete the Pirani converges on the capacitance manometer

But when has an asymptote been reached?

Schneid (2008) Aaps Pharm.sci.tech, 9, 729-739

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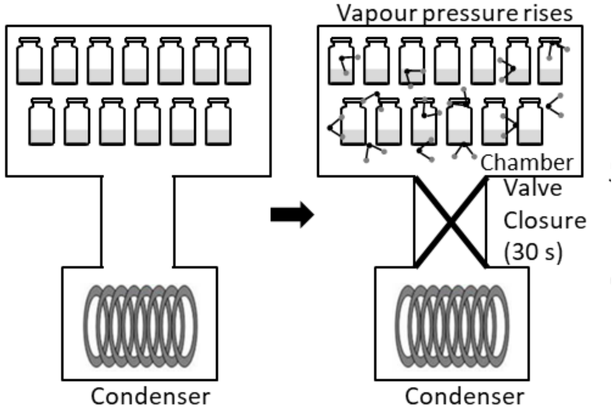
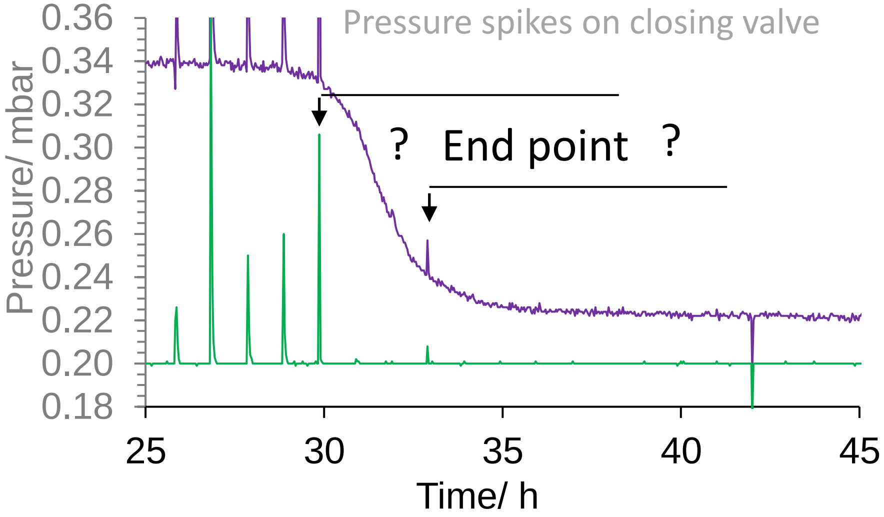
Pressure Rise Test (PRT)



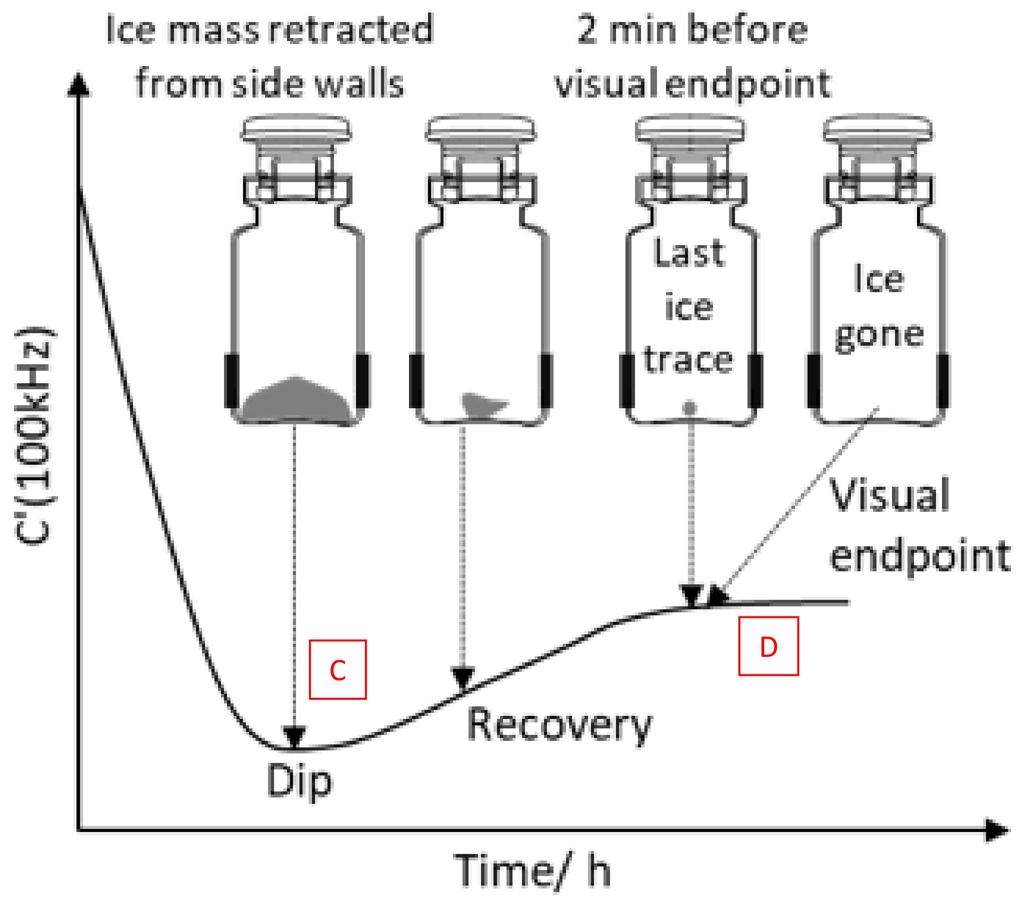


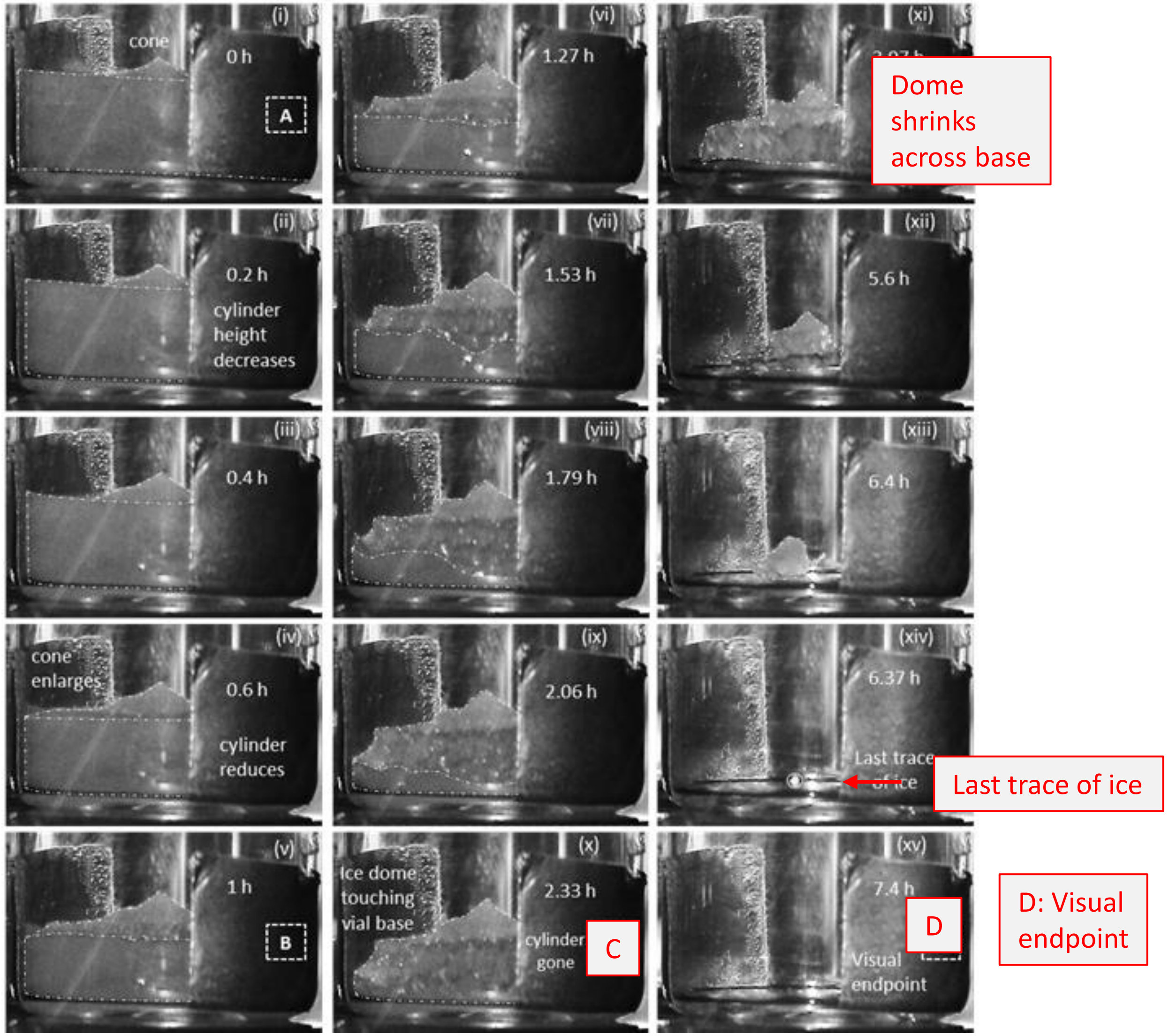
- Pressure rise testing (PRT)
  - Brief (up to 30 s) isolation of the valve between drying chamber and condenser
  - Results in spikes (pressure rises) in both Pirani and capacitance manometer readings
  - Reason :
    - water vapour is released from the product during the drying stages
    - Vapour can not vent to the condenser when the valve is closed
    - Pressure rise occurs until the valve is opened again

Schneid (2008) AAPS Pharm Sci Tech, 9, 729-739

Through Vial Impedance Spectroscopy

TVIS Sublimation end point

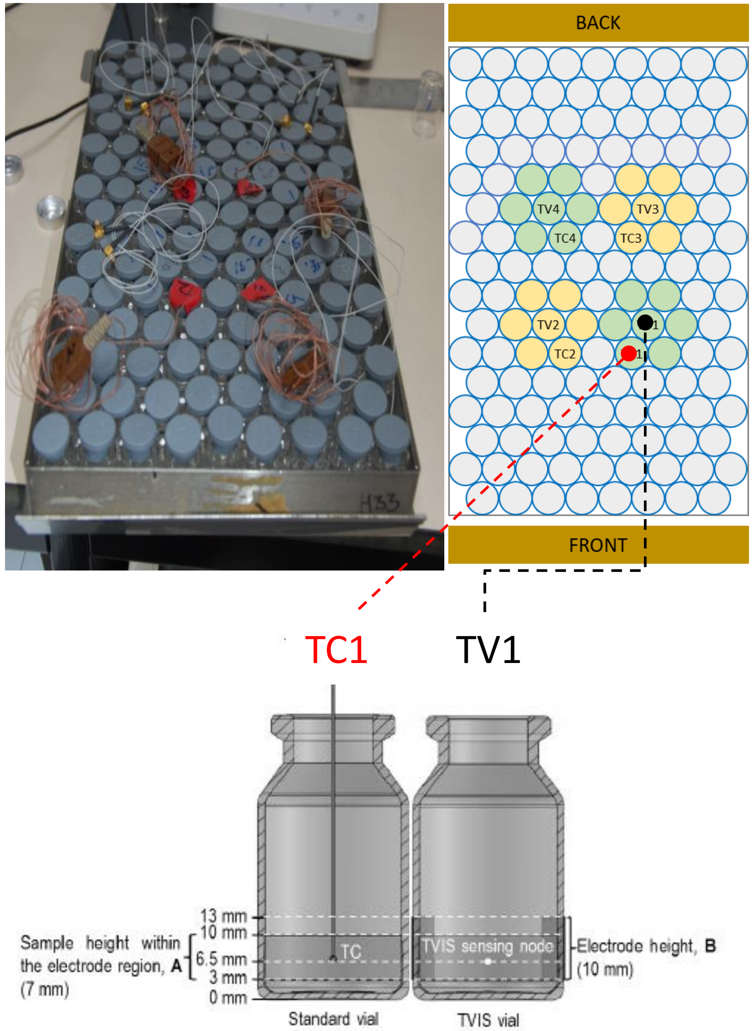


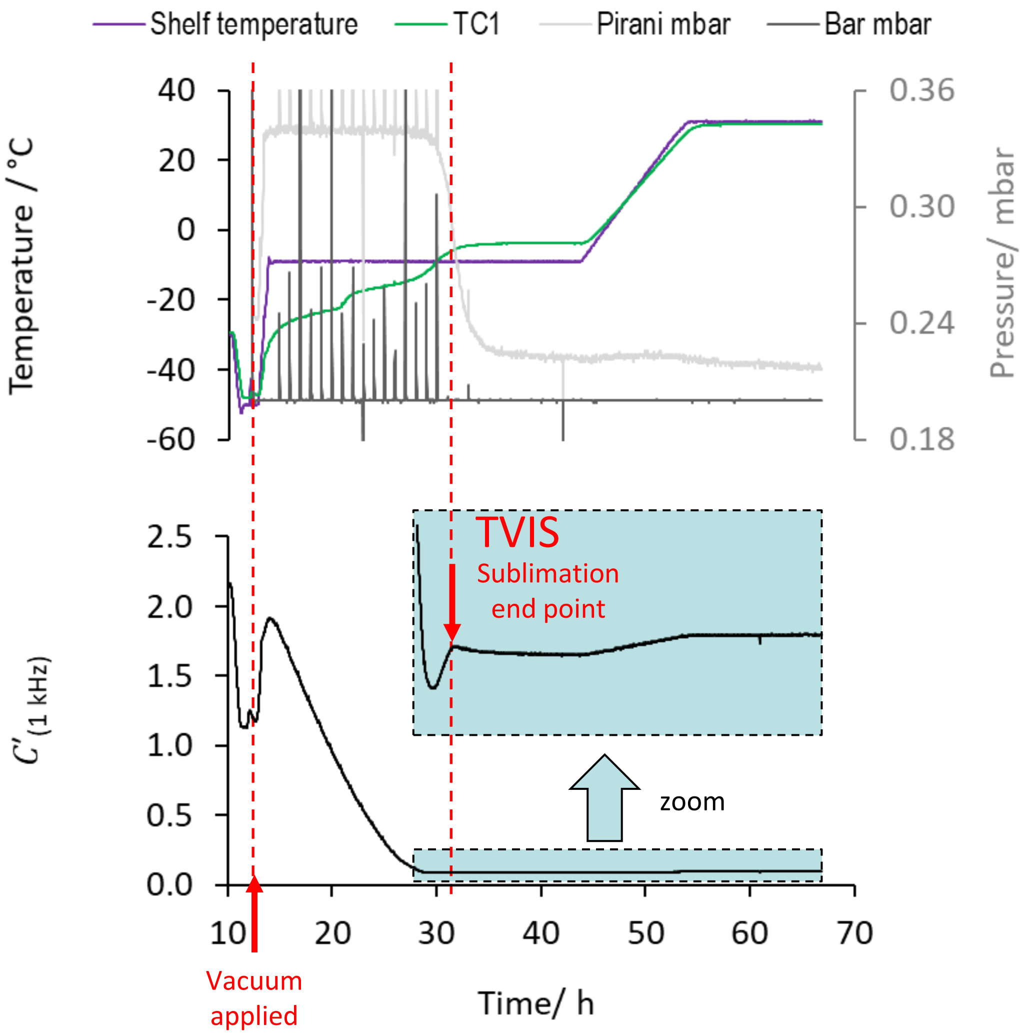


C: Ice mass no longer in contact with the side wall

DMU LyoGroup

Drying of a protein formulation 15% IgG, 1% Sucrose, 4% Mannitol, 20 mM Histidine, 0.01% Tween 20





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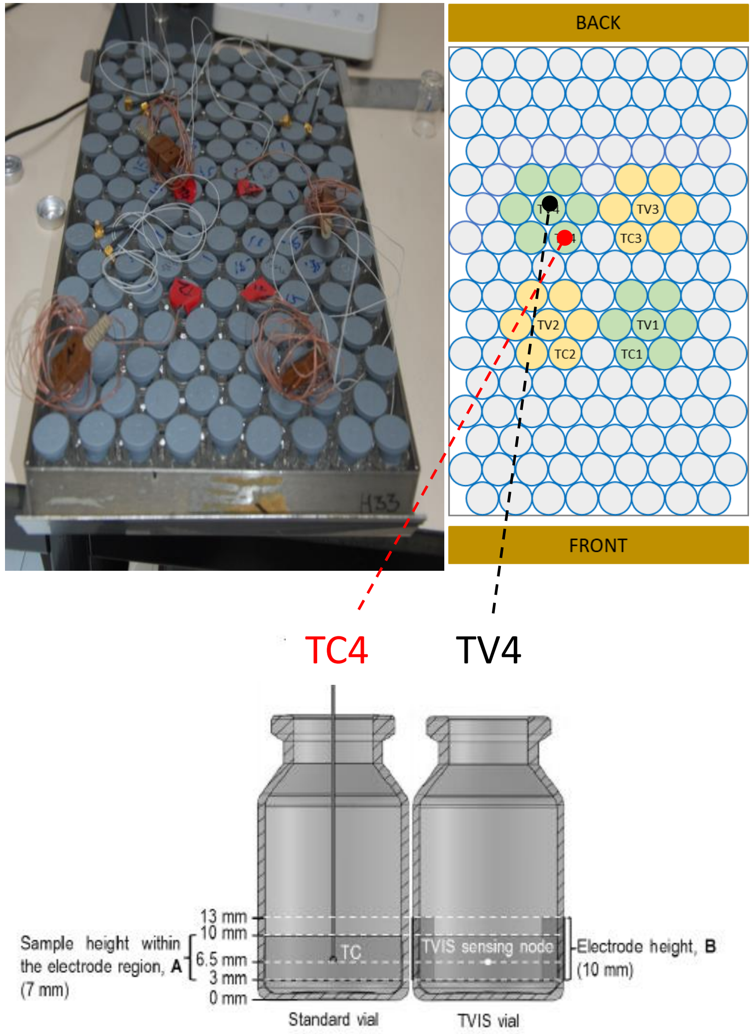
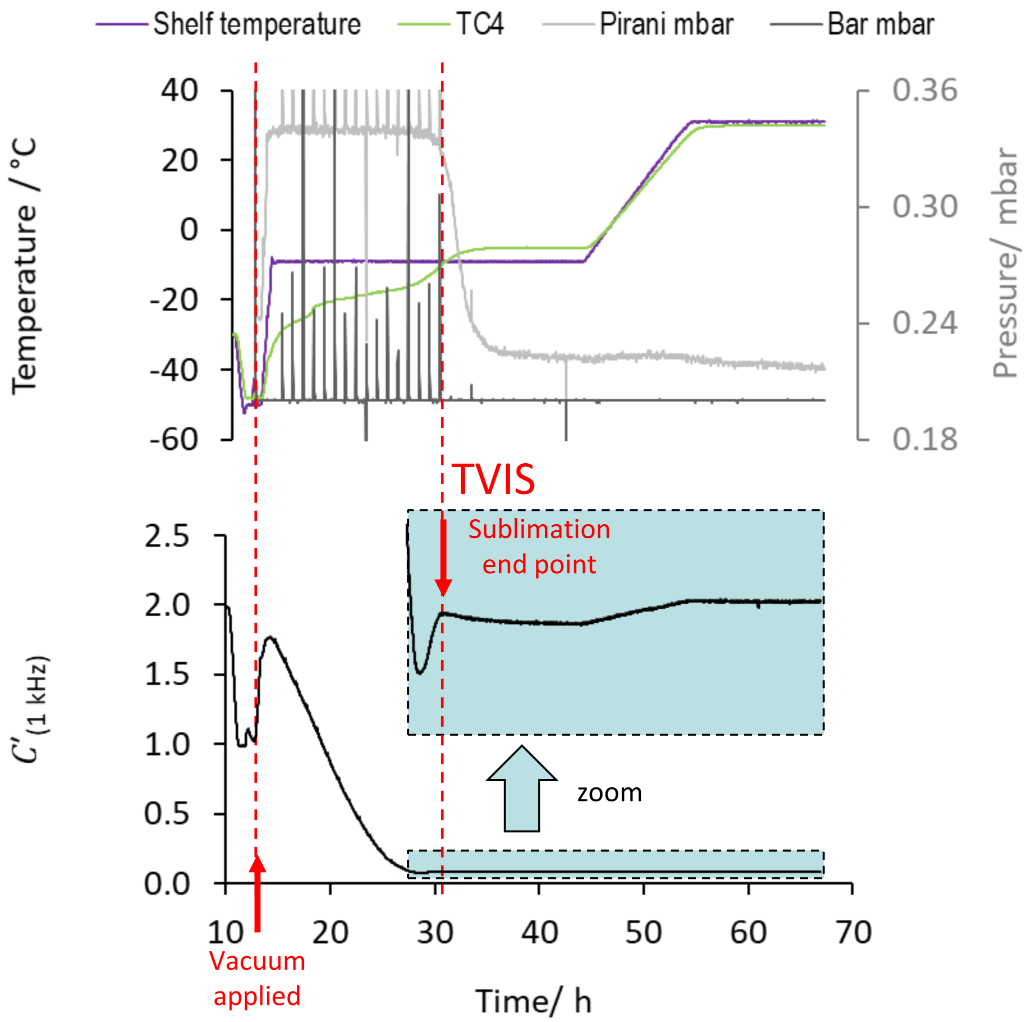
NIBSC Confidence in Biological Medicines

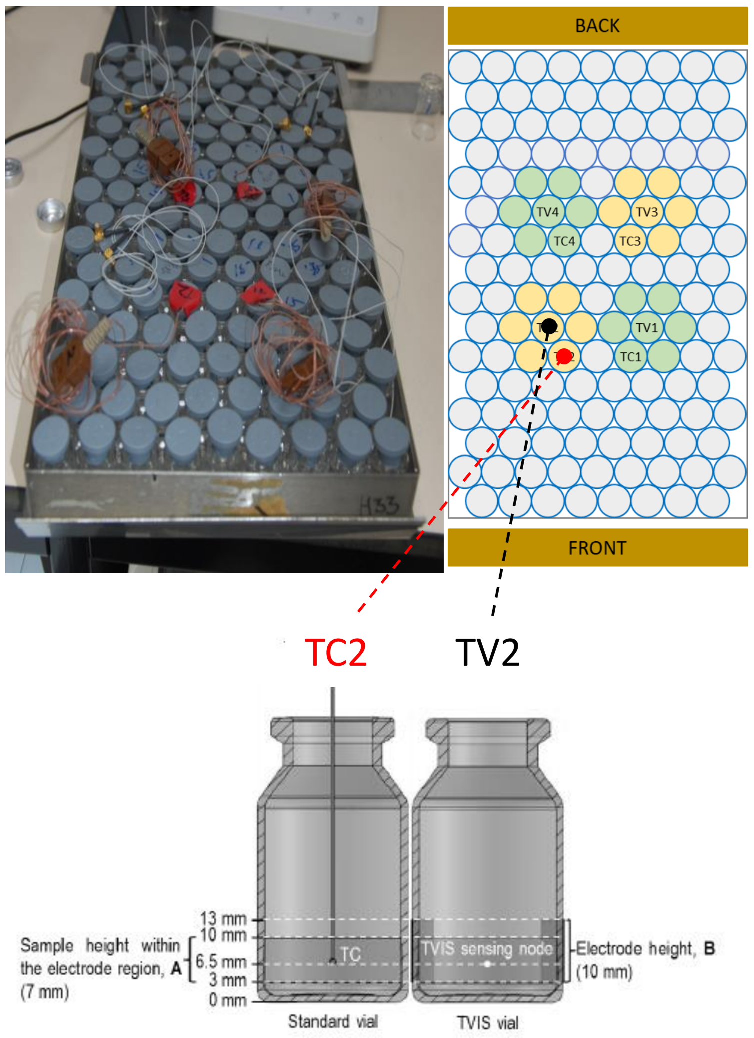
DMU LyoGroup

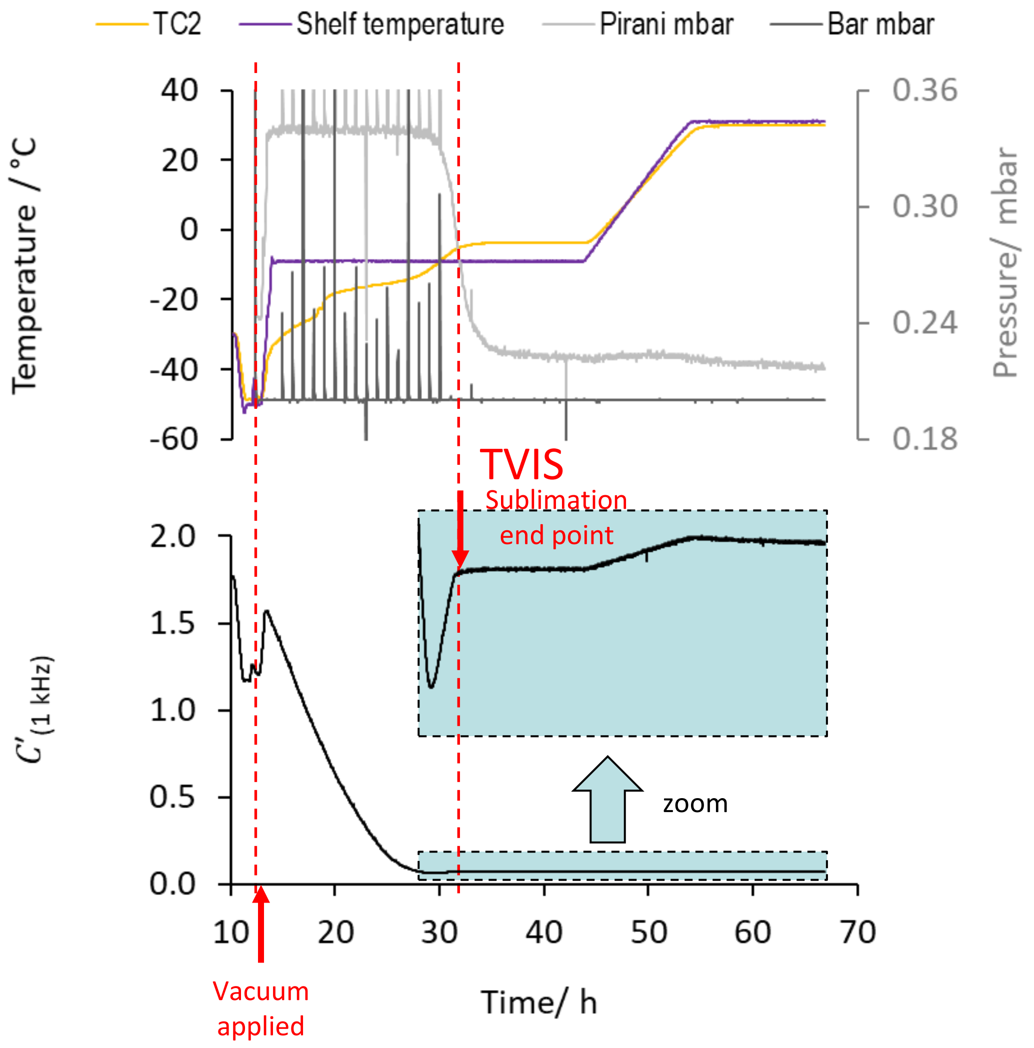
Primary drying **15% IgG, 1% Sucrose, 4% Mannitol, 20 mM Histidine, 0.01% Tween 20**



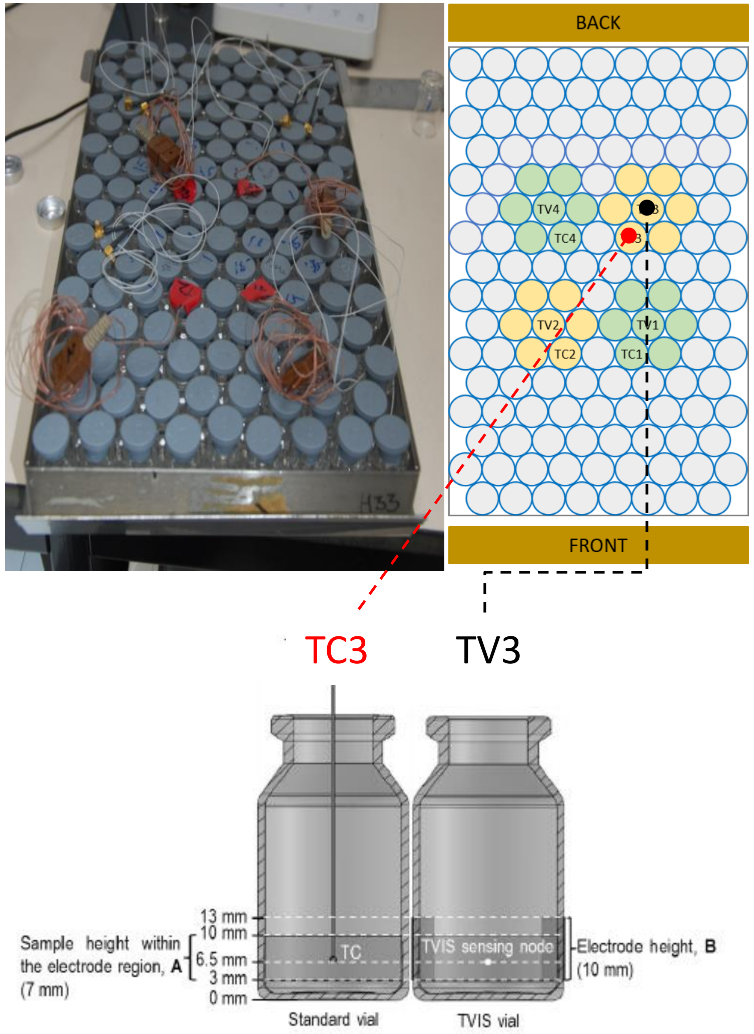


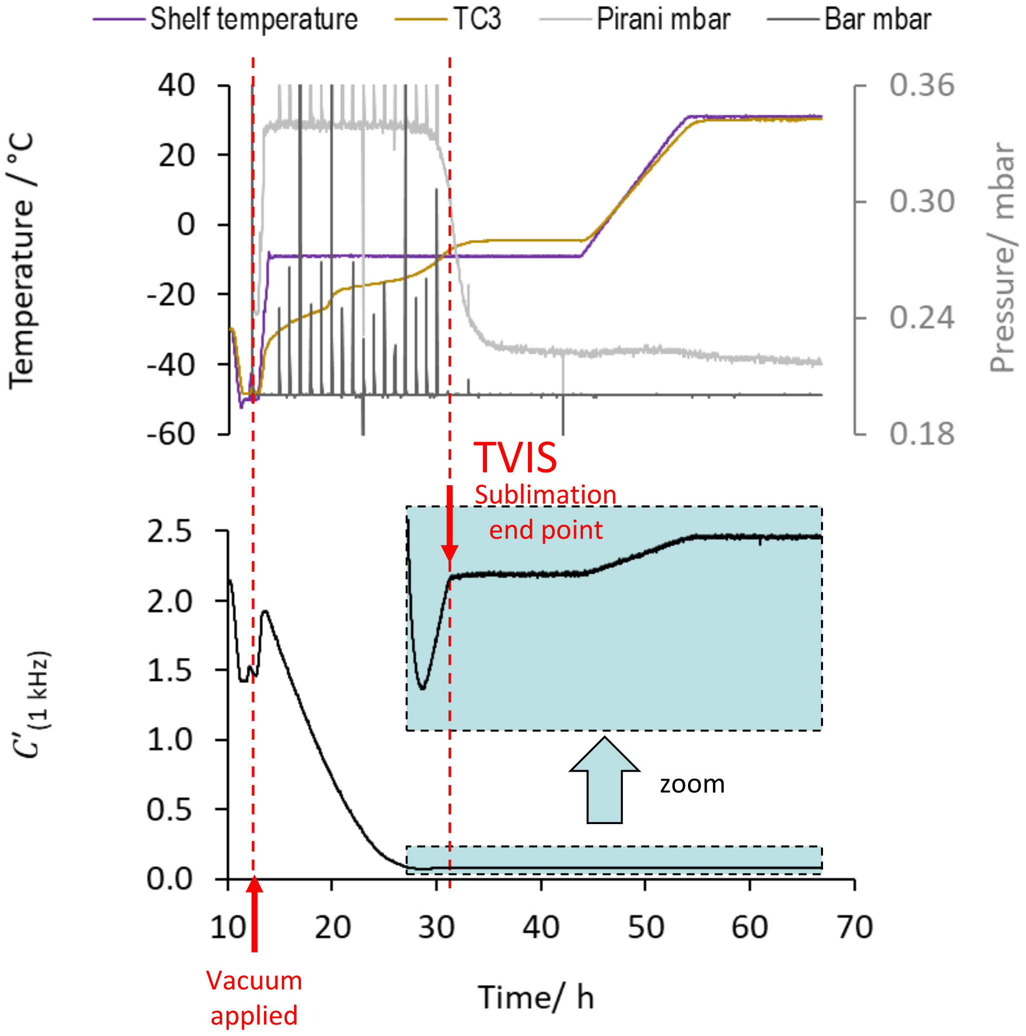
Primary drying 1% IgG, 1% Sucrose, 4% Mannitol, 20 mM Histidine, 0.01% Tween 20





Primary drying 1% IgG, 1% Sucrose, 4% Mannitol, 20 mM Histidine, 0.01% Tween 20





Take home messages from this talk

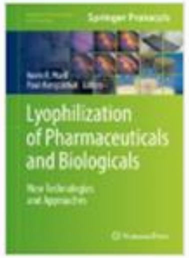
TVIS provides ….

- Identification of 'real', in-vial thermal transitions (critical events, such as devitrification of amorphous phases)
- Non-invasive determination of ice nucleation temperature (and ice solidification end point)
- Identification of true sublimation (primary drying) end point
    - Vapour sensing technologies, such as CPM, can not differentiate between source of water vapour (ice or adsorbed water)
    - Thermal measurements can also detect cooling from desorption of water adsorbed in the unfrozen fraction

Summary of Applications

Dielectric loss peak		Dielectric constant	
Log peak frequency (F_{PEAK})	Temperature calibration (ice phase) Spatial measurements of ice temperature possible with multiple nodes	**Low frequency (100 Hz)**	Ice nucleation onset time and temperature
Peak amplitude (C''_{PEAK})	Ice mass & sublimation rate Annealing end-point	**High frequency (100-200 kHz)**	Ice solidification end point Glass transition temperature Devitrification Sublimation end point

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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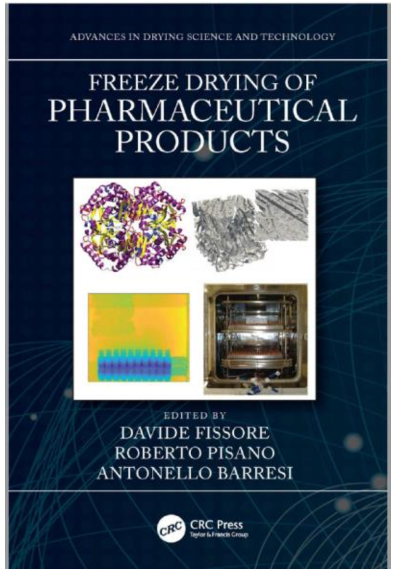

Freeze Drying of Pharmaceutical Products

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TVIS publications

- Jeeraruangrattana, Y., Smith, G., Polygalov, E. and Ermolina, I. (2020) Determination of ice interface temperature, sublimation rate and th **Nucleation Temperature and the Solidification End Point** ıent of microcollapse using through-vial impedance spectroscopy. European Journal of Pharmaceutics and Biopharmaceutics, 152, pp. 144-163
- 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
- Smith, G., Arshad, M.S., Polygalov, E., Ermolina, I., McCoy, T.R., Matejtschuk, P. (2017). Process Understanding in Freeze-Drying Cycle Development: Applications for Through-Vial Impedance Spectroscopy (TVIS) in Mini-pilot Studies. Journal of Pharmaceutical Innovation, 12 (1), pp. 26-40 **Key observation was the potential to measure temperature non-invasively**
- Arshad, M.S., Smith, G., Polygalov, E., Ermolina, I. (2014). 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**. European Journal of Pharmaceutics and Biopharmaceutics, 87 (3), pp. 598-605
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- Smith, G., Arshad, M.S., Polygalov, E. and Ermolina, I. (2013) An application for impedance spectroscopy in the characterisation of the **glass transition** during the lyophilization cycle: The example of a 10% w/v maltodextrin solution. European Journal of Pharmaceutics and Biopharmaceutics, 86 (3 Part B), pp. 1130-1140.

Acknowledgements

Evgeny Polygalov
Physicist and Inventor of TVIS
1952-2020

Dr Paul Matejtschuk
Head of Standardization
Science in the Analytical &
Biological Sciences Division

Pathum Wijesekara
PhD student, School of Pharmacy
De Montfort University Leicester

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Grant awards

Innovate UK
Government Support for industry

LyoDEA
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By dielectric analysis

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