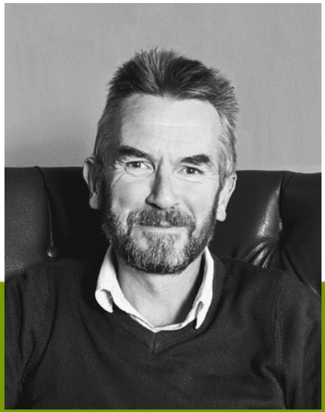
12th Edition

Biologics Formulation Development and Drug Delivery Forum

Non-invasive spectroscopic methods for single-vial PAT in biopharmaceutical freeze-drying

Prof. Geoff Smith

DMU LyoGroup



In collaboration with NIBSC

Confidence in Biological Medicines

marcusevans conferences

Tuesday June 15th 2021

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Overview

Introduction to
freeze-drying

Introduction to
process analytical technologies

Through-vial impedance spectroscopy (TVIS)

Multiplexing with
impedance measurements

Characterization of critical
process parameters

Benefits of Lyophilization

“30% of therapeutic proteins are freeze dried”

“80% are lyophilized in vial”

Lyophilization commonly used for

- Small Molecules Drugs (e.g., acyclovir)
- Large Molecule Drugs (e.g., proteins, DNA)
- Vaccines
- Blood factors

Azithromycin injection. (Zithromax®)

Zoster vaccine (Zostavax®)

Lyophilization

Freezing

Sublimation

Desorption

Powder

- *Low moisture content*
- *More surface area & porous*

Easy to transport

Increased Stability

Easy to Dissolve

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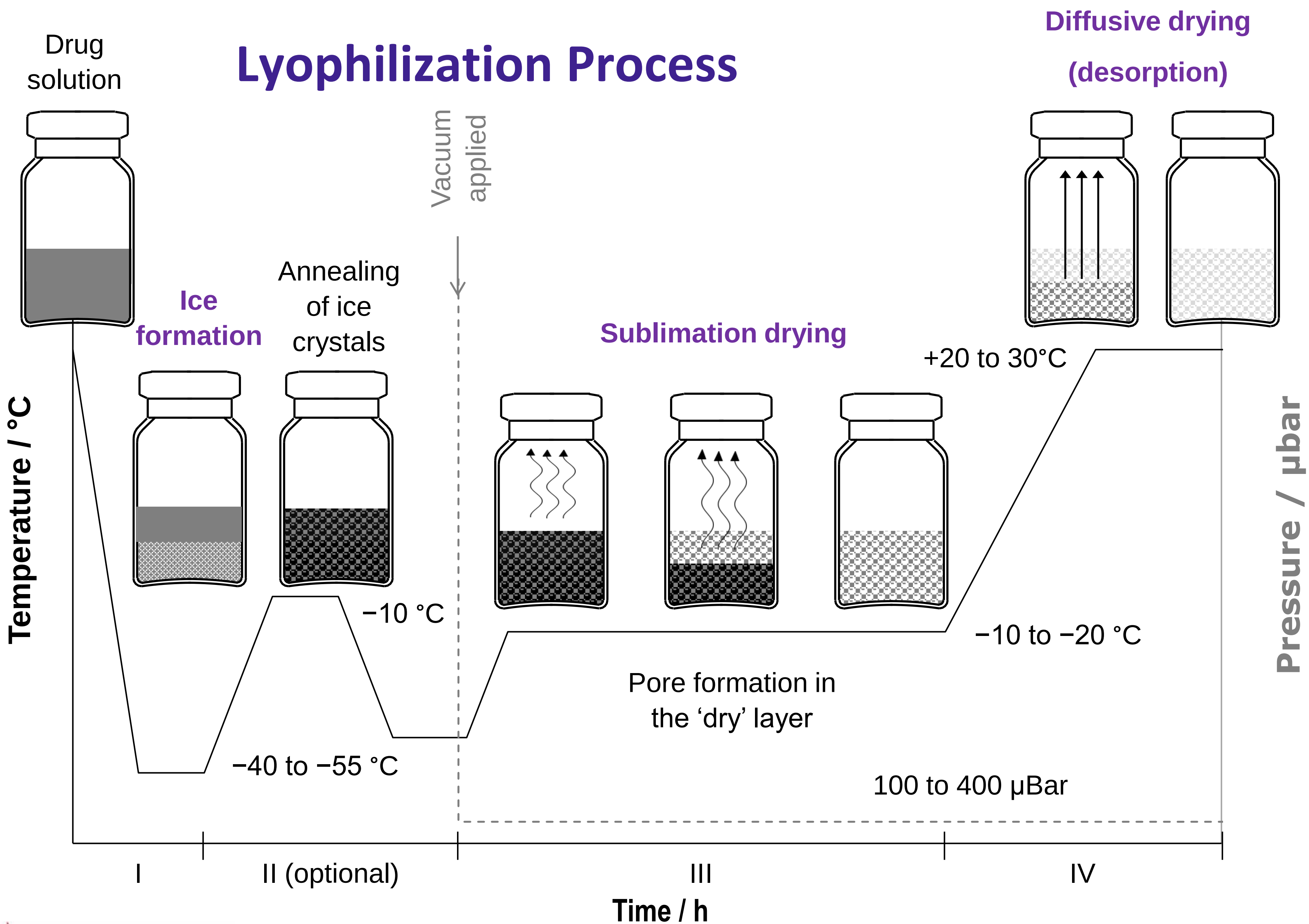
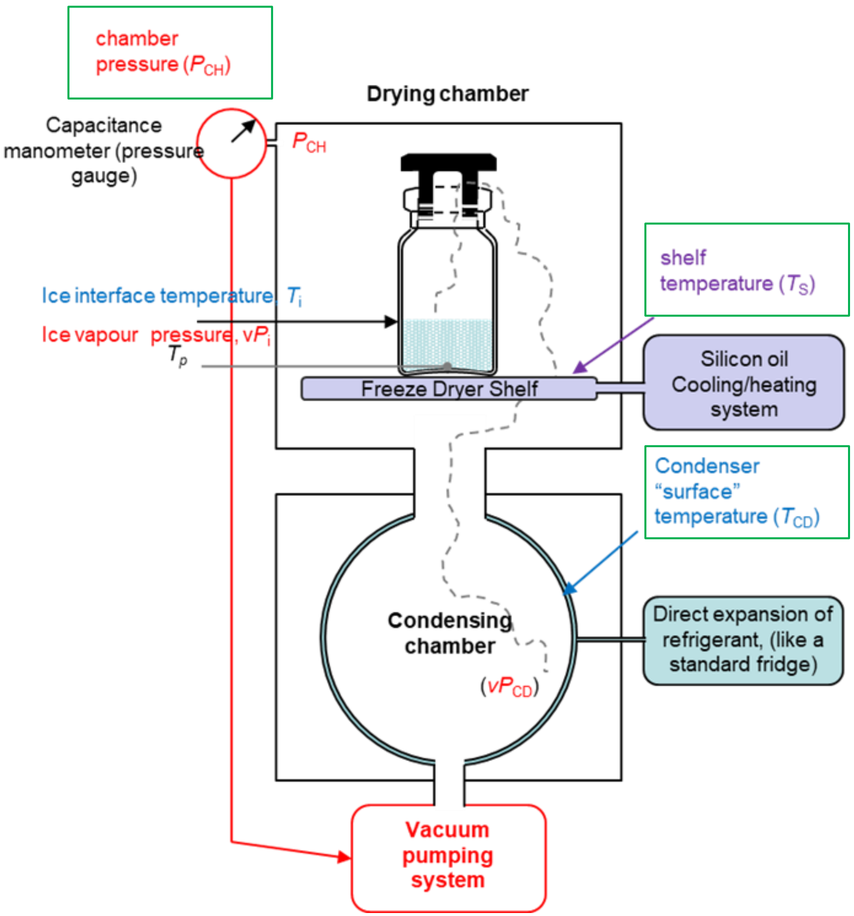
Lyophilization Process



Lyophilization process



Operating parameters :

(A) shelf temperature (ramp)

(B) chamber pressure

(C) condenser temperature

Critical process parameters:

- Ice nucleation temperature (T_n)
- Rate of change of the product temperature (dT_p/dt):
- Phase behaviour of solid/solute fraction
- Critical temperature (e.g. collapse), T_c
- Vial heat transfer coefficient
- Porosity of the 'dry' fraction of the product that develops during primary drying (R_p = 1/ Porosity)
- Ice interface temperature (T_i) < T_c
- Primary and secondary drying end points

Process Analytical Technology (PAT)

PAT, as defined by the ICH, is "a system for **designing, analysing and controlling** the manufacturing through timely measurement (during the process) of critical quality and performance attributes of raw and in-process materials and the process with the goal of ensuring final product quality"

ICH, 2009. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Topic Q8(R2): Pharmaceutical Development.

Single vial (new) techniques

- Through vial impedance spectroscopy

Single vial (existing) techniques

- Probe probes
- Microbalance
- Heat flux transducers

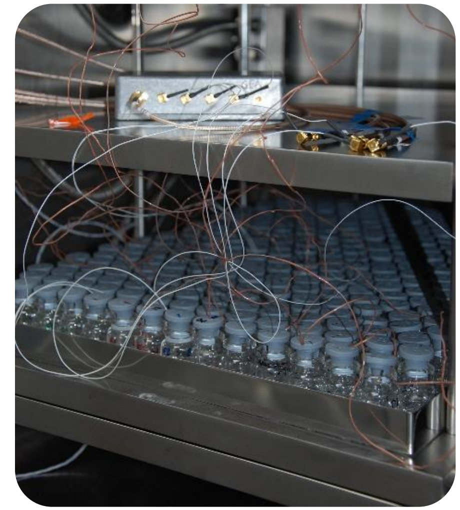
Batch techniques

- Pressure rise test (PRT)
- Manometric temperature measurement (MTM)
- Comparative pressure measurement (CPM)
- Time domain laser absorption spectroscopy (TDLAS)

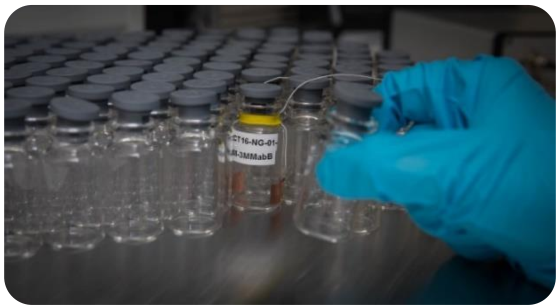
Through Vial Impedance Spectroscopy

Single Vial PAT

Multichannel



Non- perturbing to packing of vials



Thin flexible cables (0.5 - 2 m)

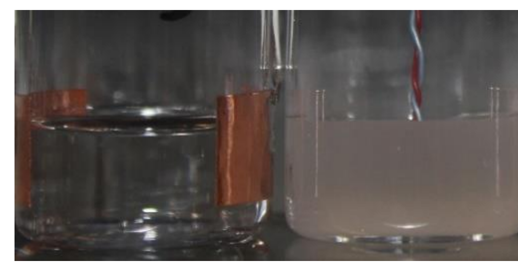
- Stoppering unaffected

Temperature calibration

- using nearest neighbour vial(s)

Low thermal mass of electrodes

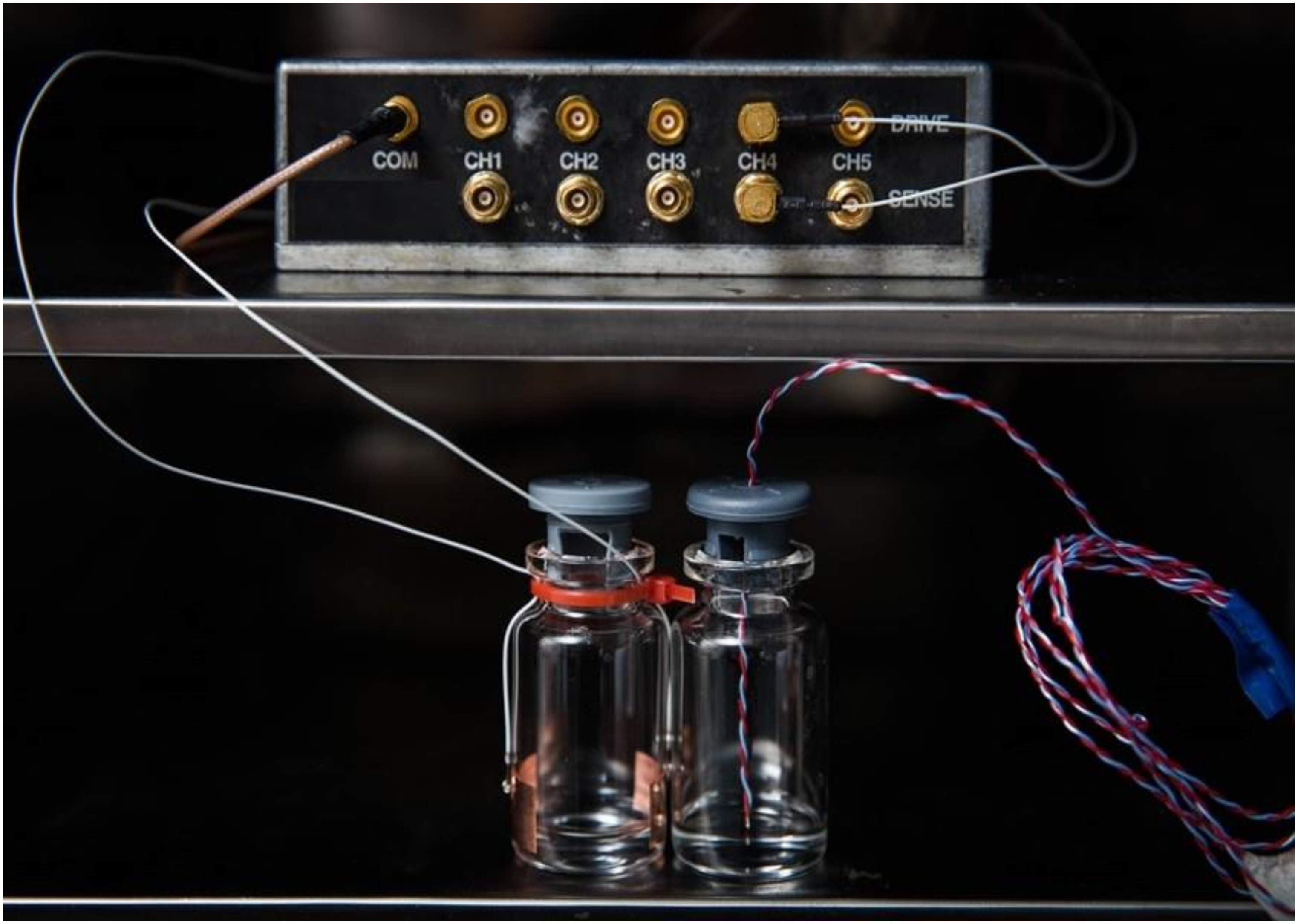
- no interference with heat transfer & drying rates



Non-sample invasive

- no impact on ice nucleation

Junction box



CASE STUDY 1

TVIS temperature calibration

Method 1 : Triangulation

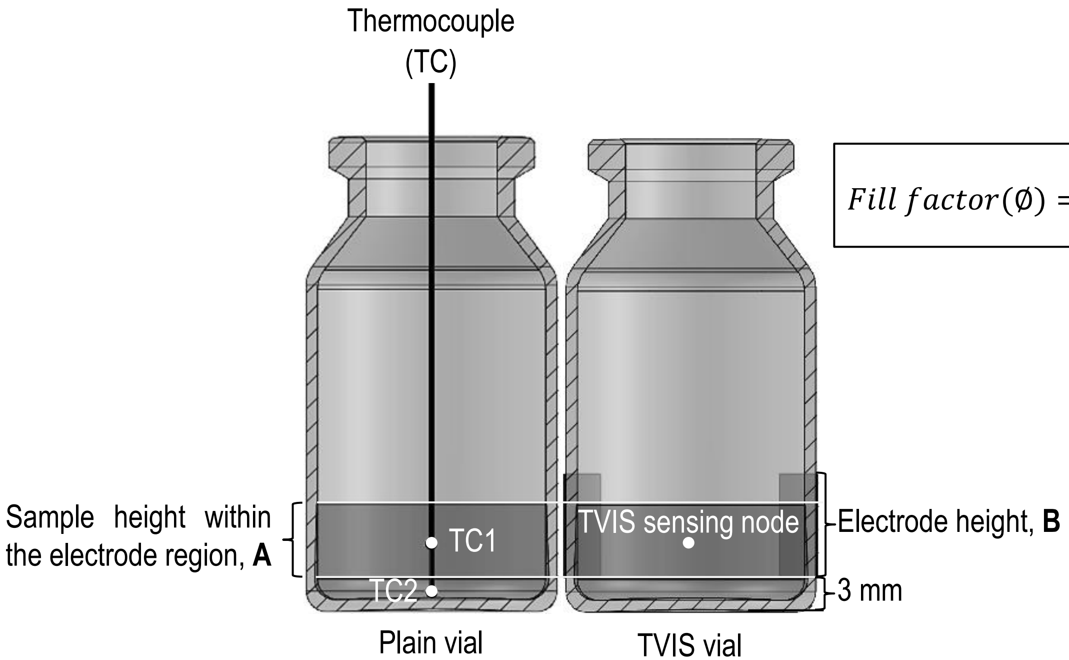
Mehod 2 : Tempris®

1. Triangulation method

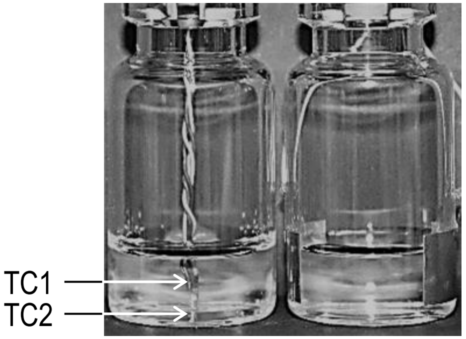
Placing a thermocouple at the TVIS sensing node allows for the calibration of the temperature inside the TVIS vial to a precision of +/- 0.4 C

(see next two slides)

TC in nearest neighbour vial

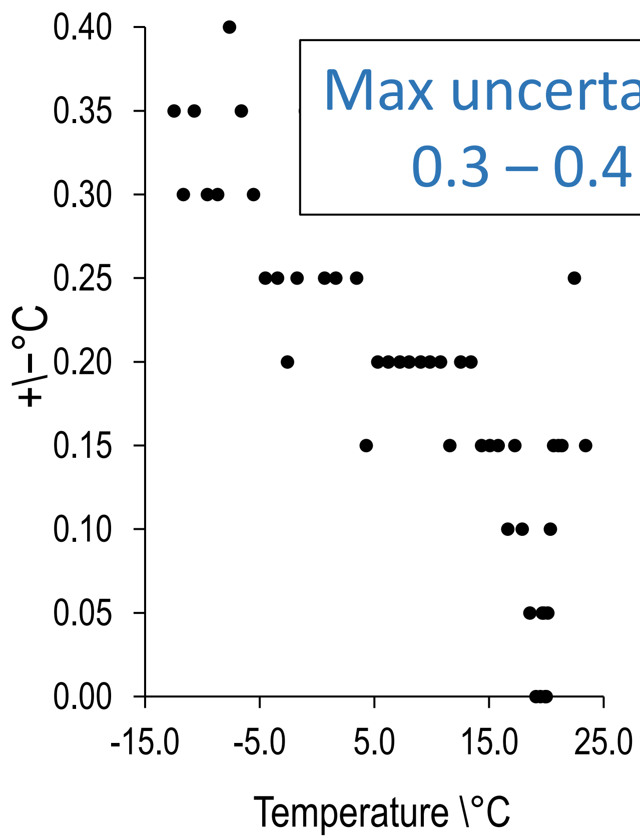


$$Fill\ factor(\emptyset) = \frac{A}{B}$$

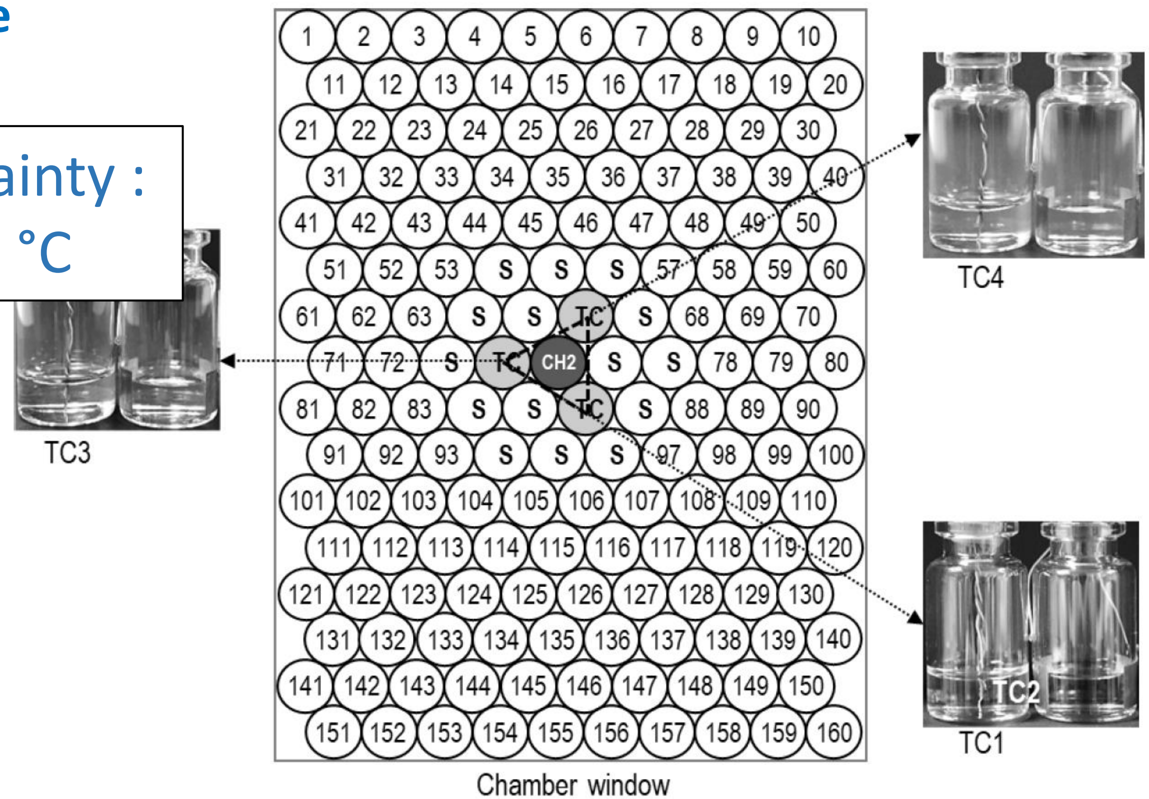


1. Triangulation method

Temperature uncertainty during freezing phase

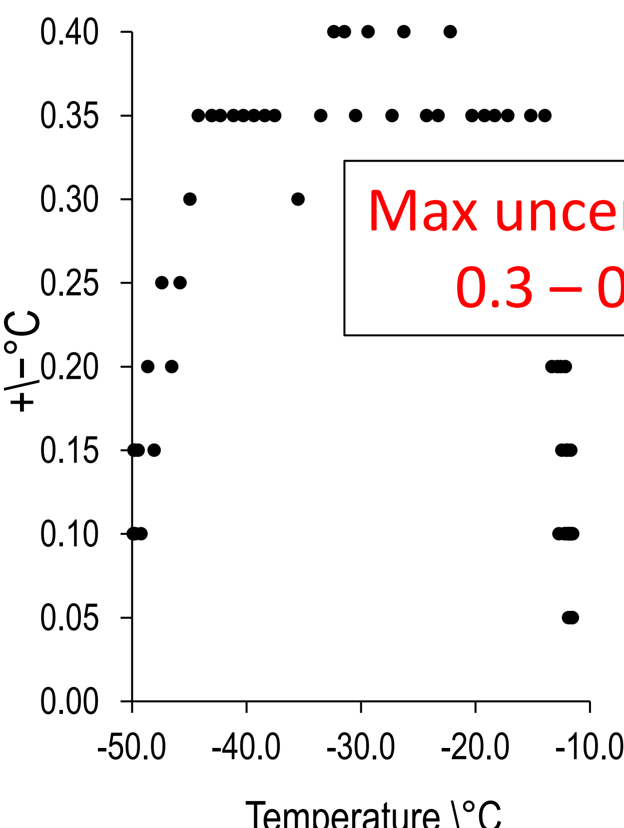


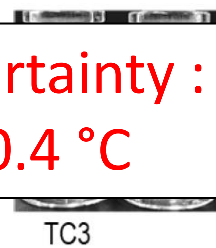
TC in nearest 3 neighbour vials



Temperature calibration for the TVIS vial:
1. Triangulation method

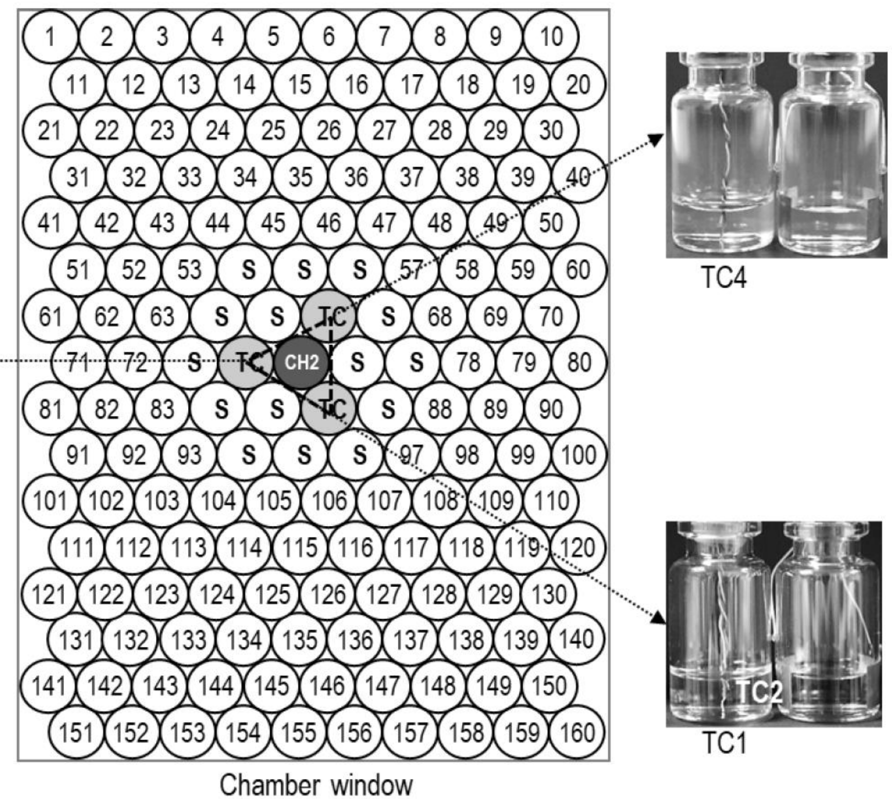
Temperature uncertainty during re-heating phase





Max uncertainty : 0.3 – 0.4 °C

TC in nearest 3 neighbour vials



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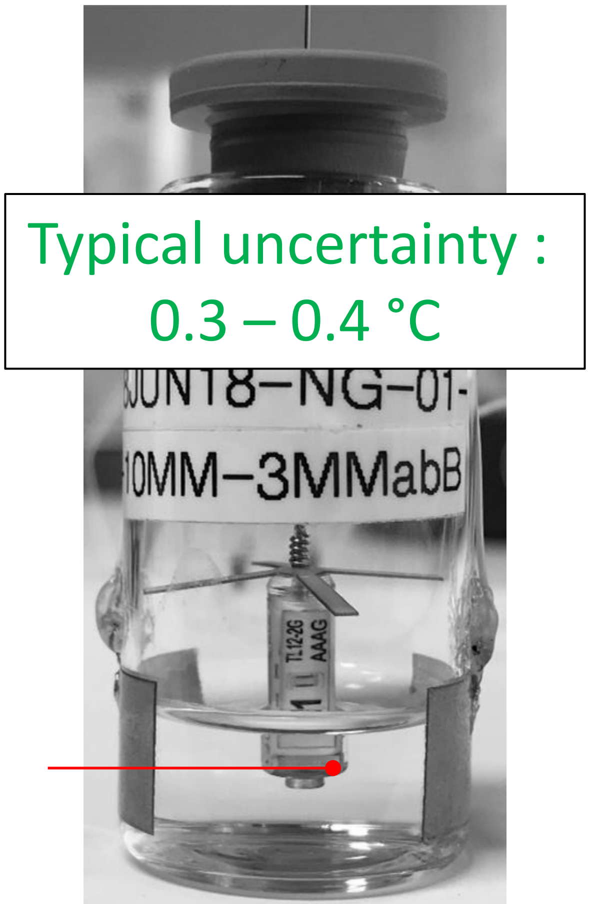
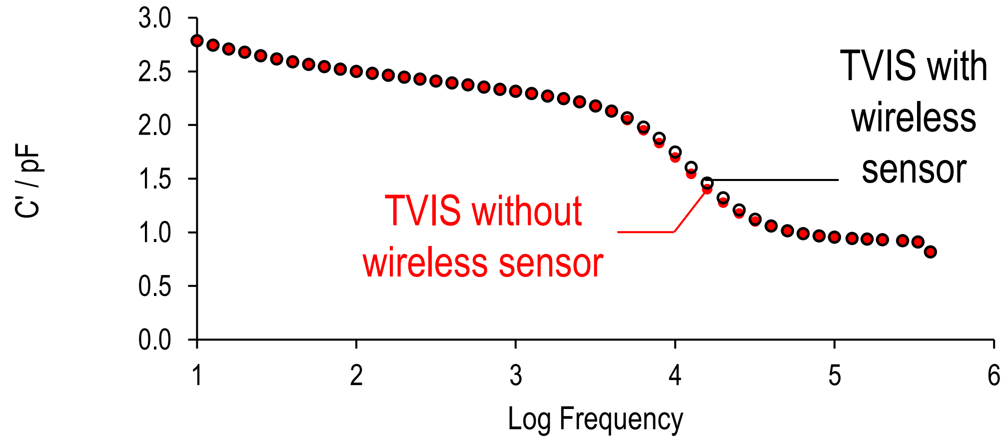
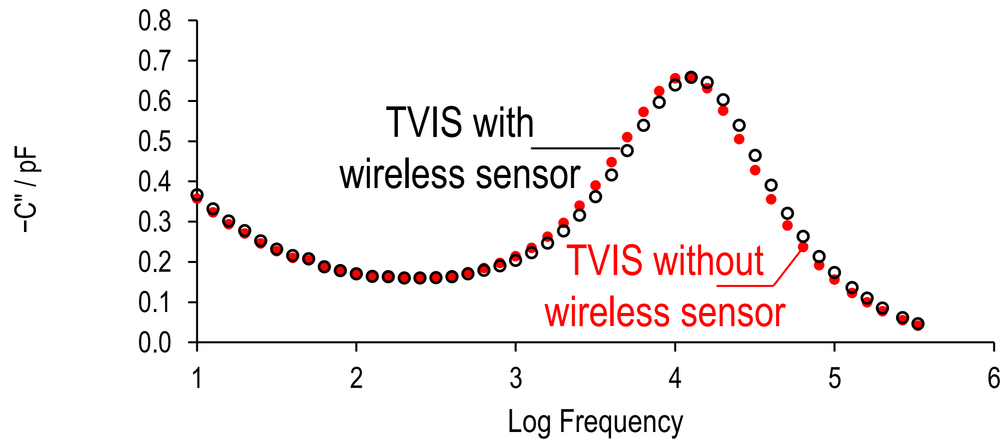
Temperature calibration for the TVIS vial:
2. Tempris® method

TVIS spectra







tempris® sensor technology

DMU LyoGroup

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

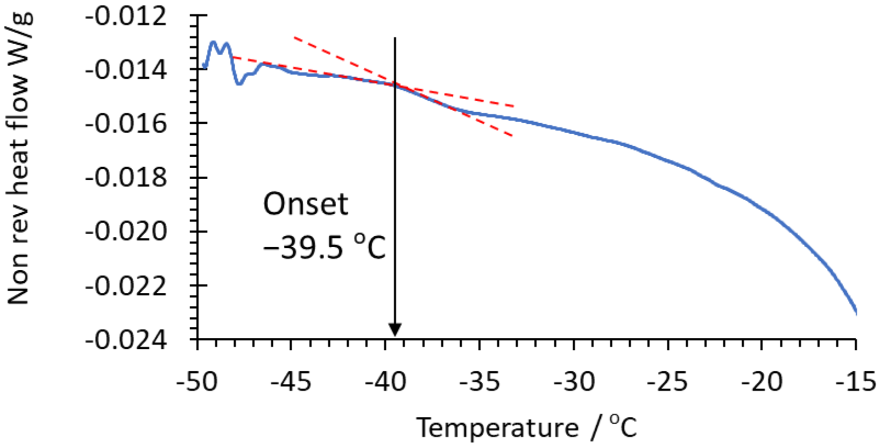
Sample	Amount (mg)
1% IgG	51.2
15% IgG	77.3
Excipients	82.3

DSC Q2000 V24.11 Build 124
(TA Instruments)

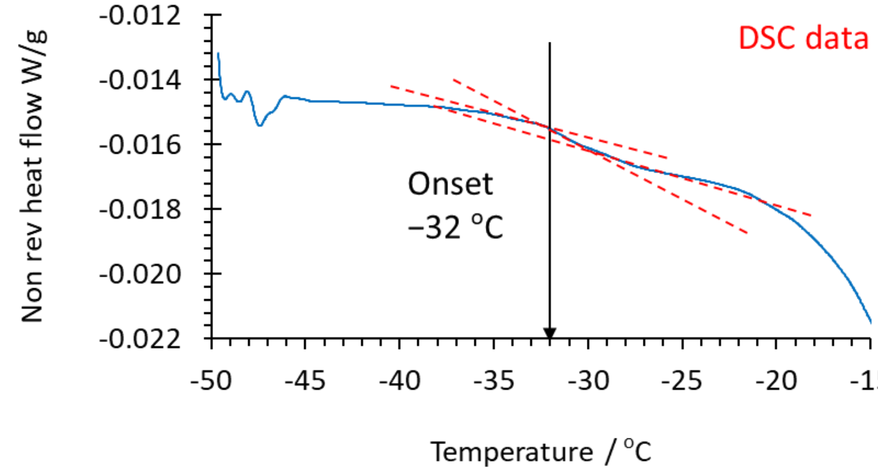
Step	Description
1	Isothermal for 2 min
2	Ramp 10 °C/min to -50 °C (mark end of cycle 1, data storage off)
3	Isothermal for 5 min
4	Ramp 1.5 °C/min to -15 °C
5	Isothermal for 10 min
6	Ramp 1.5 °C/min to -50 °C (data storage on, sampling interval 1 s/pt, modulate ± 0.23 °C every 60 s)
7	Isothermal for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

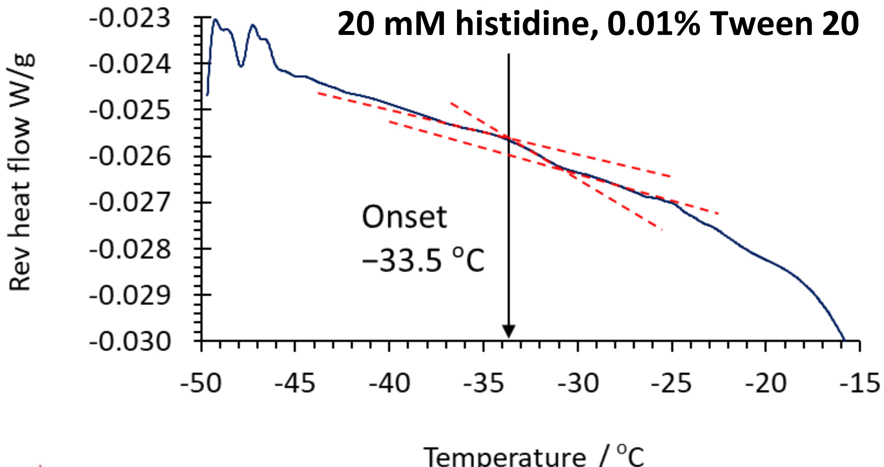
0% IgG
1% sucrose, 4% mannitol
20 mM histidine, 0.01% Tween 20



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

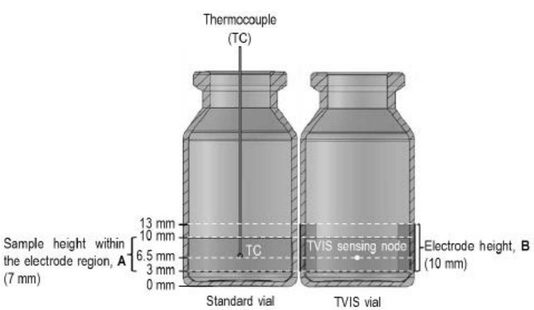
Junction box

Vial array

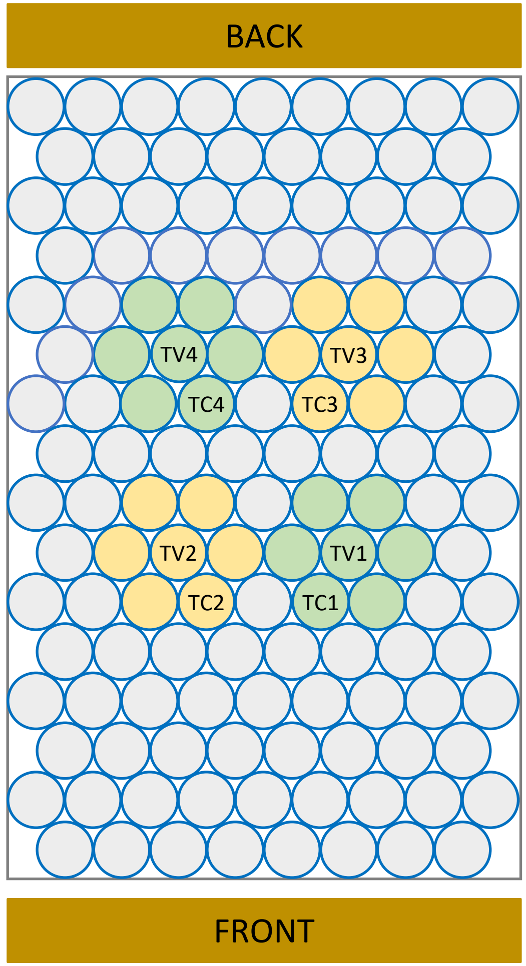
Telstar LyoBeta Pilot Freeze Dryer

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

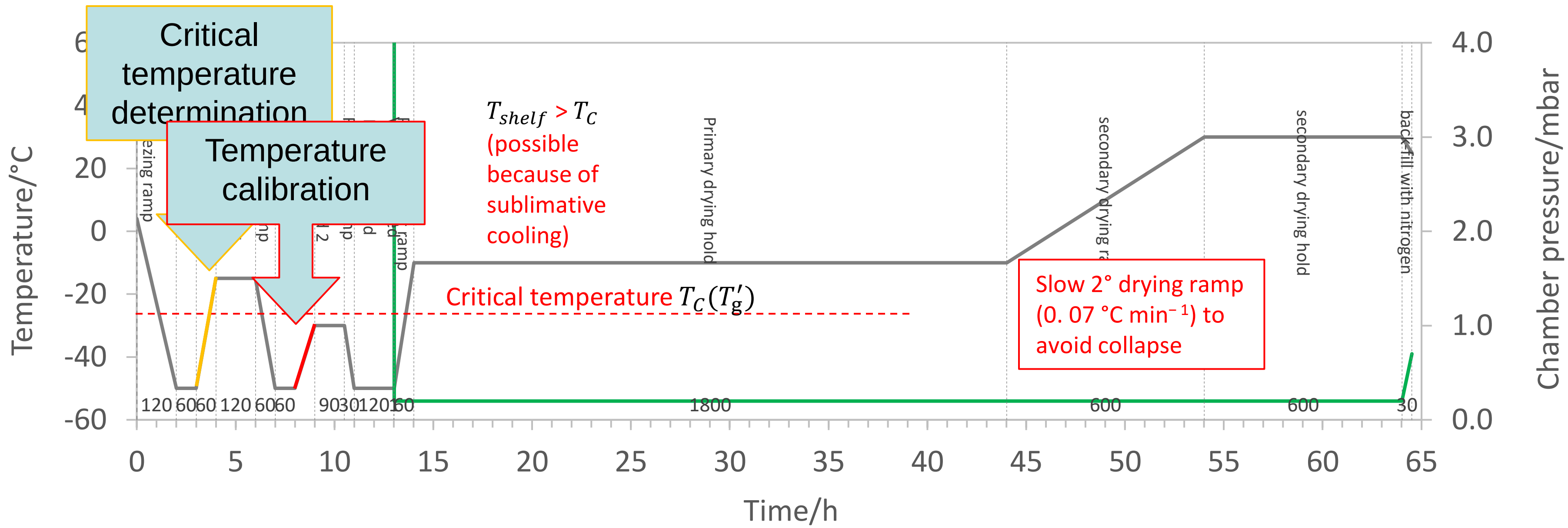
TV4 - TVIS-modified vial connected to CH4

TC4 - Standard-unmodified vial with TC4

- Standard-unmodified vial

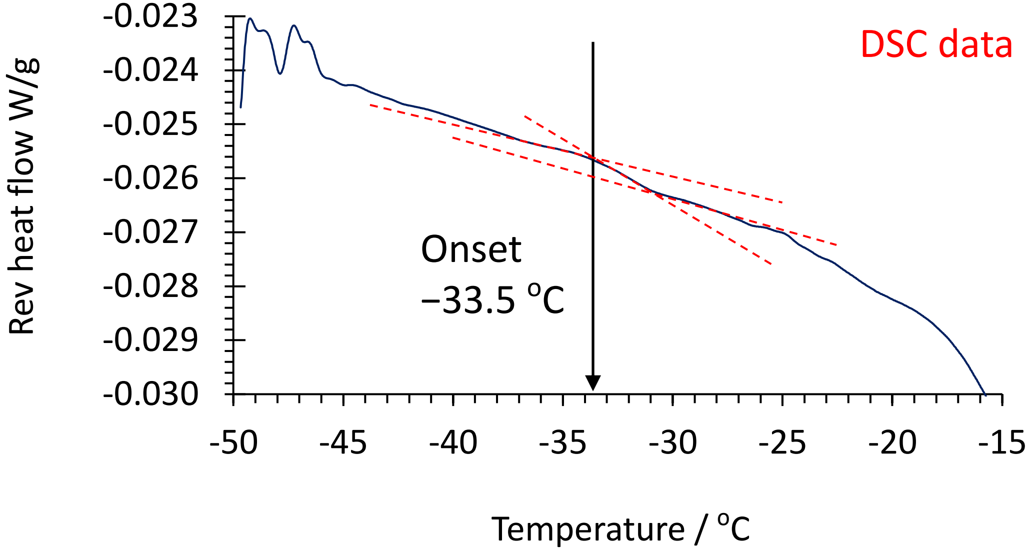
Freeze drying cycle

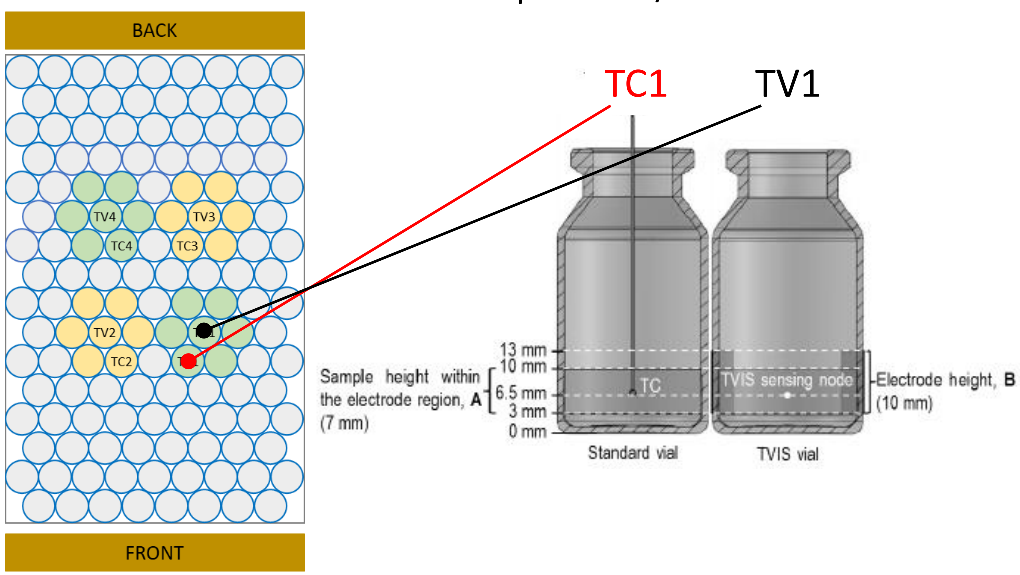
Step	Temperature (°C)	Ramp (°C/min)	Time (min)	Cumulative Time (h)	(mbar/min)	Set pressure (mbar)	Notes
Equilibrium phase	4		30	0		1000	Equilibrate
Freezing ramp	-50	-0.45	120	2		1000	Freeze to below maximal solidification point (determined by FDM/thermal m
Freezing hold	-50		60	3		1000	Soak to equilibrate 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

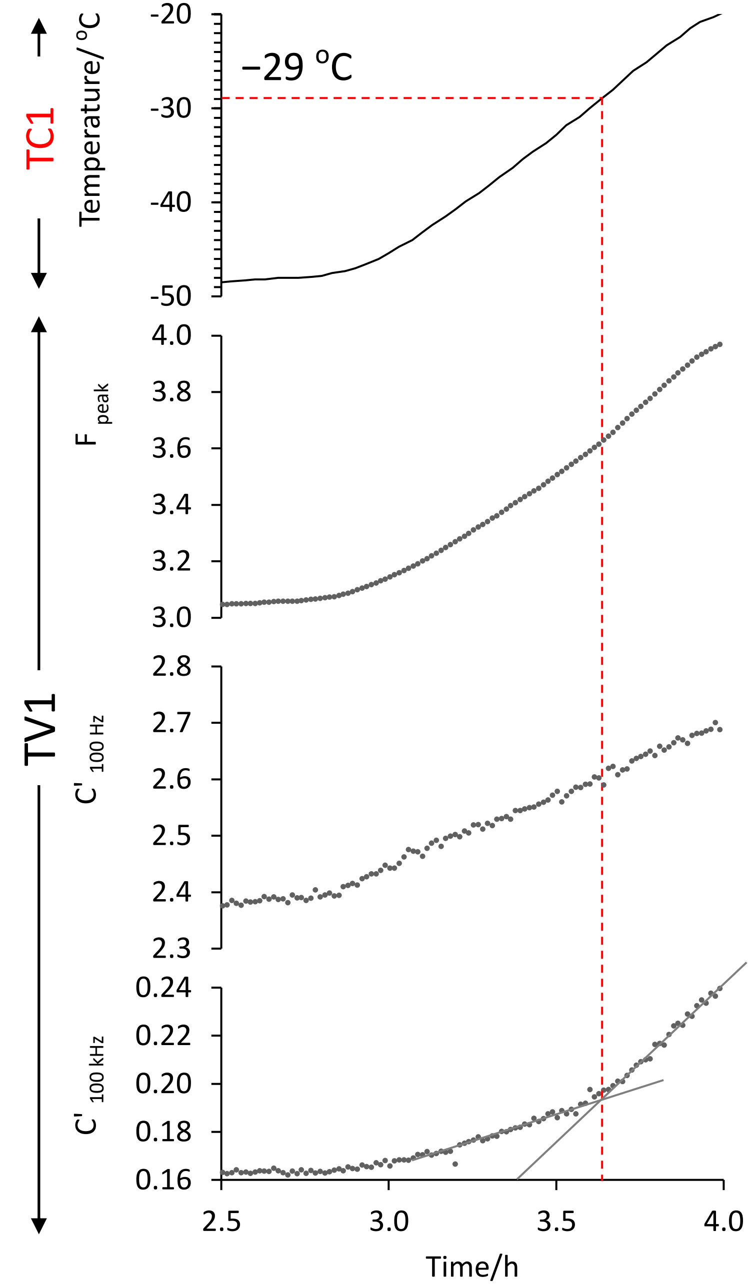


Anneal temperature and time and critical $T_C(T_g')$ need to be determined empirically .Condenser temperature (not shown) should be 10-20°C below minimum shelf T,e.g. −70 °C

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







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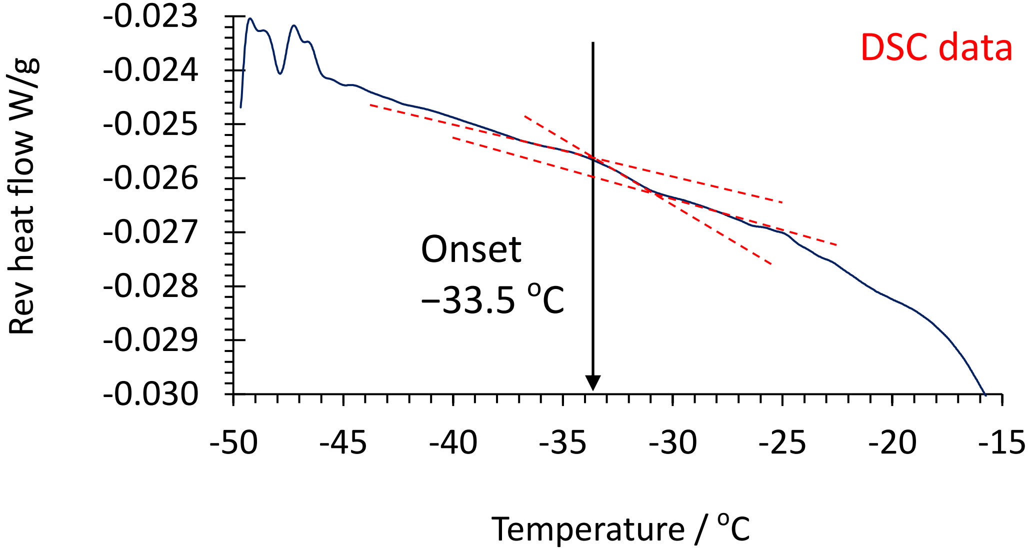
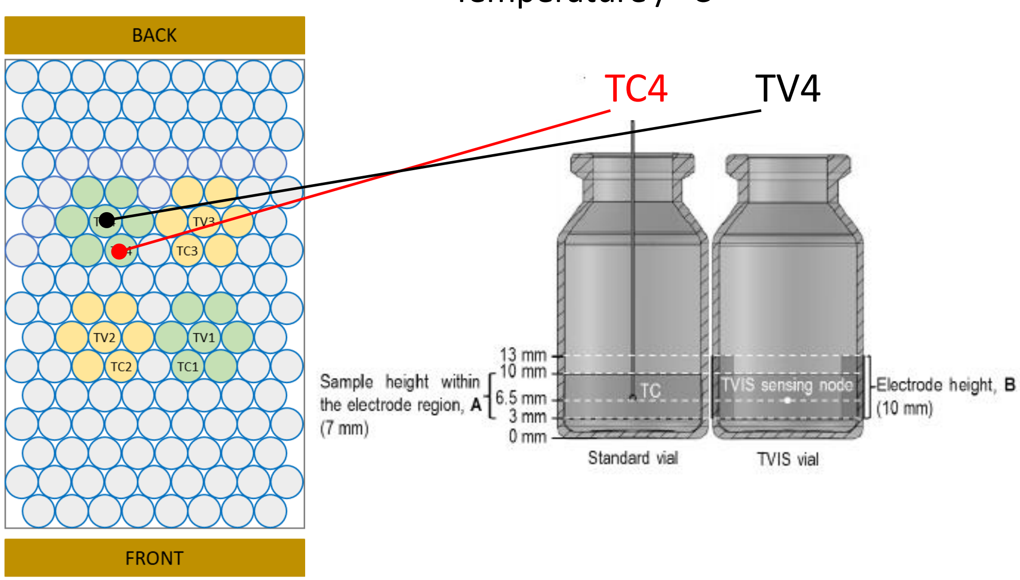
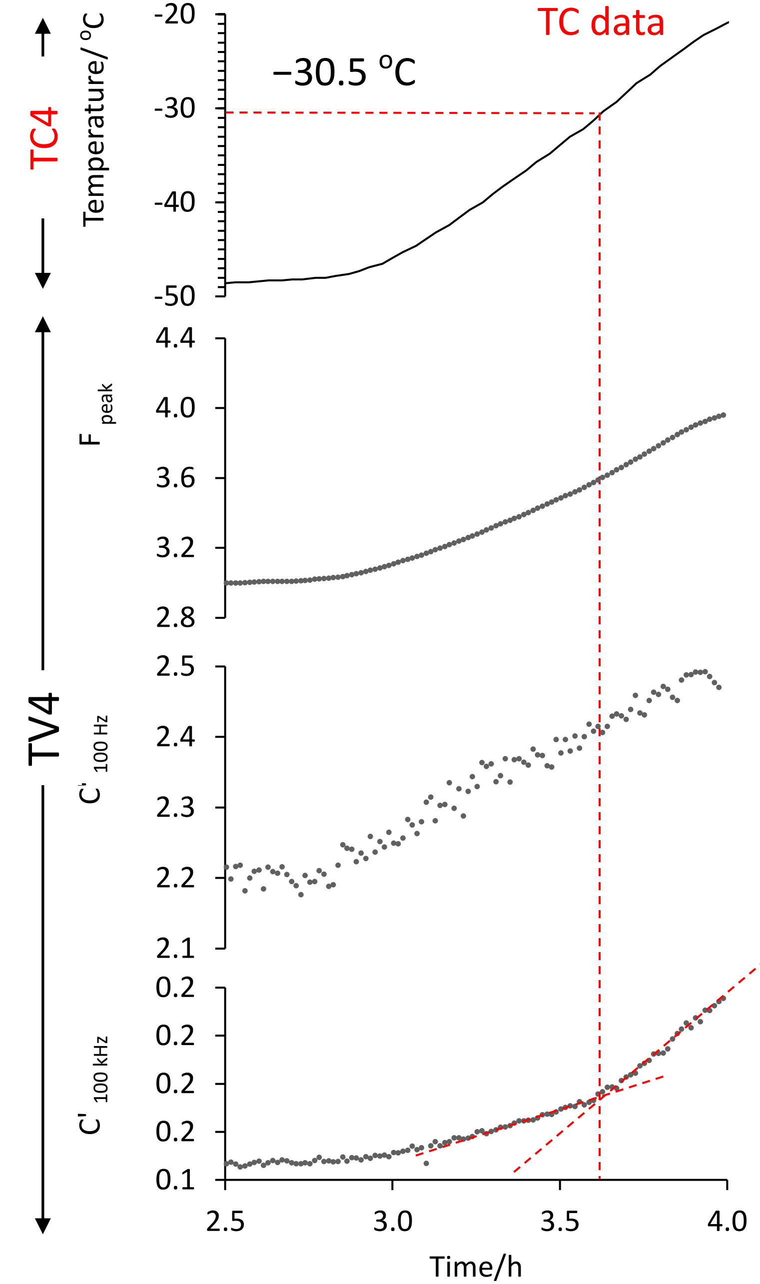
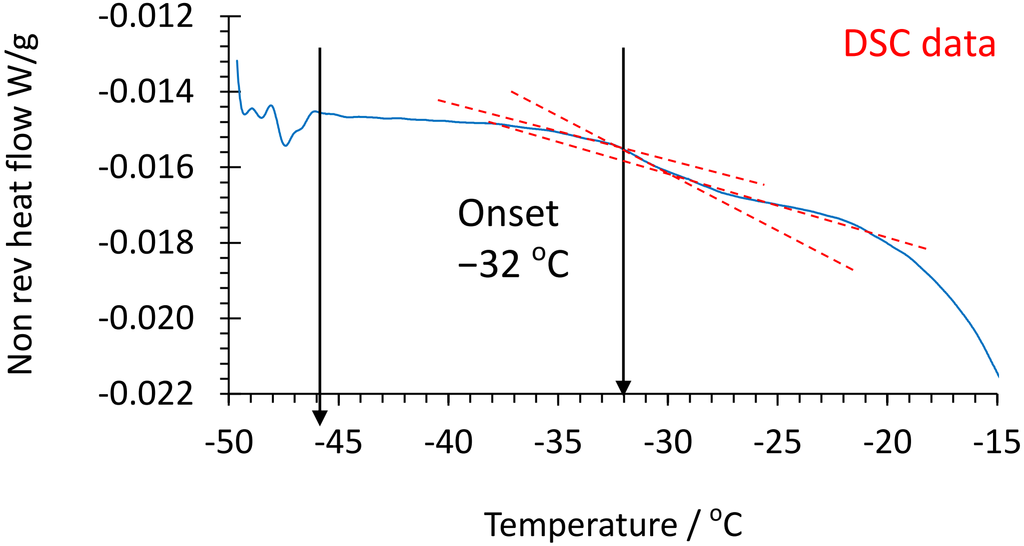
Re-heating of 15% IgG, 1% sucrose, 4% mannitol, 20 mM histidine, 0.01% Tween 20

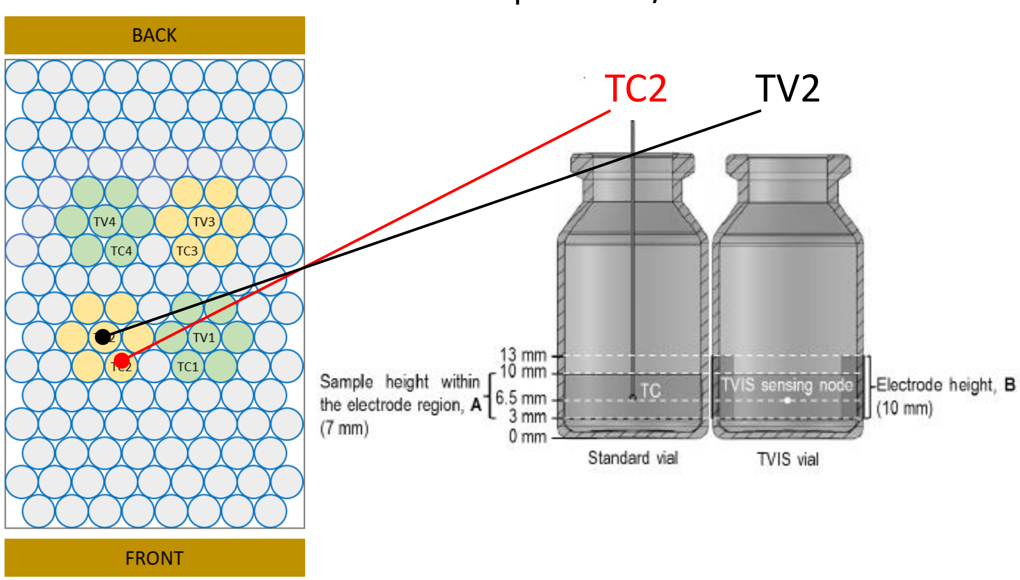


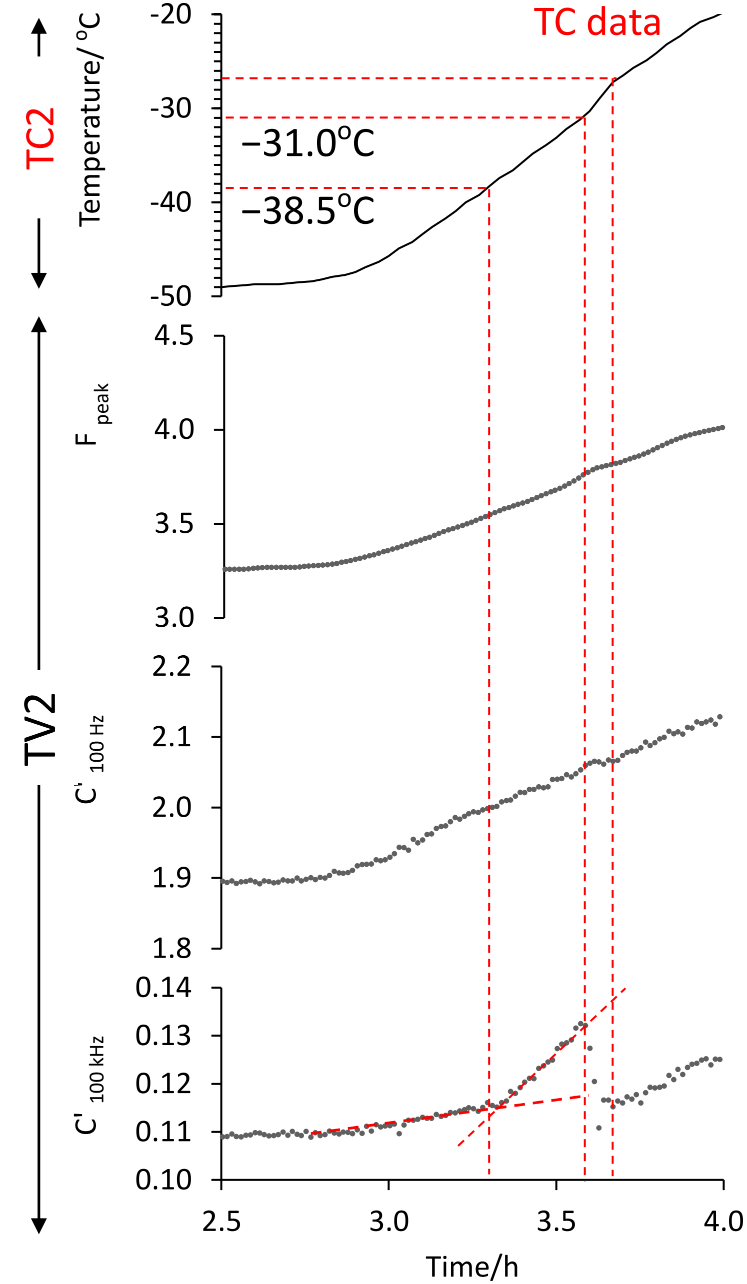




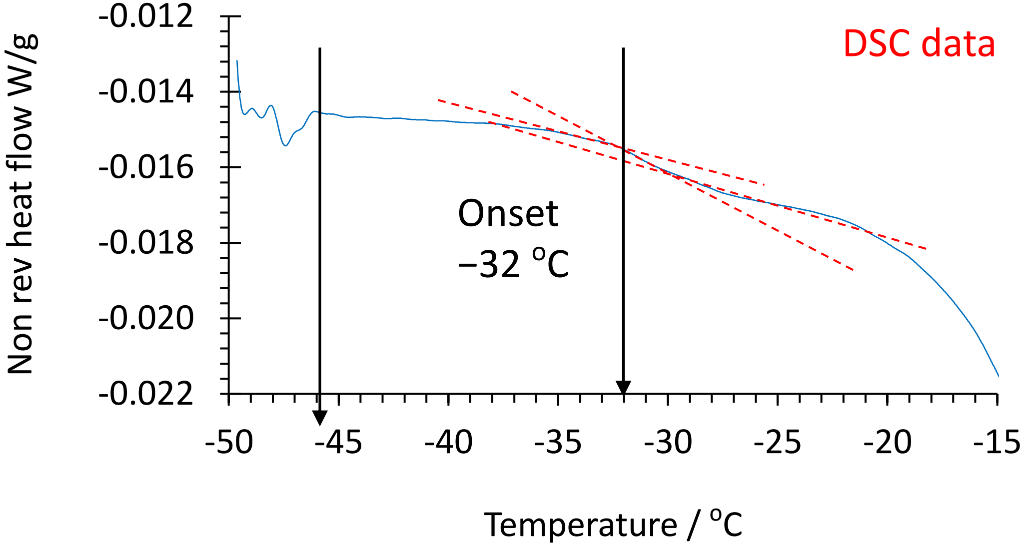
Re-heating of 1% IgG, 1% sucrose, 4% mannitol, 20 mM histidine, 0.01% Tween 20

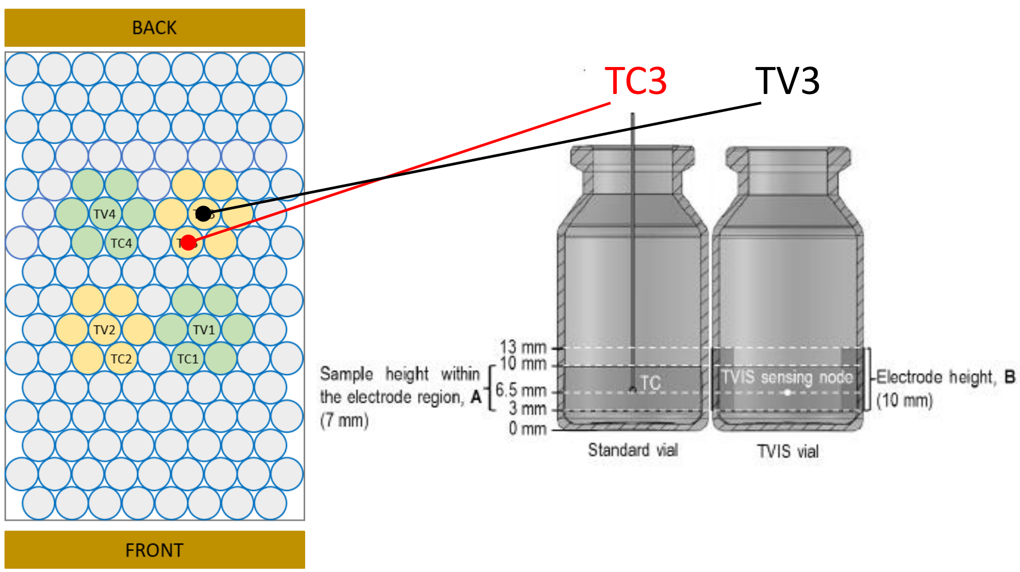


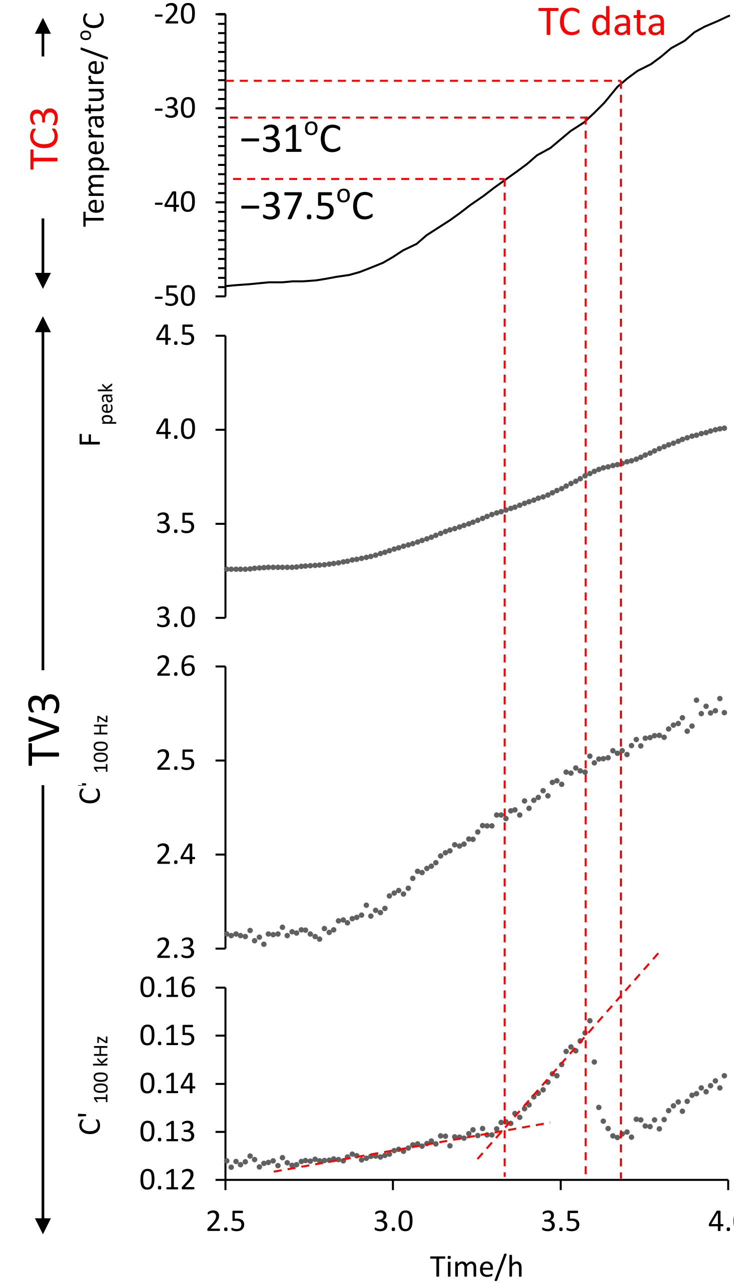




Re-heating of 1% IgG, 1% sucrose, 4% mannitol, 20 mM histidine, 0.01% Tween 20

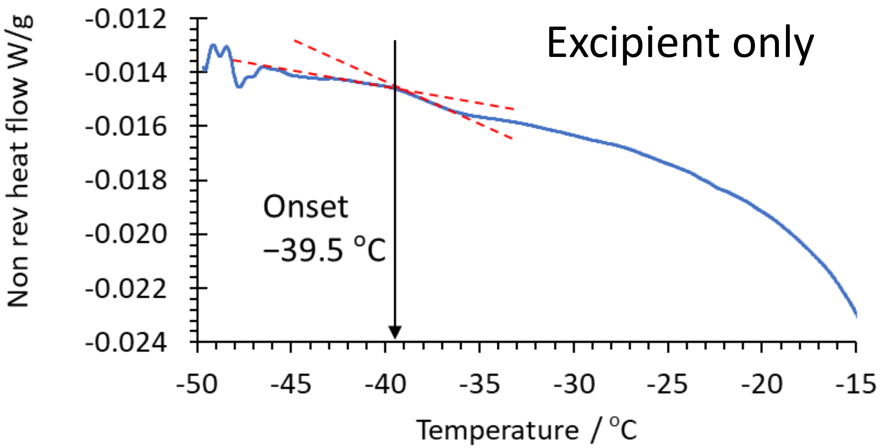


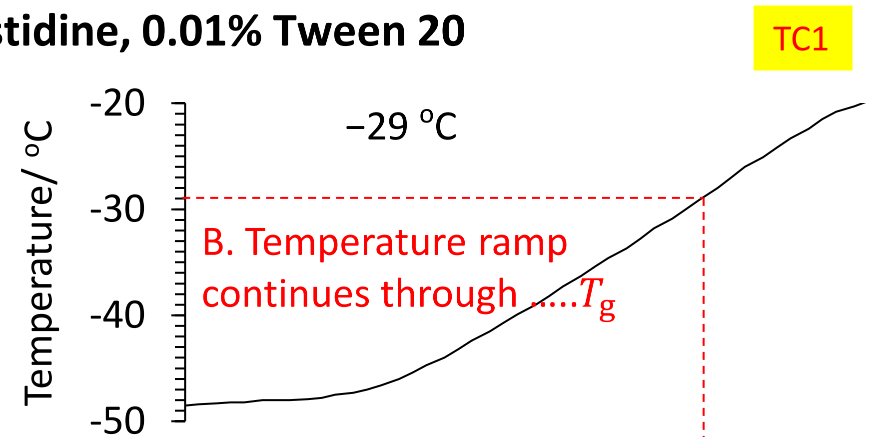




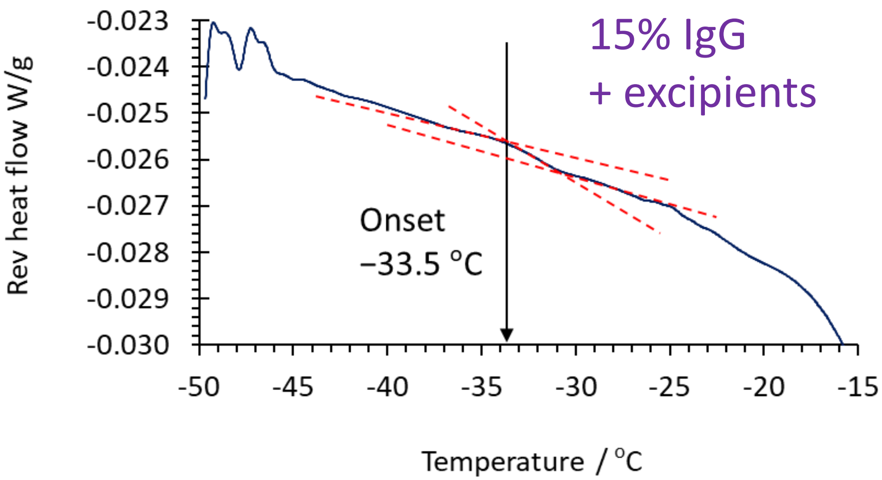
What does this mean?

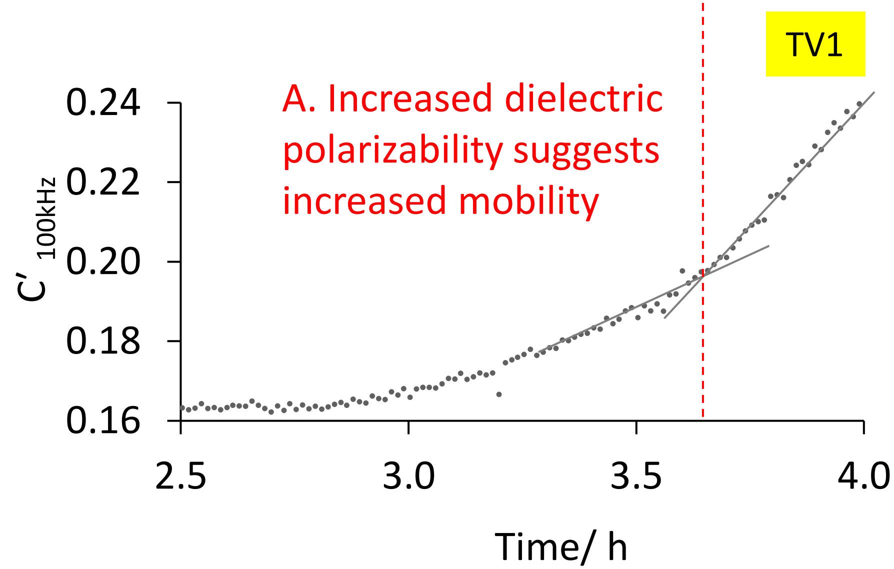
15% IgG, 1% sucrose, 4% mannitol, 20 mM histidine, 0.01% Tween 20





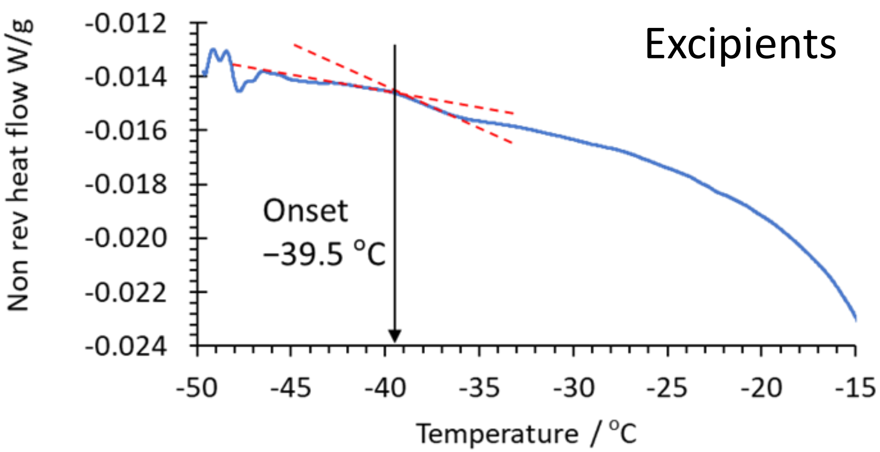
A with B suggests a glass transition

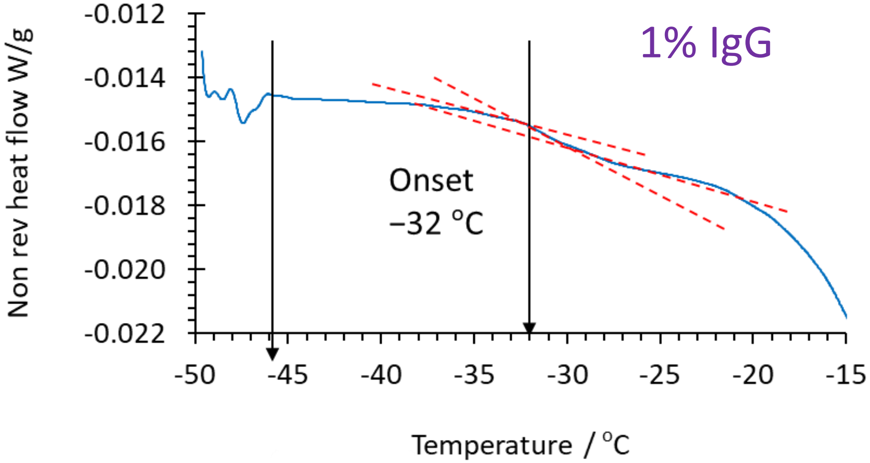


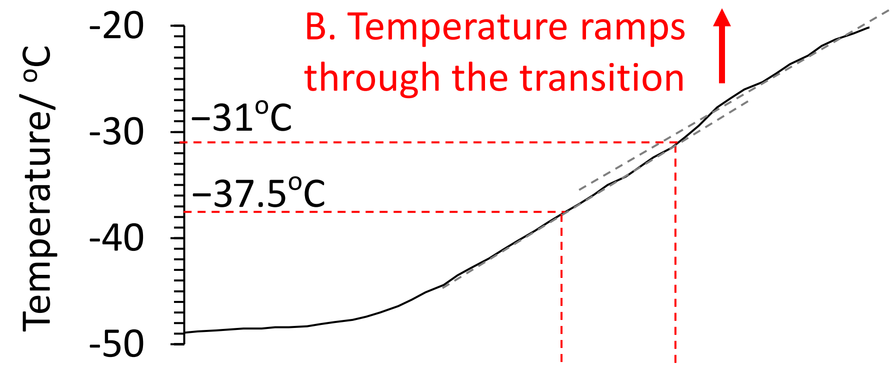


What does this mean?

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

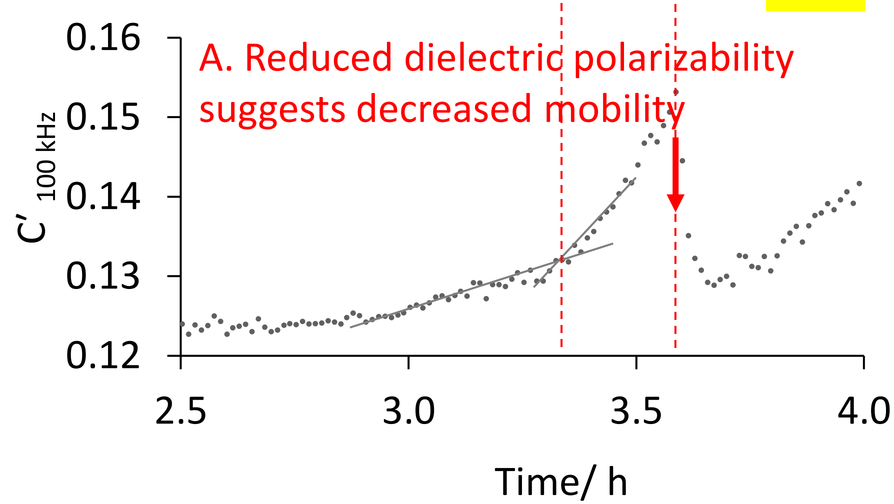






A with B suggests crystallization (i.e. devitrification)

TV3



Summary: “unexpected” phase behaviour at low IgG

CPP	0% IgG	15% IgG		1% IgG	
DSC T_g (Onset) (°C)	−39.5	−33.5		−32	
TVIS data		TV1	TV4	TV2	TV3
devitrification (°C)	N/A	-	-	−31	−31
glass transition (°C)	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)

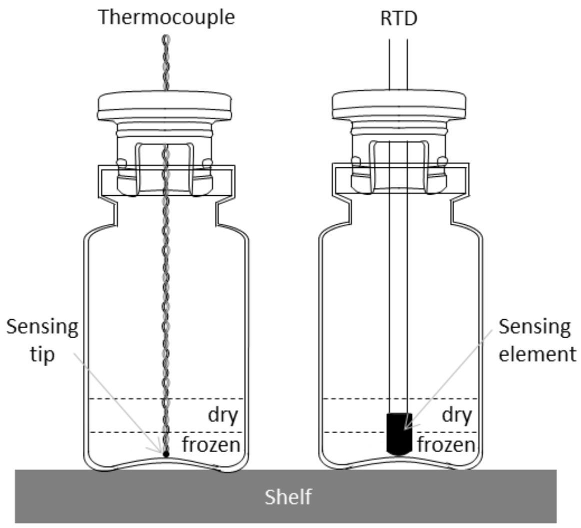
CASE STUDY 3

Temperature determination by product probes

Invasive nature of probes produces non-representative behaviour in freezing and primary drying

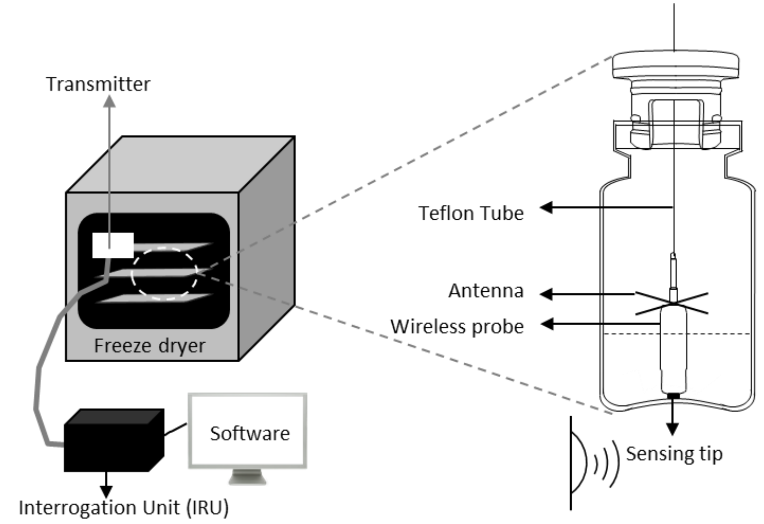
Product probes

Conventional thermocouple and Resistance temperature detector (RTD)



- RTD : steam sterilizable
- TCs : small more pin point
- Both placed at the front

Temperature Remote Interrogation System



- Wireless
- Can be used across the whole batch and in production scale

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

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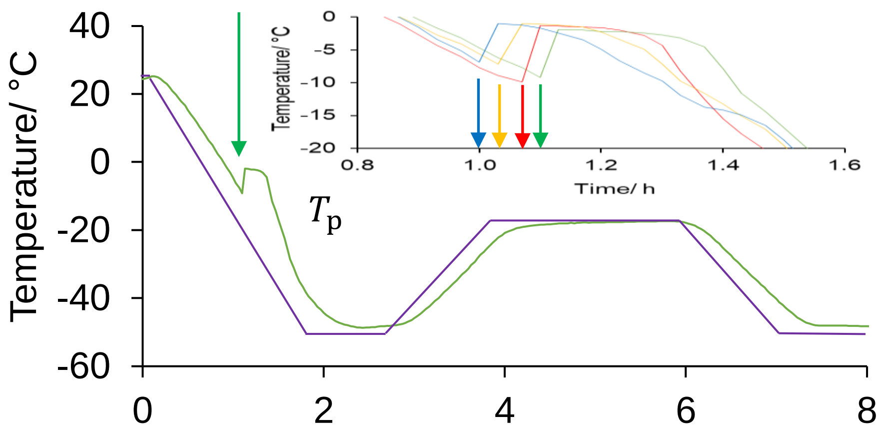
Results from TC probe

Freezing and annealing

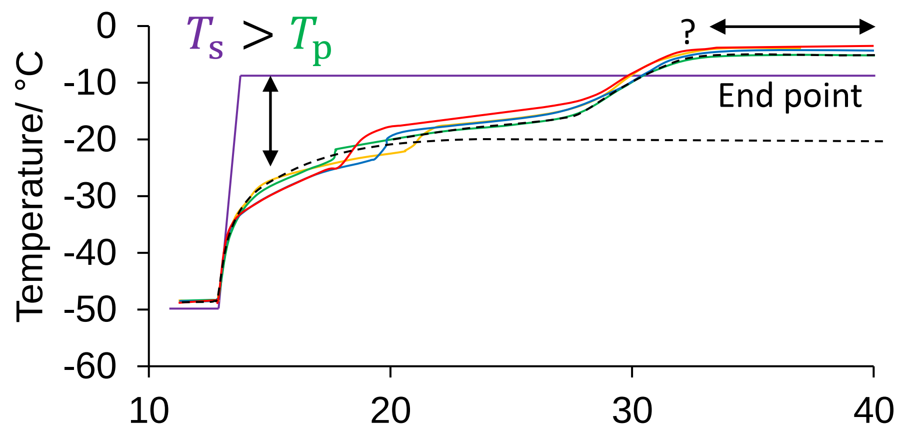
Ice nucleation (stochastic process)



- Product temperatures (T_p) > Shelf temperature (T_s) during cooling
- Ice nucleation temperature, T_n determined by a by spike in T_p
- $T_p < T_s$ during annealing ramp up
- $T_p < T_s$ during annealing ramp down

Primary drying

End point determined by plateau in temperature



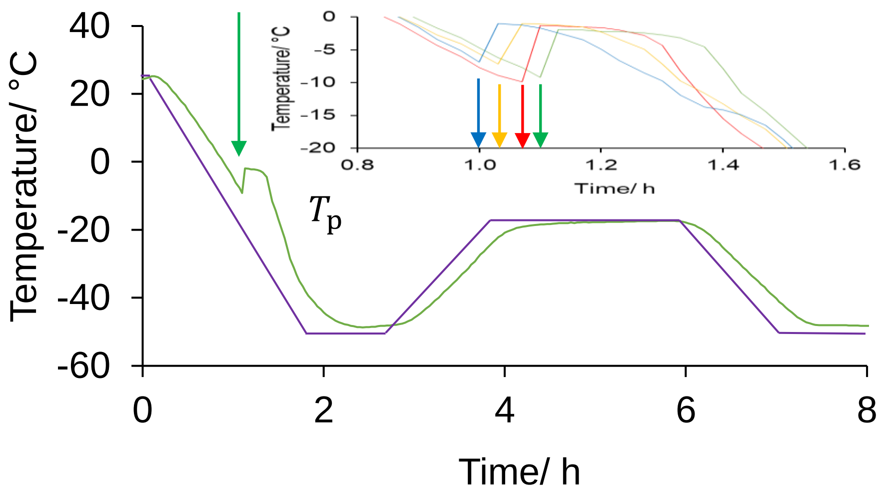
$T_p < T_s$ during drying associated with absorption of latent heat (self cooling of the vial)

Primary drying end point determined by probe temperature (T_p) increasing above the shelf temperature (T_s)

Results from TC probe

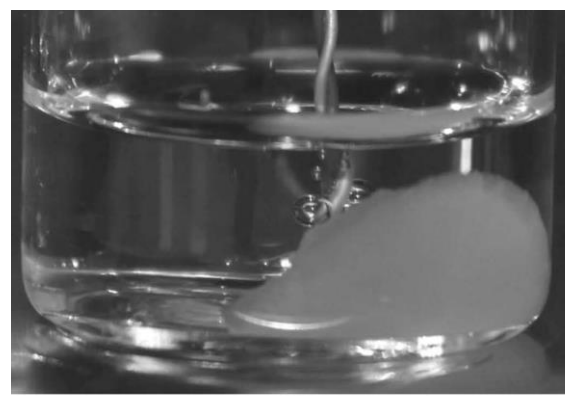
Freezing and annealing

Ice nucleation (stochastic process)



Primary drying

- Product probe provides additional nucleation sites and generally results in higher nucleation temperature
- Alters the way the ice forms
- Changes the dry layer resistance



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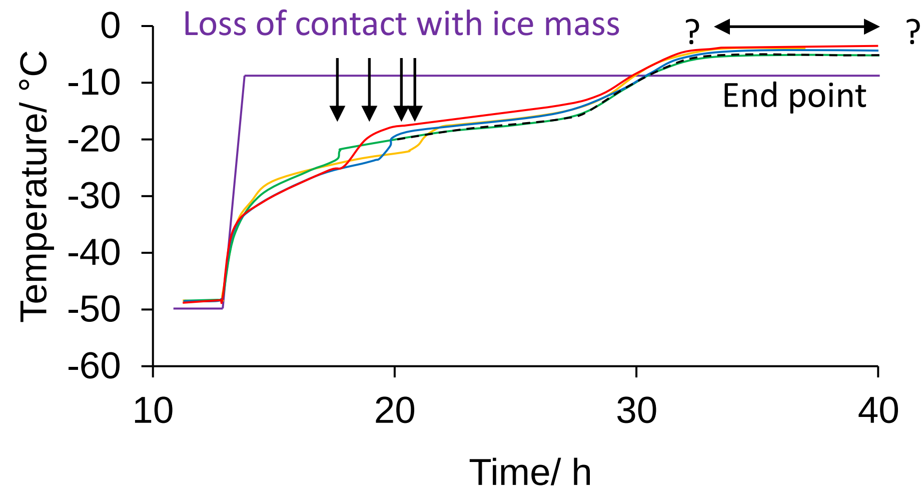
Results from TC probe

Freezing and annealing

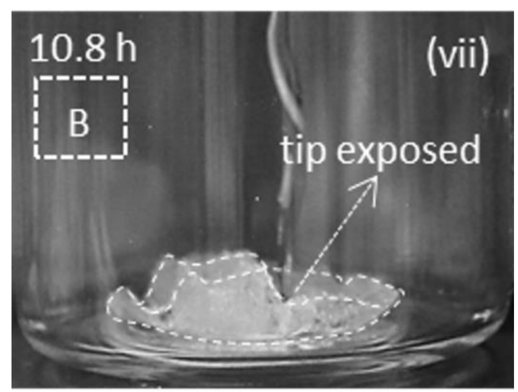
Ice nucleation (stochastic process)

Primary drying

End point determined by plateau in temperature



1. Apparent increase in product temperature is an artefect from the disconnection of the probe from the ice mass
2. End point could be earlier as a result of heat input down the TC wires

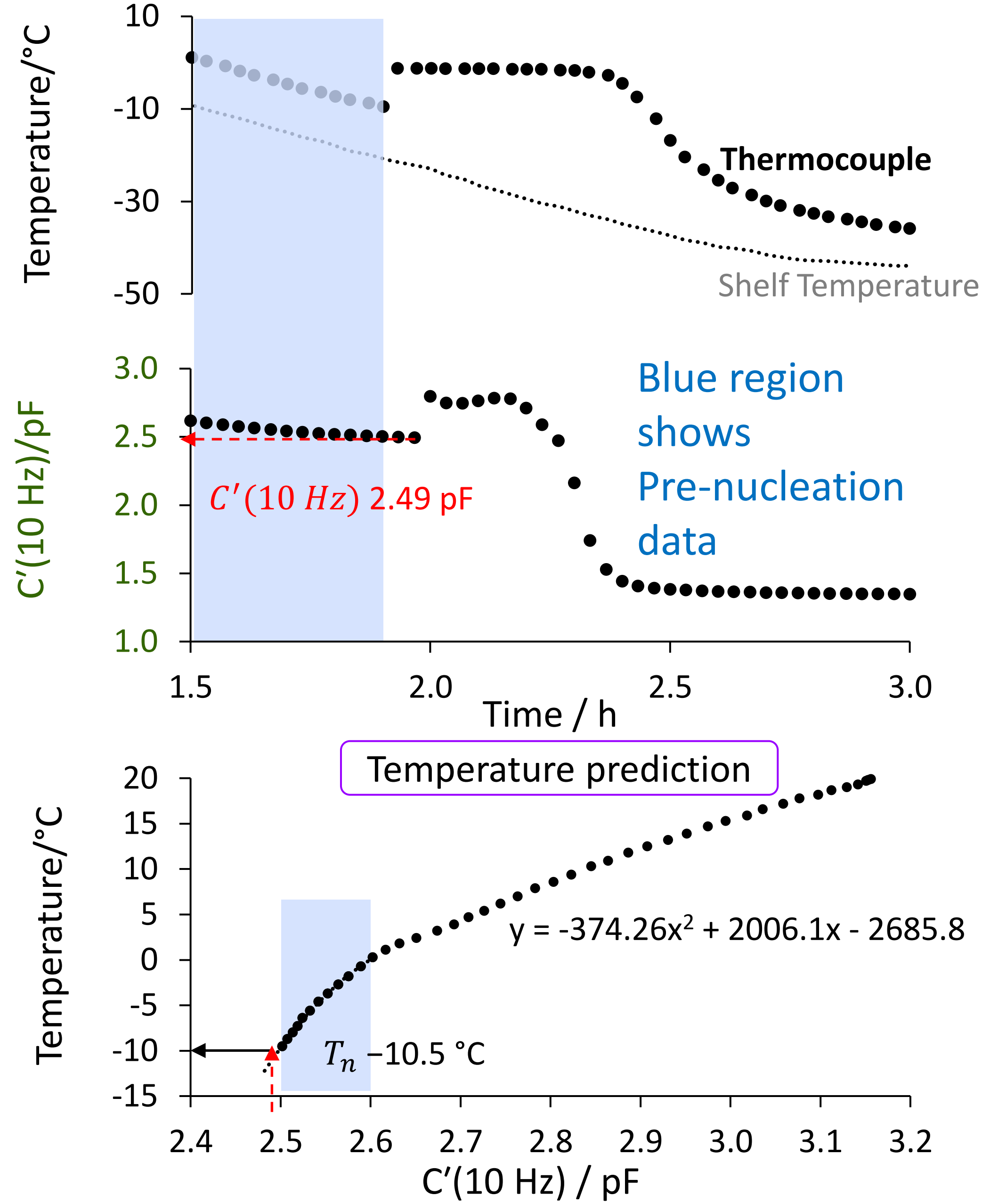


Photograph courtesy
B Pandya
PhD Thesis 2020

A non-invasive TVIS solution for the freezing stage?

Nucleation Temperature by TVIS

- 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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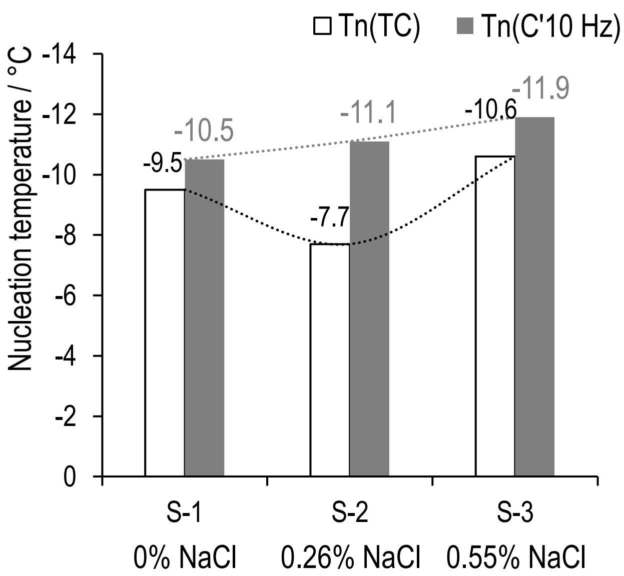
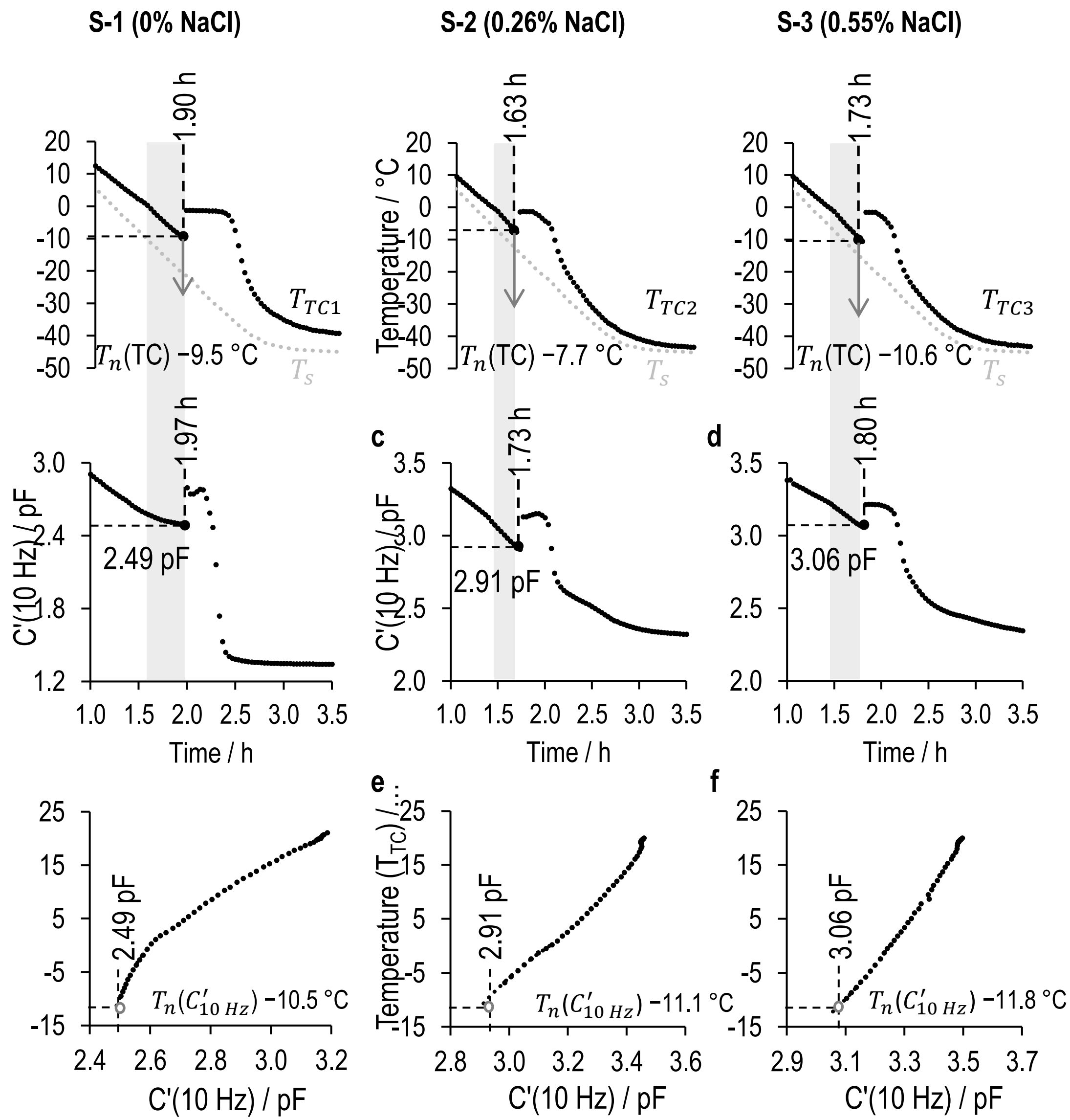
Nucleation temperature





CASE STUDY 4

Primary drying end point

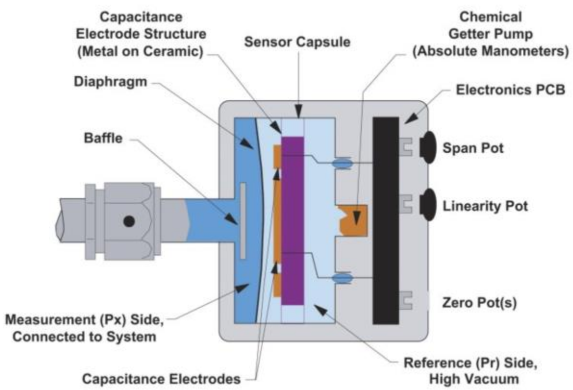
Separation between sublimative drying and diffusive desorption (secondary drying)

0%; 1% and 15% IgG

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

Batch primary drying end-point

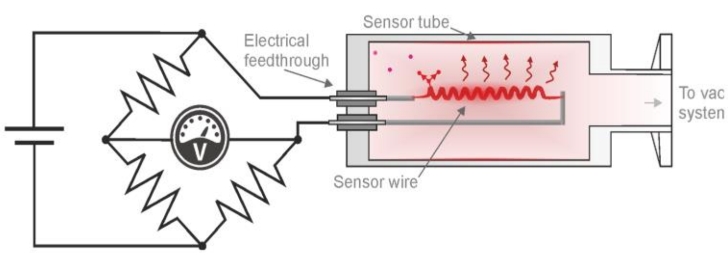
Capacitance manometer



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

Sensitive to total pressure

Priani gauge

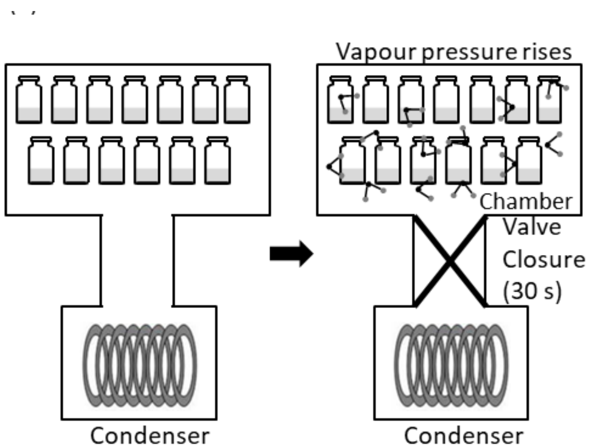


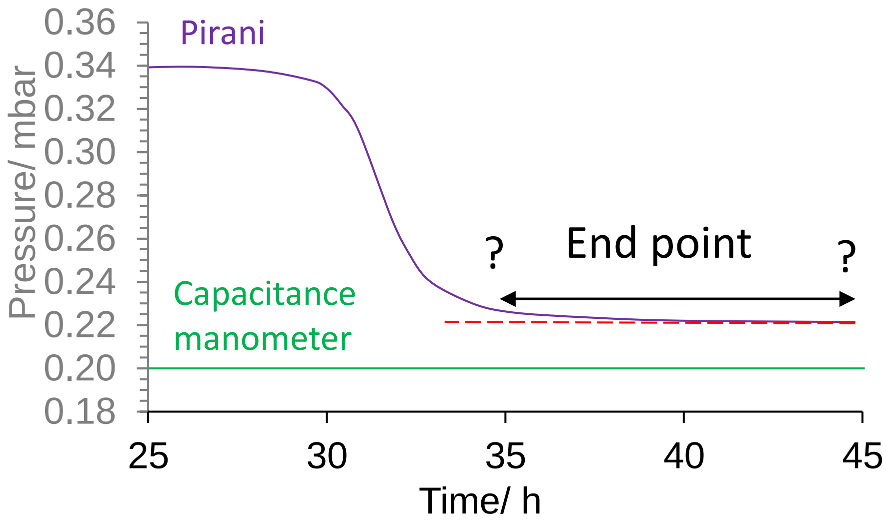
Gas molecules collide with the element and removes heat changing the resistance

Sensitive to type of gas,

e.g., N_2, H_20

Comparative pressure measurement (CPT)



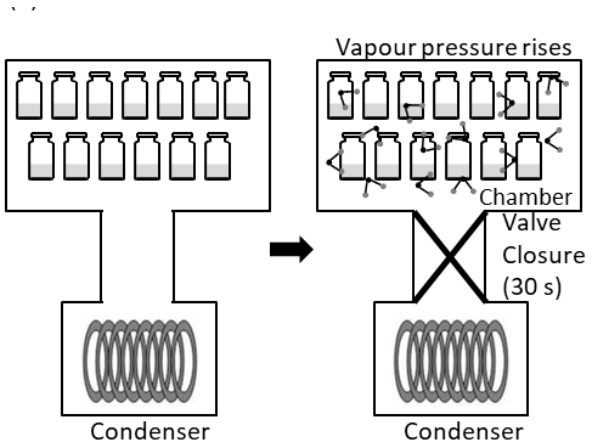


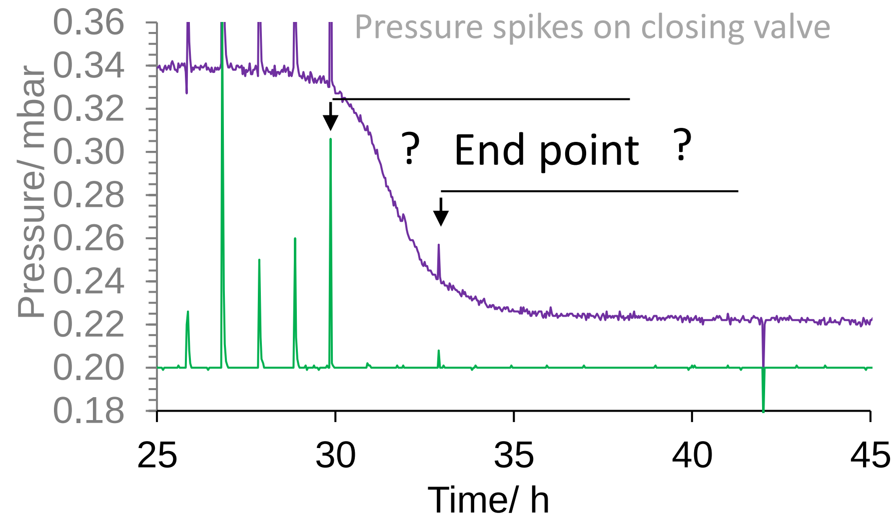
- Comparative pressure measurement (CPM):
  - Capacitance manometer responds to absolute gas pressure
  - Pirani response to water vapour is ~ 1.6 x that of the capacitance manometer
  - Therefore, Pirani output is higher than the CM while water vapour is being generated
- When drying is complete the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

But when has an asymptote been reached?

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

Pressure rise test (PRT)

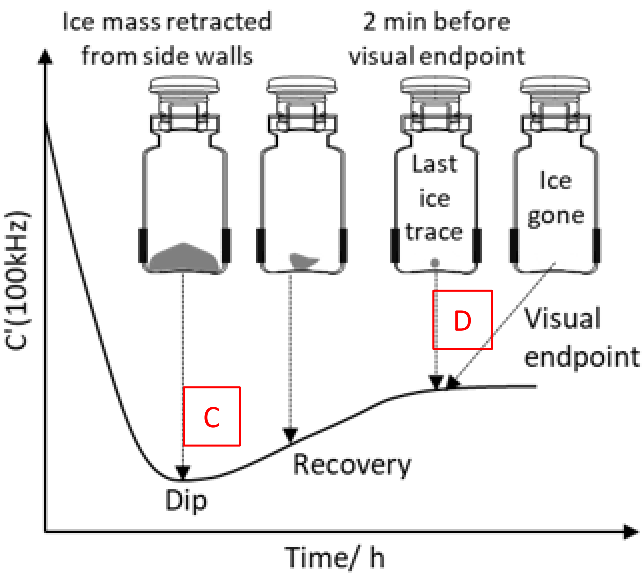


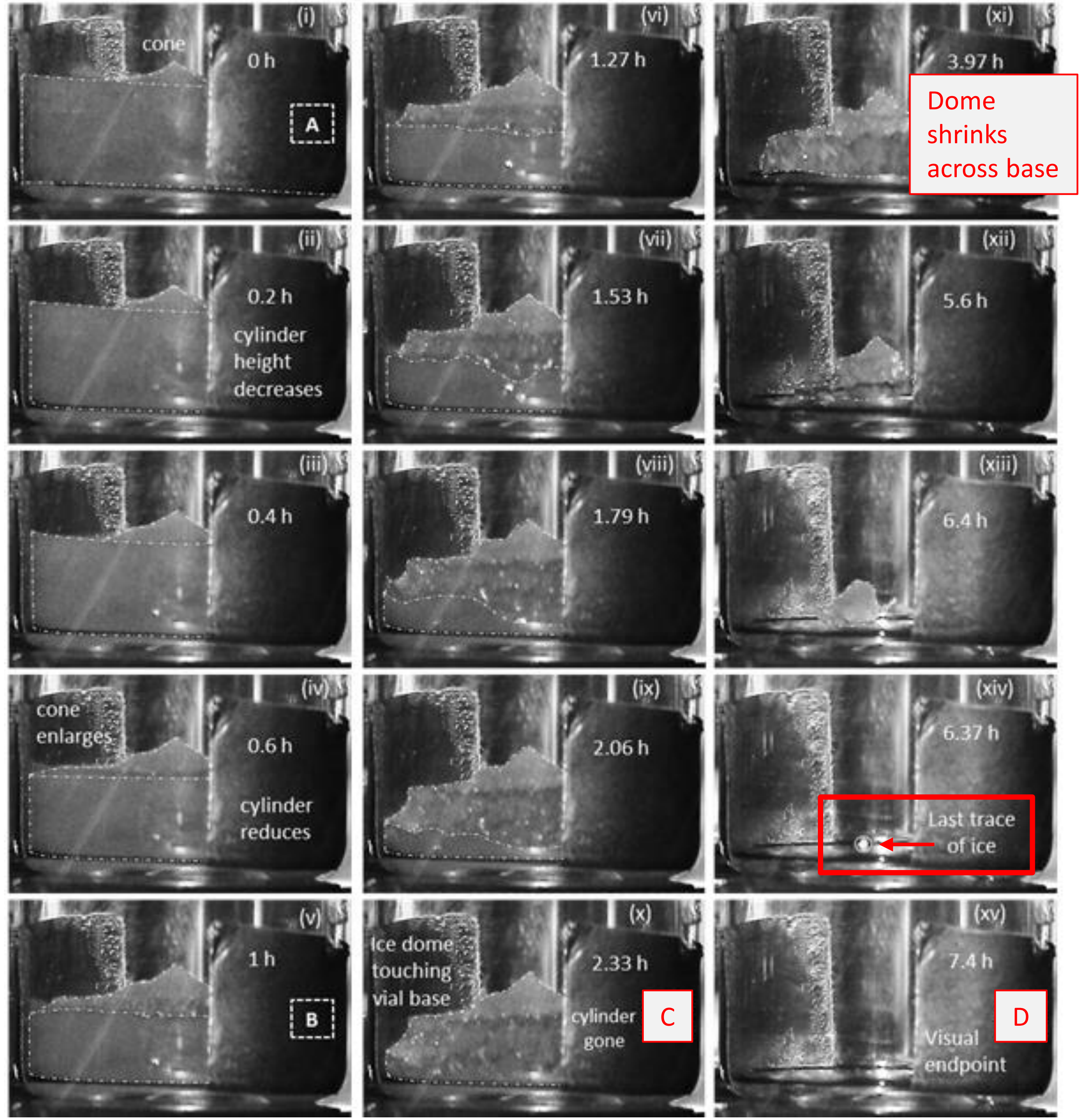


- Pressure rise testing (PRT)
  - Brief (up to 30 s) isolation of the valve between drying chamber and condenser
  - Results in spikes (pressure rises) in both Pirani and capacitance manometer readings
  - Reason :
    - water vapour is released from the product during drying stages
    - can not vent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

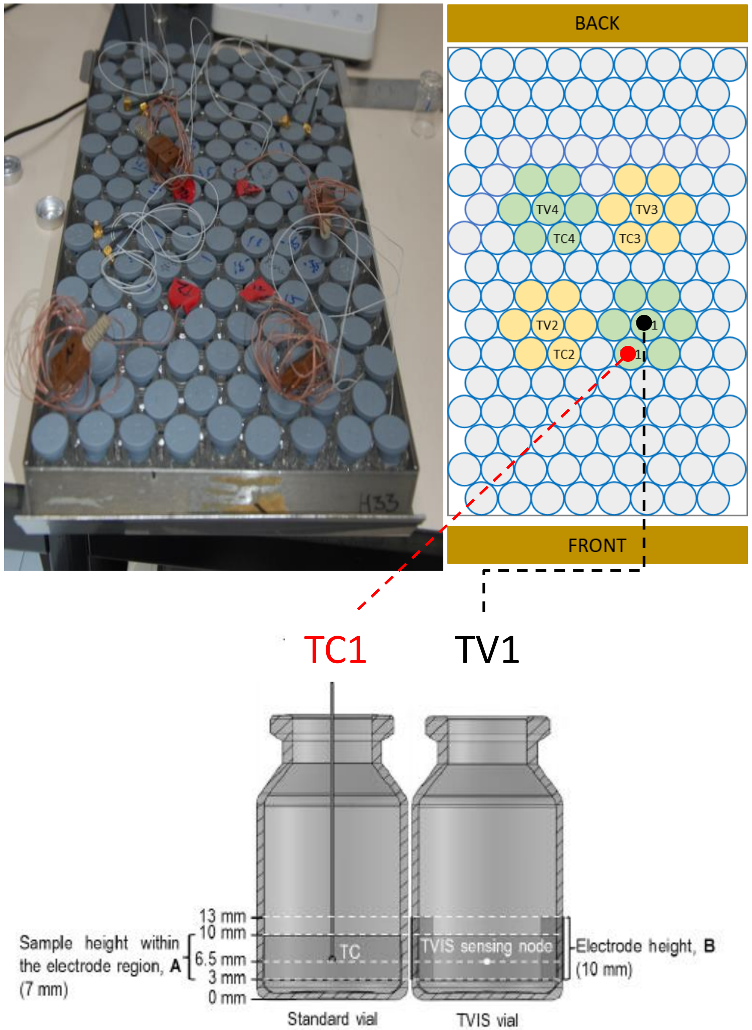
Schneid (2008) AAPS Pharm Sci Tech, 9, 729-739

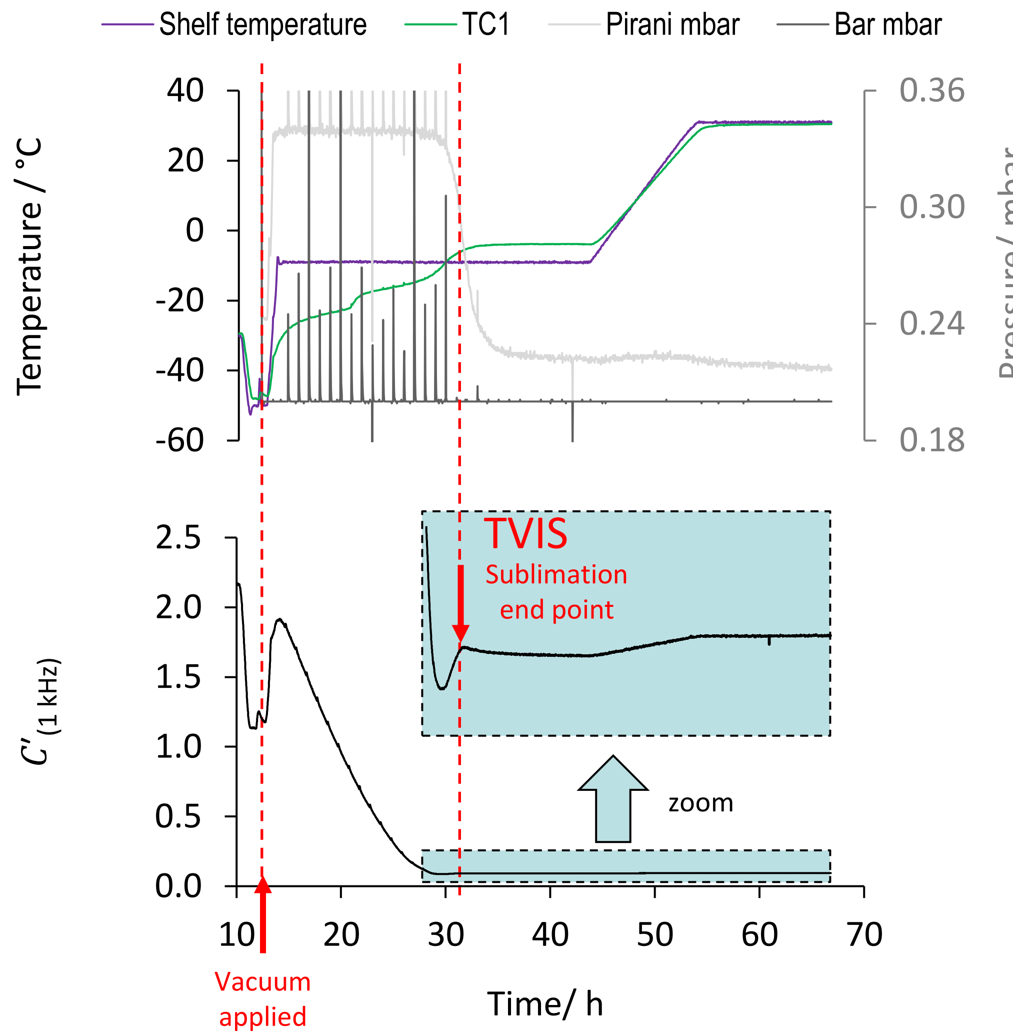
TVIS
Sublimation end point



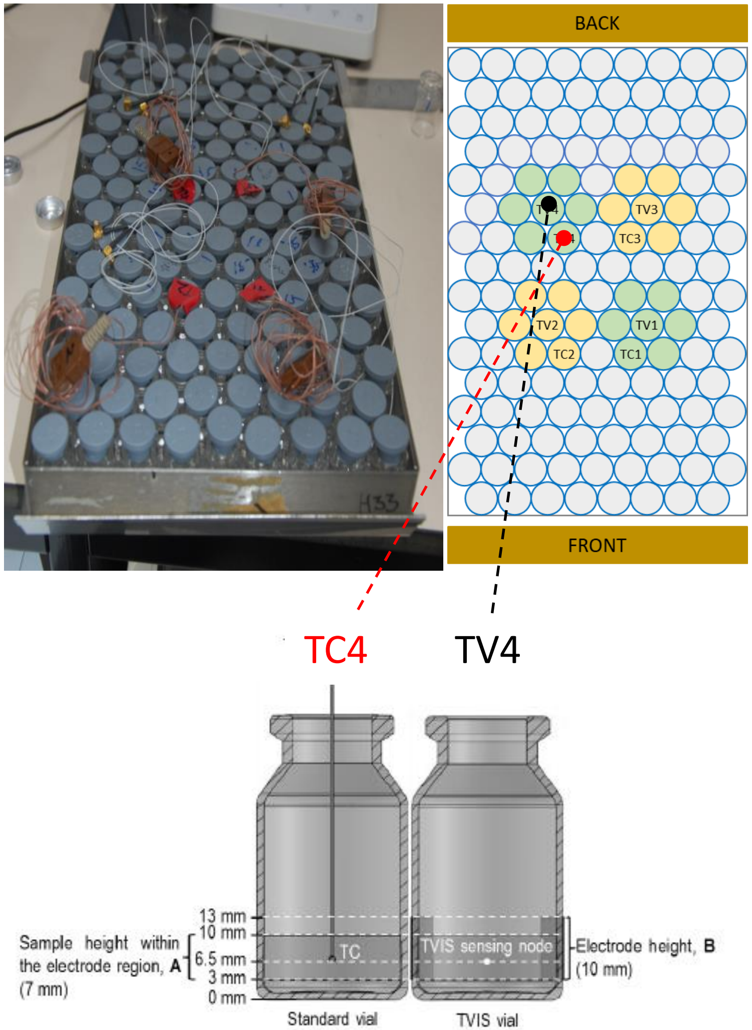


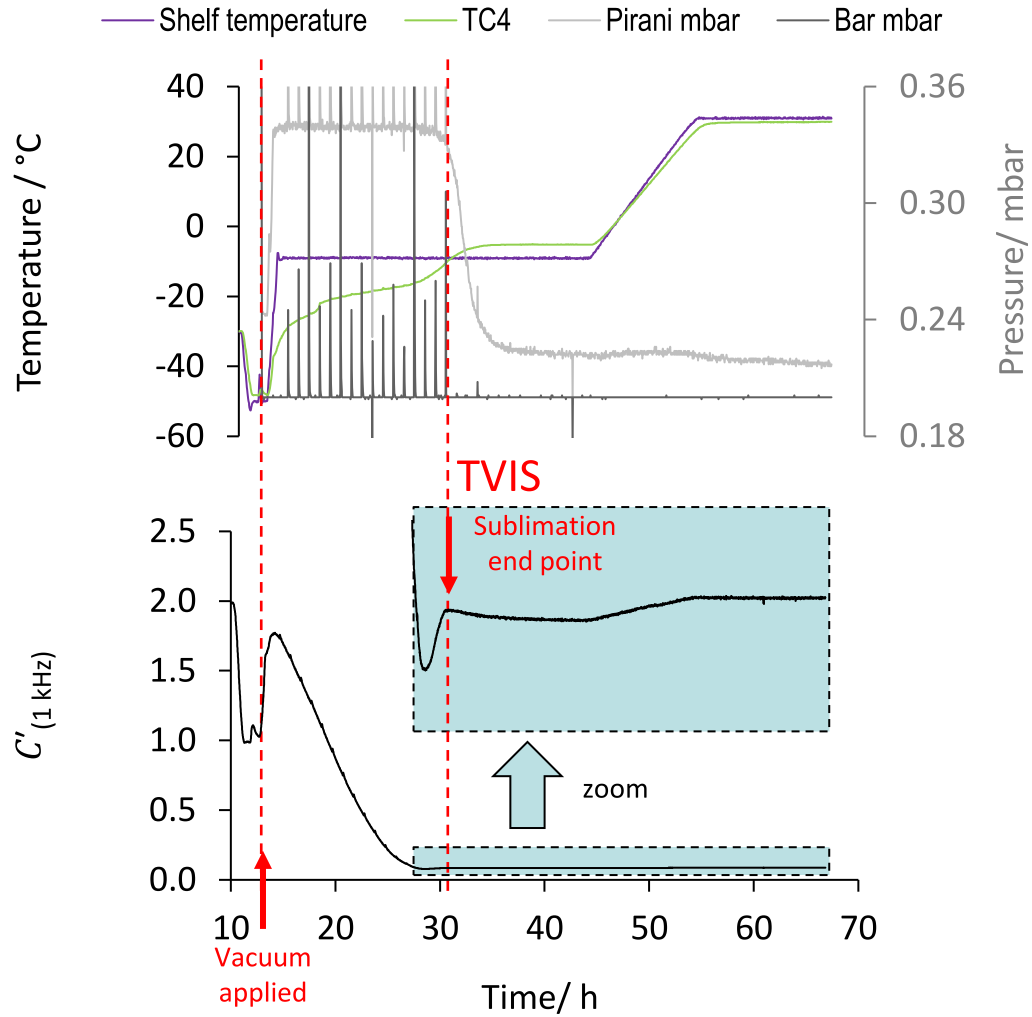
Primary drying 15% IgG, 1% Sucrose, 4% Mannitol, 20 mM Histidine, 0.01% Tween 20





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





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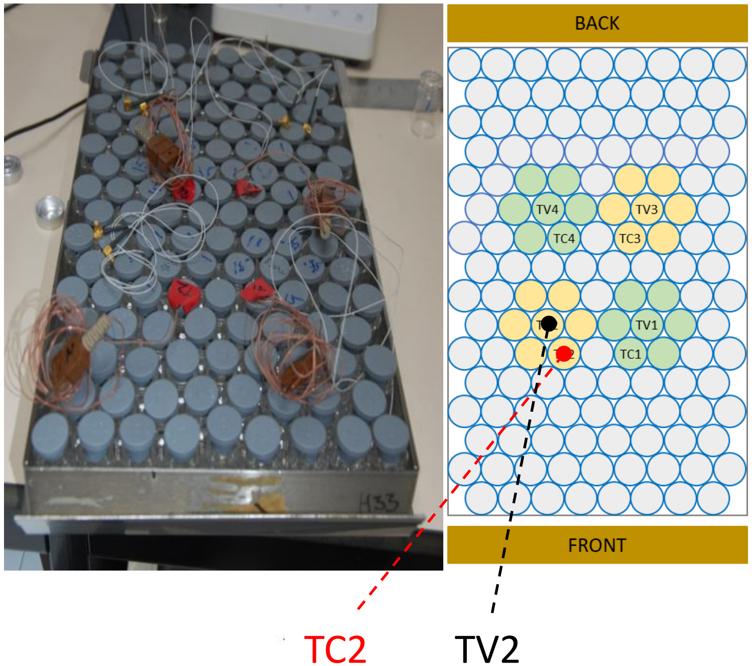
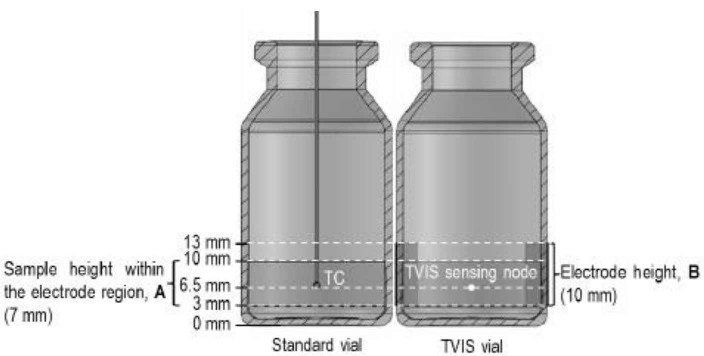
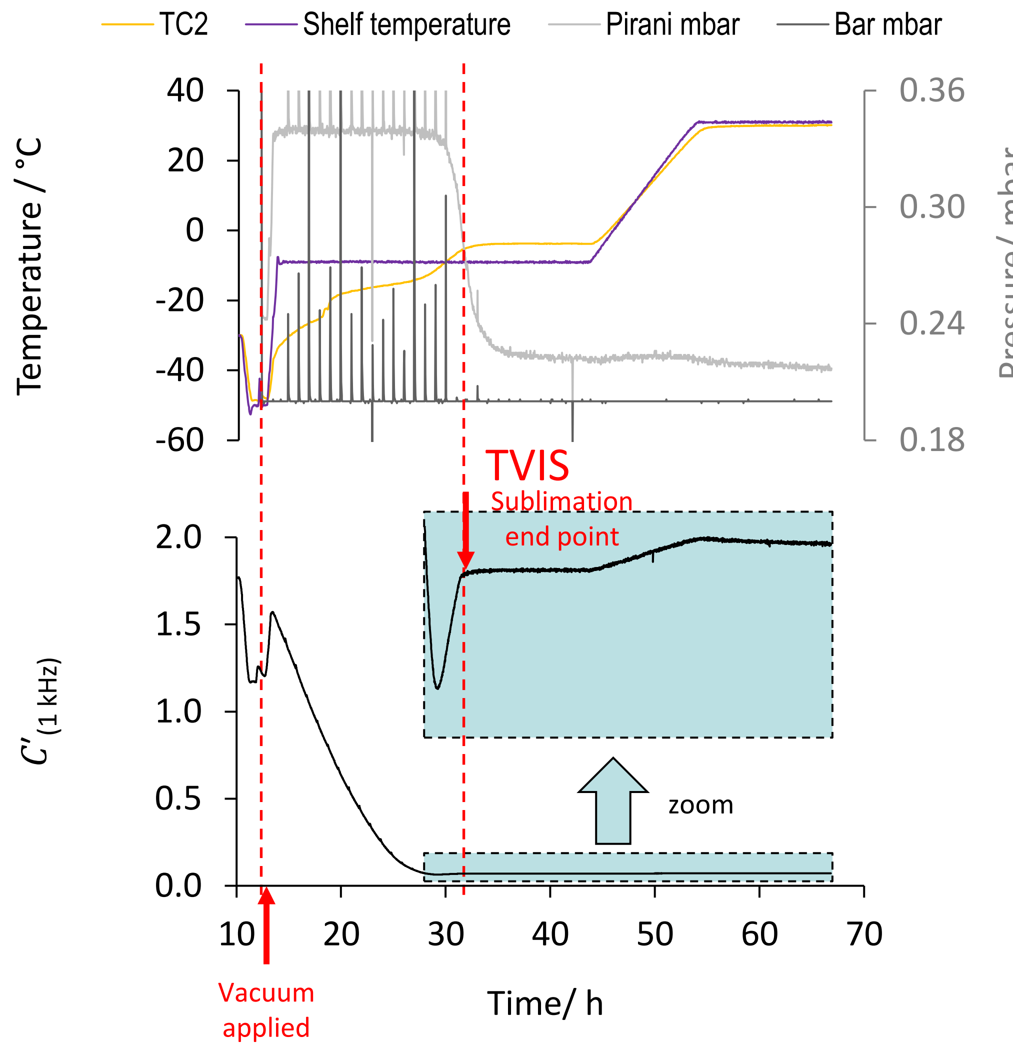
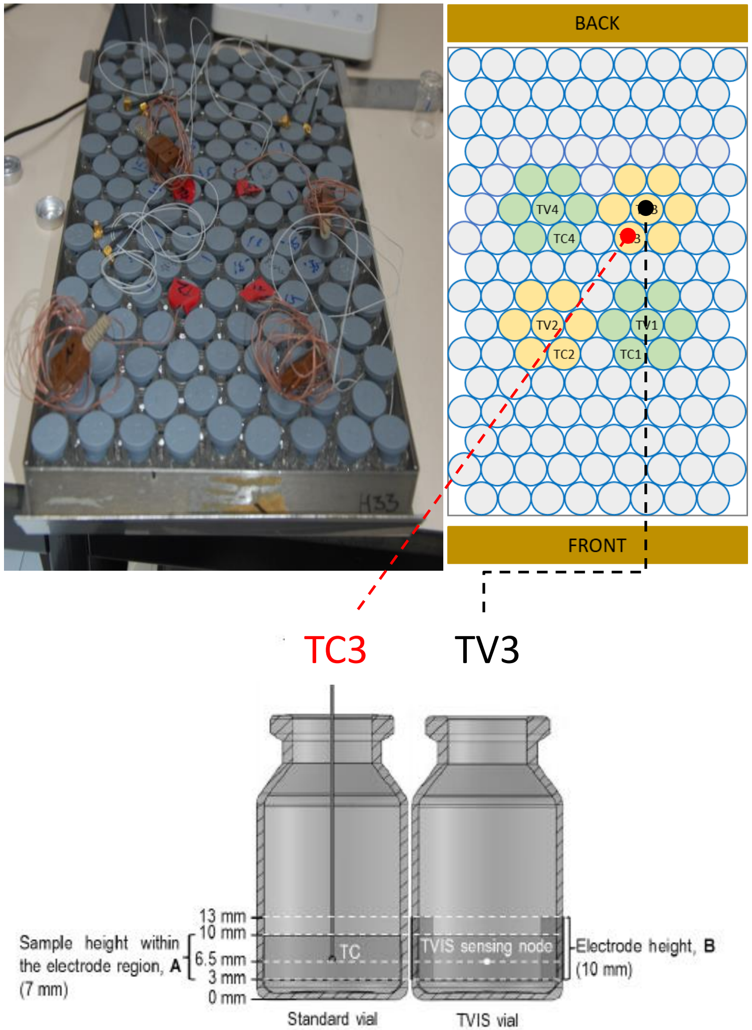
Primary drying **1% IgG, 1% Sucrose, 4% Mannitol, 20 mM Histidine, 0.01% Tween 20**

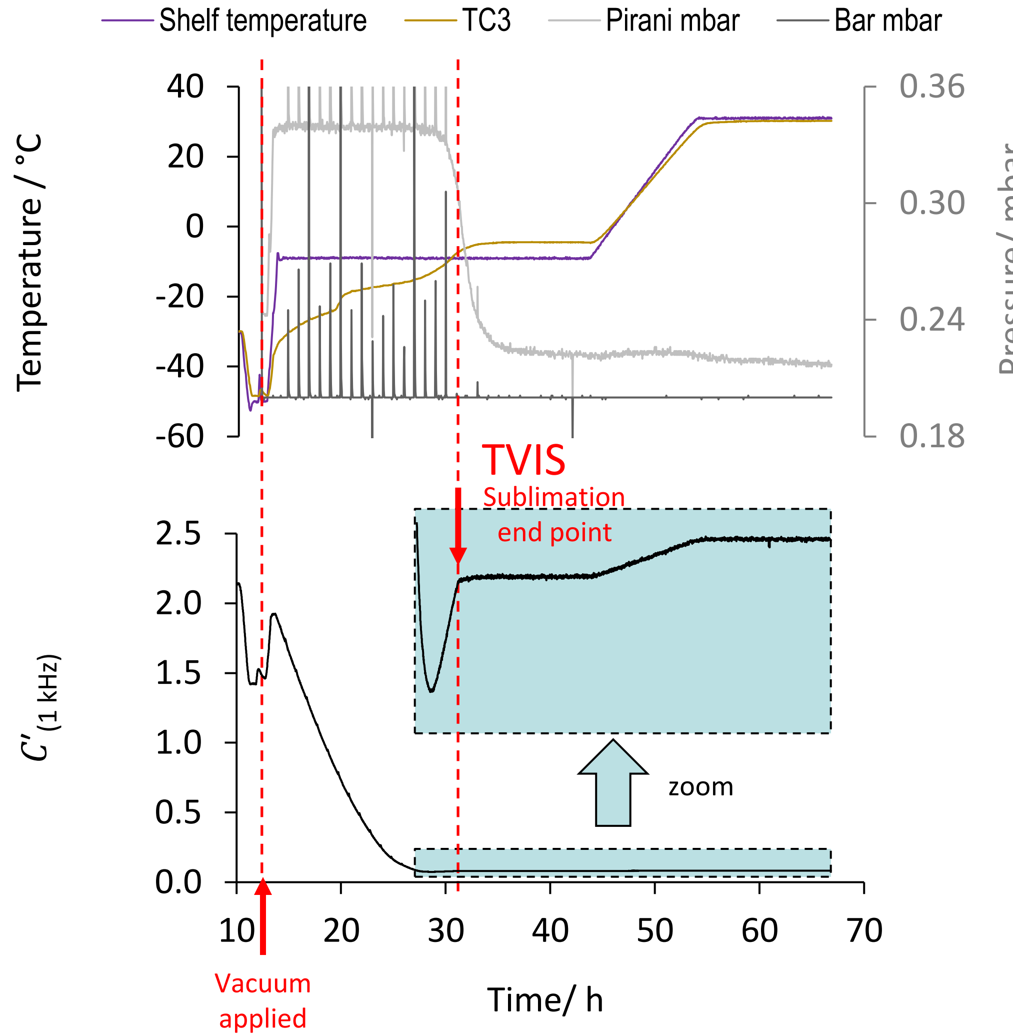






Primary drying **1% IgG, 1% Sucrose, 4% Mannitol, 20 mM Histidine, 0.01% Tween 20**





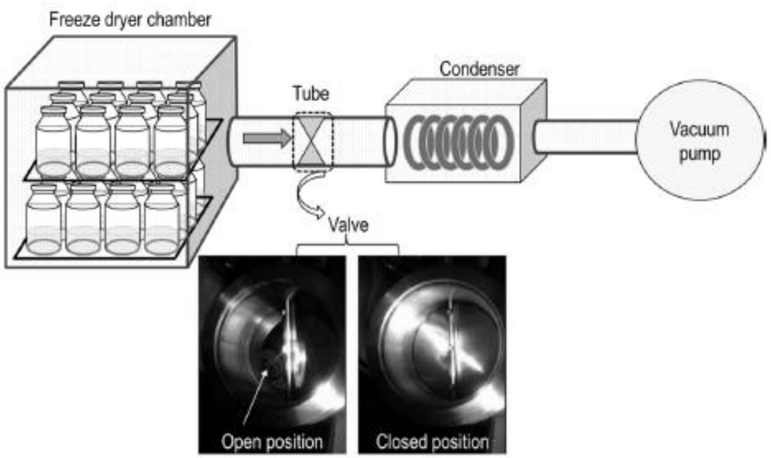
CASE STUDY 5

Primary drying rate models

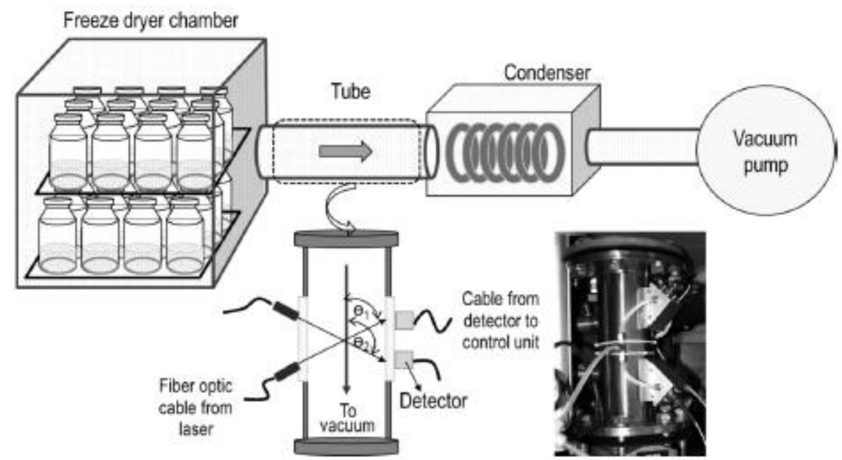
Assumptions of a planar ice interface

Drying rate based on vapour pressure measurement

MTM



TDLAS

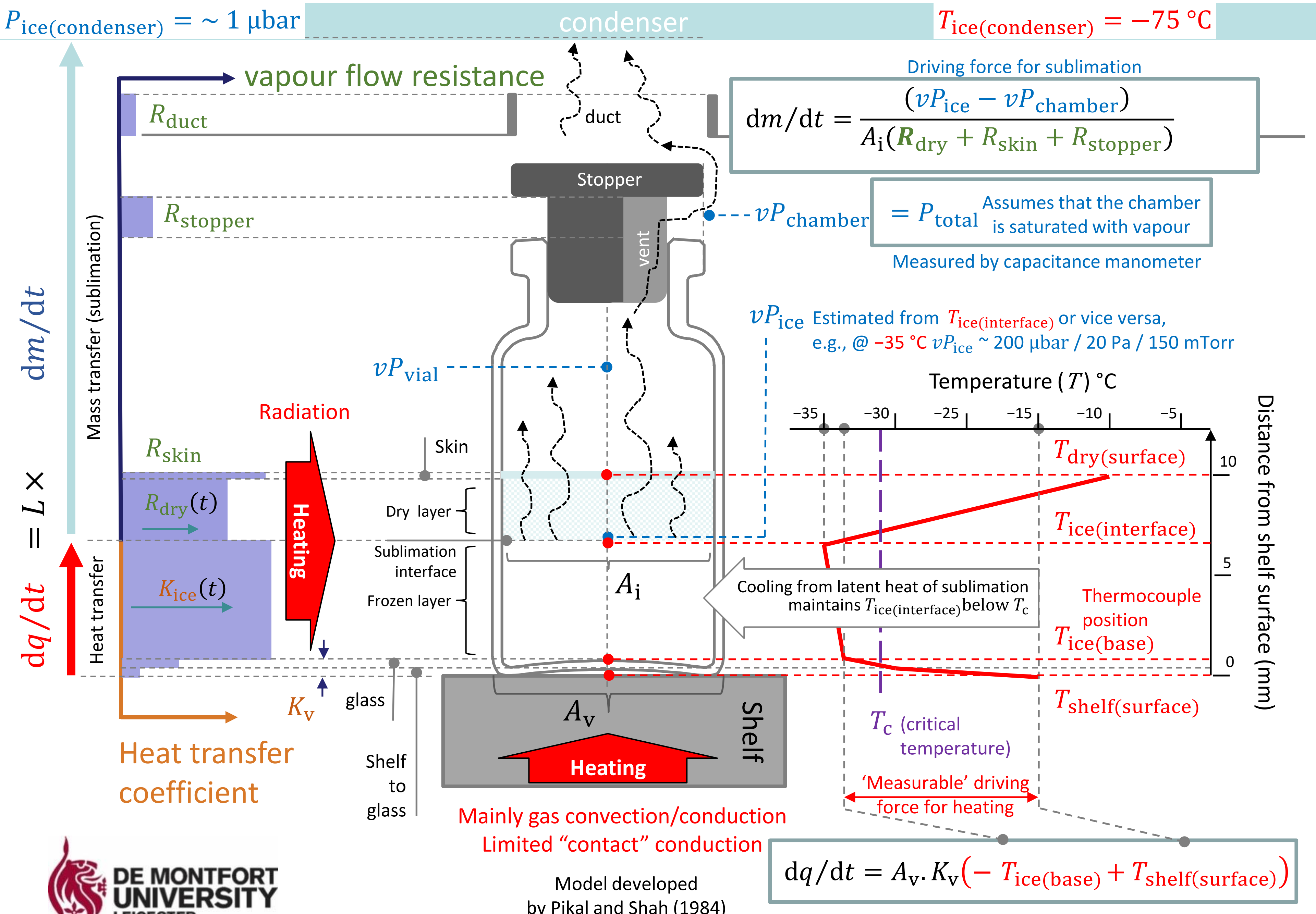


- Increase the pressure in the freeze dryer (same as PRT)
- MTM combines the pressure rise data with a mathematical equation to predict drying rates

- Laser assembly tube is connected between chamber and condenser
- Drying rate determined from
  - Laser light absorbed is proportional to the concentration of gas/water vapour
  - Doppler effect used to determine velocity of the vapour

From drying rate calculate:

(i) heat transfer coefficient; (ii) batch 'average' temperatures (@ ice front & ice base), (iii) drying endpoints, (iv) dry layer resistance

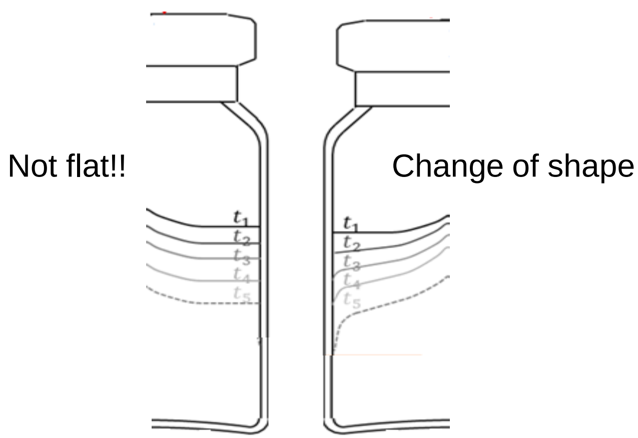


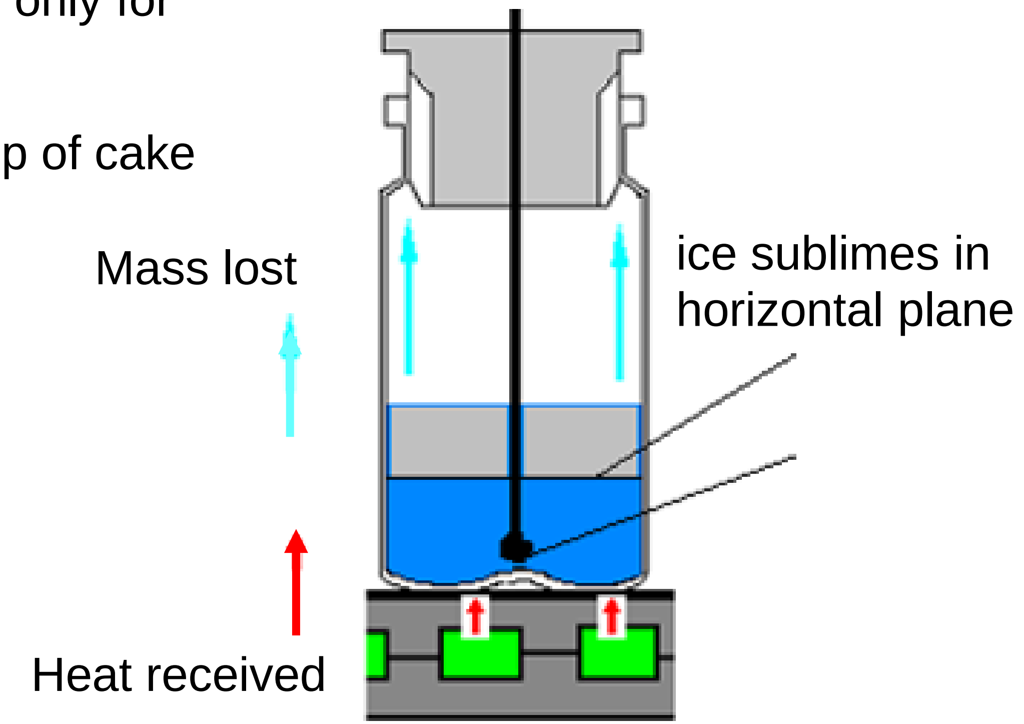
$P_{ice(condenser)} = \sim 1$ µbar
condenser
$T_{ice(condenser)} = -75$ °C
vapour flow resistance
R_{duct}
duct
Driving force for sublimation
$dm/dt = \frac{(vP_{ice} - vP_{chamber})}{A_i(R_{dry} + R_{skin} + R_{stopper})}$
Stopper
$R_{stopper}$
vent
$vP_{chamber}$
$= P_{total}$
Assumes that the chamber is saturated with vapour
Measured by capacitance manometer
vP_{ice} Estimated from $T_{ice(interface)}$ or vice versa,
e.g., @ −35 °C vP_{ice} ~ 200 µbar / 20 Pa / 150 mTorr
vP_{vial}
dm/dt
Mass transfer (sublimation)
$= L \times$
dq/dt
Heat transfer
Radiation
R_{skin}
Skin
$R_{dry}(t)$
Dry layer
Heating
Sublimation interface
$K_{ice}(t)$
Frozen layer
A_i
Cooling from latent heat of sublimation maintains $T_{ice(interface)}$ below T_c
Temperature (T) °C
−35
−30
−25
−15
−10
−5
$T_{dry(surface)}$
$T_{ice(interface)}$
Thermocouple position
$T_{ice(base)}$
$T_{shelf(surface)}$
10
5
0
Distance from shelf surface (mm)
K_v
glass
Shelf to glass
A_v
Shelf
Heating
T_c (critical temperature)
'Measurable' driving force for heating
Heat transfer coefficient
Mainly gas convection/conduction
Limited "contact" conduction
$dq/dt = A_v . K_v(- T_{ice(base)} + T_{shelf(surface)})$
Model developed by Pikal and Shah (1984)

Heat and Mass Balance: Assumptions

1. All heat received by product is used only for sublimation of water.
2. Sublimation front moves from the top of cake parallel to the vial bottom

Reality:





3. The contribution of radiation component to the vial heat transfer coefficient is constant within entire operation temperature range

Pikal et al. (1984) J Pharm Sci 73:1224
Temperature measurements have to be completed before 15% of the ice mass is removed before the assumption of a planar ice-surface interface is seriously violated

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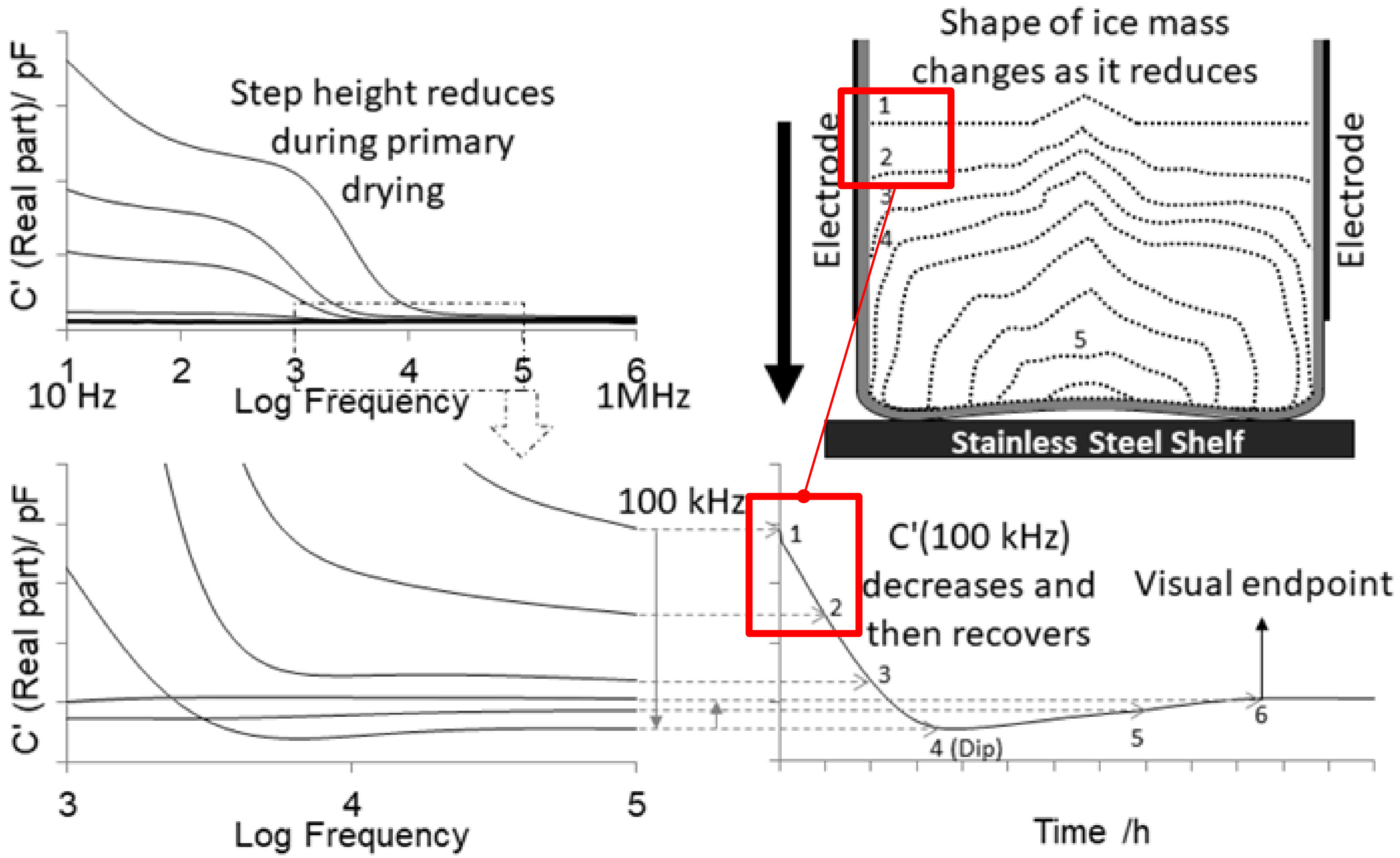
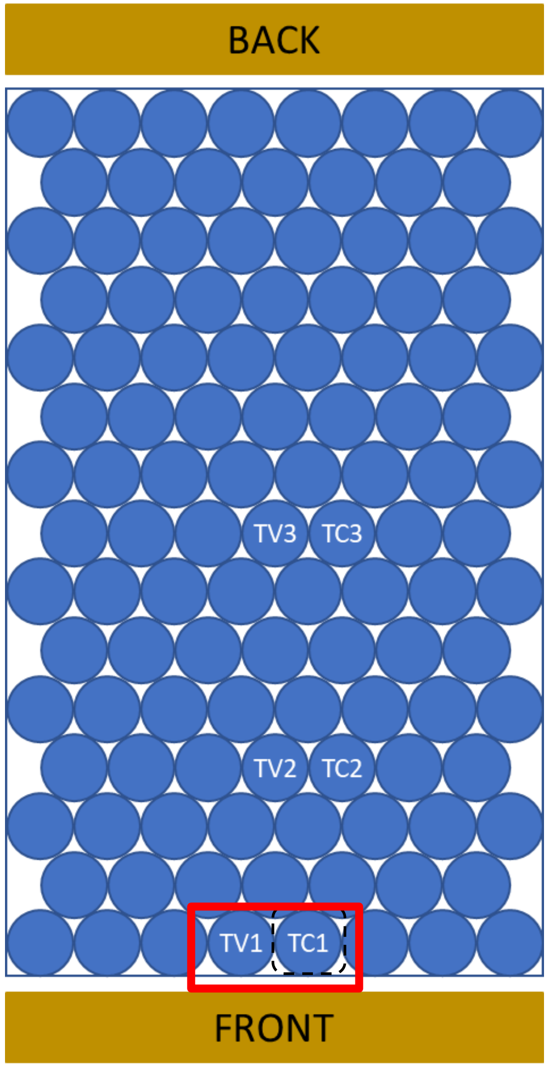
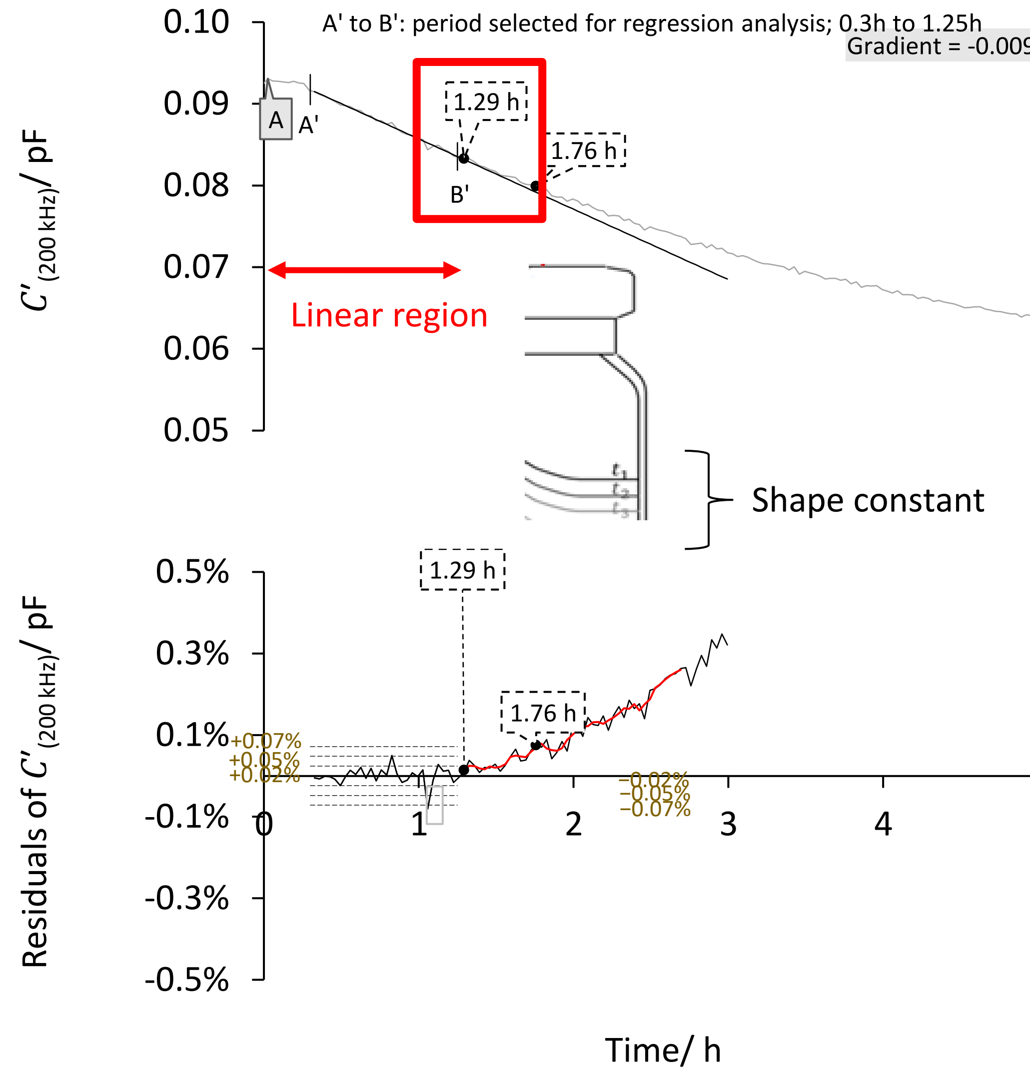
TVIS application in studying ice mass shape

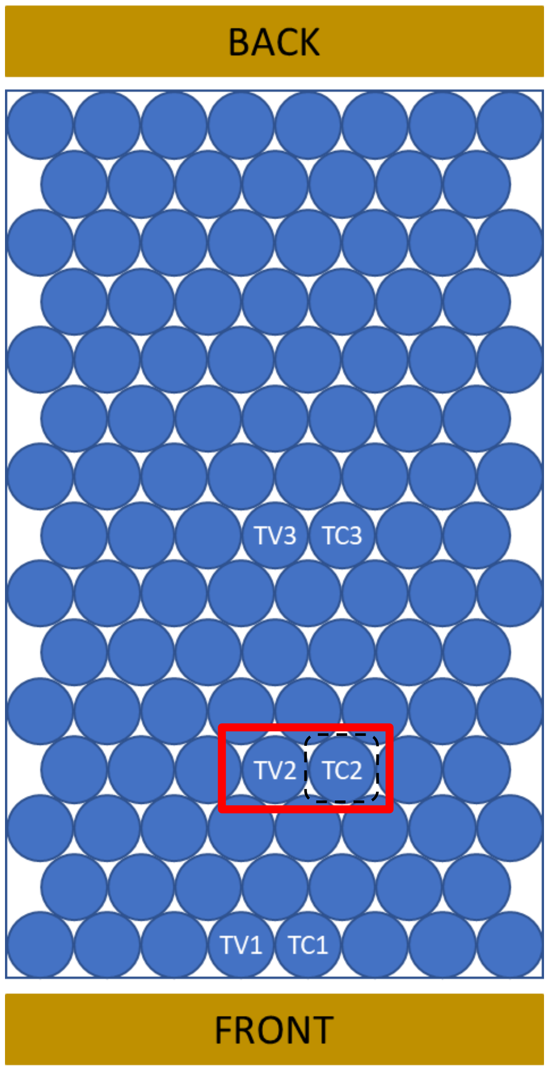


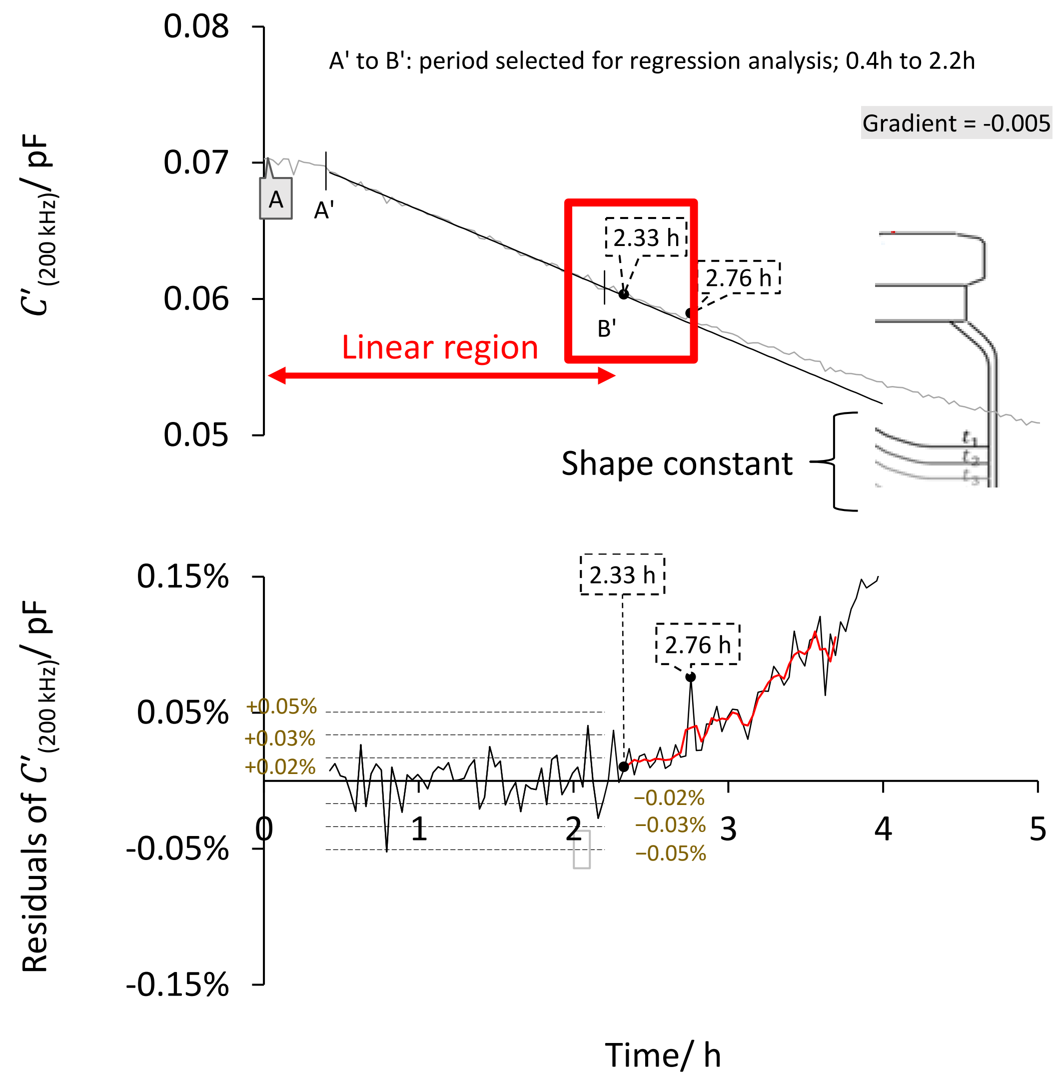
Front of shelf: linear for 1.29 h



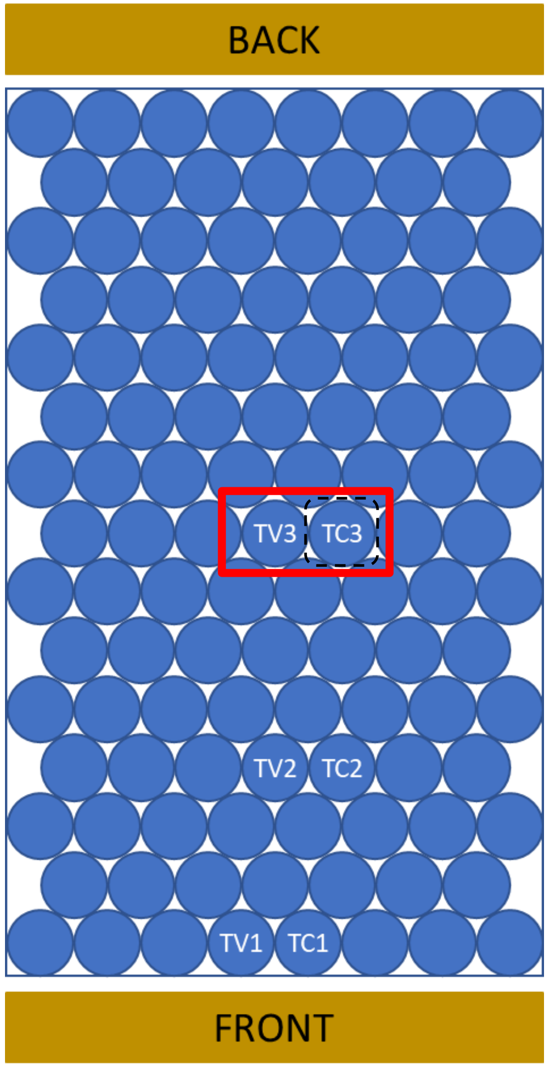


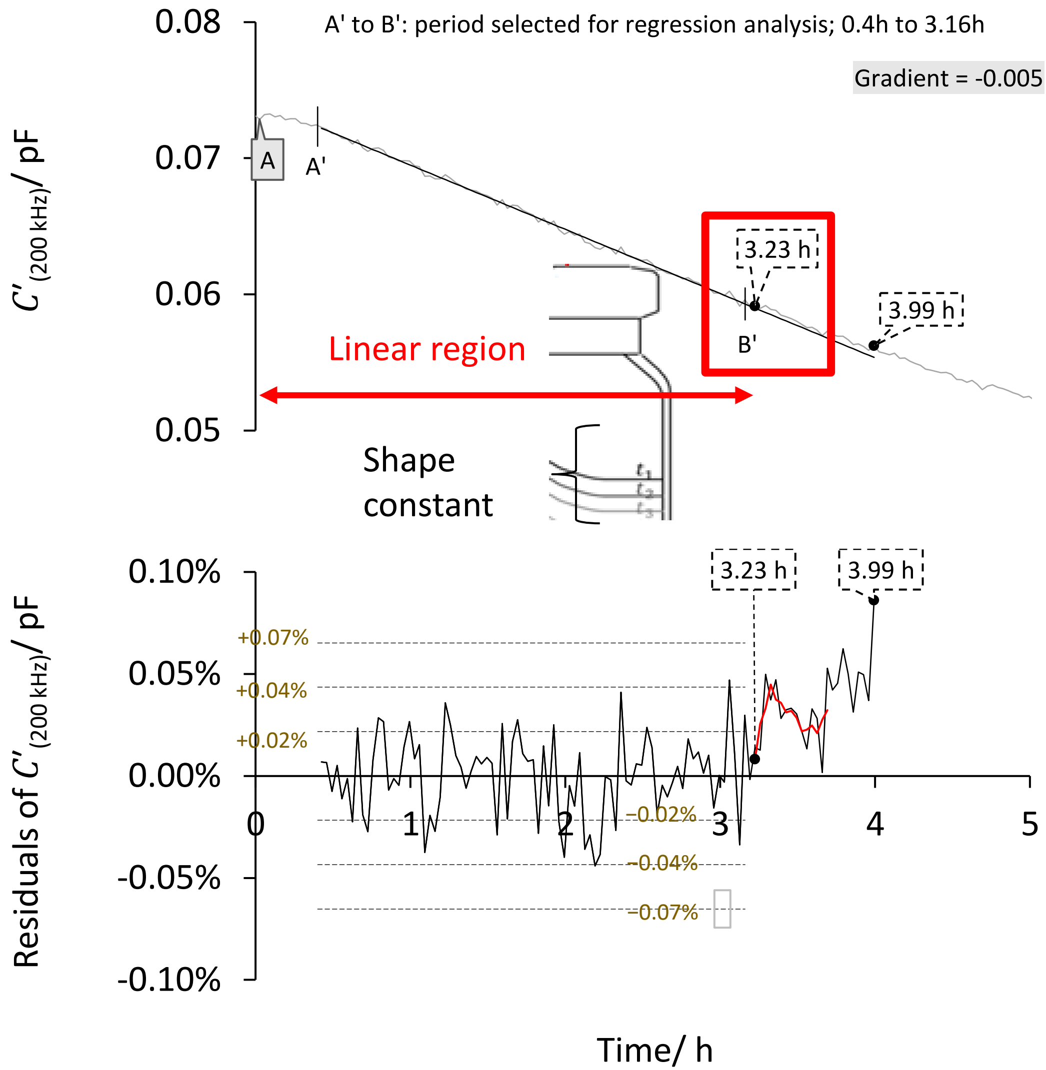
Mid-way to the centre : linear for 2.33 h





Centre of the shelf : linear for 3.23 h





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Take home messages from this talk

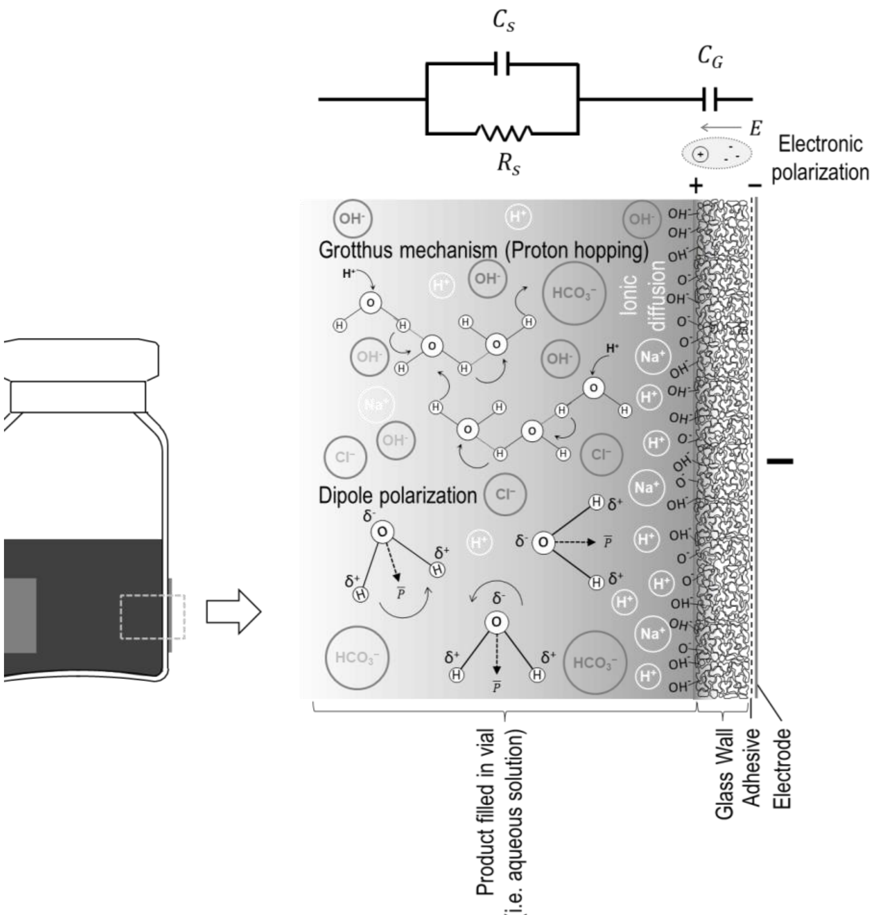
TVIS provides ….

- 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 MTM and TDLAS, can not differentiate between source of water vapour (ice or adsorbed water)
- Qualification of batch process models (MTM, TDLAS) in terms of the assumptions in the model (planar ice interface)

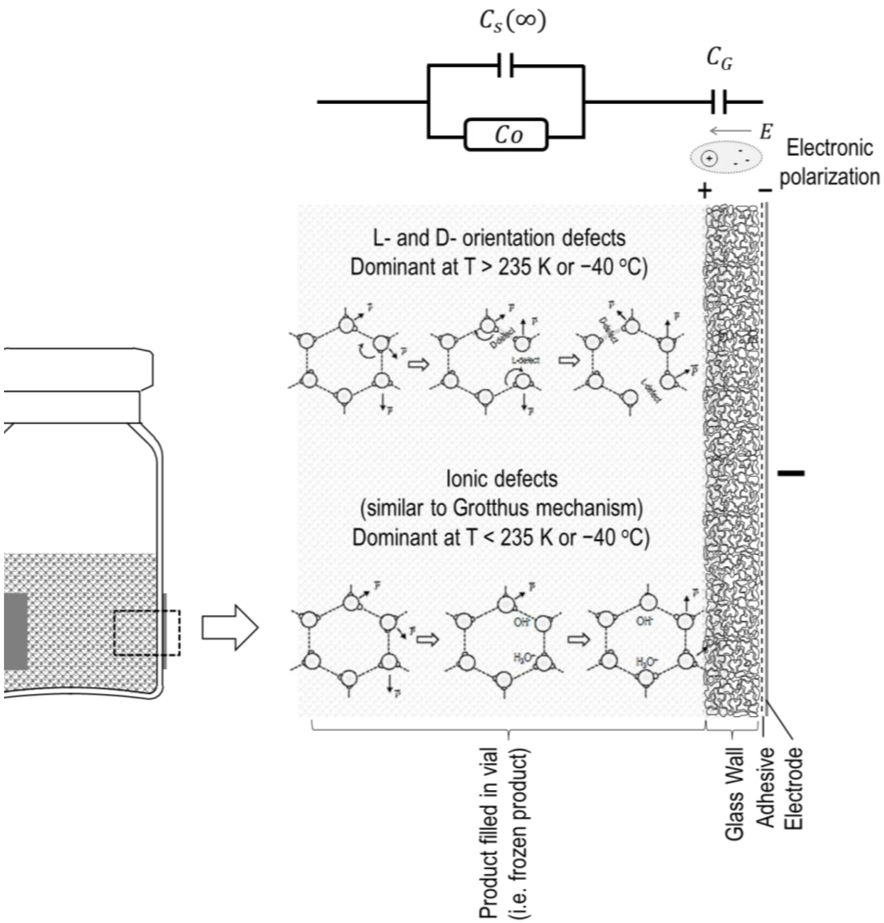
TVIS theory

Electrical impedance and material attributes

Liquid state (Maxwell-Wagner)



Frozen state (dielectric relaxation)



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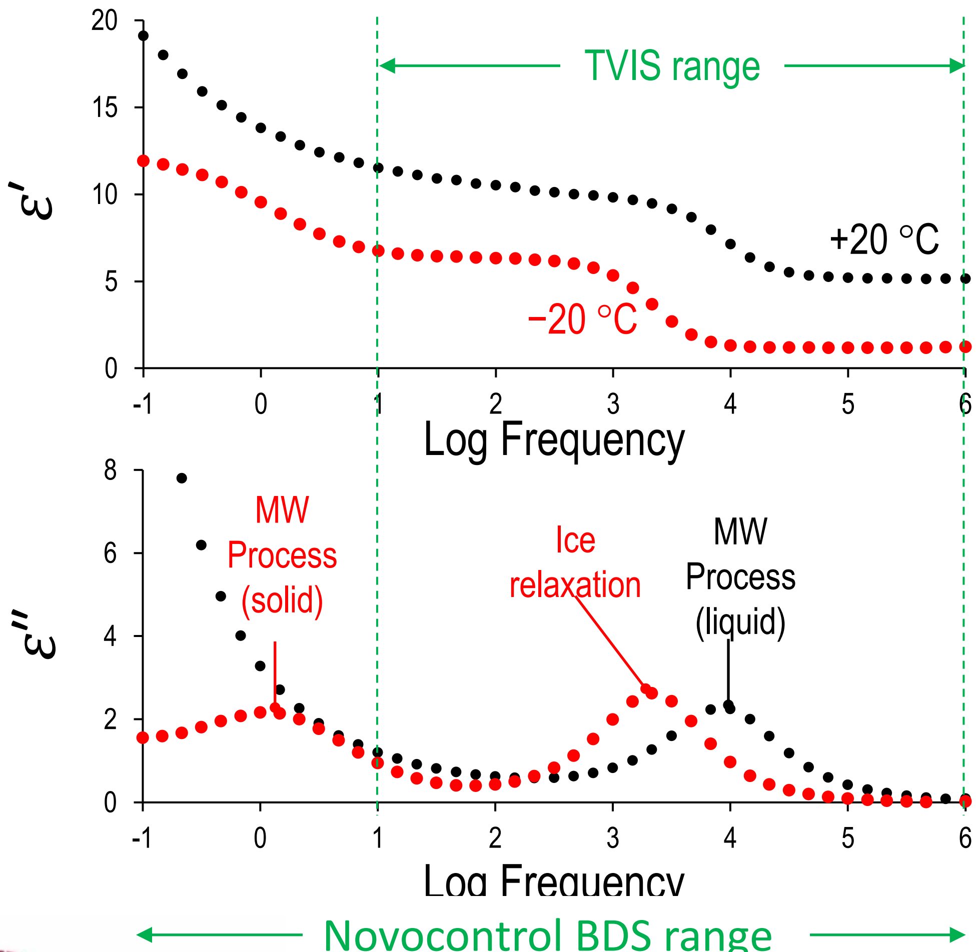
Electrical impedance and material attributes

Maxwell-Wagner & ice relaxation



b

TVIS vial on cradle

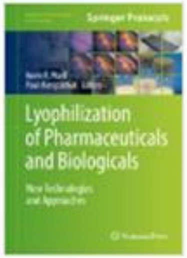
To be placed in the cryostat

of Novocontrol BDS

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

CRC Press
Taylor & Francis Group

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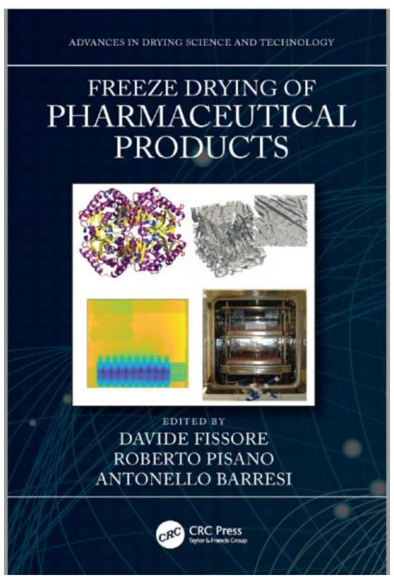

Freeze Drying of Pharmaceutical Products

1st Edition

Davide Fissore, Roberto Pisano, Antonello Barresi

Hardback
£118.00

CRC Press

November 13, 2019 **Forthcoming**

Reference - 214 Pages - 4 Color & 66 B/W Illustrations

ISBN 9780367076801 - CAT# K405807

Series: Advances in Drying Science and Technology

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** ment 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
- Smith, G., Arshad, M.S., Polygalov, E., Ermolina, I. (2014). Through-Vial Impedance Spectroscopy of the **Mechanisms of Annealing** in the Freeze-Drying of Maltodextrin: The Impact of Annealing Hold Time and Temperature on the Primary Drying Rate. Journal of Pharmaceutical Sciences, 103 (6), pp. 1799-1810
- 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.

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1952-2020

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

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The end ….

….. Or the beginning?

Grant awards

Innovate UK
Government Support for industry

LyoDEA
Lyophilization process analytics
By dielectric analysis

BIOSTART
Biopharmaceutical Stability at
Room Temperature

AtlasBio
Analytical Technologies for the
Stabilization of Biopharmaceuticals

Dissemination

figshare
Our data

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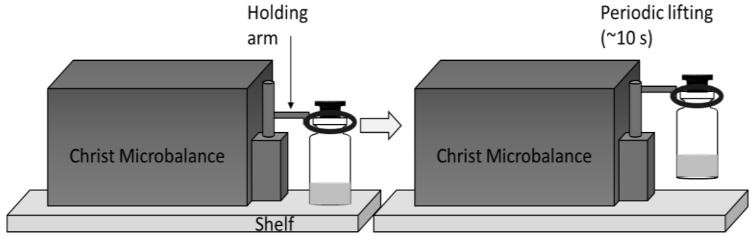
Our Twitter Page

TVIS
Through Vial Impedance Spectroscopy
Our WebPage

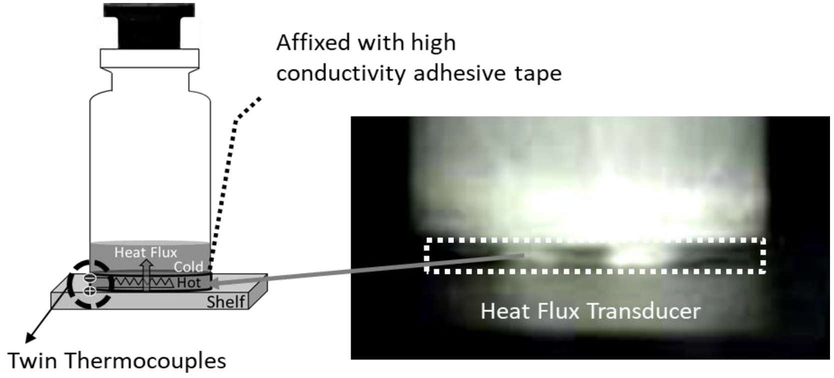
Drying rate based on mass loss or heat input

Christ Microbalance



- A gravimetric method to determine the loss of mass (ice and moisture) during the drying stages
- Sublimation and diffusive rates
- Primary & secondary drying endpoints

Heat flux transducer

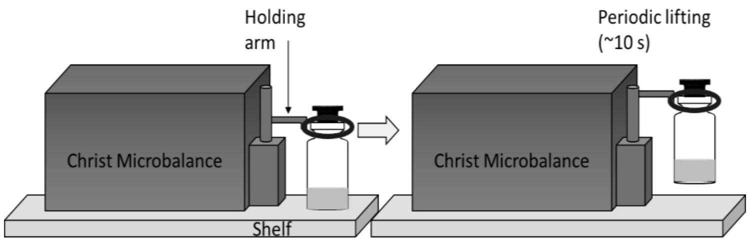


- Paired thermocouples attached to the top surface of the shelf and the bottom of the vial to determine the heat flux
- Non-invasive determination of:
  - Ice nucleation
  - Drying rates
  - End points

Roth (2001) Pharm. Sci., 90, 1345-1355
Chen (2008) Pharm. Dev. Technol., 13, 367-374

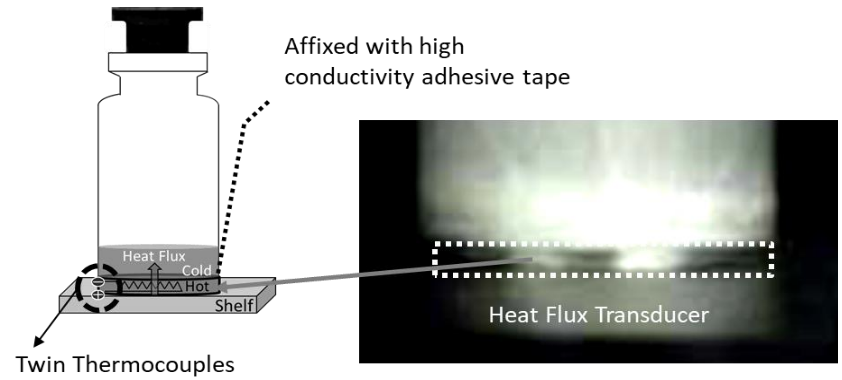
Drying rate based on mass loss or heat input

Christ Microbalance



- A gravimetric method to determine the loss of mass (ice and moisture) during the drying stages
- Interrupts the process and the packing of the vials and so is non-representative of the drying process

Heat flux transducer



- Paired thermocouples attached to the top surface of the shelf and the bottom of the vial to determine the heat flux
- The cabling to the sensor below the vial requires routng through the vial stack

Roth (2001) Pharm. Sci., 90, 1345-1355
Chen (2008) Pharm. Dev. Technol., 13, 367-374