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Through-Vial Impedance Spectroscopy (TVIS)

A novel process analytical technology for the development of pharmaceutical products and processes

2nd Annual Pharmaceutical
Lyophilisation Summit
#pharmalyo18

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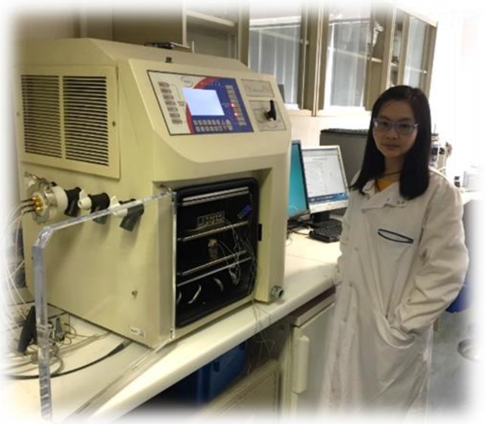
Outline

- Description of TVIS measurement system
- Applications in Brief
- First time report on the use of dual-electrode system and its applications
    - Ice region specific temperature prediction (T_i, T_b)
    - Drying rate determination
    - Heat transfer coefficient (K_v) determination
- Acknowledgements
- TVIS dielectric loss mechanisms



Through Vial Impedance Spectroscopy (TVIS)

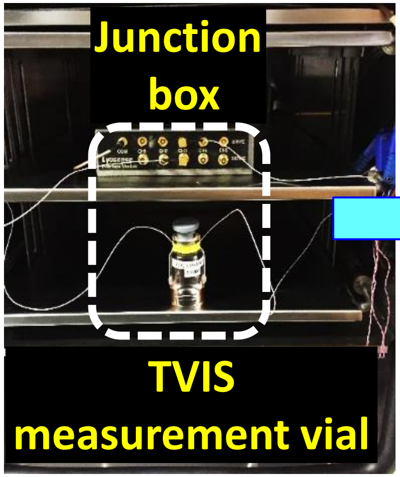
Description of Measurement System

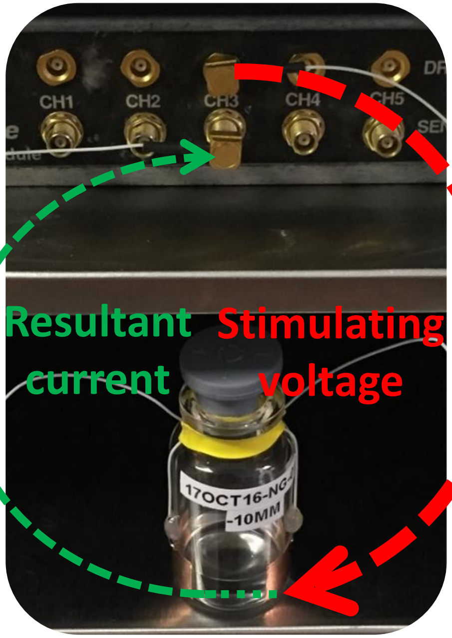
Introduction to the TVIS System

- Impedance spectroscopy characterizes the ability of materials to conduct electricity under an applied an oscillating voltage (of varying frequency)
- Impedance measurements across a vial rather than within the vial
- Hence **"Through Vial Impedance Spectroscopy"**

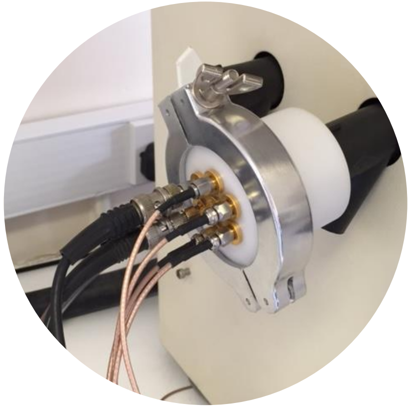
- Features
  - Single vial "non-product invasive"
  - Both freezing and drying characterised in a single technique
  - Non-perturbing to the packing of vials
  - Stopper mechanism unaffected

Freeze drying chamber



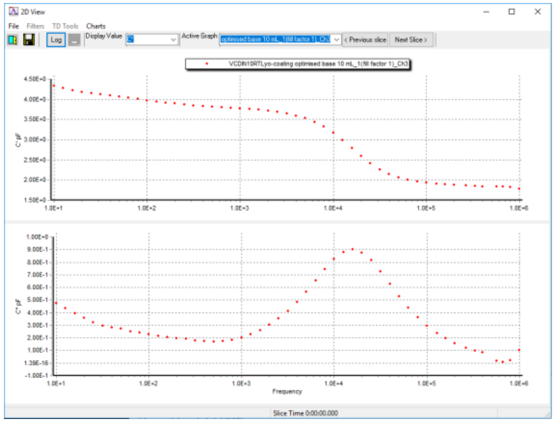


Pass-through

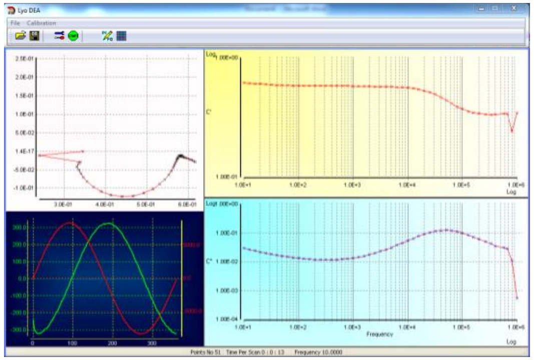


TVIS system (I to V convertor)

LyoView^{TM} analysis software



LyoDEA^{TM} measurement software

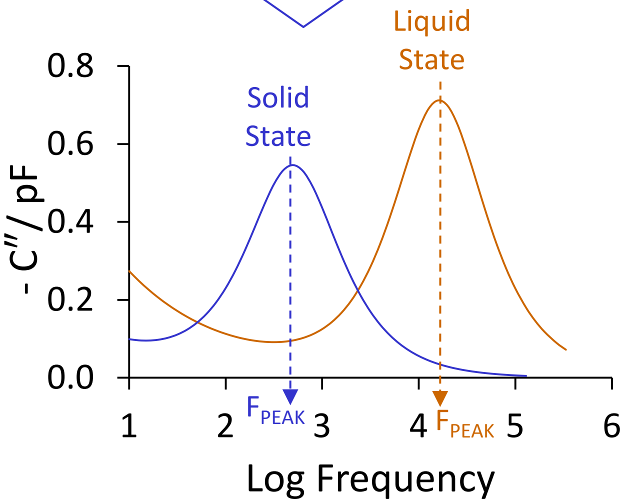


Through Vial Impedance Spectroscopy (TVIS)

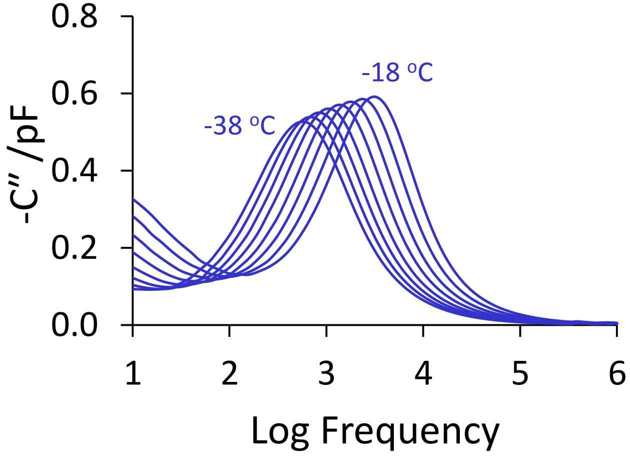
Applications

Through Vial Impedance Spectroscopy (TVIS)

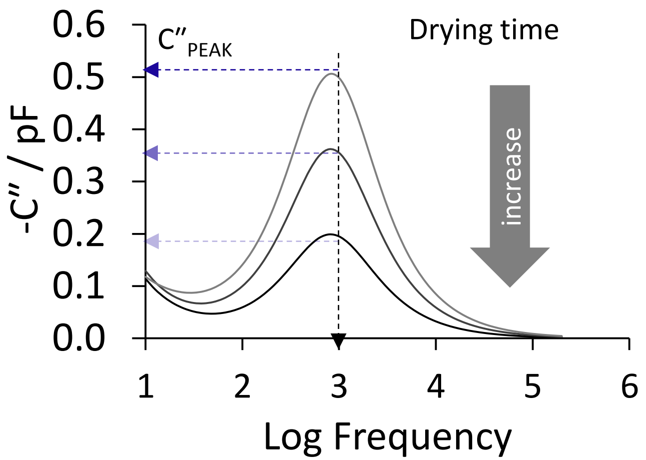
Monitoring **Phase Behaviour** (ice nucleation temperature and solidification end points by using F_{PEAK}



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



Surrogate **drying rate** (from $\frac{dC''_{PEAK}}{dt}$)



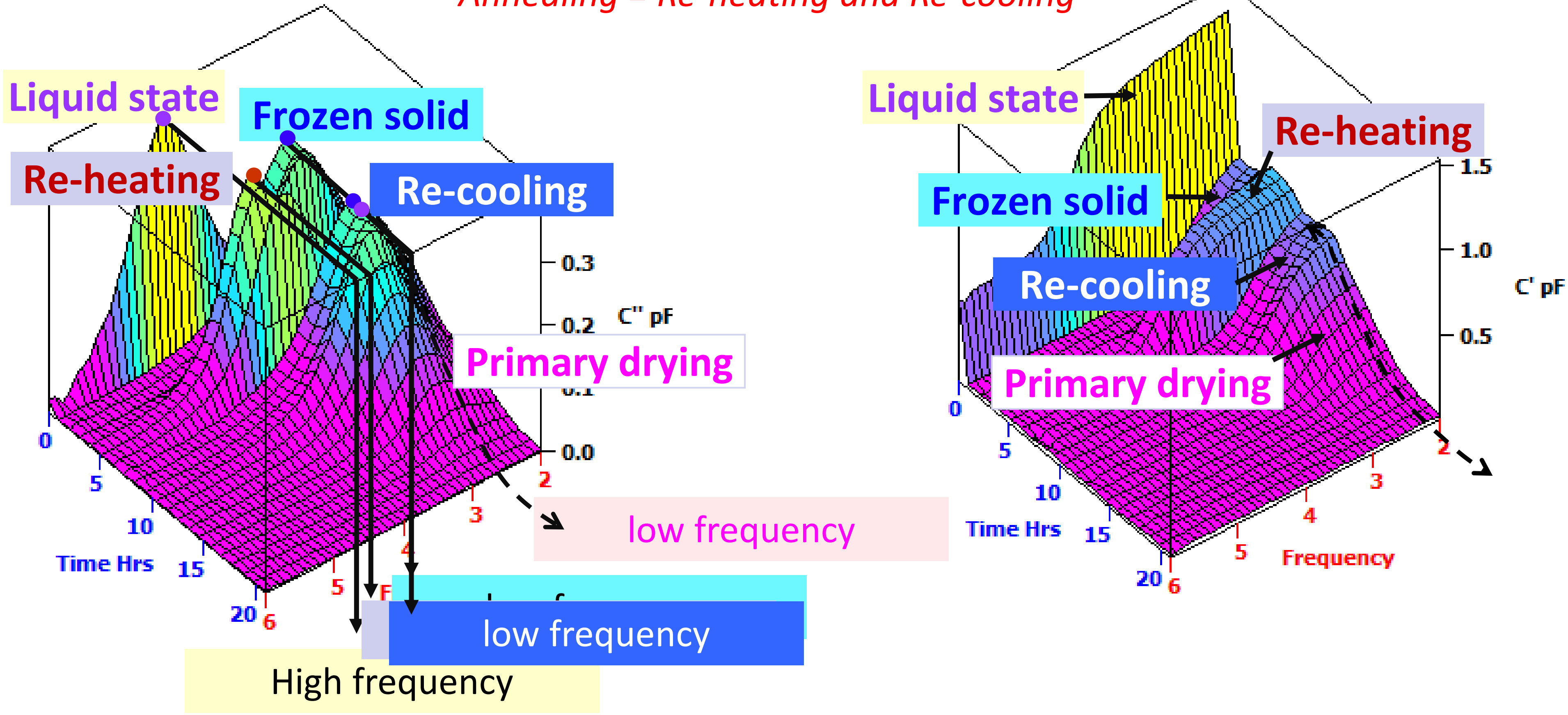
C'(~ 100 kHz) is highly sensitive to low ice volumes; therefore it could be used for determination **end point** of primary drying

TVIS Response Surface (3D-Plot)

Imaginary Part of Capacitance

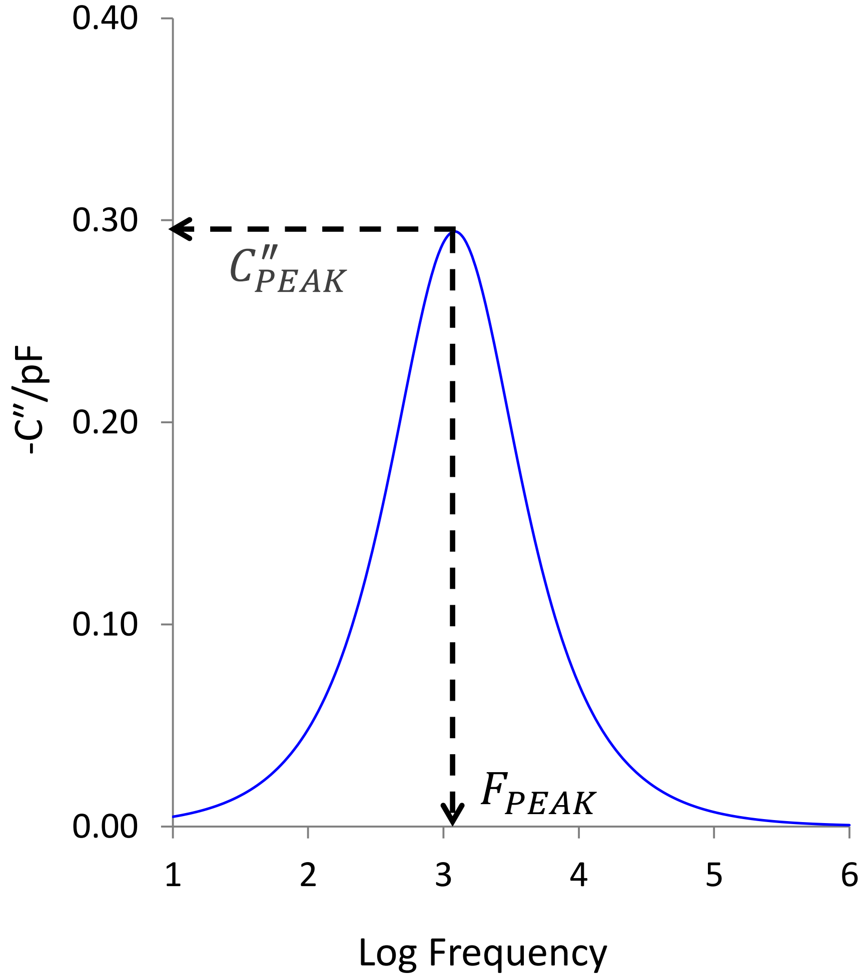
Real Part of Capacitance

Annealing = Re-heating and Re-cooling



Dielectric loss spectrum

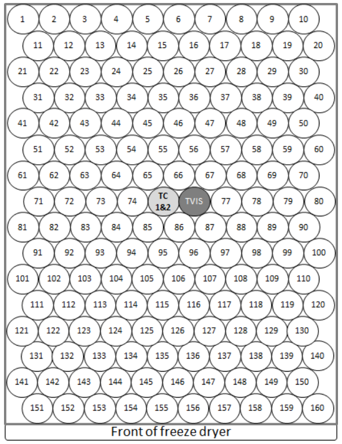
- *Data analysing software (LyoView ™) identifies the peak frequency (F_{PEAK}) and peak amplitude (C''_{PEAK}) in the imaginary part of the capacitance spectrum*



Through Vial Impedance Spectroscopy (TVIS)

Dual-electrode system and its applications

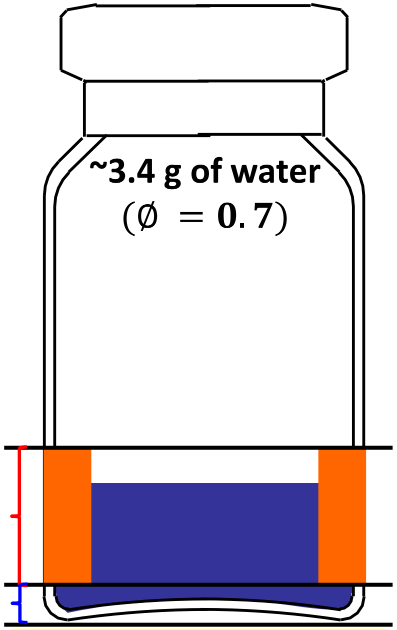
(Ice temperature, Drying rate and Heat transfer coefficient)



Dual-electrode system

Standard TVIS vial

(Single electrode system)



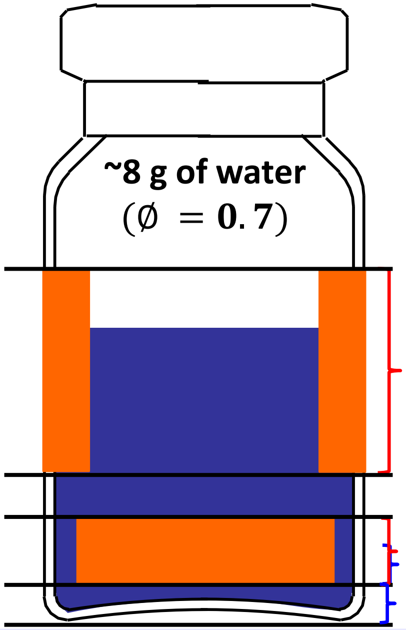
Electrode height ~10 mm

Electrode distance from base ~3 mm

Electrode Dimension
10 x 19 mm

New feature of TVIS vial

(Dual electrode system)



Top electrode height ~15 mm

Gap between electrode ~3 mm

Bottom electrode height ~10 mm

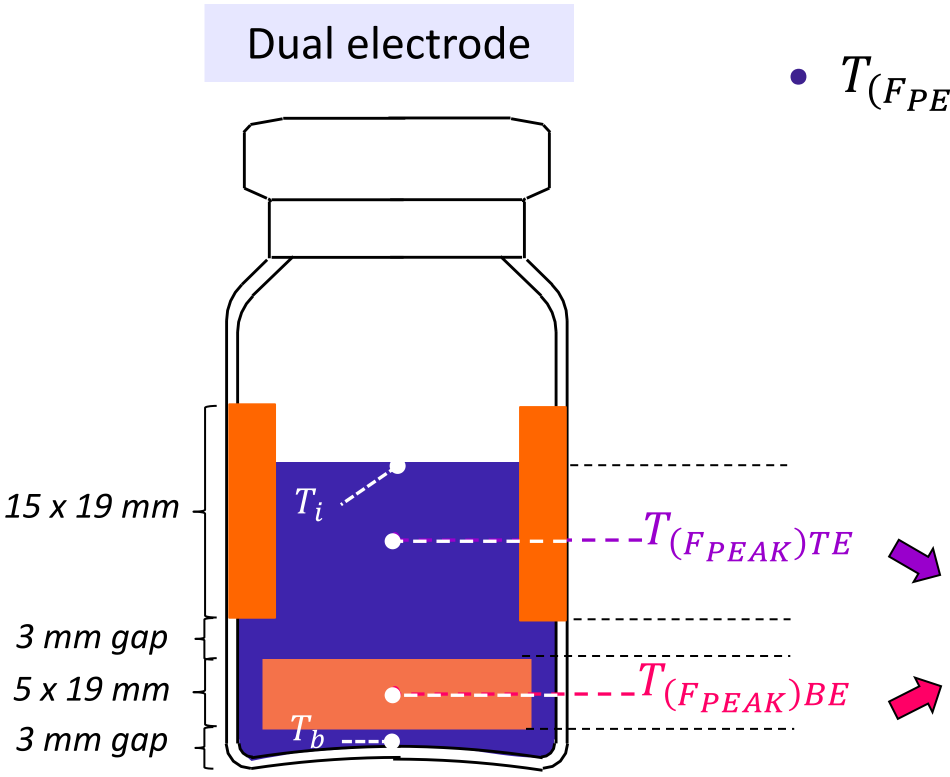
Electrode distance from base ~3 mm

Electrode Dimension
Top electrode (TE): 10 x 19 mm
Bottom Electrode (BE): 5 x 19 mm

- A dual electrode system comprises two pairs of copper electrode glued to the external surface of a Type I tubular glass vial.
- This option is suitable for large volume samples, including those used for K_v determination.

Temperature Determination

- $T_{(F_{PEAK})TE}$: TVIS predicted temperature from top electrode (TE)
- $T_{(F_{PEAK})BE}$: TVIS predicted temperature from bottom electrode (BE)



Both T_i and T_b can be estimated by extrapolating from the temperatures predicted from the centers of top electrode ($T_{(F_{PEAK})TE}$) and bottom electrode ($T_{(F_{PEAK})BE}$).

Aims & Objectives

Aims

To determine the heat transfer coefficient (K_v) by using a novel dual electrode TVIS approach

- I Temperature calibration of log F_{PEAK} of top electrode ($T_{(F_{PEAK})TE}$) and bottom electrode ($T_{(F_{PEAK})BE}$)
- II Prediction ice temperatures for both electrodes during primary drying
- III Temperature calibration of C''_{PEAK}
- IV Compensation of C''_{PEAK} during primary drying
- V Calibration of C''_{PEAK} for ice layer height
- VI Estimation of ice layer height during primary drying
- VII Prediction ice temperatures at (i) sublimation interface (T_i) and (ii) vial's base (T_b) including qualification TVIS technique ($T_i = T_{(P_i=P_c)}$)
- VIII Comparison of TVIS drying rate ($\Delta m/\Delta t$) with gravimetric method (weight loss)
- IX Determination (i) the drying rate ($\Delta m/\Delta t$) and (ii) ice base temperature (T_b) during the steady state period
- X Heat transfer coefficient (K_v) calculation

Objective

I

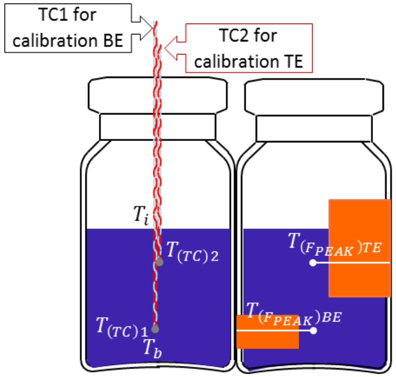
Temperature calibration of log F_{PEAK} of top electrode ($T_{(F_{PEAK})TE}$) and bottom electrode ($T_{(F_{PEAK})BE}$)

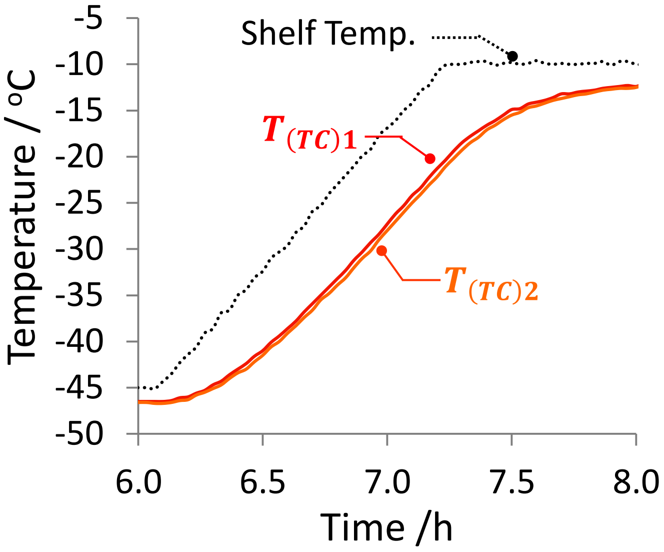
- Annealing the sample
- In-line TVIS measurement
- Identifying peak frequency (F_{PEAK}) using LyoView ™ software
- Calibration plot (temperature vs Log F_{PEAK})
- Predicting product temperature using calibration plot

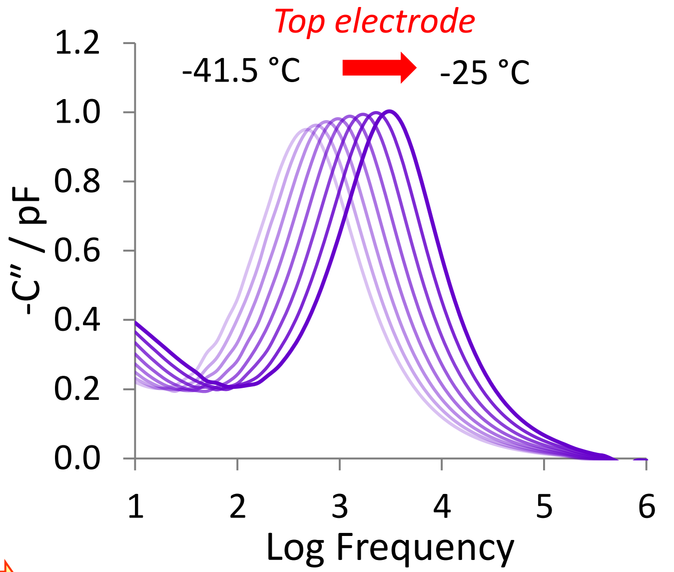
Objective

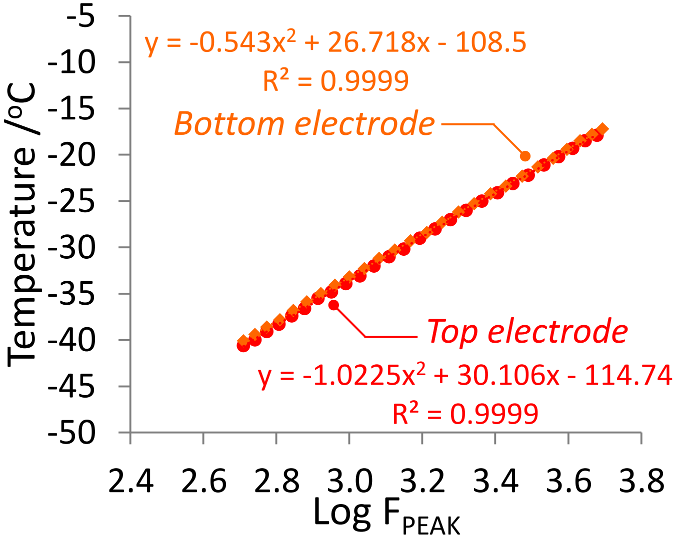
I

Temperature calibration of log F_{PEAK} of top electrode ($T_{(F_{PEAK})TE}$) and bottom electrode ($T_{(F_{PEAK})BE}$)









Polynomial coefficient from $Log\ F_{PEAK}$ − temperature calibration

	a	b	c
TE	*-1.02*	*30.1*	*-114*
BE	*-5.43 x 10^{-1}*	*26.7*	*-109*

Objective

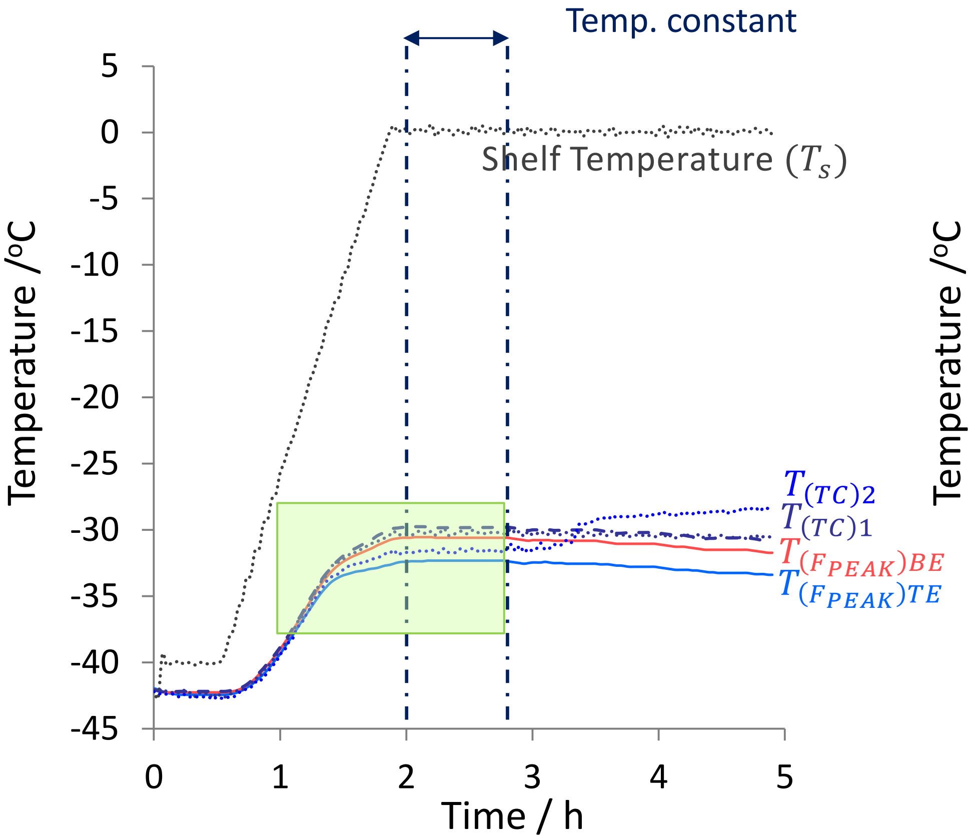
II

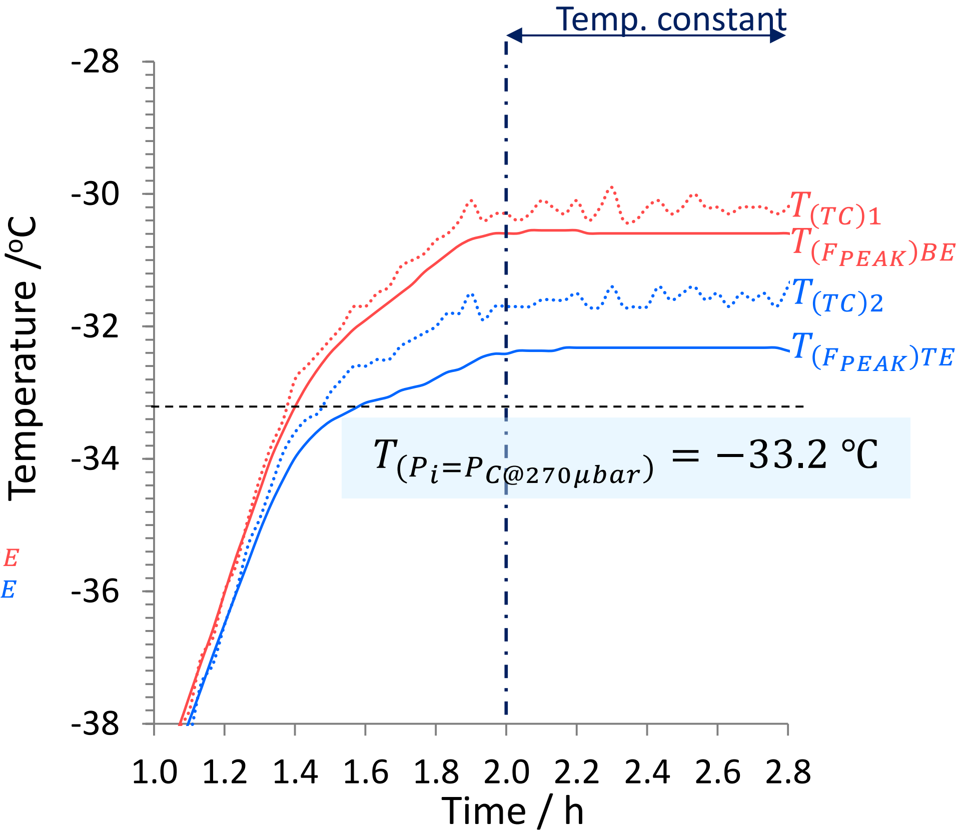
Prediction ice temperatures for both electrodes during primary drying

Objective

II

Prediction ice temperatures for both electrodes during primary drying



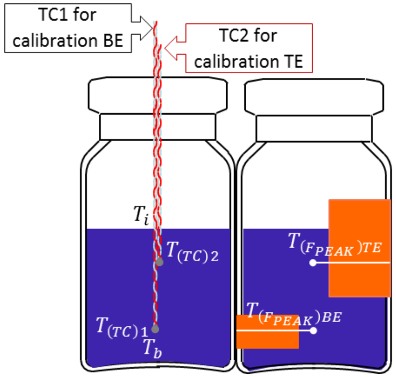


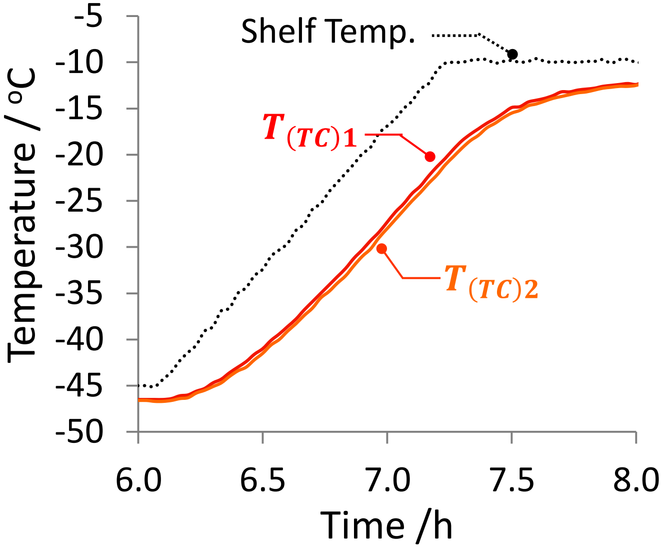
The product temperature predicted by TVIS can demonstrate the temperature gradient across ice cylinder height

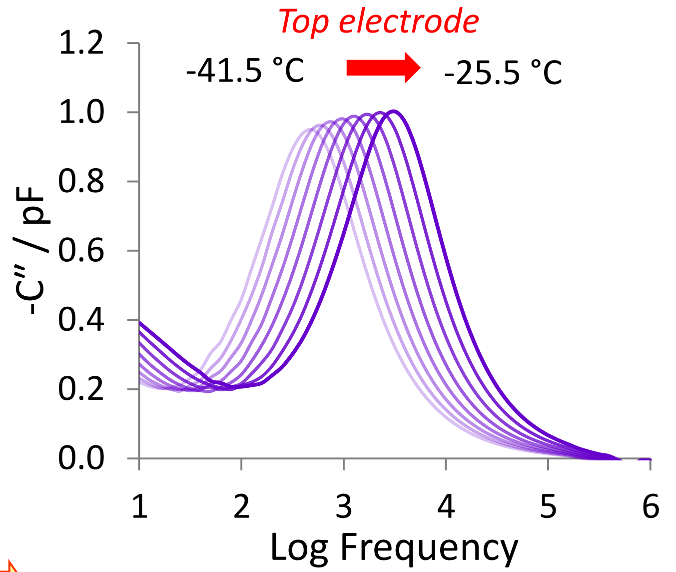
Objective III Temperature calibration of C''_{PEAK}

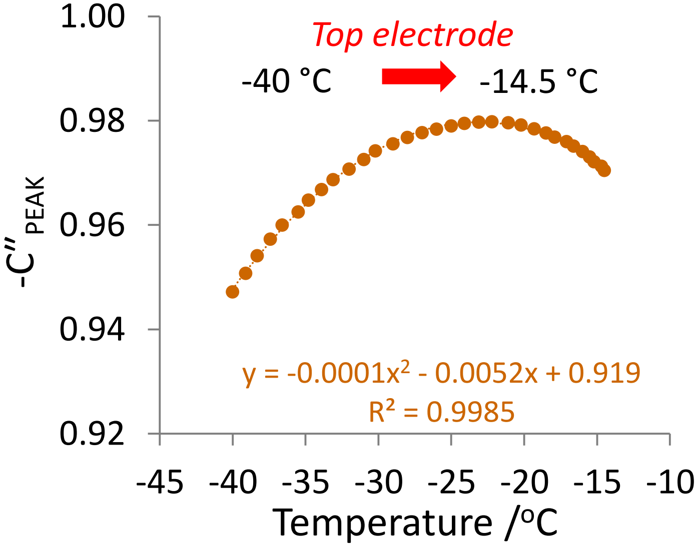
- Annealing the sample
- In-line TVIS measurement
- Identifying peak amplitude (C''_{PEAK}) using LyoView ™ software
- Calibration plot (C''_{PEAK} vs temperature)
- Temperature compensation of C''_{PEAK} using calibration plot

Objective III Temperature calibration of C''_{PEAK}









Polynomial coefficient from C''_{PEAK} − temperature calibration

a	b	c
-1.00 x 10^{-4}	*-5.20 x 10^{-3}*	*9.19 x 10^{-1}*

Objective IV Compensation of C''_{PEAK} during primary drying

Objective IV

Compensation of C''_{PEAK} during primary drying

- During primary drying, C''_{PEAK} is attributed to both the loss of ice and product temperature; therefore, it requires a standardization factor (Ø) for temperature compensation:

$$\varnothing(T) = \frac{C''_{PEAK}(T)}{C''_{PEAK}(T_{ref})}$$

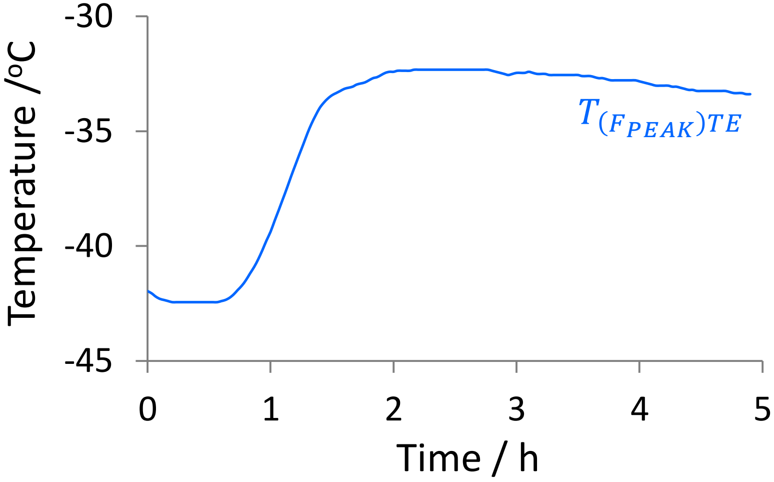
$C''_{PEAK}(T)$ and $C''_{PEAK}(T_{ref})$ are the peak amplitudes at temperatures (T) and reference temperature (T_{ref}) during the re-heating ramp. In this presentation, a temperature of -20 °C is used as the reference temperature value

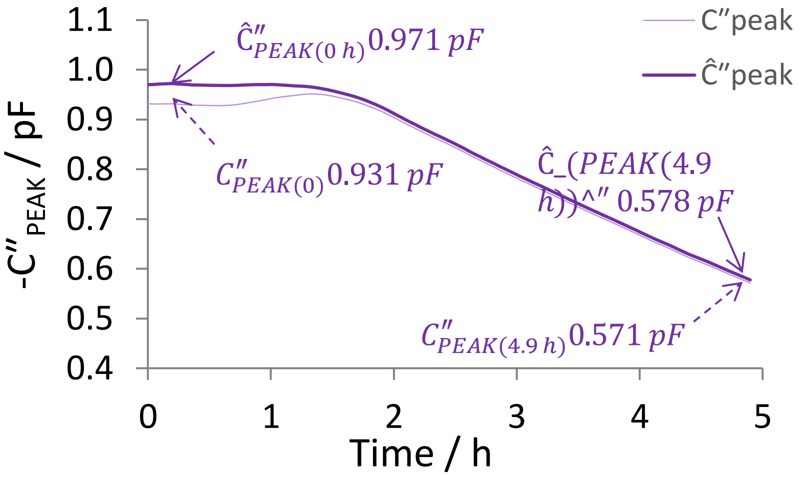
- The expression for $\varnothing(T)$ can be re-written in terms of the polynomial coefficients (slide 22):

$$\varnothing(T) = \frac{aT^2+bT+c}{a{T_{ref}}^2+bT_{ref}+c}$$

- Values of C''_{PEAK} during primary drying are then standardized to the reference temperature by dividing by $\varnothing(T)$ to give a standardized peak amplitude of $\hat{C}''_{\boldsymbol{PEAK}}$

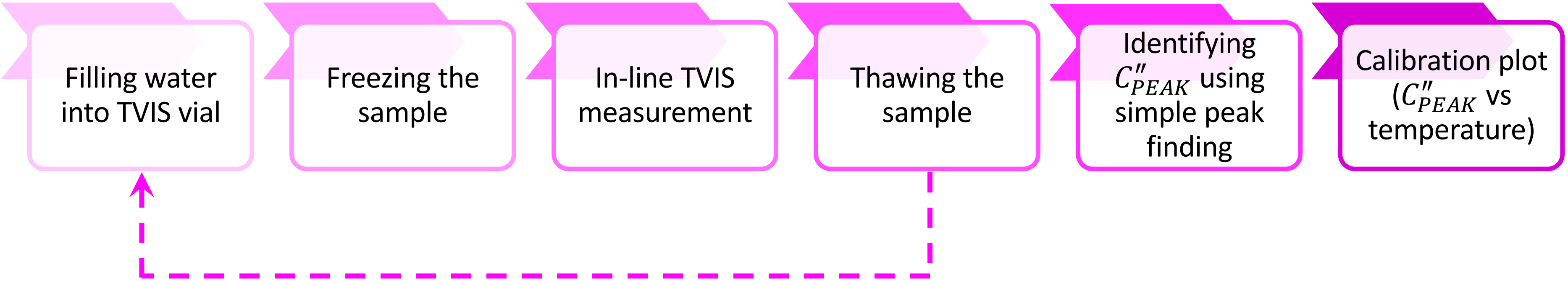
$$\hat{C}''_{\boldsymbol{PEAK}} = \frac{C''_{PEAK}(T)}{\varnothing(T)}$$





The standardized C''_{PEAK} is defined as $\hat{C}''_{\boldsymbol{PEAK}}$

Objective V Calibration of C''_{PEAK} for ice layer height


Filling water into TVIS vial

Freezing the sample

In-line TVIS measurement

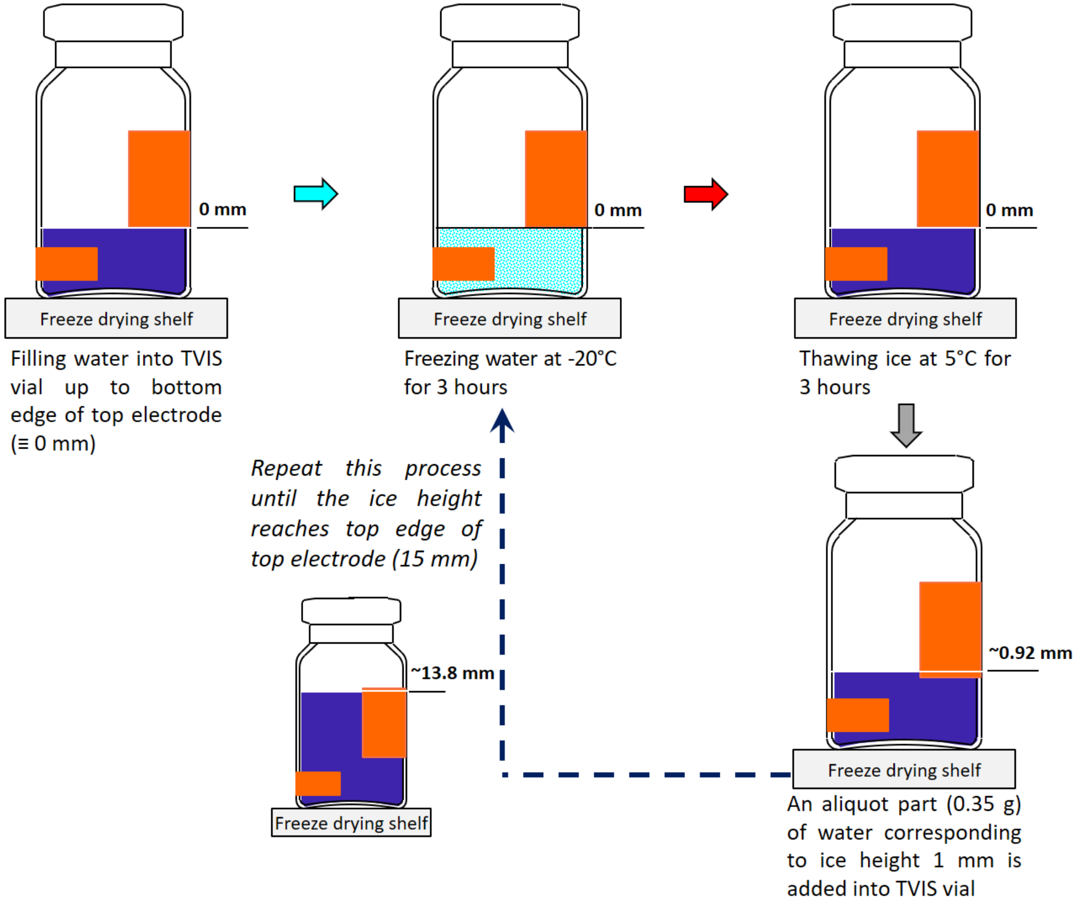
Thawing the sample

Identifying C''_{PEAK} using simple peak finding

Calibration plot (C''_{PEAK} vs temperature)

Objective

V Calibration of C''_{PEAK} for ice layer height



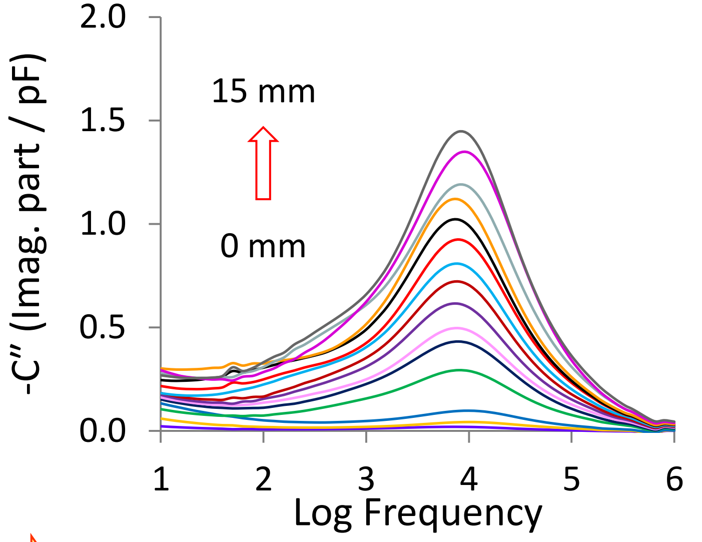
Filling water into TVIS vial up to bottom edge of top electrode (≡ 0 mm)

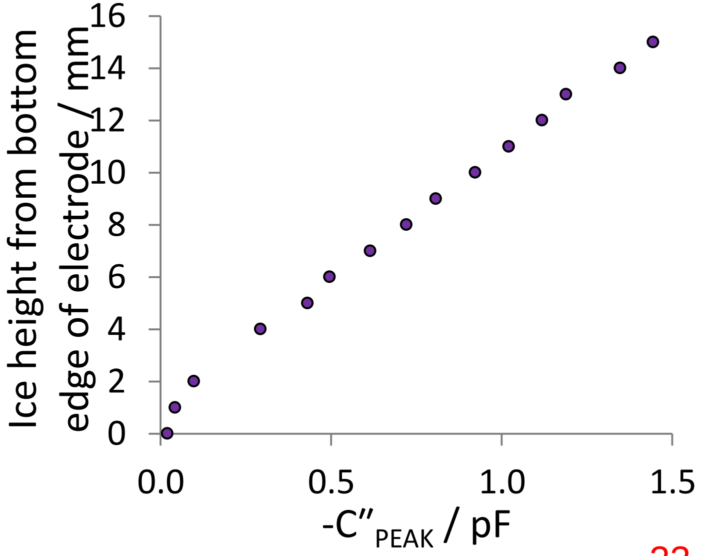
Freezing water at -20°C for 3 hours

Thawing ice at 5°C for 3 hours

An aliquot part (0.35 g) of water corresponding to ice height 1 mm is added into TVIS vial

Repeat this process until the ice height reaches top edge of top electrode (15 mm)

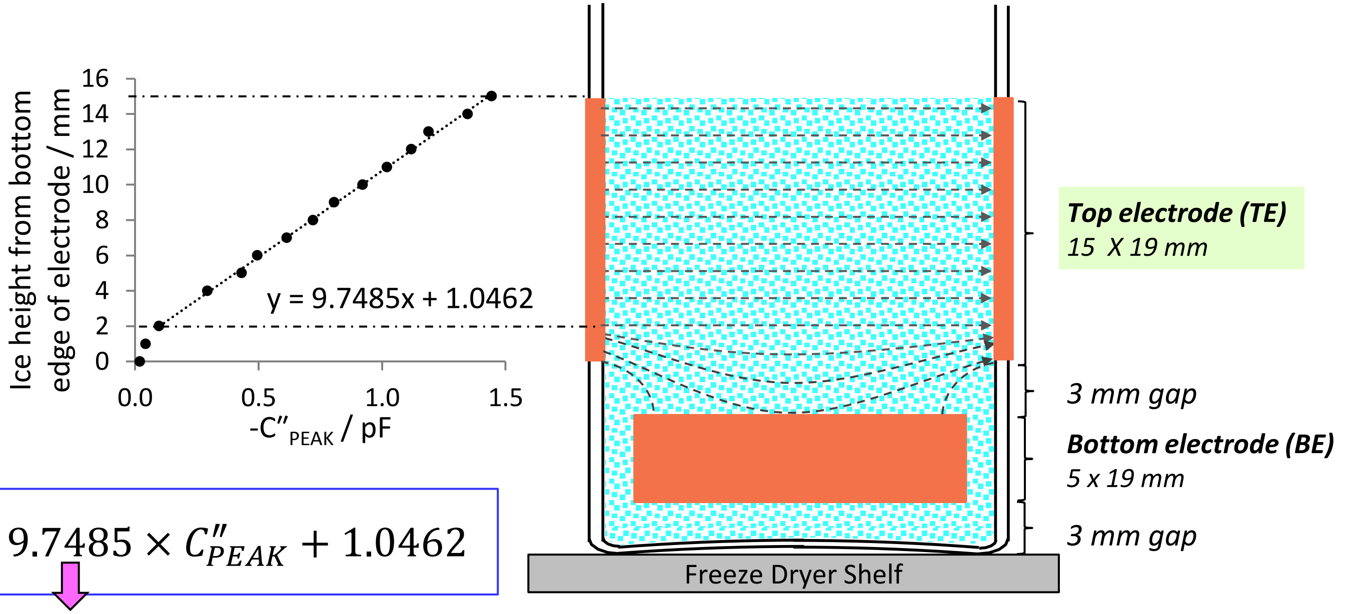




Objective VI Estimation of ice layer height during primary drying

Objective VI Estimation of ice layer height during primary drying

At -20 °C



$$Ice\ height(h) = 9.7485 \times C''_{PEAK} + 1.0462$$

Gradient of the line ($m_{h/c}$)

At 2.4 h into primary drying

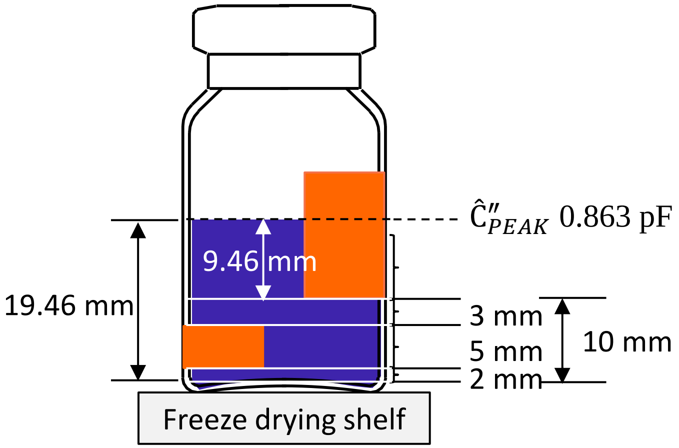
$\hat{C}''_{PEAK}$ = 0.863 pF

Ice height = 9.7485 x 0.863 + 1.0462

= 9.459 mm (from the bottom edge of TE)

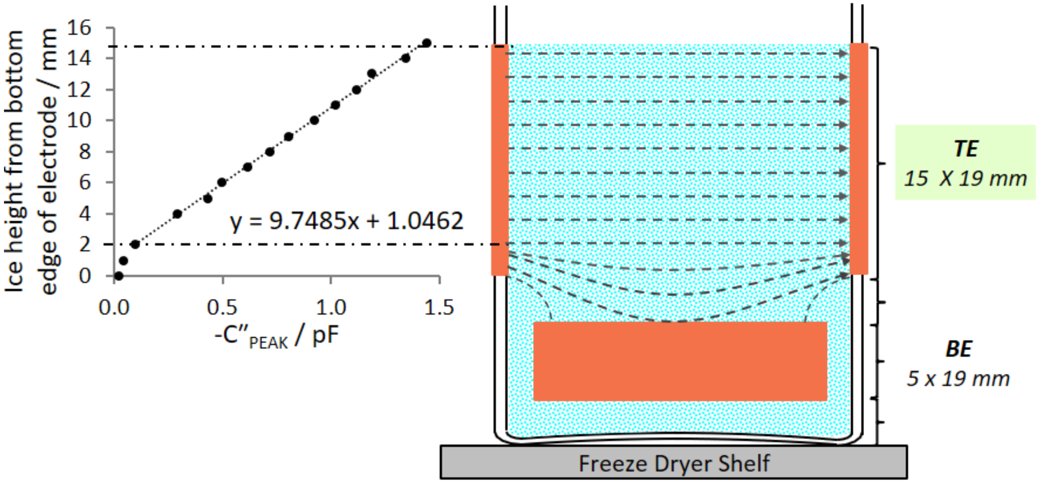
Ice front height = 9.459+(2+5+3)

= 19.46 mm



Objective VI Estimation of ice layer height during primary drying

- The dependency of C''_{PEAK} on the ice cylinder height in linear region
- Surrogate drying rate can be estimated in terms of decreasing ice height

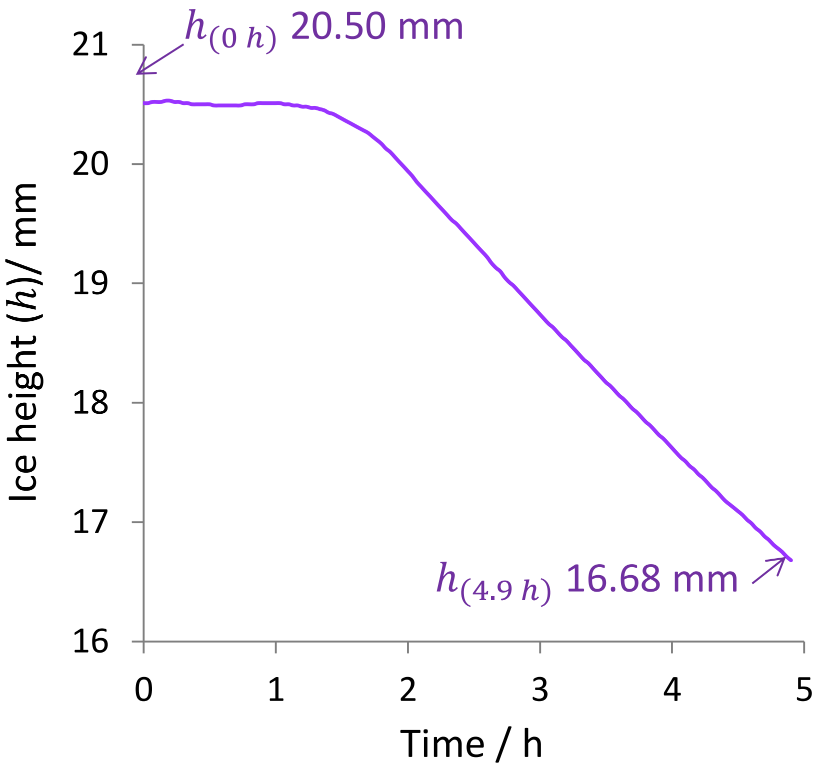


$$y = 9.7485x + 1.0462$$

C''_{PEAK}

Linear gradient $(m_{h/c})$

Ice height (h)

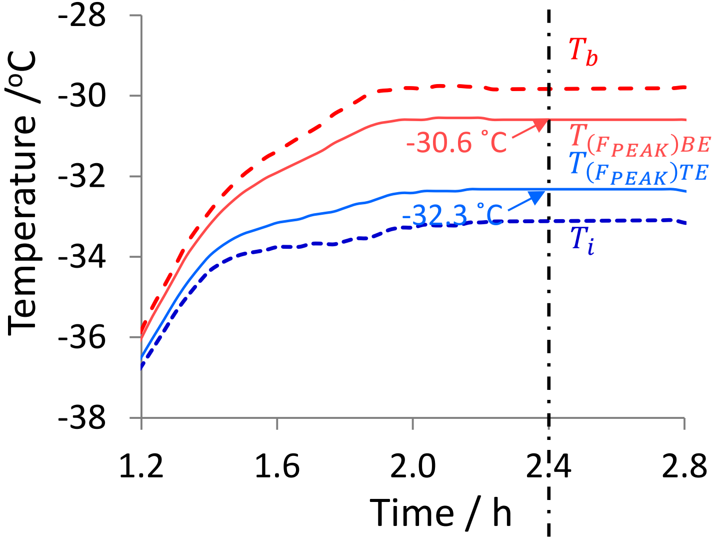


Objective

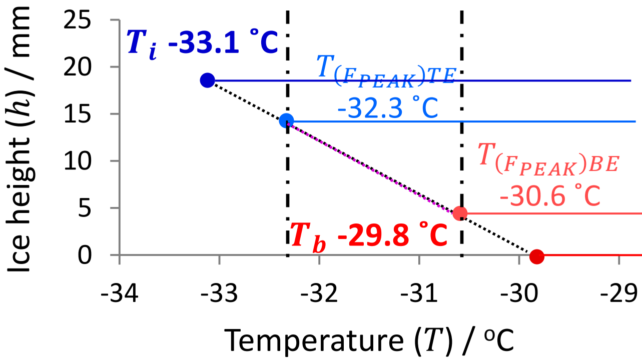
VII

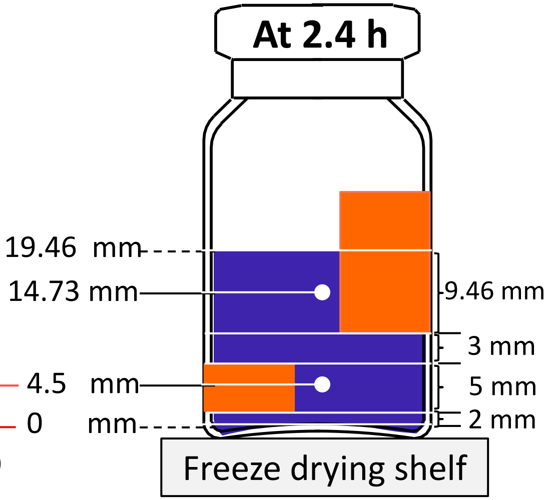
Prediction ice temperatures at (i) sublimation interface (T_i) and (ii) vial's base (T_b) including qualification TVIS technique ($T_i = T_{(P_i=P_c)}$)

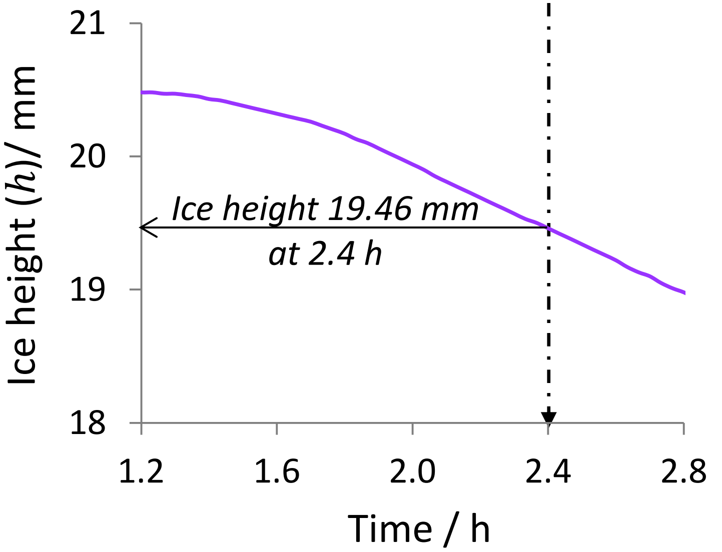
Objective VII Prediction ice temperatures at (i) sublimation interface (T_i) and (ii) vial's base (T_b) including qualification TVIS technique ($T_i = T_{(P_i=P_c)}$)



$$h = -5.93 \times T - 176.79$$







Ice height for $T_{(F_{PEAK})TE}$ $= 2 + 5 + 3 + (\frac{9.46}{2}) = 14.73$ mm

Ice height for $T_{(F_{PEAK})BE}$ $= 2 + (\frac{5}{2}) = 4.50$ mm

$$h = -5.93 \times T - 176.79 \Rightarrow T = \frac{h + 176.79}{-5.93}$$

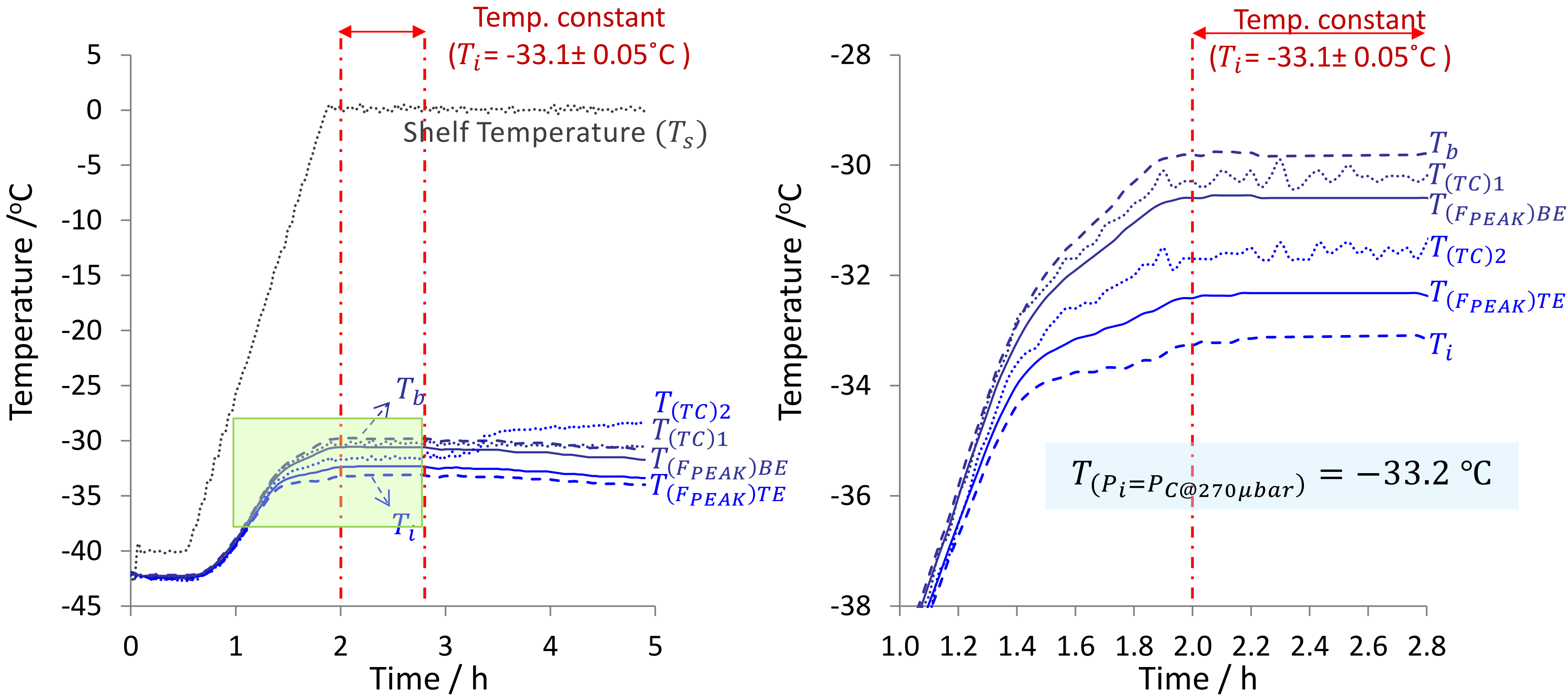
Ice Temperature

At interface (T_i, 19.46 mm) $= \frac{h+176.79}{-5.93} = \frac{19.46+176.79}{-5.93} =$ **-33.1 ˚C**

At vial's base (T_b, 0 mm) $= \frac{h+176.79}{-5.93} = \frac{0+176.79}{-5.93} =$ **-29.8 ˚C**

Objective VII Prediction ice temperatures at (i) sublimation interface (T_i) and (ii) vial's base (T_b) including qualification TVIS technique ($T_i = T_{(P_i=P_c)}$)

TVIS



$T_{(P_i=P_{C@270\mu bar})} = -33.2\ ℃$

The product temperature at ice interface predicted by using a 2-points temperature extrapolation close to the temperature of ice vapour at chamber pressure of 270 µbar ($T_{(P_i=P_{C@270\mu bar})}$)

Objective VIII

Comparison of TVIS drying rate ($\Delta m/\Delta t$) with gravimetric method (weight loss)

Objective VIII Comparison of TVIS drying rate ($\Delta m/\Delta t$) with gravimetric method (weight loss)

- Drying rate is based on the assumption of a planar sublimation front
- The change in ice cylinder height (h) can be equated to the change in ice volume (v)

$$\mathrm{v}\ (cylinder) = \pi r^2 h = Ah$$

Where r is internal radius of vial and A is internal cross section area of vial ($= \pi r^2$)

- Ice volume can be converted to ice mass (m) by multiplying with ice density (ρ_i)

$$m = \rho_i \cdot \pi r^2 h = \rho_i \cdot Ah$$

- Hence; drying rate ($\frac{\Delta m}{\Delta t}$) can be expressed by

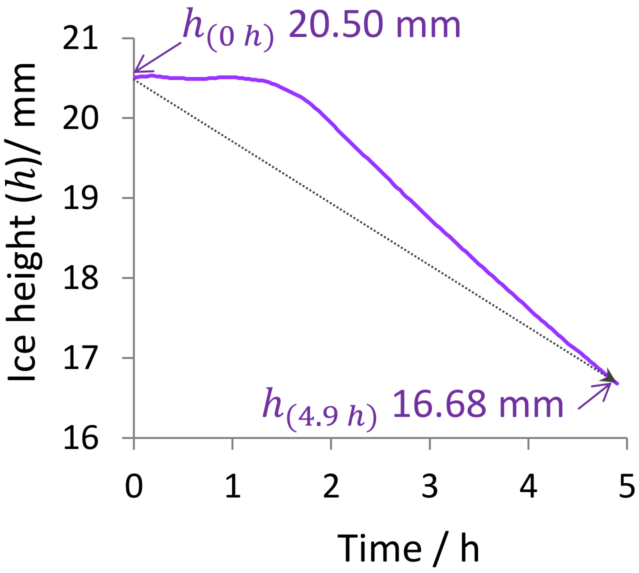
$$\boldsymbol{Drying\ rate\ (\frac{\Delta m}{\Delta t}) = \rho_i \cdot A \cdot \frac{h_{(t1)} - h_{(t2)}}{t_2 - t_1}}$$

Objective VIII Comparison of TVIS drying rate ($\Delta m/\Delta t$) with gravimetric method (weight loss)

- An average surrogate drying rate calculation

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

Ice density (ρ_i)at -32 ˚C	= 0.920 g·cm^{-3}
Internal vial diameter (VC010-20C)	= 2.21 cm
Cross-section area (A)	= 3.80 cm^2
Ice height at 0 h ($h_{(0\ h)}$)	= 20.50 mm
Ice height at 4.9 h ($h_{(4.9\ h)}$)	= 16.68 mm



$$Drying\ rate\ = 0.920\ g \cdot cm^{-3} \times 3.80\ cm^2 \times \frac{(20.50 - 16.68) \times 10^{-1} cm}{(4.9 - 0)h}$$

$$= \mathbf{0.27\ g \cdot h^{-1}}$$

	Drying rate
TVIS	0.27 g/h
Gravimetric	0.25 g/h

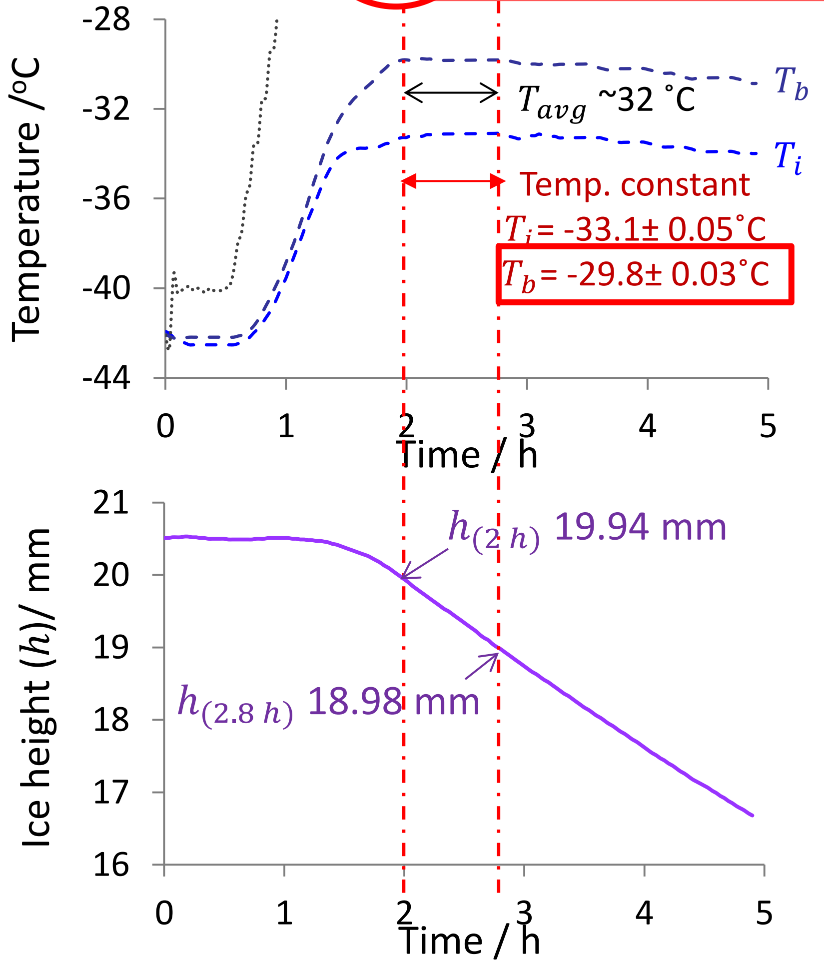
Objective

IX

Determination (i) the drying rate ($\Delta m/\Delta t$) and (ii) ice base temperature (T_b) during the steady state period

Objective IX

Determination (i) the drying rate ($\Delta m/\Delta t$) and (ii) ice base temperature (T_b) during the steady state period for heat transfer coefficient (K_v) calculation



- 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:

$$\frac{\Delta m}{\Delta t} = 0.42\ \mathrm{g{\cdot}h^{-1}}$$

T_b= -29.8˚C

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

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

Objective

X

Heat transfer coefficient (K_v) calculation

Objective X Heat transfer coefficient (K_v) calculation

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

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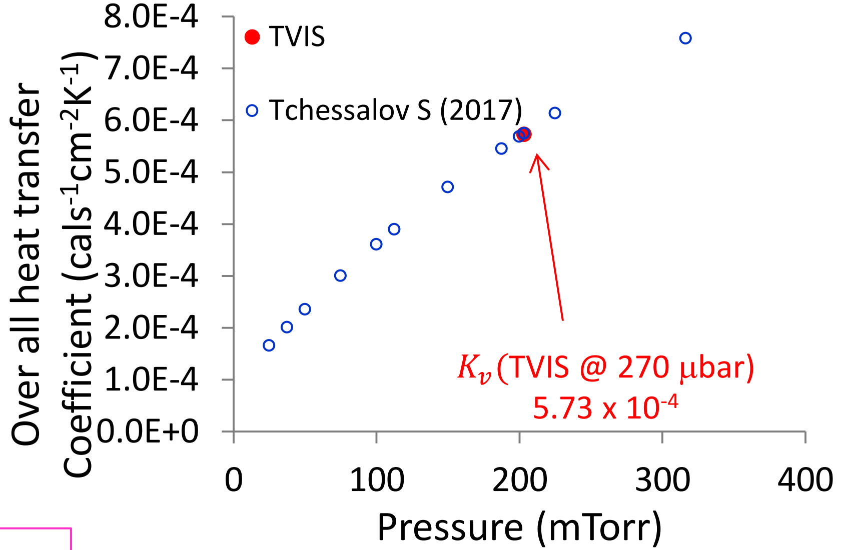


$$L\frac{\Delta m}{\Delta t} = A_e K_v (T_s - T_b) \Rightarrow \boxed{K_v = \frac{L\frac{\Delta m}{\Delta t}}{A_e(T_s - T_b)}}$$

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)

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

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

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

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

Pikal, et al. (1984)

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

Additional comments

Qualification of steady state heat transfer mechanisms

A single vial technique

Pikal, et al. (1984)

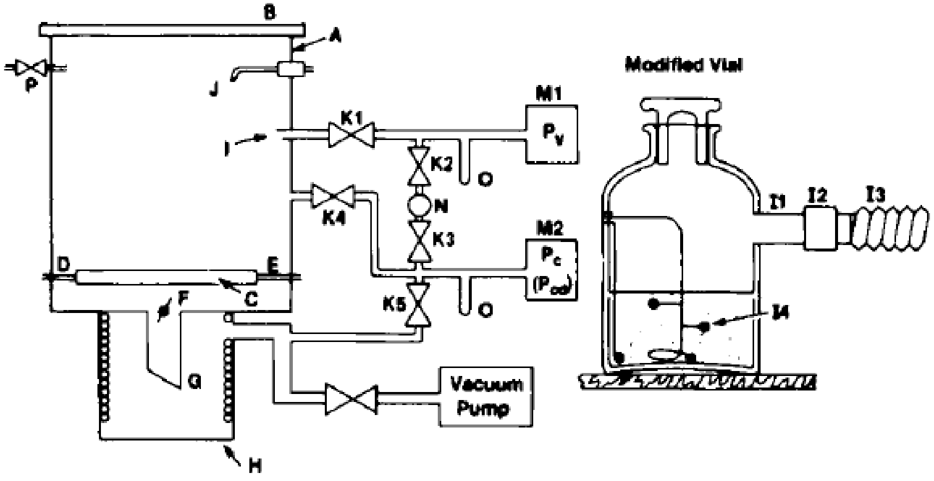


Figure 1—*Schematic of the laboratory freeze-dryer (see text for key).*

The mean sublimation rate was calculated from the mass of ice sublimed and the time required for sublimation.

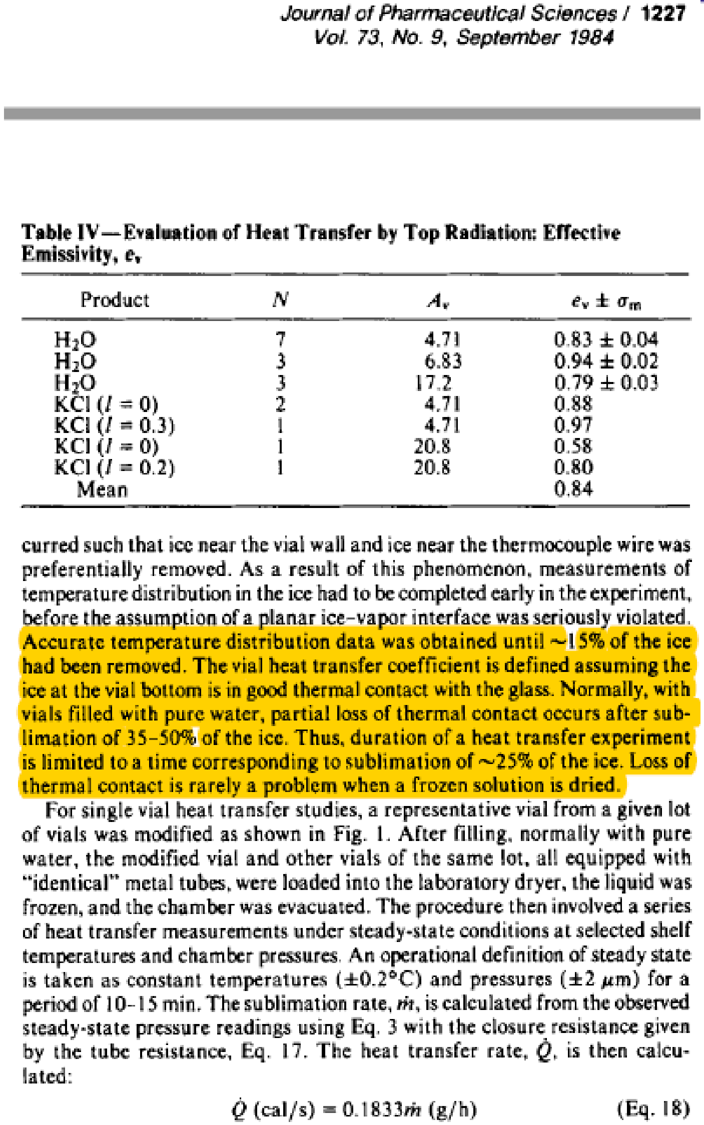

Journal of Pharmaceutical Sciences / **1227**
Vol. 73, No. 9, September 1984

Table IV—Evaluation of Heat Transfer by Top Radiation: Effective Emissivity, e_v

Product	N	A_v	$e_v \pm \sigma_m$
H_2O	7	4.71	0.83 ± 0.04
H_2O	3	6.83	0.94 ± 0.02
H_2O	3	17.2	0.79 ± 0.03
KCl (l = 0)	2	4.71	0.88
KCl (l = 0.3)	1	4.71	0.97
KCl (l = 0)	1	20.8	0.58
KCl (l = 0.2)	1	20.8	0.80
Mean			0.84

curred such that ice near the vial wall and ice near the thermocouple wire was preferentially removed. As a result of this phenomenon, measurements of temperature distribution in the ice had to be completed early in the experiment, before the assumption of a planar ice-vapor interface was seriously violated. Accurate temperature distribution data was obtained until ~15% of the ice had been removed. The vial heat transfer coefficient is defined assuming the ice at the vial bottom is in good thermal contact with the glass. Normally, with vials filled with pure water, partial loss of thermal contact occurs after sublimation of 35–50% of the ice. Thus, duration of a heat transfer experiment is limited to a time corresponding to sublimation of ~25% of the ice. Loss of thermal contact is rarely a problem when a frozen solution is dried.

For single vial heat transfer studies, a representative vial from a given lot of vials was modified as shown in Fig. 1. After filling, normally with pure water, the modified vial and other vials of the same lot, all equipped with "identical" metal tubes, were loaded into the laboratory dryer, the liquid was frozen, and the chamber was evacuated. The procedure then involved a series of heat transfer measurements under steady-state conditions at selected shelf temperatures and chamber pressures. An operational definition of steady state is taken as constant temperatures (±0.2°C) and pressures (±2 μm) for a period of 10–15 min. The sublimation rate, $\dot{m}$, is calculated from the observed steady-state pressure readings using Eq. 3 with the closure resistance given by the tube resistance, Eq. 17. The heat transfer rate, $\dot{Q}$, is then calculated:

$$\dot{Q}\ (\text{cal/s}) = 0.1833\dot{m}\ (\text{g/h}) \qquad \text{(Eq. 18)}$$

Assumption for K_v determination

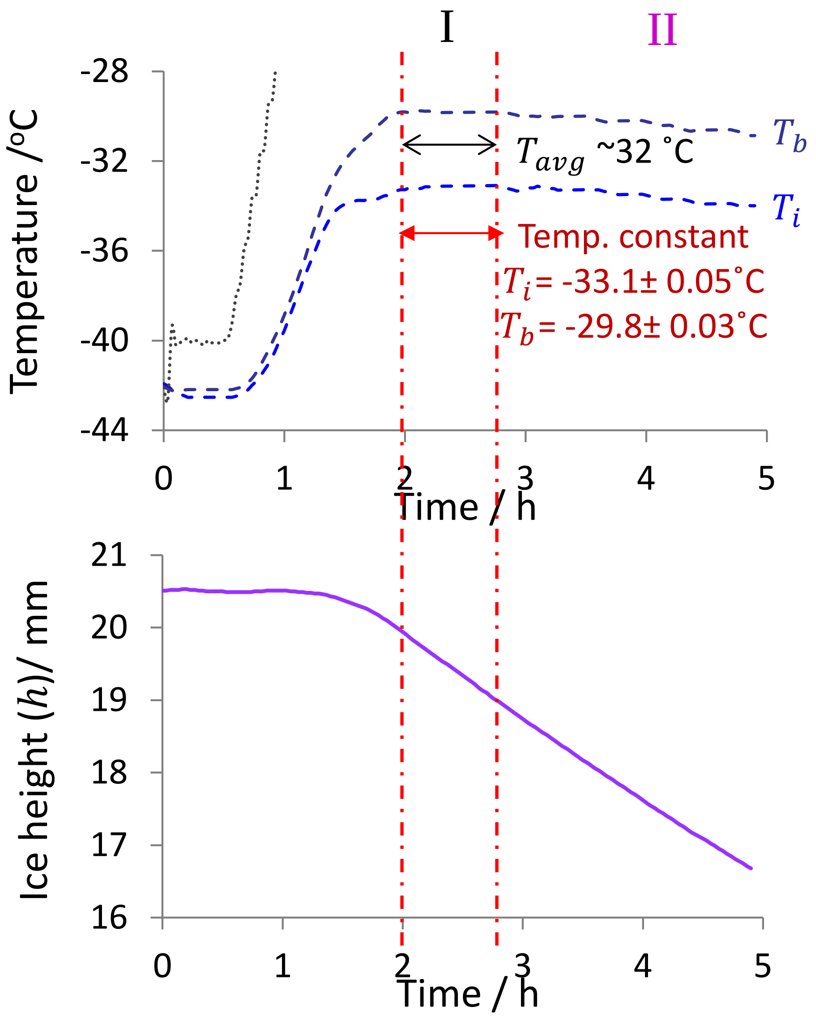
- How do we know that the heat transfer mechanisms are constant up to 25% loss of ice mass?

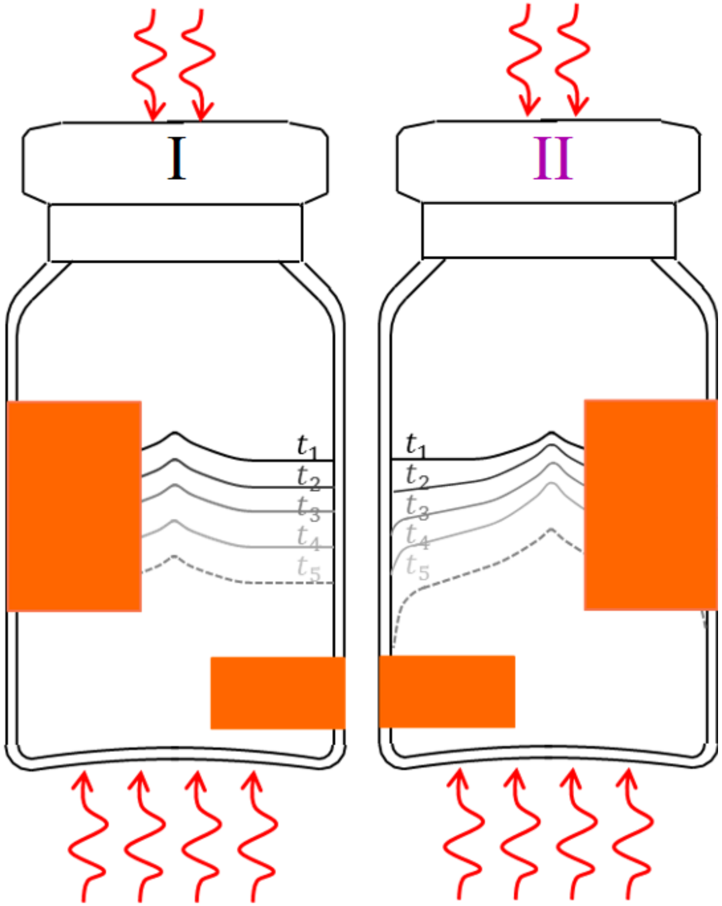
- If the heat transfer mechanisms change because of ice- glass interface contact or because of the change of ice shape (surface area) then surely heat transfer coefficient will change?

- It requires a technique to <u>qualify</u> when the heat transfer mechanisms change

- So can TVIS demonstrate when ice leaves the glass wall interface?

Limitation of TVIS System ?





Discussion

- Decrease in F_{PEAK} suggests that the temperature may be decreasing after the steady state period, contrary to accepted knowledge that the temperature starts to increase owing to a reduction in drying rate and hence the degree of self cooling
- Decrease in F_{PEAK} is more likely to be due to a change in the ice-glass contact associated with a change in the shape of the ice cylinder.

Conclusion

- The period for determining the drying rate should be decreased from 25% ice loss to 10% for TVIS to give reliable estimates for Kv
- Opportunity to cycle through shelf temperature and chamber pressure to create the design space for Kv determinations as a function of shelf position.

Limitations

- C''_{PEAK} and F_{PEAK} parameters rely on intimate contact of ice cylinder with glass wall
- Cable length limited to 1m at present
- C-TVIS not compatible with front loading system
- Incompatible with TCs in same TVIS vial (use fibre optic sensors – INFAP)

Future Work

- Development dryer mapping of sublimation characteristics
  - heat transfer coefficients (K_V)
  - dry layer resistance (R_P)

- Instrument Development
  - Contact C-TVIS instrument (2018)
  - Non-contact TVIS (2018-19)
    - Micro-well screening
    - Vial clusters in batch FD
  - TVIS - Shuttle (2019-20)

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Thank you