



Through Vial Impedance Spectroscopy (TVIS)

A novel process analytical technology for the development of freeze-drying processes and products

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Leicester School of Pharmacy, De Montfort University,
United Kingdom

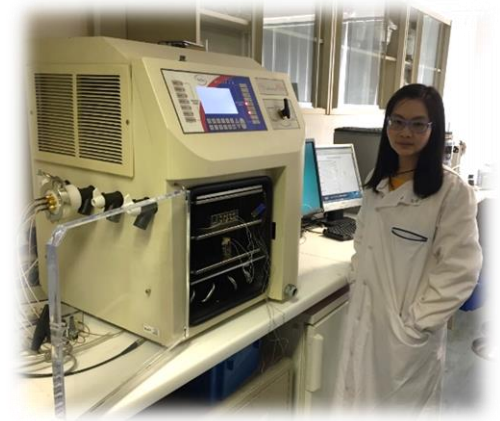
Through Vial Impedance Spectroscopy



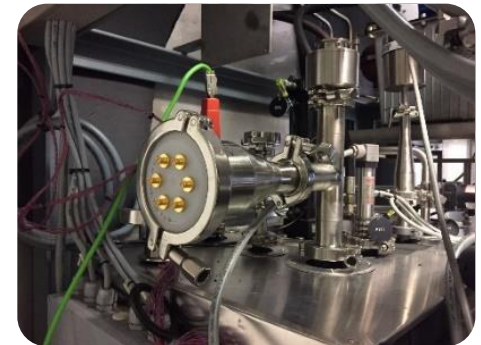
Outline



- Introduction
 - Description of Measurement System
 - Theory (Dielectric loss mechanisms)
- TVIS Applications
 - Ice Formation and phase separation in freezing
 - Temperature calibration and prediction
 - Drying rate estimation
 - Heat transfer coefficient calculation
 - End-point determination
 - Dry Layer resistance and collapse (time permitting)
- Acknowledgements



Yowwares Jeeraruangrattana
GPO Thailand



TVIS pass through on
GEA Lyophil dryer, Hurth, Cologne

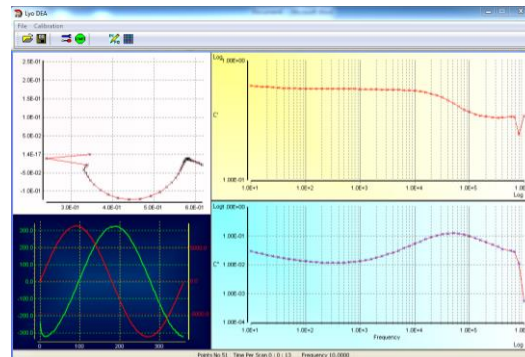
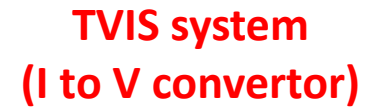
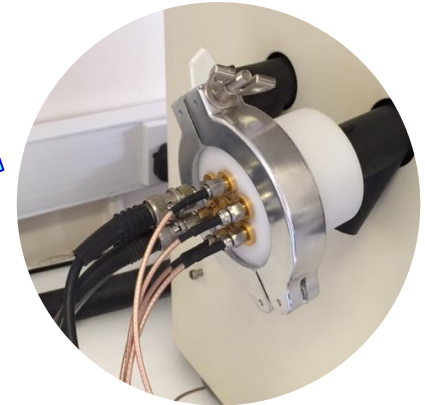
Introduction to the TVIS System

- 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

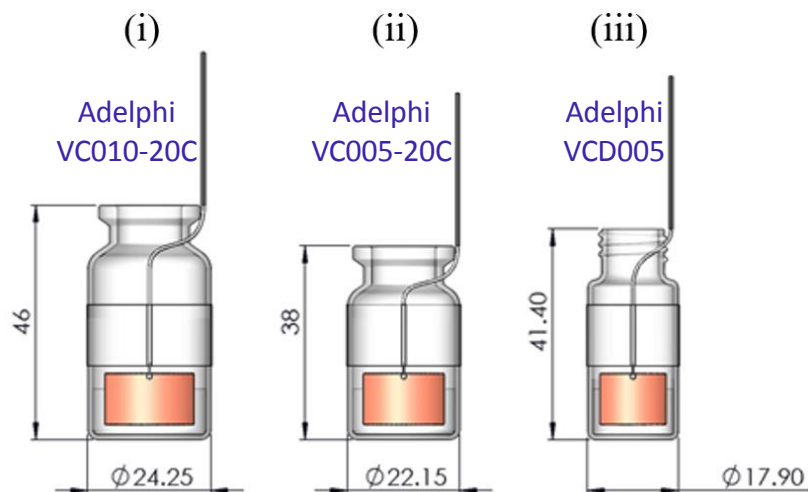


Through Vial Impedance Spectroscopy (TVIS)

Description of Measurement System



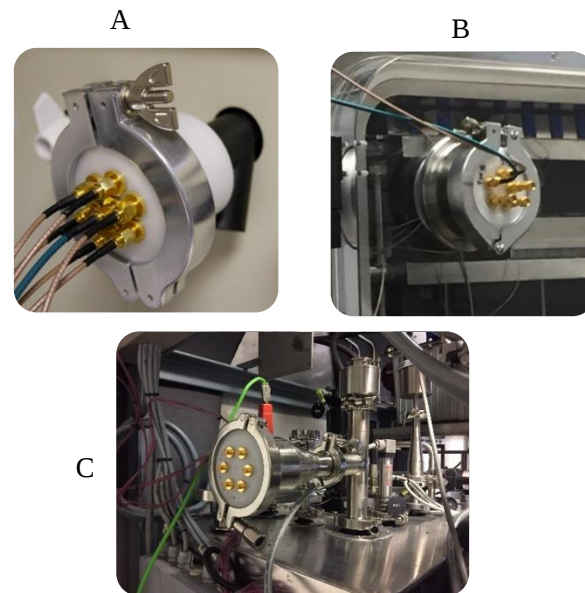
TVIS Measurement System



- The designs of various vials that have been modified with copper foil electrodes (10 mm in height and 3 mm from the base of each container)
 - 20 mm crimp-neck vial with 10 ml nominal capacity
 - 20 mm crimp-neck vial with 5 ml nominal capacity
 - screw-neck vial with 5 ml nominal capacity

- The different styles of a bespoke pass-through for TVIS systems

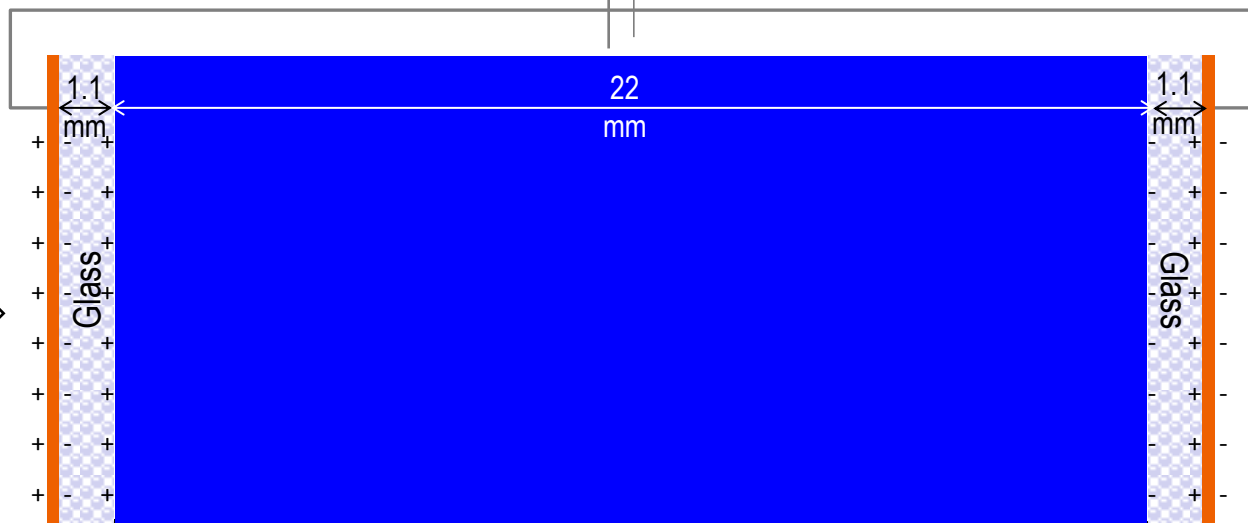
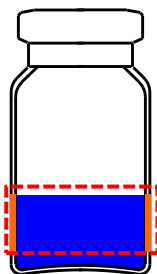
- Connected via the manifold hose on the outside of the dryer
- Connected via the port on top left side of the door on the dryer
- Connected to a port on the top of the drying chamber



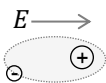
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Dielectric Loss Mechanisms

Measurement vial



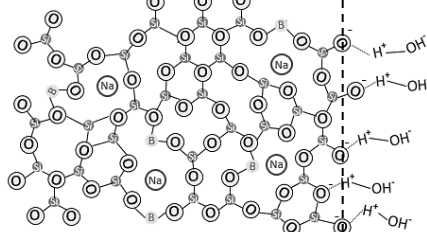
Electronic polarization
distortion of electrons
relative to the nuclei



Atomic polarization
distortion of nuclei across
a heteroatom bond by
stretching and bending



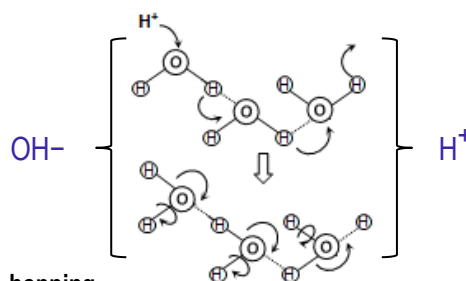
**Instantaneous polarization dominant
mechanism in the glass wall**



**Space charge polarization
(weak frequency dependence)**

**MW (space-charge) polarization at glass
wall – sample interface**

TVIS response for empty vial



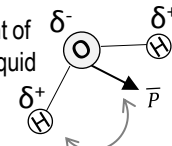
Proton-hopping

Conduction of protons in liquid water occurs
through the Grotthuss "hop-turn" mechanism

Conductivity in pure water

Dipolar polarization

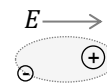
re-orientation/alignment of
permanent dipoles in liquid
water (Debye-like
relaxation)



**Polarization mechanisms in liquid water
(relaxation time, $\tau \sim 9$ ps at 20°C)**

TVIS response for liquid water

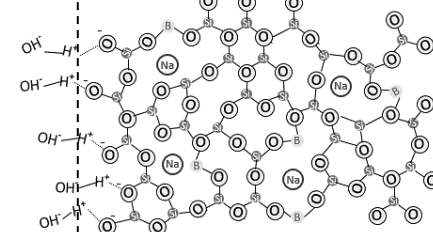
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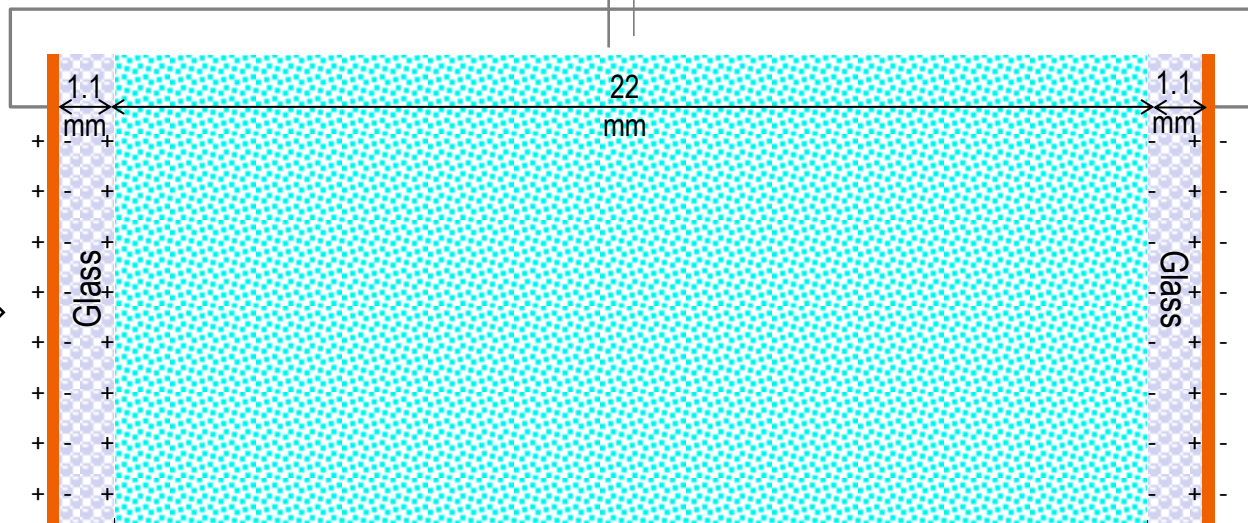
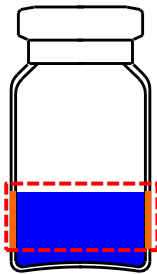


**Space charge polarization
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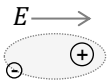
**MW (space-charge) polarization at glass
wall – sample interface**

TVIS response for empty vial

Measurement vial



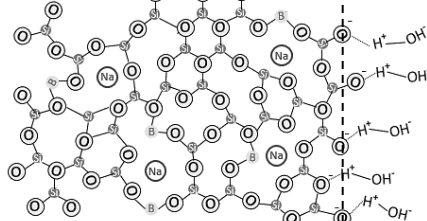
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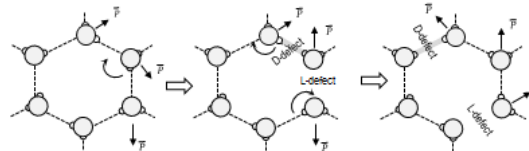


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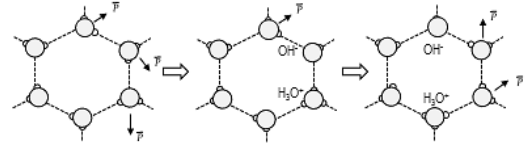
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TVIS response for empty vial

Dominant at $T > 235$ K (approx. -40 °C)
Generation/migration of L- and D- orientation defects
in ice Ih



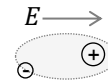
Dominant at $T < 235$ K (approx. -40 °C)
Generation/migration of H_3O^+ / OH^- ion pairs (ionic
defects) in ice Ih (similar to the Grotthuss mechanism)



Polarization mechanism in ice

TVIS response for frozen water (ice)

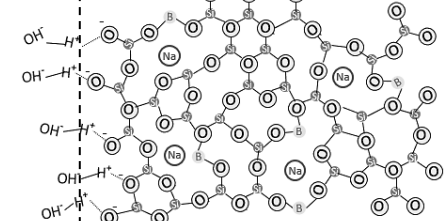
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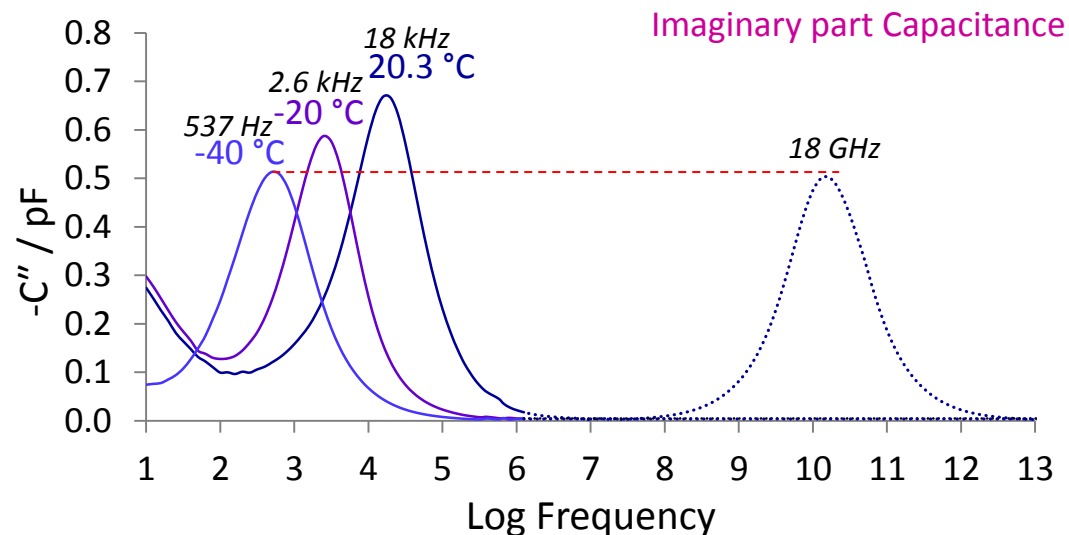
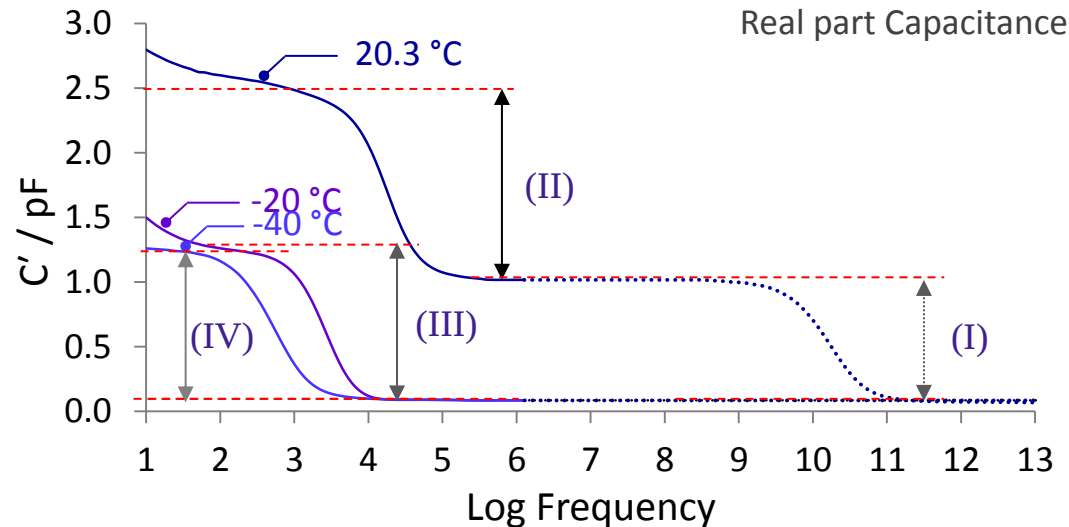
**MW (space-charge) polarization at glass
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TVIS response for empty vial

Frozen Water and Dielectric Relaxation of Ice



- I. : The polarization of the water dipole in liquid water at 20 °C, with a dielectric loss peak frequency of ~ 18 GHz
- II. : The Maxwell-Wagner (MW) polarization of the glass wall of the TVIS vial at 20 °C, with a dielectric loss peak frequency of 17.8 kHz
- III. : The dielectric polarization of ice at -20 °C, with a dielectric loss peak frequencies of 2.57 kHz
- IV. : The dielectric polarization of ice at -40 °C with a dielectric loss peak frequencies of 537 Hz.



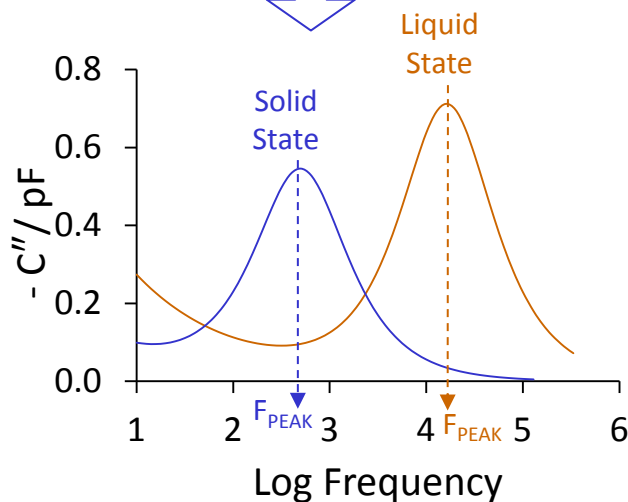
Through Vial Impedance Spectroscopy (TVIS)

Applications

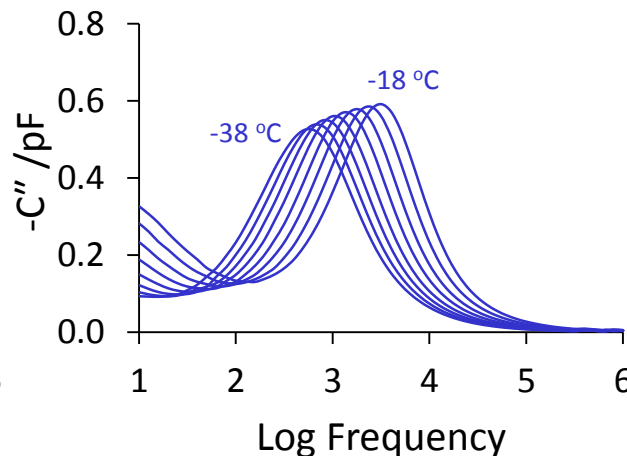
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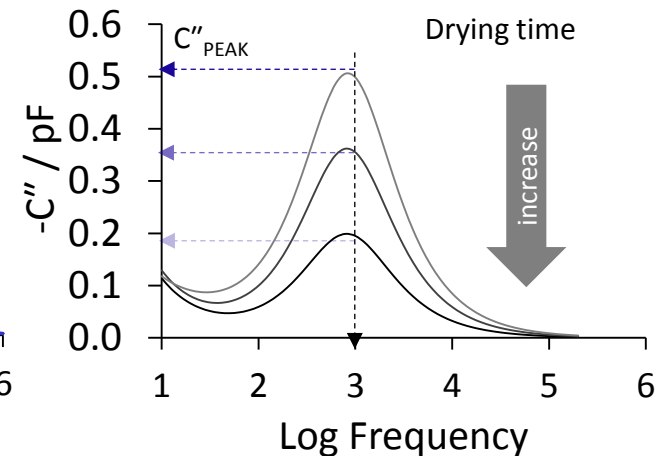
Monitoring **Phase Behaviour**
(ice nucleation temperature
and solidification end points
by using F_{PEAK})



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

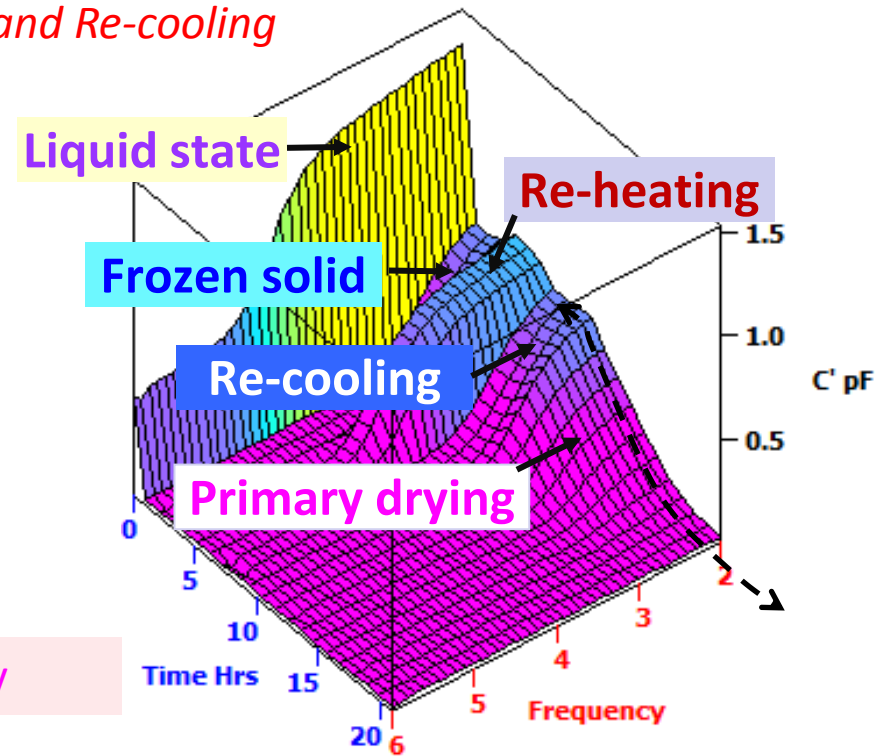
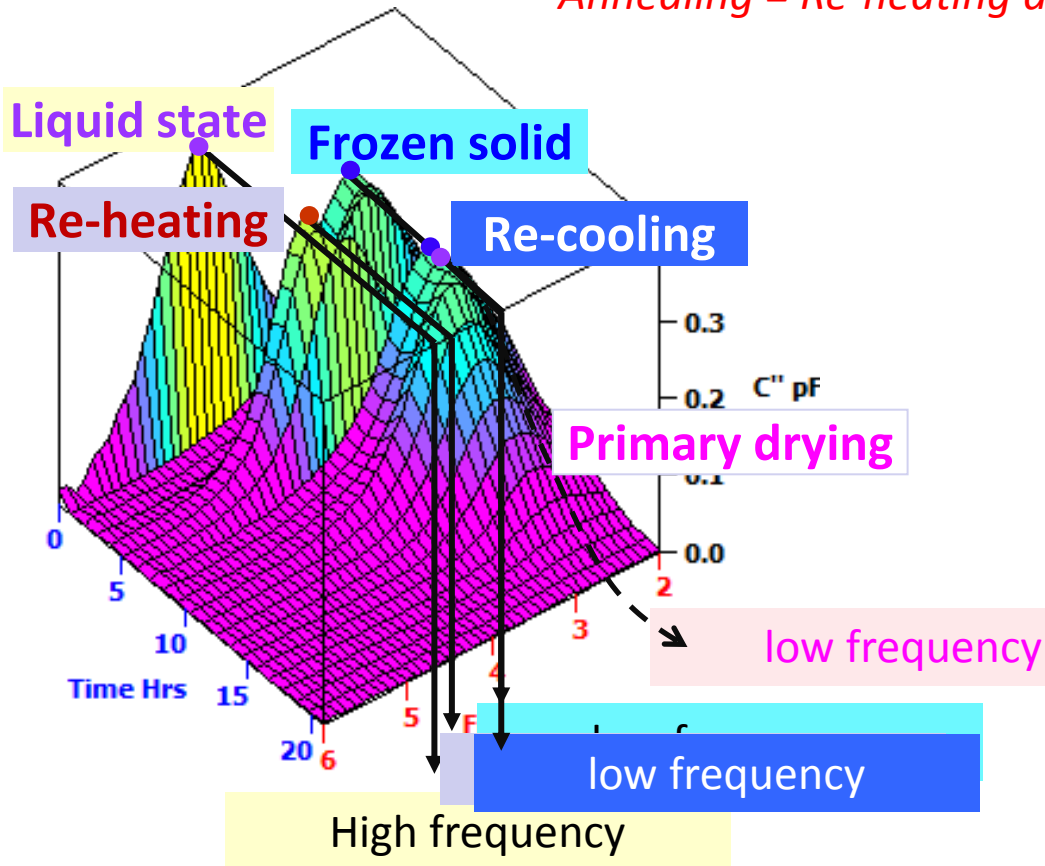
TVIS Response Surface (3D-Plot)



Imaginary Part of Capacitance

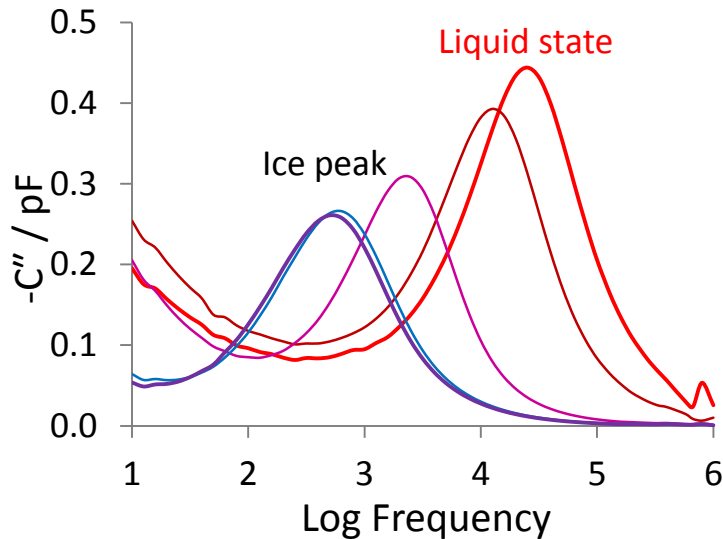
Real Part of Capacitance

Annealing = Re-heating and Re-cooling

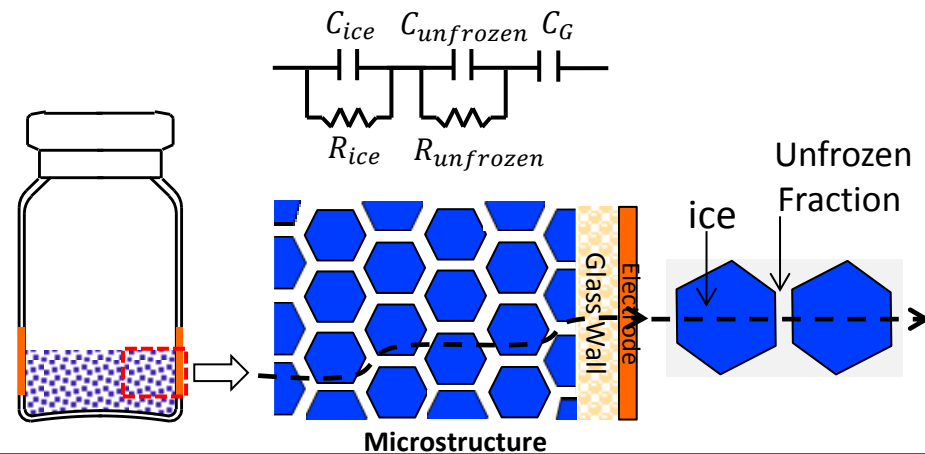
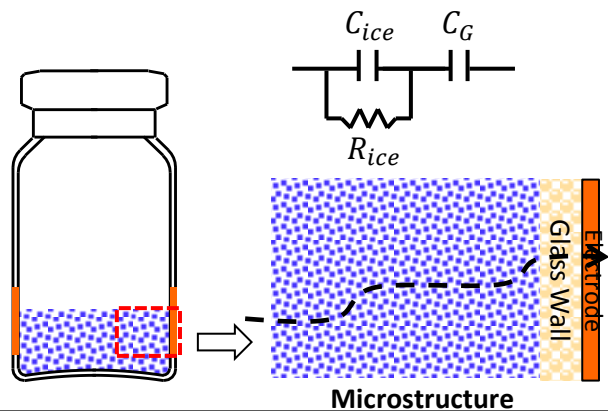
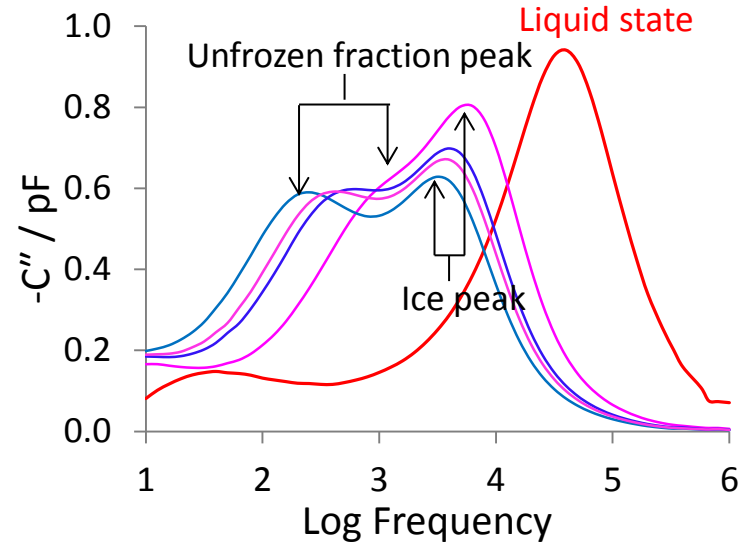


Phase Separation in Freezing Step

Water (frozen)

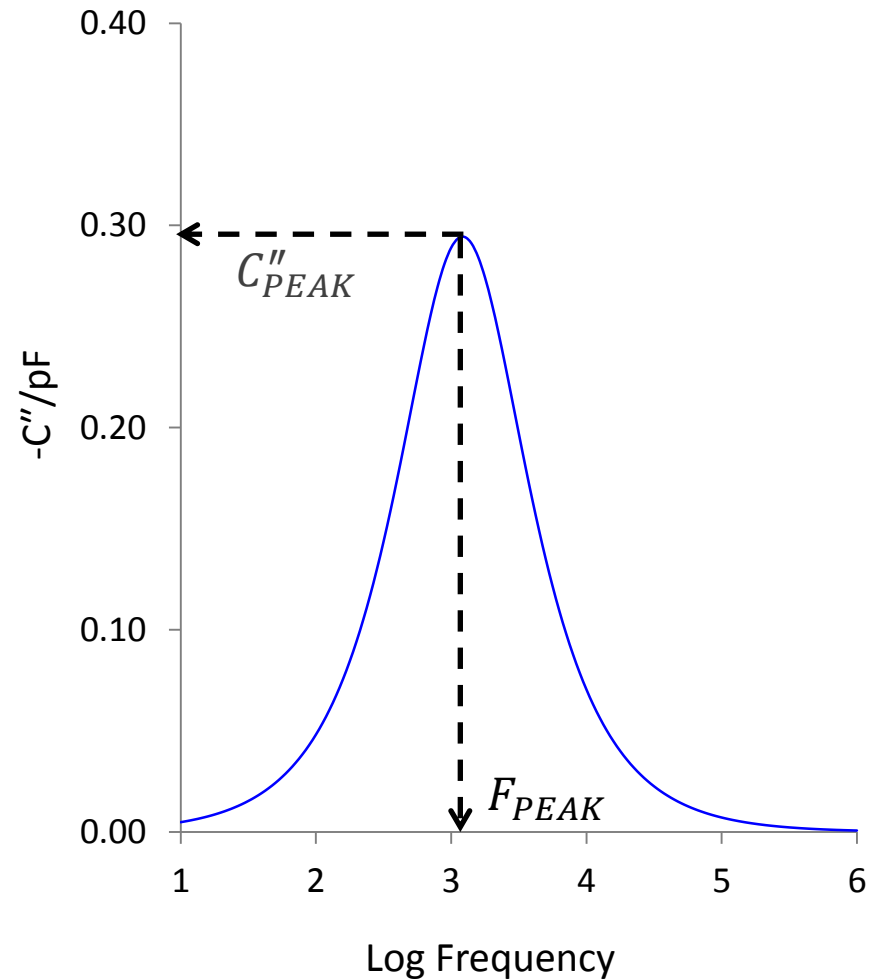


5%w/v Lactose solution (frozen)



Dielectric loss spectrum

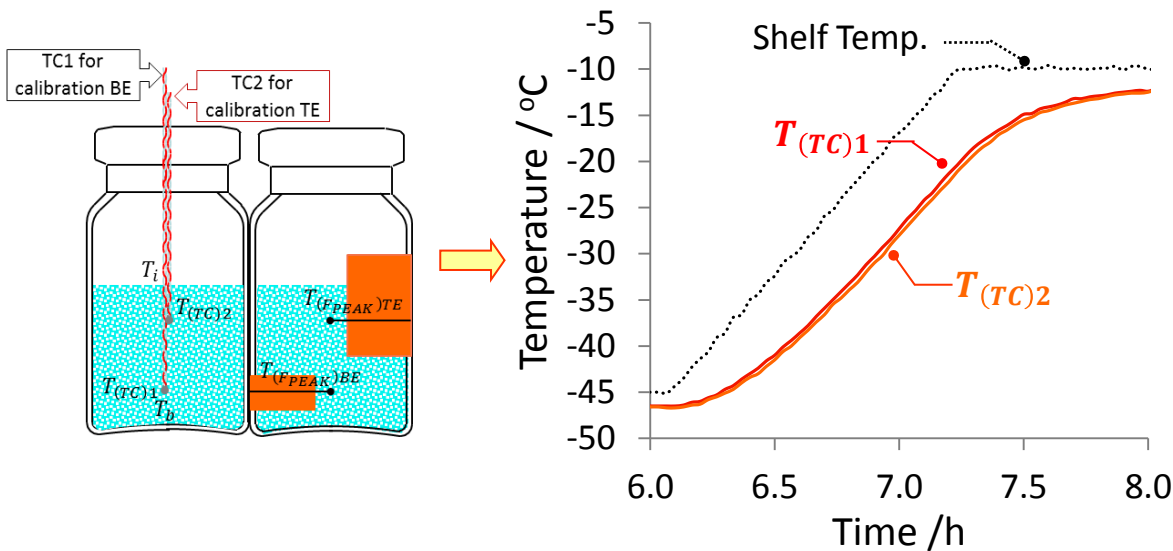
- Data analysing software (*LyoView™*) identifies the peak frequency (F_{PEAK}) and peak amplitude (C''_{PEAK}) in the imaginary part of the capacitance spectrum



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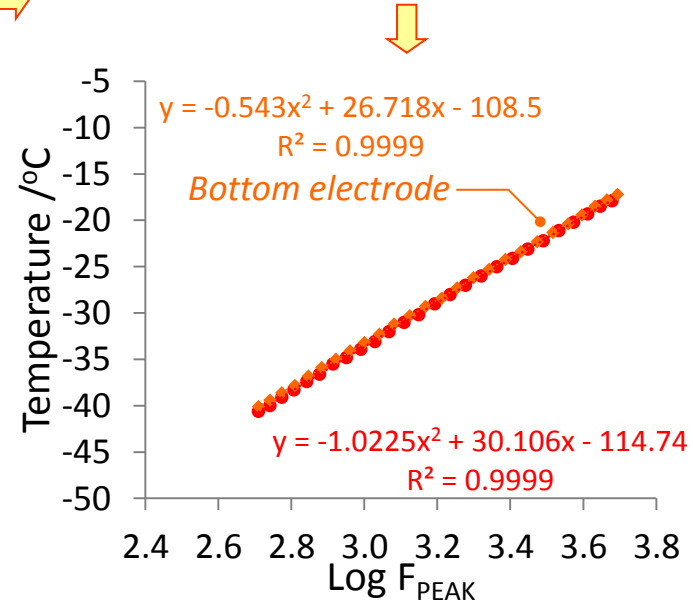
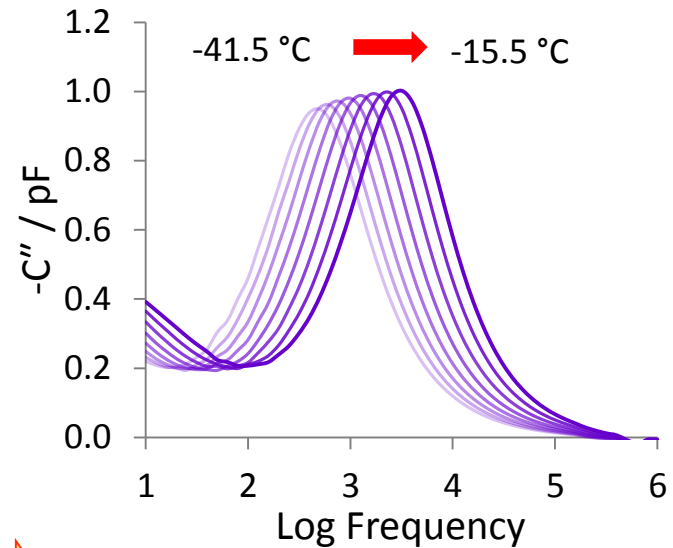
Temperature calibration & Temperature prediction

Temperature Calibration

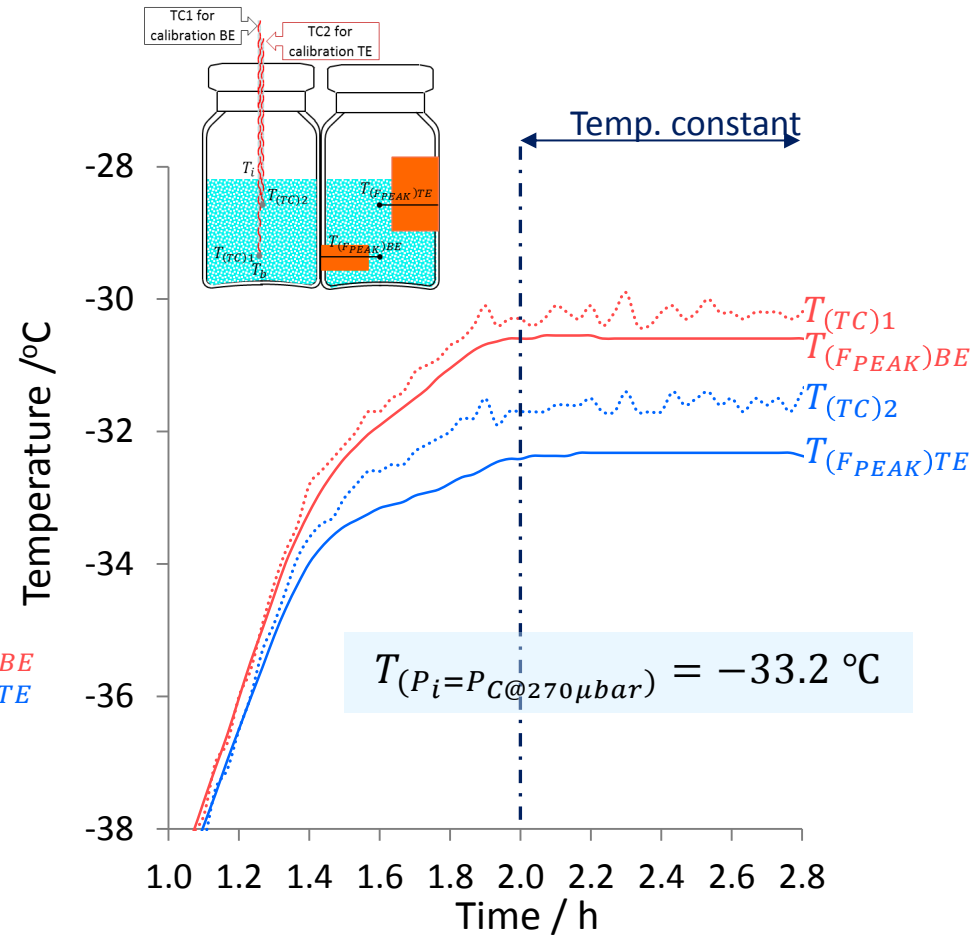
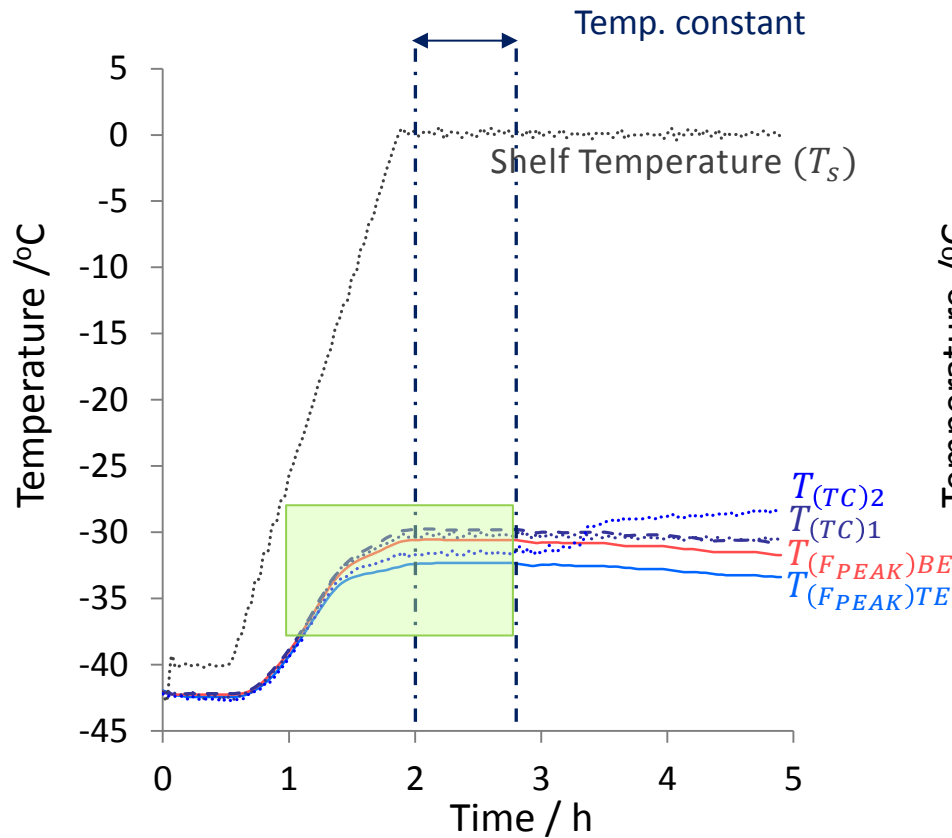


Polynomial coefficient from $\text{Log } F_{PEAK}$ – temperature calibration

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



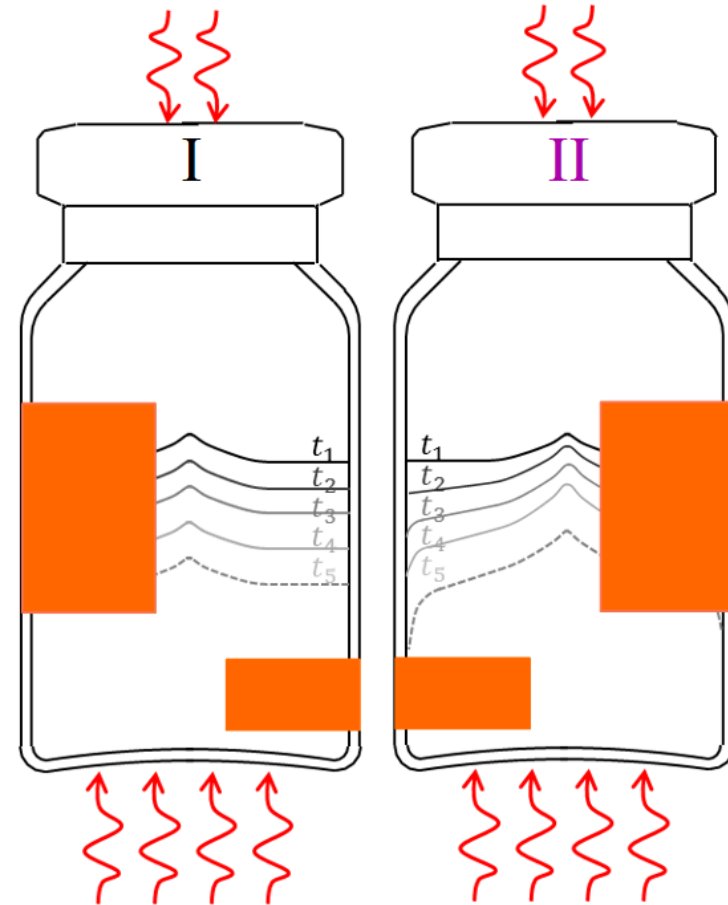
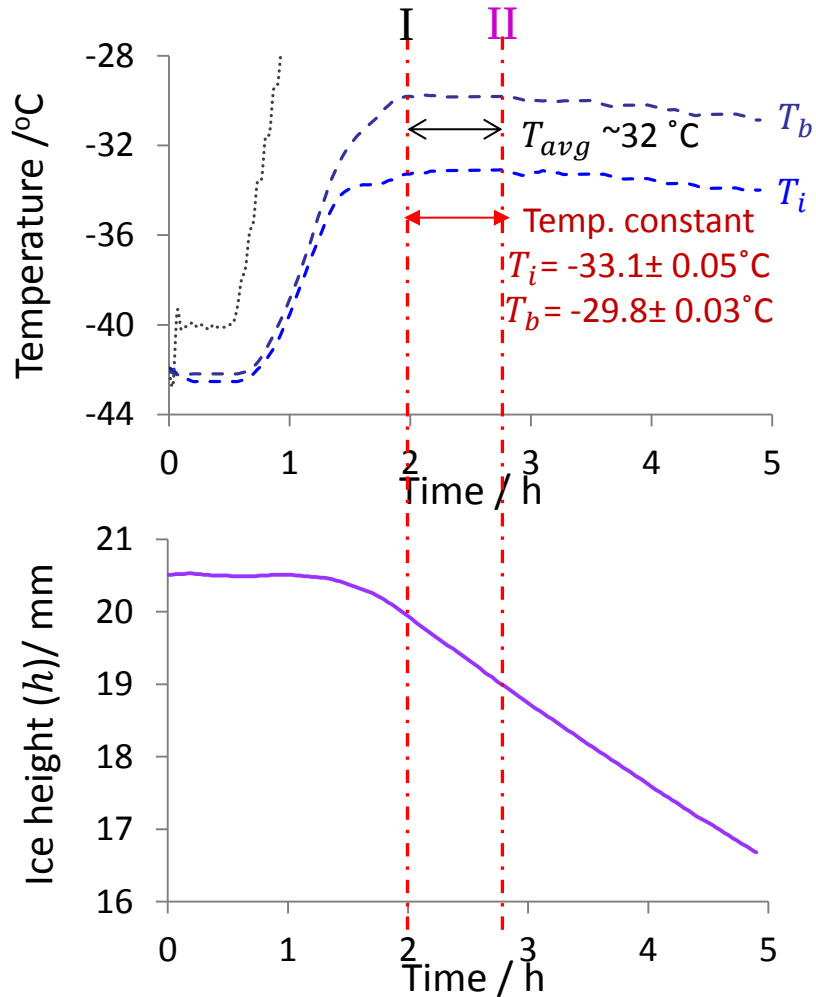
Temperature Prediction



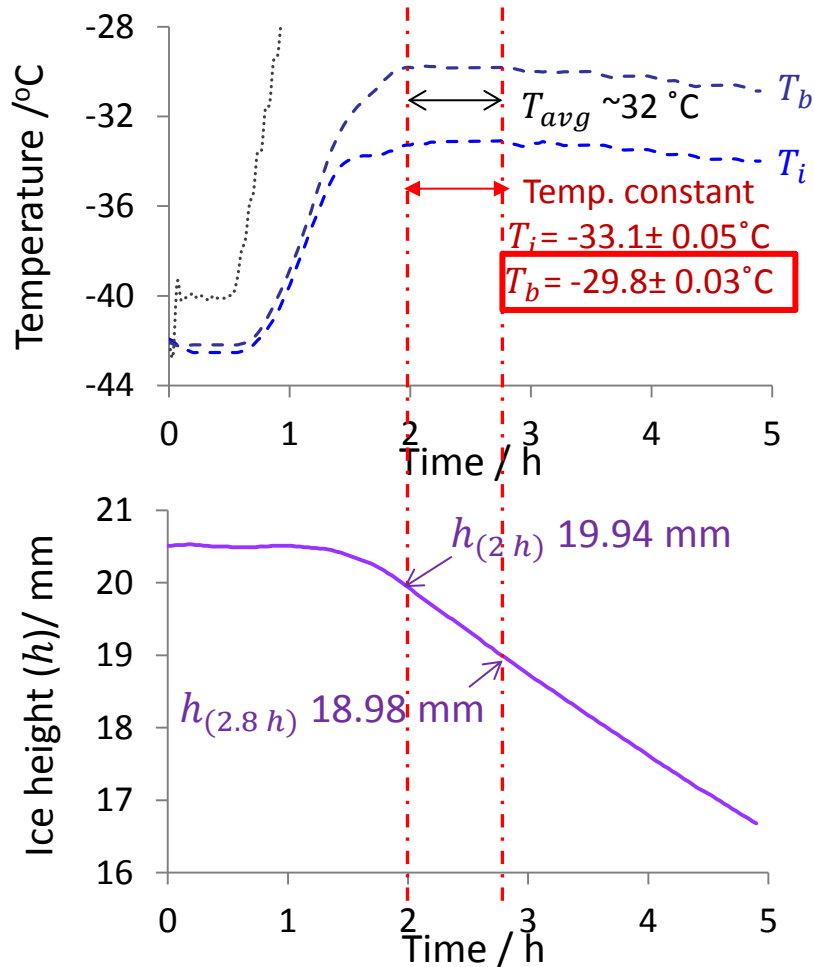
Through Vial Impedance Spectroscopy (TVIS)

Drying rate estimation

Drying Rate Estimation



Drying Rate Estimation



- Drying rate during the steady state

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

Ice density (ρ_i) at -32°C = $0.920\text{ g}\cdot\text{cm}^{-3}$

(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 ($h_{(2\text{ h})}$) = 19.94 mm

Ice height at 2.8 h ($h_{(2.8\text{ h})}$) = 18.98 mm

TVIS parameters used for determination:

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

$$T_b = -29.8^\circ\text{C}$$

$$\begin{aligned} \text{Drying rate} &= 0.920\text{ g}\cdot\text{cm}^{-3} \times 3.80\text{ cm}^2 \times \frac{(19.94 - 18.98) \times 10^{-1}\text{ cm}}{(2.8 - 2.0)\text{ h}} \\ &= \mathbf{0.42\text{ g}\cdot\text{h}^{-1}} \end{aligned}$$

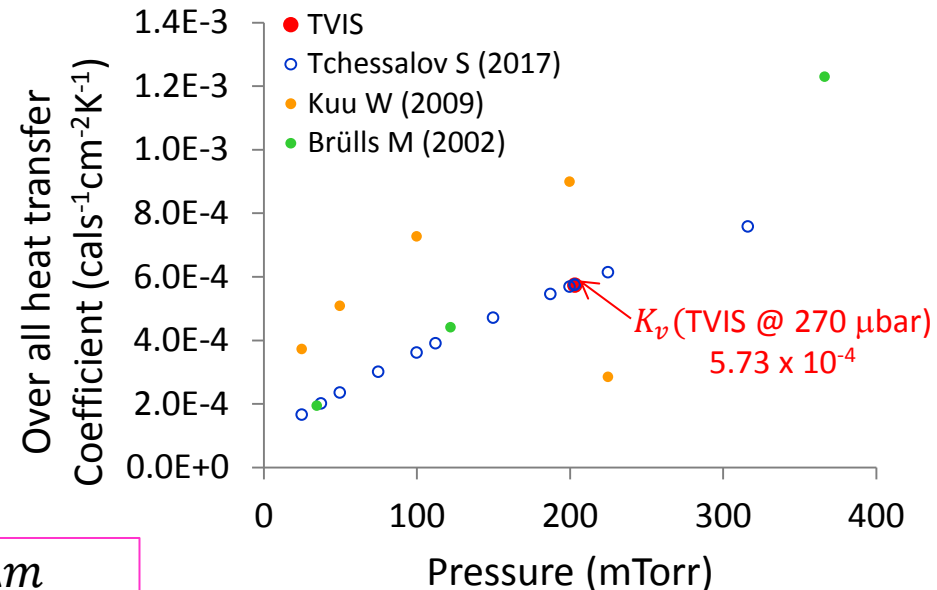
Through Vial Impedance Spectroscopy (TVIS)

Heat Transfer Coefficient Determination

Heat Transfer Coefficient (K_v) Determination



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



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

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

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

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

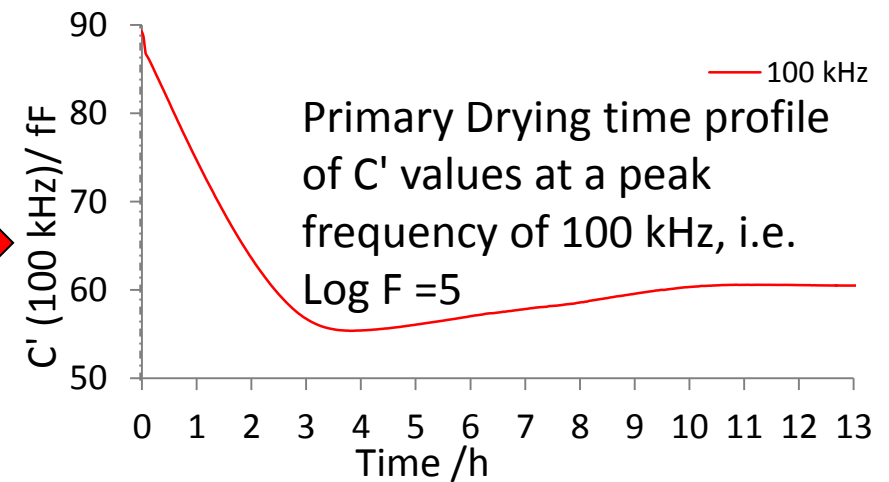
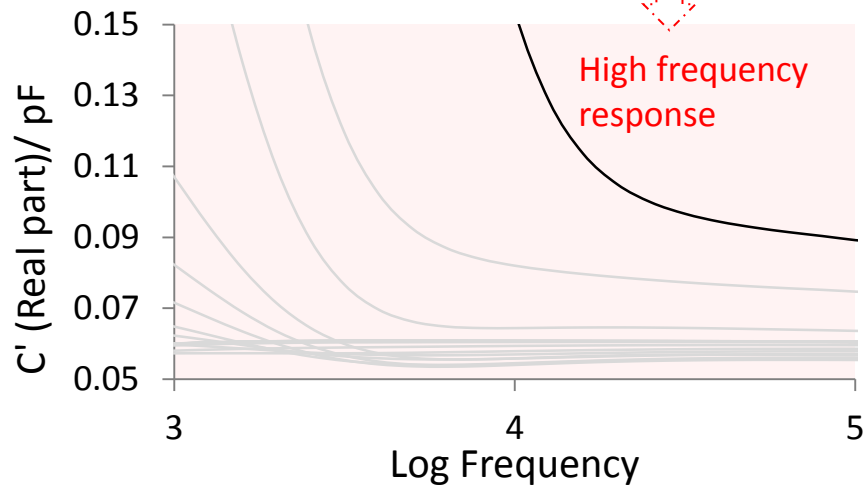
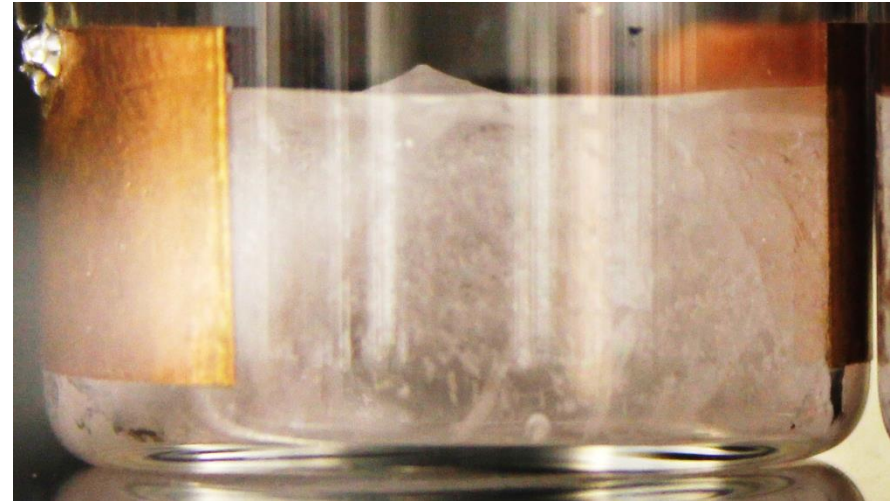
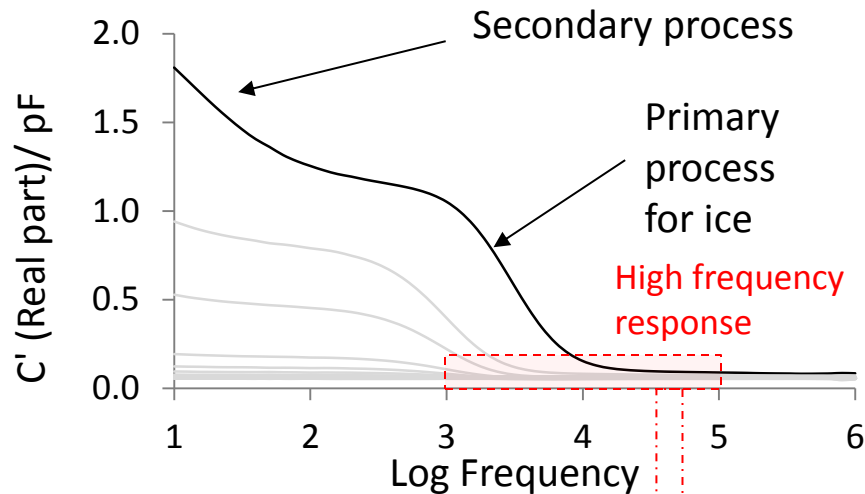
$$\begin{aligned} &= \frac{679.7 \text{ cal} \cdot \text{g}^{-1} \times 0.42 \text{ g} \cdot \text{h}^{-1}}{4.62 \text{ cm}^2 \times (273.3 - 243.3) \text{ K}} \\ &= 2.06 \text{ cal} \cdot \text{h}^{-1} \cdot \text{cm}^{-2} \cdot \text{K}^{-1} \\ &= 5.73 \times 10^{-4} \text{ cal} \cdot \text{s}^{-1} \cdot \text{cm}^{-2} \cdot \text{K}^{-1} \end{aligned}$$

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

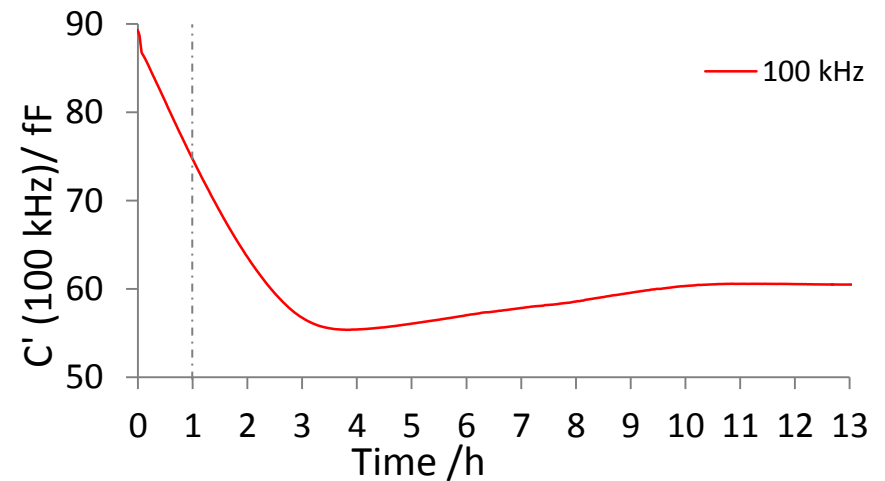
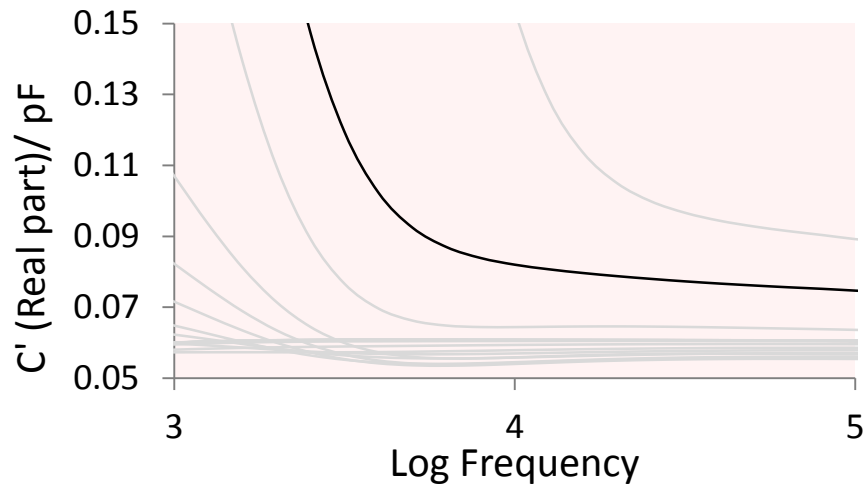
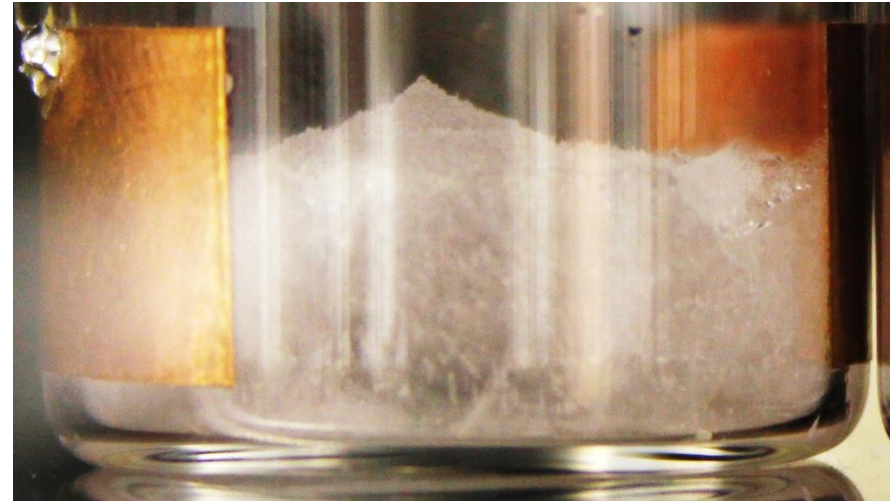
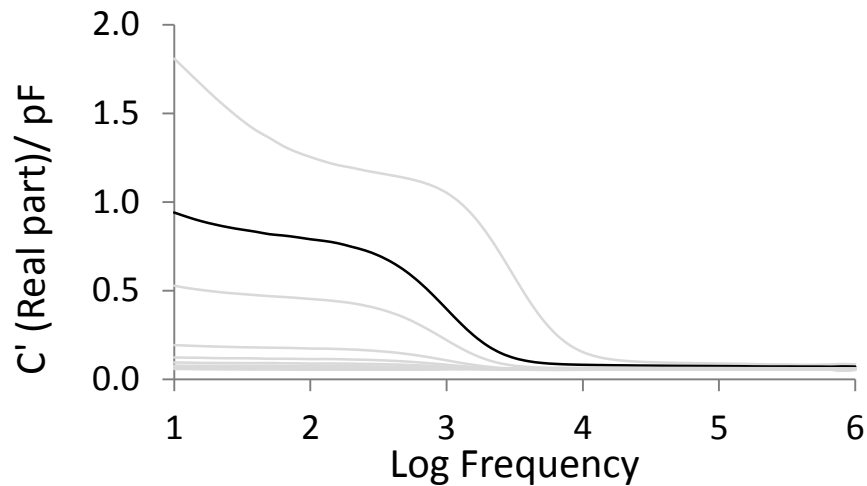
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End-point Determination

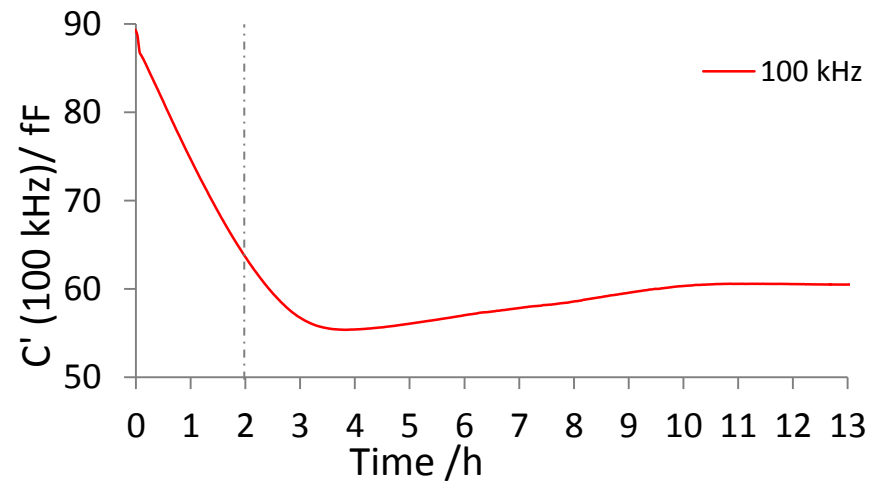
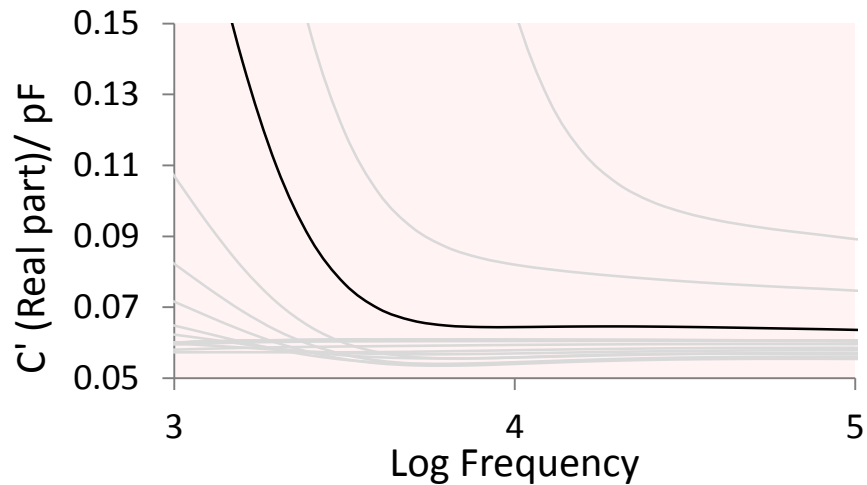
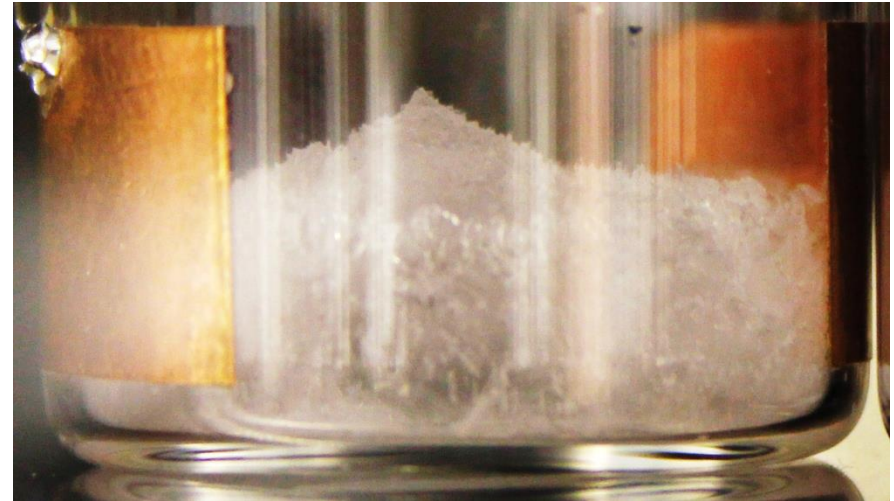
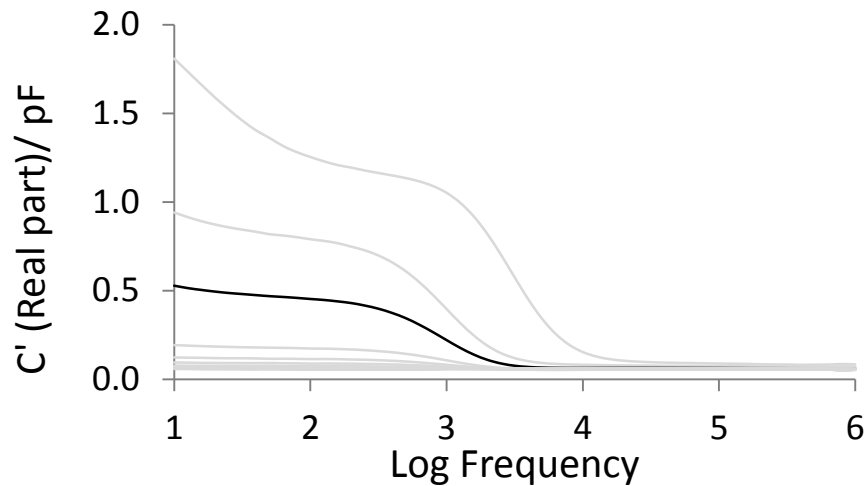
End-Point Determination (T_s -15 °C and P_c 400 μ bar)



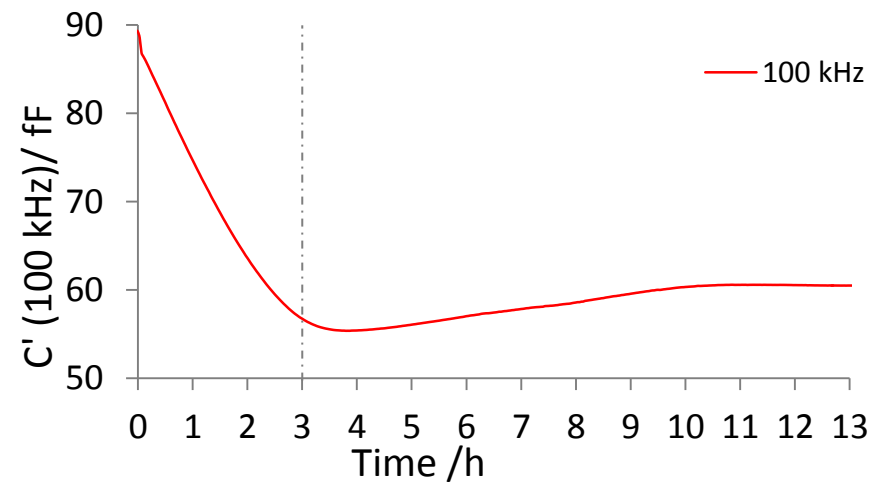
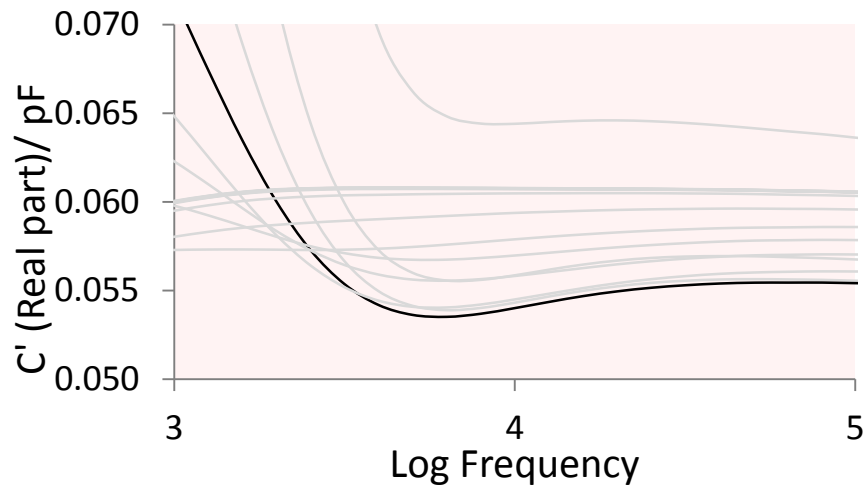
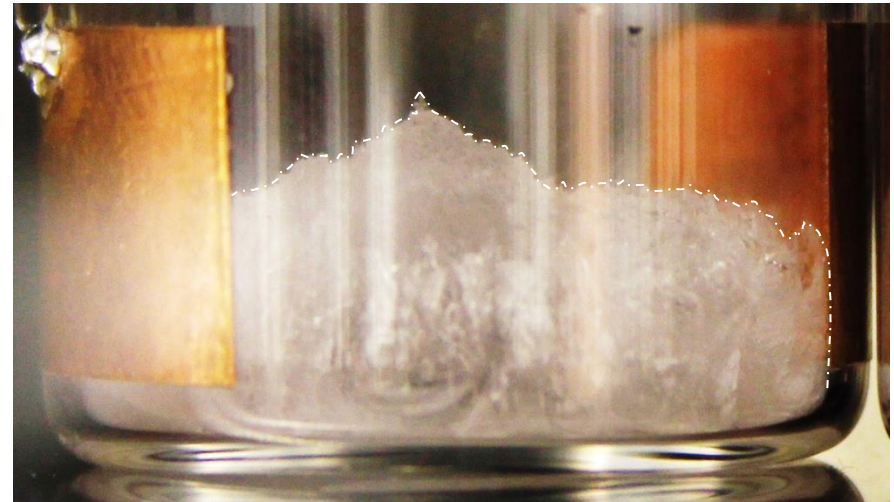
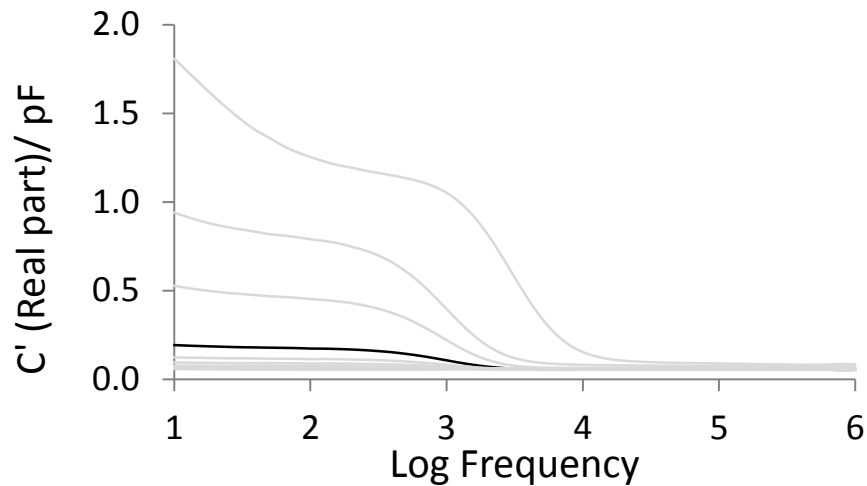
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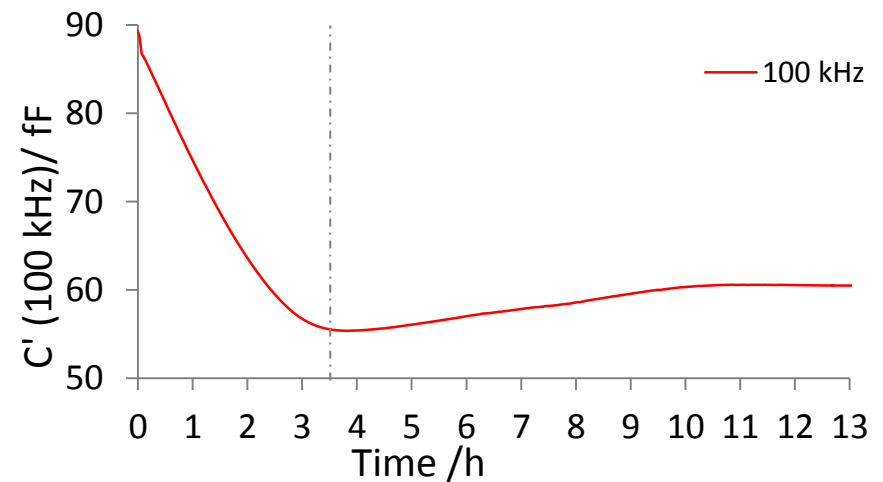
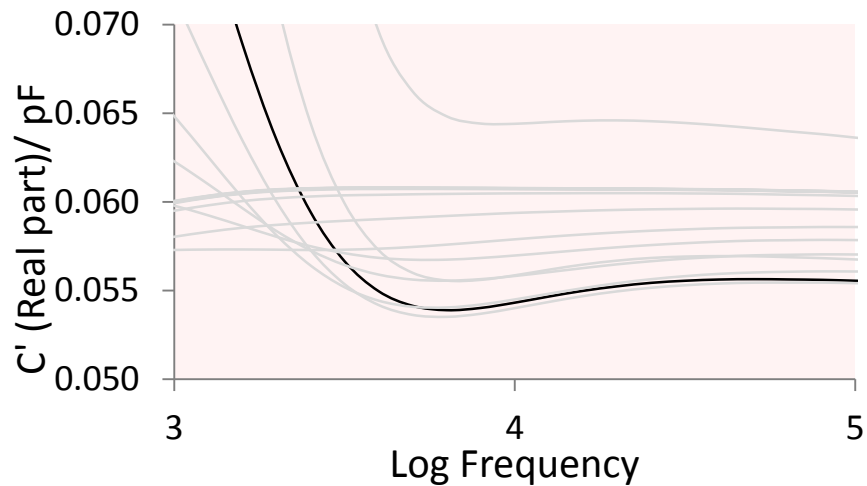
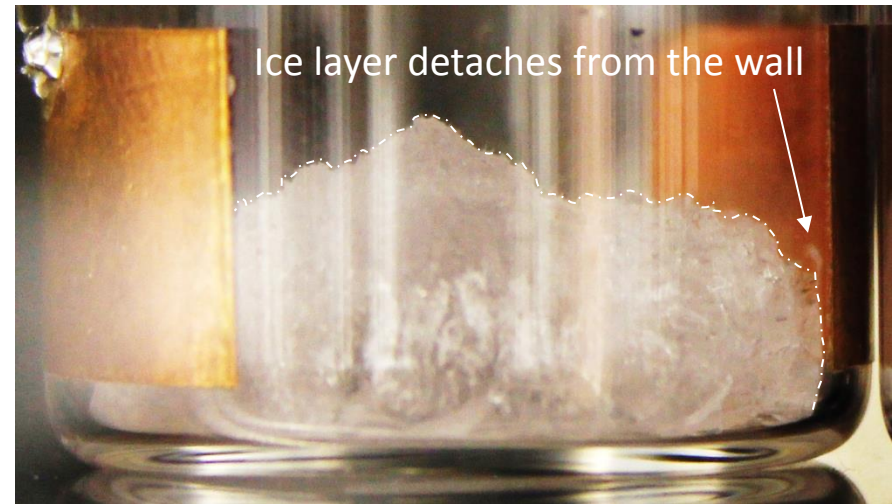
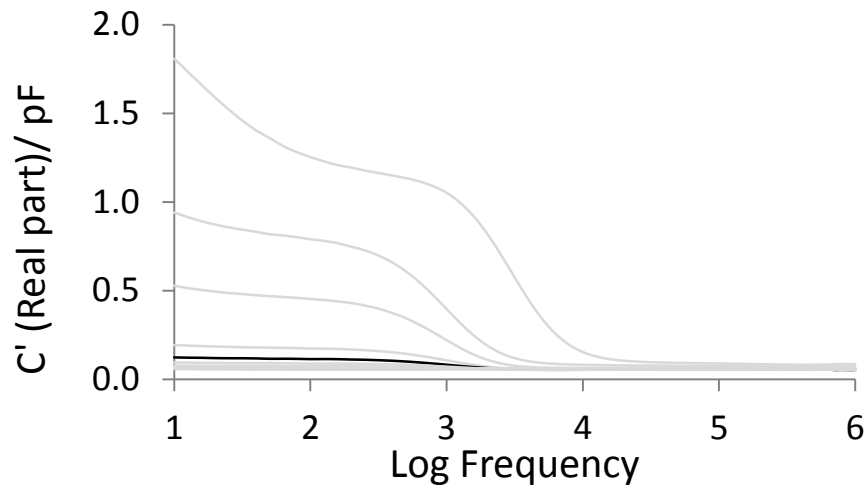
End-Point Determination (T_s -15 °C and P_c 400 μ bar)



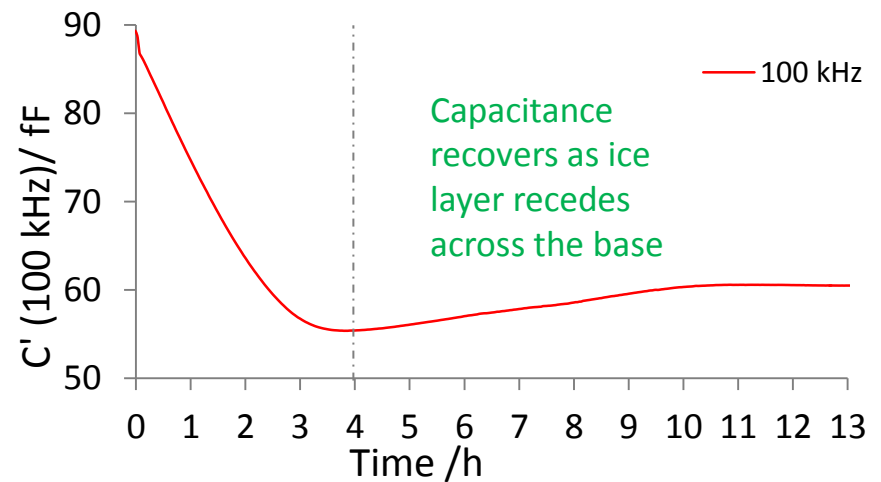
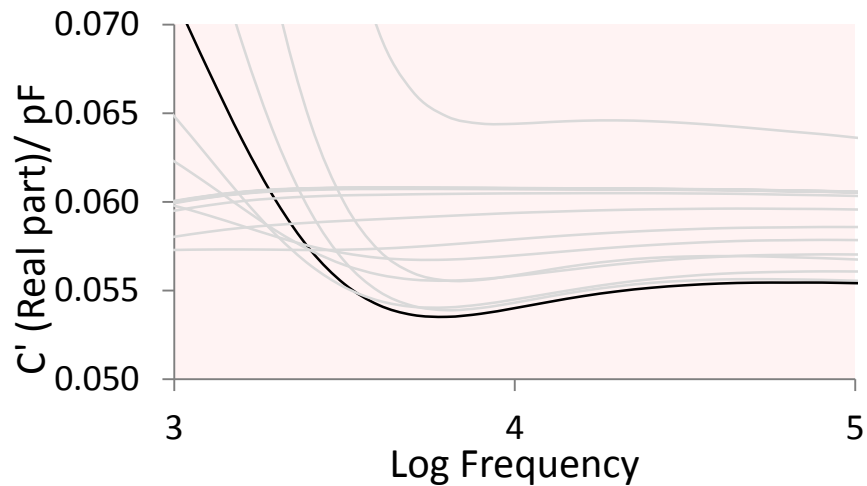
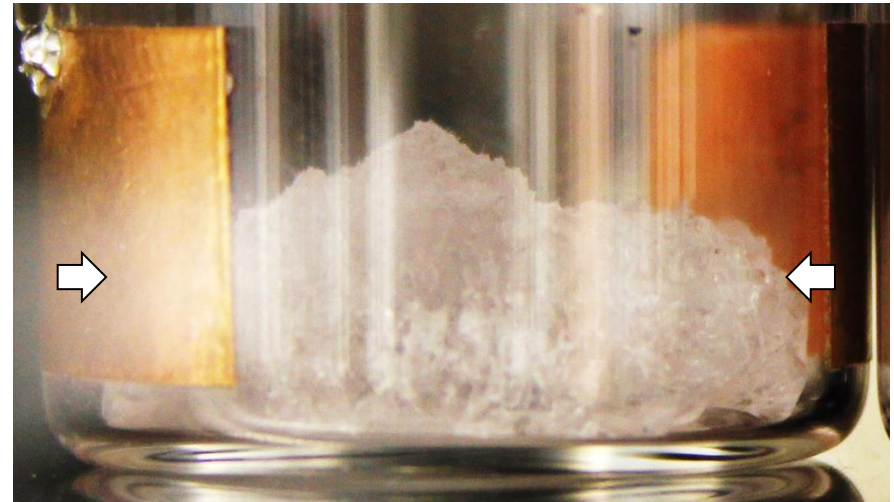
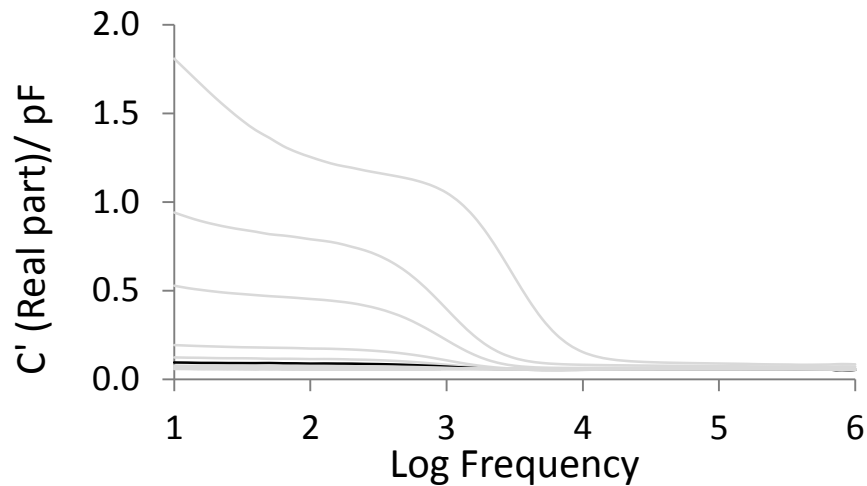
End-Point Determination (T_s -15 °C and P_c 400 μ bar)



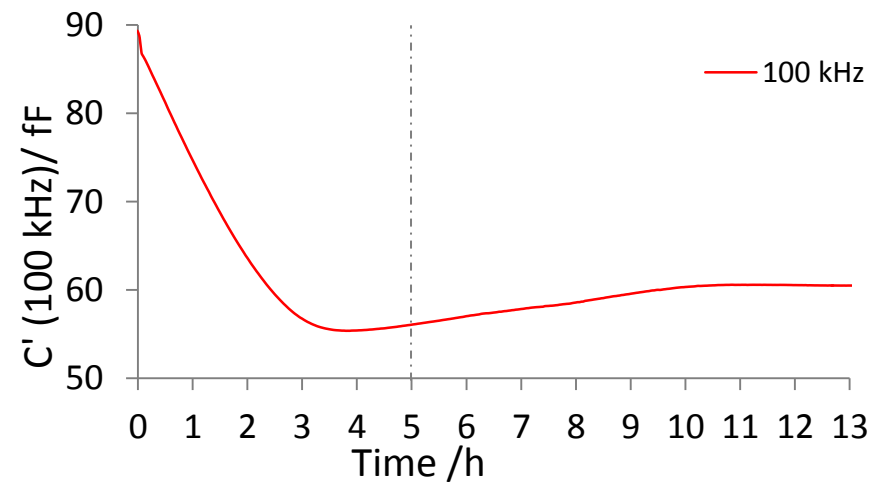
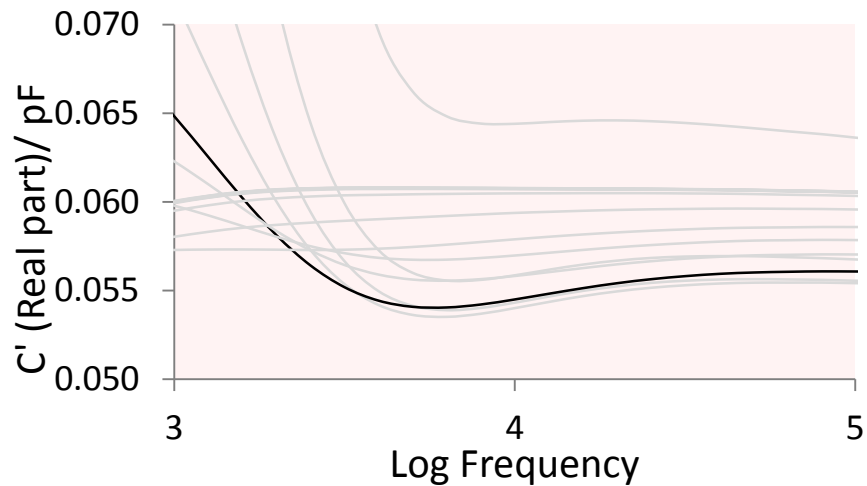
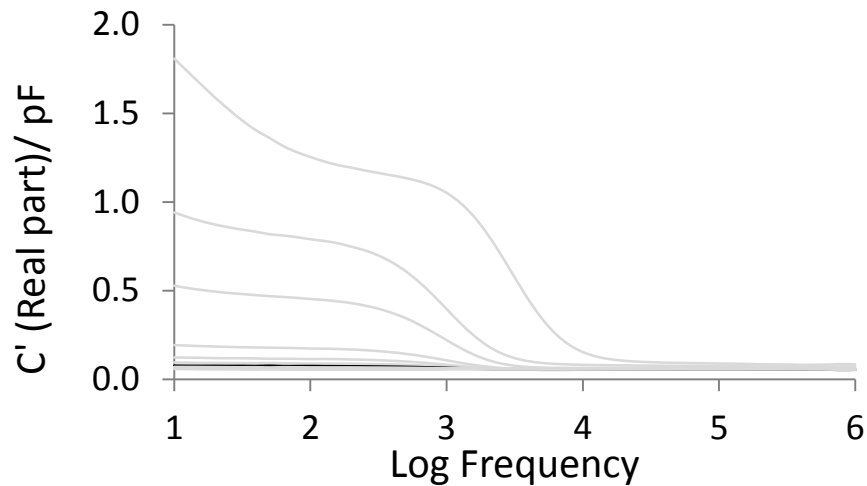
End-Point Determination (T_s -15 °C and P_c 400 μ bar)



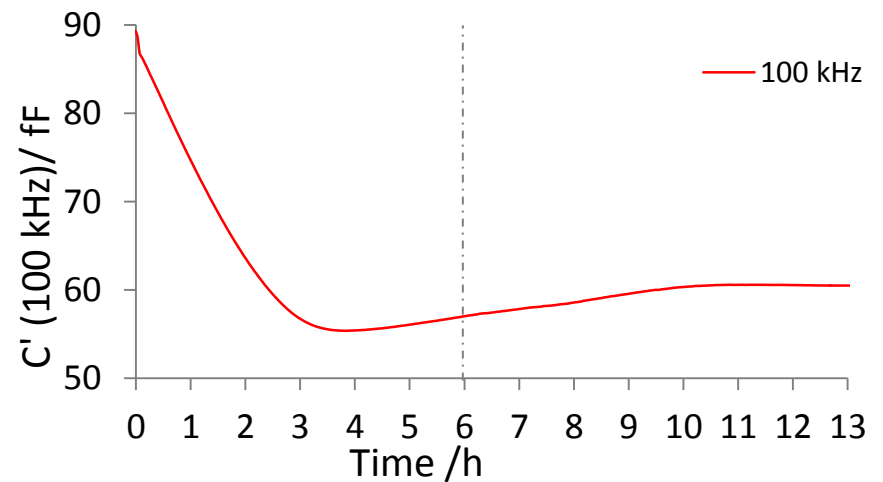
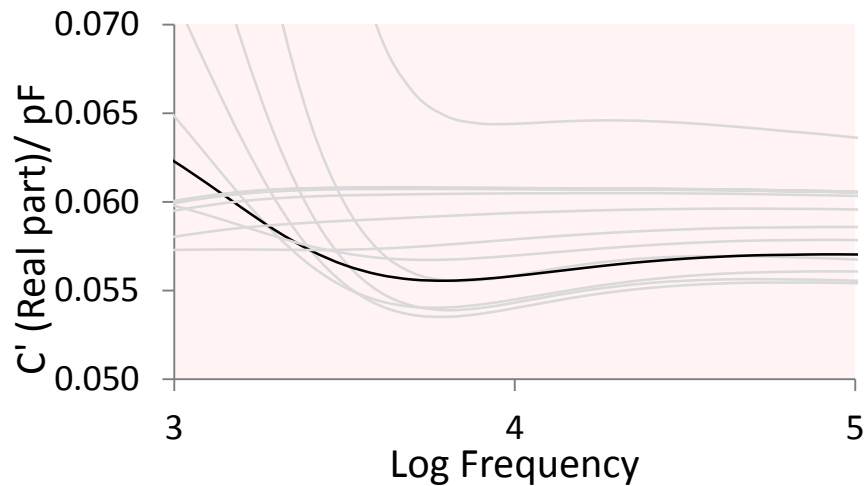
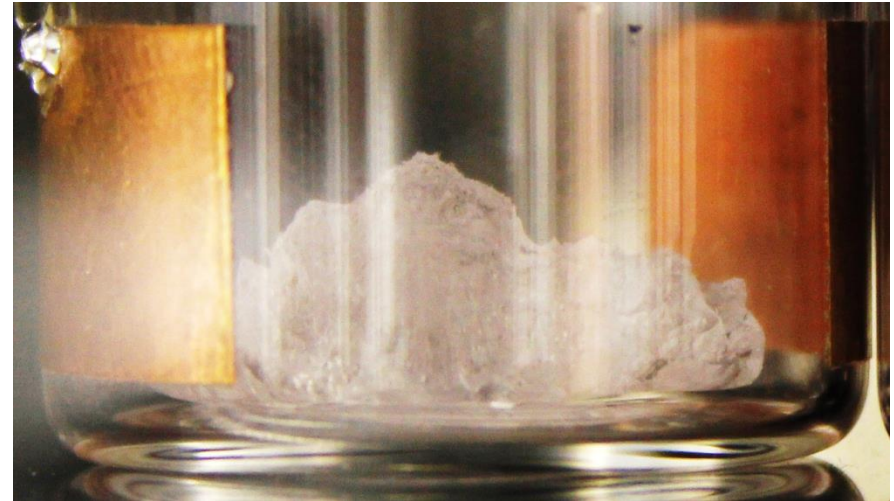
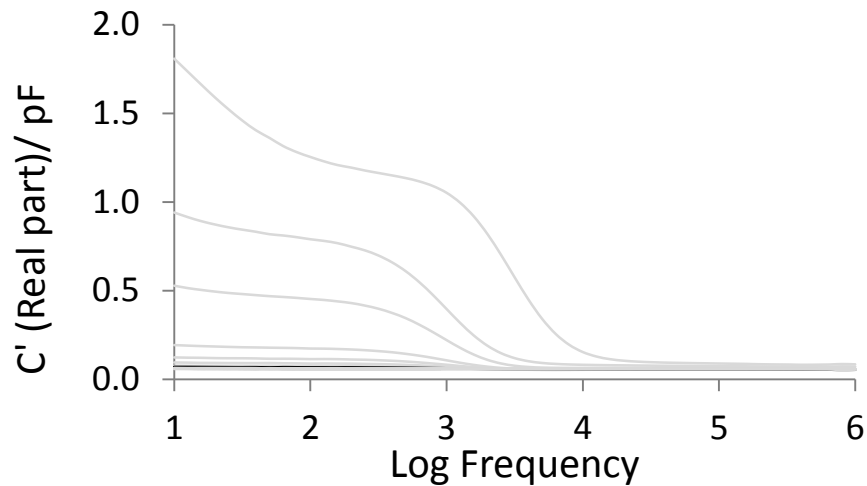
End-Point Determination (T_s -15 °C and P_c 400 μ bar)



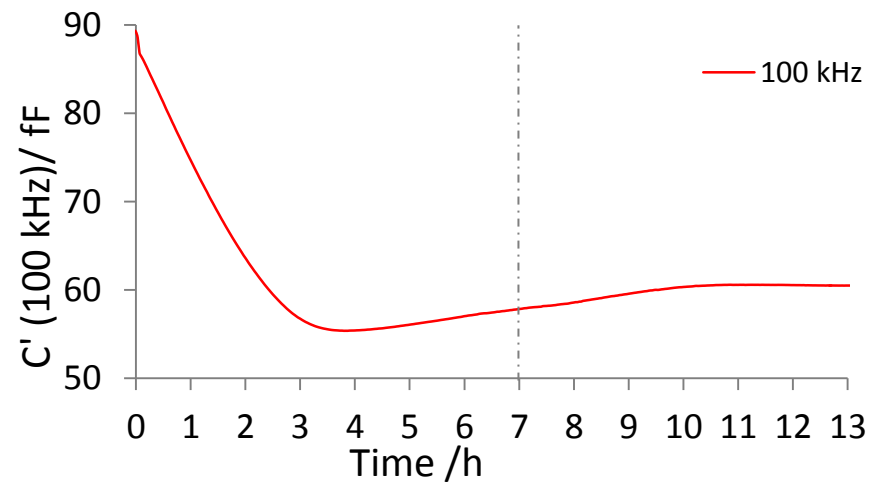
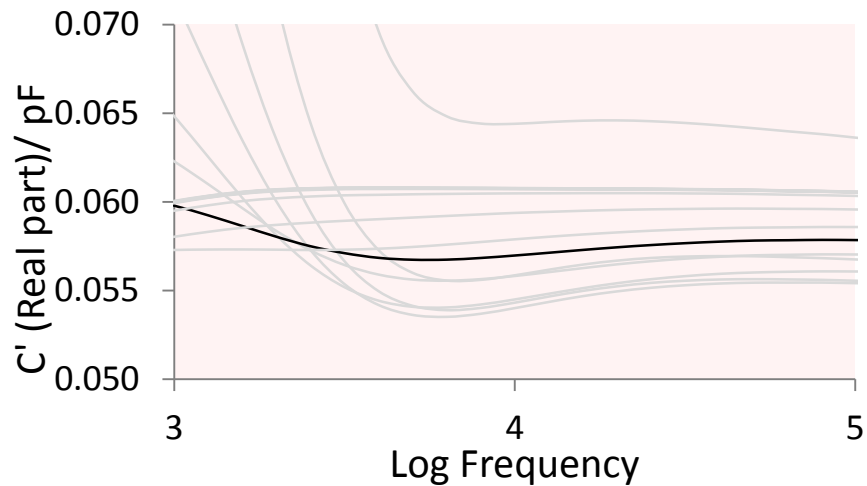
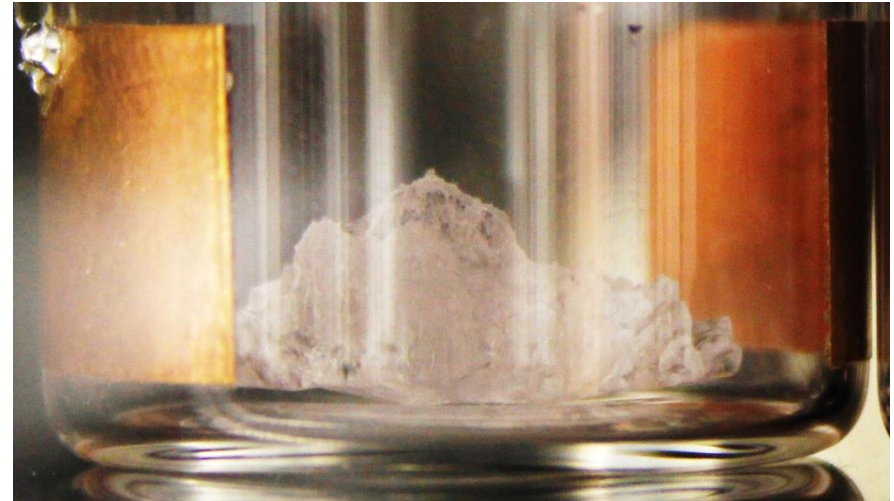
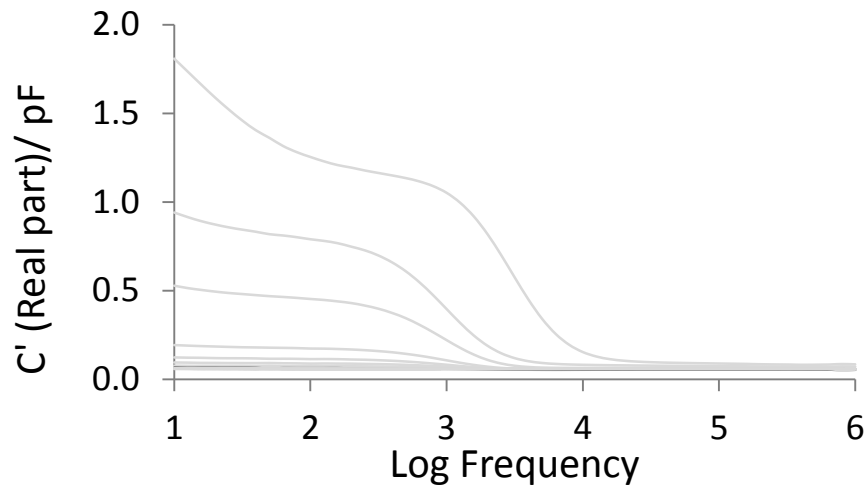
End-Point Determination (T_s -15 °C and P_c 400 μ bar)



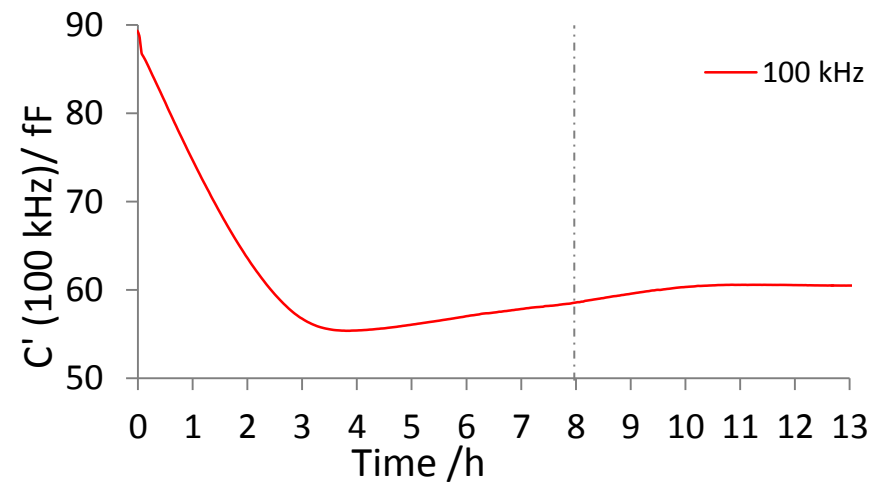
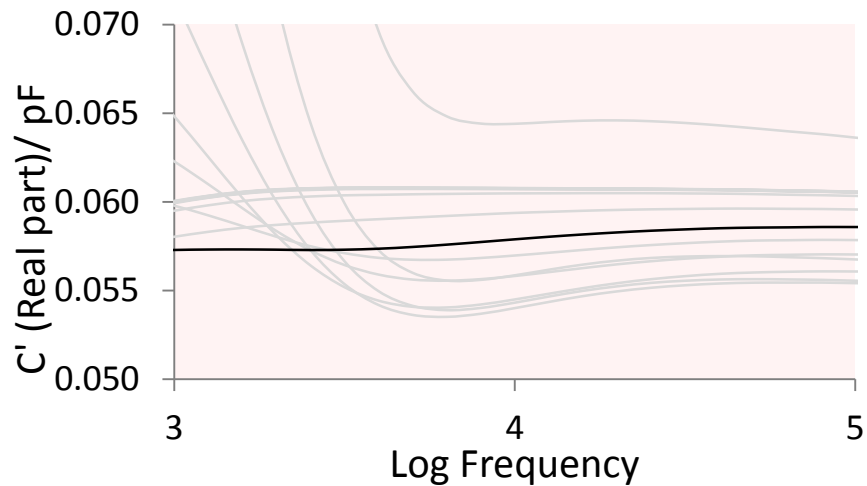
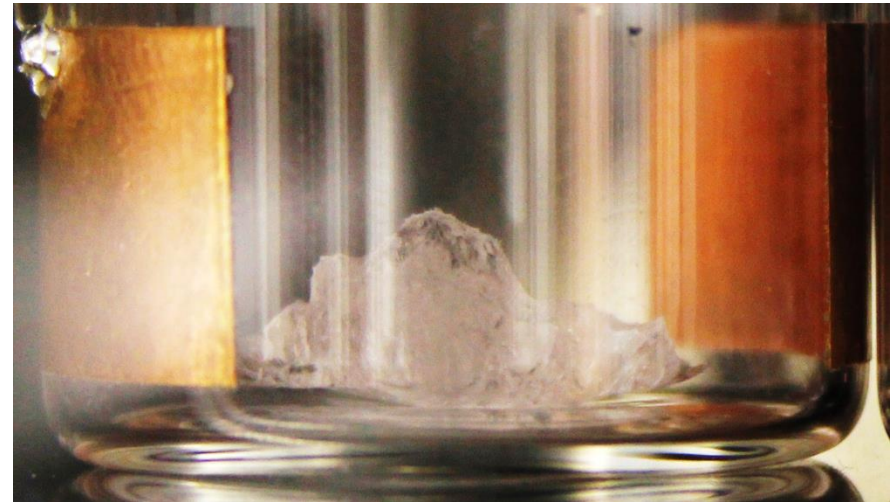
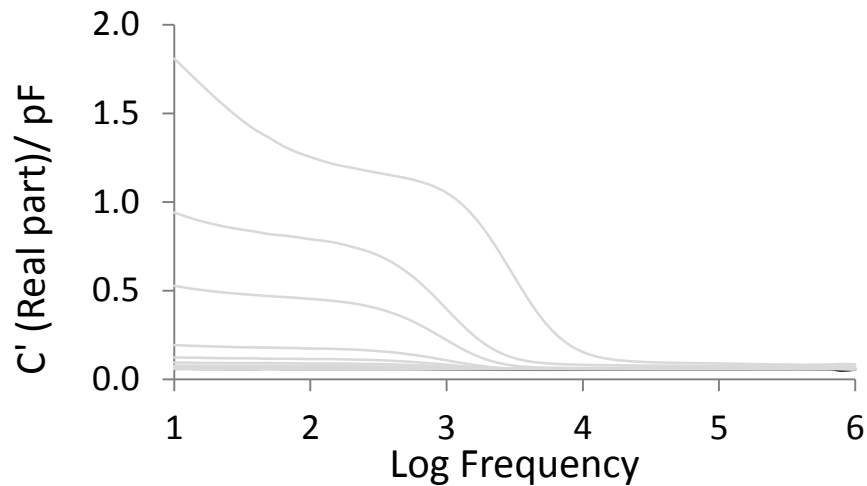
End-Point Determination (T_s -15 °C and P_c 400 μ bar)



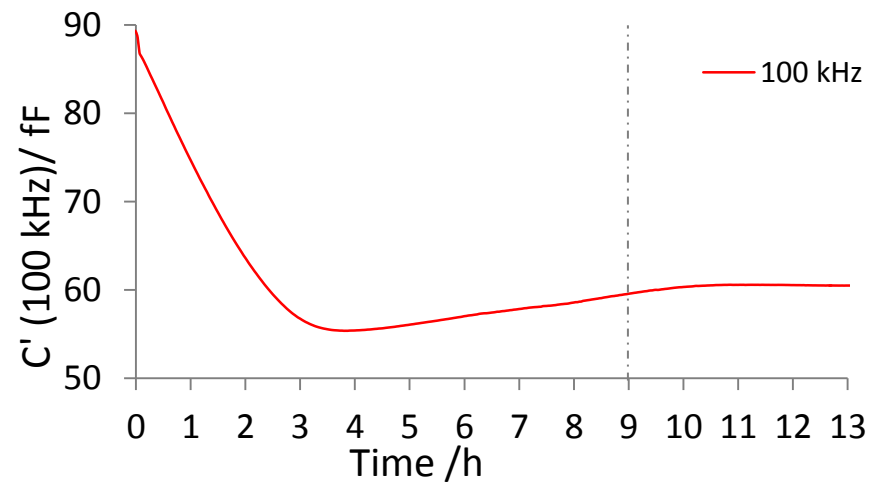
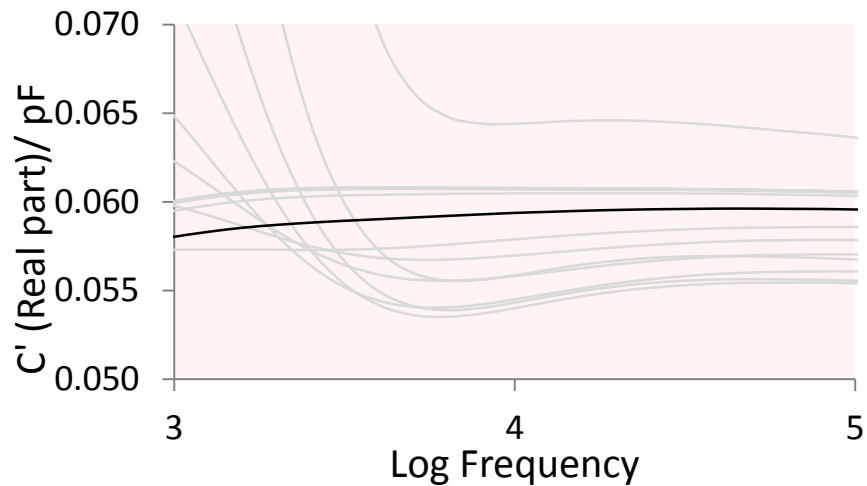
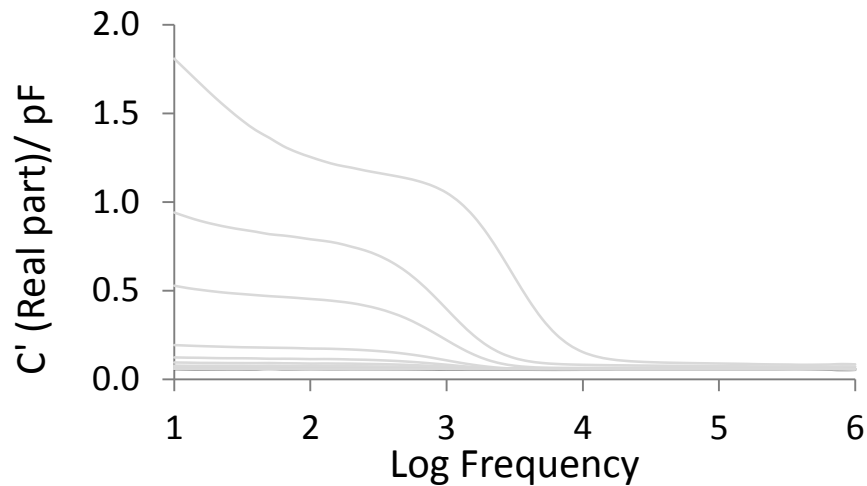
End-Point Determination (T_s -15 °C and P_c 400 μ bar)



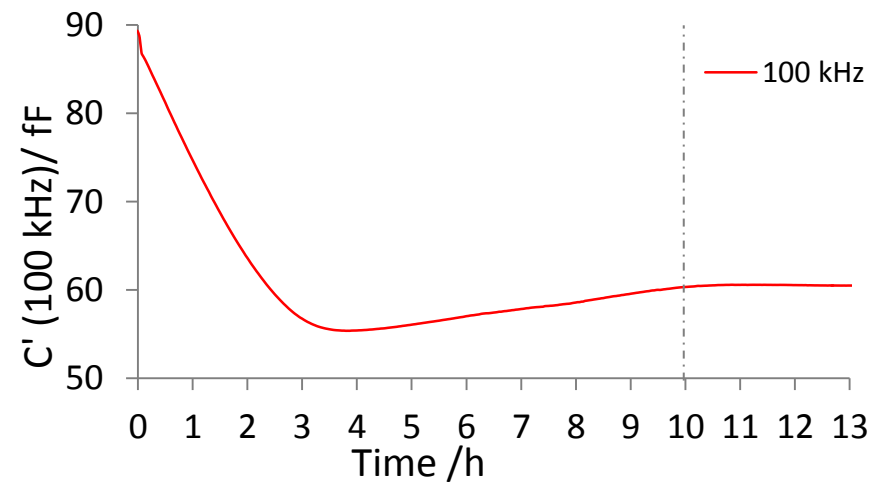
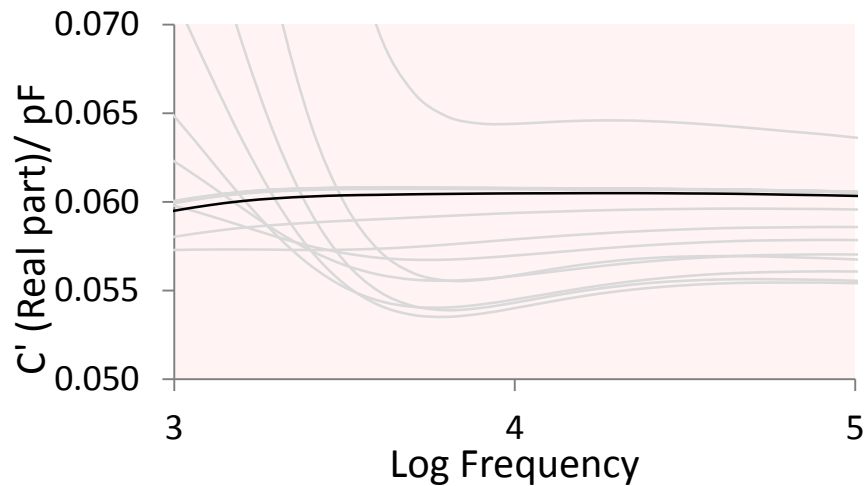
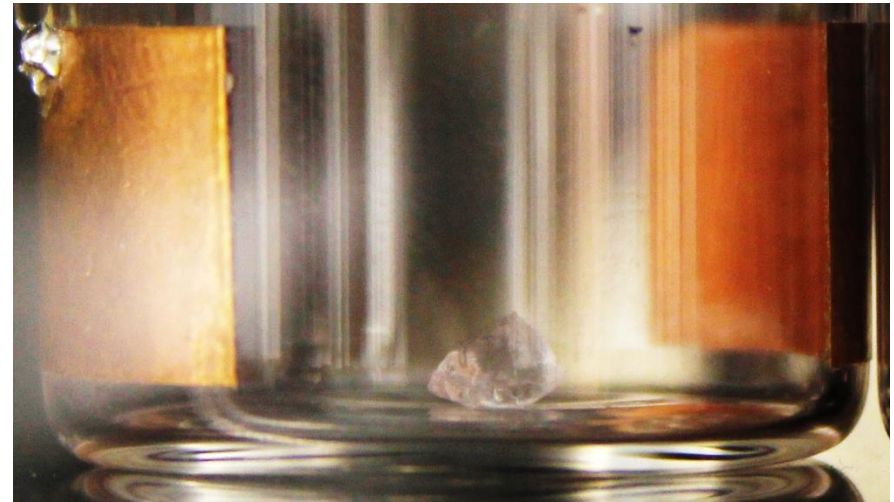
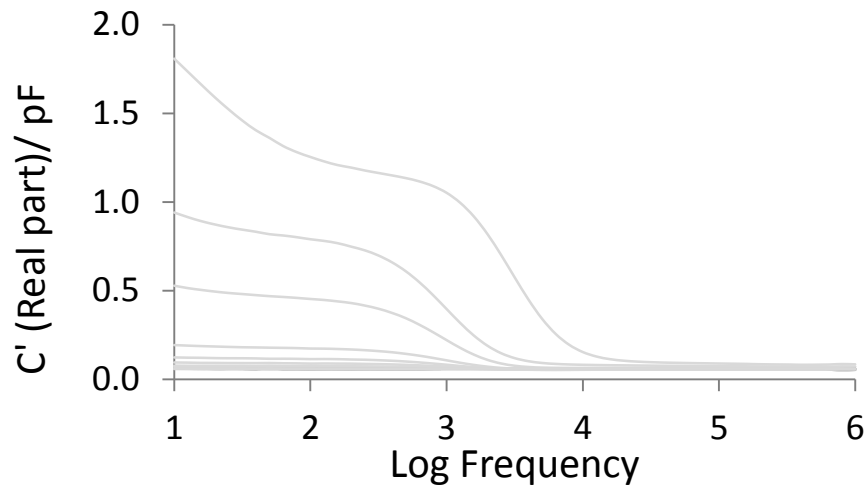
End-Point Determination (T_s -15 °C and P_c 400 μ bar)



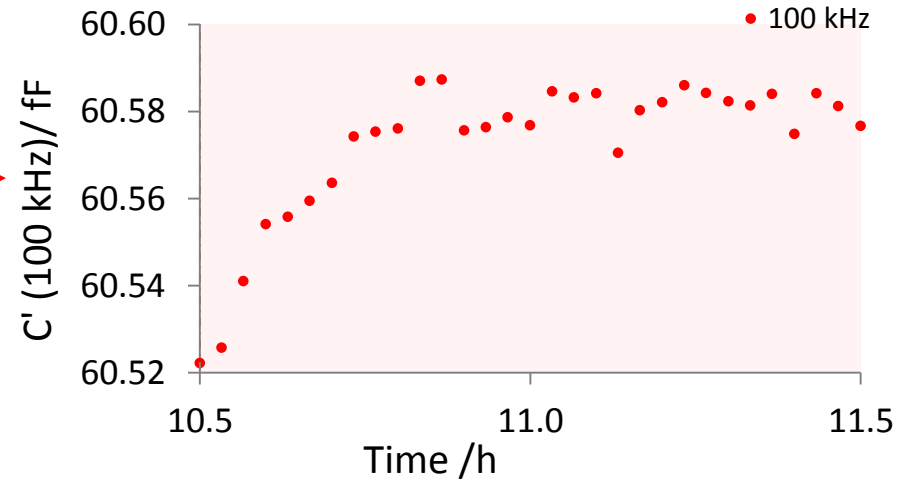
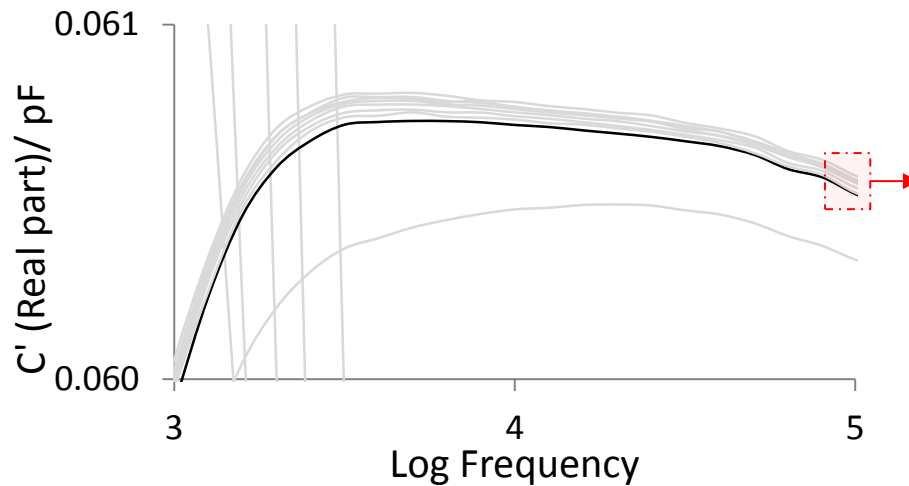
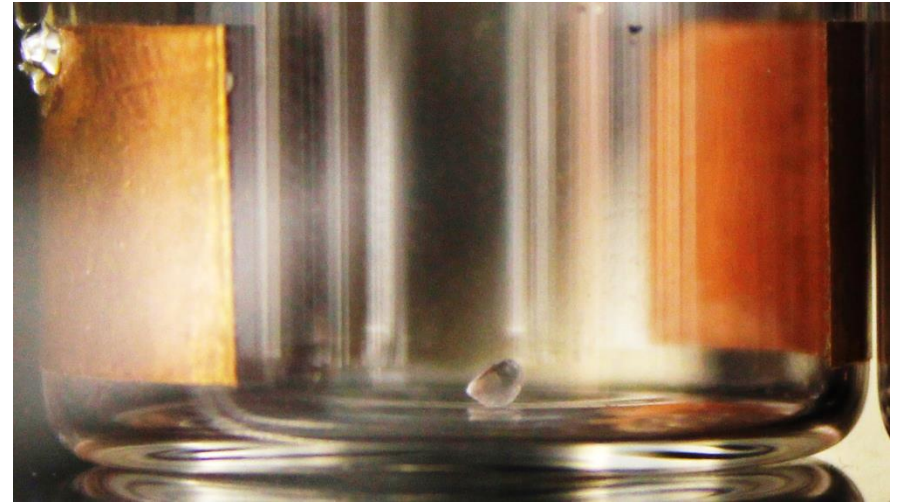
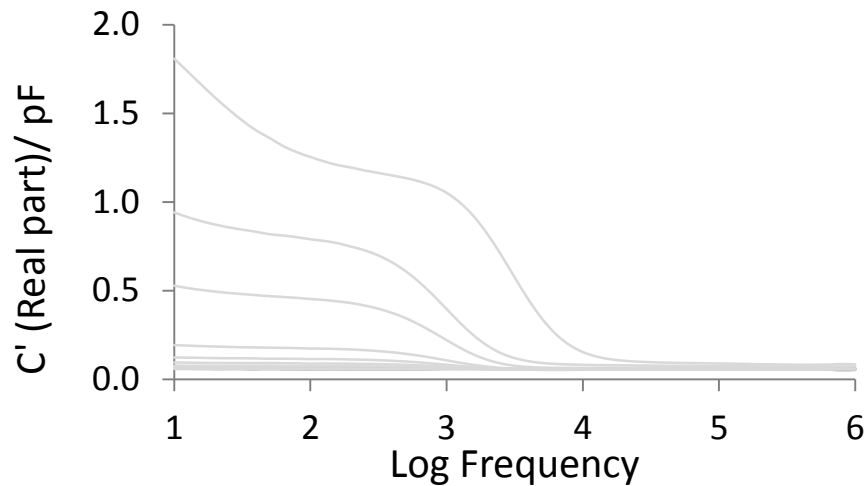
End-Point Determination (T_s -15 °C and P_c 400 μ bar)



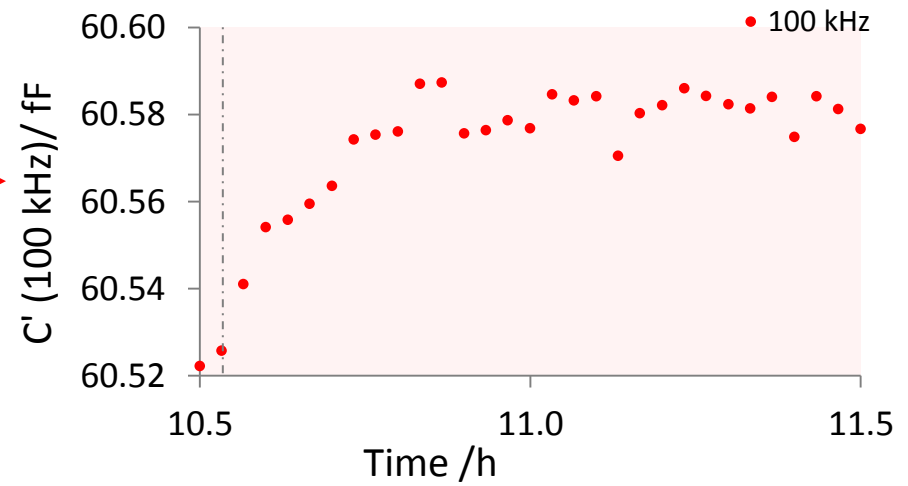
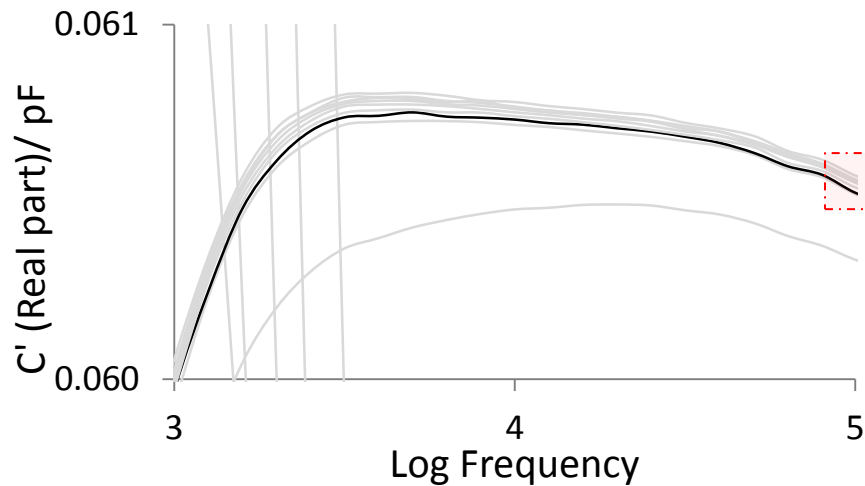
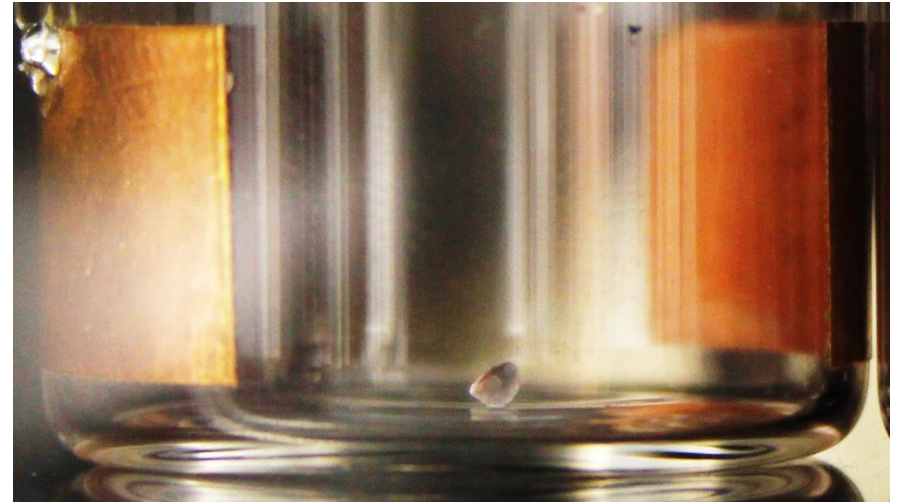
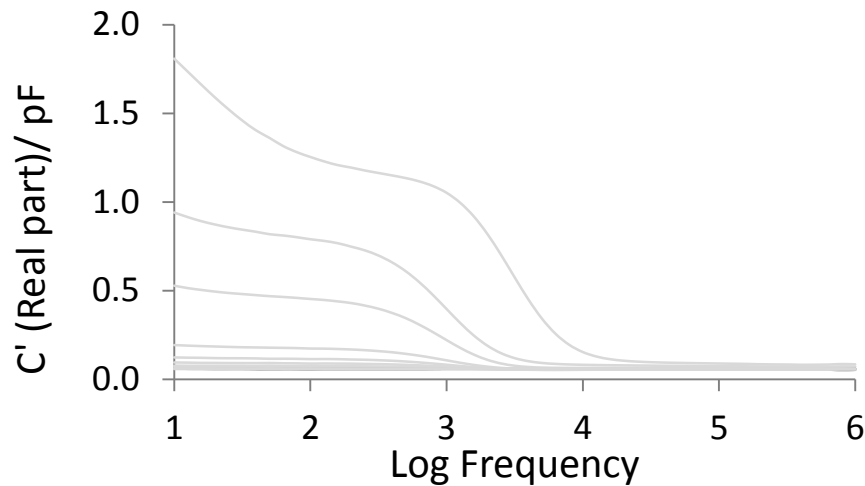
End-Point Determination (T_s -15 °C and P_c 400 μ bar)



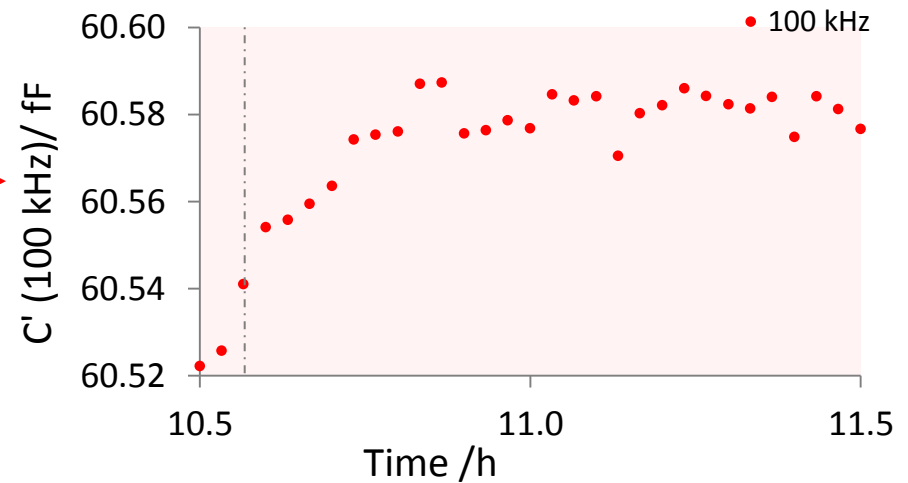
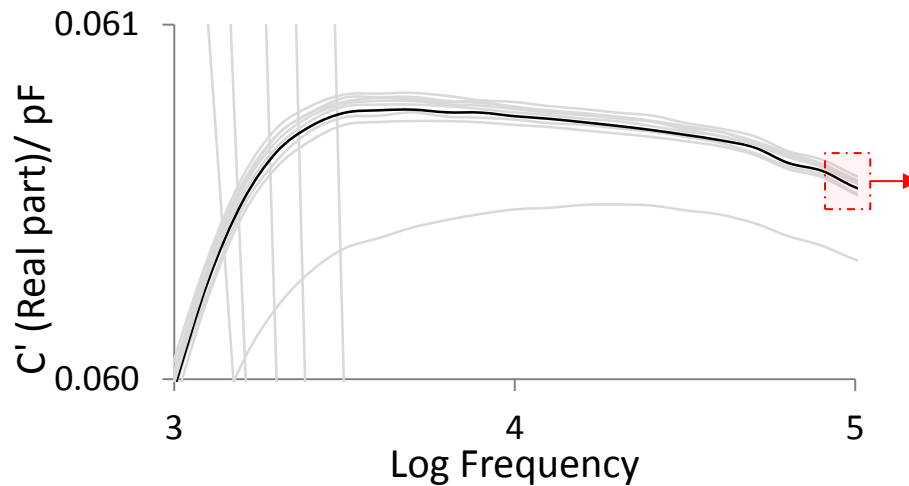
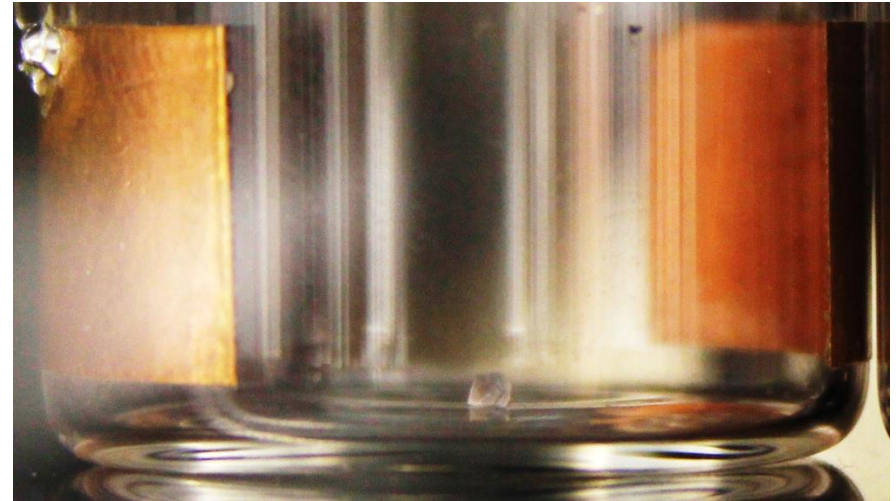
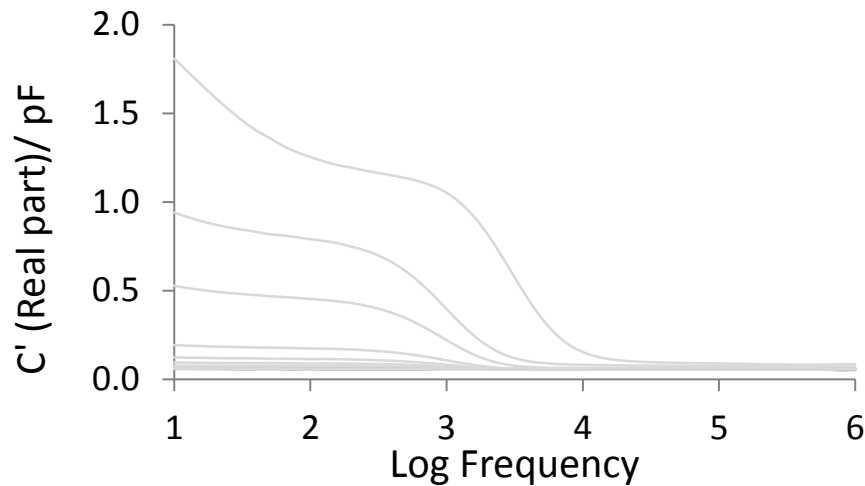
End-Point Determination (T_s -15 °C and P_c 400 μ bar)



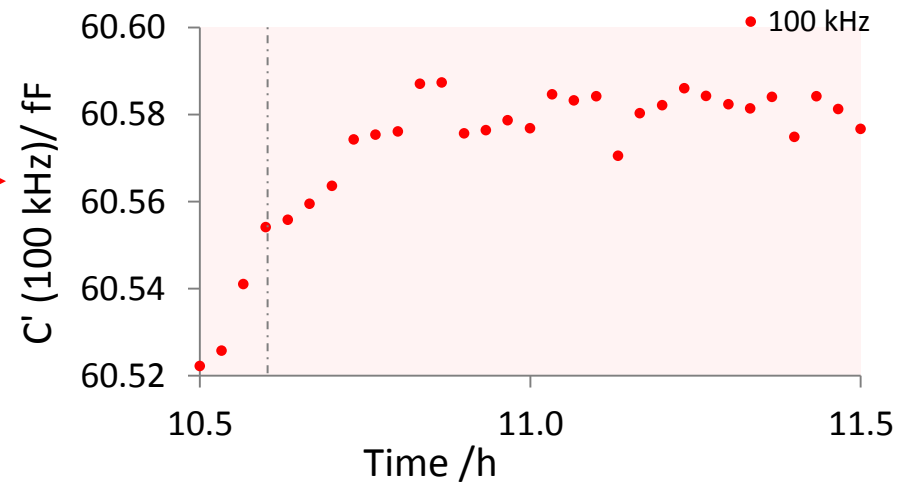
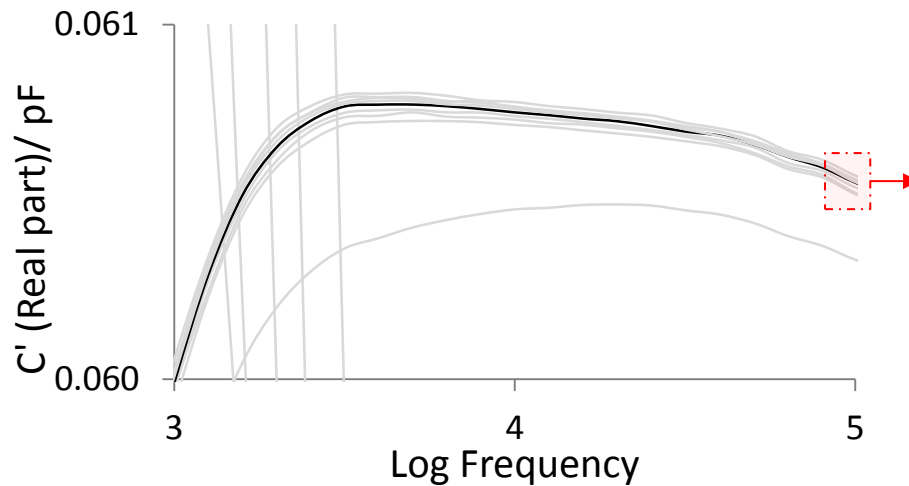
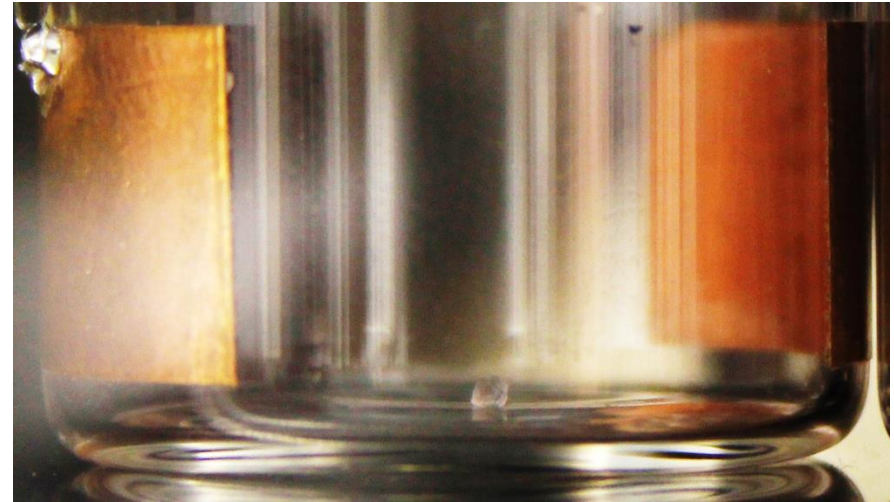
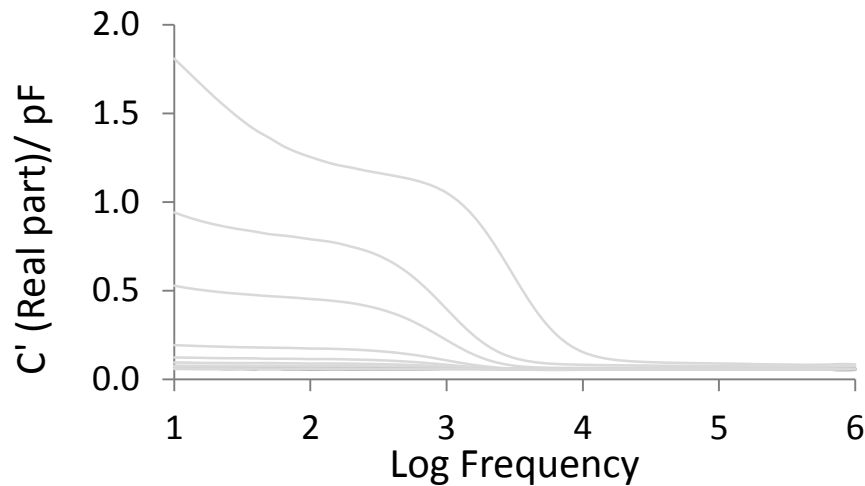
End-Point Determination (T_s -15 °C and P_c 400 μ bar)



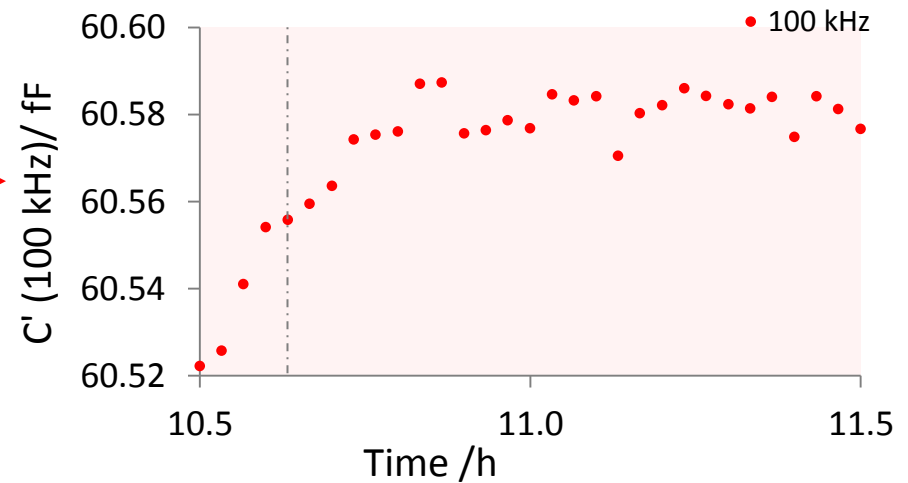
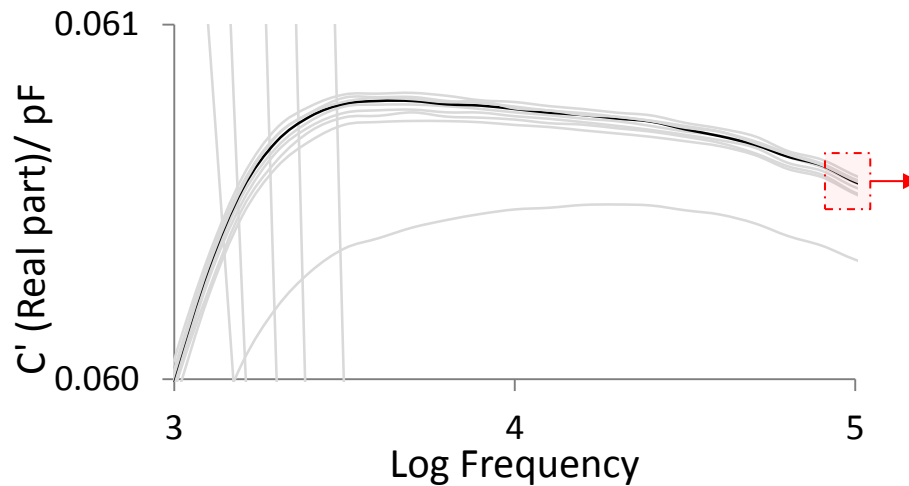
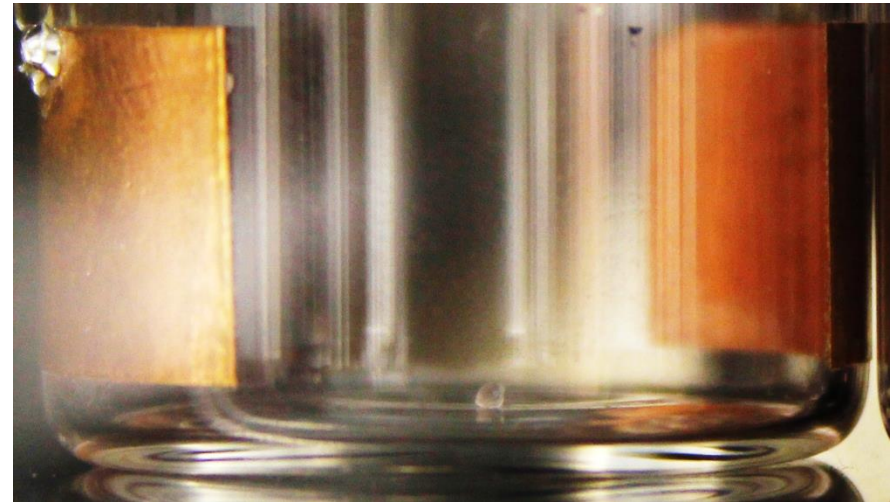
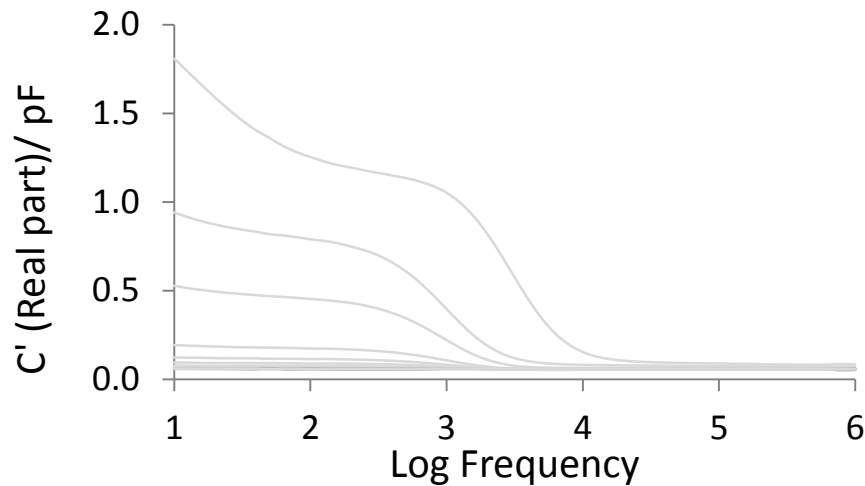
End-Point Determination (T_s -15 °C and P_c 400 μ bar)



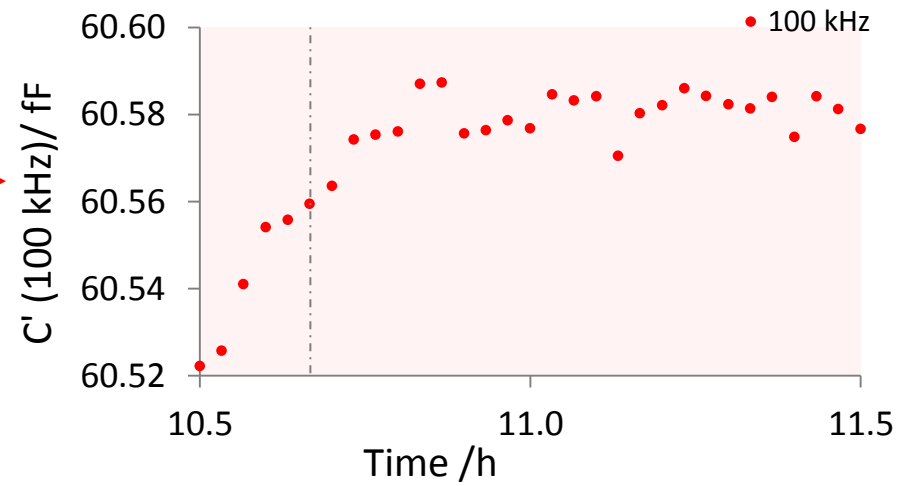
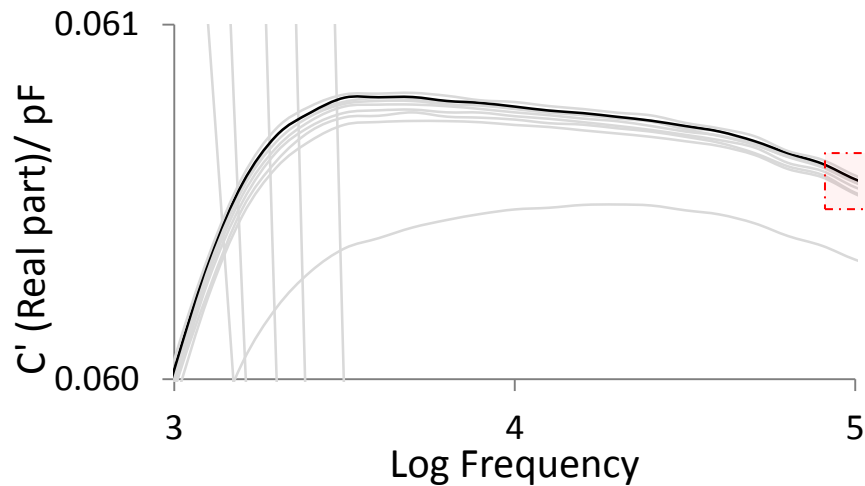
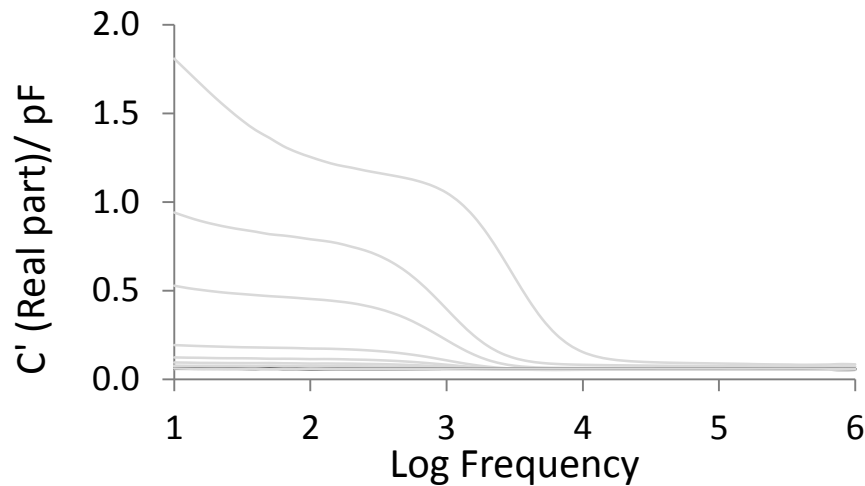
End-Point Determination (T_s -15 °C and P_c 400 μ bar)



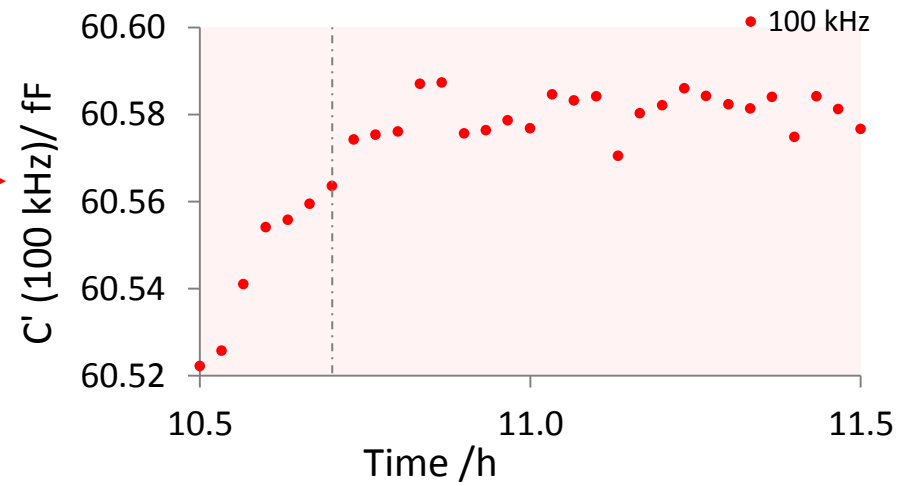
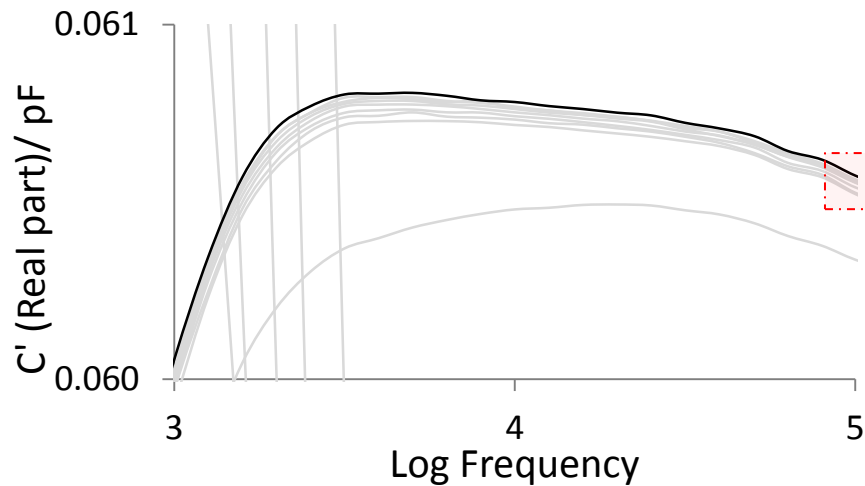
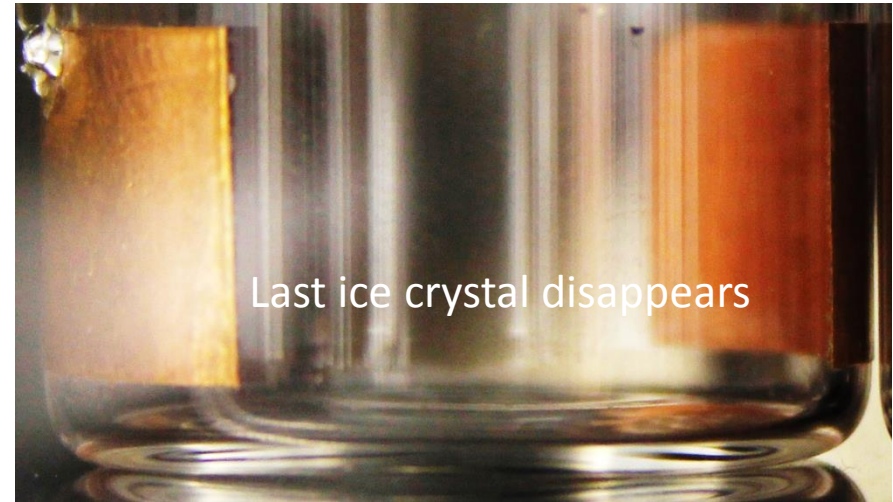
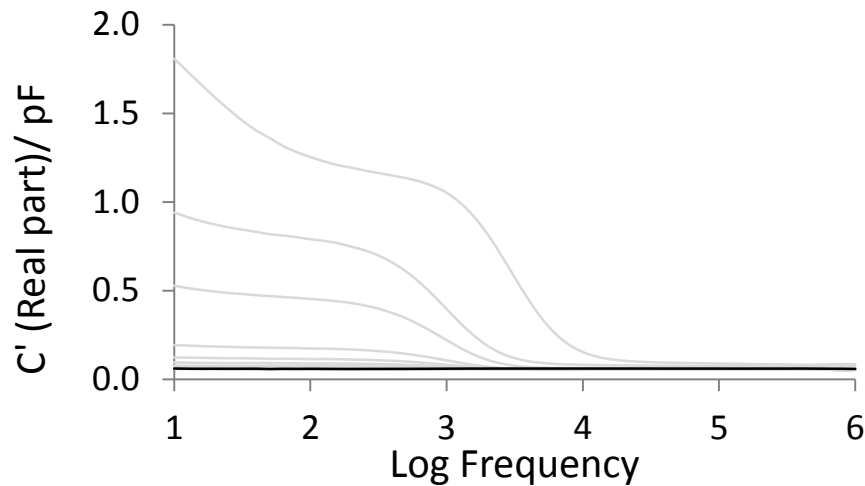
End-Point Determination (T_s -15 °C and P_c 400 μ bar)



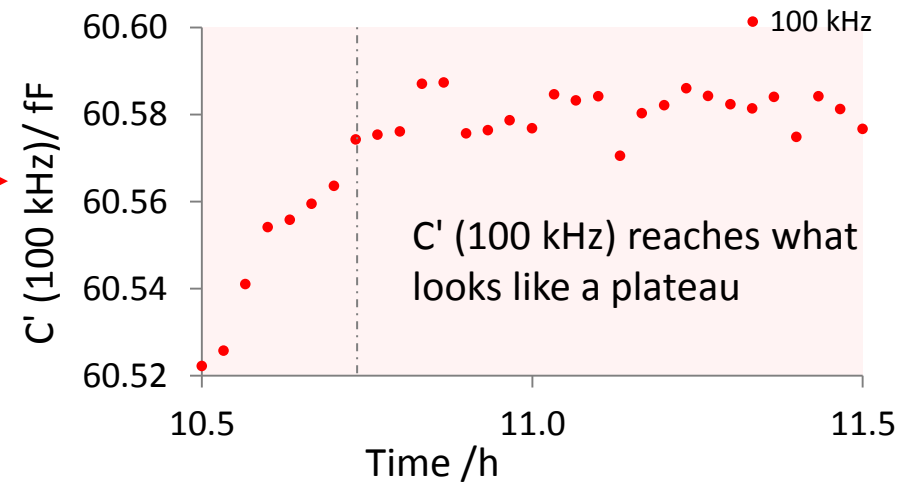
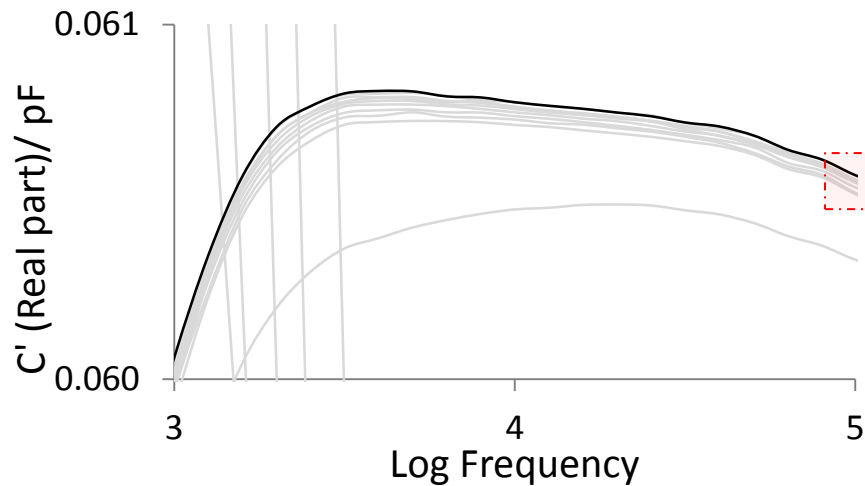
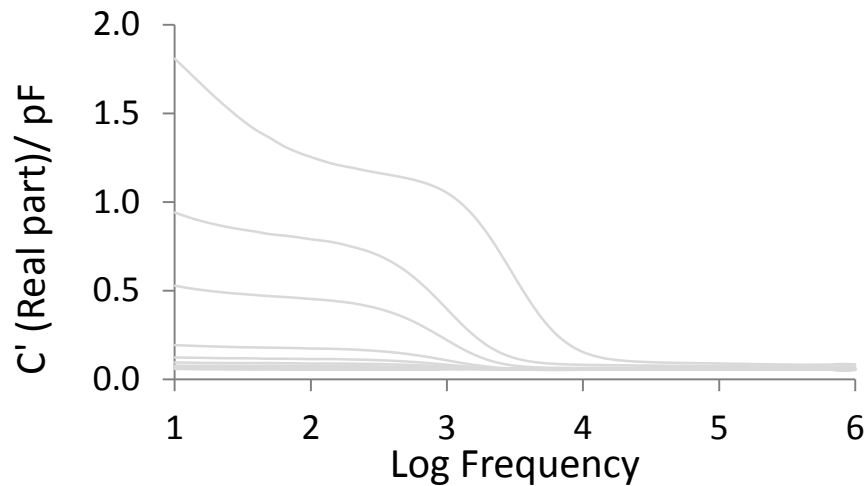
End-Point Determination (T_s -15 °C and P_c 400 μ bar)



End-Point Determination (T_s -15 °C and P_c 400 μ bar)

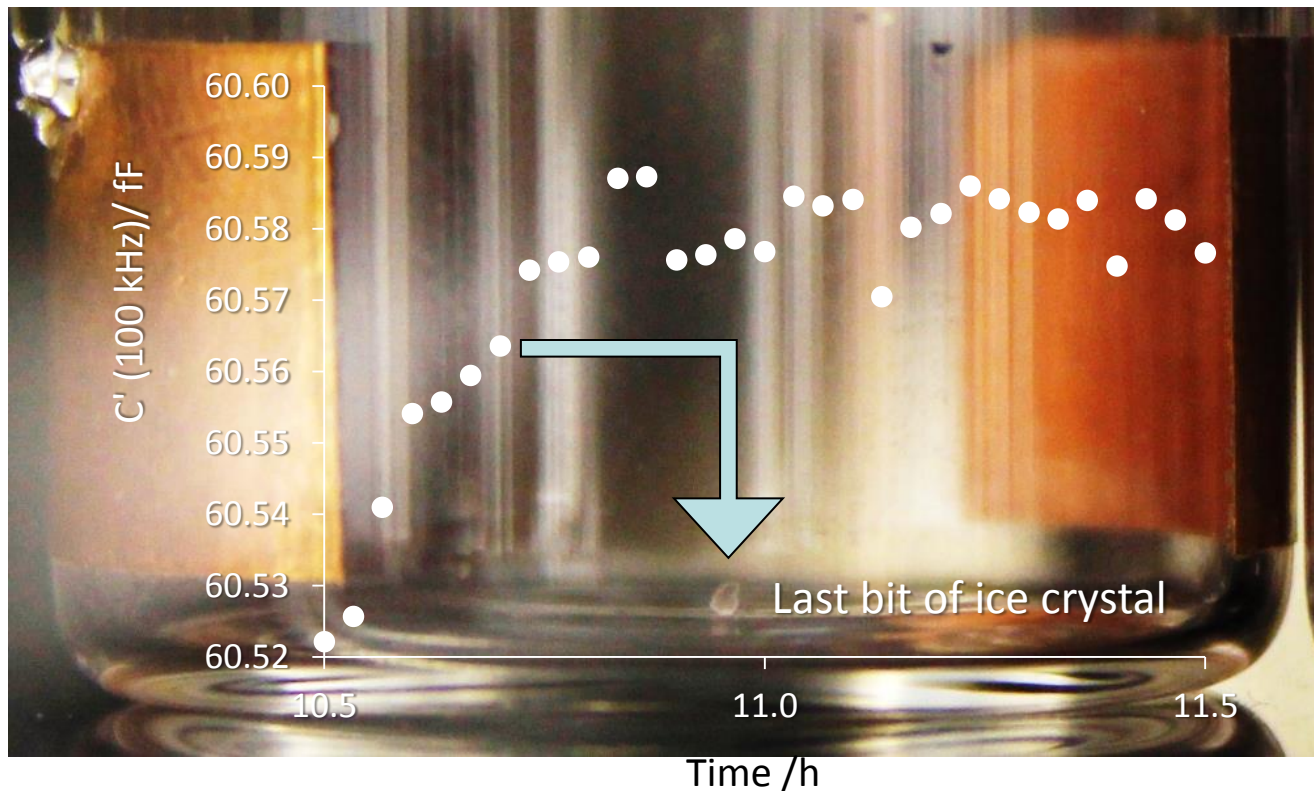


End-Point Determination (T_s -15 °C and P_c 400 μ bar)



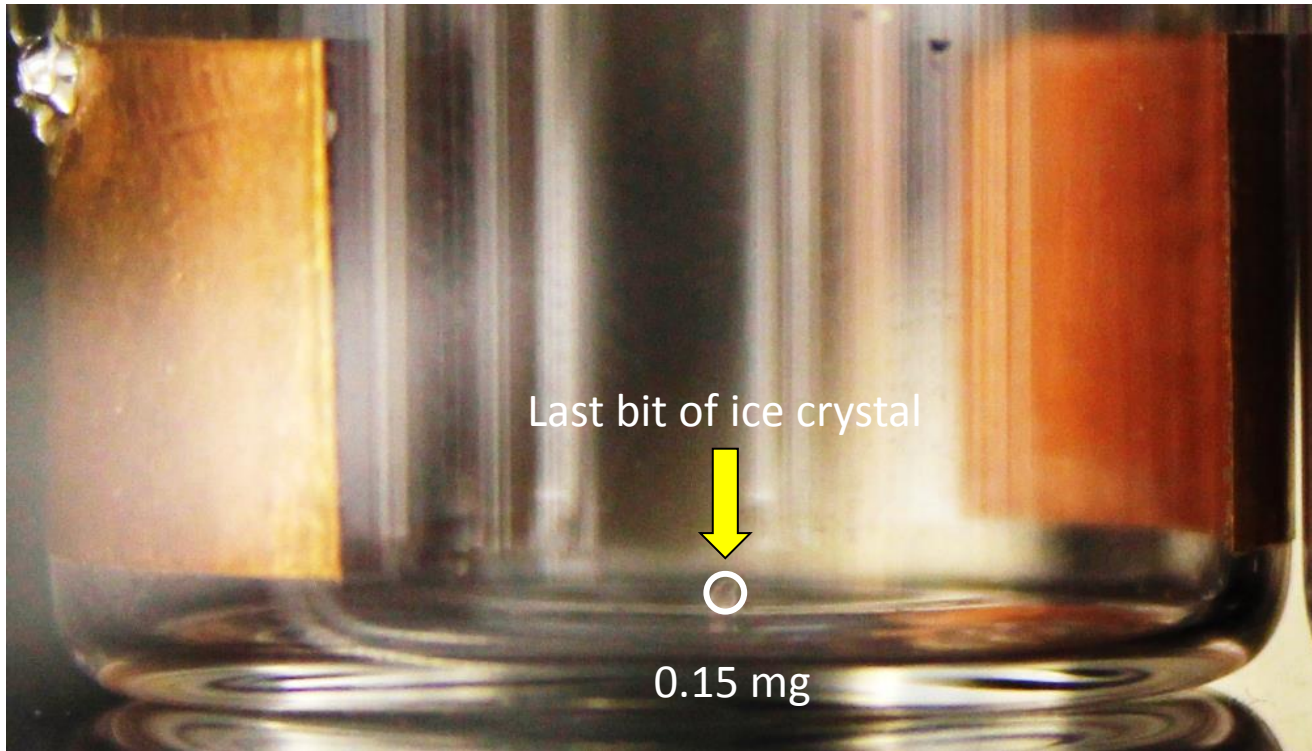
Summary

- End point determine by high frequency (i.e. 100 kHz for ice) real part capacitance (i.e. 100 kHz for ice)



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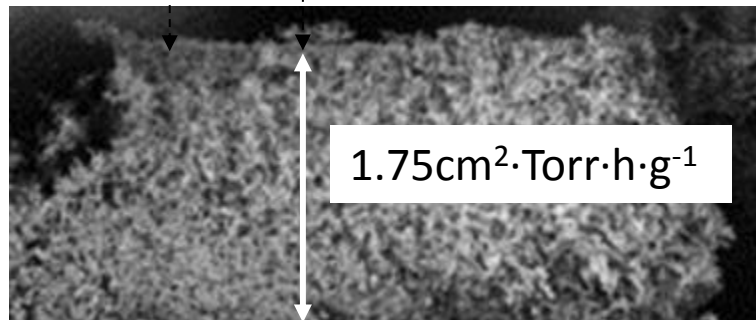
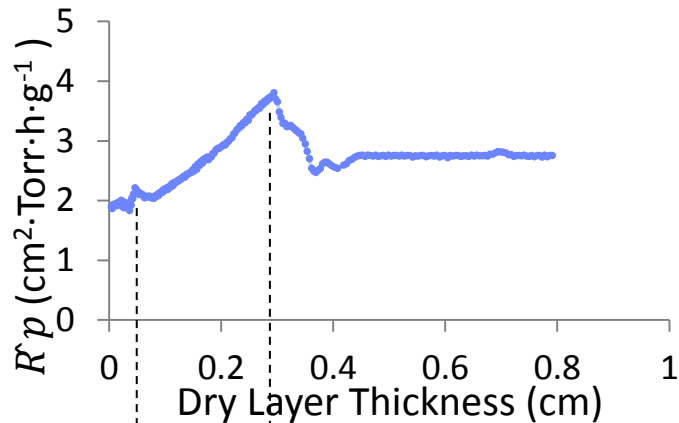


Through Vial Impedance Spectroscopy (TVIS)

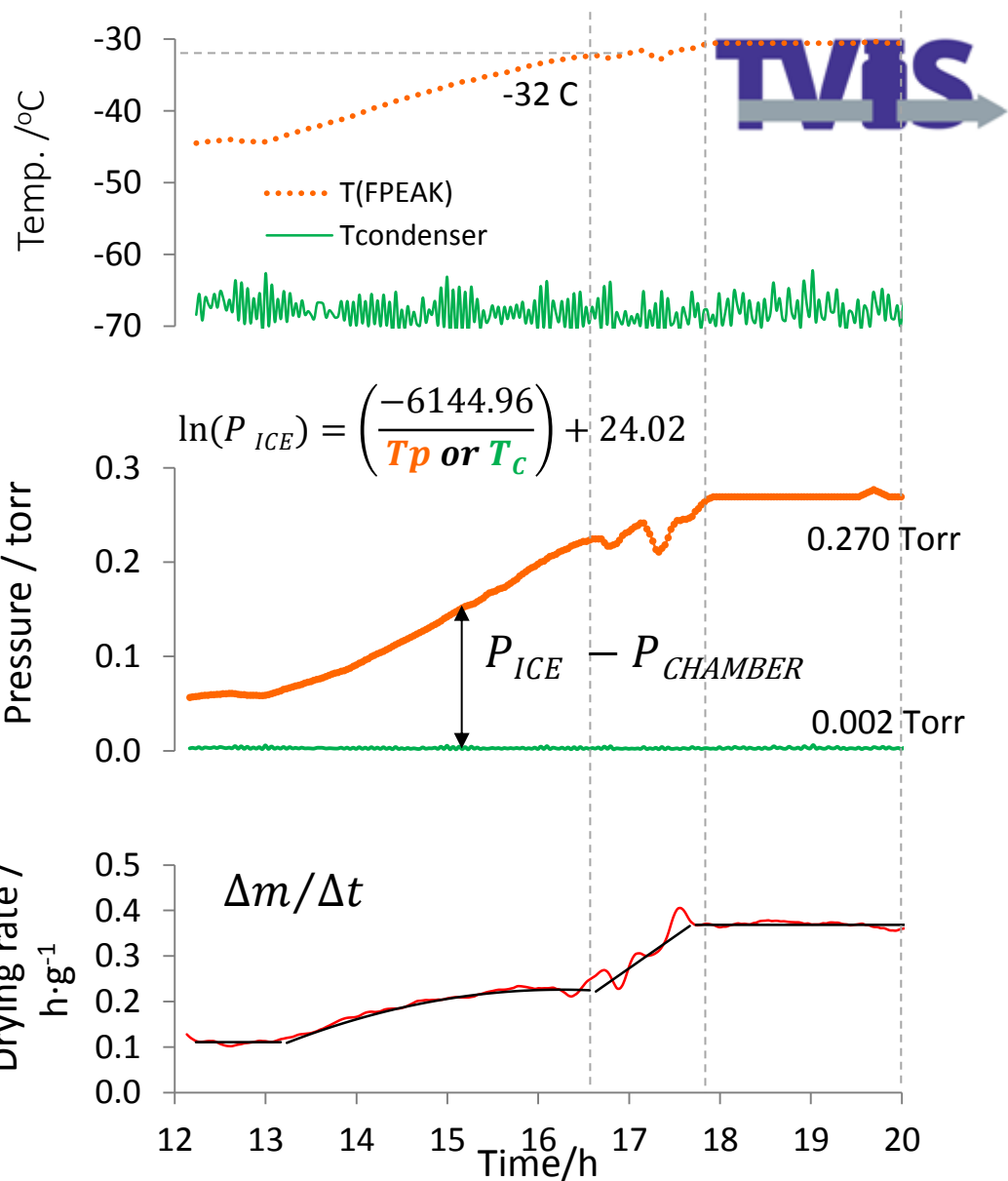
Product Resistance Determination

Product Resistance (R_p) Determination

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

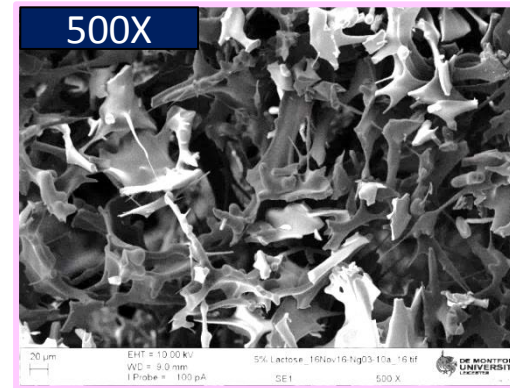
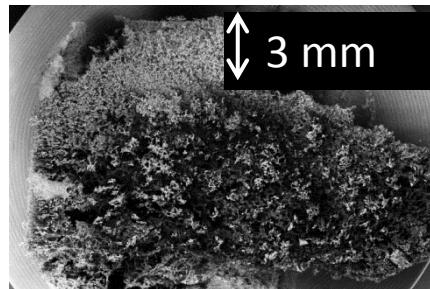
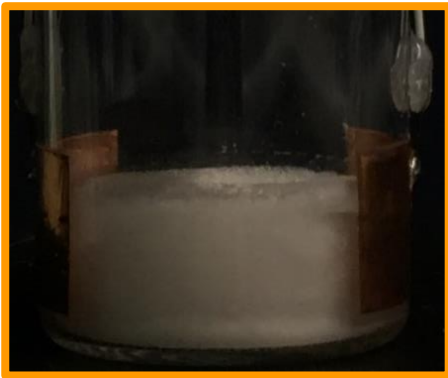
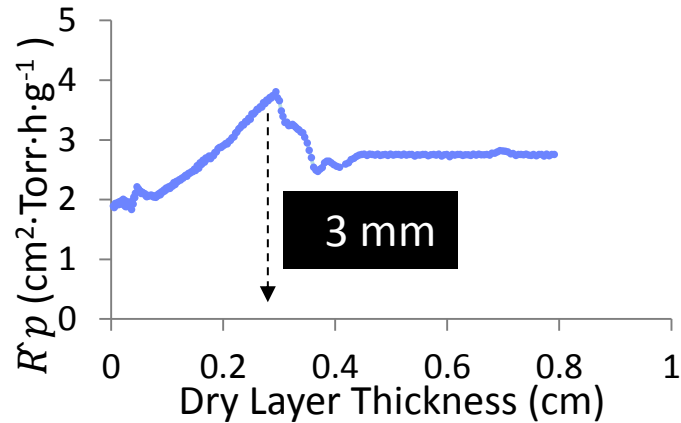


Lactose freeze-dried matrix

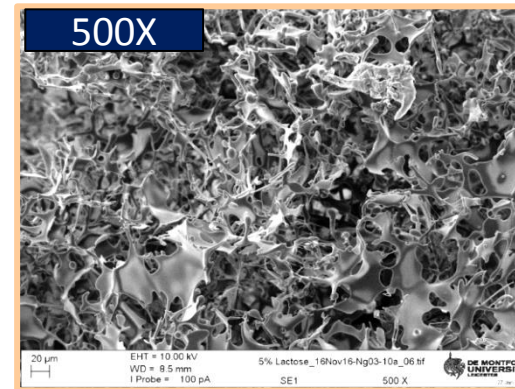


Product Resistance (R_p) Determination

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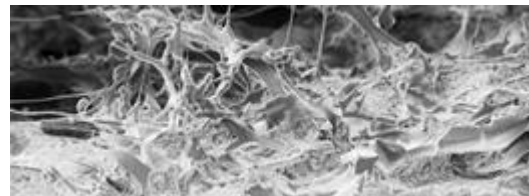


Top layer
Fine pores



Middle layer
Micro-collapse

500X

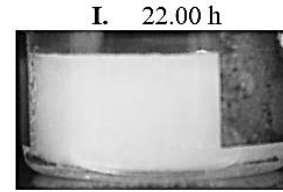
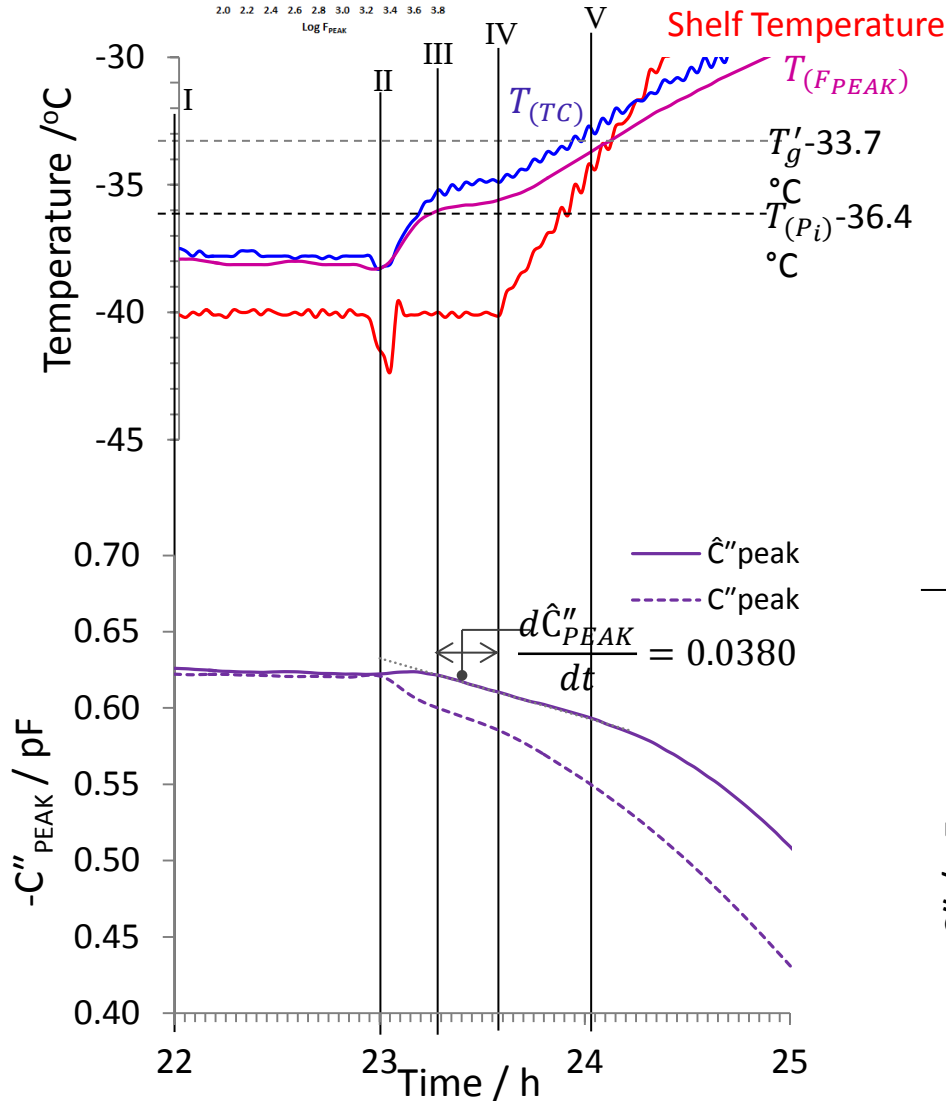
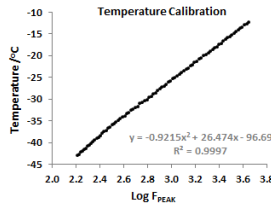


Bottom layer
Full collapse

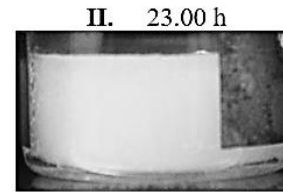
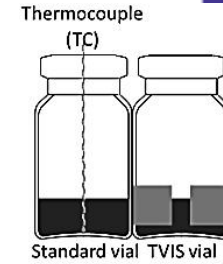
Through Vial Impedance Spectroscopy (TVIS)

Collapse Phenomena

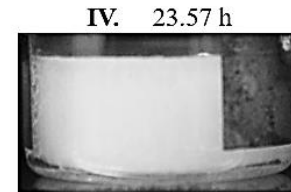
5% Sucrose



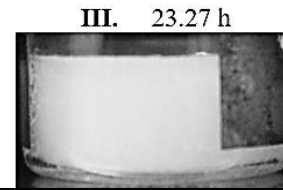
$T_{(TC)} = -37.8$ °C;
 $T_{(FPEAK)} = -38.2$ °C



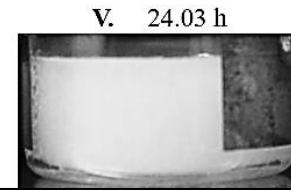
$T_{(TC)} = -38.2$ °C;
 $T_{(FPEAK)} = -38.2$ °C



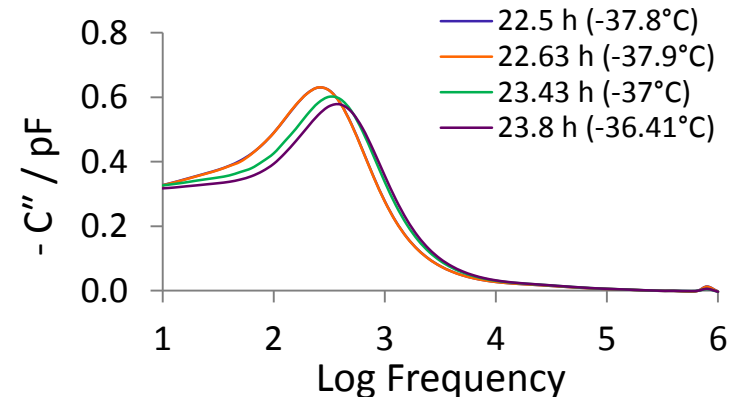
$T_{(TC)} = -34.9$ °C;
 $T_{(FPEAK)} = -35.6$ °C



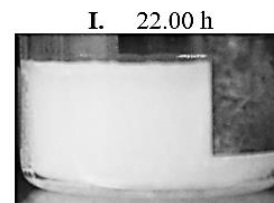
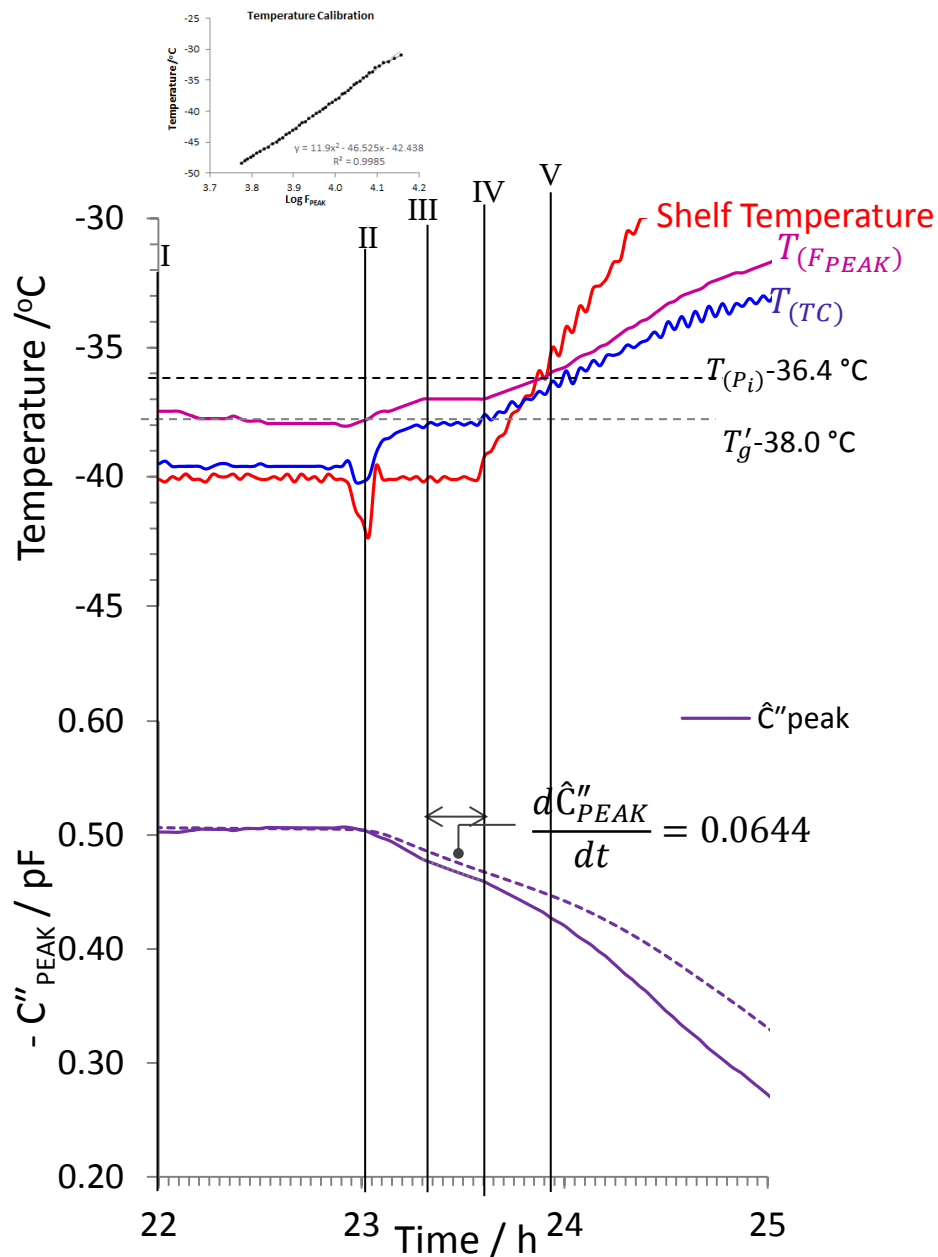
$T_{(TC)} = -35.2$ °C;
 $T_{(FPEAK)} = -36.0$ °C



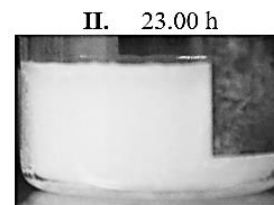
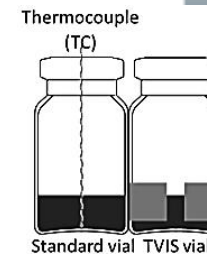
$T_{(TC)} = -33.0$ °C;
 $T_{(FPEAK)} = -33.6$ °C



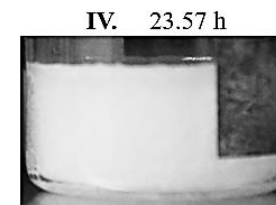
5% Sucrose in 0.26% NaCl



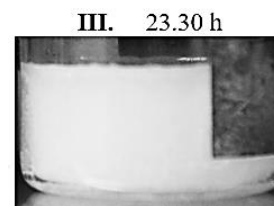
$T_{(TC)} = -39.5\text{ °C};$
 $T_{(FPEAK)} = -37.5\text{ °C}$



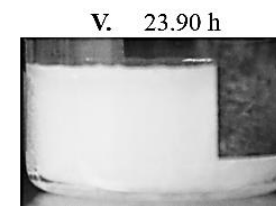
$T_{(TC)} = -40.2\text{ °C};$
 $T_{(FPEAK)} = -37.8\text{ °C}$



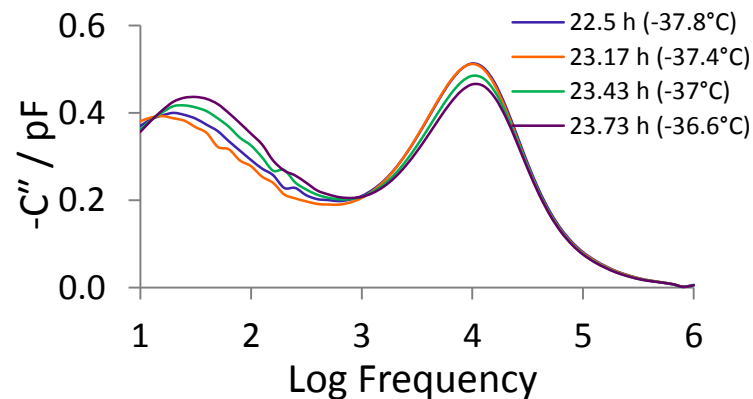
$T_{(TC)} = -38.0\text{ °C};$
 $T_{(FPEAK)} = -37.0\text{ °C}$



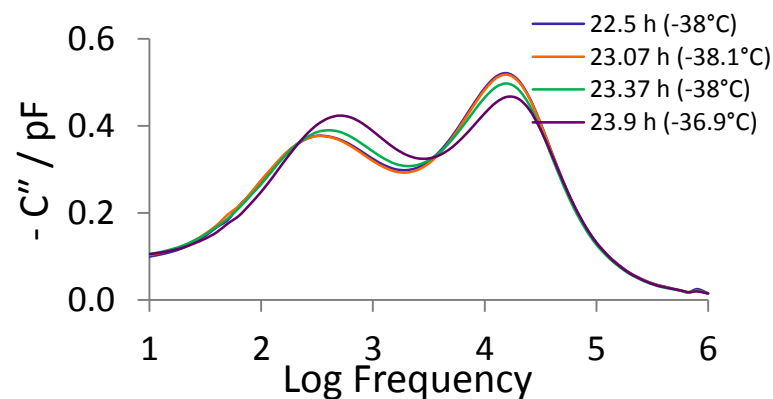
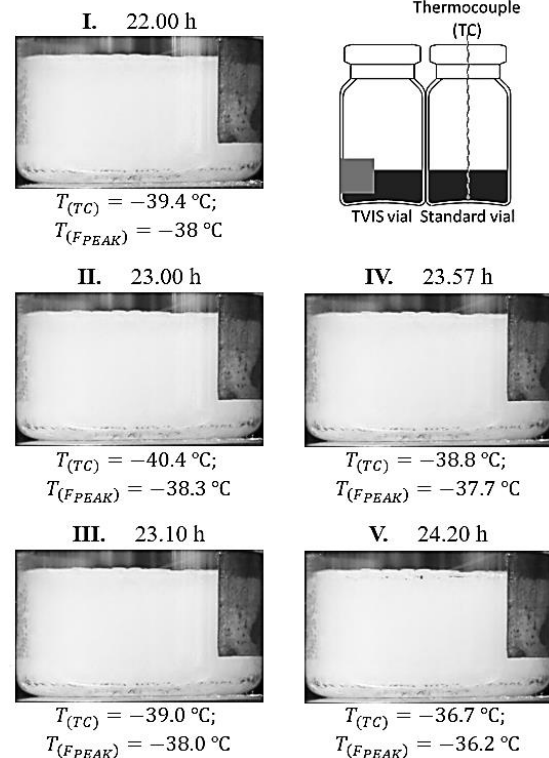
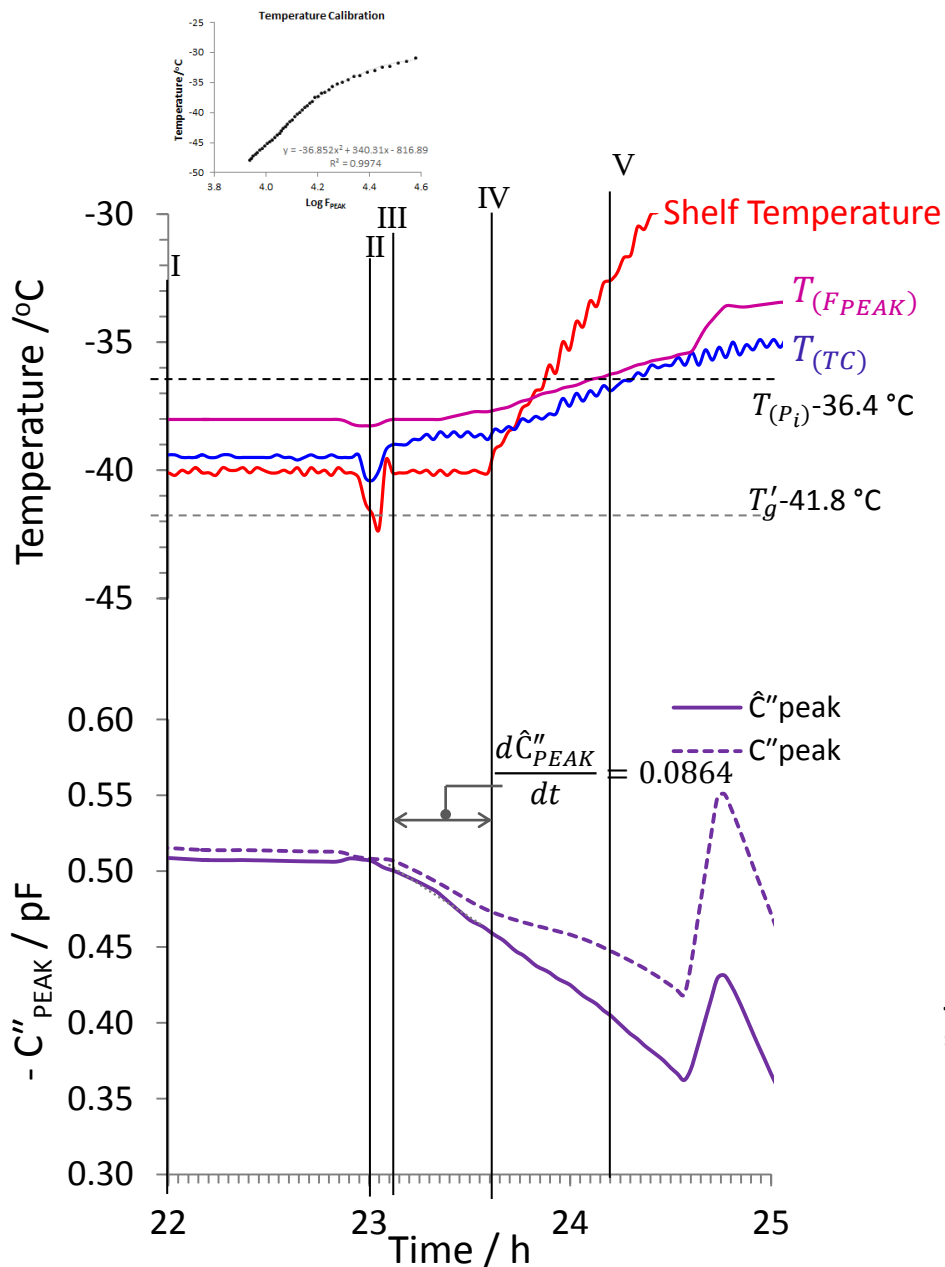
$T_{(TC)} = -38.1\text{ °C};$
 $T_{(FPEAK)} = -37.0\text{ °C}$



$T_{(TC)} = -36.8\text{ °C};$
 $T_{(FPEAK)} = -36.1\text{ °C}$



5% Sucrose +0.55% NaCl



Summary results of sugar- salts solutions



Parameters	Unit	S-1	S-2	S-3
Component				
Sucrose	%w/v	5	5	5
Sodium chloride	%w/v	-	0.26	0.55
T'_g (DSC)	°C	-33.7	-38.0	-41.8
Temperature stabilization period (Before ramping shelf temperature)		III to IV	III to IV	III to IV
	h	23.3 - 23.6	23.3 - 23.6	23.1 - 23.6
$T_{(F_{PEAK})}$	°C	-36.0 to -35.6	-37.0	-38.3 to -37.7
Surrogate drying rate ($d\hat{C}_{PEAK}/dt$)	pF/h	0.0380	0.0644	0.0864
Structural state		Non-collapse	micro-collapse?	Micro-collapse
		VII to VIII	VII to VIII	VII to VIII
Temperature stabilization period (After shelf temperature constant)	h	26.0 - 26.8	26.0 - 26.4	26.0 - 26.2
	°C	-26.4 to -25.6	-30.1 to -30.0	-32.8 to -32.7
Surrogate drying rate ($d\hat{C}_{PEAK}/dt$)	pF/h	0.2243	0.1227	0.1569
Structural State*		Micro-collapse	Collapse	Collapse

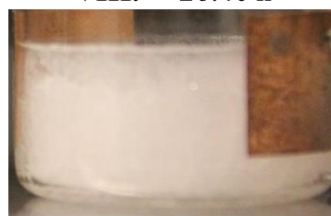
5% Sucrose in Salt Solutions

VI. 23.90 h



$T_{(TC)} = -36.8\text{ }^{\circ}\text{C};$
 $T_{(FPEAK)} = -36.1\text{ }^{\circ}\text{C}$

VIII. 26.40 h



$T_{(TC)} = -31.7\text{ }^{\circ}\text{C};$
 $T_{(FPEAK)} = -30.0\text{ }^{\circ}\text{C}$

VII. 26.03 h

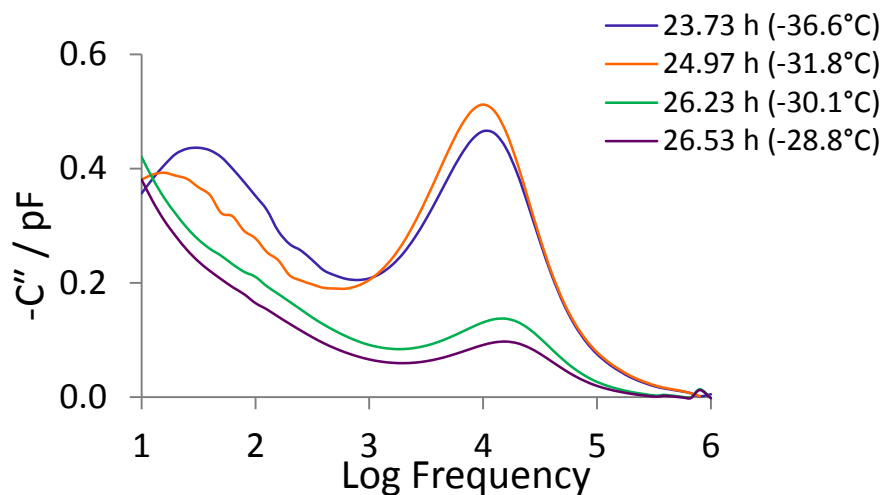


$T_{(TC)} = -31.5\text{ }^{\circ}\text{C};$
 $T_{(FPEAK)} = -30.1\text{ }^{\circ}\text{C}$

IX. 26.67 h



$T_{(TC)} = -31.4\text{ }^{\circ}\text{C};$
 $T_{(FPEAK)} = -27.9\text{ }^{\circ}\text{C}$



5% sucrose in 0.26% NaCl

VI. 24.20 h



$T_{(TC)} = -36.7\text{ }^{\circ}\text{C};$
 $T_{(FPEAK)} = -36.2\text{ }^{\circ}\text{C}$

VIII. 26.20 h



$T_{(TC)} = -34.4\text{ }^{\circ}\text{C};$
 $T_{(FPEAK)} = -32.7\text{ }^{\circ}\text{C}$

VII. 26.03 h

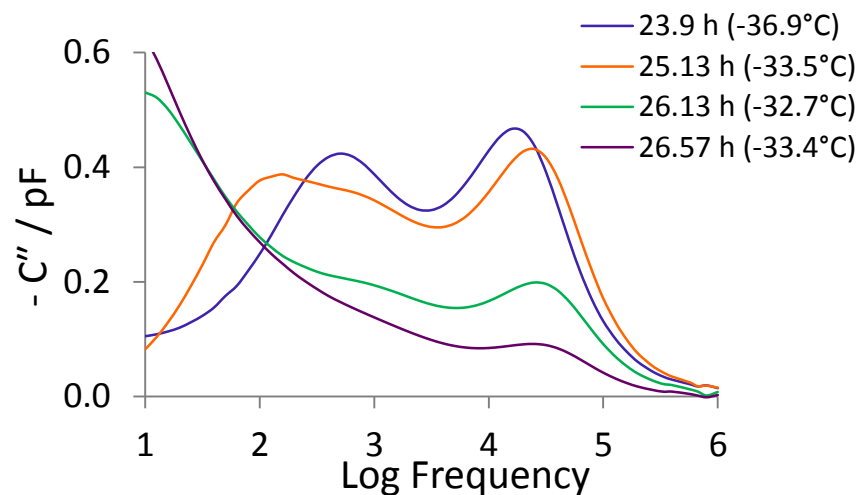


$T_{(TC)} = -34.1\text{ }^{\circ}\text{C};$
 $T_{(FPEAK)} = -32.8\text{ }^{\circ}\text{C}$

IX. 26.90 h



$T_{(TC)} = -34.7\text{ }^{\circ}\text{C};$
 $T_{(FPEAK)} = -32.5\text{ }^{\circ}\text{C}$



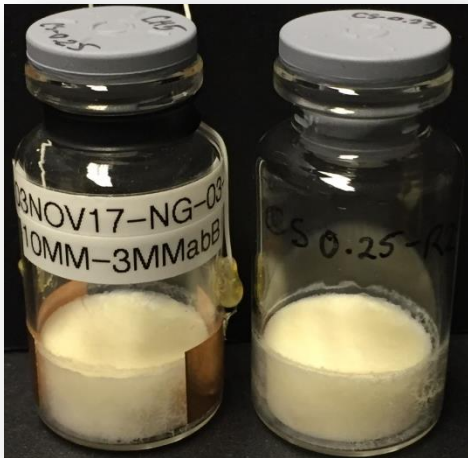
5% sucrose in 0.55% NaCl

Limitations

- C''_{PEAK} and F_{PEAK} parameters rely on intimate contact of ice cylinder with glass wall
- $C'(100\text{ kHz})$ parameter does not depend on contact and can be used for end point but relationship between $C'(100\text{ kHz})$ ice constant is non-linear
- 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 mapping a drying characteristics
 - heat transfer coefficients (K_V)
 - dry layer resistance (R_P)



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

Non-invasive real time information for characterising the freeze drying

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