



# Application of a novel impedance-based freeze drying microscopy for formulation development

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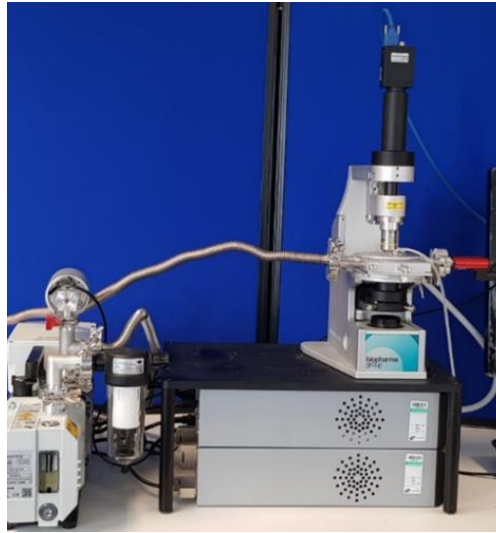
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Ghent, Belgium, 2-6 September 2019

# Outline

- Background
  - Development of Z-FDM
- Application of Z-FDM
  - Study 1: Freezing drying without collapse
    - a) Freezing
      - Nucleation onset
      - Ice growth & Solidification end-point
      - Loss of excess heat and thermal equilibrium
    - b) Primary drying
      - Drying rate
      - End of drying
  - Study 2: Freeze drying with collapse
- Acknowledgements

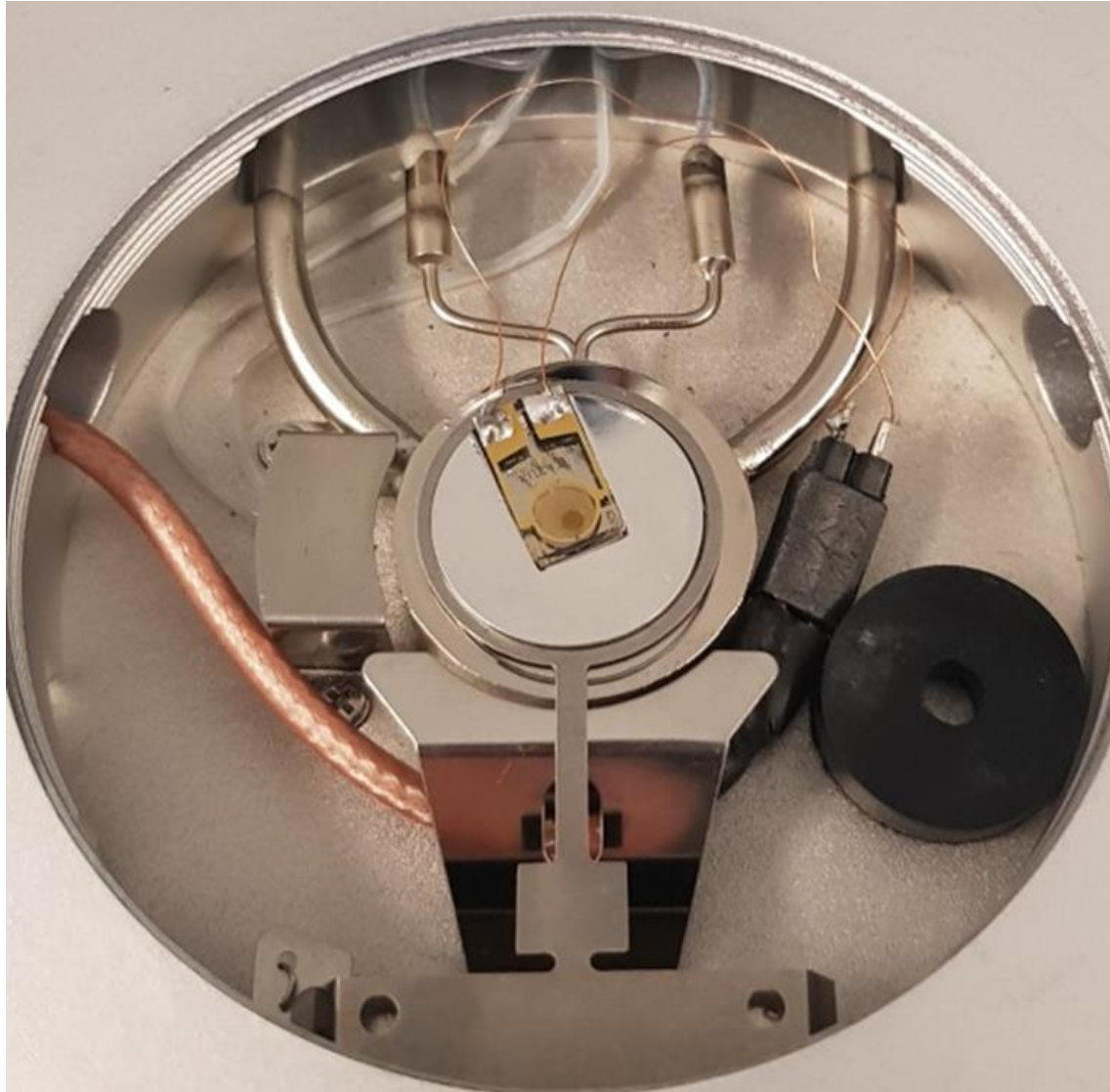
# Background

- Impedance spectroscopy essentially measures the ability of material to conduct electricity under an applied oscillating voltage at a bound frequency
- Our group works with 'Through Vial Impedance Spectroscopy' (TVIS)
- Freeze drying microscopy (FDM) is used to study critical parameter of freeze drying process (i.e. collapse temperature or eutectic temperature)



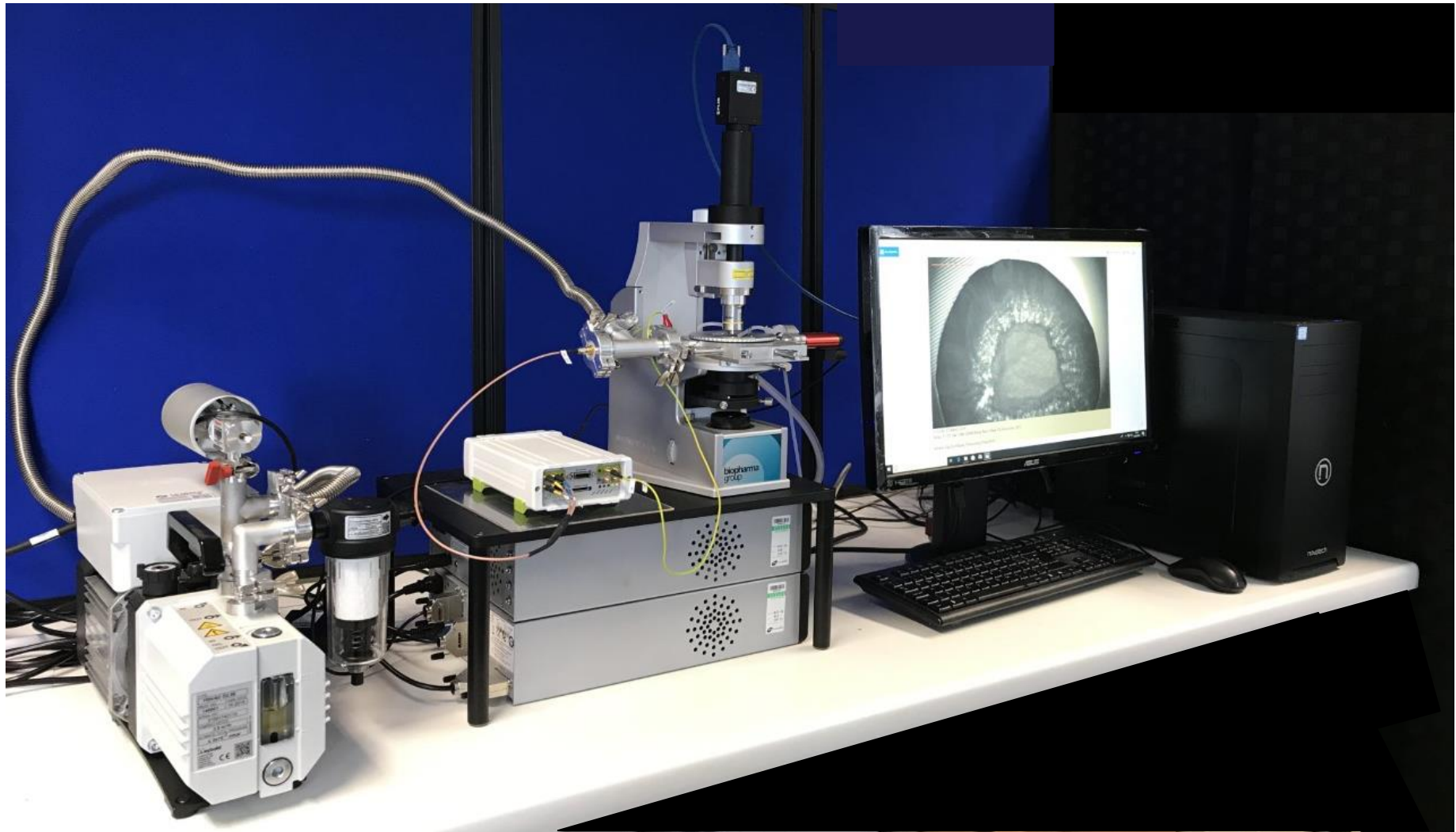
**Task:** Integration of FDM with impedance measurement system

# Modified FDM Chamber





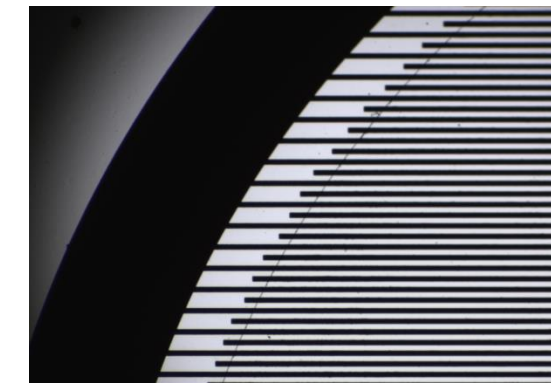
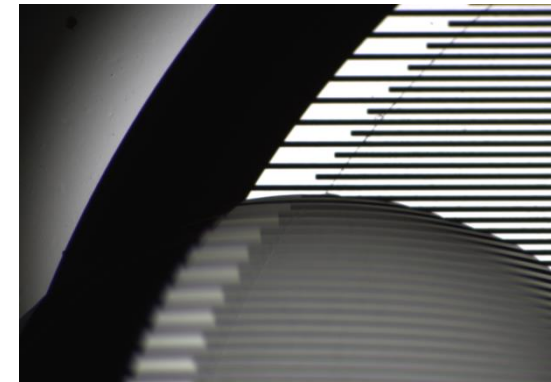
# A single analytical instrument – Z-FDM



## IDE (ED-IDE1-Au) under the FDM

Room temperature analysis

- Top image: Blank IDE
- Middle image: IDE with 1  $\mu\text{L}$  water (no coverslip)
- Bottom image: IDE with water and coverslip on top



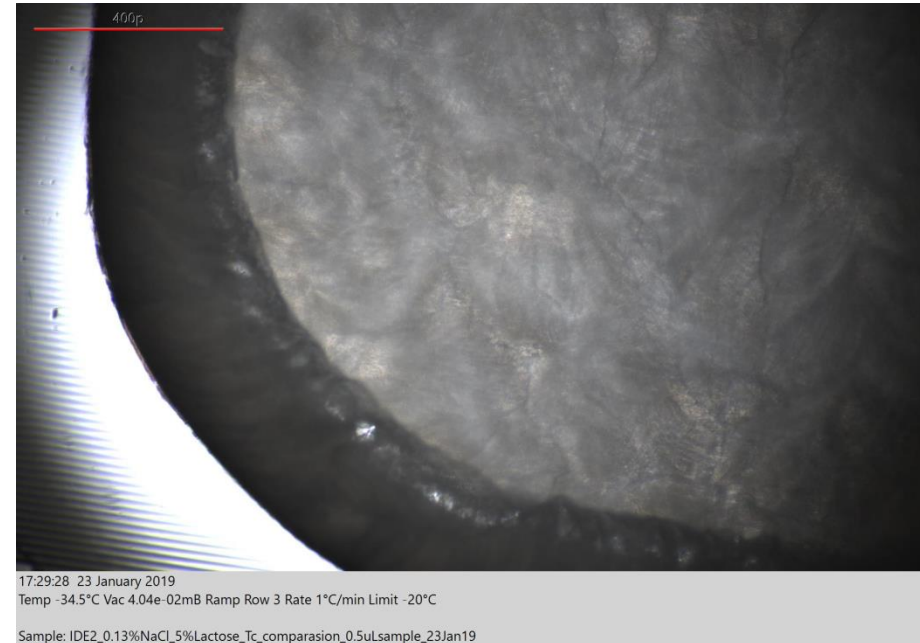
# Initial experimental work: Compatibility test

*5% Sucrose with 0.13% NaCl collapse temperature study*



Collapse temperature: -34.6° C

Typical FMD study (i.e sample without IDE)



Collapse temperature: -34.5° C

(sample with IDE)

# Study 1a: Freezing



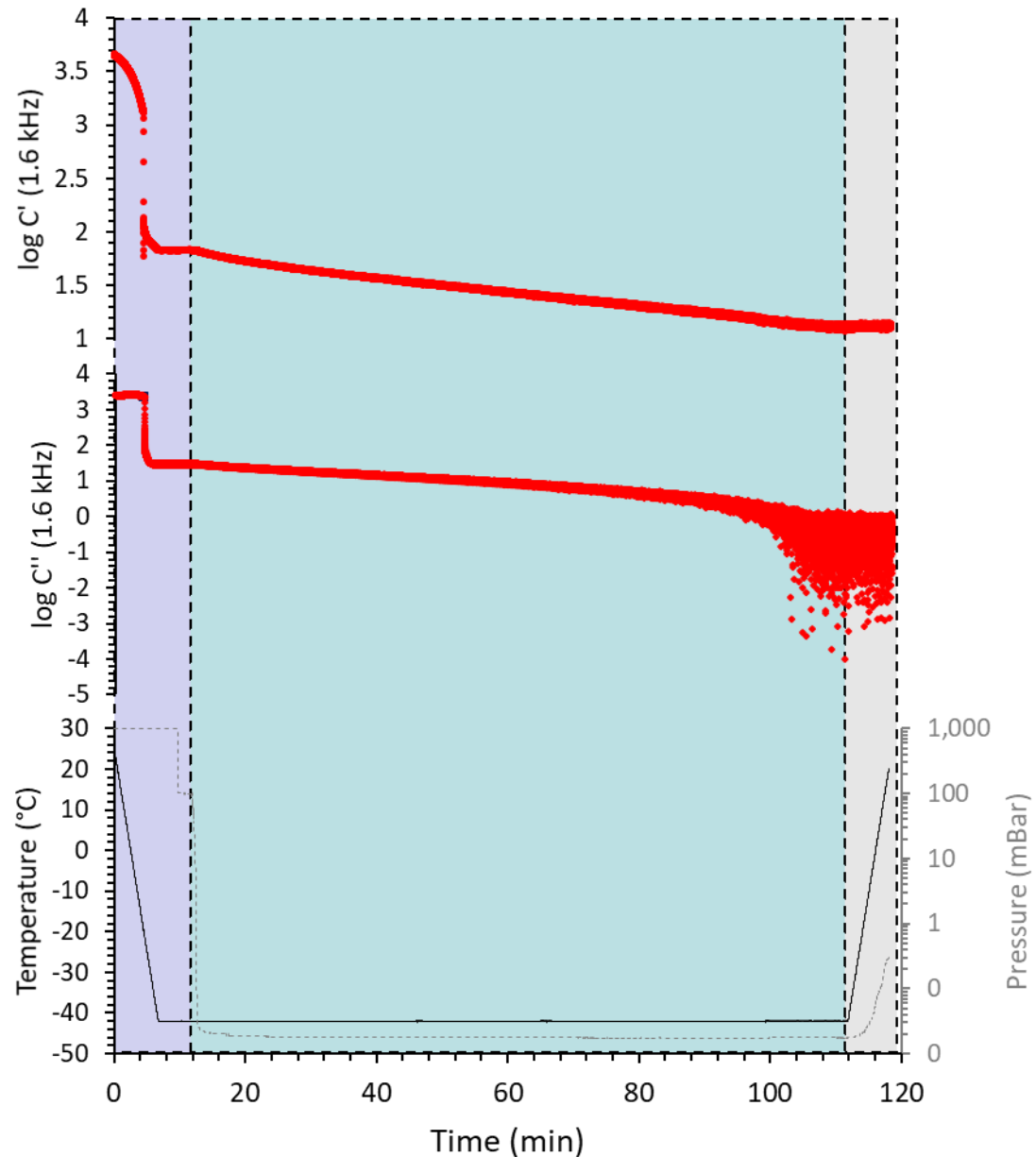
# Freeze drying using 5% Sucrose solution

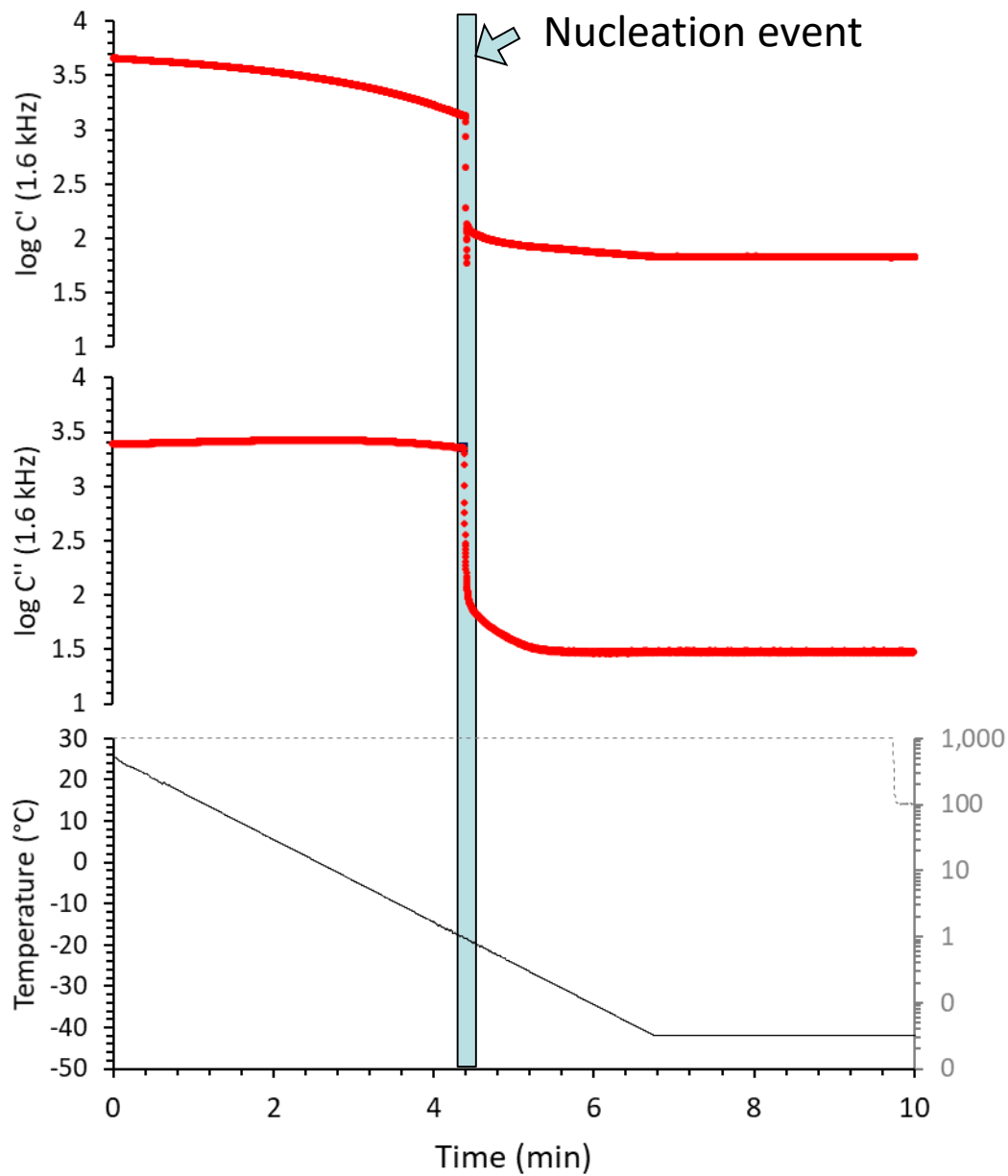
Step no	Rate (°C/min)	Limit (°C)	Time (hh:mm:ss)	Vac (mBar)	Image capture delay (s)
1	10	-42	00:05:00*	1E+3	0.1
2	1	-42	01:40:00^	1E-3	0.1, 10 and 30
3	10	20	00:00:00	1E-3	0.1

\* At after 3 min of hold the pump was switched on  
 ^ after 40 min of initial drying, 1 hour extra added

Note: Liquid nitrogen speed set to AUTO throughout the experiment

- Freezing and Nucleation
- Drying
- Ramp to RT

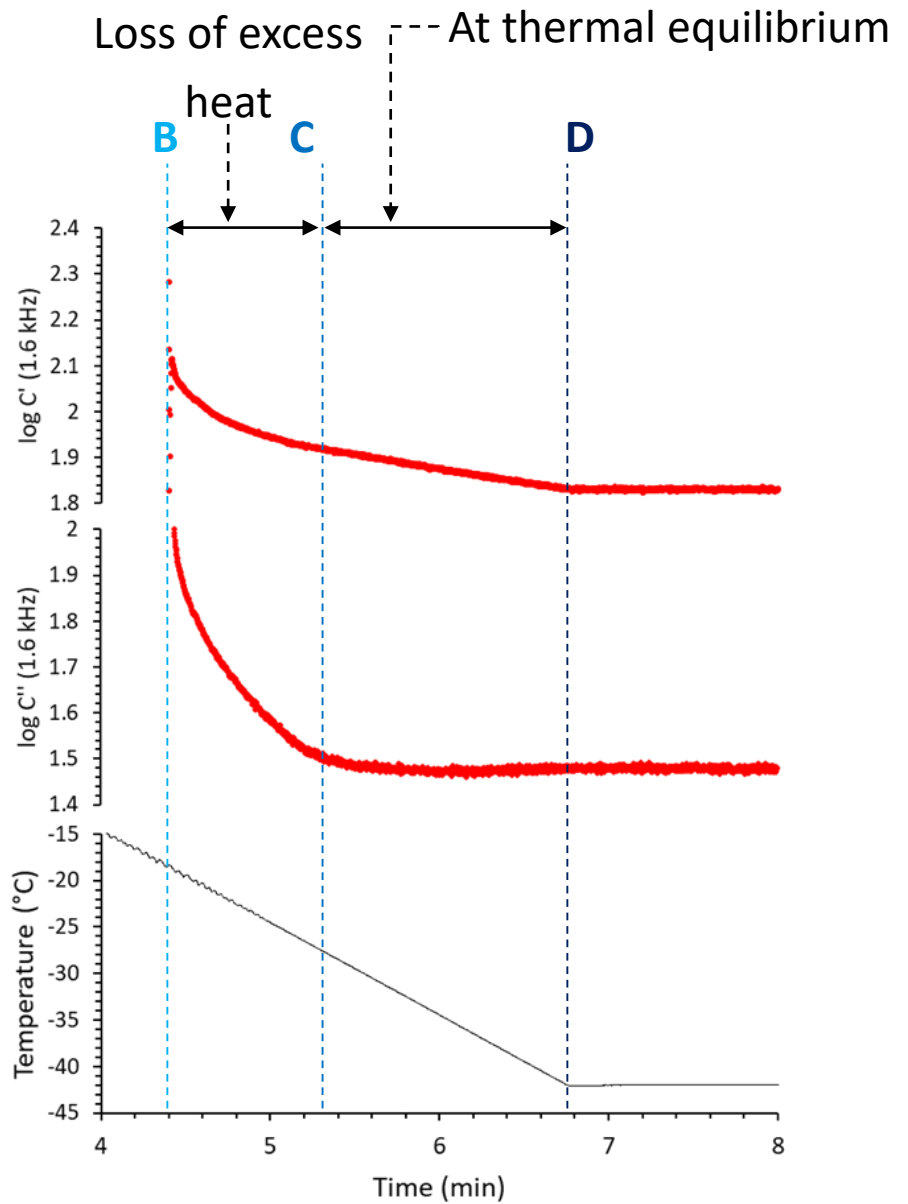
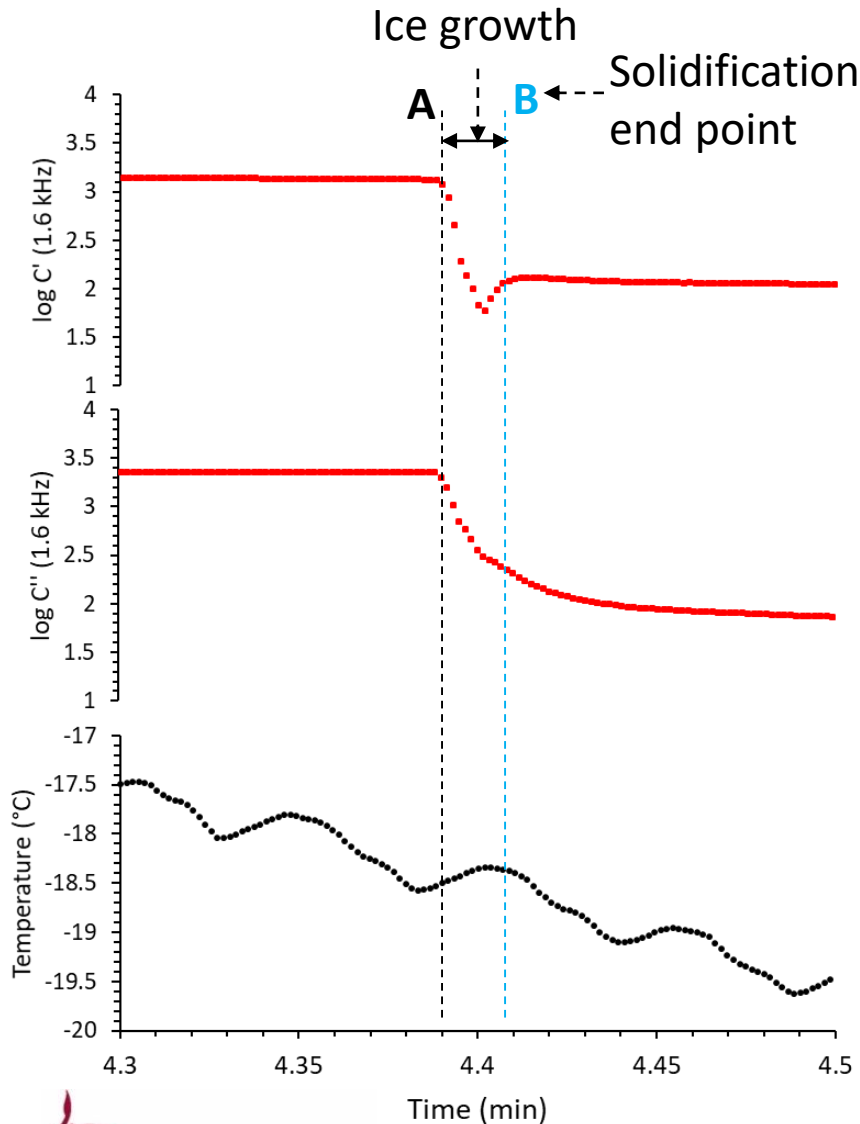




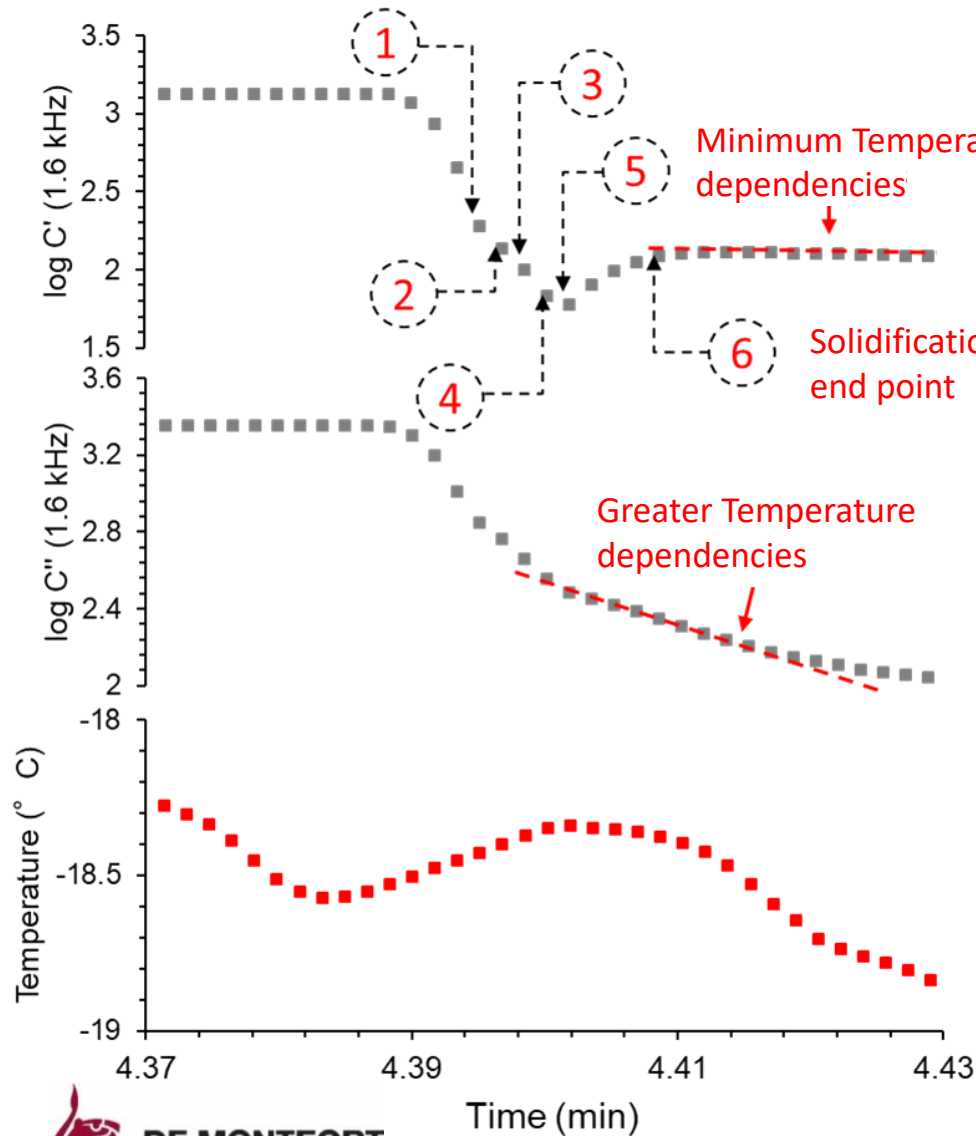
## Freezing



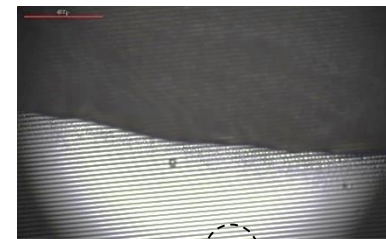
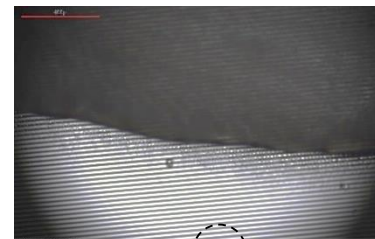
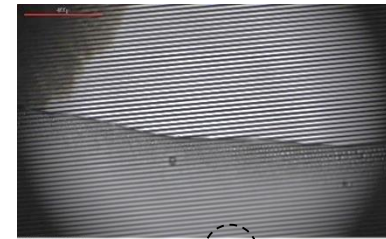
# Freezing in detail



# Nucleation onset & Solidification endpoint



Z-FDM is sensitive and captures minute changes in the freezing step. At point 6 (solidification end-point), the  $C'$  has minimum temperature dependency.



## Study 1b: Primary Drying



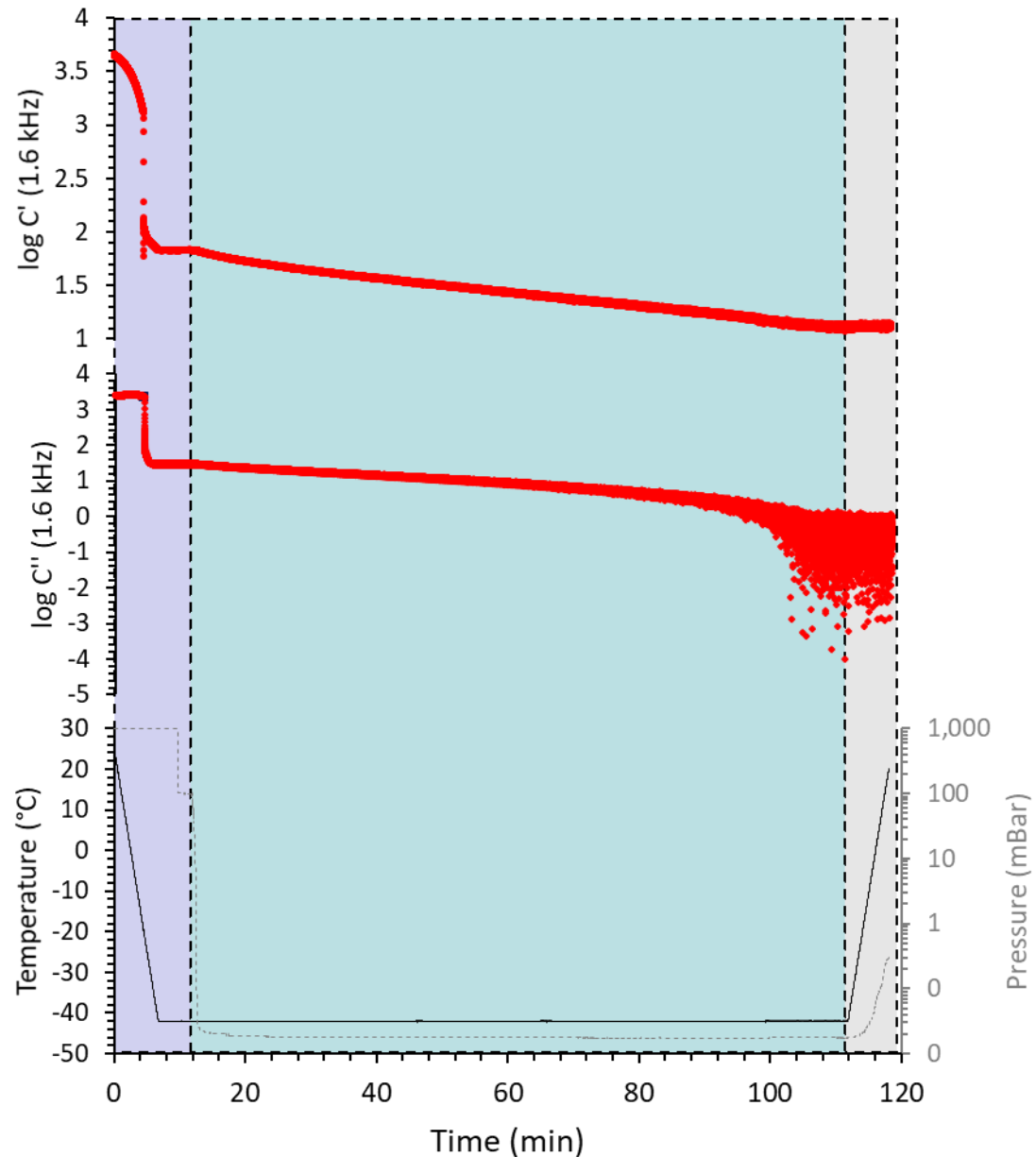
# Drying study of 5% Sucrose solution

Step no	Rate (°C/min)	Limit (°C)	Time (hh:mm:ss)	Vac (mBar)	Image capture delay (s)
1	10	-42	00:05:00*	1E+3	0.1
2	1	-42	01:40:00^	1E-3	0.1, 10 and 30
3	10	20	00:00:00	1E-3	0.1

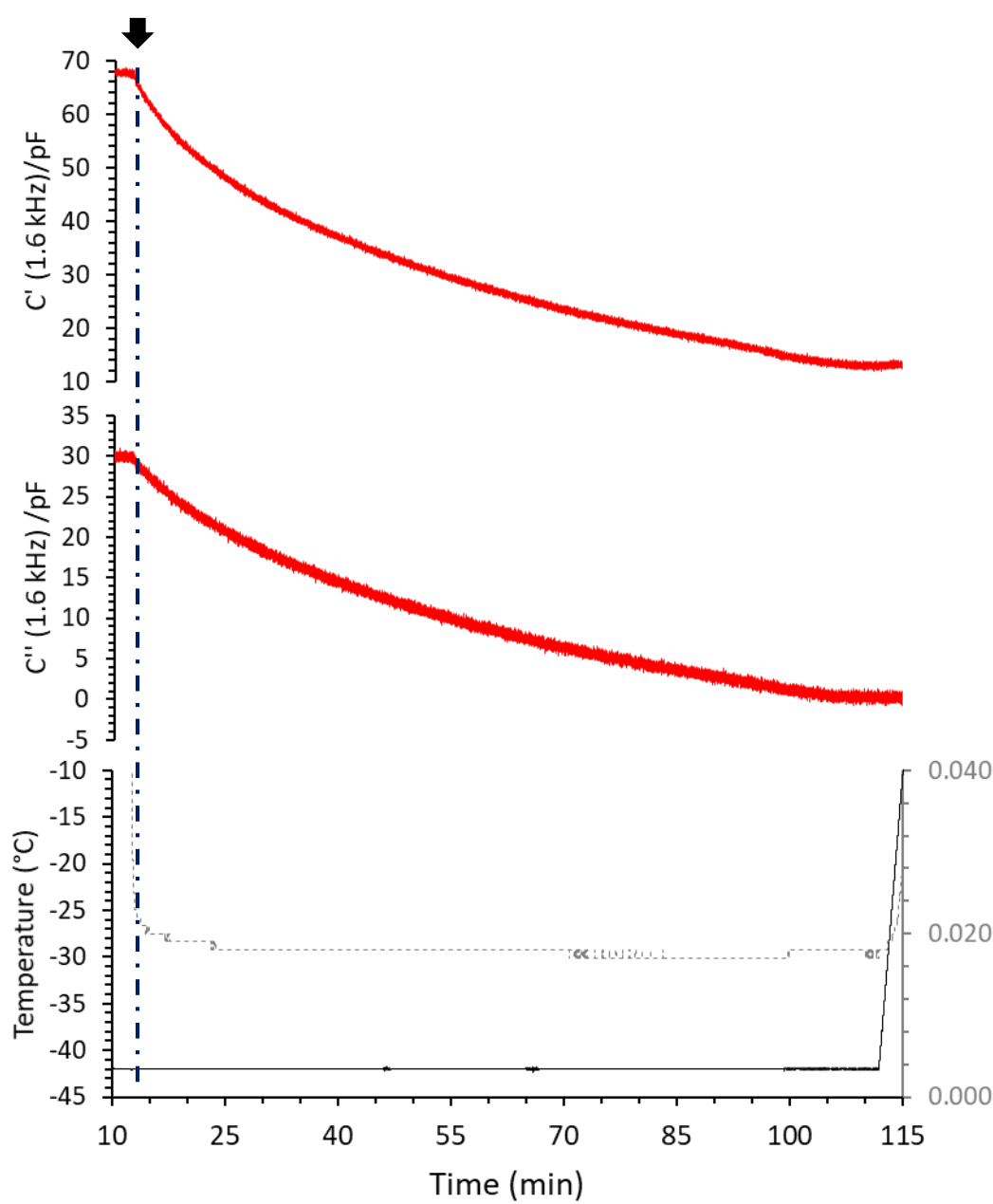
\* At after 3 min of hold the pump was switched on  
 ^ after 40 min of initial drying, 1 hour extra added

Note: Liquid nitrogen speed set to AUTO throughout the experiment

- Freezing and Nucleation
- Drying
- Ramp to RT



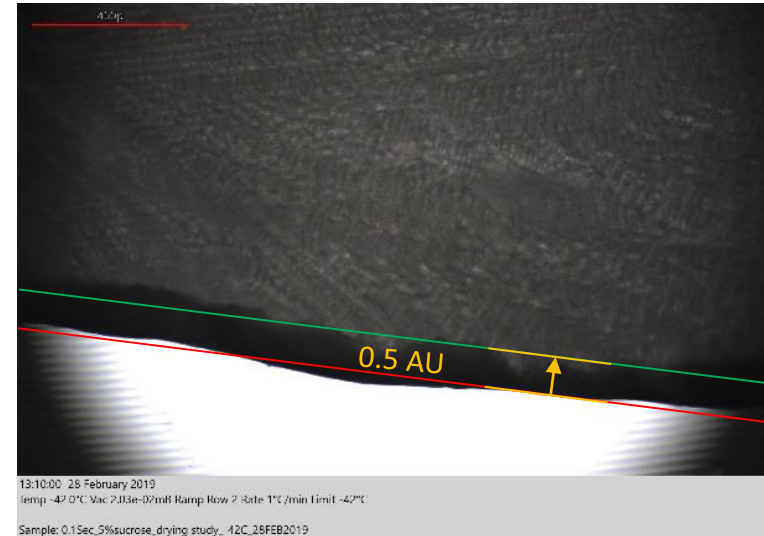
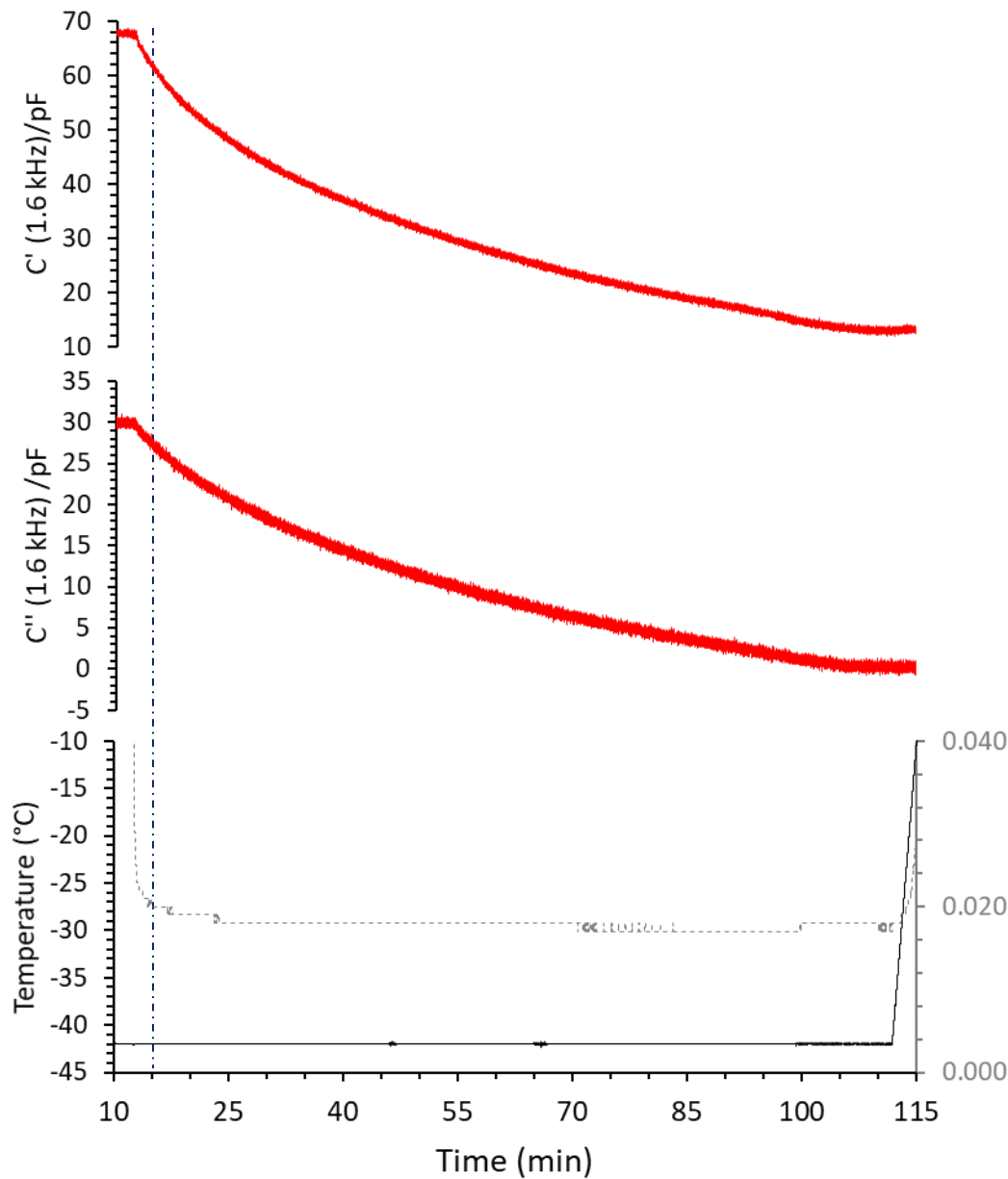
## Drying (vacuum applied)



Time: 11min 45 sec

NB: Distance is an arbitrary unit

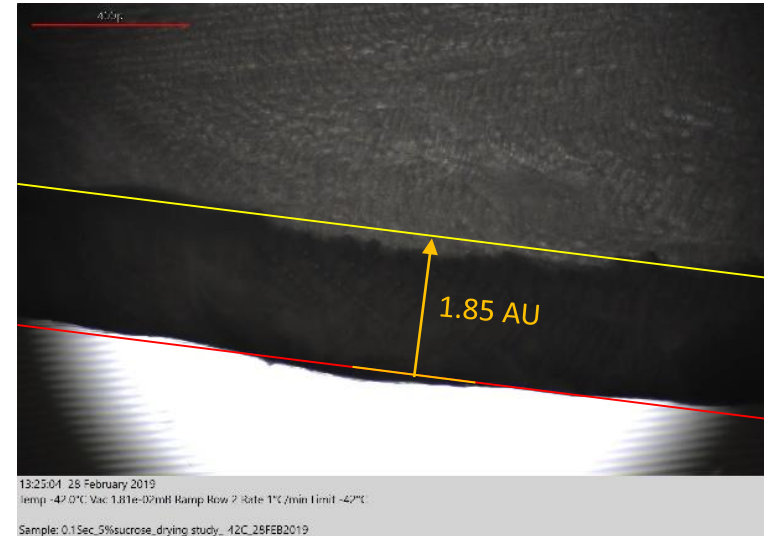
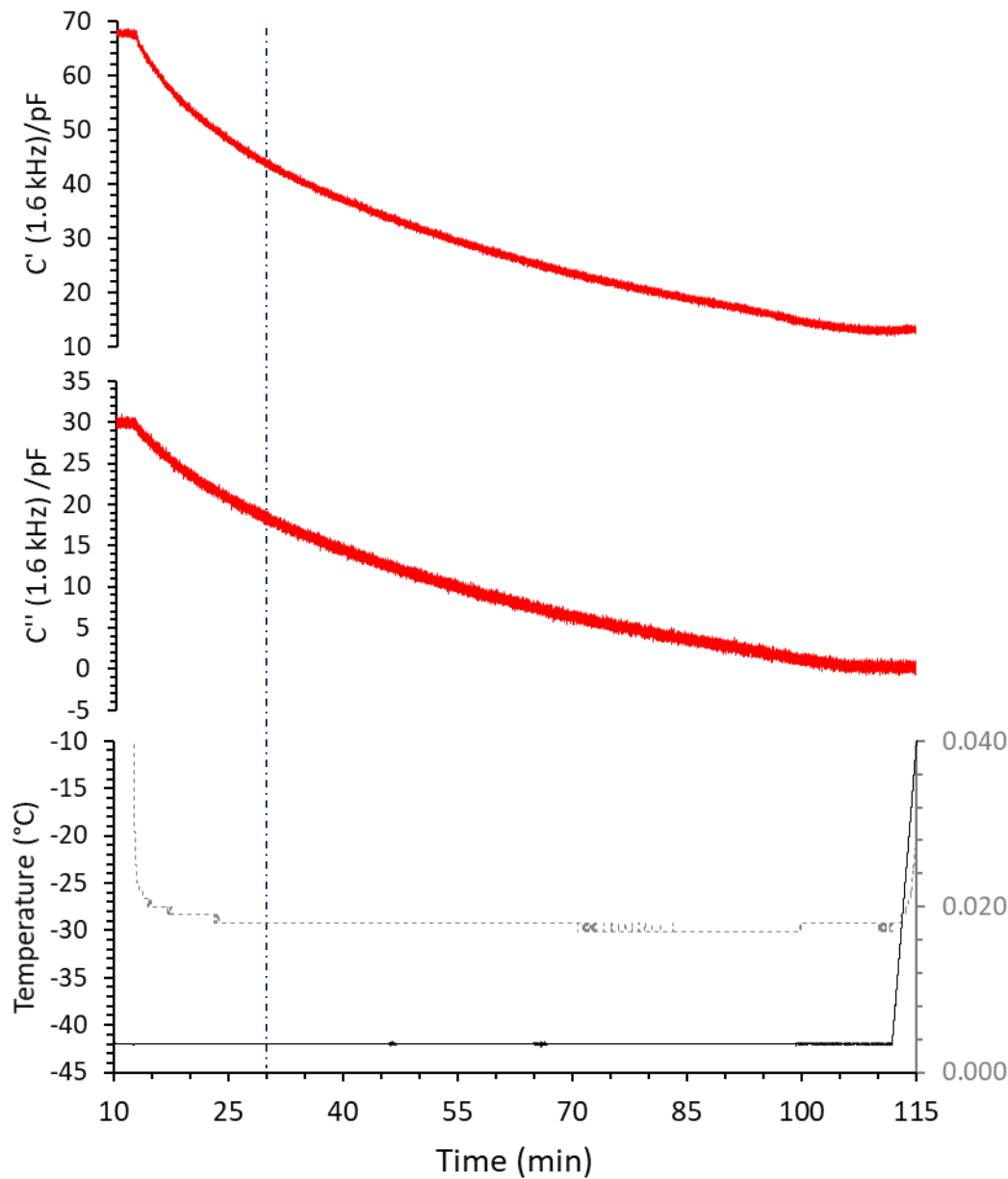
Drying time: 3 min 15 sec



Time: 15 min

NB: Distance is an arbitrary unit

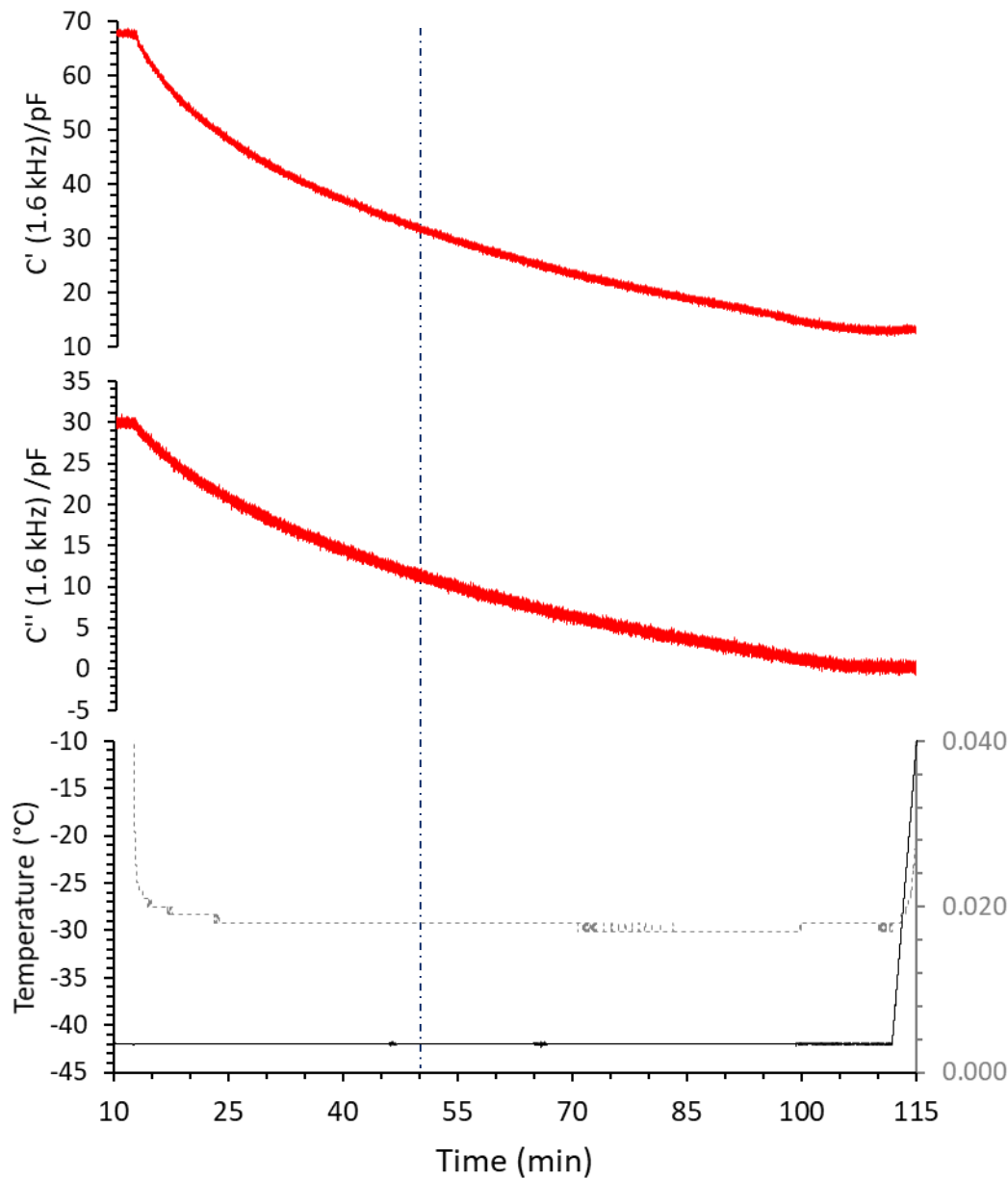
Drying time: 17 min 19 sec



Time: 30 min

NB: Distance is an arbitrary unit

Drying time: 37 min 18 sec

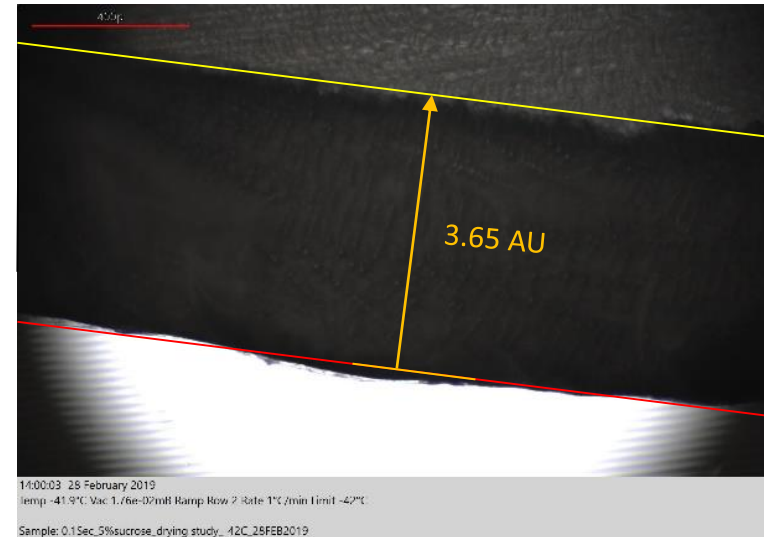
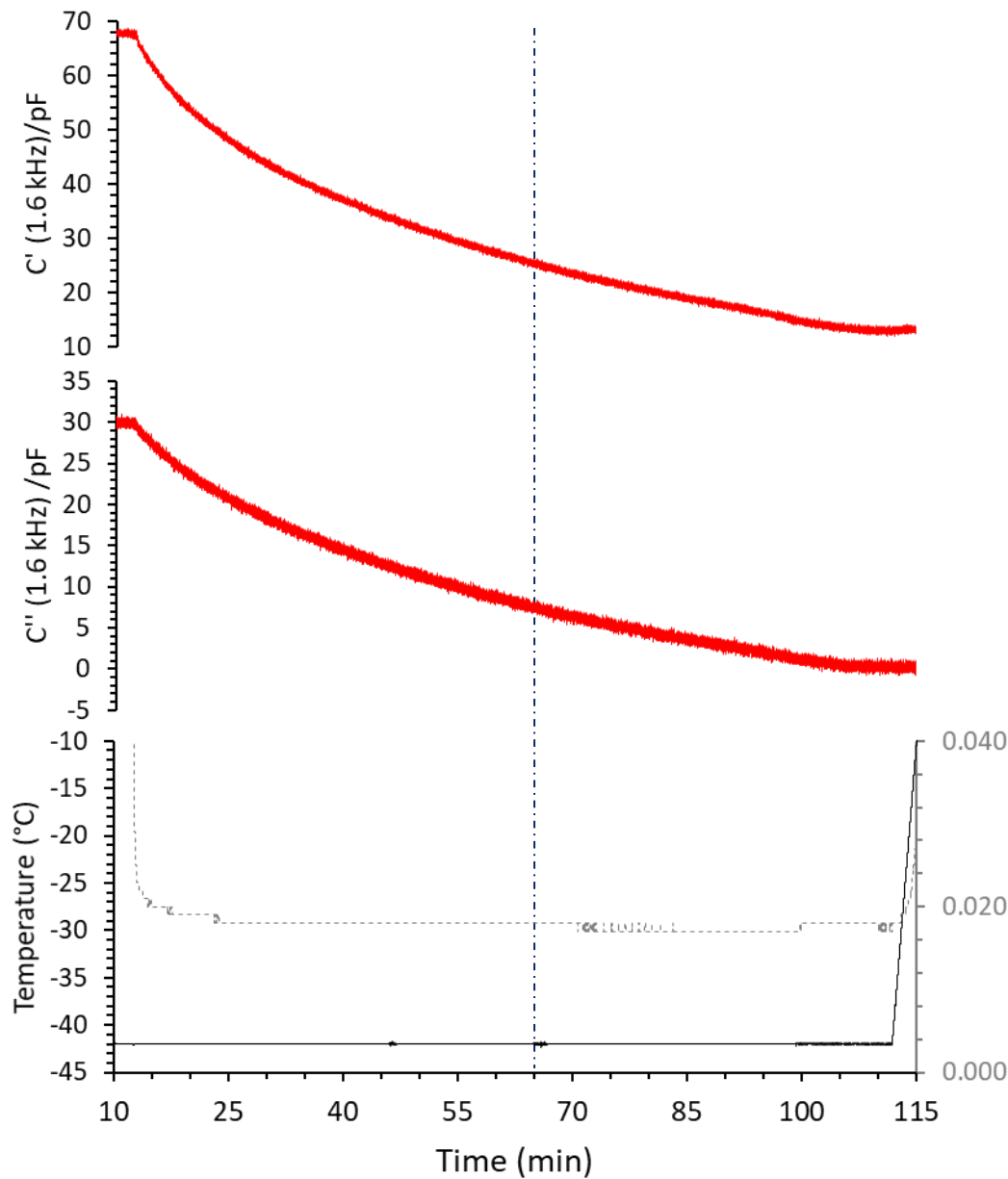


Time: 50 min

NB: Distance is an arbitrary unit



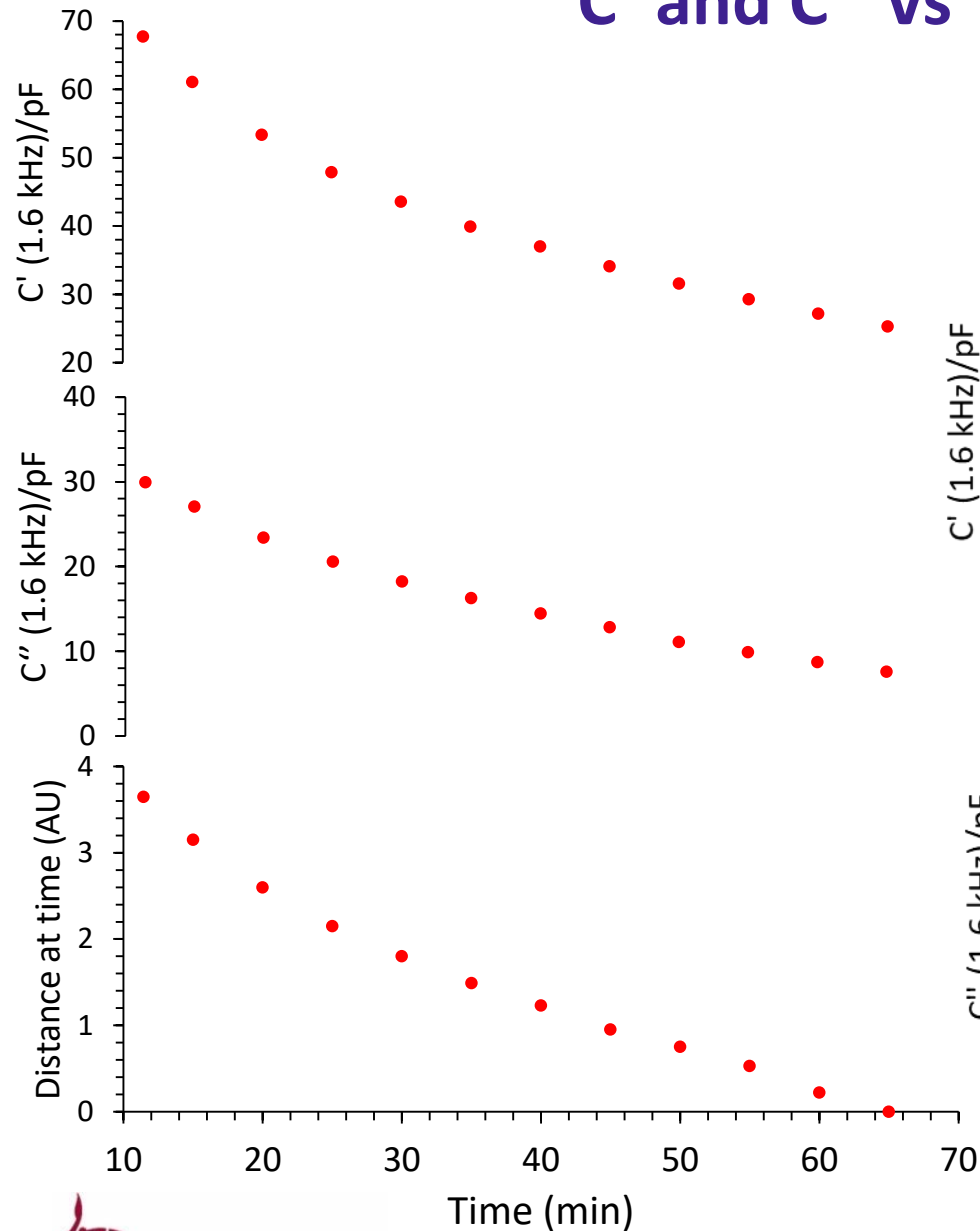
Drying time: 52 min 18 sec



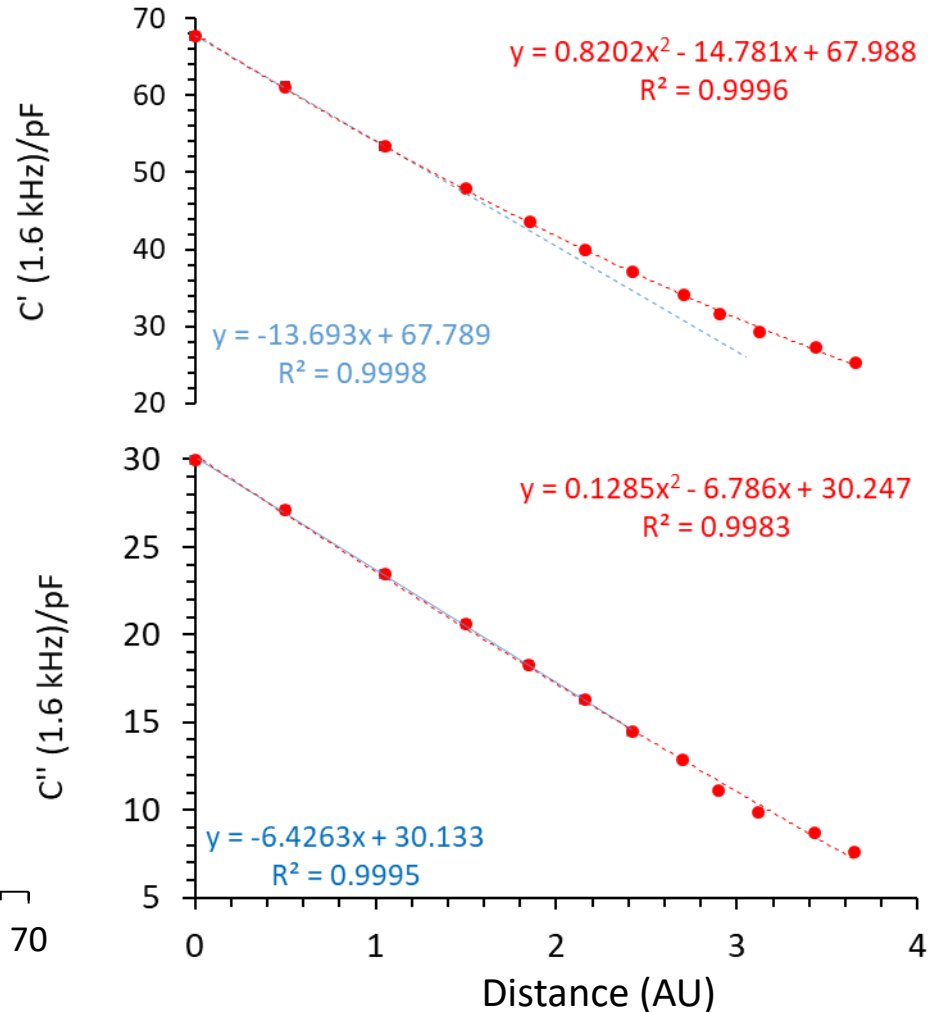
Time: 65 min

NB: Distance is an arbitrary unit

# C' and C'' vs Distance

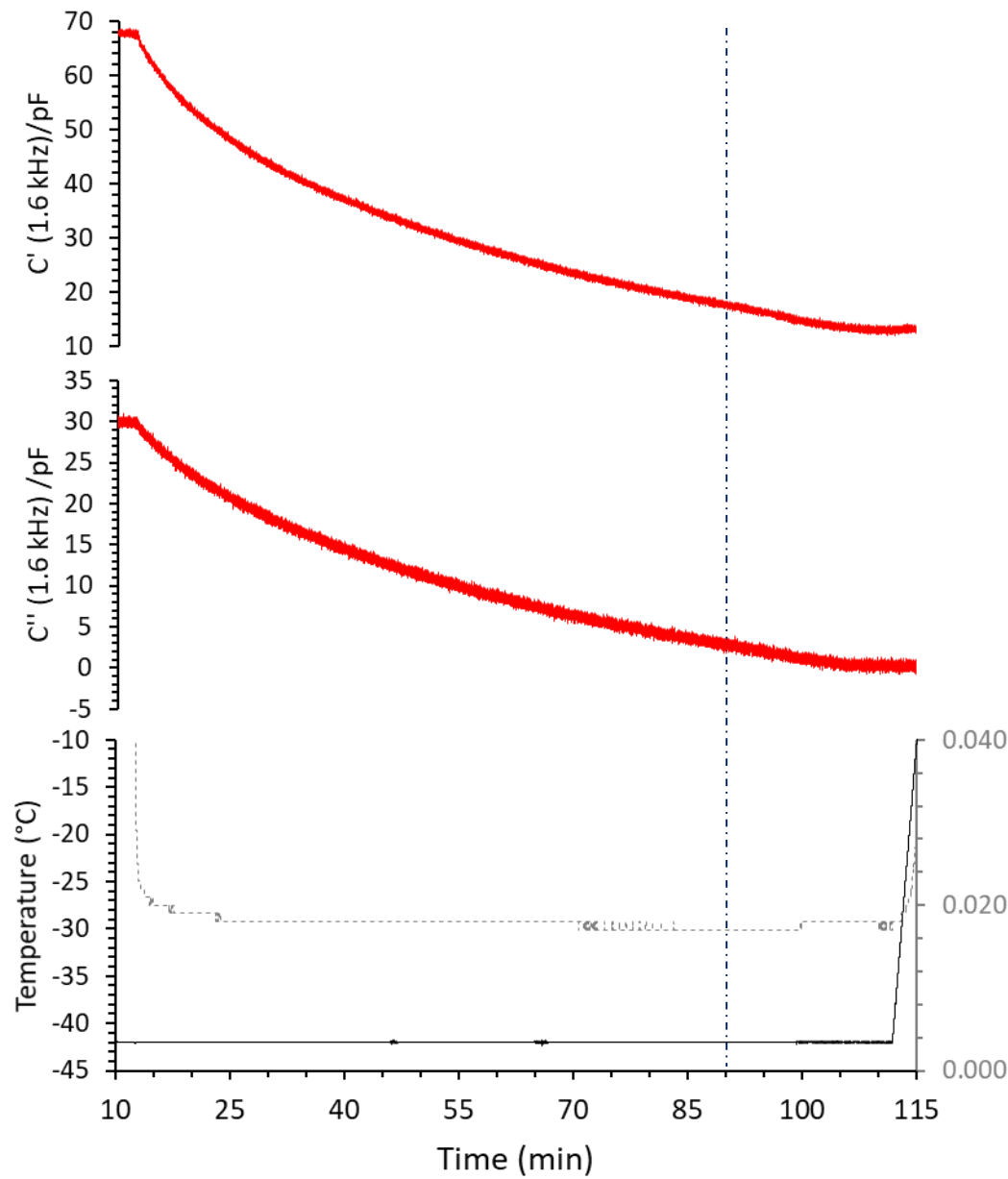


**C''** is more **linear** with the dry layer length and therefore more suited to drying rate calibration



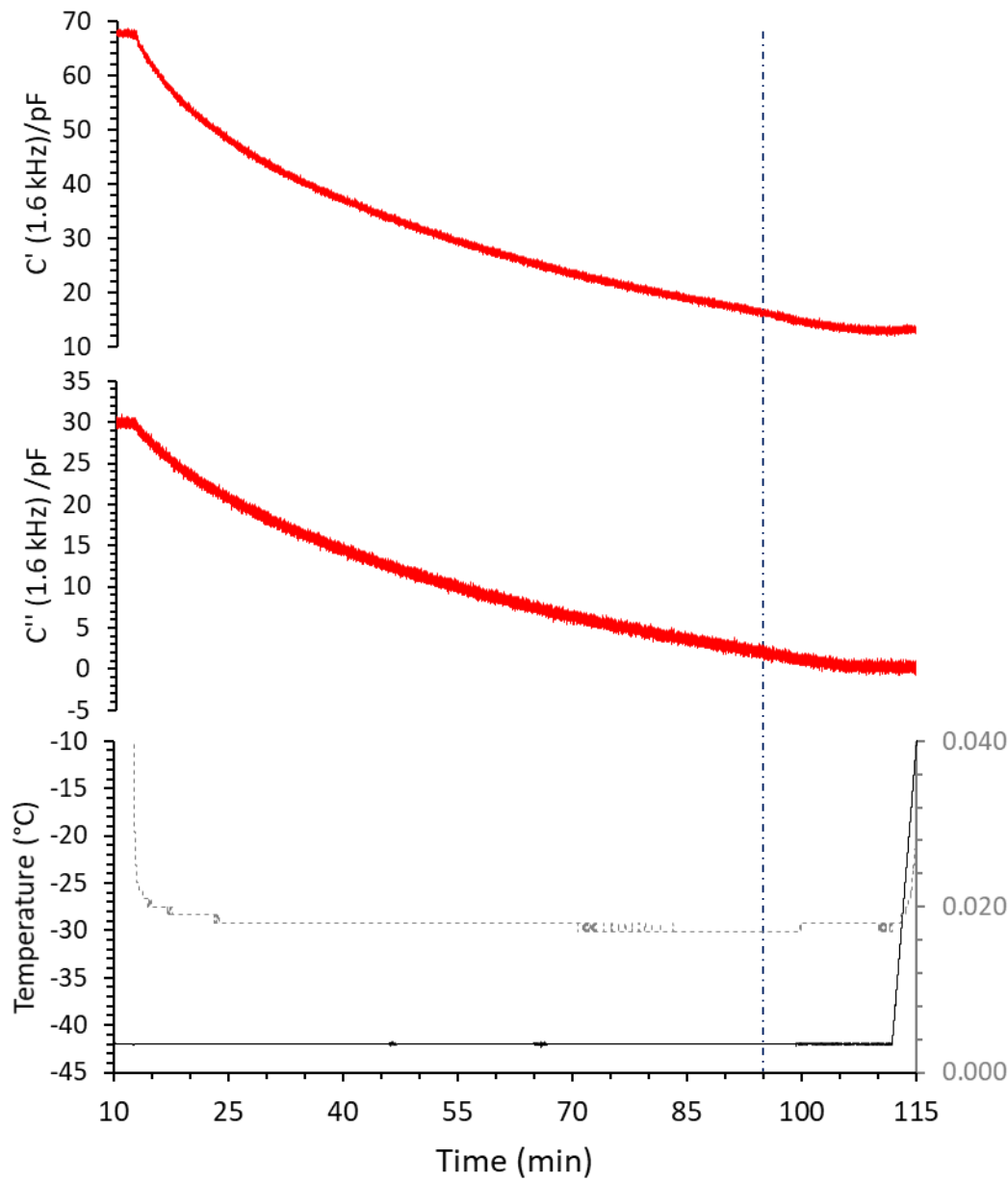
End point

Drying time: 77 min 18 sec



Time: 90 min

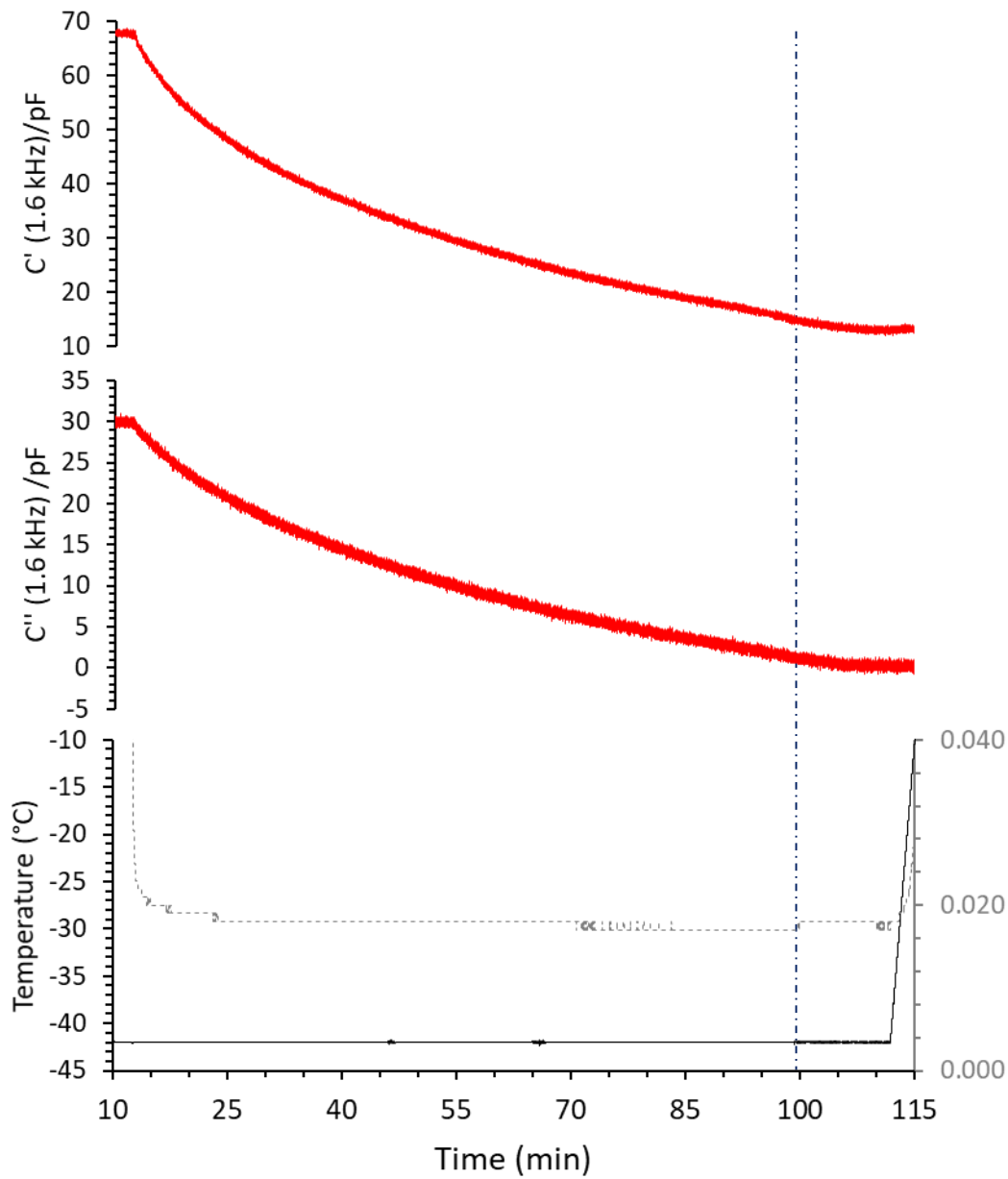
Drying time: 82 min 18 sec



Time: 95 min

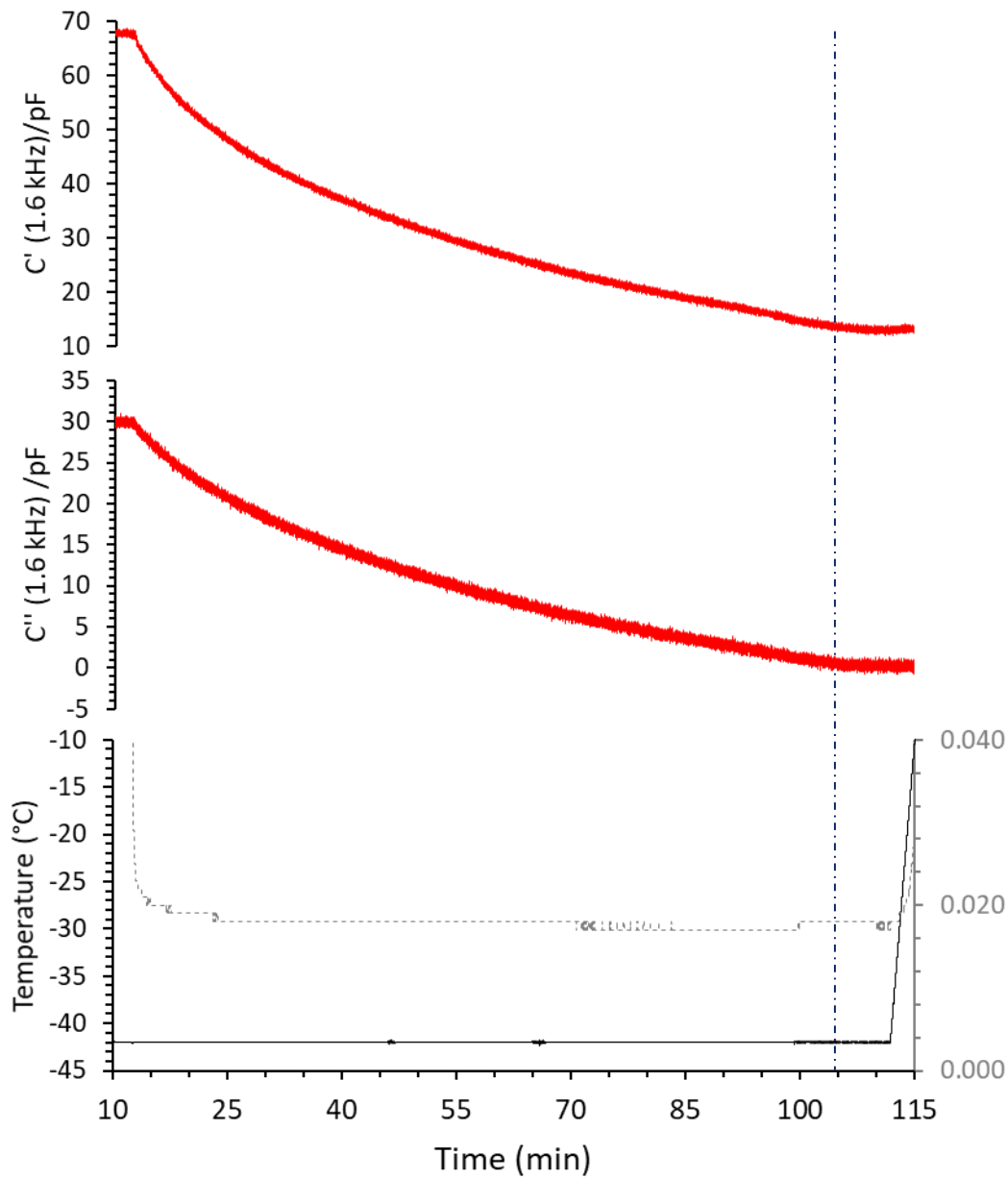


Drying time: 87 min 18 sec



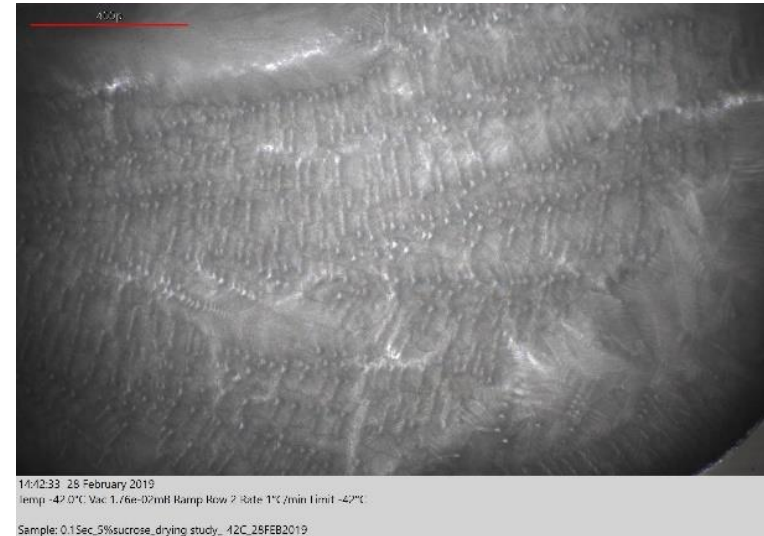
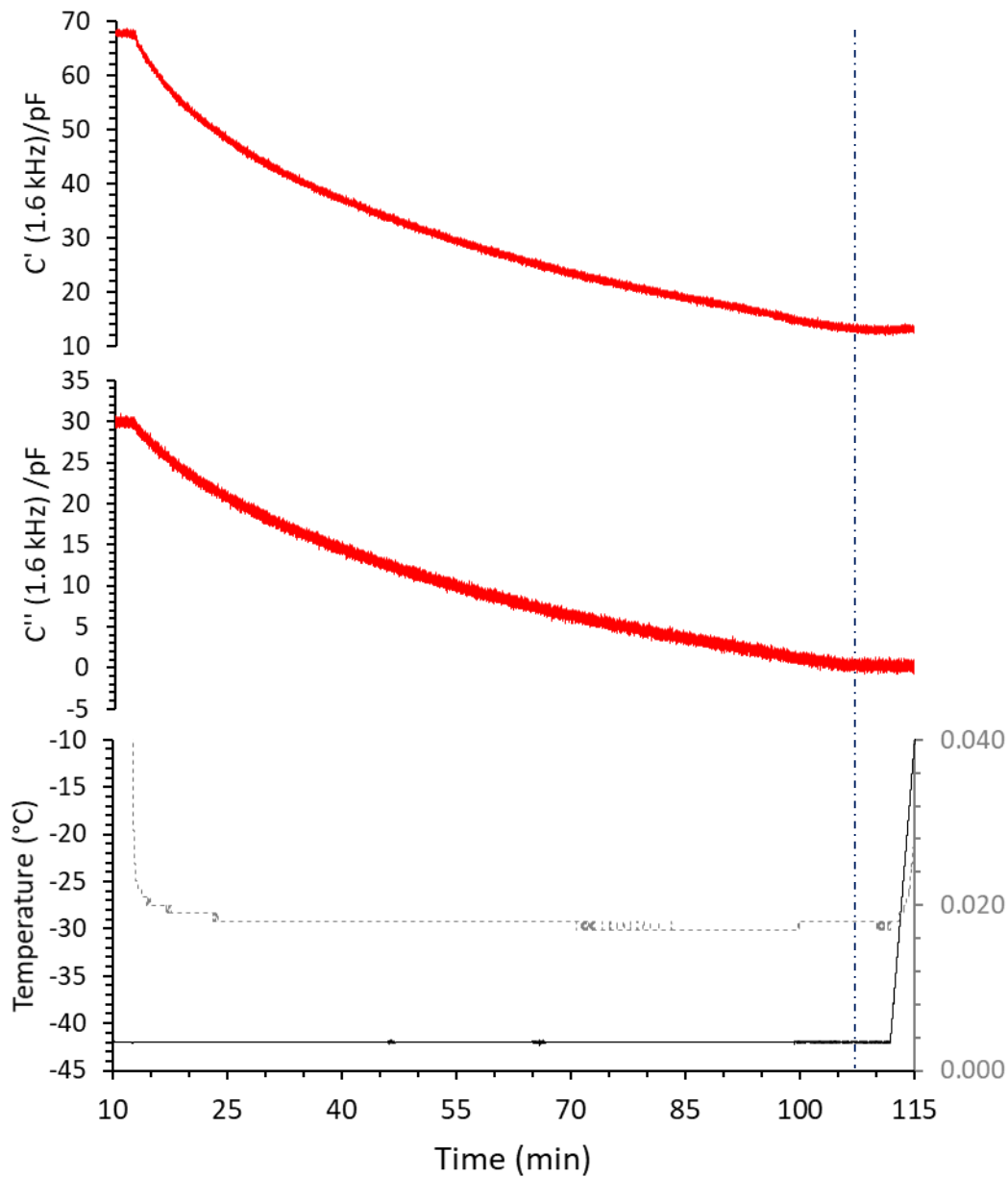
Time: 100 min

Drying time: 92 min 18 sec



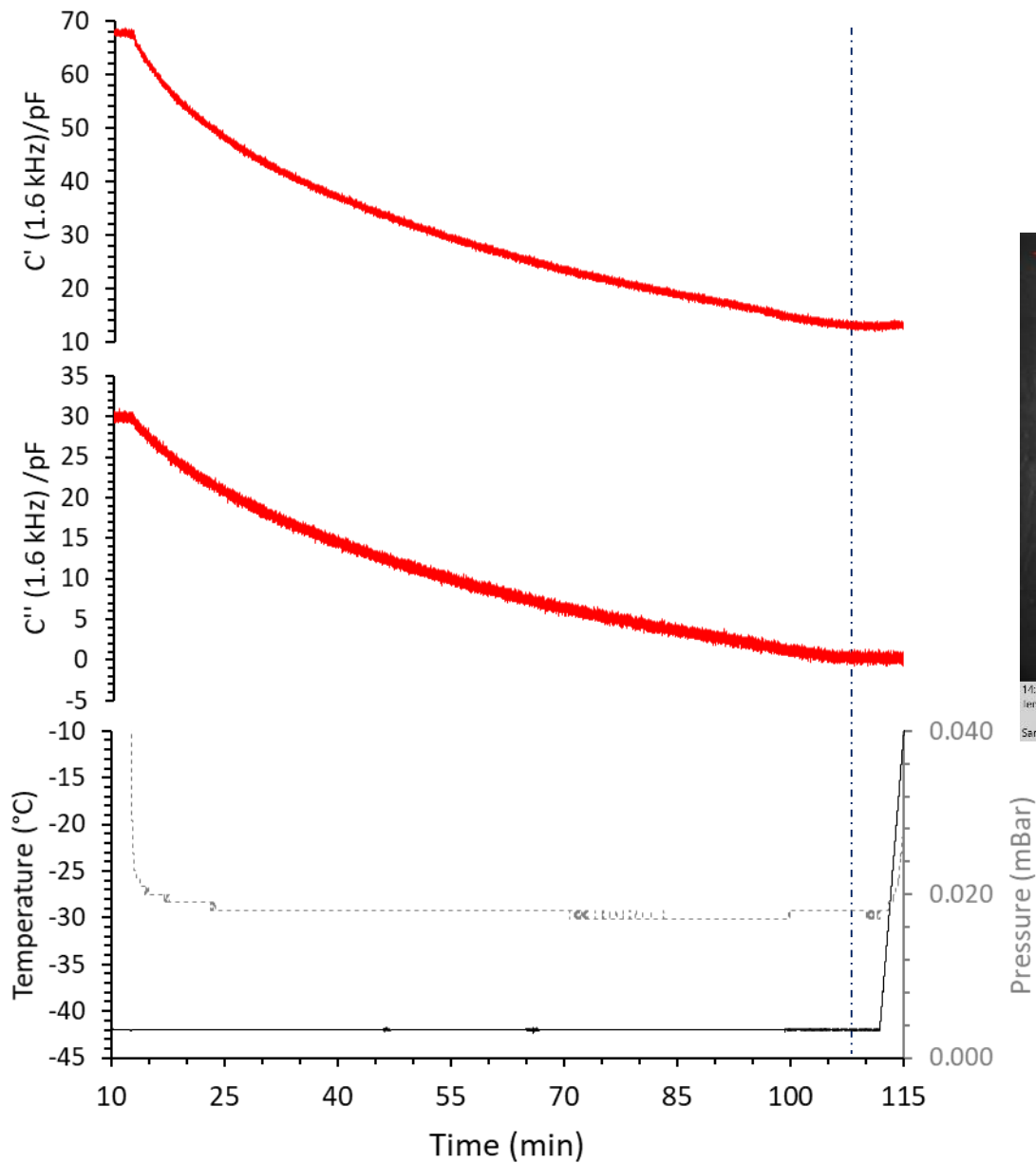
Time: 105 min

Drying time: 94 min 48 sec, last remaining ice



Time: 107.5 min

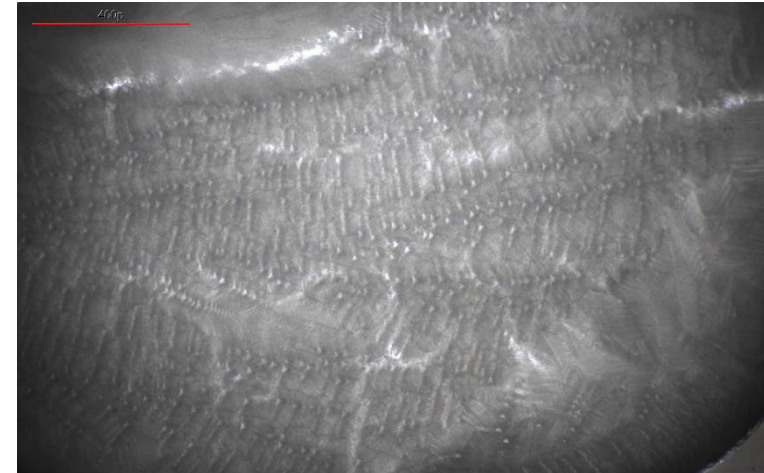
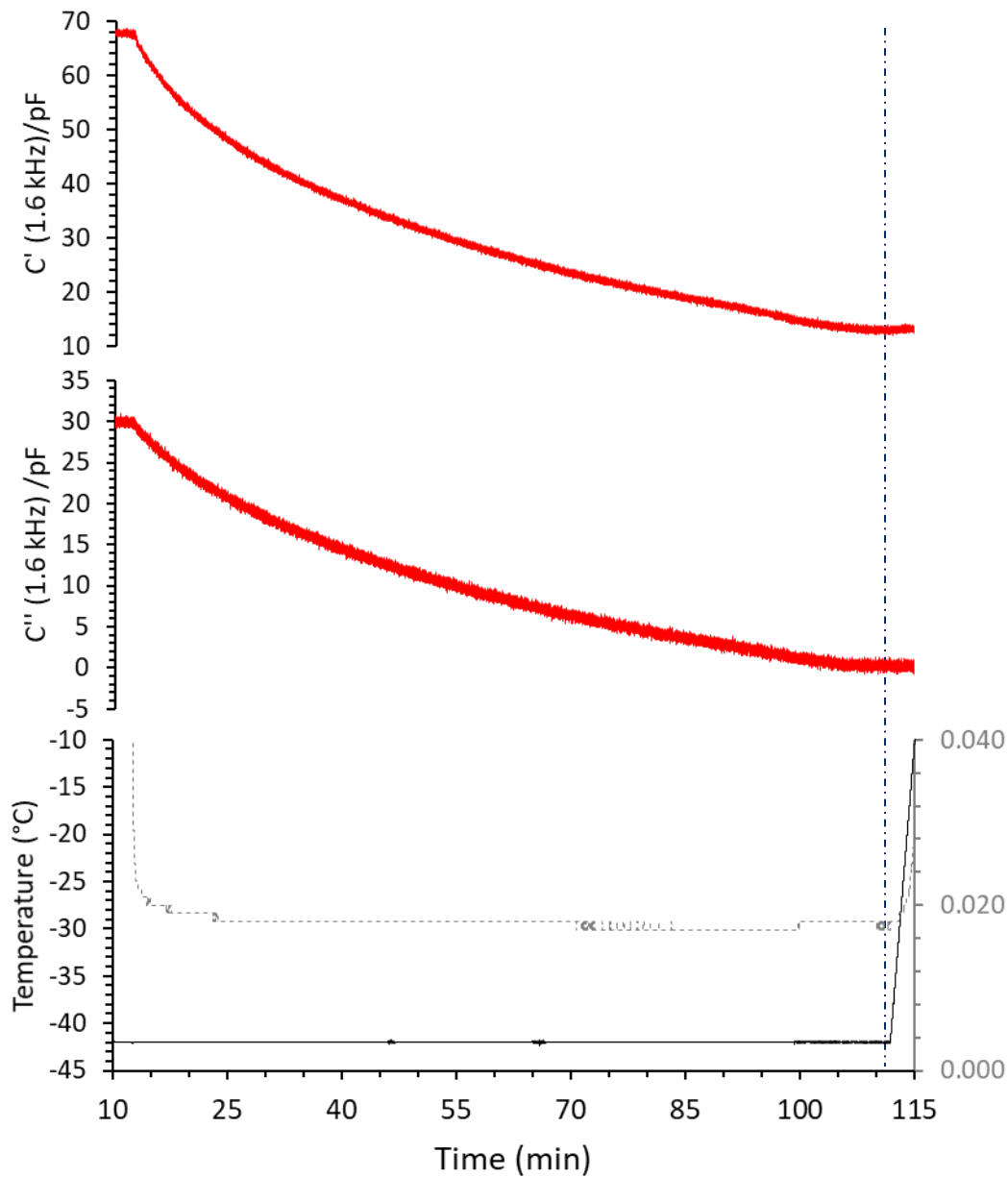
Drying time: 95 min 18 sec,  
visually last ice gone



Time: 108 min

Drying time: 99 min 01 sec,

Drying End-point



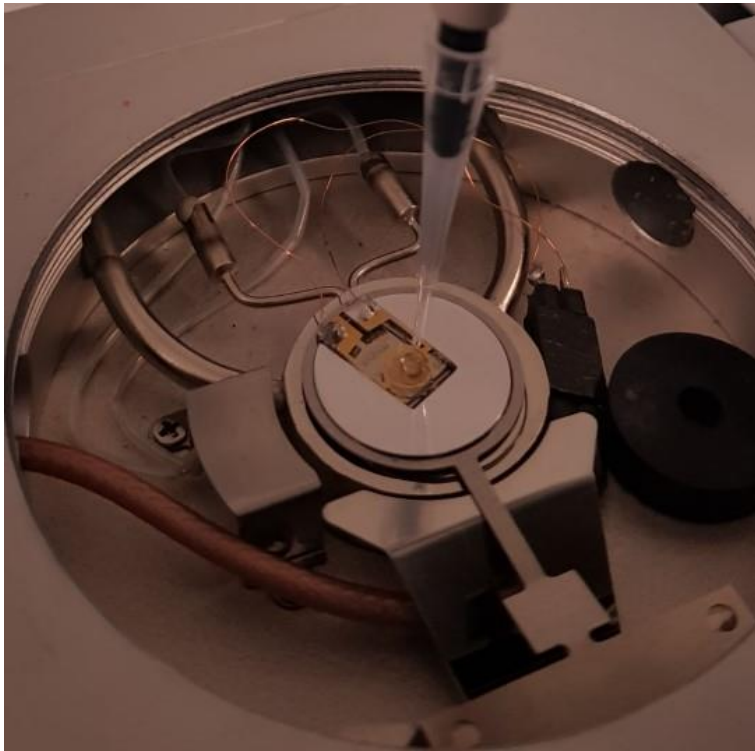
14:46:46 28 February 2019  
Temp -42.0°C Vac 1.75e-02mB Ramp Row 3 Rate 10°C/min Limit 20°C  
Sample: 0.1Sec\_5%sucrose\_drying study\_-42C\_28FEB2019

Time: 111 min 43 sec

## Study 2: Collapse

# 5% w/v sucrose analysed using Z-FDM

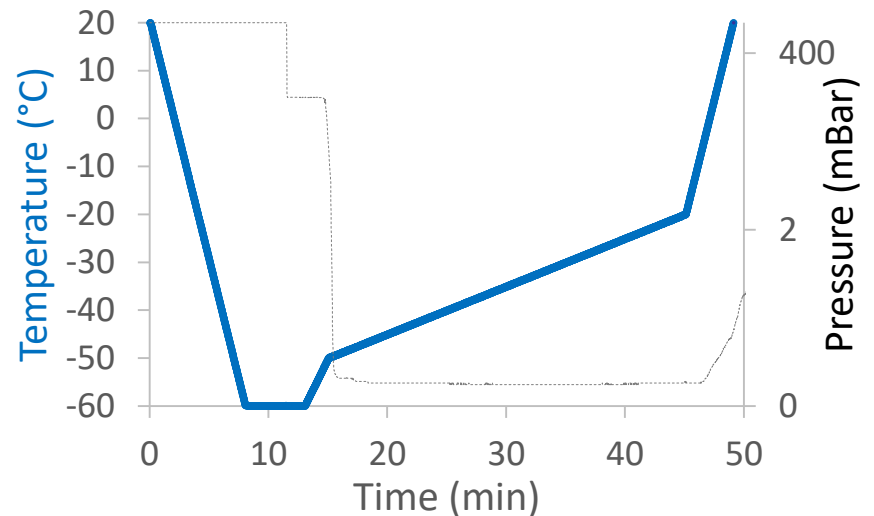
- ED-IDE1-Au with 0.5  $\mu\text{L}$  of 5% w/v sucrose solution



- ISX-3 impedance analyser measurement setup

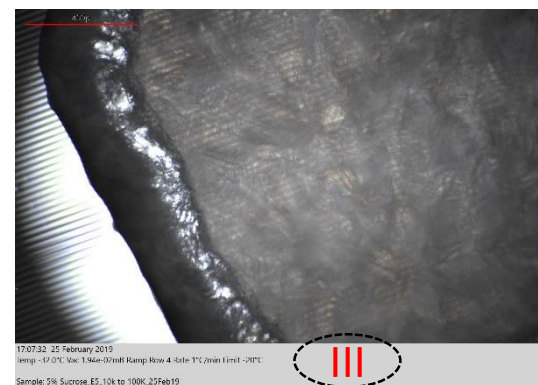
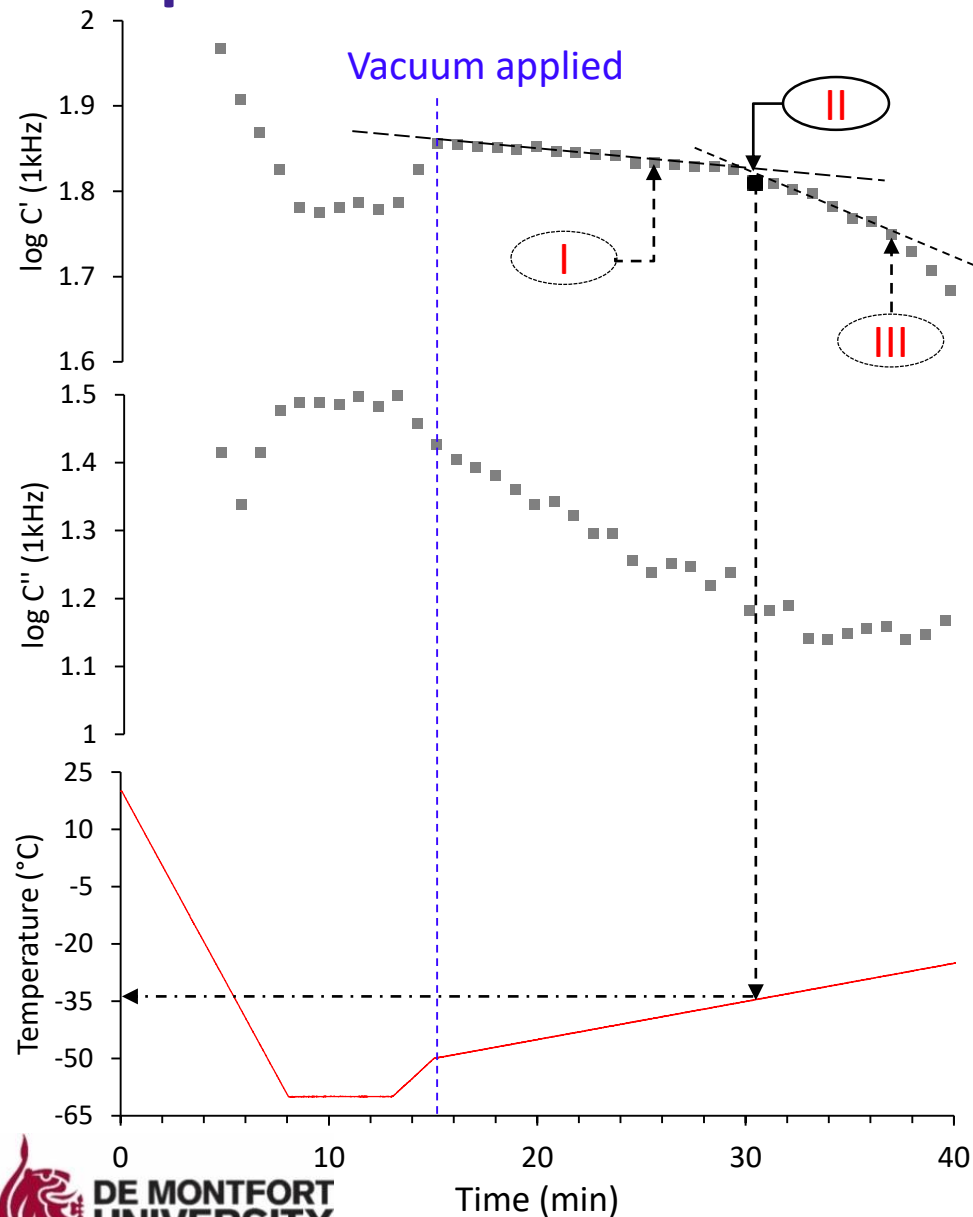
Range		1M	Amplitude [mV]		400	
Mean Count		1	Repeat		0	
Min f [Hz]	Max f [Hz]	Steps	Scale	Precision	P. Delay [μs]	Ph. Sync
10	100k	31	log	1.0	0.0	Disable
Measurement Time: 56.5sec			Calibration load: 22pF		File name: setup1	

- FDM process log





# Collapse Observation at 1 kHz



# *To conclude*

Parameter	$C'$	$C''$
Nucleation onset	✓	✓
Solidification end-point	✓	-
Drying rate	-	✓
Collapse temperature	✓	-

$C'$  : Real part capacitance

$C''$  : Imaginary part capacitance

# Acknowledgements

- De Montfort University
  - Professor Geoff Smith
  - Dr Neill Horley
  - Dr Glen McCann
  - Yowwares Jeeraruangrattana
- Biopharma Process Systems
  - Dr Kevin Ward
- University College London
  - Professor Paul Dalby



Thank you for your attention



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