Lyophilization Process Development for Biopharmaceuticals

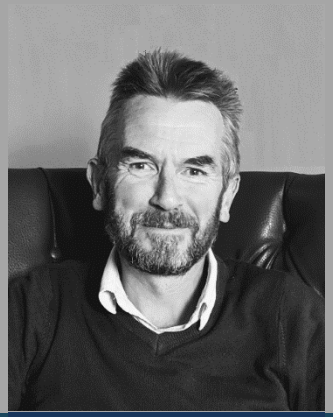
Applications for eis PAT

Electrical Impedance Spectroscopy

Process Analytical Technology

Prof. Geoff Smith

DMU LyoGroup



Overview

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Lyophilization

Benefits : Applications : Challenges

Design space solutions ……

Electrical Impedance Spectroscopy Process Analytical Technology

Z-FDM
Impedance-enabled freeze-drying microscopy

TVIS
Through-vial impedance spectroscopy

Formulation development

Process development

Benefits of Lyophilization

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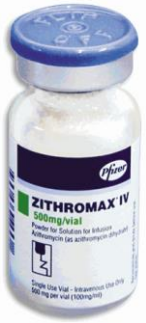
"40% of biologically based products have to be freeze dried"
http://www.genengnews.com/gen-articles/lyophilization-growing-with-biotechnology/1083

"80% of the available products lyophilized in vial"
https://www.pharmpro.com/article/2017/03/lyophilization-basics

Lyophilization commonly used for
- Small Molecules Drugs (e.g. penicillin)
- Large Molecule Drugs (e.g. proteins, DNA)
- Microorganisms (e.g. bacteria, virusus)
- Blood products

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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Applications (in the news) …… Remdesivir

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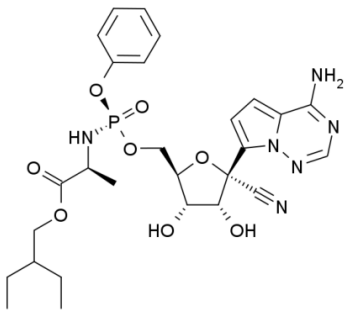
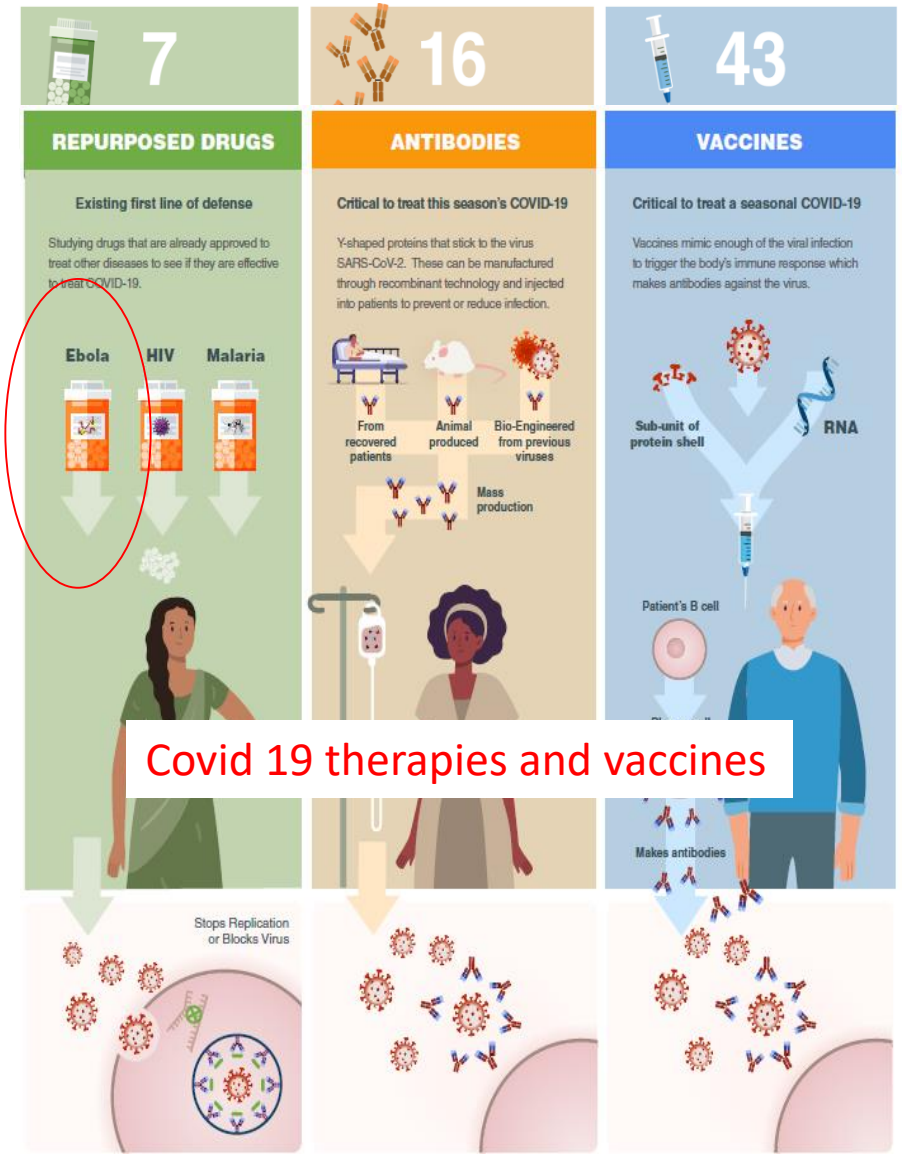


- Developed for Ebola (2008)
- Re-purposed experimental drug treatment for Covid-19
- co-formulated with cyclodextrin for solubility & freeze-dried



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Challenges of Lyophilization

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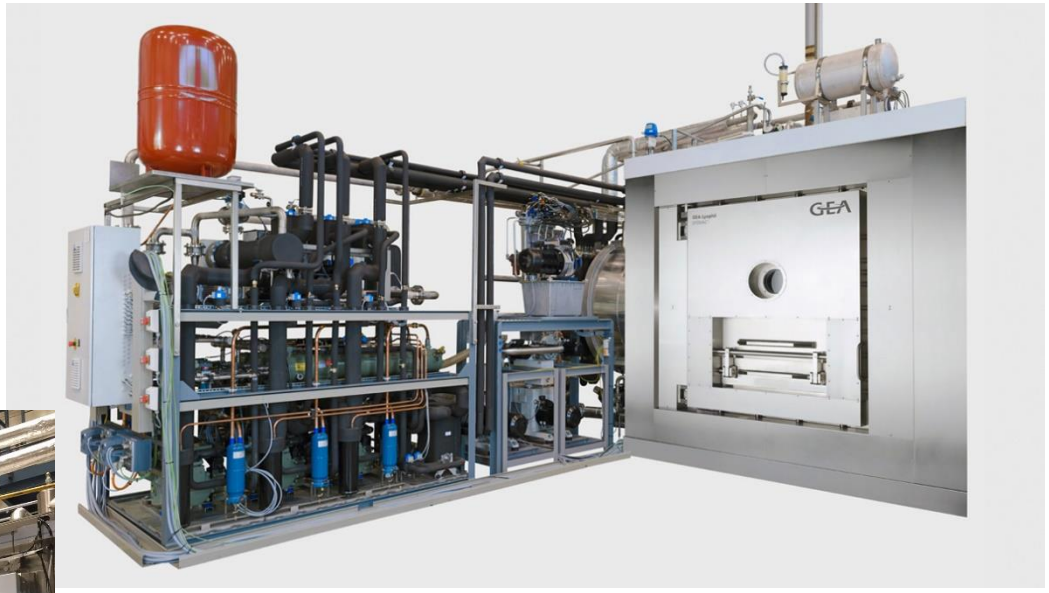
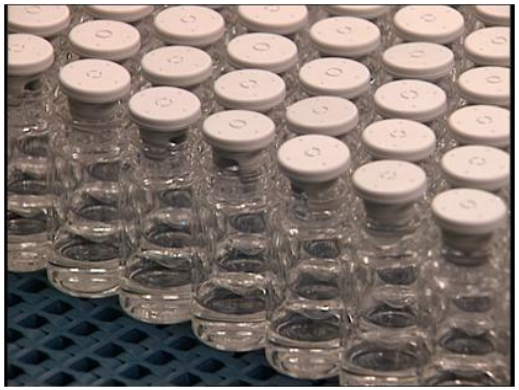
1. Complex 3 stage process
2. Cost: energy & GMP
   Long process (up to 5 days)
3. Difficult to scale-up
4. Variation within batch





Design space

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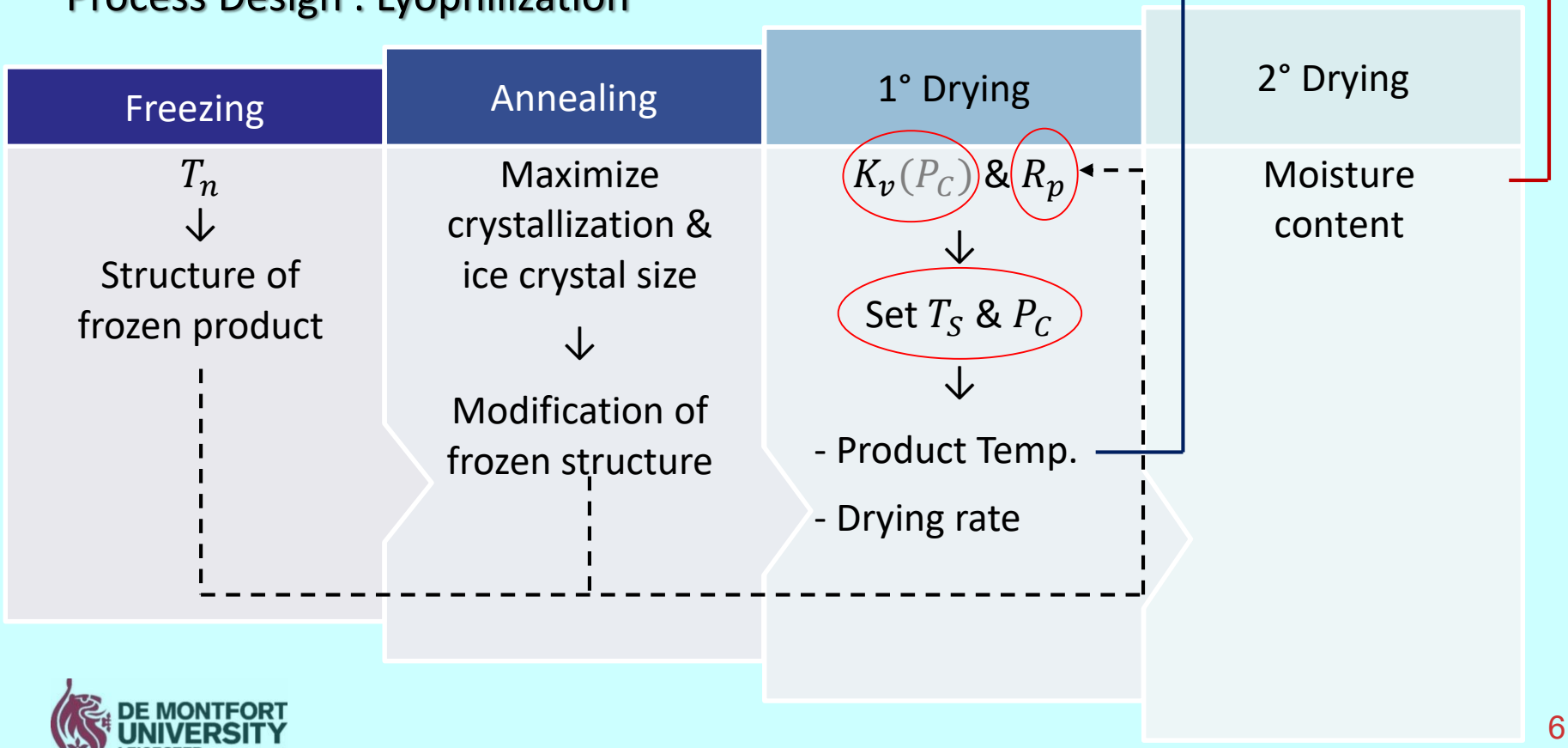
Product Design : Formulation

- Stability (chemical & physical) and packaging compatibility
- Critical product temperature T_c (~T_g' and/or T_{eu})

Process Design : Lyophilization



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Louis Rey 1960s

STUDY OF THE FREEZING AND DRYING OF TISSUES AT VERY LOW TEMPERATURES

L. R. Rey

Laboratoire de Zoologie-Physiologie, Ecole Normale Supérieure, Paris

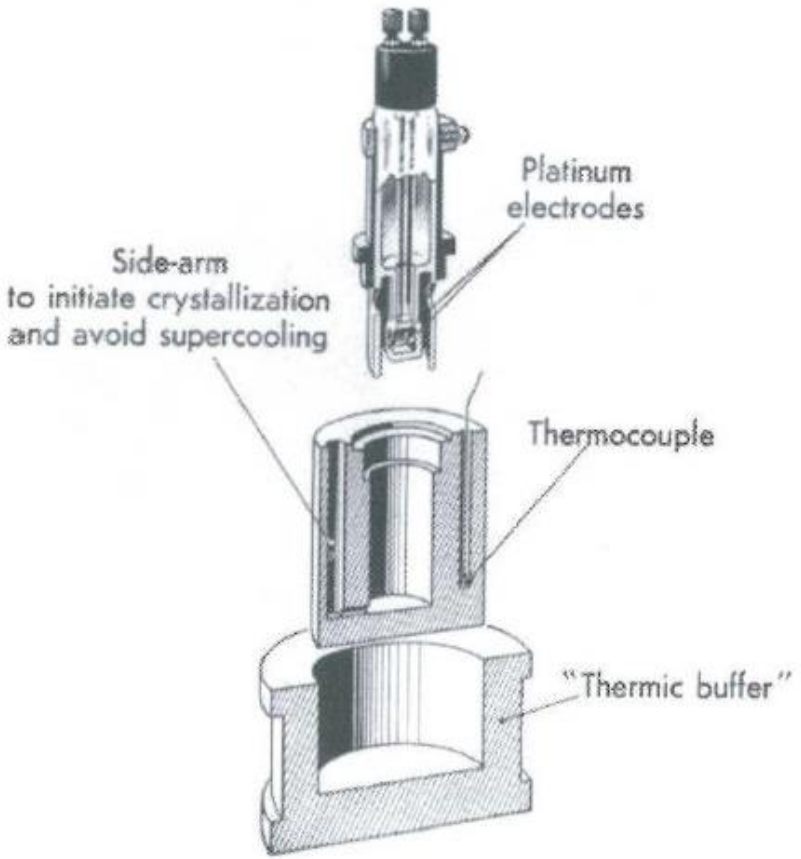
The outstanding interest of the freeze-drying technique is that it provides a possibility for long-term preservation of highly alterable structures. The method has had a great number of applications in the field of histology and histochemistry since the pioneer work of Altmann (1890) and Gersh (1932).

Many authors have thought, too, that it would be possible to try to preserve life in frozen and dried animal tissues. It has been shown long ago, by Becquerel (1936) that, as far as the cells of certain plants and lower animals are concerned, highly dehydrated material could be kept over very long periods of time and would resist extreme conditions of temperature.

Unfortunately, animal cells are not very resistant and they are not able to loose a great amount of water. Luyet and Hartung (1941), Rostand (1946), Parkes (1951) and Polge, Smith and Parkes (1949), have shown that different chemical substances and especially glycerol offer very good protection against cold injury. We have done similar experiments in our laboratory, and we have studied the protective action of glycerol by the use of tissue-culture and organ-culture techniques (Rey, 1957, b and d).

In a second group of researches, our intention was to find out the conditions of lyophilization which would be able to give the best preservation of the fine cytological structures of the tissue-cells, and which, if possible, would preserve life.

At first, and according to what we said in 1957 at the Royal Society, the freezing must be done in a very precise way, because there is no use drying with great care a tissue which has undergone denaturation in the course of freezing. It is likely that a glycerol preimpregnation would be necessary. However, we have had much evidence in our work (1957 d) and we agree perfectly well with Meryman (1957) that the most harmful period of the action of low temperatures on living tissues is during thawing. One could think then, that, if we avoid thawing by previous drying, it would be possible not to use glycerol impregnation, provided that the freezing period is short. This is a theoretical point of view, compromise solutions are not excluded and we can reasonably



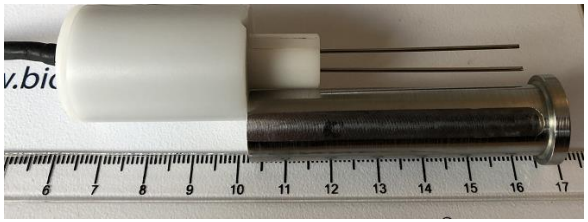
Rey (1960) Study of freezing and drying of tissues at very low temperatures. In Parkes and Audrey eds. Recent research in freezing and drying, Blackwell, Oxford.

Lyotherm

Biopharma Process Systems

Impedance analysis (Zsinϕ) at a single frequency (1 kHz) with differential thermal analysis (DTA)

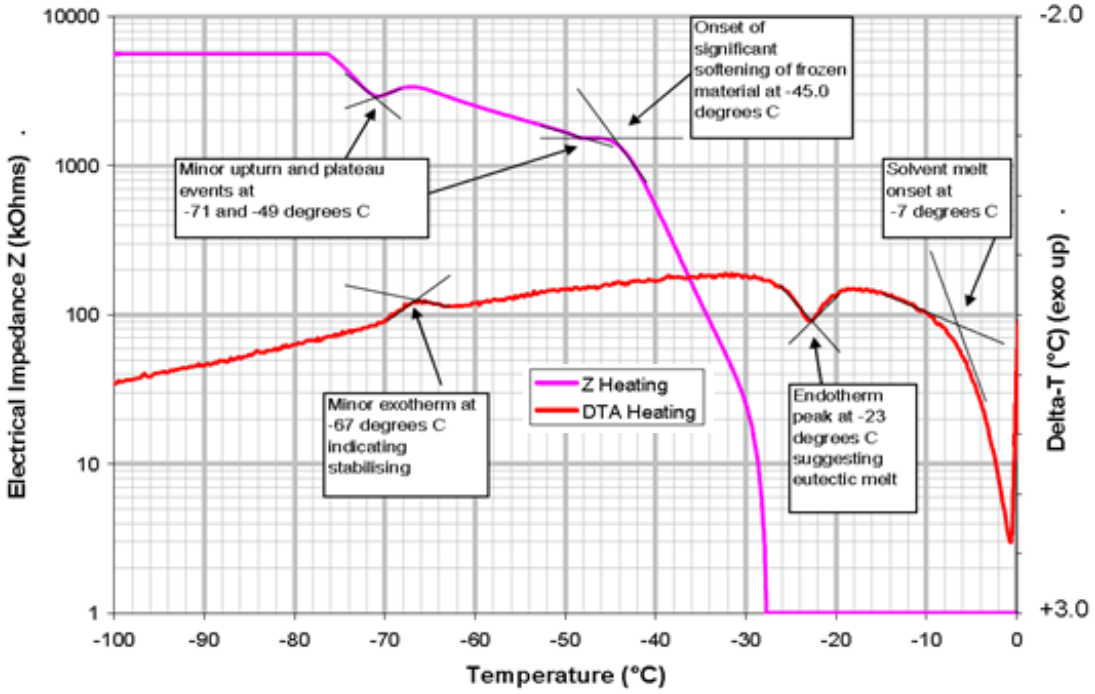
- Pin electrode (pair)



- Integrated within cryostat

Designed to measure temperatures relevant to freeze-dried formulations

- glass transition (T_G')
- ice melting (T_M) and eutectic (T_{EU})



Ward & Matejtschuk , 2010 *in Freeze Drying/ Lyophilization of Pharmaceutical & Biological Products* 3rd ed. Rey,L & May JC eds, Informa Press, New York

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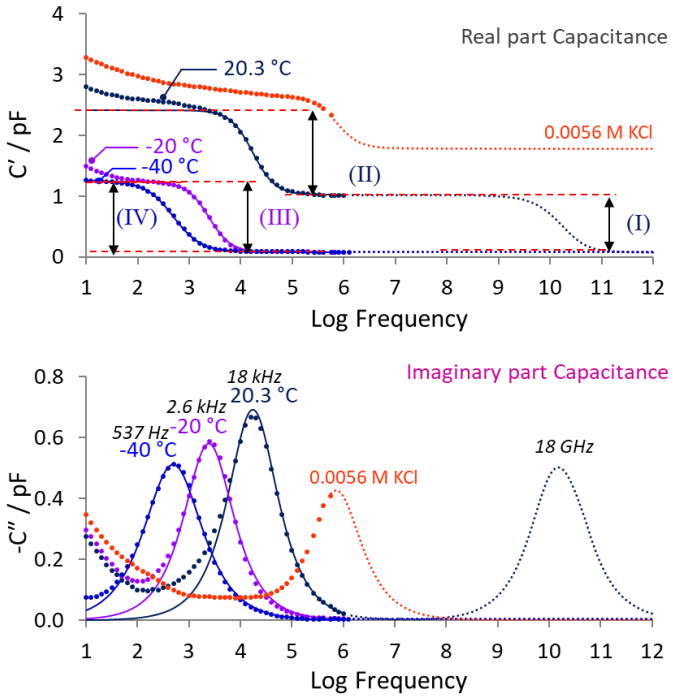
Design space solutions ……

Electrical Impedance Spectroscopy Process Analytical Technology

Test object is measured at a range of discrete frequencies



Design space solutions ……

Electrical Impedance Spectroscopy Process Analytical Technology

Test object is measured at a range of discrete frequencies

Novocontrol BDS
Broad Band Dielectric Spectroscopy (sub Hertz to 10 MHz)

Formulation development

IDE
Inter-digitated electrodes
Micro-sample measurement

Process development

TVIS
Through-vial impedance spectroscopy
for in vial measurement

Spectroscopy Systems (sub Hz to 10 MHz)

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Spectroscopy Systems (sub Hz to 10 MHz)

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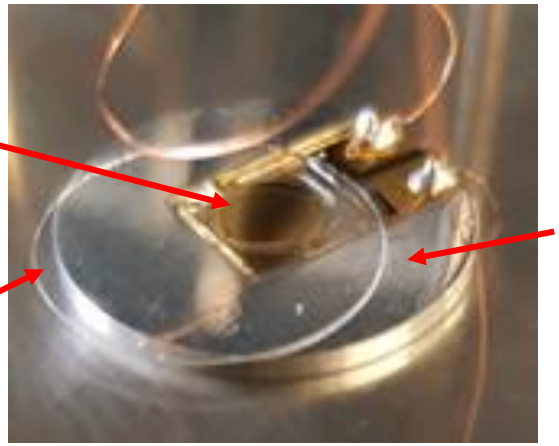
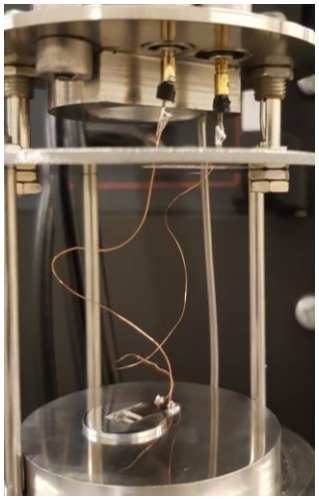
Spectroscopy Systems (sub Hz to 10 MHz)

OPTION 1 Inter-digitated microelectrode array
IDE: 2 µL volume



Placed on a cradle

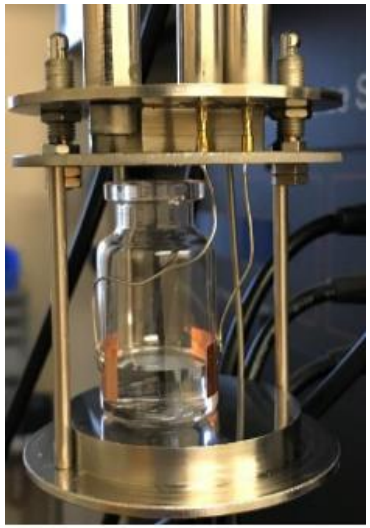


Spectroscopy Systems (sub Hz to 10 MHz)

OPTION 2 TVIS vial 2-3 ml volume

Copper foil electrodes

Placed on the cryostat “cradle”



The story so far ……..

- Note that the technologies described so far are only capable of measurements during freeze-thawing cycles
- A bit like a DSC style measurement

Design space solutions ……

Electrical Impedance Spectroscopy Process Analytical Technology

Bespoke instrumentation
Integrated within freeze-drying platforms

Process development

TVIS
Through-vial impedance spectroscopy

Formulation development

Z-FDM
Impedance-enabled freeze-drying microscopy

Innovate UK
Government Support for industry

bps
biopharma process systems

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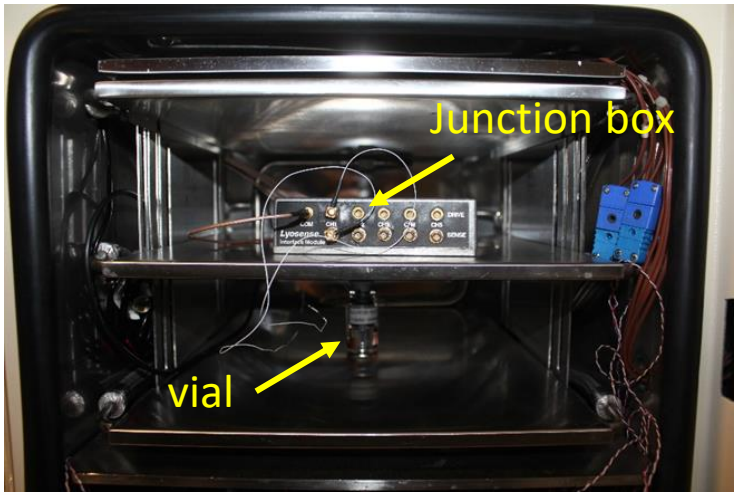
Spectroscopy Systems : TVIS

Modified glass vial

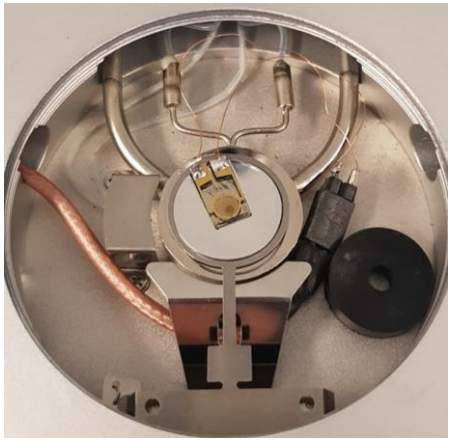
Placed within the dryer



TVIS (Through-Vial Impedance Spectroscopy)

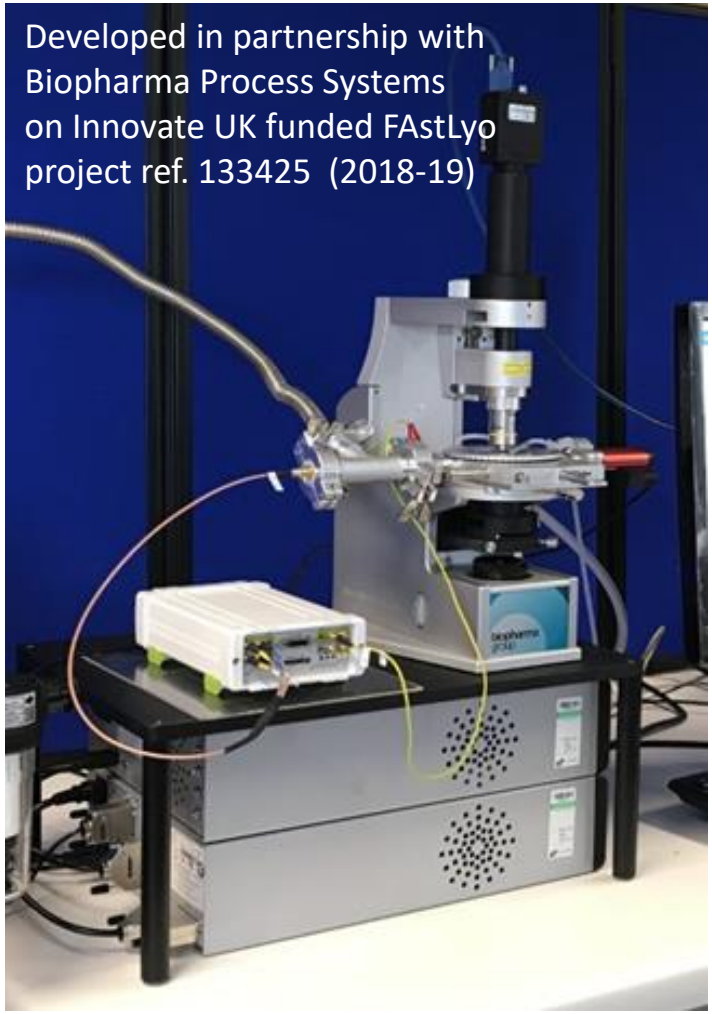
Spectroscopy Systems : Z-FDM

Integrated within the FDM stage



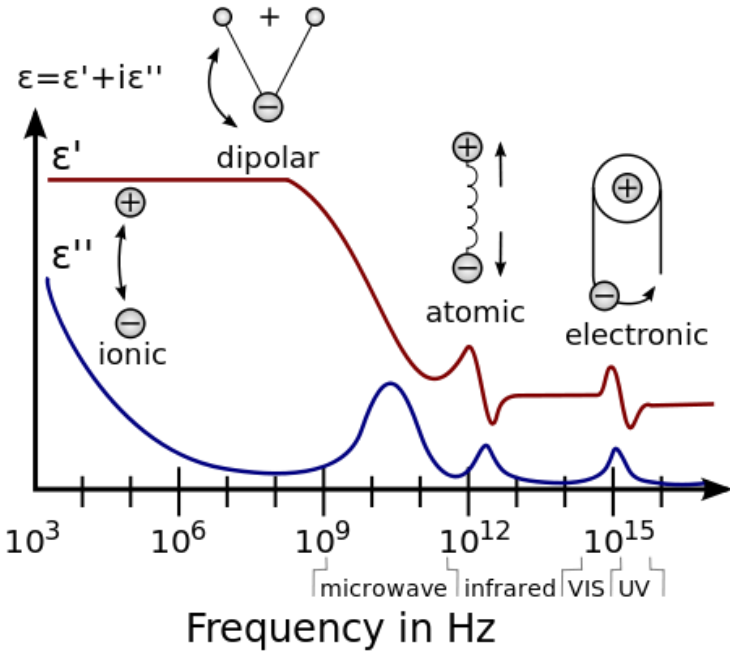
Inter-digitated electrode

Developed in partnership with Biopharma Process Systems on Innovate UK funded FAstLyo project ref. 133425 (2018-19)

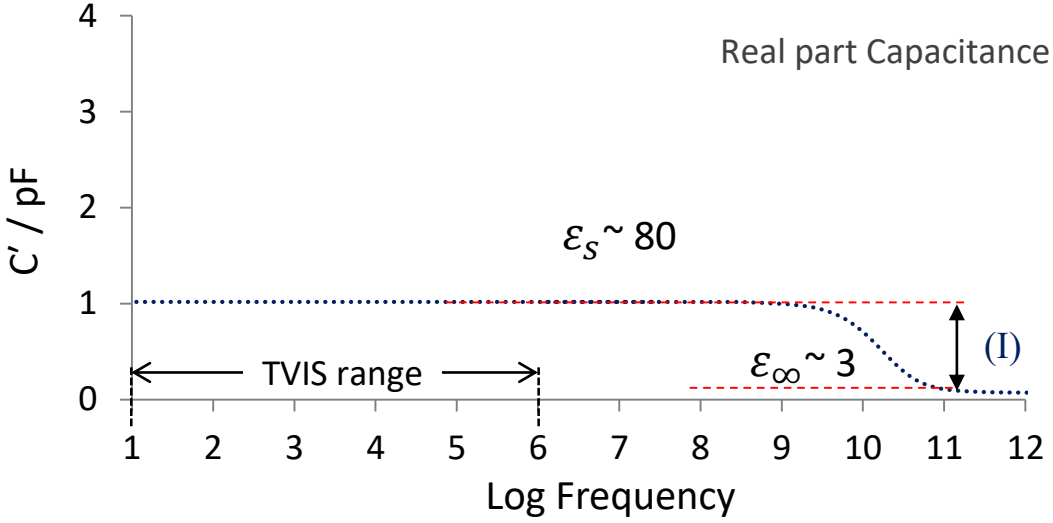


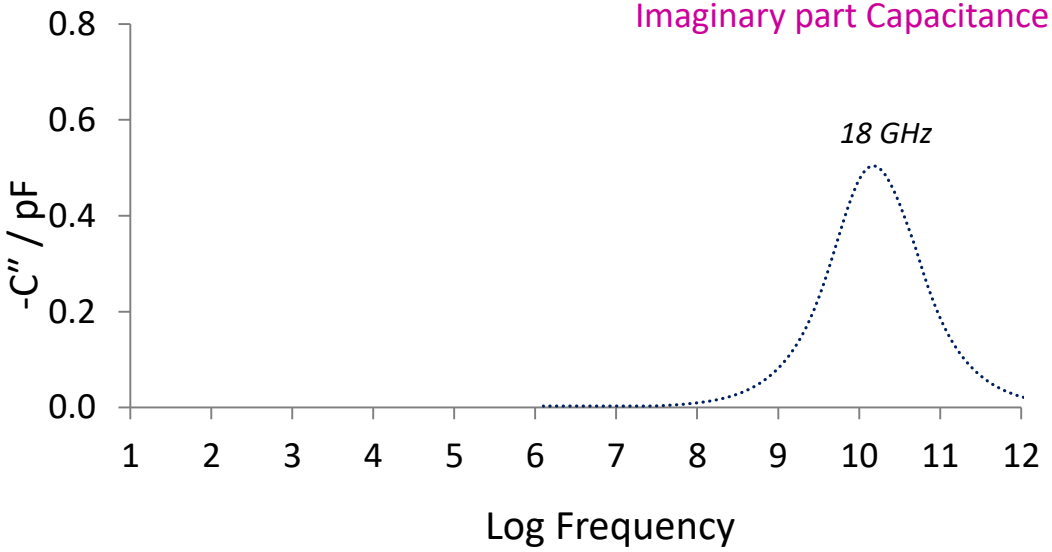
Dielectric Loss Mechanisms

I. The polarization of the water dipole in liquid water at 20 ℃, with a dielectric loss peak frequency of ~ 18 GHz



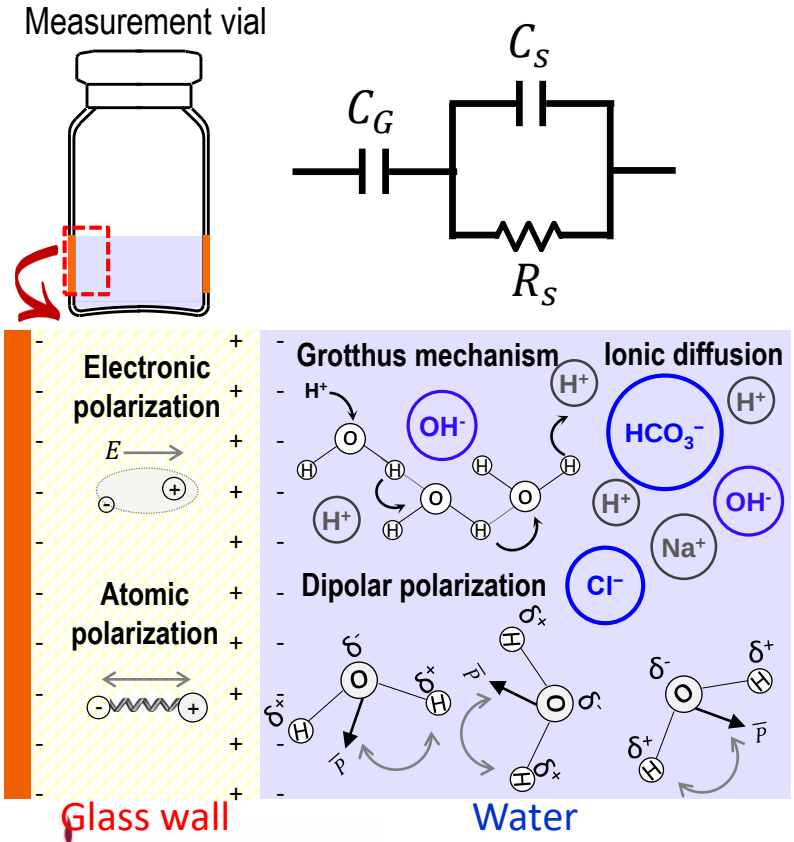
https://en.wikipedia.org/wiki/Permittivity

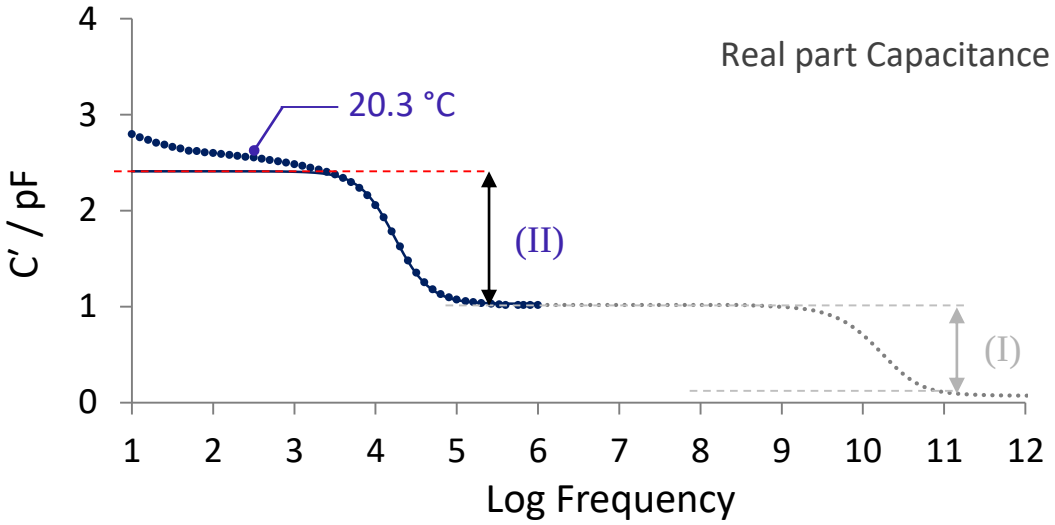


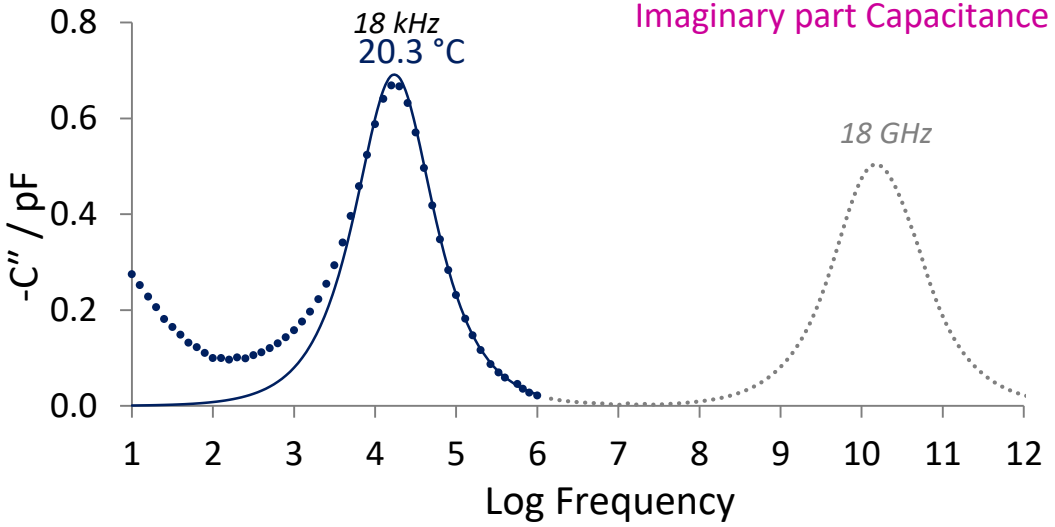


Dielectric Loss Mechanisms

II. Maxwell-Wagner (MW) polarization of the glass wall of the TVIS vial at +20 ℃, with a dielectric loss peak frequency of 17.8 kHz







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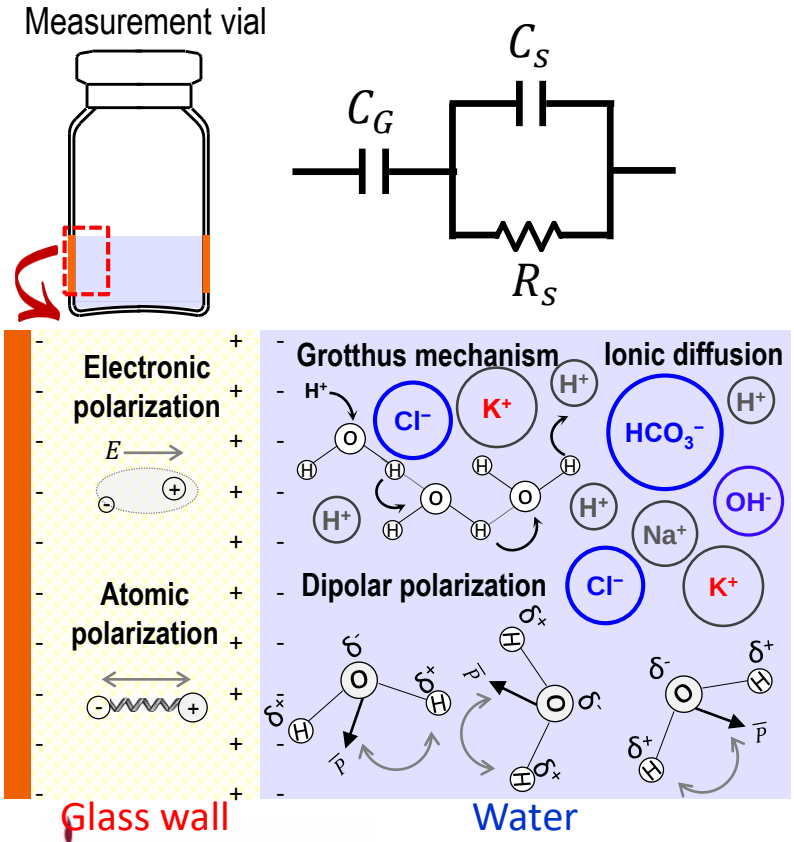
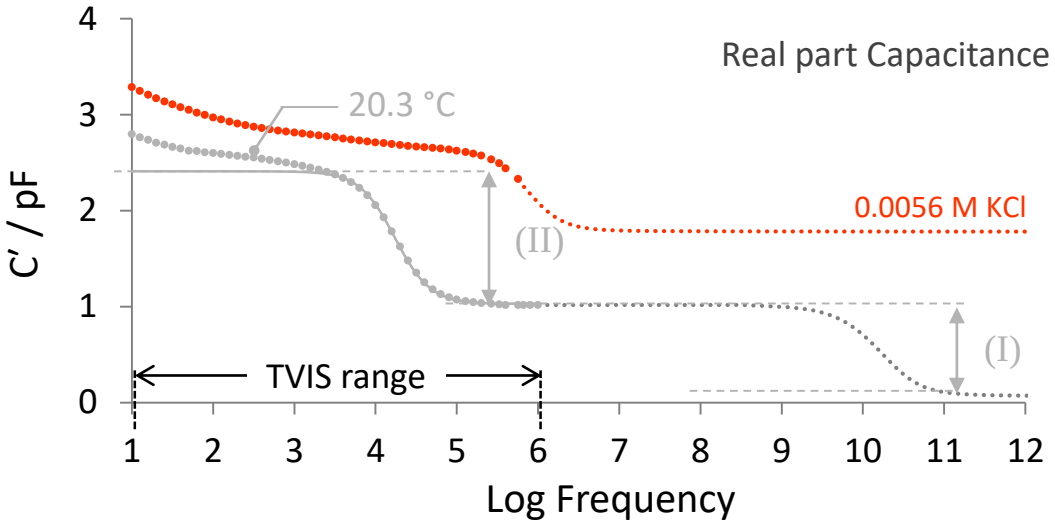
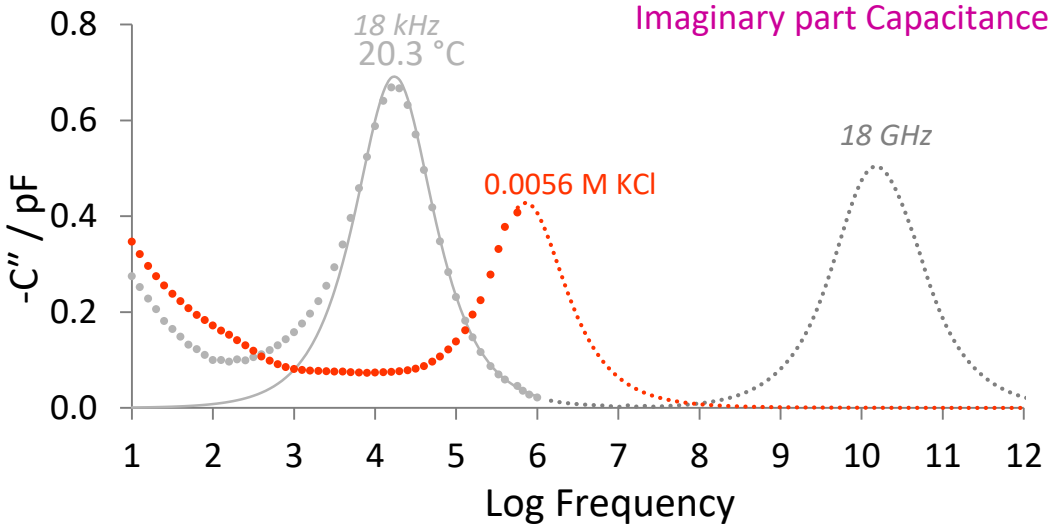
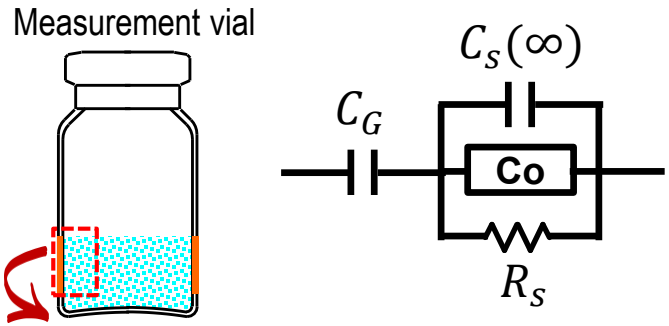


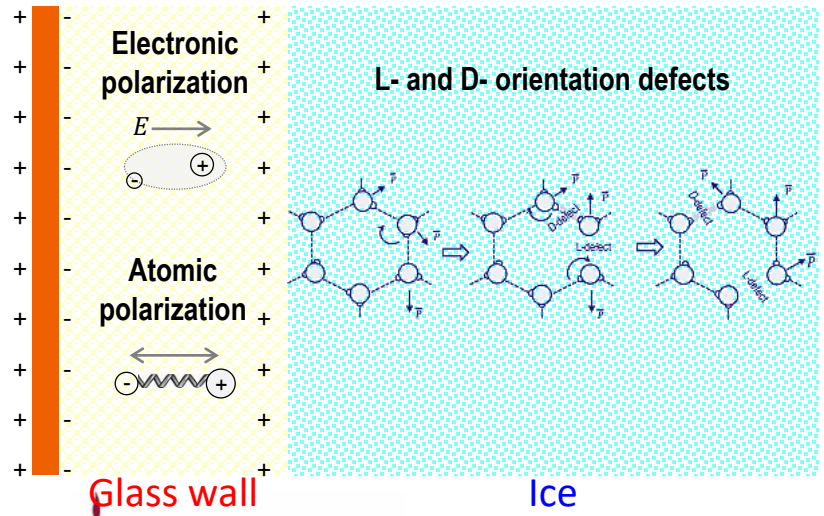


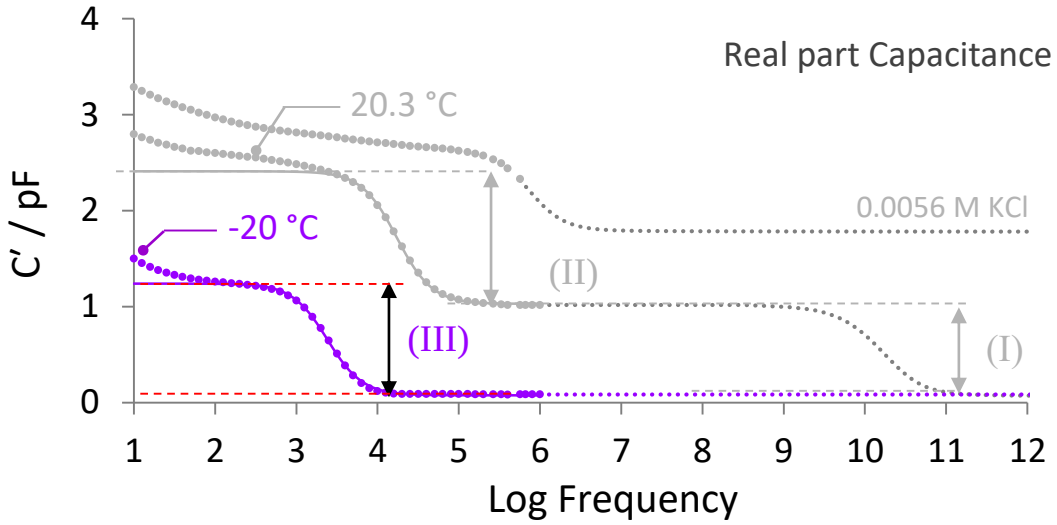


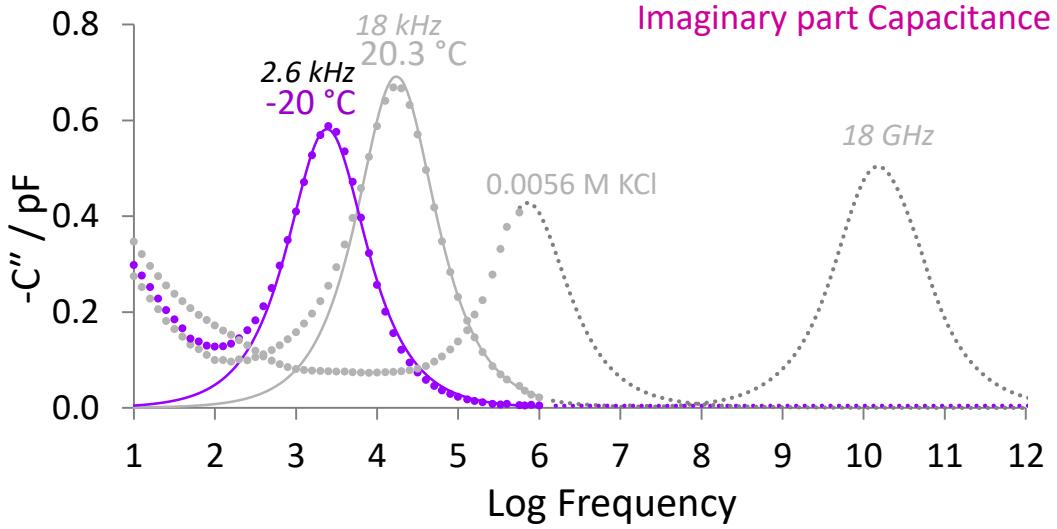
Dielectric Loss Mechanisms

III. The dielectric polarization of ice at −20 ˚C, with a dielectric loss peak frequencies of 2.57 kHz



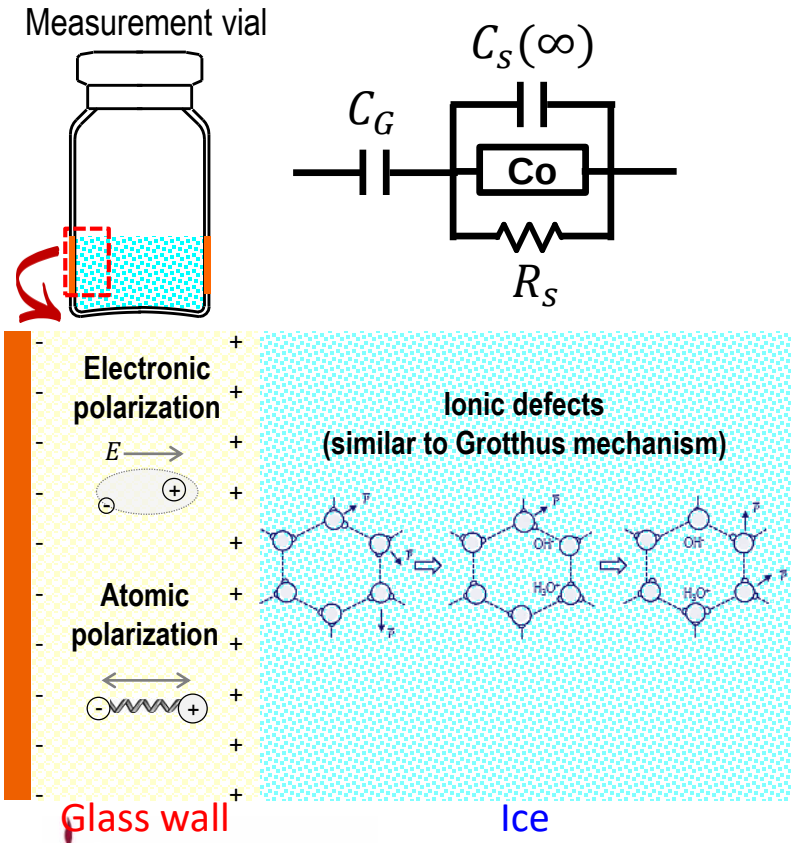


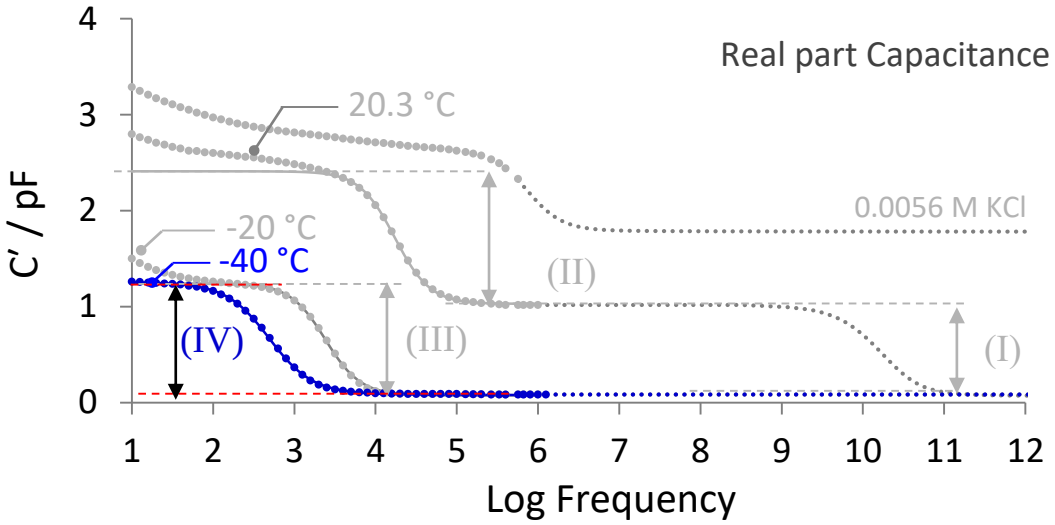


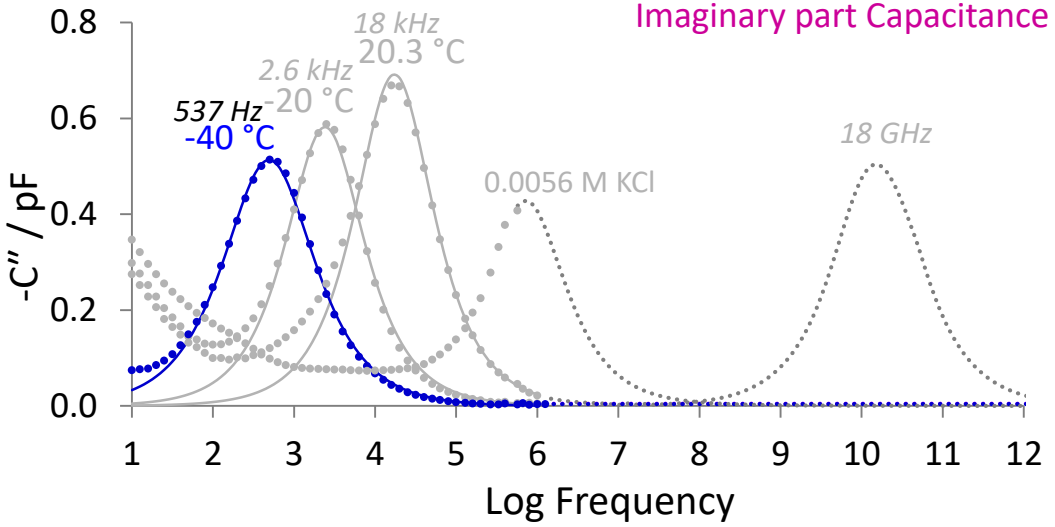


Dielectric Loss Mechanisms

IV. The dielectric polarization of ice at −40 ℃ with a dielectric loss peak frequencies of 537 Hz.







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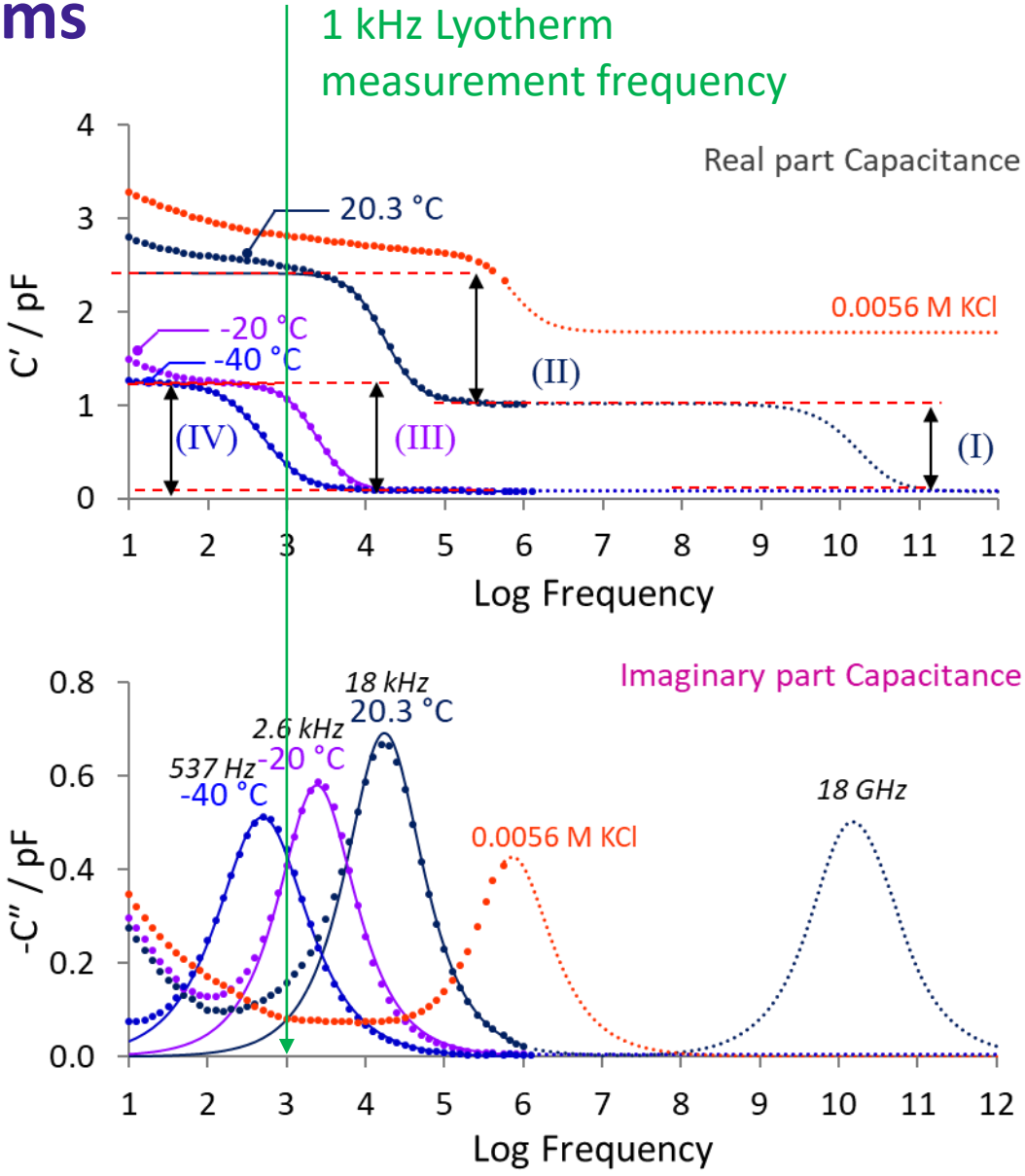
III. The dielectric polarization of ice at −20 ℃, with a dielectric loss peak frequencies of 2.57 kHz

IV. The dielectric polarization of ice at −40 ℃ with a dielectric loss peak frequencies of 537 Hz.

Note: Process II only seen in TVIS vial; in Z-FDM process II is replaced by electrode polarization impedance)



TVIS publications suggestive of Z-FDM applications

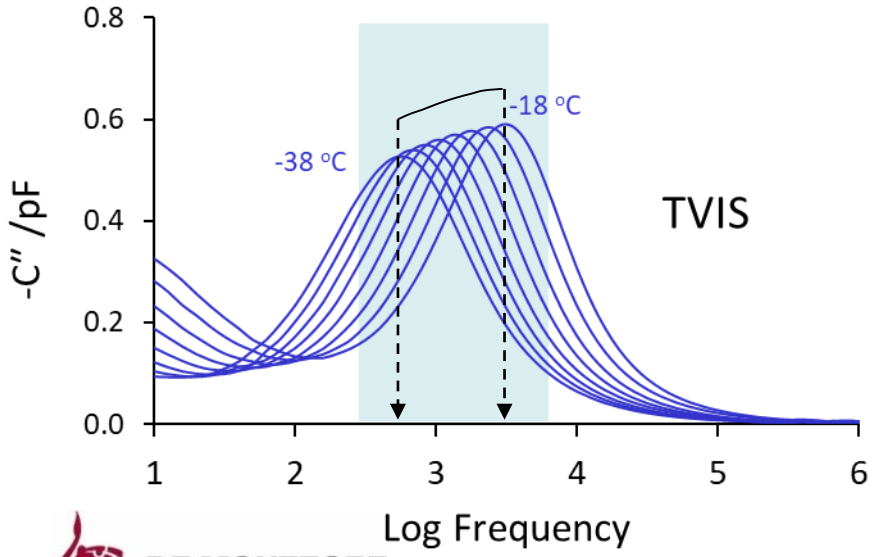
- Smith, G. & Jeeraruangrattana, Y. 2019, "Chapter 5 Through-Vial Impedance Spectroscopy (TVIS): A New Method for Determining the Ice **Nucleation Temperature and the Solidification End Point** n Freeze Drying of Pharmaceutical Products, eds. D. Fissore, R. Pisano & A. Barresi, 1st edn, CRC Press, Florida, United States
- Jeeraruangrattana, Y., Smith, G., Polygalov, E. and Ermolina, I. (2020) Determination of ice interface temperature, sublimation rate and **the dried product resistance**, and its application in the assessment 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

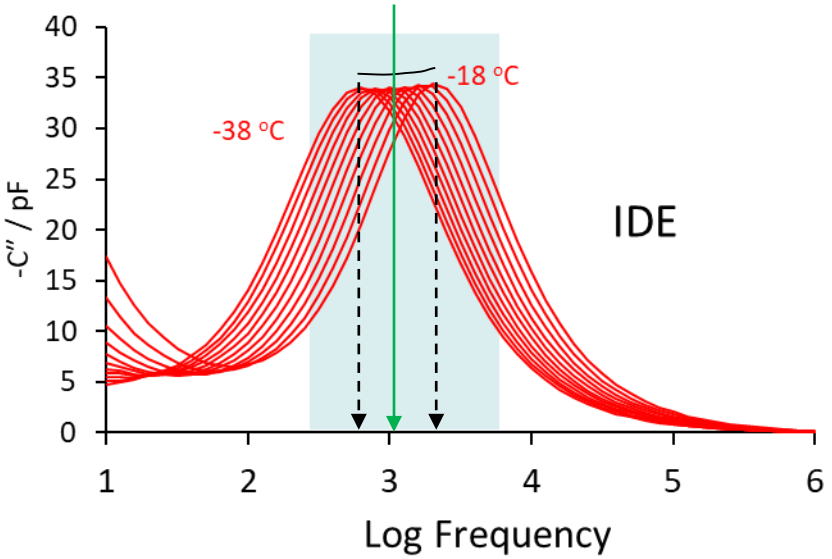
- Freeze-Drying Cycle Development: Applications for Through-Vial Impedance Spectroscopy (TVIS) in Mini-pilot Studies. Journal of Pharmaceutical Innovation, 12 (1), pp. 26-40 **Key observation was the potential to measure temperature non-invasively**
- Arshad, M.S., Smith, G., Polygalov, E., Ermolina, 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.

Dielectric relaxation of ice

5 mL water in
10 mL glass TVIS vial
(1 pair of 10/19 mm
height/width electrodes)

2 µL water over IDE
(90 pairs of gold interdigitated electrodes)
1.6 kHz temperature sensitive





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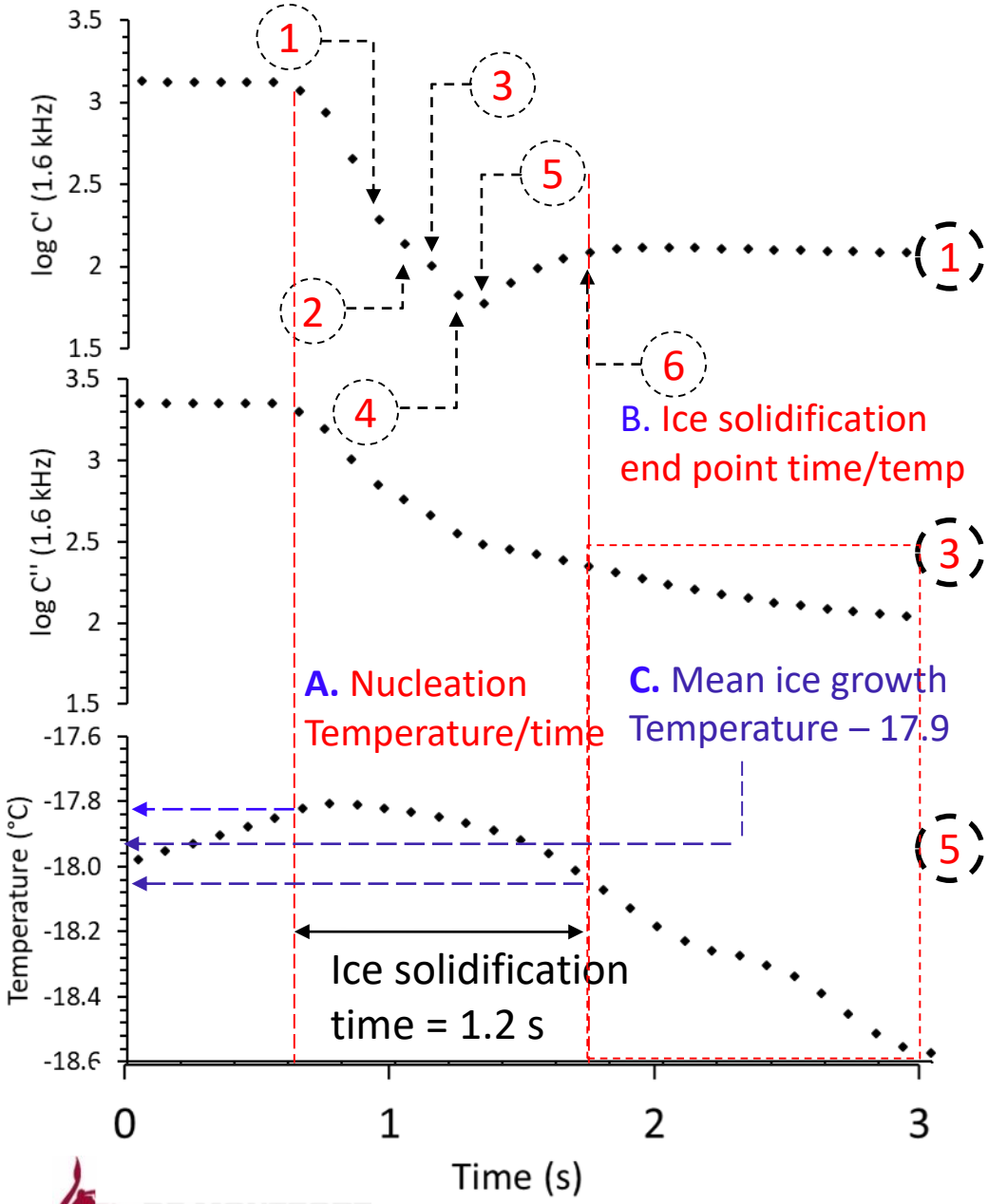
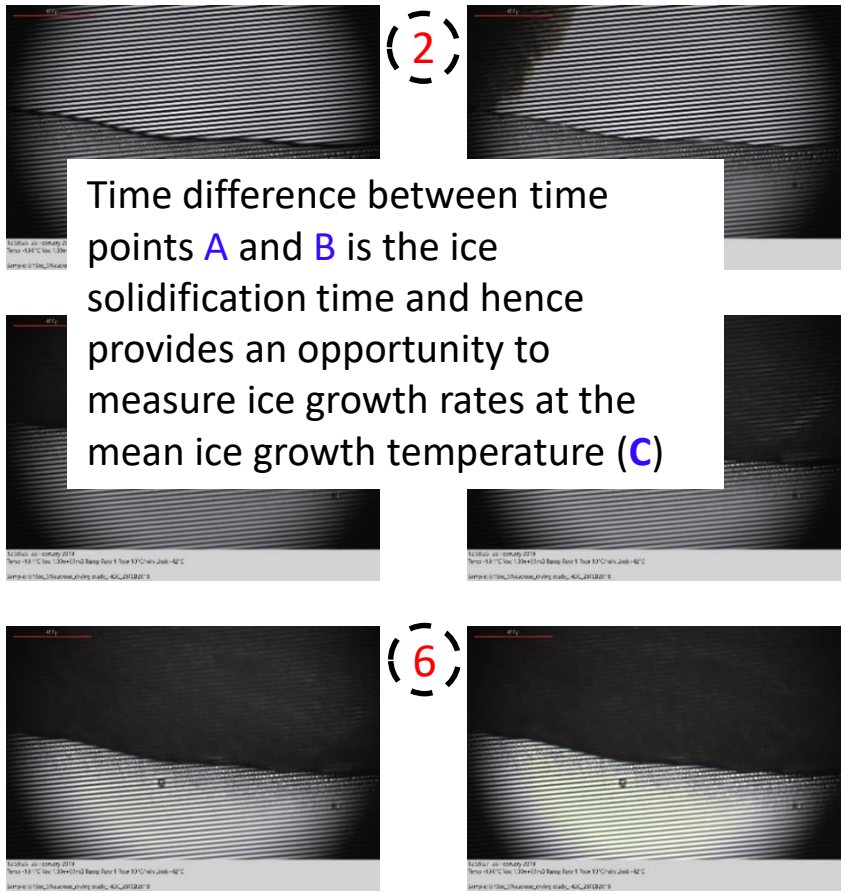
Applications in freezing (nucleation temperature, ice growth rates, solidification end point)

Observations on Sample Size

Case study of 5% w/v Sucrose Solution

Nucleation of 0.5µL of 5% Sucrose





Time difference between time points A and B is the ice solidification time and hence provides an opportunity to measure ice growth rates at the mean ice growth temperature (C)

Ice growth rates

- 1 mL of 5% w/w sucrose has 0.95 g water
- Assumption: unfrozen fraction comprises 80:20 ratio of sucrose to water
- It follows that 0.0125 g (0.05 x 20/80) is bound and produces 0.9375 g ice

Estimated from:

0.5 µL of 5% sucrose (produces 4.688E-04 g ice)

- Ice formation time = 1.2 s (12 data points)
- Ice growth rate: 4.688E-04 / 1.2 = 0.39 mg/s

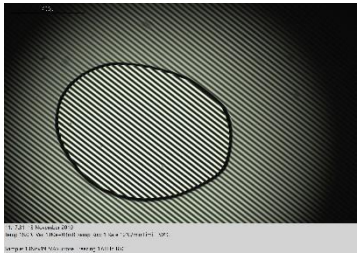
Relevance : ice crystal size? Rp and drying rates

Applications in primary drying
(drying rate, product collapse)

Freeze drying of 5% sucrose (0.05µL)

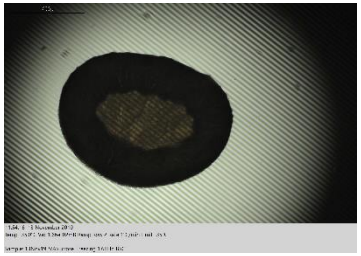
Studied by Image analysis

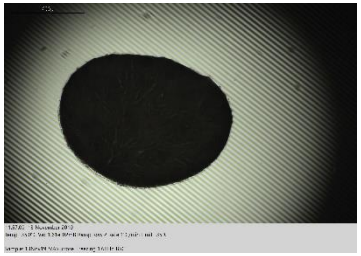
FDM protocol


Liquid state

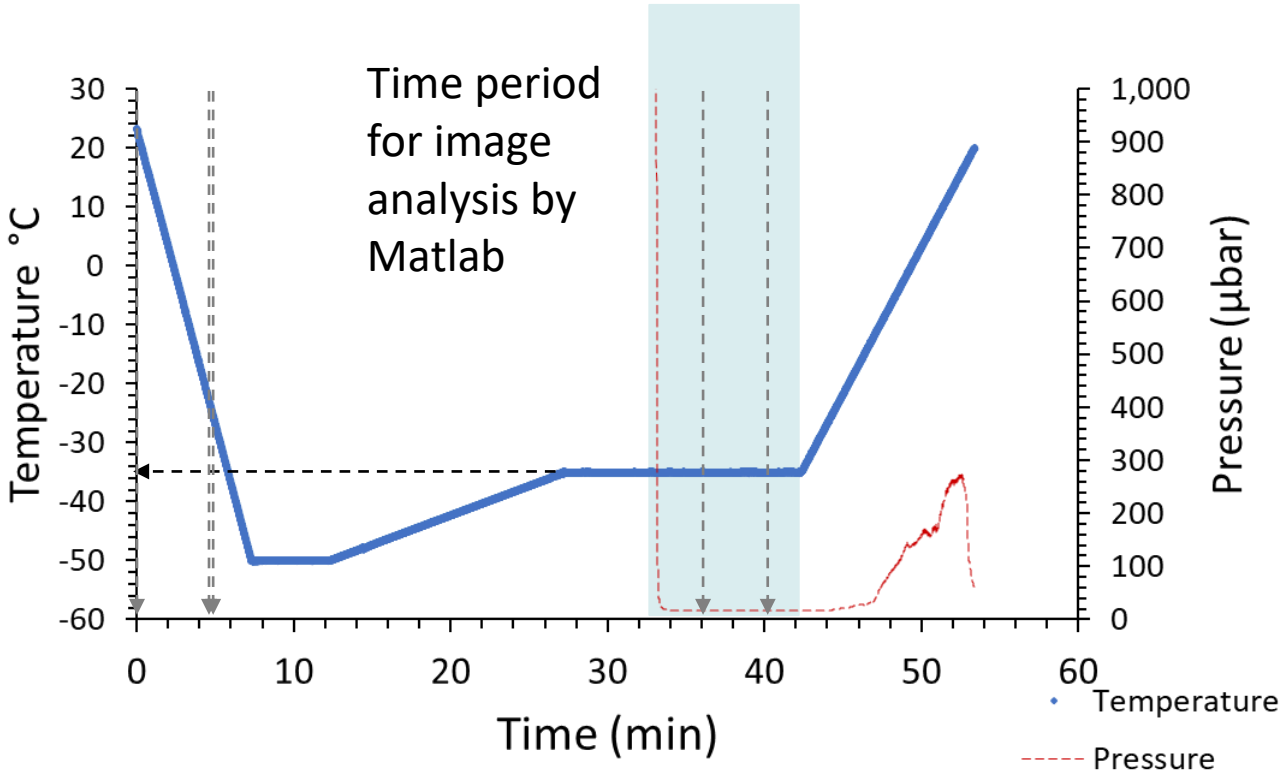

ice growth


ice solidification


sublimation


end of primary drying

FDM freeze-drying of 5% sucrose solution (0.05 µL)

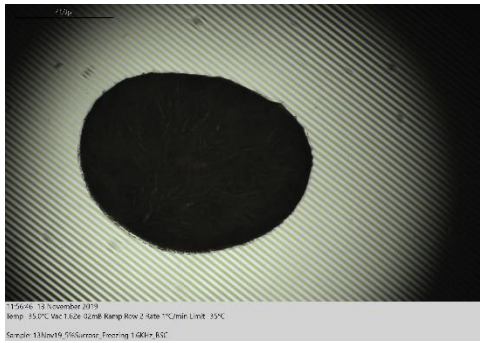


NB: Temperature and pressure measured on FDM every 100 ms

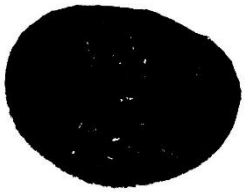
MATLAB® Image analysis (pixel counting)

FDM primary-drying of 5% sucrose soln (0.05 µL) at -35˚C

1. **Global templet generation** – dried product image



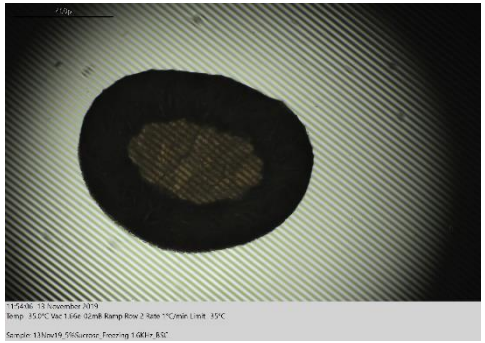
MATLAB®



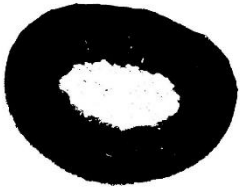
Global pixel : 527515

Dried product image

2. **Threshold test image** – frozen image or drying stage image



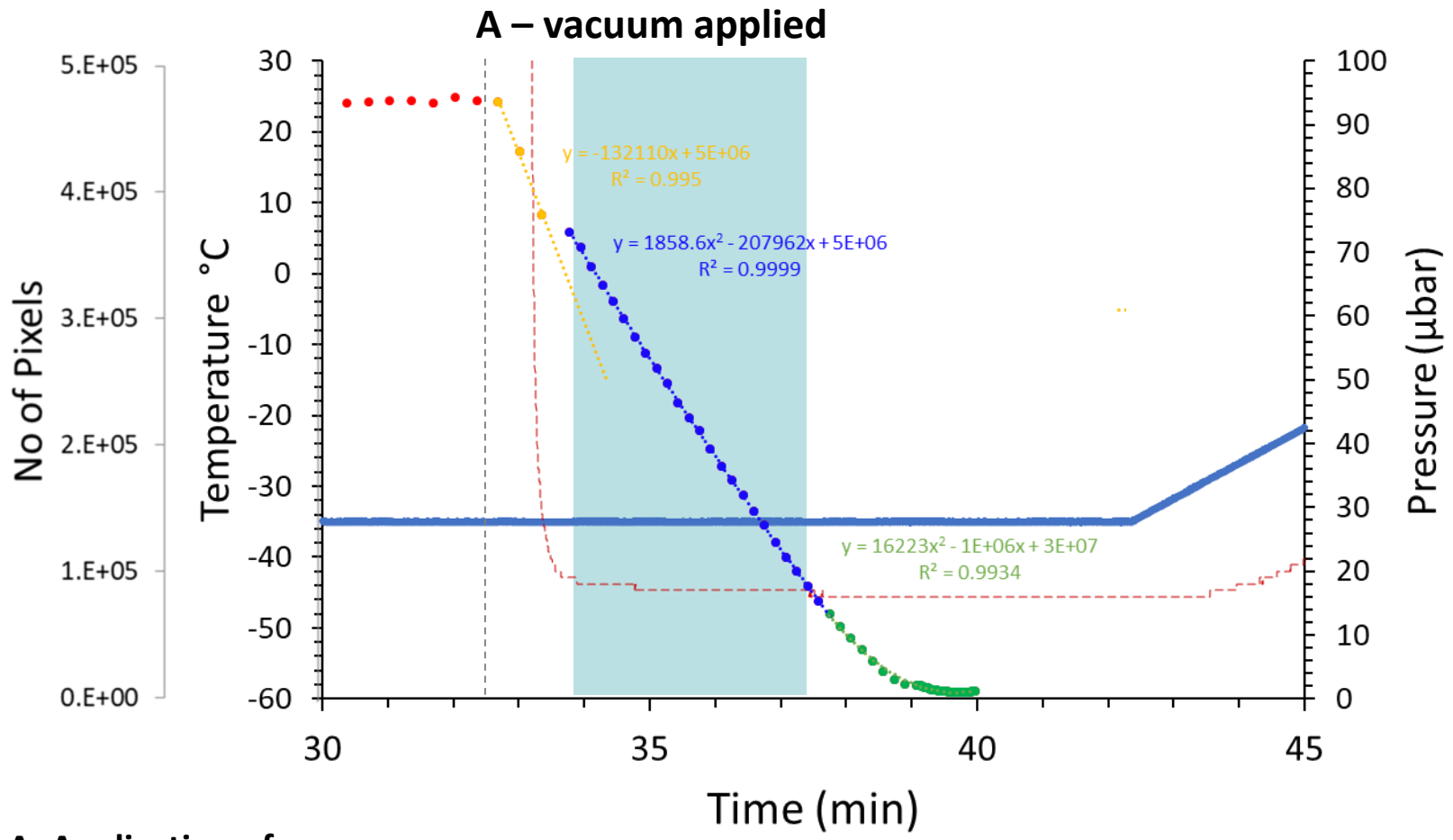
MATLAB®



Pixel for central area: 86317

Product during drying

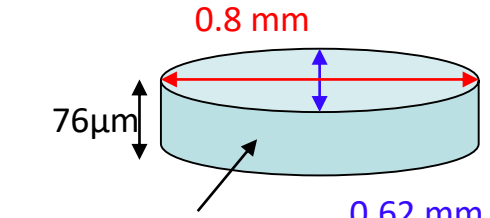
Pixel analysis



A: Application of vacuum

NB: Temperature and pressure measured every 100 ms

Drying rate determination



Area of perimeter
0.00342 cm²

Weight fraction of sucrose	0.05	(5% Sucrose)
Weight fraction of water	0.95	i.e. 95 % water
Weight fraction of bound water (1)	0.0125	
Weight fraction of freezable water	0.9375	

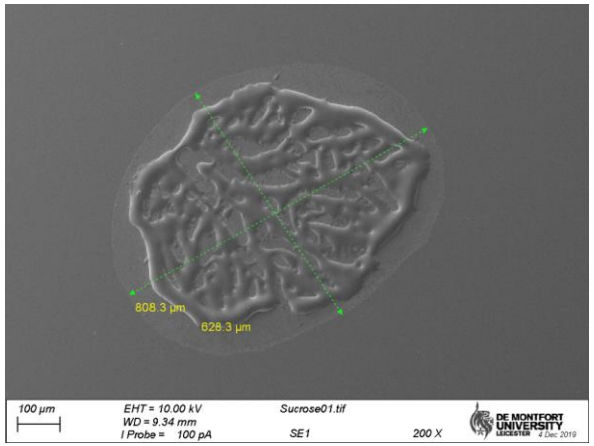
(1) based on 80:20 ratio of sugar to water in freeze-concentrated solution

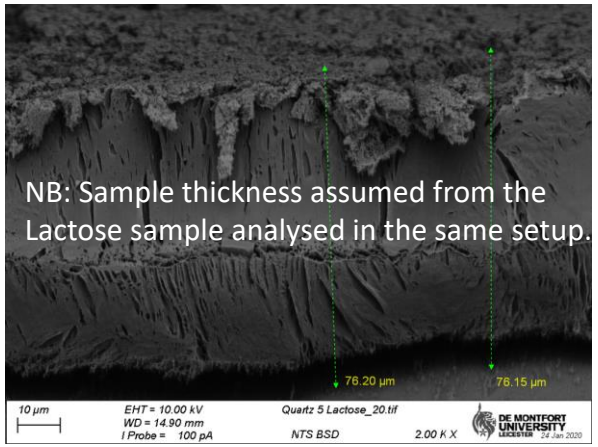
Sample volume	0.05	µL
Freezable water	0.0469	µL
Freezable water in mg	0.0469	mg of ice

Total pix before drying starts	466873	
1 pixel (a)	1.004E-07	mg of ice

Gradient of linear part (b)	132110	pixel per min (yellow line)
Drying rate (a x b)	0.0133	mg min^{-1}
Drying rate (B)	**0.00080**	**g h^{-1}**

Area of perimeter of sample (A)	0.00342	cm^2
Specific drying rate (B/A)	**0.233**	**g h^{-1} cm^{-2}**





Example drying rate from a 10 mL glass tubing vial is 0.25 g h^{-1}
Vial diameter : 22 mm Internal area : 3.8 cm^{-1}
Specific drying rate : 0.065 g h^{-1} cm^{-2}
Difference due to differences in heat transfer etc.

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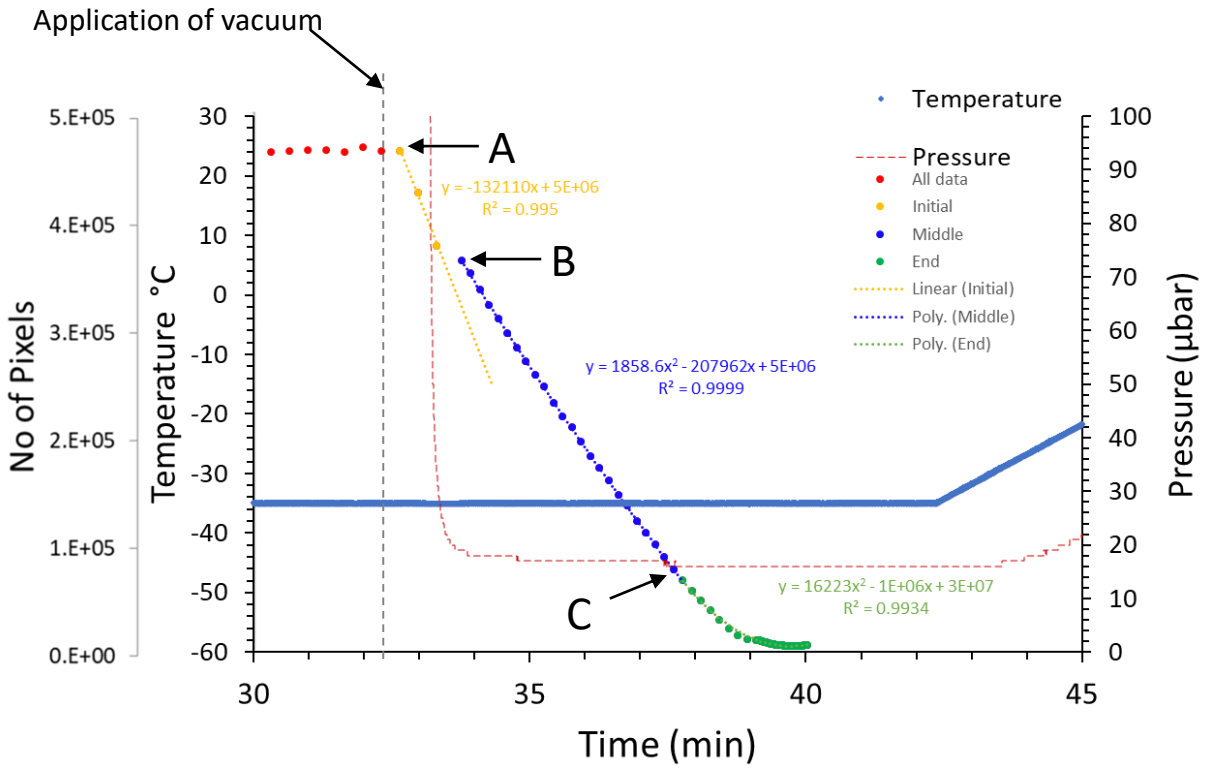
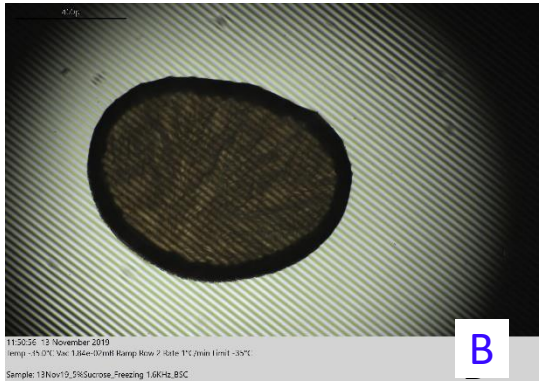
Drying rate at different gradient





Drying Rates

- At A Initial – 0.00080g h^{-1}
- At B: Middle – 0.00050 g h^{-1}
- At C: Middle – 0.00041 g h^{-1}

NB: Temperature and pressure measured every 100 ms

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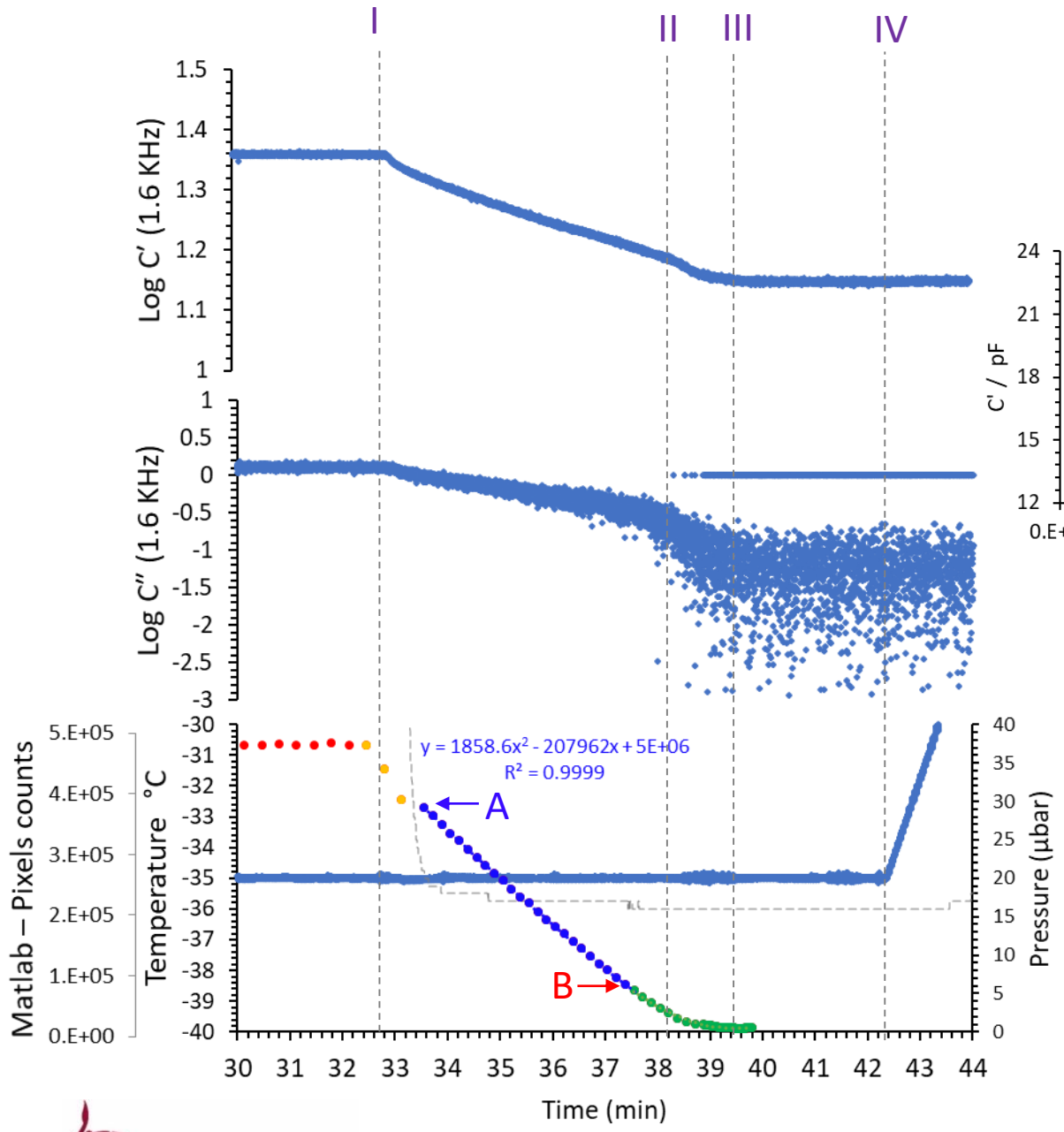
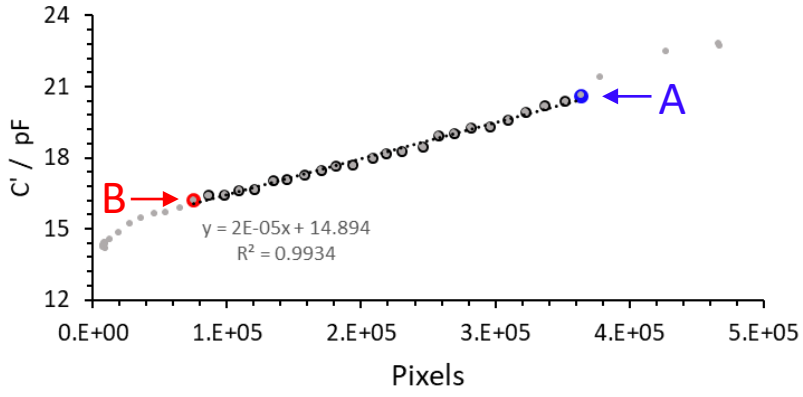
Freeze drying of 5% sucrose (0.05µL)

Studied by Z-FDM

Drying: Image analysis vs Capacitance during drying of 0.05 µL 5%sucrose





Linear relationship between real part capacitance C' and pixel count (ice content) confirms the opportunity to use Z-FDM for drying rate estimation

I: Application of vacuum. Primary drying starts
II: Both gradients of imaginary and real part capacitance change towards the end of drying
II : end of primary drying
IV: Ramped to RT and capacitance remains unchanged with temperature

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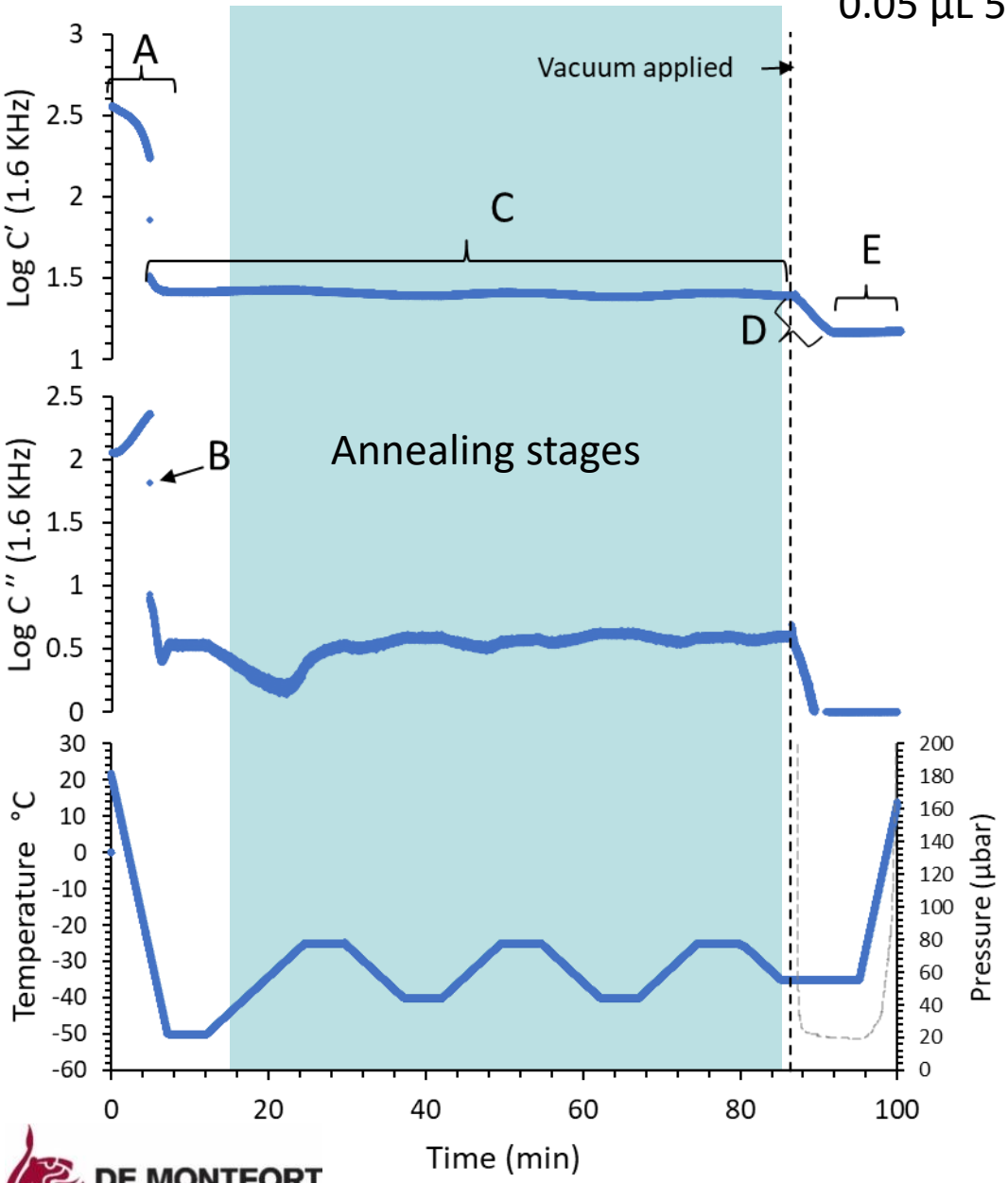
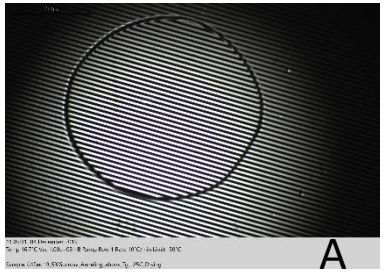
Annealing of 5% sucrose (0.05µL)

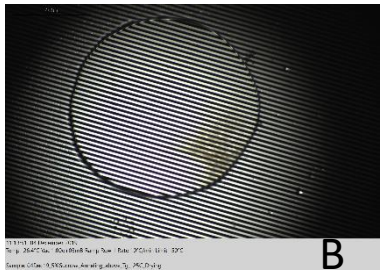
Studied by Z-FDM

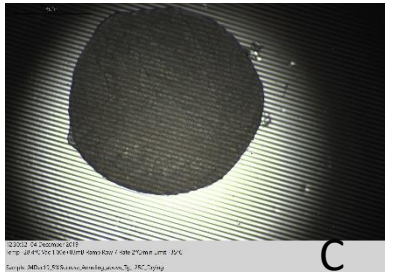
0.05 µL 5%sucrose

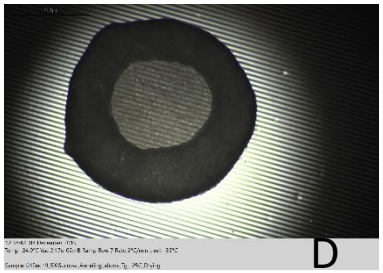
Full process

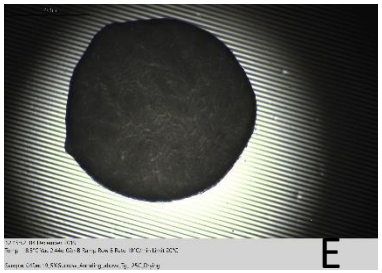












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Capacitance data measured at 1.6KHz

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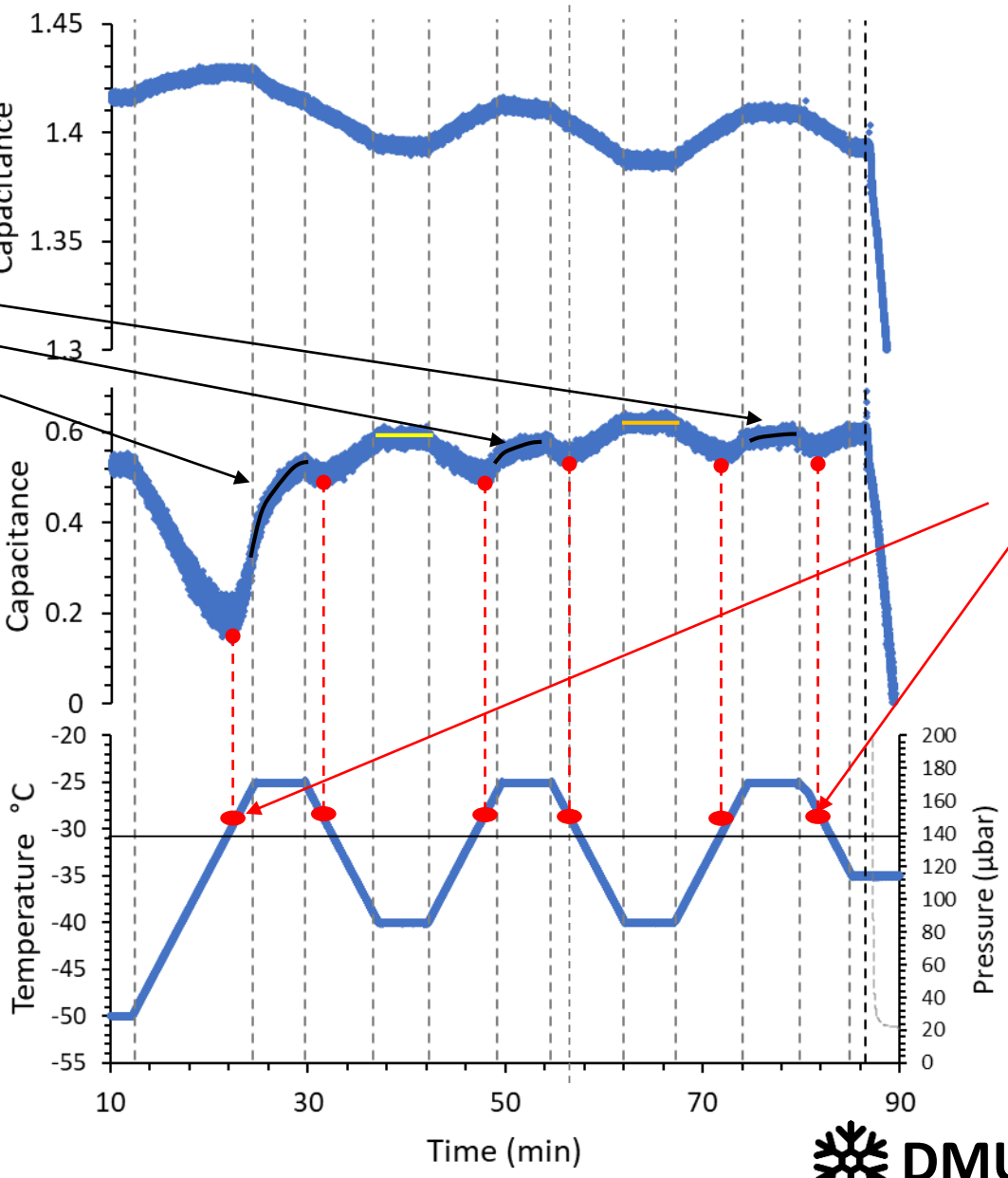
Annealing (1.6KHz)

0.05 µL 5%sucrose

Structural changes on re-heating decrease with each annealing



Excursions in temperature just above the glass transition

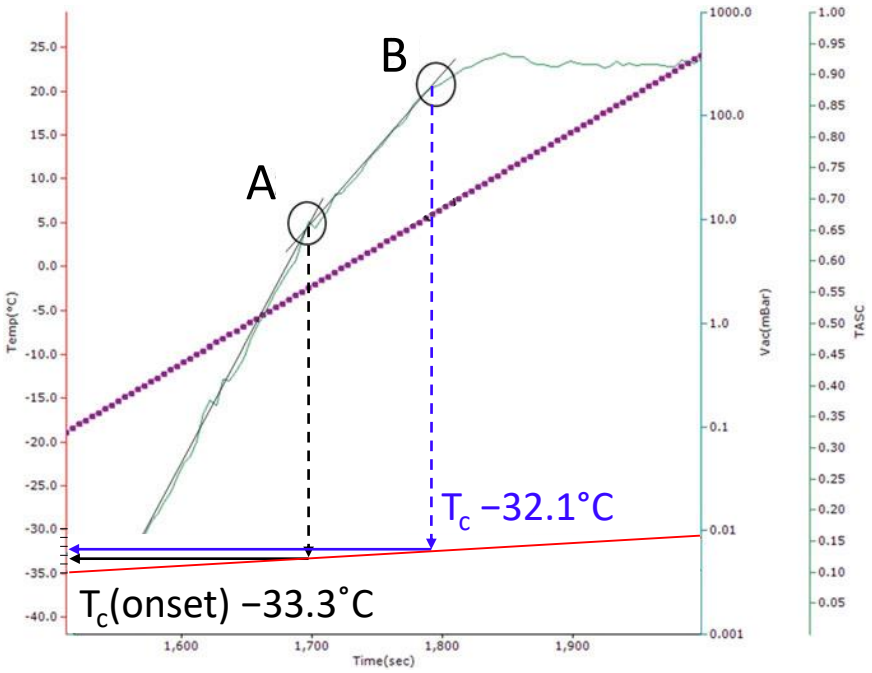
Applications in primary drying : product collapse

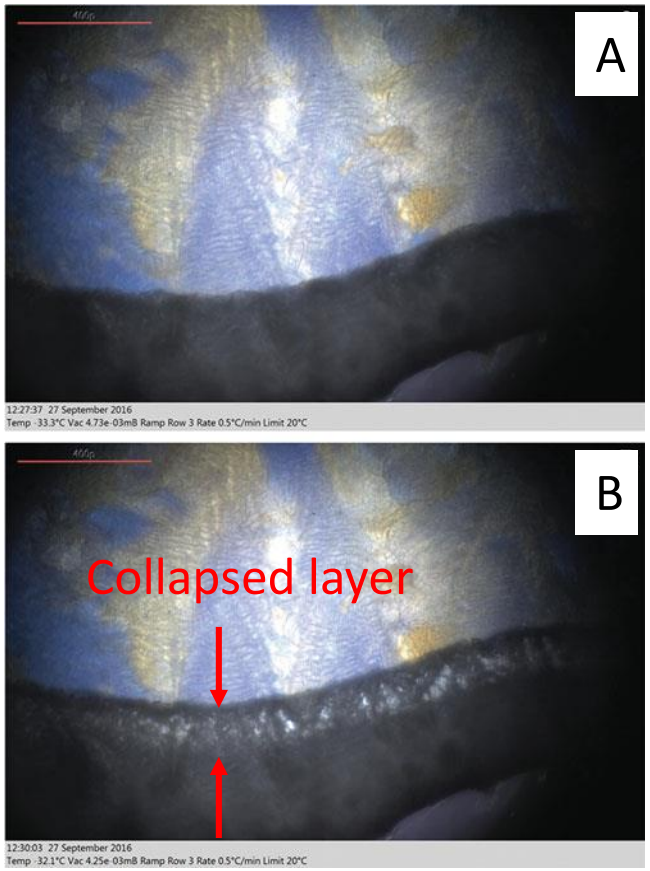
Collapse of 5% sucrose (0.5 µL)

Studied by Z-FDM

TASC – image analysis of sucrose solution

Reduces operator error in the analysis of the collapse temperature and can use for drying rate.





Adapted from: Ward, K. and Matejtschuk, P., 2019. Chapter 1 Characterization of Formulations for Freeze-Drying In: K. R. WARD and P. MATEJTSCHUK, eds, Lyophilization of Pharmaceuticals and Biologicals: New Technologies and Approaches. 1 edn. New York: Humana Press, pp. 1-33.

Images coinciding with TASC features
(A) onset of collapse at −33.3°C, and
(B) full collapse occurring at −32.1°C

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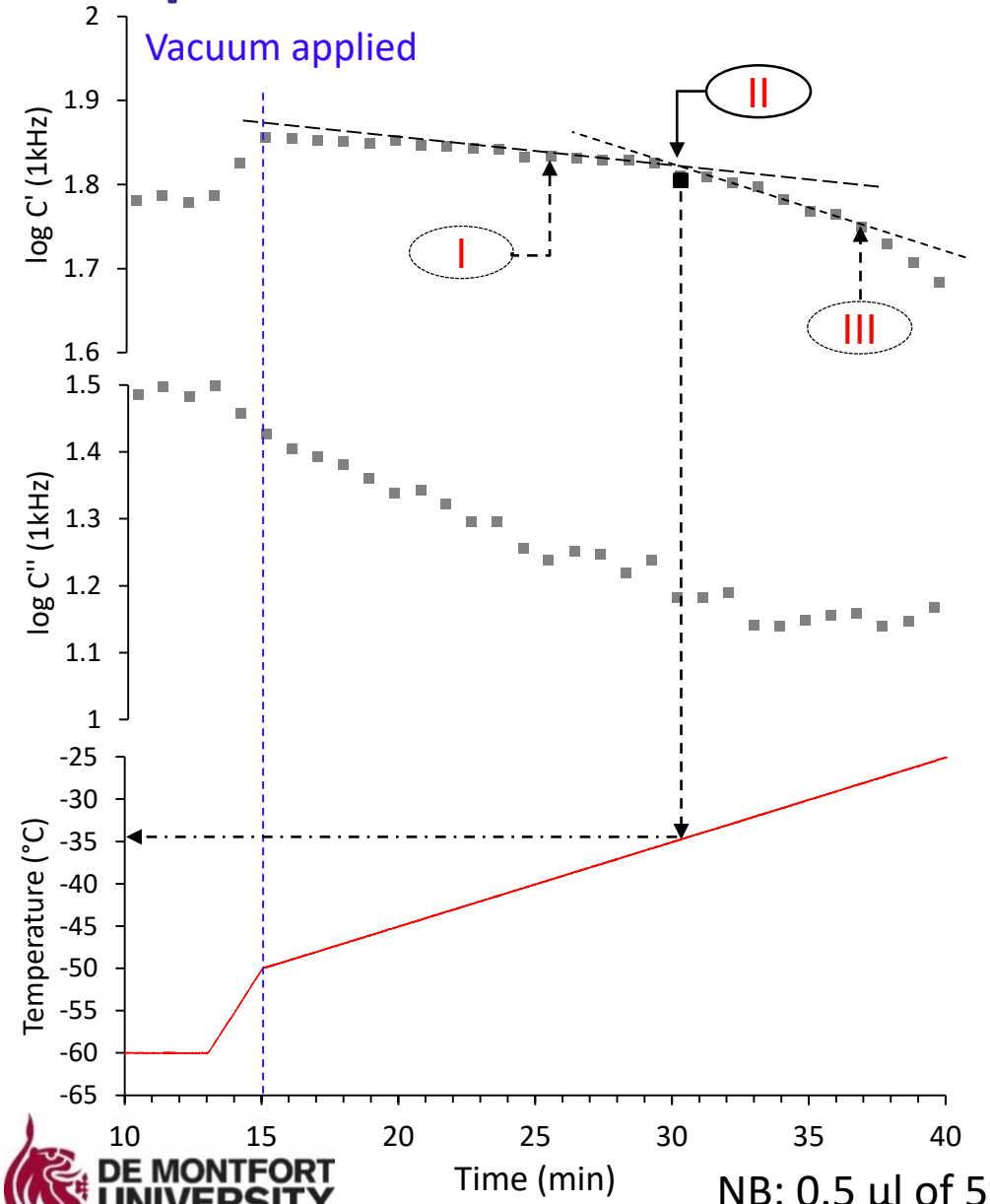
Collapse Observation at 1 kHz



NB: 0.5 µl of 5% Sucrose soluiton

Take home messages (from measurements at 1.6 KHz)

- Real and imaginary part capacitances can be used for the determination of ice nucleation and ice growth rates
- Pixel analysis works for drying rate determination
- Real capacitance has a linear relationship with pixel count, and hence ice mass, so can be used for drying rate determination
- Imaginary part capacitance can be used to study the annealing process but requires further work in order to be able to determine the glass transition temperature.
  - Selection of a higher measurement frequency is likely to provide the answer to the glass transition temperature assessment
- Step changes in drying rate (observed from real part capacitance) can be used to determine the collapse temperature
- Relevance of the results is questionable because of differences in sample size, heat transfer etc. to product container

Acknowledgements, Recent Projects & Collaborators

- De Montfort University, School of Pharmacy
  - Anand Vadesa. PhD student
  - Neill Horley. Senior Lecturer
  - Glen McCann: Lecturer
- University College London
  - Prof. Paul Dalby
- Biopharma Process Systems
  - Kevin Ward

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LyoDEA

Lyophilization process analytics
By dielectric analysis

BIOSTART

Biopharmaceutical Stability at
Room Temperature

AtlasBio

Analytical Technologies for the
Stabilization of Biopharmaceuticals

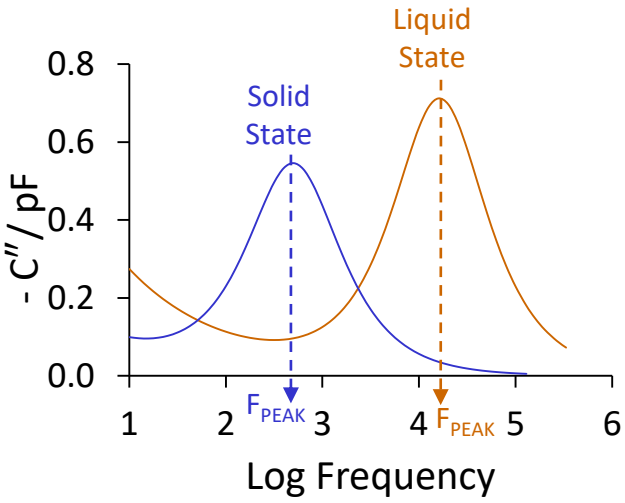
Through Vial Impedance Spectroscopy (TVIS)

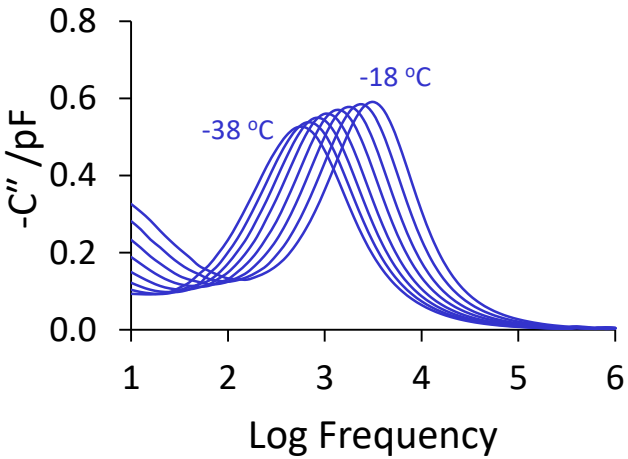
- TVIS measurement relate to both the *electrical resistance* and *electrical capacitance of the vial contents.*

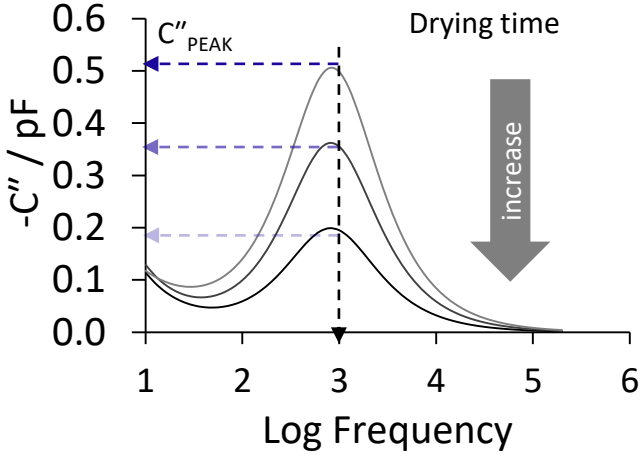
Monitoring Phase Behaviour (ice nucleation temperature and solidification end points

FPEAK temperature calibration for predicting temperature of the product in primary drying

Drying rate surrogate (from dC''_{PEAK} /dt)







C' (real part of the complex capacitance) is highly sensitive to low ice volumes; therefore it could be used for determination end point of primary drying

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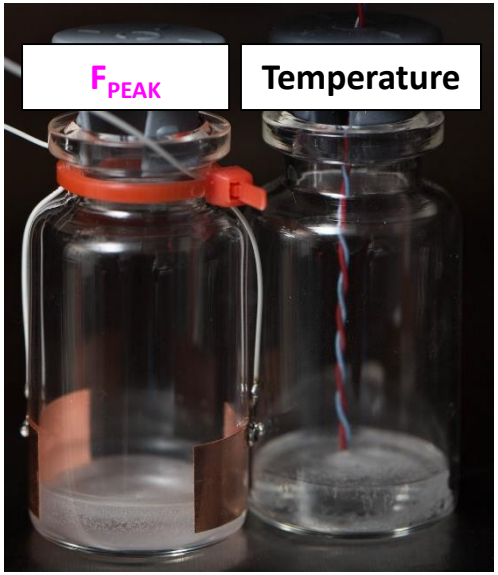
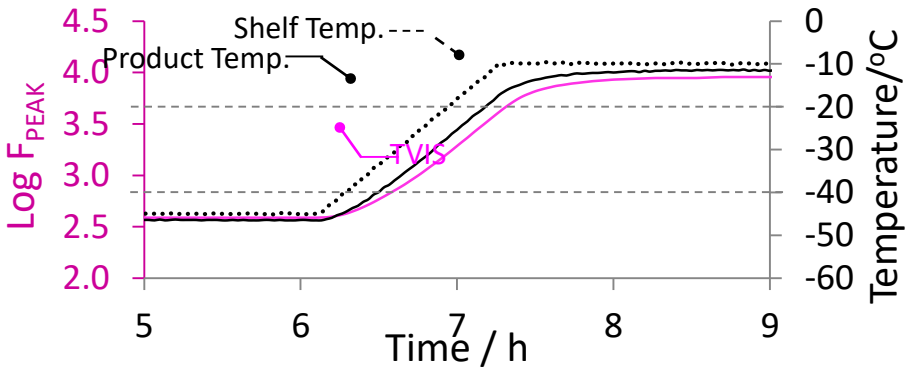
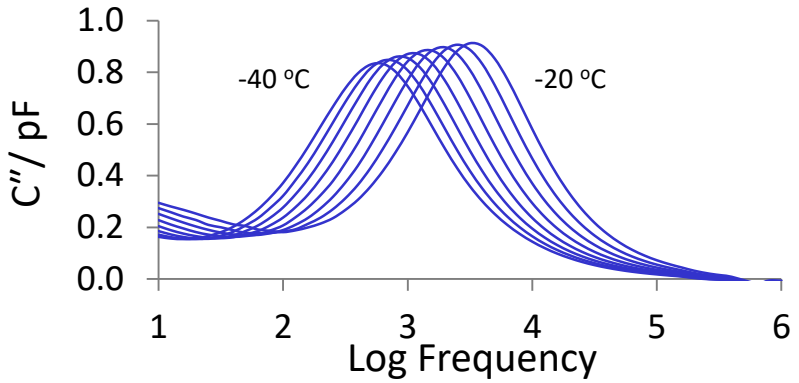
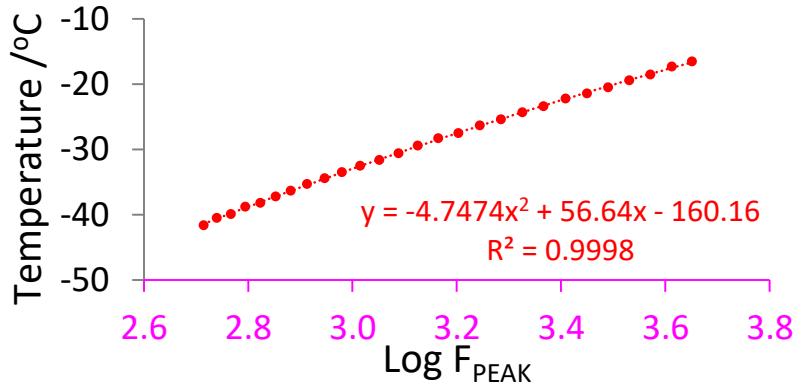
Temperature Calibration

- F_{PEAK} profile during annealing has 'similar' profile with product temperature.
- Assuming thermal equivalence between the thermocouple (TC) vial and TVIS vial, then the temperature calibration from annealing might be employed for the prediction of temperature during primary drying



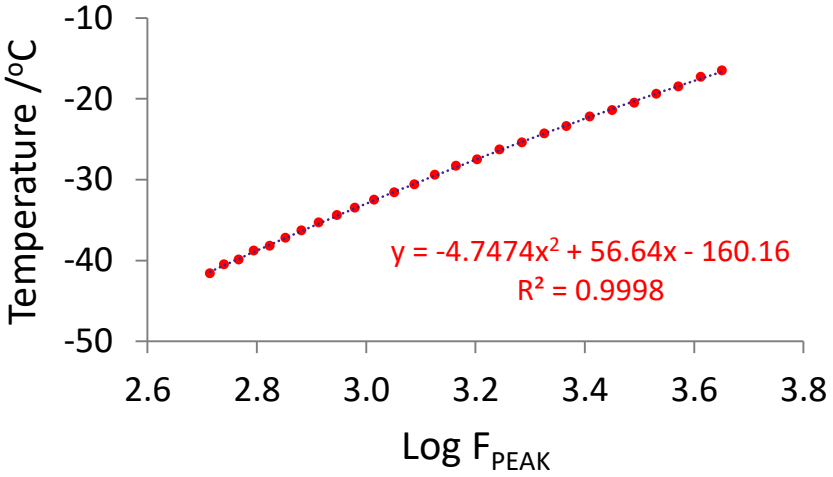




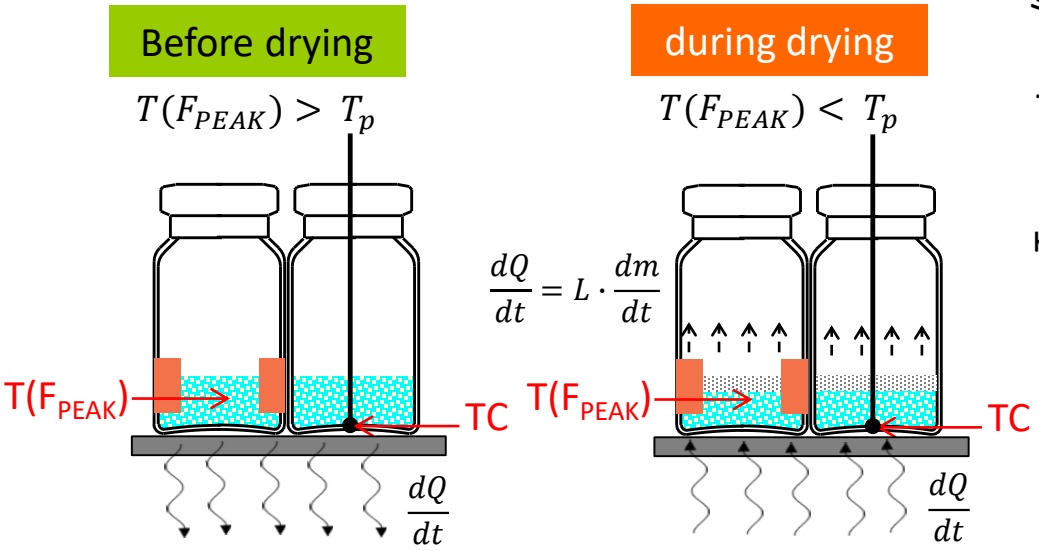


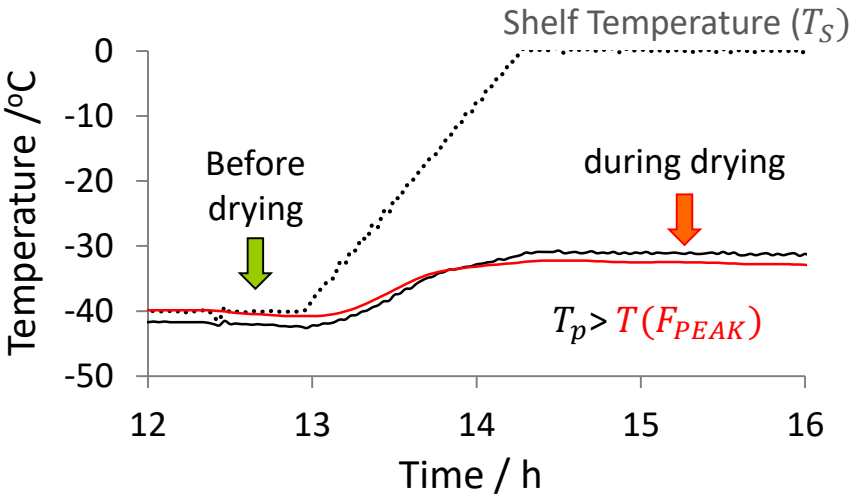
Temperature Prediction in Primary Drying

- Temperature calibration curve selected for temperature prediction in primary drying : $T(F_{PEAK})$



- Good agreement between product temperature (by TC) and $T(F_{PEAK})$





Compensation of C"PEAK by T(F_{PEAK})

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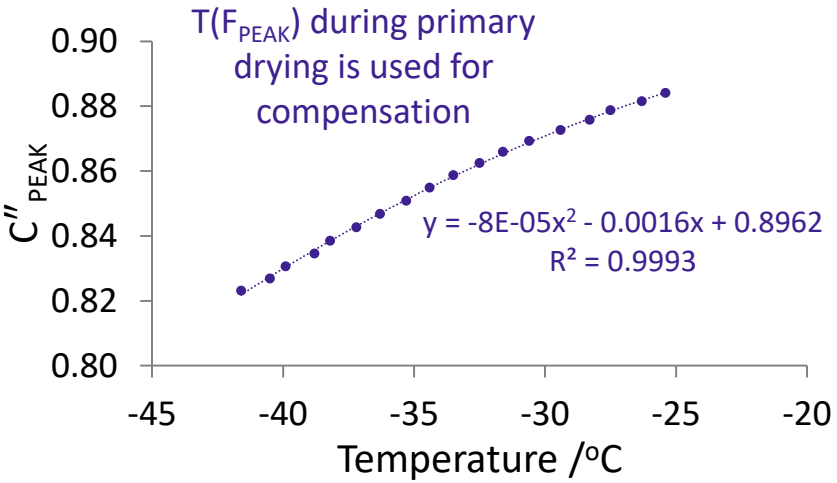

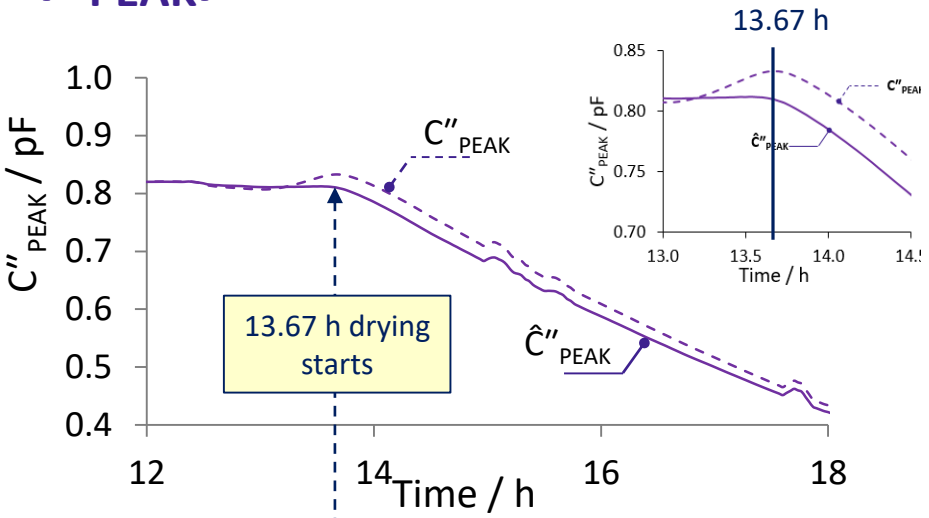

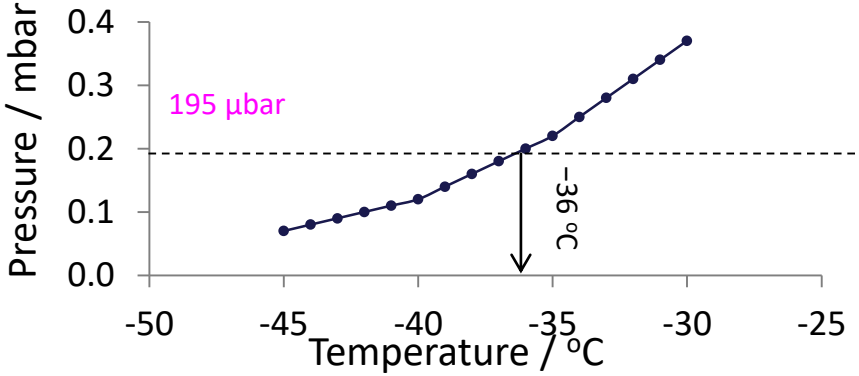

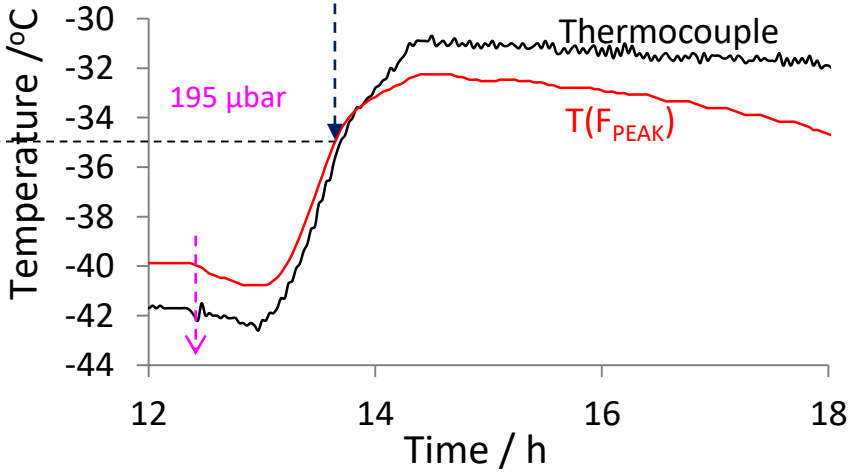

Drying rate calculation

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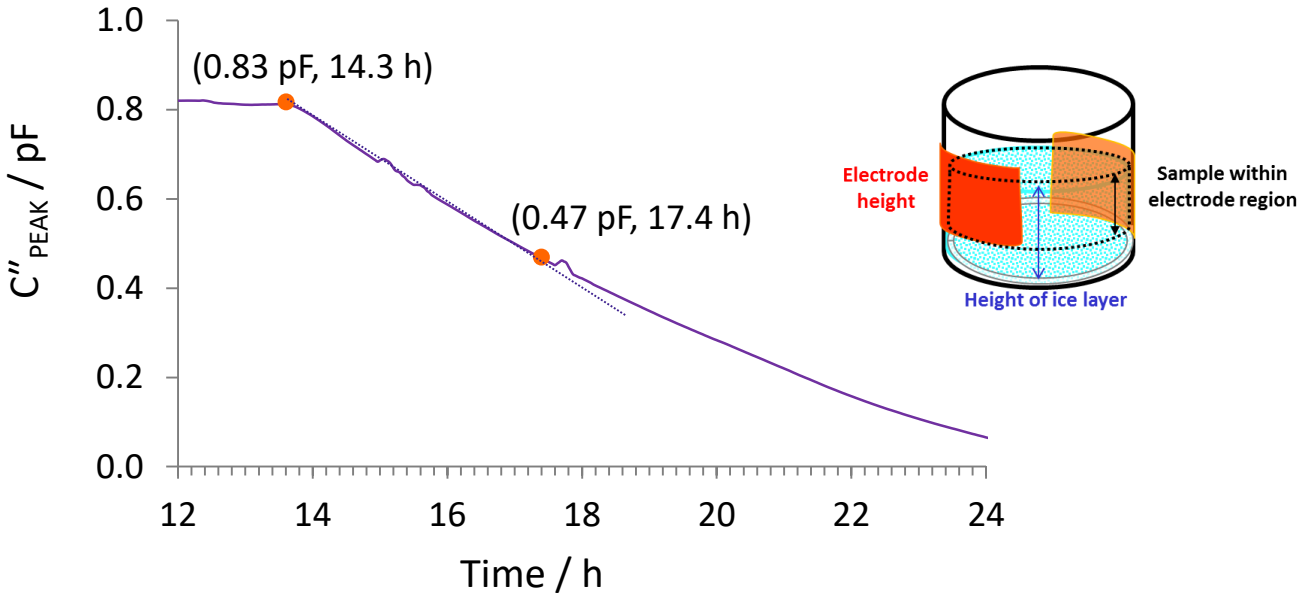

- Drying rate (g/h) for $\hat{C}''_{PEAK}$

$$Drying\ rate = \left(\frac{\hat{C}''_{PEAK(initial)} - \hat{C}''_{PEAK(end)}}{Time_{(end)} - Time_{(initial)}}\right) \times \frac{ice\ mass\ within\ electrode\ region}{\hat{C}''_{PEAK(initial)}}$$

$$Drying\ rate = \left(\frac{0.83 - 0.47}{17.4 - 14.3}\right) \times \frac{3.69}{0.83} = 0.52\ g \cdot h^{-1}$$

Summary

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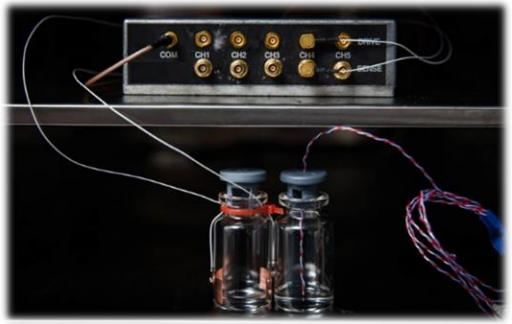
- Temperature calibration of the TVIS parameter (F_{PEAK}) for ice during an additional temperature cycling stage applied to a prediction of ice temperatures during the initial (few hours) of primary drying
- Temperature compensation of TVIS parameter (C''_{PEAK}) allows for an accurate estimation of ice mass during primary drying as evidenced by comparable results of drying rate between the determined by TVIS and that determined (gravimetrically) by loss weight

Non-invasive real time information for characterising the freeze drying



Future Work

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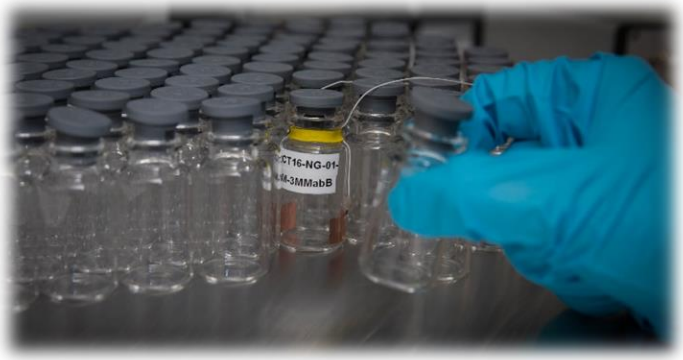
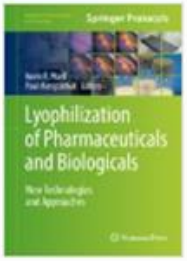
- Development mapping a drying characteristics from lab scale to production
  - Determination of heat transfer coefficients (K_V)
  - Determination of dry layer resistance (R_P) to predict drying efficiency



- Investigation the molecular dynamic of the unfrozen fraction
  - Monitoring product stability
  - Examine the mechanical strength of the freeze dried product (i.e. collapse behaviour)

- Develop (new) continuous drying technologies



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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

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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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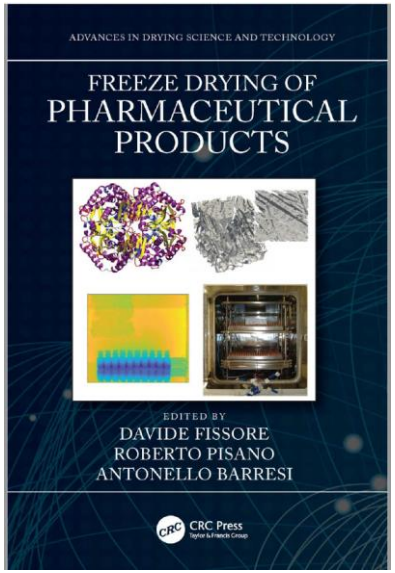

Freeze Drying of Pharmaceutical Products

1st Edition

Davide Fissore, Roberto Pisano, Antonello Barresi

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Glass Transition (T_g') Determination

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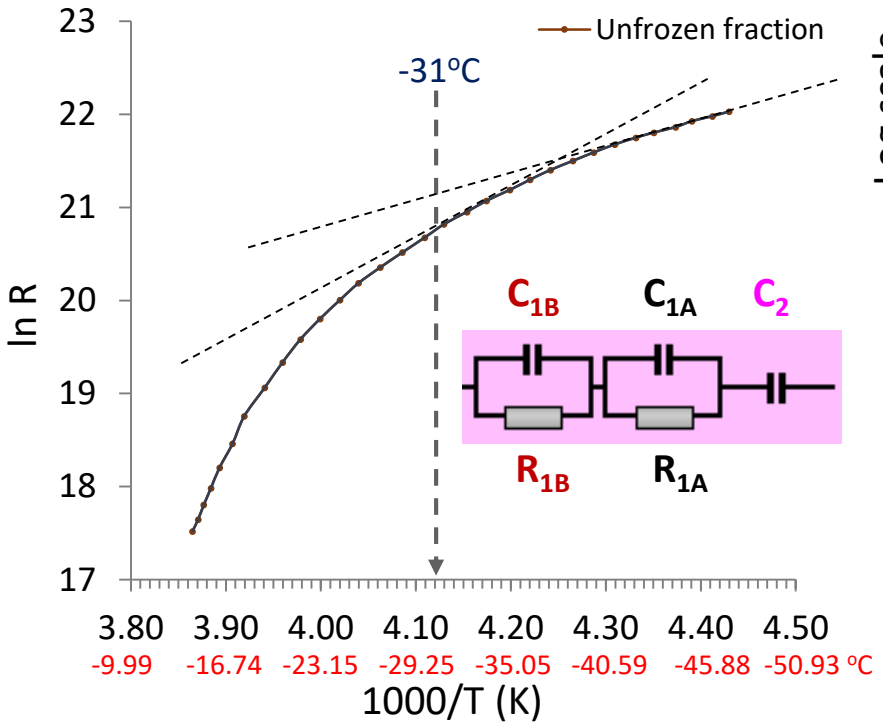
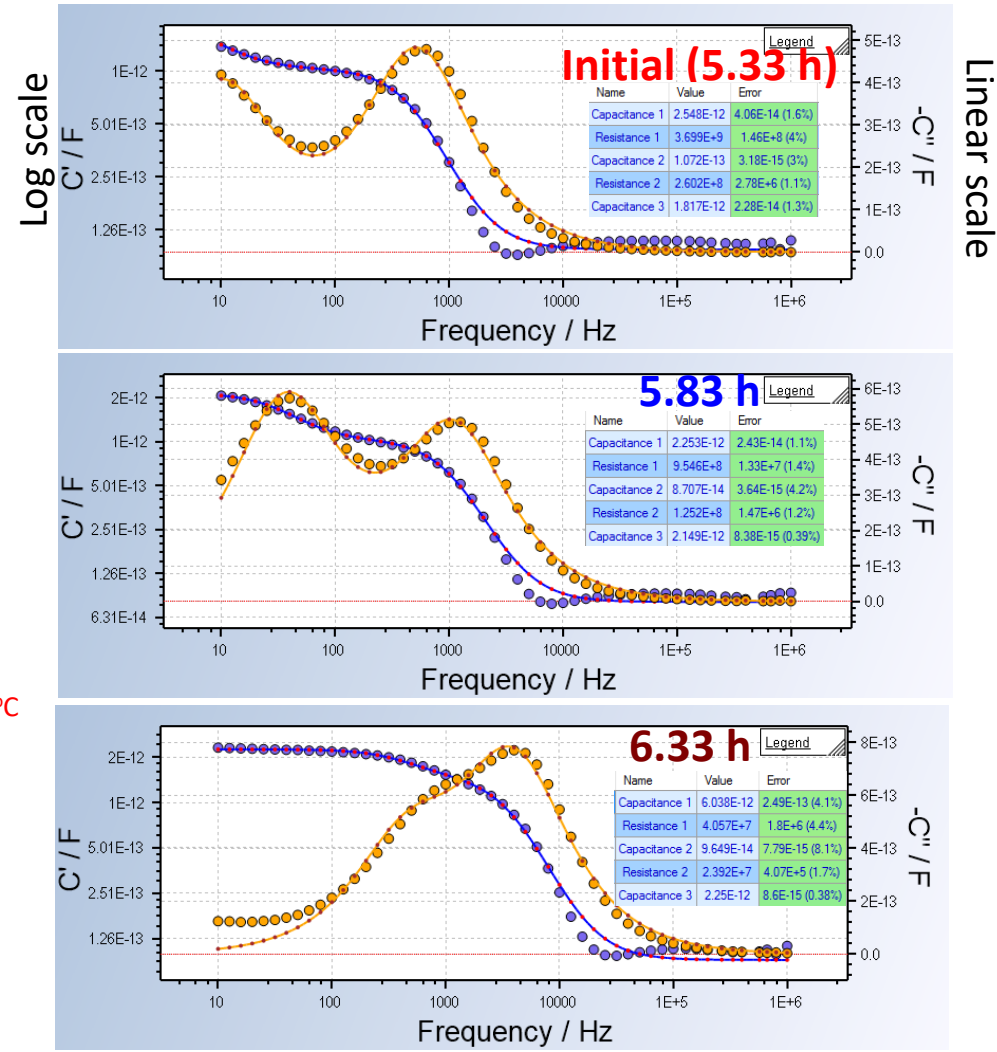
5% w/v Lactose solution





- Below T_g' the changes in product resistance follows Arrhenius
- Above T_g' VTF function models the resistance profile.

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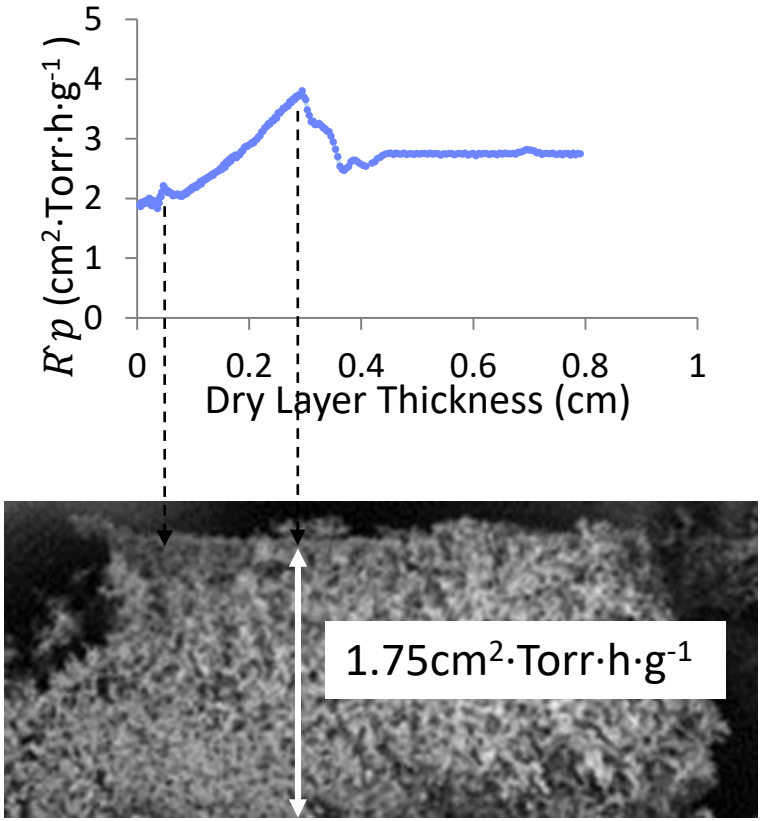
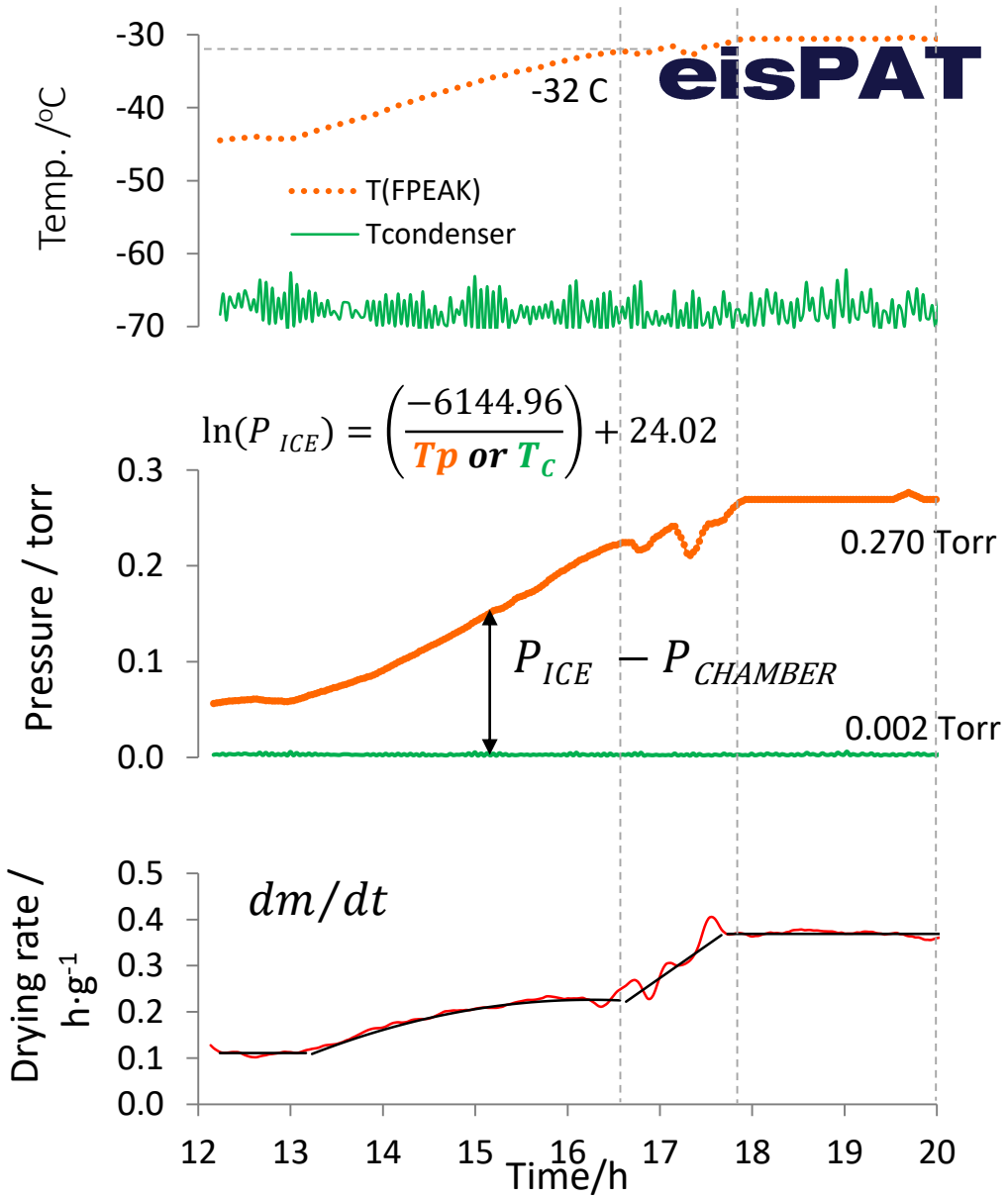
Lactose Dried Product Resistance (R_P)

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





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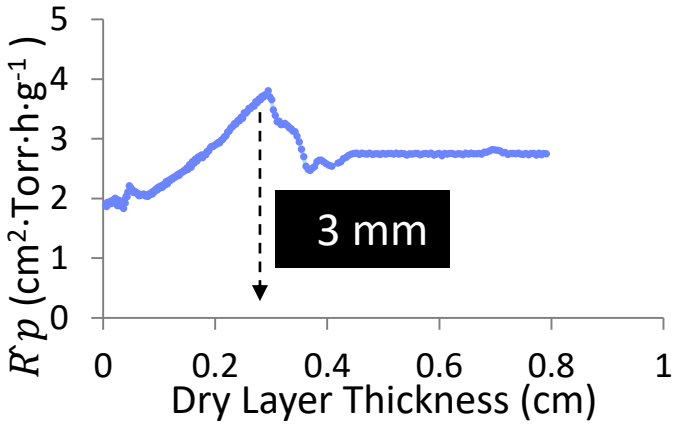

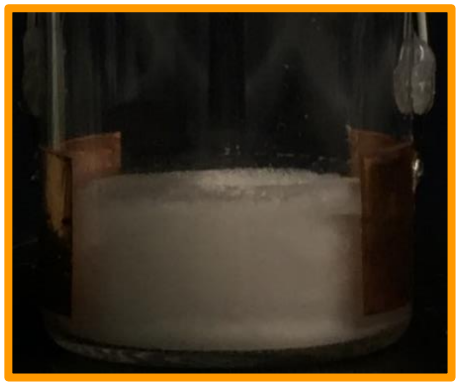

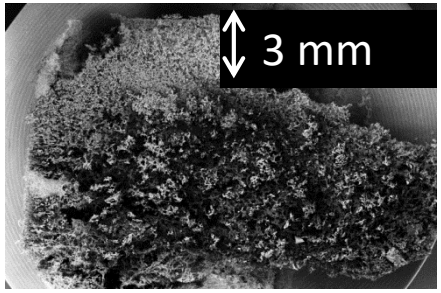

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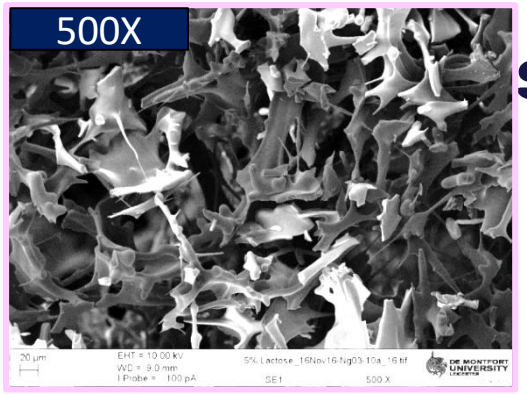
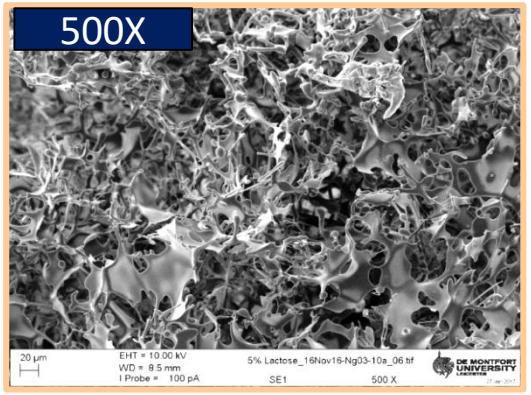
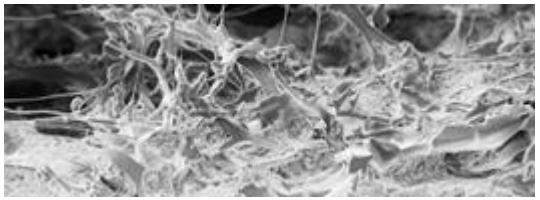


Top layer
Fine pores



Middle layer
Micro-collapse

500X



Bottom layer
Full collapse

Examples of Biopharmaceuticals Therapy

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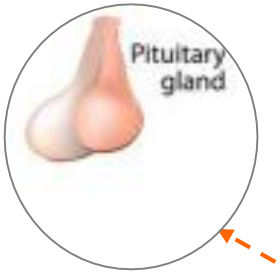
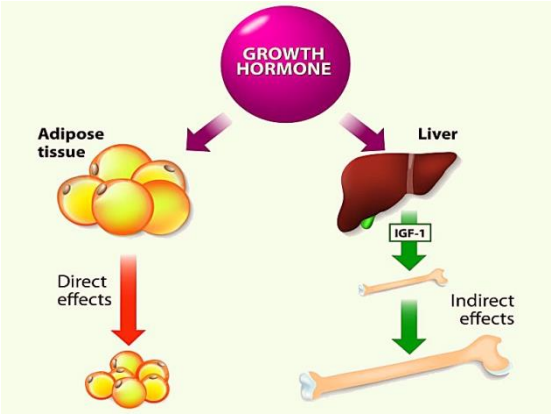
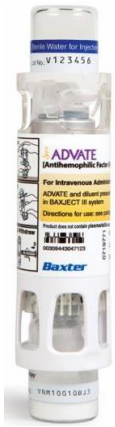
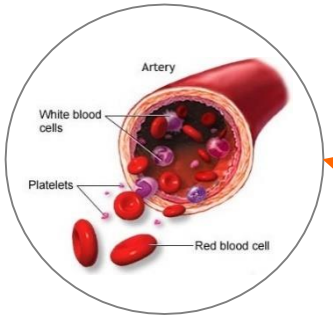


Endocrine system

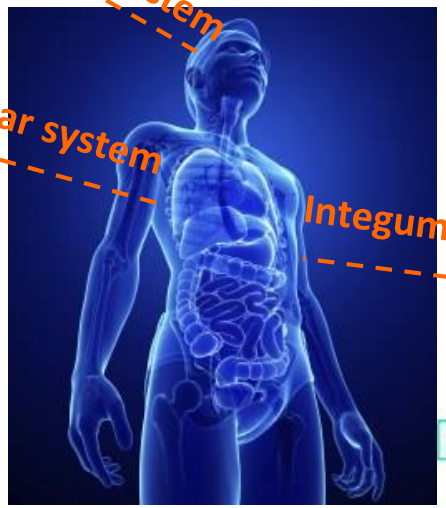
Growth hormone



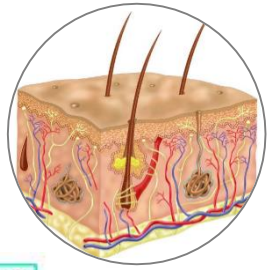




Cardiovascular system



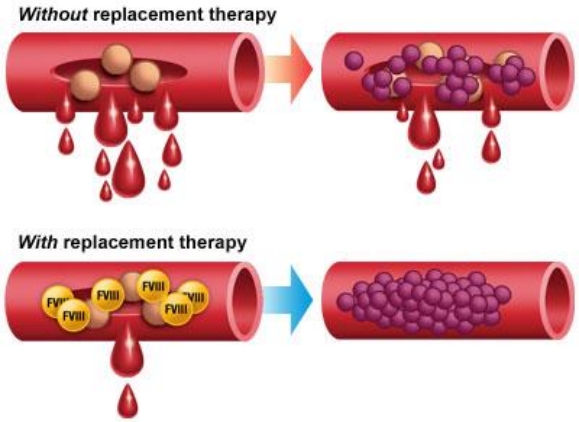
Integumentary system

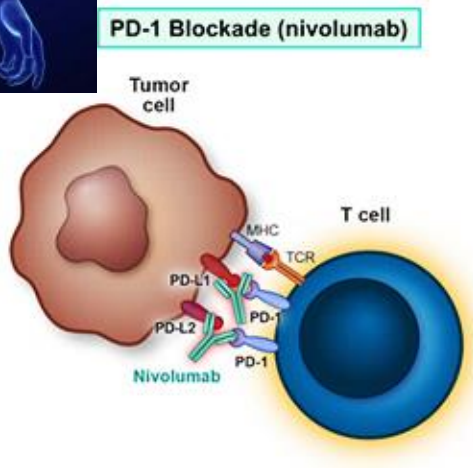


Factor VIII helps blood to clot

Treatment hemophilia

Nivolumab





Monoclonal antibodies (mAb)

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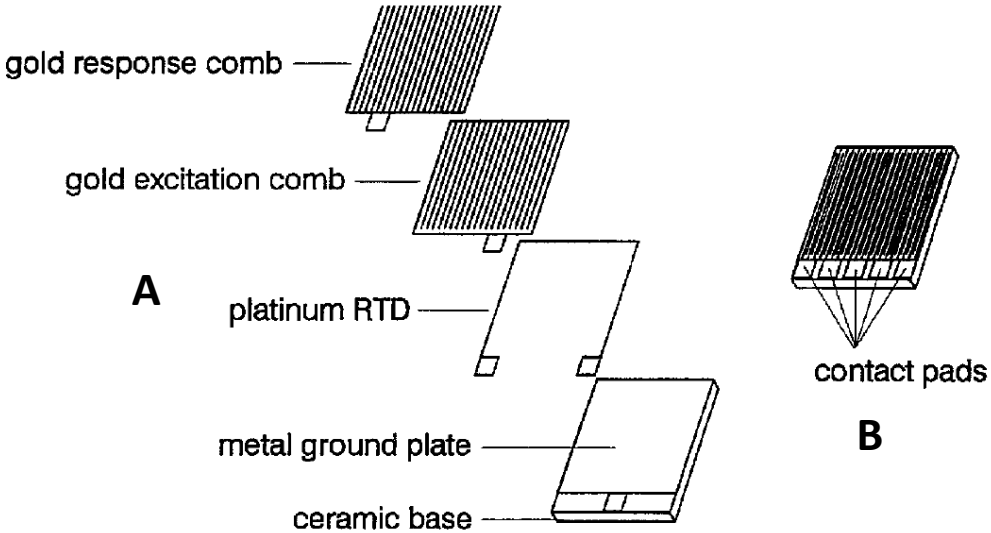
mAbs used for treatment cancer

Table 1 FDA-approved mAbs for use in oncology

Name	Marketed by	Class	Target	First approved indication	Reported mechanisms of action	Approval year
Rituximab (Rituxan)	Biogen Idec/ Genentech	Chimeric IgG1	CD20	Non-Hodgkin's Lymphoma	ADCC, CDC, Induction of Apoptosis[4]	1997
Trastuzumab (Herceptin)	Genentech	Humanized IgG1	HER2	Breast Cancer	Signal Inhibition, ADCC[5]	1998
Alemtuzumab (Campath)	Sanofi-Aventis	Humanized IgG1	CD52	B cell Chronic Lymphocytic Leukemia	CDC, Induction of Apoptosis[6]	2001
Ibritumomab tiuxetan (Zevalin)	Biogen Idec	Murine IgG1	CD20	Non-Hodgkin's Lymphoma	Radioisotope Delivery (^{90}Y)	2002
Tositumomab (Bexxar)	GlaxoSmithKline	Murine IgG2a	CD20	Non-Hodgkin's Lymphoma	Radioisotope Delivery (^{131}I), ADCC, CDC, Induction of Apoptosis[7]	2003
Cetuximab (Erbitux)	Bristol-Myers Squibb/Eli Lilly	Chimeric IgG1	EGFR	Squamous Cell Carcinoma of the Head and Neck	Signal Inhibition, ADCC, CDC[8]	2004
Bevacizumab (Avastin)	Genentech	Humanized IgG1	VEGF	Colorectal Cancer	Signal Inhibition[9]	2004
Panitumumab (Vectibix)	Amgen	Human IgG2	EGFR	Colorectal Cancer	Signal Inhibition, ADCC[10]	2006
Ofatumumab (Arzerra)	Genmab/GSK	Human IgG1	CD20	Chronic Lymphocytic Leukemia	ADCC, CDC[11]	2009
Denosumab (Xgeva)	Amgen	Human IgG2	RANKL	Bone Metastases	Signal Inhibition	2010
Ipilimumab (Yervoy)	Bristol-Myers Squibb	Human IgG1	CTLA-4	Metastatic Melanoma	Signal Inhibition[12]	2011
Brentuximab vedotin (Adcetris)	Seattle Genetics	Chimeric IgG1	CD30	Hodgkin Lymphoma	ADC	2011
Pertuzumab (Perjeta)	Genentech	Humanized IgG1	HER2	Breast Cancer	Signal Inhibition, ADCC[13]	2012
Trastuzumab emtansine (Kadcyla)	Genentech	Humanized IgG1	HER2	Breast Cancer	ADC, Signal Inhibition, ADCC[14]	2013

Interdigitated electrodes

- Interdigitated electrodes have been used in past for the prediction of lyophile collapse temperature



A: Showing individual components of a single surface, co-planer, interdigitated-comb sensor and **B:** the complete sensor

RESEARCH ARTICLE

Prediction of Lyophile Collapse Temperature by Dielectric Analysis

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ABSTRACT: A new method for predicting lyophile collapse temperatures based upon dielectric analysis (DEA) of frozen two component systems is presented. The method, called the take off frequency model (TOF), relies both on the inherent ability of DEA to detect molecular motion and on the abrupt change in viscosity experienced by a frozen sample undergoing a glass-liquid transition. Collapse temperatures for binary glass forming systems (an antibiotic, sucrose, trehalose, or sorbitol, with water) were in good agreement with the values reported in the literature. DEA was easily able to detect glass transitions poorly defined by differential scanning calorimetry (DSC). Conservative lyophilization cycles for simple systems can be quickly determined on the basis of the TOF model.

Introduction

Dielectric analysis (DEA) has been used extensively in polymer science for determining the characteristics of polymer films (1). There is also a considerable history of DEA in the study of molecular properties including those of biological molecules (2–6). With the advent of commercially available instruments (see Experimental), some preliminary pharmaceutical applications have been explored in our lab. The current work summarizes efforts to characterize representative frozen aqueous systems intended for lyophilization for the purpose of determining the highest allowable temperature for primary drying without collapse.

Pikal (7) has shown that there is a correlation between collapse temperature (Tc) and the glass transition temperature (Tg′) of glass forming systems. There are, however, difficulties in the determination of Tg′ by the common methods such as differential scanning calorimetry (DSC), conductivity, etc. DSC may require relatively high concentrations in systems with very low energy transitions and direct current or single frequency resistivity measurements depend on ionic content and do not easily distinguish first order from higher order transitions. It has also been documented that the Tg′ may precede the observed Tc by varying intervals up to several degrees C (7). It was thought that DEA might provide a more sensitive and accurate measure of Tg′ for reasons described below. As with most techniques, we have come to view DEA as complementary to classical thermal techniques for the complete characterization of such transitions. This report will present the basis of our "model" for predicting the Tc based on DEA results. This is a new application of the technique and the development of our model may provide an approach that will prove useful in the study of other pharmaceutical processes and systems.

Background

Basically, DEA involves the construction of a capacitor in which the sample to be examined is the dielectric material between the capacitor plates. A sinusoidal voltage of fixed amplitude and known frequency is impressed across the capacitor and the resulting current is followed with time. Changes in the phase of the current relative to that of the applied voltage are then used to calculate the dielectric constant (ε). Since ε is ultimately a function of frequency and temperature, it is not a constant and is simply referred to as permittivity or relative permittivity. This concept may be described mathematically in terms of the force that the dielectric material experiences in the capacitor. For a static field Maxwell's relationship (cgs system) (8) for a non polar dielectric is

$$\vec{D} = \epsilon_r \vec{E} \qquad (1)$$

where D is the displacement force, E is the electric field inside the capacitor ($D = E$ in vacuo), and ϵ_r is the

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This work was presented in part on 5/14/92 in Newark, DE at the Spring Thermal Analysis Symposium & Exhibition on Applications in the Food, Pharmaceutical and Cosmetic Industries sponsored by the Thermal Analysis Forum of Delaware Valley and as a poster at the Eastern Regional AAPS Meeting on 6/2/92 in New Brunswick, NJ.
Author to whom correspondence should be addressed: Dr. Sean A. Evans, ImmuLogic Pharmaceutical Corp., 610 Lincoln Street, Waltham, MA, 02154.

Mackenzie, A. P., Evans, S. A. and Morris,. Prediction of Lyophile Collapse Temperature by Dielectric Analysis Prediction of Lyophile Collapse Temperature by Dielectric Analysis, *PDA J Pharm Sci and Tech* **1994**, *48* 318-329.

Example interdigitated electrode (gold on glass)

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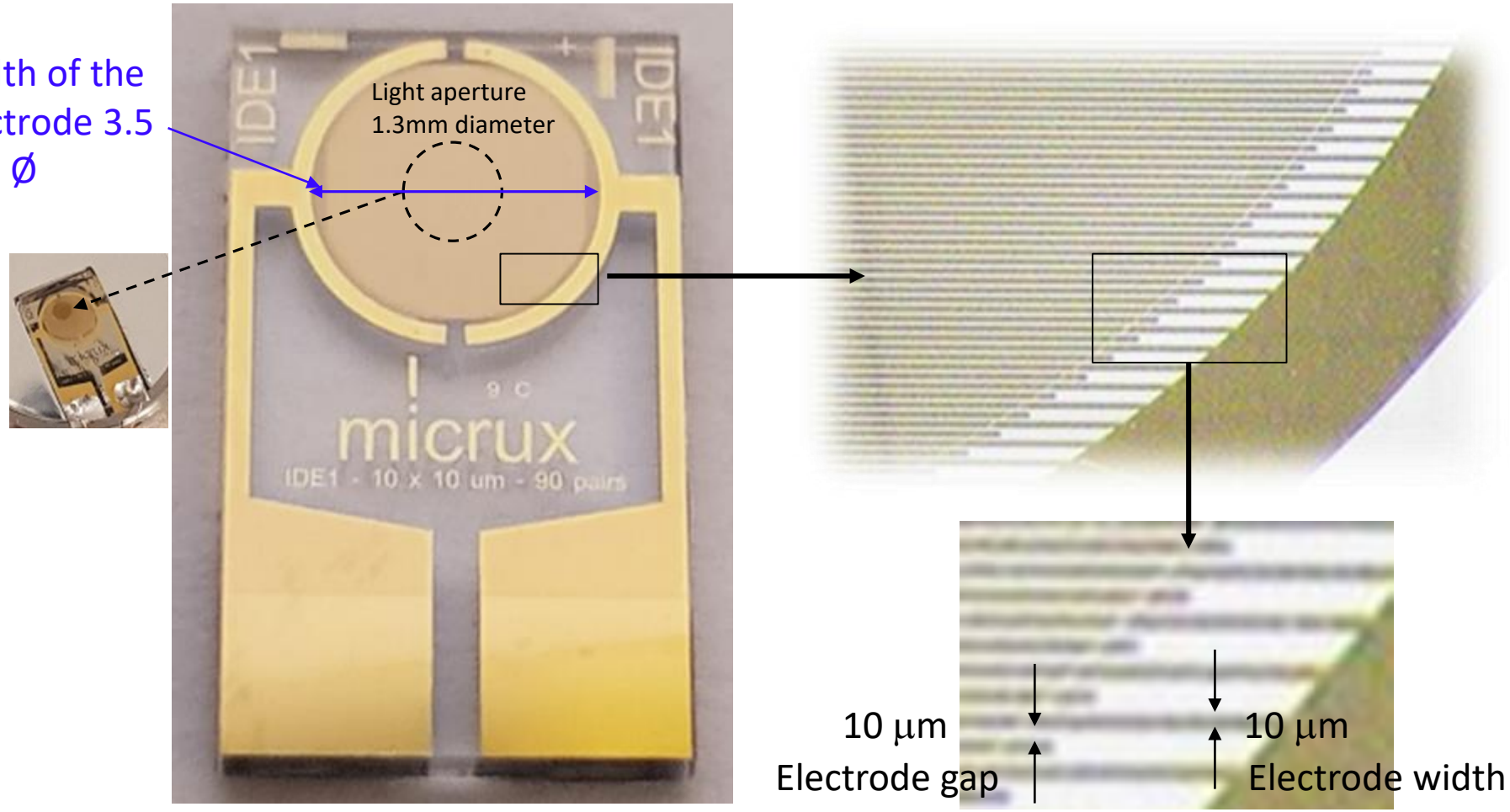

Commercial IDE – Micrux™

Design of IDE holder

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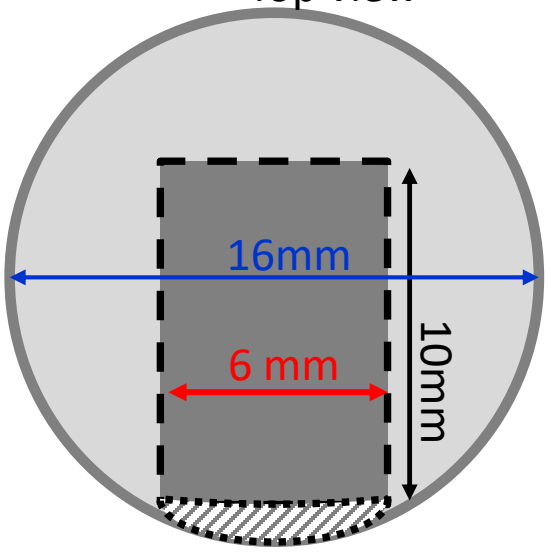
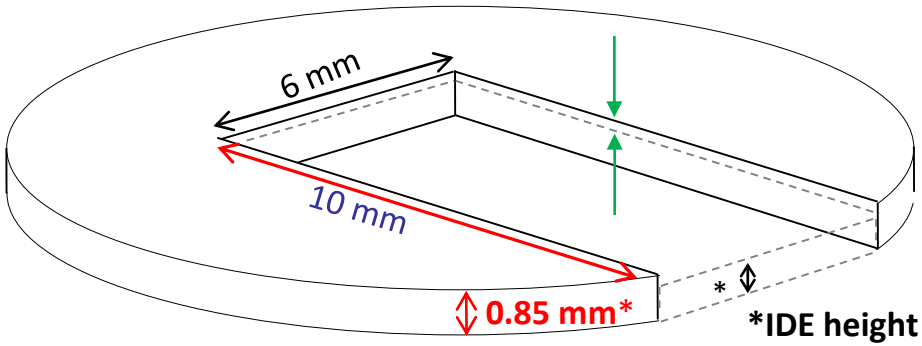
Top view



IDE dimensions:
10 x 6 x 0.75 mm

Theoretical sample height



*IDE height
0.75 mm

* different height of IDE adaptors used for initial assessment:

- 0.85 mm
- 0.90 mm
- 0.95 mm
- 1.00 mm

IDE is lower than the adapter and sample height derived between difference between then IDE adaptor size