New Impedance Based Methodologies to Determine the Vial Heat Transfer Coefficient and the Endpoint of Primary Drying

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SUMMARY

Aims: To propose a new methodology to determine the vial heat transfer coefficient (K_V) and the endpoint of primary drying. Methods: Convergence of the peak imaginary capacitance (C''_{PEAK}) and the high frequency permittivity, C'(100 kHz) was used as a new method to calculate the drying rate and K_V and the time profile of C'(100 kHz) was used to determine the endpoint. Results: Convergence was true only within the first 5 % of ice sublimation; C'(100 kHz) plateau coincided with the visual endpoint; Conclusions: K_V should be calculated only within the first 5% of primary drying and C'(100 kHz) can be followed to detect the endpoint.

INTRODUCTION

The freeze-drying cycle comprises (1) freezing to form ice and crystallise out any solutes, (2) primary (1°) drying to remove the ice phase by sublimation and (3) secondary drying to remove the remaining unfrozen water which is bound to the remaining matrix of crystalline and amorphous solids, Smith (2017).

A better fundamental understanding of the coupled heat and mass transfer processes in 1° drying requires the characterisation of the vial heat transfer coefficient (K_V). In industry, K_V is determined after the completion of ~30% of ice sublimation from the classic heat/mass balance equation,

$$dq/dt = L.\ dm/dt = A.\ K_V.\ \Delta T$$

where dm/dt is the drying rate, dq/dt is the rate of heat transfer from the shelf to the bottom of a given vial; ΔT is the difference between the product and the shelf temperature; A is the vial's cross-sectional area; and L is the latent heat of sublimation, Pikal (1984). However, this calculation assumes that heat is transferred only via the base of the vial and the ice layer has been drying in a horizontal plane from the beginning to the time corresponding to 30% of ice sublimation. *The first objective of this work is to present a new methodology based on Through Vial Impedance Spectroscopy (TVIS) that was used to test whether the assumption is true.*

Frequently, the endpoint of 1° drying is determined from product thermocouples among several other Process Analytical Technologies (PATs), none of which are free from limitations. *The second objective of this work is to present a new methodology using TVIS to determine the endpoint of primary drying.*

MATERIALS AND METHODS

Double distilled water from "all glass apparatus" was used in this study. The TVIS system comprises a bespoke multichannel high precision impedance analyser which was connected to a TVIS measurement vial, which is a standard 10 mL freeze drying vial (manufactured by Schott) that has been modified with copper electrodes (19 x 10 mm) attached to the outside of the glass wall, thus making the measurement non-product invasive. One clear vial (with 3 Type K thermocouples submersed at a range of heights within the liquid) and a TVIS vial each containing 3 g distilled water, were freeze dried in a Virtis Advantage Plus benchtop freeze dryer, by freezing at a shelf temperature of −40 °C at a ramp of ~43 °C h^{-1}, then annealing to −10 °C at a ramp of 30°C h^{-1}, (with a hold time of 1 h) and then subjected to 1° drying at −15 °C until all of the ice disappeared. TVIS capacitance spectra and photographs of the ice sublimation process (using a Canon EOS 550D) were collected every two minutes throughout the freeze-drying process. Two parameters, C"PEAK and C'(100 kHz), of the real and the imaginary capacitance spectra of the TVIS vial (example spectrum not shown) are considered to be proportional to the amount of ice remaining in the vial. It is assumed that C"PEAK is proportional to the height of the ice layer that is in contact with the glass wall whereas C'(100 kHz) measures the bulk of the ice in the vial whether in contact with the vial wall or not. The premise for assuming that the ice layer is drying in a horizontal plane, and therefore the surface area of the ice may be equated to the cross-sectional surface area of the vial (A), is that both C"PEAK and C'(100 kHz), when normalised to one another, should follow the same trajectory in time.

RESULTS AND DISCUSSION

C"PEAK was found to be proportional to C'(100 kHz) on the normalised scale (Figure 1) over the first ~5 min of primary drying (equivalent to 5% ice sublimation).

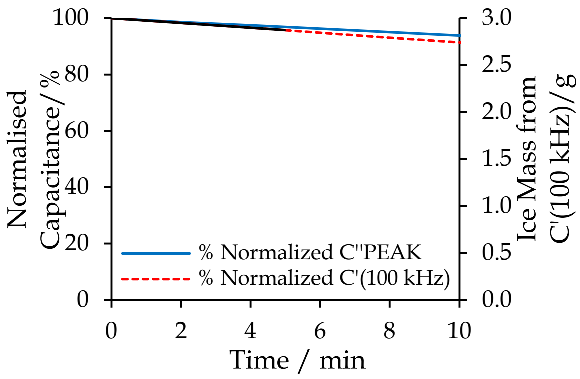

Fig. 1. Convergence of C"PEAK and C'(100 kHz) parameters form the real and the imaginary capacitance spectrum over the first 4 minutes of primary drying

During this brief period the gradient (i.e. drying rate: 1.512 g/h) was determined from the assumption C"PEAK and C'(100 kHz) are both proportional to the amount of ice remaining in the vial. The K_V (~ 318 W m^{-2} K^{-1}) value was determined from the heat/mass balance equation, where L = 2844 Jg^{-1} and dq/dt = 4300 Jh^{-1}, ice temperature was 242 K (recorded from a thermocouple placed in the top region of the ice layer), shelf temperature was 258 K and A = 0.00045 m^{-2}. As expected, K_V was much higher than the range of values found in the literature (15-25 W m^{-2} K^{-1} at 40 Pa), Brülls (2002) as a consequence of the fact that the current study was undertaken on an isolated vial whereby the radiant heat from the side walls would contribute significantly to the heat transfer co-efficient.

The second objective of this work was to present a new methodology for determining the endpoint of primary drying based on the parameter C'(100 kHz) (Figure 2).

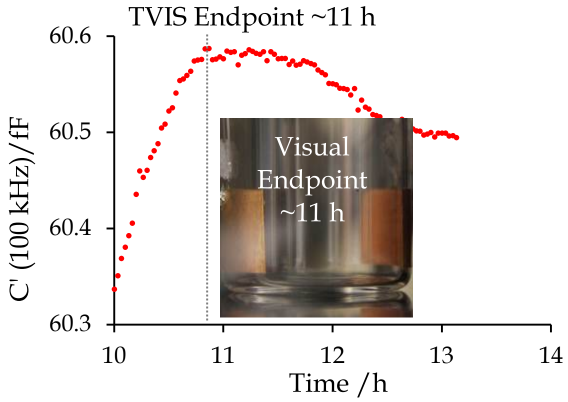

Fig. 2. TVIS endpoint from (C'100 KHz) vs Visual Endpoint

This plot is an enlarged version of a plateau in the high frequency region of the real capacitance spectrum (which is towards the end of 1º drying). The point at which the C'(100 kHz) parameter reaches a plateau (before decreasing) corresponds to the point at which the ice disappears by the photographic evidence.

CONCLUSIONS

Two conclusions may be made from this work (i) In the case of an isolated vial, K_V should be determined within the first 5% of primary drying before the ice interface starts to deviate from a planar drying that would otherwise result in uncertainties in the estimation of the surface area of the ice interface, (ii) The time profile of C'(100 kHz) may be used to detect the endpoint of primary drying.

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