# Application of Through Vial Impedance Spectroscopy for Lyophilization Process Development

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## 1. INTRODUCTION

### Freeze drying process and critical factors

Freeze- drying or lyophilisation is a widely used stabilisation strategy for the downstream processing of several pharmaceutical and biological compounds. A sound understanding of the various heat transfer mechanisms (conduction, convection and radiation) is important for delivering products with the required critical quality attributes. The overall heat contribution from these heat sources is represented by a numerical value termed "vial heat transfer coefficient" ($K_v$). Vial location is one of the key factors that impacts the value of $K_v$ particularly for the edge vials and the centre/core vials.[1]

### Single vial and batch techniques to determine $K_v$

In practice, $K_v$ is most commonly determined by a gravimetric method and less frequently by the batch techniques such as the Tuneable Diode Laser Absorption Spectroscopy (TDLAS) (Fig 1).

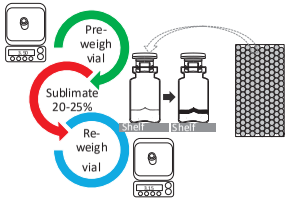


**Fig 1A:** Illustration of the Gravimetric method for individual vial $K_v$ after 20-25 % ice sublimation

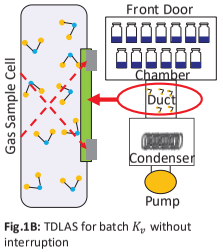


**Fig.1B:** TDLAS for batch $K_v$ without interruption

The gravimetric method (Fig.1A) involves loading the dryer with pre-weighed vials and weighing them individually after interrupting the primary drying stage following the sublimation of 20-25 % of ice. This approach assumes that the shape of the sublimation interface and the contact of the ice with the walls of the vial won't have changed over this period and therefore the contributions from the various heat transfer mechanisms also won't have changed and therefore drying will have occurred at a constant rate.

In contrast, TDLAS has an advantage over the gravimetric method in that with TDLAS, it is possible to determine $K_v$ without interrupting primary drying. Nevertheless, it doesn't allow one to obtain $K_v$ from individual vials. Further, the application of this technique to model the entire batch relies on a numerical factor that accounts for the edge vial effect.[1] For example, it is assumed that the edge vials dry 50 % faster (i.e. a factor of 1.5) than the core vials.

### Through vial impedance spectroscopy (TVIS)

Through vial impedance spectroscopy (TVIS) measures the electrical properties of the glass vial and the contents of the vial. It comprises an electrode system attached on the outside of a standard glass vial. With a dual electrode system, it has been possible to determine $K_v$ over a steady state period for a core vial.[2] The peak imaginary amplitude, $C''_{PEAK}$, is a direct measure of the ice mass in the vial, and the peak frequency, $F_{PEAK}$, serves two important roles: (i) it is an indicator of the point when the sublimation interface changes shape and therefore, informs one of a finite time period over which $K_v$ can be determined, (ii) its sensitivity to temperature makes it a reliable parameter for estimating the product temperature during primary drying.

## 2. AIM

The aim of this work is to demonstrate the application of TVIS for the determination of surrogate drying rate (dC"PEAK/dt) across the shelf.

## 2. OBJECTIVES

- To calibrate $F_{PEAK}$ from the electrode system with the temperature from a thermocouple in the neighbouring vial during re-heating
- To predict ice temperature, $T(F_{PEAK})$, during primary drying
- To compensate for the temperature dependency of $C''_{PEAK}$ during primary drying
- To define a period of steady state during primary drying
- To assess the impact of vial location on the steady state period and the surrogate drying rate

## 3. MATERIALS AND METHODS

160 standard 10 mL vials (manufactured by Schott) containing ~3g of double distilled water were used in this work, out of which 5 were modified TVIS measurement vials with copper electrodes (19 by 10 mm), with 4 out of the 5 accompanied by the nearest neighbour vials containing a thermocouple submersed in the liquid at a height corresponding to the midpoint of the liquid bound by the electrodes (Fig. 2A&B). The freeze drying cycle (Fig. 2C) was executed in a Virtis Advantage Plus laboratory freeze dryer equipped with a pass-through for TVIS measurement (Fig. 2D).

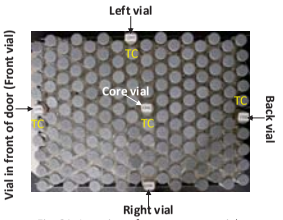


Fig. 2A: Location of measurement vials

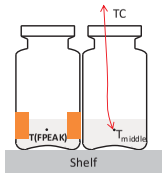


Fig. 2B: Position of thermocouple

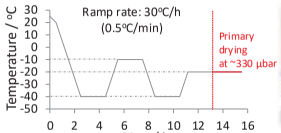


Fig. 2C: Freeze drying cycle

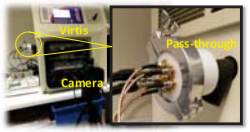


Fig. 2D: Virtis Advantage Plus freeze dryer with a pass-through for TVIS measurement

## 4. RESULTS AND DISCUSSION

### Temperature calibration

The relationships of both $F_{PEAK}$ and $C''_{PEAK}$ with temperature follow a 2nd order polynomial function during re-heating. Fig. 3 demonstrates the temperature dependency for the front TVIS vial.

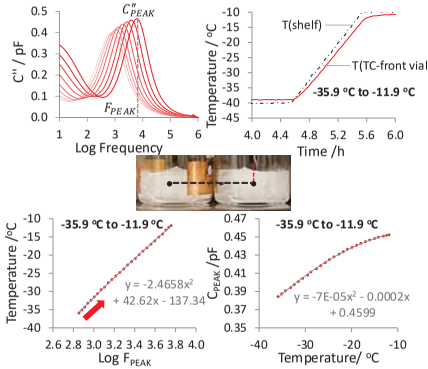


Fig. 3: Temperature Calibration of $F_{PEAK}$ and $C''_{PEAK}$

### Prediction of ice temperature and standardization of $C''_{PEAK}$ in primary drying

The polynomial coefficients from the temperature calibration of $F_{PEAK}$ are used to predict ice temperature, $T(F_{PEAK})$, during primary drying. Fig. 4A shows the ice temperature predicted for the front TVIS vial.

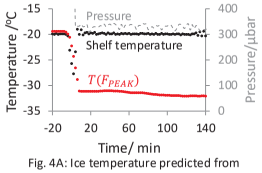


Fig. 4A: Ice temperature predicted from the calibration routine for the front vial

In Fig. 4B, it is clear that $C''_{PEAK}$ is also sensitive to temperature over the first 12 min of primary drying when the shelf temperature and the chamber pressure stabilize. Therefore, $C''_{PEAK}$ requires a standardization factor ($\emptyset$) for temperature compensation:

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

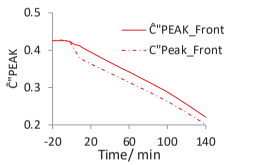


Fig. 4B: Temperature compensation of $C''_{PEAK}$ in primary drying

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

The expression for $\emptyset(T)$ can be re-written in terms of the polynomial coefficients from the temperature calibration of $C''_{PEAK}$:

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

Values of $C''_{PEAK}$ during primary drying are then standardized to the reference temperature by dividing $C''_{PEAK}(T)$ by $\emptyset(T)$ to give a standardized peak amplitude of $\hat{C}''_{PEAK}$ *(Fig. 4B)*

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

### Determination of the period of steady state during primary drying

It is clear from the photographic images of the front TVIS vial (Fig. 5A) that the shape of the sublimation interface changed over the course of primary drying such that the ice developed a more prominent cone or a dome shaped top surface owing to the additional heat contribution from radiation. It follows that the contact between the ice and the side wall of the glass vial degraded over time. This phenomenon was registered by $F_{PEAK}$ whose time profile suggested the point when the curvature of the sublimation interface started to change (80 min), as in Fig. 5B(i). This becomes clearer when one looks at the trajectory of $T(F_{PEAK})$ which decreases as the ice temperature, sensed by the thermocouple in the neighbouring vial, increases as shown in Fig. 5B(ii).

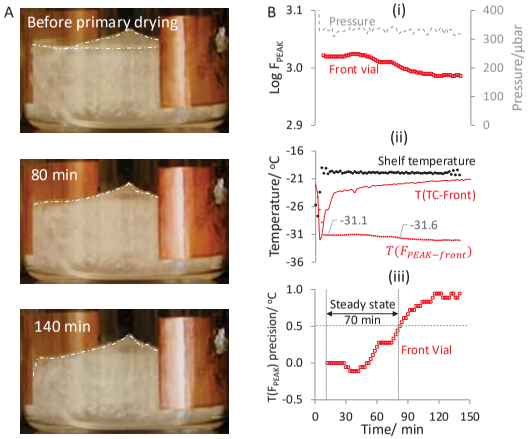


Fig. 5: (A) Images of the sublimation interface in the front vial; (B) Determination of steady state

It is true that as the contact between the ice and the glass wall degrades, the drying rate decreases and the ice temperature increases which is sensed by the thermocouple. However in this case, the thermocouple appeared to sense the gas temperature in the void formed around the tip of the thermocouple's sensing bead.

In order to define the period of steady state (Fig. 5Biii), a pre-defined precision of 0.5 °C for the change in $T(F_{PEAK})$ from -31.1 °C was considered because that corresponded to the first point (12 min) when the shelf temperature and the chamber pressure stabilised. The steady state period lasted for the next 70 min when $T(F_{PEAK})$ was -31.6 °C (82 min) and therefore, agreed with the pre-defined temperature limit.

### Assessment of the rate of change in $\hat{C}''_{PEAK}$ during steady state primary drying

It is important to recognize that the methodologies discussed in the previous sections for the front edge vial were also used for studying the other TVIS vials except for the right edge vial which did not accompany a thermocouple in the neighbour vial due to an equipment limitation. The data in Fig. 6 are summarised in Table 1 which clearly demonstrates the heterogeneity of the heat transfer process across the batch.

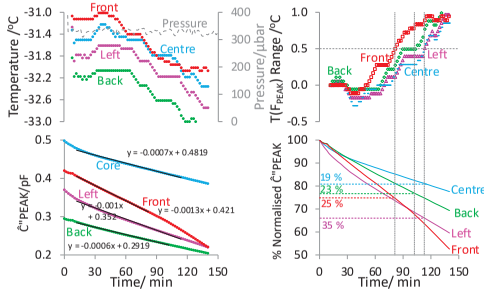


Fig. 6: Heterogeneity in the surrogate drying rate across the shelf

Table 1: Comparison of drying behaviour of TVIS vials over the steady state period

| Vial | Steady state period/min | % reduction in $\hat{C}''_{PEAK}$ | d($\hat{C}''_{PEAK}$)/dt Factor |
|---|---|---|---|
| Front edge | 82 | 25 | 1.86 |
| Left edge | 114 | 35 | 1.43 |
| Back edge | 102 | 23 | 1.16 |
| Core | 114 | 19 | 1.00 |

The use of $T(F_{PEAK})$ to define the steady state period for the vials located in different positions of the shelf is justified when one considers the % reduction in $\hat{C}''_{PEAK}$ which agrees with the gravimetric approach of interrupting primary drying after 20-25 % removal of ice. This reaffirms that over the estimated steady state period, the contributions from the heat sources did not change and therefore drying occurred at a constant rate. Further, the knowledge of the relative differences in the d($\hat{C}''_{PEAK}$)/dt factor across the shelf can be used to allow for a more precise modelling of the freeze-drying process.

## 5. CONCLUSION

The relative measurements of the surrogate drying rate could provide a more precise definition of the factor that accounts for the edge vial effect.

## 6. REFERENCES

1. Tchessalov, S. 2017, "Application of modeling to lyophilization process design and scale up: process validation approaches"
2. Smith, G., Jeeraruangrattana, Y. & Ermolina, I. 2018, "The application of dual-electrode through vial impedance spectroscopy for the determination of ice interface temperatures, primary drying rate and vial heat transfer coefficient in lyophilization process development", European Journal of Pharmaceutics and Biopharmaceutics, vol. 130, pp. 224-235.