# Multiplexing Through Vial Impedance Spectroscopy (TVIS) with Comparative Pressure Measurement for the Determination of the Primary Drying Endpoint of Immunoglobulin (IgG)

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## Abstract

Two IgG formulations, one with 5% sucrose and the other with 5% Mannitol:Sucrose (ratio 4:1) both in 20mM Histidiine 0.01% Tween 20 pH 6.5, were freeze dried in a Telstar freeze dryer equipped with Pirani and Baratron sensors and a Sciospec® five-channel through vial impedance spectroscopy (TVIS) system. The TVIS parameter C'(100kHz) (i.e. the real part electrical capacitance measured at 100 kHz) is sensitive to the amount of ice in the vial. By following the recovery of its time profile during primary drying, it was possible to determine the primary drying endpoint. The TVIS endpoint of the sucrose edge vial occurred well before the onset of the Pirani endpoint suggesting that Pirani was more sensitive to the core vials. The TVIS endpoint in the core vials also occurred somewhere close to the midpoint of the Pirani endpoint suggesting that other core vials were still in primary drying.

## Introduction

Comparative pressure measurement using the Pirani and the Capacitance Manometer (MKS Baratron) sensors is most popular among the batch techniques that have been utilised for the determination of the primary drying endpoint [1]. Through vial impedance spectroscopy (TVIS) is a single vial technique that 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, thereby making the measurement non-product invasive. Previously, it has been shown that it is possible to determine the endpoint of a sucrose formulation using the imaginary capacitance at 1 kHz. The aim of this study is to use the time-line of the real capacitance at 100 kHz, i.e. C'(100kHz) to determine the range of primary drying endpoints for a complex protein formulation located at the edge and the core; and to compare the endpoint from TVIS with the endpoint given by the comparative pressure measurement.

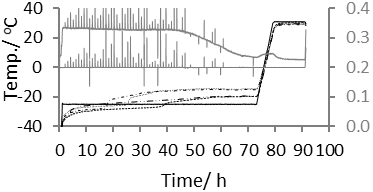
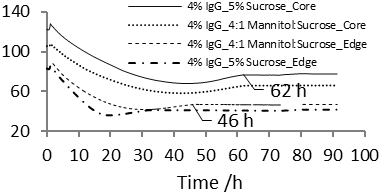
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## Materials and Methods

A batch of 308 x 5 mL vials (Adelphi VC005-20C) were filled with 3g of 20 mM Histidine Buffer and 0.01% Tween 20 pH 6.5, containing either (i) 4% IgG with 5% sucrose; (ii) 4% IgG with 5% of a 4:1 mannitol:sucrose mixture; or (iii) their placebo equivalents. Two vials from (i) and two vials from (ii) were modified with copper electrodes (19 mm by 10 mm; copper adhesive tape 1181 3M) attached externally to the glass wall at a distance of 3 mm from the vial baseline. One TVIS vial from each IgG containing formulation were placed in the middle of the first row of the edge vials facing the dryer door and the other two TVIS vials were placed in the core. Each TVIS vial was accompanied by two Type T thermocouples placed in the immediate neighbor vials. Freeze drying was carried out in a Telstar Pilot dryer equipped with Pirani and Capacitance Manometer pressure sensors and a 5-channel TVIS system (Sciospec, Germany). The lyo cycle consisted of a freezing ramp from 20 oC to -50 oC at 0.2 oC/min, two annealing steps (to -15 oC and -28 oC), followed by a 73 h primary drying step at a shelf temperature of -25 oC and finally a secondary drying step at a shelf temperature of 30 oC. The total cycle time for the recipe was approx. 113 h.

## Results and Conclusions

Fig. 1(i) shows the time-lines of the Pirani and Baratron sensors and the thermocouple product temperatures. Fig. 1(ii) shows the characteristic dip and recovery of the TVIS parameter C'(100kHz) that we take as the sublimation end-point. The TVIS endpoint for the sucrose-IgG edge vial occurred 12 h earlier than the onset of the reduction in the Pirani vapour pressure (43 h). In addition, the TVIS endpoint for both core TVIS vials occurred at 62 h and yet the Pirani was still active until 73 h. This may be due to one or both of two factors: (i) other core vials were still drying (most probable) and/or (ii) the Pirani continues to sense water vapour in the dryer even when all the ice has sublimed (least probable).



Pirani

Baratron

Shelf Temperature

32h h

(i) Batch

(ii) Single Vial TVIS

C'(100kHz)/ fF

Pressure/ mbar

TCs

**Fig. 1** *Primary drying endpoint determination using (i) comparative pressure measurement (i.e. Pirani and Baratron) and (ii) through vial impedance spectroscopy for two IgG formulations*

**References**

1. S.M. Patel, T. Doen, M.J. Pikal, Determination of End Point of Primary Drying in Freeze-Drying Process Control, Aaps Pharmscitech 11 (2010) 73-84.