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Research paper

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

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ABSTRACT

Through vial impedance spectroscopy (TVIS) is a product non-invasive process analytical technology which exploits the frequency dependence of the complex impedance spectrum of a composite object (i.e. the freeze-drying vial and its contents) in order to track the progression of the freeze-drying cycle. This work demonstrates the use of a dual electrode system, attached to the external surface of a type I glass tubing vial (nominal capacity 10 mL) in the prediction of (i) the ice interface temperatures at the sublimation front and at the base of the vial, and (ii) the primary drying rate. A value for the heat transfer coefficient (for a chamber pressure of 270 μbar) was then calculated from these parameters and shown to be comparable to that published by Tchessalov (2017).

1. Introduction

One of the dehydration techniques commonly used for drying of heat sensitive biopharmaceuticals, such as therapeutic proteins, is freeze drying or lyophilization. This multi-step process is costly, time-consuming and difficult to transfer technology from R&D scale to commercial scale manufacturing due to the differences in equipment scale/design and the impact of these factors on heat and mass transfer [2,3].

An example of the impact of scale, is that the proportion of the so-called 'edge' vials (i.e. those exposed to the radiant heat from the door and the walls of the primary drying chamber) to those considered to be core vials (i.e. those which are surrounded by vials at similar temperatures to each other) will be higher in the smaller dryer compared to the larger dryer, resulting in differences in the average drying rates of the two populations of vials.

One simple example of a difference in design is that a lab scale freeze dryer (which only has a capacity of 200–500 vials) often has an acrylic glass door which has a thermal radiation coefficient which is greater than that of the stainless steel doors used in the larger dryers (which can have capacities of up to 200,000 vials, depending on their size). It follows that the product temperature of the vials in the first few rows of a laboratory scale dryer (close to the chamber door) will be higher than the front row of vials in the commercial dryer [4] and therefore the former will again experience faster drying rates for the same freeze-drying protocol (e.g. shelf temperature set value).

Other factors associated with dryer design and scale are the distribution in shelf temperatures (both across an individual shelf and between shelves), the chamber pressure (especially the build-up of water vapor towards the center of the large shelves of a commercial dryer), the fill volume (or more specifically the fill height) and the product characteristics (such as dry layer resistance). Each and all of these have a direct influence on the distribution of product temperatures both within an individual vial and across the population of vials within the dryer. For example, the greater the fill height and the faster the drying rate (either because of a lower dry layer resistance and/or because the vial location is close to the chamber wall) then the larger will be the temperature gradient from the bottom of the vial to the ice interface.

None of these issues would be so important, were it is not for the fact that an increase in product temperature above the glass transition of the freeze concentrated solution, $T_g^{'}$, may cause a collapse of the cake microstructure at a specific formulation related temperature known as collapse temperature, T_c. The possible consequences of exceeding the collapse temperature are reduced rates of drying (if collapse increases the dry layer resistance) and increased product temperatures (owing to reduce self-cooling rates). These factors can then impact the critical quality attributes of product stability, final moisture content and

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appearance, and even lead to the rejection of an entire commercial batch. In order to avoid such dramatic consequences, the product is usually dried at temperatures much lower than the theoretical limit, in order to maintain a safe margin between the product temperature and the collapse temperature but at the additional cost of a more prolonged primary drying time.

It is not surprising therefore that effort to improve process efficiencies have focused on the development and effective use process analytical technologies (PAT) for the determination of product temperature, as a significant process parameter [5–10]. These PATs can be divided into single vial techniques, which are characterized by having some forms of probe (usually inserted inside the vial) and batch techniques which are based on some direct or indirect measurement of drying rate from which mathematical models may be developed to predict the temperature at the ice sublimation interface (T_i) and at the base of the ice (T_b). It is not the intention here to fully appraise the strengths and weaknesses of currently available process analytical technologies as this information can be found in the recent reviews on process monitoring tools for pharmaceutical freeze drying [11–13].

1.1. Single vial techniques

Thermocouples (Type-T is generally used for pharmaceutical lyophilization) and resistance temperature detectors (abbreviated to RTD) are the traditional temperature sensors used for both laboratory and production scale investigations. It is recommended that these sensors are positioned inside and at the center of the base of the vial where one expects the last vestiges of the ice mass will be removed [14]. To achieve this, it requires a fastening device to avoid the misplacement of the probe. The positioning of the sensor at the base of the vial is an appropriate strategy for witnessing the end point of primary drying and for determining the vial heat transfer coefficient (K_v) but less useful when trying to predict the closeness of the sublimation interface temperature (T_i) to the temperature at which the dry layer will collapse (T_c) when trying to drive process efficiencies using elevated shelf temperatures. For that application, it might be necessary to have two 'point' sensors positioned at two heights within the ice layer and to predict ice base and ice interface temperatures assuming a linear temperature gradient across the ice layer.

In primary drying, the heat absorbed at the sublimation interface creates a temperature gradient within the ice layer, such that the ice interface temperature (T_i) is lower than the base of the ice cylinder (T_b) by as much as 10 °C, depending on factors such as the drying rate and the height of the product being dried [8,15]. Both temperatures are of interest to the development scientist, as the base temperature (T_b) along with the shelf temperature allows one to calculate the heat transfer coefficient (provided the drying rate is known) whereas monitoring of the sublimation interface temperature (T_i) enables one to maintain the temperature of top layer product below the critical limit known as the collapse temperature, in order to ensure that the dry layer can maintain the porous structure and thereby facilitate vapour loss during both primary and secondary drying. If the target is to measure the temperature at the bottom of the vial (T_b) e.g. for end point determination or K_v calculations, then the thermocouple may suffice. However, if the target is to determine the ice interface temperature (T_i) using a thermocouple then it will be possible only during the initial period of drying owing to the fact that, once the top layer of ice has been removed, the thermocouple will lose contact and begin to sense the temperature of the gas above the ice layer rather than the layer itself. This is one of the incidental observations we have made in this study (see Fig. 10B in Section 3.5).

1.2. Batch techniques

The first batch technique to be developed was the manometric temperature measurement (MTM) [6]. MTM combines data from the increase in pressure within the freeze drying chamber (that results from a transient closing of the isolation valve between the drying chamber and the condenser) with a mathematical equation to predict the 'batch average' temperatures at both the ice front and at the ice base within the vial. Some years following the introduction of MTM, Gieseler and coworkers [16] evaluated the potential of tunable diode laser absorption spectroscopy (TDLAS) for monitoring the sublimation rate during product development and process scale-up. Both MTM and TDLAS provide information on drying rates, as well as the temperatures at the base of the ice and at the sublimation interface, and so both techniques have been used successfully to characterize critical parameters of the system, such as heat transfer coefficients and dry layer resistances [6,16–21]. Both methods are also non-invasive methods and therefore won't alter the 'natural' characteristics and progression of the freeze-drying cycle. However, these techniques are limited in one sense, that they only provide a collective 'average' measurement of the batch and so if there is any significant heterogeneity in temperature and drying rates across the dryer and between shelves then these factors need to be accounted for in order to ensure that the process is modeled effectively. One way to account for this heterogeneity is to make certain assumptions concerning (i) the number of vials that can be considered as edge vials in proportion to the overall size of the batch, and (ii) the impact of radiant heating; and to introduce factors which model the faster drying rates of these vials [1]. An alternative and indeed complimentary approach would be to combine a non-invasive batch method such as MTM or TDLAS with a number of single measurements in the edge vial populations. An example of this approach is the "LyoMonitor" which multiplexes data from MTM and thermocouples in order to control the primary drying cycle [22].

Returning to a consideration of the single vial approaches, there appears to be a gap in the market for a sensor which can determine the ice interface temperature and the ice base temperature in a single vial (in a non-invasive manner) but is also able to measure the drying rate in a way that doesn't interfere with the hexagonal packing of the vials (as would be the case if using a microbalance to determine drying rates). Such a device could be deployed at key locations in the dryer and then multiplexed with MTM or TDLAS in order to qualify and validate the batch models which have incorporated factors for batch heterogeneity.

1.3. Through-vial impedance spectroscopy (TVIS)

TVIS has been developed in the first instance as a non-invasive process analytical technology for determining critical process parameters within individual vials, at user-defined locations across a small scale development dryer. The basis for the TVIS technology is the measurement of the electrical impedance of a freeze-drying vial containing the product, i.e. the opposition to current flow when an alternating voltage is applied to the vial, using a pair of electrodes which are attached to the external surface of the glass wall (hence the term "through-vial"). With a through vial impedance measurement it is the changes in the electrical properties of the composite object (comprising the product and the glass wall) that reflect the physical condition of the product during the freeze drying process [23]. Using a simple empirical approach in the first instance (as opposed to more sophisticated modeling of the electrical behavior of the composite object) it is possible to extract useful information about the sublimation of ice from the amplitude (C''_{PEAK}) and characteristics frequency (F_{PEAK}) of the dielectric loss peak that results primarily from the dielectric relaxation of ice. The C''_{PEAK} parameter is sensitive to the height of the ice cylinder within the electrode space (i.e. the internal volume of the vial which is bounded by the external electrodes) from which one can predict the rate of primary drying, whereas the F_{PEAK} parameter can be calibrated through the incorporation of an annealing stage and then used to predict the product temperature in a subsequent primary drying stage [24]. Both parameters also lend themselves to the determination of phase behavior (e.g. ice formation and eutectic formation) [25,26].