Freeze Drying from Small Product Containers and its Implication on Freeze Drying Process Design: Evaluation of Heat Transfer Coefficients of a New 96-Well Freeze Drying System in Comparison to 2R Tubing Vials and Polypropylene 96-Well PCR-Plates

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Delicate biological or pharmaceutical products such as proteins often require special handling in order to preserve their original characteristics and their activity. Freeze drying has become a method of choice to achieve long-term stability of such products. Many of these agents are of high potency so that only small quantities (i.e., a few μg) are needed per application. Moreover, production costs for these active ingredients are often excessive and therefore an additional demand for heat and mass transfer at the freeze drying process which in turn affects the product quality over time and the total primary drying time. The purpose of this study was to evaluate the efficiency of heat transfer in a new 96-well freeze drying system and comparison of these data to 2R tubing glass vials and 96-well PCR-plates manufactured by polypropylene which have been analyzed in earlier studies. Derivation of guidelines for freeze drying process design in small, atypical container systems is another intention.

MATERIALS & METHODS

Sublimation Tests

Sublimation tests with pure water were performed to determine vial heat transfer coefficients ($K_v$) of the new 96-well freeze drying systems (2R, 96-well, NY, USA) which consisted of 96 0.5 mL round bottom vials inserted into a single aluminum (Al) block with circular drillings designed for a tight fit of these vials (figs. 1 and 2). Vial inner cross-sectional area $A_p$ was 0.40 cm², vial outer cross-sectional area ($A_v$) was 0.60 cm². Experiments were conducted with a maximum number of six Al-blocks consisting of 96 0.5 mL polypropylene (PP) sublimation freeze dryer (FTS Systems, WA, USA) each filled with 0.4 mL of double-distilled water. Selected vials (roughly 10% of the batch) in center and edge positions of each Al-block were weighed before and after each run. Thermocouples (TC, Omega Engineering GmbH, copper-constantan, 0.08 mm wire diameter) were placed on the shelf surface beneath the two (of the Al-blocks as well as at the center bottom position of six selected vials in the batch. Tests were performed using a standard freezing protocol, a shelf temperature ($T_s$) setting of -5°C, and five pressure setpoints ranging from 0.03 to 0.5 Torr. The sublimation process was cut off after approximately two hours (removal of ice: ~ 30-40%) by rapidly increasing chamber pressure to ~ 3 Torr. The remaining ice was then thawed and the selected vials washed or weighed. Offset runs were conducted to account for the amount of ice removed during non-steady-state conditions in the initial ramping phase of the sublimation process. Additional testing included print tests to determine contact areas and Al-block.

Calculation of Heat Transfer Coefficients

Heat transfer coefficients were calculated from steady-state mass flux (dm/dt), heat of sublimation of ice, $\Delta H = 670$ cal/g, TC data, and the effective contact area between vial and Al-block. $\Delta H$ is the average temperature of the cavity surface of the Al-block. The temperature gradient from lower Al-block surface to inner cavity surface is assumed to be negligible (i.e., $< 1$ K) because the thickness of the Al-block bottom is low (0.3 mm) and specific thermal conductivity of aluminum is high. $T_v$ is the average temperature of product ice measured at center bottom position of the vials. The contact area, $A_{contact}$, of a vial inserted into an Al-block cavity with the Al-block was averaged over contact area at the beginning of the sublimation process and contact area for fill volume at the end of the process. Fill volume at the end of the sublimation phase was calculated from density of ice and vial weight at the end of the process.

Equation 1

$$ K_v = \frac{\Delta H \cdot dm}{\Delta T \cdot A_p} $$

Equation 2

$$ A_{contact} = A_p \cdot \left(1 - \frac{A_v}{A_p}\right) $$

Equation 3

$$ A_{fill} = \frac{A_p \cdot \rho \cdot v}{\rho_v} $$

Equation 4

$$ \Delta T = T_v - T_b $$

Equation 4a

$$ \Delta T = T_v - T_b $$

Equation 5

$$ Q_v = \left(\frac{A_{contact} \cdot \rho_v}{A_p \cdot \rho \cdot v}ight) \cdot \frac{d(T_s - T_b)}{dt} $$

Equation 5a

$$ Q_v = \left(\frac{A_{contact} \cdot \rho_v}{A_p \cdot \rho \cdot v}ight) \cdot \frac{d(T_s - T_b)}{dt} $$

Equation 6

$$ K_v = \frac{Q_v}{(\rho_v \cdot v \cdot \Delta T)} $$

Equation 6a

$$ K_v = \frac{Q_v}{(\rho_v \cdot v \cdot \Delta T)} $$

Equation 7

$$ K_v = \frac{Q_v}{(\rho_v \cdot v \cdot \Delta T)} $$

Equation 7a

$$ K_v = \frac{Q_v}{(\rho_v \cdot v \cdot \Delta T)} $$

Equation 8

$$ K_v = \frac{Q_v}{(\rho_v \cdot v \cdot \Delta T)} $$

Equation 8a

$$ K_v = \frac{Q_v}{(\rho_v \cdot v \cdot \Delta T)} $$

Equation 9

$$ K_v = \frac{Q_v}{(\rho_v \cdot v \cdot \Delta T)} $$

Equation 9a

$$ K_v = \frac{Q_v}{(\rho_v \cdot v \cdot \Delta T)} $$

RESULTS & DISCUSSION

$K_v$ data were statistically significant below $K_v$ values found for vials and slightly lower than $K_v$ values for 96-well PCR-plates inserted into Al-blocks with drillings adjusted to fit the conic shape of vial walls (table 1). There are several factors which might explain these differences. First, heat transfer for vials might be essentially from the vial bottom which is greatly different for PCR-plates and FDS. Here, the containers are inserted into Al-blocks which serve as heat transfer enhancers. For this reason, the Al-block is attached to the bottom but also from the side because the vial is completely “immersed” into the heat source. Note that heat transfer should be more efficient if a larger area can be used for transfer of energy. However, sublimation is found vertically and not only horizontally as in traditional heat transfer models. When the ice product directly adjacent to the container wall has sublimated, an isolation layer is created between the vial and the sublimation chamber which then greatly hinders heat transfer. Note that heat transfer from one side of the vial to the ice layer had a more impact on a vial plate due to a different effective surface. For the plates the formation of “ice pillars” with very little contact remaining to well walls has been observed. To take this change into account, the calculation of $K_v$ was adapted to these changed circumstances (eq. 4b). Al-blocks with drillings in the paint elevates the emissivity factor of the Al-blocks to nearly unity. In comparison to the emissivity of a shelf in direct line of view to 2R vials placed upon it, 0.6 and emissivity of slightly oxidized custom made Al-blocks used with PCR-plates is approximately 0.3. Based on the theoretical considerations of radiative heat transfer, the zero pressure intercept should be higher for FDS than for PCR-plates. However, the calculation of the zero pressure intercept for the Al-blocks with drillings were for the Al-blocks with drillings are plausible for this could be a significant decrease in radiation from the top shelf (shelf above FDS) caused by the Al-blocks which “block out” all perpendicular radiation. Contribution of $K_v$ also contributes to zero pressure intercept. Print tests of vials inserted in Al-blocks showed that, that total area of direct contact (bottom and wall of vial) between vial and block cavity was approximately 20% which is comparable to the contact area of PCR-plates inserted in Al-blocks (25%). Thirdly, it is to be expected that the energy accommodation coefficient $\alpha$ (eq. 6) is different for vials (0.67) than for the FDS and polypropylene PCR-plates: A relatively small variation in $\alpha$ may have a large impact on $K_v$ and therefore strongly affect efficiency of heat conduction through the gas. This assumption is supported by the difference in curve fitting of fitting functions (fig. 3). The increase of $K_v$ for small pressure (0.03 and 0.05 Torr) is much less pronounced than for vials at high pressure settings (0.03 and 0.5 Torr) the curve remains almost the same for vials as for Al-blocks. As compared to the decreasing inclination of fits for $K_v$ as $v$ and $K_v$. Results of the fitting equation for all three container systems are given in eq. 7, 8, and 9.

<table>
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<tr>
<th>Value of fitting constant source</th>
<th>kPCR</th>
<th>kFDS</th>
<th>k(2R)</th>
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<tr>
<td>0.03</td>
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<td>0.71</td>
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CONCLUSIONS

- The present results suggest that heat transfer in Al-blocks is greatly affected by the increase in total area for heat flow. In addition to heat flow through the bottom, heat flow from the Al-block wall to the side of the product promotes atypical (i.e. vertical) drying behavior in which one might reduce heat transfer while drying proceeds. Application of a simple heat and mass transfer model might not be sufficient to delineate the heat flow for such systems.
- A change in the energy accommodation coefficient must be considered when introducing a new material to enhance heat transfer to the product. The total value of $\alpha$ might also be affected by differences in the surface of the material (paint or finish of material under consideration).
- For all tested container systems, heat transfer in 2R tubing systems can be described best by existing heat and mass transfer models. Vials unite entire handling and good heat transfer characteristics.

REFERENCES

[2] Breckenridge, Colorado (USA)
[6] CPPR Freeze Drying of Pharmaceuticals and Biologicals Conference • August 6-9, 2008 • Breckenridge, Colorado (USA)