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## Finite elements model of heat transfer predicts the edge vial effect in different freeze-drying configurations

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Bernadette Scutella, Stéphanie Passot, Erwan Bourlés, Fernanda Fonseca, Artemio Plana-Fattori, et al.. Finite elements model of heat transfer predicts the edge vial effect in different freeze-drying configurations. 2016 CPPR Conference Freeze-Drying of Pharmaceuticals and Biologicals, Jul 2016, Breckenridge, United States. hal-01567200

**HAL Id: hal-01567200**

**<https://hal.science/hal-01567200v1>**

Submitted on 5 Jun 2020

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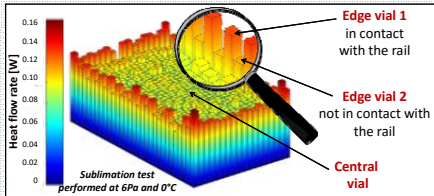
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## What is the "edge vial effect"?



### What is the "edge vial effect"?

During freeze-drying process, products in vials located at the periphery of the shelf are warmer and have an higher sublimation rate of about 15% compared to vials in the centre [1]. This phenomenon results from the combined effects of radiation from external sources (walls, rail) and conduction due to direct contact of the vial with the rail.

### Which are the consequences?

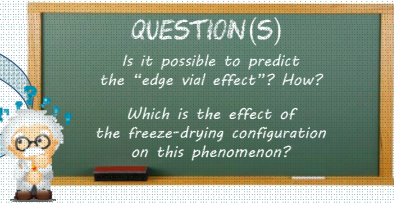
The "edge vial effect" results in different thermal histories among the vials and thus in a non-homogeneous final quality of the product.

## Why this study and which strategy?

The "edge vial effect" causes...

- Heterogeneity within product batch
- Issues in process control
- Problematic scale-up

Mathematical model of heat transfer in freeze-drying in 3D using COMSOL MULTIPHYSICS



## Mathematical model of heat transfer in freeze-drying

### Main hypotheses

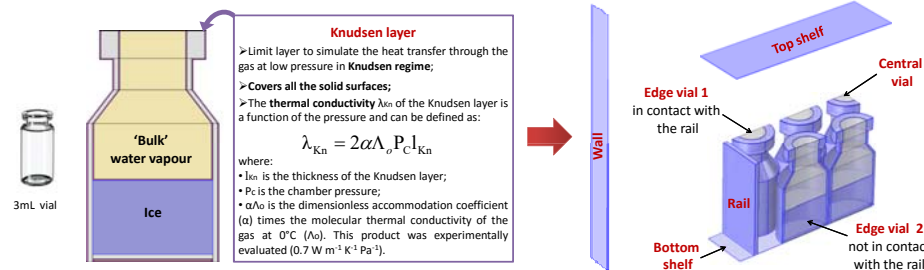
- > Pseudo-stationary state: all the heat received from the vial is used for ice sublimation;
- > Constant ice thickness in the vials and flat ice-vapour interface;
- > Pure water vapour in the drying chamber;
- > Heat transfer by convection is negligible.

### Relevant parameters

Parameter	Symbol	Value
'Bulk' vapour conductivity	$\lambda_w$	0.025 [W m <sup>-1</sup> K <sup>-1</sup> ]
Knudsen layer conductivity	$\lambda_{Kn}$	$2 \cdot 10^{-3} P_c$ [W m <sup>-1</sup> K <sup>-1</sup> ]
Depth of vial bottom curvature	$l_w$	0.1 [mm]
Knudsen layer thickness	$l_{Kn}$	0.1 [mm]

### From the vial...

### ...to the system



**Knudsen layer**  
 > Limit layer to simulate the heat transfer through the gas at low pressure in Knudsen regime;  
 > Covers all the solid surfaces;  
 > The thermal conductivity  $\lambda_{Kn}$  of the Knudsen layer is a function of the pressure and can be defined as:

$$\lambda_{Kn} = 2\alpha\lambda_w P_c l_{Kn}$$

where:

- $l_{Kn}$  is the thickness of the Knudsen layer;
- $P_c$  is the chamber pressure;
- $\alpha$  is the dimensionless accommodation coefficient (a) times the molecular thermal conductivity of the gas at 0°C ( $\lambda_w$ ). This product was experimentally evaluated (0.7 W m<sup>-1</sup> K<sup>-1</sup> Pa<sup>-1</sup>).

### Heat transfer in solid and gaseous bodies

$$\vec{q}_c = -\lambda_i \nabla T$$

•  $\vec{q}_c$ : heat flux by conduction in the solid or gas [W m<sup>-2</sup>];  
 •  $\lambda_i$ : thermal conductivity of the body material [W m<sup>-1</sup> K<sup>-1</sup>];  
 •  $\nabla T$ : gradient of temperature [K].

### Heat transfer by contact conduction

$$q_{cc} = K_{cc} (T_1 - T_2)$$

•  $q_{cc}$ : heat flux by contact conduction [W m<sup>-2</sup>];  
 •  $K_{cc}$ : heat transfer coefficient of contact conduction [W m<sup>-2</sup> K<sup>-1</sup>];  
 •  $T_{1,2}$ : temperatures of the bodies [K].

### Heat transfer by radiation

$$q_r = F_{1 \rightarrow 2} \sigma (T_1^4 - T_2^4)$$

•  $q_r$ : heat flux by radiation [W m<sup>-2</sup>];  
 •  $F_{1 \rightarrow 2}$ : visualization factor [-];  
 •  $T_{1,2}$ : temperatures of the bodies [K];  
 •  $\sigma$ : Stephen-Boltzmann constant [W m<sup>-2</sup> K<sup>-4</sup>].

## "Edge vial effect" in different freeze-drying configurations

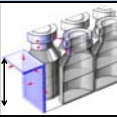
### A. Edge vials completely shielded by the rail

- Heat transfer by radiation from the wall to the rail;
- Heat transfer by contact conduction and radiation from the rail to the vials.



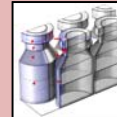
### B. Edge vials partially shielded by the rail

- Heat transfer by radiation from the wall to the rail and vials;
- Heat transfer by contact conduction and radiation from the rail to the vials.



### C. Edge vials completely exposed to the wall

- Heat transfer by radiation from the wall to the vials.



## Experimental procedure

### Gravimetric method

- Fill the vials with 1.8ml of purified water...
- ...weight them to evaluate the initial mass ( $m_1$ )...
- ...freeze-dry them until 30% of ice is sublimated...
- ...re-weight them to evaluate the final mass ( $m_2$ )...

$$\dot{m} = \frac{m_1 - m_2}{\text{sublimation time}}$$

$\dot{m}$ : mass flow rate [kg s<sup>-1</sup>].

### Sublimation test

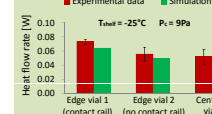
- Freezing step: 2h at -50°C;
- Ramp: 1°C/min;
- Sublimation:
  - > 9Pa and -25°C for configuration A and C (MillRock freeze-dryer);
  - > 6Pa and -40°C and 0°C for configuration B (Aqua-Finn GT6 freeze-dryer).

$$\dot{Q} = \Delta H \dot{m}$$

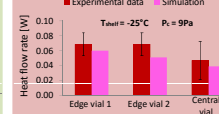
$\dot{Q}$ : heat flow rate [J s<sup>-1</sup>];  
 $\Delta H$ : latent heat of sublimation [J kg<sup>-1</sup>].

## Model validation

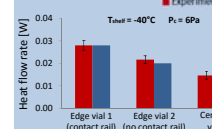
### Configuration A – vials fully shielded



### Configuration C – vials not shielded

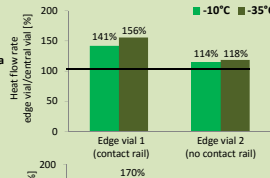


### Configuration B – vials partially shielded

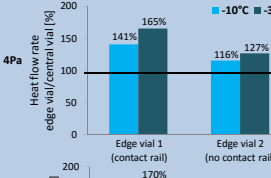


## Virtual experiments

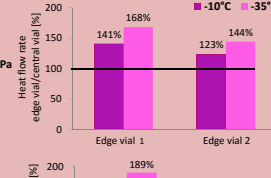
### Configuration A – vials fully shielded



### Configuration B – vials partially shielded



### Configuration C – vials not shielded



### Impact of the operating parameters

- The heat flux difference between central and edge vials...
- ... is higher if the shelf temperature is lower (in a range of -10 to -25°C);
- ... is higher if the chamber pressure is higher (in a range of 4 to 9Pa).

### Impact of the edge configuration

- Configurations A and B are equivalent (±5%) except at low shelf temperature (-35°C) and pressure (4Pa);
- The best edge configuration appears to be the configuration A, in all the possible combination of operating parameters.

## Conclusions and perspective

- ✓ The developed model predicts the heat flow rate in edge and central vials in different freeze-drying configurations;
- ✓ The edge effect is less important if the edge vials are shielded by the rail but not in contact with it;

- ✓ The edge effect is more important at low shelf temperature and high chamber pressure (for a range of -10 to -35°C and 4 to 9Pa);
- ✓ Next step will involve the use of the model as smart tool to predict the "edge vial effect" in freeze-dryers at commercial scale.

### References

- [1] Rambhatla, S. & Pikal, M. J., 2003. Heat and mass transfer scale-up issues during freeze-drying. I: atypical radiation and the edge vial effect. *Aaps PharmSciTech* 4, 22–31;
- [2] Ganguly, A., Nail S., Alexeenko A., 2013. Experimental determination of the key heat transfer mechanisms on pharmaceutical freeze-drying. *J Pharm Sci* 102(5).

### Acknowledgement

Thanks to Benoit Moreau and Yves Mayeresse (GSK Vaccines) for their contributions in reviewing this work.  
 Erwan Bourlés is an employee of the GSK group of companies. This study was financially supported by GlaxoSmithKline Biologicals SA.