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Ioan-Cristian Trelea, Fernanda Fonseca, Stéphanie Passot, Denis Flick. A binary gas transport model Improves the prediction of mass transfer in freeze drying. *Drying Technology*, 2015, 33 (15-16), pp.1849-1858. 10.1080/07373937.2015.1040025 . hal-01269386

HAL Id: hal-01269386

<https://hal.science/hal-01269386>

Submitted on 11 Jul 2017

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Title:

A binary gas transport model improves the prediction of mass transfer in freeze-drying

Short title: Binary gas transport model in freeze-drying

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Abstract

Monitoring partial vapor pressure in the freeze-drying chamber is a cheap, global and non-intrusive way to assess the end of the primary drying stage. Most existing dynamic freeze-drying models which predict this partial pressure describe mass transfer between the product and the condenser via a mass transfer resistance or a mass transfer coefficient. Experimental evidence suggests that such models can be significantly in error for some

values of the sublimation flux, leading to physically inconsistent predictions and possibly incorrect assessment of primary drying termination, with potential risk of product damage if moving to secondary drying and increasing shelf temperature while some ice is still present. Assuming a binary gas transport model for vapor and inert gas leads to improved and consistent predictions and explains the apparent variation of the mass transfer resistance with total pressure, shelf temperature and product sublimation area.

Keywords: lyophilization, dynamic model, mass transfer, convection, diffusion

INTRODUCTION

Freeze-drying (lyophilization) is widely used for long term preservation of thermosensitive biological material and pharmaceuticals, such as proteins, vaccines, bacteria, mammalian cells and high quality food.^[1, 2] It removes water or an organic solvent in a way that minimizes the modification of the molecular structure of the active ingredient and creates a porous matrix with high rehydration properties. Freeze-drying remains a costly process, however, and lot of research was devoted to its optimization, often based on mathematical modeling.^[2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12]

The process consists of three main steps: freezing, ice removal by sublimation (primary drying) and unfrozen water removal by desorption from the solid matrix (secondary drying). The primary drying stage is usually the most time and energy consuming part of a freeze-drying cycle. A lot of research has been devoted to the development of methods to precisely and consistently identify the end of the primary drying. Most of these methods rely on the monitoring of the vapor partial pressure in the freeze-drying chamber, either directly (moisture sensors such as aluminum oxide probes) and/or indirectly (Pirani gauge, mass spectrometer, Tunable Diode Laser Absorption Spectroscopy (TDLAS)).^[13, 14] Moreover, abundant literature is available concerning modeling of primary freeze-drying for optimizing

this step of the process off line and also more recently in real time.^[11, 12, 15] Models often predict the product temperature and the sublimation flux. The rate of solvent vapor removal from the product is usually described as being governed by three barriers or resistances: resistance of the dried-product layer, resistance of the containers (vials and stoppers), and resistance of the chamber to condenser pathway. Since the gas phase is mainly vapor during the primary drying and gradients of concentrations are small, true diffusion, or flow under the influence of a concentration gradient, is often considered of minor importance and models focus on bulk flow mechanisms.^[16] The resistance of the dried product layer and of the containers has been studied both theoretically and experimentally by many groups. These studies present two limitations, however. Firstly, the chamber resistance is usually neglected because of measurement difficulties, or it is estimated by rather complex approaches involving Computational Fluid Dynamics (CFD) simulations.^[17, 18, 19, 20] Secondly, the partial vapor pressure is usually not predicted but taken as fixed and equal to the total chamber pressure, despite its importance for real time optimization and freeze-drying control.^[3, 10, 21, 22, 23, 24]

Our group previously developed a one-dimensional heat and mass transfer model, which can accurately represent both the primary and secondary drying stages and the gradual transition between them.^[9] When adapting it to other freeze-dryers and to bacterial suspensions, however, it turned out that the determined chamber resistance strongly varied with total pressure and shelf temperature. Moreover, for a sufficiently high sublimation flux, e.g. generated by a high shelf temperature at the beginning of the primary drying, the model can predict a partial vapor pressure higher than the total one, which is obviously incorrect.

In the present study the chamber resistance was experimentally determined and a model of mass transfer between the freeze-drying chamber and the condenser is proposed for the solvent vapor and inert gas pair. The model is based on the mass transfer theory in binary gas mixtures and includes bulk flow and mutual diffusion terms. This model improved the prediction of the chamber vapor pressure and of the primary drying termination. It also accounted for apparent variations of the effective mass transfer resistance with total pressure, shelf temperature and product sublimation area.

MATERIALS AND METHODS

Determination of the mass transfer resistance (vapor flow) of the chamber to condenser pathway

Experiments were carried out on a LyoBeta special freeze-dryer (Telstar, Terrassa, Spain) equipped with 5 thermocouples, a capacitive manometer and a Pirani gauge. Purified water and bacterial cell suspensions were successively considered.

A stainless steel tray was filled with purified water to a thickness of 3 cm. The evaporative flow was determined using the gravimetric method. After freezing the water at -50°C (cooling rate of 0.6 °C/min), and sublimation time between 4 and 8 hours depending on the experimental conditions, the process was stopped and the tray was weighted to determine the amount of water removed and thus the evaporative flux (F_v , in kg s⁻¹). The mass transfer coefficient (k_m , kg s⁻¹ Pa⁻¹), or, equivalently, resistance of the chamber to condenser pathway (r_m , Pa s kg⁻¹) was determined from Eq. 1:

Eq. 1
$$F_v = k_m (P_{v1} - P_{v2}) = \frac{P_{v1} - P_{v2}}{r_m}$$

with P_{v1} , the water vapor partial pressure just above the product (Pa), estimated from the ice temperature and P_{v2} , the water vapor partial pressure at the condenser (Pa), estimated from the condenser temperature.

The effect of three process variables on the effective mass resistance (r_m) value was investigated: sublimation area (0.033, 0.074 and 0.15 m²), chamber pressure (10, 20, 40 and 60 Pa) and shelf temperature (-15, 0 and 15°C).

Freeze-drying experiments with bacterial suspensions

Lactic acid bacteria were produced by fermentation in controlled conditions of pH and temperature.^[25] After concentration, the bacterial cells were re-suspended in a 1:2 cells/protective medium ratio. The protective medium was composed of 200 g/L of sucrose and 0.15 M of NaCl. A stainless steel tray was filled with 450g of bacterial suspension and the following freeze-drying protocol was applied: freezing at -50°C (cooling rate of 0.6°C/min); primary drying at -20, 0 or 25°C; secondary drying at 25°C for 8 hours. The total chamber pressure was controlled at either 20 or 60Pa. Thermocouples were placed at the bottom of the product in the centre of the tray.

Estimation of partial vapor pressure from the Pirani gauge

The reading of a Pirani gauge in a pure gas is proportional to the pressure of the gas and to the molecular heat conductivity of the gas.^[26] The main gases present in the freeze-drying chamber are solvent vapor (usually water) and an inert gas such as nitrogen or air. Let

Eq. 2
$$\alpha = \frac{\lambda_v}{\lambda_N}$$

be the ratio of the molecular heat conductivities. This ratio is equal to 1.6 for the water vapor and nitrogen pair. If the Pirani gauge is calibrated with inert gas, nitrogen in the present case, then the reading in pure solvent vapor will be:

Eq. 3
$$P_v^p = \alpha P_v$$

In a gas mixture, the Pirani gauge will measure the sum of heat fluxes due to conduction in each gas. The reading will be:

Eq. 4
$$P^p = \alpha P_v + P_N$$

In contrast, the capacitive sensor will give the true total pressure:

Eq. 5
$$P_t = P_v + P_N$$

From these two readings, one can determine the partial pressures of vapor and inert gas:

Eq. 6
$$P_v = \frac{P^p - P_t}{\alpha - 1}$$

Eq. 7
$$P_N = \frac{\alpha P_t - P^p}{\alpha - 1}$$

Numeric calculations

Calculations were performed with Matlab™ 8 software (The MathWorks Inc., Natick, MA) equipped with the Statistics Toolbox and the Global Optimization Toolbox.

MASS TRANSFER MODELS BETWEEN CHAMBER AND CONDENSER

Mass transfer resistance model

In most previously developed freeze-drying models, the mass flux between the freeze-drying chamber containing the product (location 1) and the condenser (location 2) was either

ignored, considering the vapor pressure in the freeze-drying chamber as given,^[3, 10, 21, 22, 23] or expressed via a mass transfer coefficient (k_m) or, equivalently, via a mass transfer resistance (r_m),^[9, 12, 27, 28, 29] as given by Eq. 1.

Note that in Eq. 1 the mass flux is proportional to the partial vapor pressure difference between the two locations. Vapor pressure P_{v2} is usually fixed by the condenser temperature, while the mass flux F_V is mostly determined by the heat transfer flux from the temperature-controlled shelf to the product, i.e. by the shelf temperature and the product sublimation area. If the mass transfer resistance was constant, as it is usually assumed, then the partial vapor pressure in the chamber P_{v1} would result from Eq. 1. If the mass flux was high enough, due for example to high shelf temperature, a model based on Eq. 1 could even give a vapor pressure higher than the total chamber pressure, which is obviously impossible. A more consistent mass transfer model is developed in the next section.

Binary gas transport model

Consider a mixture of two gases at low pressure; in the case of freeze-drying these gases would be solvent vapor, usually water, released from the product and captured by the condenser and the inert gas, usually nitrogen, used to control the total chamber pressure. To determine the relevant mass transport theory, the Knudsen number, defined as the ratio of the free mean path of the molecules and the characteristic dimension of the system, was estimated. In the considered conditions, the free mean path is of order of 0.5mm at 20Pa, while the typical diameter of the chamber to condenser duct is 100mm. Knudsen diffusion can thus be safely neglected for the chamber to condenser pathway considered here, since $K_n \approx 5 \times 10^{-3}$. Note that this is usually not the case in the porous product layer where the pore size can be much less than 0.5mm, but mass transport in the porous layer is out of the scope of the present study.

The classical theory of binary diffusion in gases states that the molar flux density of solvent vapor, in stationary coordinates, is given by:^[30]

$$\text{Eq. 8} \quad N_V = x_V(N_V + N_N) - (c_V + c_N)D_{VN}\nabla x_V$$

where N_V and N_N are molar flux densities, c_V and c_N molar concentrations of vapor and nitrogen respectively, x_V is the molar fraction of vapor and D_{VN} is the mutual diffusion coefficient. The first term on the right-hand side of Eq. 8 results from the bulk motion of the fluid while the second one expresses the diffusion of vapor due to its molar fraction gradient.

Assuming pseudo-stationary conditions, compared to the duration of a freeze-drying cycle which is of one or several days, and assuming insignificant leaks in the freeze-drying chamber, the net inert gas flux is negligible compared to the vapor flux:

$$\text{Eq. 9} \quad N_N \approx 0$$

Usual variables in freeze-drying are mass fluxes instead of molar fluxes and partial pressures instead of molar fractions and concentrations. Using the ideal gas law one gets:

$$\text{Eq. 10} \quad x_V = \frac{P_V}{P_V + P_N} = \frac{P_V}{P_t}$$

$$\text{Eq. 11} \quad c_V + c_N = \frac{P_V + P_N}{RT} = \frac{P_t}{RT}$$

$$\text{Eq. 12} \quad f_V = M_V N_V$$

With these substitutions, and assuming that the variation of total pressure between freeze-drying chamber and condenser is small compared to the variation in vapour partial pressure, Eq. 8 becomes:

$$\text{Eq. 13} \quad f_V(P_t - P_V) = -\frac{M_V}{RT} P_t D_{VN} \nabla P_V$$

To solve Eq. 13, it is assumed that the vapour flux between the product and the condenser is essentially one-dimensional. This assumption is relatively sound for freeze-driers equipped with a condenser separated from the main freeze-drying chamber by a pipe, as is the case in the present study, but it is questionable when the product and the condenser are situated in the same cavity. With this assumption, Eq. 13 can be integrated between the freeze-drying chamber (location 1) and the condenser (location 2) giving:

$$\text{Eq. 14} \quad F_V = A f_V = \frac{A M_V}{l_{eff} RT} P_t D_{VN} \ln \frac{P_t - P_{V2}}{P_t - P_{V1}}$$

where F_V is the vapor mass flux, while A and l_{eff} are the diffusion cross-section area and effective duct length respectively. The effective length accounts for the presence of inlet and outlet sections, bends, valve and other elements that can introduce additional resistances.

The mutual gas diffusion coefficient D_{VN} is inversely proportional to the total pressure, thus the product $P_t D_{VN}$ is constant.^[30] For a given freeze-dryer geometry (l_{eff} , A) a constant β can be introduced:

$$\beta = \frac{l_{eff} R}{AM_V P_t D_{VN}}$$

Eq. 15

so that

$$F_V = \frac{1}{\beta T} \ln \frac{P_t - P_{V2}}{P_t - P_{V1}}$$

Eq. 16

The dependence of the mass flux on the partial vapor pressures given by Eq. 16 appears quite different from Eq. 1. It can be shown, however, using a first order Taylor series expansion of the logarithm function, that Eq. 1 is an approximation of Eq. 16 in the case when the vapor pressures are much less than the total pressure:

$$\ln \frac{P_t - P_{V2}}{P_t - P_{V1}} \approx \frac{P_{V1} - P_{V2}}{P_t} \quad \begin{array}{l} \text{if } P_{V1} \ll P_t \\ \text{and } P_{V2} \ll P_t \end{array}$$

Eq. 17

It should be noted, however, than in freeze-drying the condition $P_{V1} \ll P_t$ is usually *not* satisfied as the gas in the freeze-drying chamber during primary drying is mostly solvent vapor. The approximation given by Eq. 17 is thus not expected to be valid. This can explain the mentioned inconsistency with Eq. 1 and the apparent variation of the effective mass transfer resistance with total pressure and mass flux, as further discussed below. For now, note that Eq. 16 can accommodate arbitrarily large vapor fluxes without P_{V1} exceeding P_t , provided that the difference $P_t - P_{V1}$ becomes small enough, while remaining positive.

RESULTS AND DISCUSSION

Experimental determination of chamber to condenser mass transfer resistance

Table 1 summarizes the experimental values of the mass transfer resistance of chamber to condenser pathway measured for various process conditions.

The effective mass transfer resistance appeared to increase when increasing chamber pressure, decreasing shelf temperature and decreasing sublimation area. The mass transfer resistance was thus inversely correlated with the sublimation flux. Increasing the sublimation rate

resulted in an apparent decrease of the effective mass transfer resistance of the chamber to condenser pathway. These observed variations support the idea that the mass transfer resistance is only an effective model parameter and a different perspective is needed to get a more physically meaningful description of the transfer phenomena. This is further discussed in the next sections.

Prediction of partial vapor pressure in the chamber by the two modeling approaches: resistance vs. binary gas transport

The predictions of the previously developed freeze-drying model,^[9] adapted for bacterial suspension conditioned in trays, were compared to experimental measurements acquired in freeze-drying experiments performed as described in the “Materials and methods” section. Two versions of the model were tested, one based on a mass transfer resistance between the chamber and the condenser (Eq. 1) and the other based on the binary gas transport assumption (Eq. 16). Details of the existing model^[9] adaptation to the new freeze-dryer, container and product, as well as implementation details of the new chamber-to-condenser mass transport model based on Eq. 16 are given in the Appendix. The model parameters (notably k_m and β) were determined by fitting the models to some of the experimental data obtained in bacterial suspension experiments (Appendix and Table 2)

An example of the predictions of the two versions of the model are shown in Figure 1, for two experiments performed at 0°C shelf temperature/60Pa chamber pressure and 25°C/20Pa, respectively. These are validation experiments not used for model parameter identification. Dotted lines represent calculations based on the mass transfer resistance model and solid lines correspond to the binary gas transport model.

The experiment at 0°C/60Pa (Figure 1, left panels) illustrates a situation where the prediction of the primary drying termination differs by about 2 hours between the considered models. The end of the primary drying was arbitrarily defined here as the moment when the sublimation flux (Figure 1C) decreased below 5% of its maximum value. The resistance model predicts the end of the primary drying at about 11h, in agreement with measured product temperature approaching the shelf temperature (Figure 1A), while the binary gas model predicts the end at about 13h, in agreement with the decrease of vapor pressure in the chamber (Figure 1B). Note that product temperature measurement is a local one, potentially disturbed by the presence of the probe, while partial vapor pressure measurement is a global one, representative of the whole product in the freeze-dryer. Vapor pressure should thus be

preferred to assess the end of the primary drying.^[14] It is also non intrusive and usually more conservative, minimizing the risk of premature temperature increase and product damage, if some ice was still present when starting the secondary drying step.

The experiment at 25°C/20Pa (Figure 1, right panels) illustrates a situation where both models predict the same end point of the primary drying (11h), but the vapor pressure predicted by the resistance model is completely in error. Compared to the previously described experiment (0°C/60Pa), in this case the heat transfer resistance from the shelf to the product is higher due to lower chamber pressure (lower contribution of the gas conduction), but this is nearly compensated by a higher shelf temperature, leading to a similar heat flux. The net result is a similar primary drying time and sublimation flux (Figure 1C) for both experimental conditions. As expected from Eq. 1, a similar sublimation flux implies a similar vapor pressure calculated with the resistance model, around 50Pa in this case (Figure 1B), but this value is 2.5 times higher than the total pressure, which is obviously incorrect. In contrast, the binary gas model based on Eq. 16 consistently predicts a vapor pressure close to, but slightly less than the total one, as physically expected.

Both these examples suggest that the binary gas transport model should be preferred to the resistance model. Similar trends were observed in all performed experiments with bacterial suspensions (data not shown). The properties of the proposed binary gas transport model are further examined in the following sections.

Effective mass transfer resistance of the chamber to condenser pathway

Since Eq. 1 and Eq. 14 are two different ways of expressing the same vapor flux based on different physical assumptions, these equations can be used to define an effective mass transfer resistance of chamber to condenser pathway as:

$$\text{Eq. 18} \quad r_m = \frac{1}{k_m} = \frac{l_{eff} RT (P_{v1} - P_{v2})}{AM_v P_t D_{vN} \ln \frac{P_t - P_{v2}}{P_t - P_{v1}}} = \beta T \frac{P_{v1} - P_{v2}}{\ln \frac{P_t - P_{v2}}{P_t - P_{v1}}}$$

It readily appears from Eq. 18 that this resistance is not constant but is an effective model coefficient that depends on the actual values of the total and vapor pressure.

The effective mass transfer resistance given by Eq. 18 is plotted in Figure 2 (solid line) as a function of the vapor pressure near the product (P_{v1}), for two different total pressures ($P_t = 20$

and 60Pa) used in our experiments. The vapor pressure near the condenser was fixed to a low value $P_{12} = 0.055$ Pa, corresponding to a typical condenser temperature of -80°C . For comparison, the value of r_m determined for the mass transfer resistance model in the same conditions is also given in Figure 2 (dotted line).

Firstly, Figure 2 indicates that the effective mass transfer resistance strongly increases with the total pressure. This was expected from the experimental data in Table 1 and confirms the usual practice of performing freeze-drying at low pressure to improve mass transfer.

Secondly, the effective mass transfer resistance predicted by the binary gas model approaches zero when the vapor pressure in the chamber approaches the total pressure. This was expected from the mathematical analysis of Eq. 18 and is consistent with the fact that partial vapor pressure in the chamber cannot exceed the total one, whatever the sublimation flux. Note that this is not the case with a constant mass transfer resistance, when the vapor pressure in the chamber can formally exceed the total pressure for a sufficiently high sublimation flux in Eq. 1.

Finally, Figure 2 shows that the value of the mass transfer resistance determined using the resistance model based on Eq. 1 is situated between the bounds given by Eq. 18, as expected. The effective resistance given by the binary gas transport model is close to this value for vapor pressures very close to the total pressure. This means that the vapor pressure calculated by the binary gas model for the primary drying is most of the time very close to the total pressure, as observed in Figure 1 and well known from freeze-drying practice. This is further illustrated in the following section.

Sublimation flux and predicted vapor pressure in the chamber

In usual freeze-drying conditions the sublimation mass flux is the result of several process parameters (Table 1), such as total chamber pressure (that changes both heat and mass transfer), shelf temperature and sublimation interface area, etc. For the mass transfer resistance model given by Eq. 1, the predicted vapor pressure in the freeze-drying chamber varies linearly with the mass flux (dotted line in Figure 3) and can, as already mentioned, exceed the total pressure, for example in the case of a sufficiently high shelf temperature (Figure 1, right panels). In contrast, the vapor pressure predicted by the gas diffusion model given by Eq. 16 asymptotically tends towards the total pressure for high sublimation mass fluxes, which is physically consistent (solid lines in Figure 3). This also corroborates the well

known fact that gas composition in the freeze-drying chamber is dominated by vapor during most of the primary drying stage, when sublimation fluxes are high (approaching $2 \times 10^{-5} \text{ kg s}^{-1}$ in the considered experimental setting).

Sublimation flux and effective mass transfer resistance of the chamber to condenser pathway

Considering the effect of the sublimation mass flux in the binary gas transport model gives a common framework to understand the apparent variations of the effective mass transfer resistances observed in Table 1 for different shelf temperatures and sublimation interface areas. Increasing both these variables increases the sublimation flux and this, in turn, causes an apparent reduction of the effective mass transfer resistance (Figure 4). For sublimation fluxes approaching $2 \times 10^{-5} \text{ kg s}^{-1}$, representative of the primary drying in the considered experiments (Figure 1), the mass transfer resistance determined for the resistance model is intermediate between those calculated with the binary gas model for 20 and 60 Pa total pressure. This reflects the compromise that the model fitting procedure finds to accommodate experiments performed at both these pressures, but the achieved compromise underestimates the vapor pressure at 60 Pa and overestimates it at 20 Pa, as already shown in Figure 1.

The binary gas transport model needs a unique constant parameter

As an additional difference between the two models, note that in the mass transfer resistance model the value of the resistance between the chamber and the condenser pathway is only an effective model parameter that appears to be a function of several process variables (Table 1): total pressure, shelf temperature and product sublimation area. Accounting for this would require varying the resistance in a tricky and ad-hoc manner. Considering a constant value of the mass transfer resistance ($r_m = 2.78 \times 10^6 \text{ Pa s kg}^{-1}$ in our case) leads to poor predictions and inconsistencies, such as calculated partial vapor pressure in the chamber exceeding the total one (Figure 1 and Figure 3). On the contrary, binary gas diffusion theory states that the product $P_i D_{iN}$ is constant and therefore in the binary gas transport model the analogous parameter β , given by Eq. 15, is constant. All solid plots in Figures 1–4 were obtained with the same value of $\beta = 2.66 \times 10^3 \text{ s kg}^{-1} \text{ K}^{-1}$.

In-process mass flux estimation and detection of the primary drying termination

Eq. 16 could be used in principle for obtaining vapor flow rate estimations based on total and partial pressure measurements, and thus act as an in-process mass flow meter. In practice,

however, estimations of “high” vapor flow rates (i.e. when the partial vapor pressure approaches the total one) are expected to be inaccurate due to the vapor saturation of the chamber illustrated in Figure 3: a wide range of sublimation fluxes corresponds to almost identical partial vapor pressures, very close to the total chamber pressure. For example, with the considered values of the parameters (Appendix) at a total pressure of 60Pa, a vapor pressure of 59.99Pa corresponds to a sublimation flux of $1.14 \times 10^{-5} \text{ kg s}^{-1}$, while a vapor pressure of 58.99Pa corresponds to a sublimation flux of $0.53 \times 10^{-5} \text{ kg s}^{-1}$. In other words, an uncertainty of only 1Pa in the measurement of the vapor pressure would induce a factor 2 error on the flux value, which is clearly inappropriate for practical use.

On the contrary, Figure 3 suggests that the estimation of “low” vapor fluxes (i.e. when the partial vapor pressure is well below the total one) based on pressure measurements could be quite accurate. For example, vapor pressures of 30 and 29Pa correspond to vapor fluxes of $0.091 \times 10^{-5} \text{ kg s}^{-1}$ and $0.086 \times 10^{-5} \text{ kg s}^{-1}$ respectively; a measurement uncertainty of 1Pa would induce only about 5% error on the vapor flux.

Above considerations suggest that the proposed model is appropriate for a safe detection of the primary drying termination because a decrease of the vapor pressure well below the total one indicates a strong decrease of the sublimation flux. Continuing the above numerical examples, a vapor pressure in the chamber decreasing to the half of the total pressure corresponds to a factor 10 reduction of the sublimation flux. Of course, exact significance of “high” and “low” mass fluxes and the relevant decrease of vapor pressure depend on numerical values grouped in the parameter β defined by Eq. 15, and also involved in Eq. 16.

Finally, note that the proposed in-process flow estimation method based on total and partial pressure measurements in the chamber is complementary to the method described by Patel et al.^[31], based on differential pressure measurement between the chamber and the condenser. Indeed, the former works well for low sublimation fluxes while the latter is expected to be more accurate when the sublimation flux, and hence the measured pressure difference, are large.

CONCLUSIONS

Results presented in this paper suggest that using one-dimensional mass transfer theory in binary gas mixtures to describe vapor transfer between the freeze-drying chamber and the condenser should be preferred to the mass transfer resistance approach. Advantages of the

binary gas transport model include: (i) prediction of the vapor pressure in the freeze-drying chamber closer to the experimental one, leading to more reliable prediction of the end of the primary drying; (ii) calculated values of the vapor pressure physically consistent with the total pressure, whatever the sublimation vapor flux; (iii) need to determine a single model parameter for a given freeze-dryer geometry, independent on the operating conditions (total pressure, shelf temperature, ice sublimation area).

The main drawback of the mass diffusion model is the non-linear dependence between the vapor flux and vapor pressure, which can somewhat complicate model simulations. Solution of non-linear differential and algebraic equation sets is already part of most freeze-drying models, however, and the additional difficulty introduced by the diffusion model is expected to be minor, as confirmed by the authors' experience.

The assumption of one-dimensional mass transfer between the freeze-drying chamber and the condenser could be questioned in the future, especially for freeze-dryers with the condenser situated in the freeze-drying chamber. The challenge would be to end up with a reasonably simple closed-form relationship between mass flux and pressure, in order to maintain the overall model minimalism and short simulation time.

NOMENCLATURE

c	molar concentration	kmol m^{-3}
f	mass flux density	$\text{kg s}^{-1}\text{m}^{-2}$
k	mass transfer coefficient	$\text{kg s}^{-1}\text{Pa}^{-1}$
l	diffusion length	m
r	mass transfer resistance	Pa s kg^{-1}
x	molar fraction	kmol kmol^{-1}
A	diffusion cross-section area	m^2
D	mutual diffusion coefficient	$\text{m}^2 \text{s}^{-1}$
F	mass flux	kg s^{-1}
K_n	Knudsen number	—
M	molar mass	kg kmol^{-1}

401	N	molar flux density	$\text{kmol s}^{-1}\text{m}^{-2}$
402	P	pressure	Pa
403	R	ideal gas constant	$\text{J kmol}^{-1} \text{K}^{-1}$
404	T	absolute temperature	K
405	Greek letters		
406	α	heat conductivity ratio	–
407	β	mass transfer parameter	$\text{s kg}^{-1} \text{K}^{-1}$
408	λ	heat conductivity	$\text{Wm}^{-1} \text{K}^{-1}$
409	Subscripts		
410	1	freeze-drying chamber, near product	
411	2	condenser	
412	3	ice sublimation front	
413	4	product top	
414	eff	effective	
415	m	mass	
416	t	total	
417	N	inert gas, nitrogen	
418	V	solvent vapor, water	
419	Superscript		
420	P	measured by Pirani gauge	

421

422 ACKNOWLEDGEMENT

423 The research leading to these results has received funding from the European Community's
424 Seventh Framework Programme (FP7/2007-2013) under grant agreement CAFE n° KBBE-
425 212754.

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APPENDIX: EMBEDDING THE BINARY GAS TRANSPORT EQUATION IN A COMPLETE FREEZE-DRYING MODEL

The binary gas transport equation proposed in this paper (Eq. 16) describes the mass flux between the freeze-drying chamber and the condenser, in replacement of the more classical equation involving a mass transfer resistance or a mass transfer coefficient (Eq. 1). Both equations were tested in conjunction with an existing freeze-drying model, described in full detail previously.^[9]

In a first step, the parameters of the existing model^[9] based on Eq. 1 were re-estimated to account for a different freeze-dryer (LyoBeta special freeze-dryer from Telstar, Terrassa, Spain, instead of SMH15 freeze dryer from Usifroid, Maurepas, France), a different container (metallic tray instead of glass vial) and a different product (lactic acid bacterial suspensions in sucrose medium instead of polyvinylpyrrolidone). Parameters related to the sorption isotherm and to the glass transition of the product were determined with the methodology described previously.^[25] Parameters related to the heat and mass transfer in the freeze-dryer and in the product were estimated by fitting the product temperature and vapor pressure predicted by the model to experimental measurements. Four experiments were used simultaneously for model parameter estimation, performed in the following combinations of shelf temperature and total chamber pressure: -20°C/20Pa, -20°C/60Pa, 25°C/20Pa and 25°C/60Pa. A genetic optimization algorithm (Global Optimization Toolbox for Matlab, Natick, MA) was used for parameter identification. Since the considered optimization algorithm is stochastic, the parameter set with the best fit from 8 independent optimization runs was selected. Most optimization runs consistently converged to similar sets of parameters, usually within $\pm 10\%$. Model parameters used in the present study are listed in Table 2.

In a second step, the original mass transfer equation between the chamber and the condenser (Eq. 1) was replaced by the newly proposed one (Eq. 16) and the parameter estimation procedure was repeated using the same data and the same algorithm. The estimated parameter values are also given in Table 2. As expected, the estimated values of the parameters are similar between the two models, with the exception of the parameter describing mass transfer between the freeze-drying chamber and the condenser (k_m for the resistance model and β for the binary gas transport model), which have different physical meanings.

Since the newly introduced equation is nonlinear and the vapor pressure in the chamber is unknown *a priori*, the sublimation flux cannot be determined explicitly as in the resistance

version of the model.^[9] The vapor pressure in the chamber (P_{V1}) was considered as an additional state variable and the corresponding mass balance equation in the freeze-drying chamber was added to the existing set of differential equations:

$$\text{Eq. 19} \quad \frac{M_v V_1}{RT} \cdot \frac{dP_{V1}}{dt} = F_{V31} - F_v$$

Here V_1 is the freeze-drying chamber volume, F_v is the chamber to condenser vapor flux given by Eq. 16 and F_{V31} is the sublimation vapor flux between the ice sublimation front (location 3) and the freeze-drying chamber (location 1), given by:

$$\text{Eq. 20} \quad F_{V31} = \frac{1}{\frac{1}{k_{m34}} + \frac{1}{k_{m41}}} (P_{V3} - P_{V1})$$

where k_{m34} and k_{m41} are the mass transfer coefficients between the sublimation front and the product top (location 4), and between the product top and the chamber, respectively. Thus, both mass fluxes involved in Eq. 19 can be written explicitly in terms of known (fixed or state) variables (P_{V1} , P_{V2} , and P_{V3}).

Note that in the original freeze-drying model vapor accumulation in the freeze-drying chamber was neglected, based on a time scale analysis.^[9] This is formally equivalent to setting the chamber volume $V_1 \approx 0$ in Eq. 19, which would thus become an algebraic instead of a differential equation. This version of the model was also tested but not retained, due to occasional failures in solving the equation set during parameter identification. Observed difficulties are likely to be related to the specific differential-algebraic equations (DAE) solver available in Matlab (ode15s) which had numerical problems with some sets of parameters tested by the optimisation algorithm.

- 483 1. Tang, X.; Pikal, M.J. Design of freeze-drying processes for pharmaceuticals: practical
484 advice. *Pharmaceutical Research*, 2004, 21(2), 191–200.
- 485 2. Sadikoglu, H.; Ozdemir, M.; Seker, M. Freeze-drying of pharmaceutical products:
486 Research and development needs. *Drying Technology*, 2006, 24(7), 849–861.
- 487 3. Sadikoglu, H.; Liapis, A. Mathematical modelling of the primary and secondary drying
488 stages of bulk solution freeze-drying in trays: parameter estimation and model
489 discrimination by comparison of theoretical results with experimental data. *Drying*
490 *Technology*, 1997, 15(3&4), 791–810.
- 491 4. Sadikoglu, H.; Liapis, A. I.; Crosser, O. K. Optimal control of the primary and secondary
492 drying stages of bulk solution freeze drying in trays. *Drying Technology*, 1998, 16(3-5),
493 399–431.
- 494 5. Sadikoglu, H.; Ozdemir, M.; Seker, M. Optimal control of the primary drying stage of
495 freeze drying of solutions in vials using variational calculus. *Drying Technology*, 2003,
496 21(7), 1307–1331.
- 497 6. Gan, K. H.; Bruttini, R.; Crosser, O. K.; Liapis, A. I. Heating policies during the primary
498 and secondary drying stages of the lyophilization process in vials: effects of the
499 arrangement of vials in clusters of square and hexagonal arrays on trays. *Drying*
500 *Technology*, 2004, 22(7), 1539–1575.
- 501 7. Chouvenc, P.; Vessot, S.; Andrieu, J.; Vacus, P. Optimization of the freeze-drying cycle: a
502 new model for pressure rise analysis. *Drying Technology*, 2004, 22(7), 1577–1601.
- 503 8. Boss, E. A.; Filho, R. M.; de Toledo, E. C. V. Freeze drying process: real time model and
504 optimization. *Chemical Engineering and Processing*, 12 2004, 43(12), 1475–1485.
- 505 9. Trelea, I. C.; Passot, S.; Fonseca, F.; Marin, M. An interactive tool for freeze-drying cycle
506 optimisation including quality criteria. *Drying Technology*, 2007, 25, 741–751.
- 507 10. Velardi, S. A. and Barresi, A. A. Development of simplified models for the freeze-
508 drying process and investigation of the optimal operating conditions. *Chemical*
509 *Engineering Research & Design*, 2008, 86(A1), 9–22.

- 510 11. Pisano, R.; Fissore, D.; Velardi, S. A.; Barresi, A. A. In-line optimization and control
511 of an industrial freeze-drying process for pharmaceuticals. *Journal of Pharmaceutical*
512 *Sciences*, 2010, 99(11), 4691–4709.
- 513 12. Antelo, L. T.; Passot, S.; Fonseca, F.; Trelea, I. C.; Alonso, A. A. Toward optimal
514 operation conditions of freeze-drying processes via a multilevel approach. *Drying*
515 *Technology*, 2012, 30(13), 1432–1448.
- 516 13. Gieseler, H.; Kessler, W. J.; Finson, M.; Davis, S. J.; Mulhall, P. A.; Bons, V.; Debo,
517 D. J.; Pikal, M. J. Evaluation of tunable diode laser absorption spectroscopy for in-process
518 water vapor mass flux measurements during freeze drying. *Journal of Pharmaceutical*
519 *Sciences*, 2007, 96(7), 1776–1793.
- 520 14. Patel, S. M.; Doen, T.; Pikal, M. J. Determination of end point of primary drying in
521 freeze-drying process control. *AAPS Pharmaceutical Science and Technology*, 2010,
522 11(1), 73–84.
- 523 15. Fissore, D.; Velardi, S. A.; Barresi, A. A. In-line control of a freeze-drying process in
524 vials. *Drying Technology*, 2008, 26(6), 685–694.
- 525 16. Pikal, M. Heat and mass transfer in low-pressure gases: applications to freeze-drying.
526 *Drugs and the Pharmaceutical Sciences*, 2000, 102, 611–686.
- 527 17. Alexeenko, A. A.; Ganguly, A.; Nail, S. L. Computational analysis of fluid dynamics
528 in pharmaceutical freeze-drying. *Journal of Pharmaceutical Sciences*, 2009, 98(9), 3483–
529 3494.
- 530 18. Rasetto, V.; Marchisio, D. L.; Fissore, D.; Barresi, A. A. On the use of a dual-scale
531 model to improve understanding of a pharmaceutical freeze-drying process.
532 *Pharmaceutical Technology*, 2010, 99(10), 4337–4350.
- 533 19. Ganguly, A. and Alexeenko, A. A. Modeling and measurements of water–vapor flow
534 and icing at low pressures with application to pharmaceutical freeze-drying. *International*
535 *Journal of Heat and Mass Transfer*, 2012, 55, 5503–5513.
- 536 20. Petitti, M.; Barresi, A.; Marchisio, D. L. Cfd modelling of condensers for freeze-
537 drying processes. *Sadhana-Academy Proceedings in Engineering Sciences*, 2013, 38(6),
538 1219–1239.

- 539 21. Mascarenhas, W. J.; Akay, H. U.; Pikal, M. J. A computational model for finite
540 element analysis of the freeze-drying process. *Computer Methods in Applied Mechanics*
541 *and Engineering*, 8/15 1997, 148(1-2), 105–124.
- 542 22. Sheehan, P. and Liapis, A. I. Modeling of the primary and secondary drying stages of
543 the freeze drying of pharmaceutical products in vials: Numerical results obtained from the
544 solution of a dynamic and spatially multi-dimensional lyophilization model for different
545 operational policies. *Biotechnology and Bioengineering*, 1998, 60(6), 712–728.
- 546 23. Song, C. S.; Nam, J. H.; Kim, C. J.; Ro, S. T. A finite volume analysis of vacuum
547 freeze drying processes of skim milk solution in trays and vials. *Drying Technology*, 2002,
548 20(2), 283–305.
- 549 24. Hottot, A.; Peczalski, R.; Vessot, S.; Andrieu, J. Freeze-drying of pharmaceutical
550 proteins in vials: modeling of freezing and sublimation steps. *Drying Technology*, 2006,
551 24(5), 561–570.
- 552 25. Passot, S.; Cenard, S.; Douania, I.; Trelea, I. C.; Fonseca, F. Critical water activity and
553 amorphous state for optimal preservation of lyophilized lactic acid bacteria. *Food*
554 *Chemistry*, 2012, 132, 1699–1705.
- 555 26. Jennings, T. *Lyophilization: Introduction and basic principles*. Interpharm/CRC: Boca
556 Raton, 1999.
- 557 27. George, J. P. and Datta, A. K. Development and validation of heat and mass transfer
558 models for freeze-drying of vegetable slices. *Journal of Food Engineering*, 3 2002, 52(1),
559 89–93.
- 560 28. Chouvenec, P.; Vessot, S.; Andrieu, J.; Vacus, P. Optimization of pharmaceuticals
561 freeze-drying cycles: characterization of annealing effects by the pressure rise analysis
562 method. In *Drying 2004 – Proceedings of the 14th International Drying Symposium (IDS*
563 *2004)*, São Paulo, Brazil, August 22-25, 2004; 359–365.
- 564 29. Hottot, A.; Vessot, S.; Andrieu, J. Determination of mass and heat transfer parameters
565 during freeze-drying cycles of pharmaceutical products. *PDA Journal of Pharmaceutical*
566 *Science and Technology*, 2005, 59(2), 138–153.
- 567 30. Bird, R.; Stewart, W.; Linghtfoot, E. *Transport phenomena*. Wiley: New York, 1960.

568 31. Patel, S. M.; Chaudhuri, S.; Pikal, M. J. Choked flow and importance of Mach I in
569 freeze-drying process design. *Chemical Engineering Science*, 2010, 65, 5716–5727.
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Figure captions

Figure 1. Comparison between experimental measurements and simulations with the binary gas transport and resistance models, for two experiments with lactic acid bacteria suspensions (left panel 0°C/60Pa, right panel 25°C/20Pa). (A): Shelf and product temperatures, (B): Total and vapour pressures, (C): Sublimation fluxes. Bold: shelf temperature and total pressure, symbols: measurements, solid: binary gas model, dotted: resistance model, vertical line: end of primary drying.

Figure 2. Variation of the effective mass transfer resistance with the vapor and total pressure. Numeric values are for lactic acid bacteria suspension. Solid: binary gas model, bold: total pressure 60Pa, thin: total pressure 20Pa, dotted: resistance model.

Figure 3. Predicted vapor pressure as a function of the sublimation mass flux. Numeric values are for lactic acid bacteria suspension. Solid: binary gas transport model, bold: total pressure 60Pa, thin: total pressure 20Pa, dotted: resistance model.

Figure 4. Apparent variation of the effective mass transfer resistance of the chamber to condenser pathway as a function of the sublimation mass flux. Numeric values are for lactic acid bacteria suspension. Solid: binary gas transport model, bold: total pressure 60Pa, thin: total pressure 20Pa, dotted: resistance model.

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596 Table 1. Chamber to condenser mass transfer resistance measured with pure ice.

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Total chamber pressure (Pa)	Shelf temperature (°C)	Sublimation interface area (m ²)	Chamber to condenser resistance (10 ⁶ Pa s/kg)
10 20 40 60	0	0.074	0.65 1.29 2.64 3.72
40	-15 0 15	0.074	4.31 2.64 1.61
20	0	0.033 0.074 0.15	2.34 1.29 0.67

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600 Table 2. Values of the freeze-drying model parameters

<i>Parameters defined by the experimental setup</i>		
Number of trays (–)	1	
Sublimation area (m ²)	0.0745	
Mass of dry product (kg)	0.0736	
Mass of ice (kg)	0.3763	
Product height in the tray (m)	0.0067	
Volume of the freeze-drying chamber (m ³)	0.202	
<i>Parameters specific for the product formulation, determined in separate experiments</i> ^[25]		
Sorption isotherm, wet basis (kg kg ^{−1})	$\frac{0.3190a_w}{(1 - 0.9827a_w)(1 + 6.3668a_w)}$	
Characteristic desorption time (s)	10100	
Glass transition temperature of the frozen product (°C)	-36	
Glass transition temperature of the perfectly dry product (°C)	75.6	
Gordon-Taylor coefficient for glass transition temperature (–)	8.2	
<i>Heat and mass transfer parameters determined by model fitting</i>		
	<i>Mass transfer resistance model</i>	<i>Binary gas transport model</i>
Heat transfer coefficient by contact and radiation, between shelf and product bottom (W m ^{−2} K ^{−1})	6.74	7.29
Heat transfer coefficient by gas conduction, between shelf and product bottom (W m ^{−2} K ^{−1} Pa ^{−1})	0.400	0.366
Heat conductivity between sublimation front and product top (W m ^{−1} K ^{−1})	0.0957	0.0996
Heat transfer coefficient between product top and chamber walls (W m ^{−2} K ^{−1})	3.79	3.03
Vapor conductivity between sublimation front and product top (kg s ^{−1} m ^{−1} Pa ^{−1})	2.07×10 ^{−8}	1.98×10 ^{−8}
Vapor transfer coefficient between product top and chamber (kg s ^{−1} m ^{−2} Pa ^{−1})	8.12×10 ^{−5}	3.68×10 ^{−4}
Vapor transfer coefficient between chamber and condenser <i>k_m</i> (kg s ^{−1} Pa ^{−1})	3.60×10 ^{−7}	Not applicable
Vapor transfer parameter between chamber and condenser <i>β</i> (s kg ^{−1} K ^{−1})	Not applicable	2.66×10 ³
Residual frozen layer thickness for gradual transition between primary and secondary drying (m)	0.00173	0.00170
Effective chamber wall temperature (°C)	15.3	13.9

601 Complete model equations and exact definitions of the model parameters are given in ref.^[9]

Figure 1. Comparison between experimental measurements and simulations with the binary gas transport and resistance models, for two experiments with lactic acid bacteria suspensions (left panel 0°C/60Pa, right panel 25°C/20Pa). (A): Shelf and product temperatures, (B): Total and vapour pressures, (C): Sublimation fluxes. Bold: shelf temperature and total pressure, symbols: measurements, solid: binary gas model, dotted: resistance model, vertical line: end of primary drying.

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