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A simulation model for the primary drying phase of the freeze-drying cycle

Marco P. Schoen [a], Bryan K. Braxton [b], Larry A. Gatlin [b], Raymond P. Jefferis III [c,*]

[a] *School of Mechanical Engineering, Old Dominion University, Norfolk, VA 23529, USA*
[b] *Department of Pharmaceutics, Glaxo Inc., 5 Moore Drive, Research Triangle Park, NC 27709, USA*
[c] *School of Engineering, Widener University, Chester, PA 19013, USA*

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Abstract

A lyophilization process model was adapted to fit experimental data from product vials processed using a development scale dryer. The model was evaluated with regard to how well it simulated the primary drying time and temperature conditions for product vials during the primary drying phase of the cycle. The results indicated the predicted drying time was very close to the actual drying time observed for the product. The simulated product temperature profile also compared well with the actual product temperature profile. The simulation results are presented as well as the coefficients used to fit the data.

Keywords: Freeze-drying; Simulation; Mathematical model; Primary drying time; Primary drying temperature

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1. Introduction

Extensive efforts by industry and research centers have been made to predict and predetermine the course of freeze-drying cycles in order to control the quality of the product and to minimize costs. Many different mathematical models for operating freeze-dryers have been proposed to optimize the process. Such models are a useful tool for defining freeze-drying cycles, as long as they accurately describe the process. The models presented to date described various aspects of the freeze-drying process. Zamzow (1952) and later Mujumdar (1980) modeled and simulated the drying process within the vial. Liapis and Marchello (1983), and Pikal et al. (1984), added external heat and mass transfer, while keeping the chamber pressure constant. A broader understanding can perhaps be achieved by deriving equations that describe the primary drying phase of the freeze-drying process and include other major physical influences such as the influence of the condenser, so that simulation of the model would represent the behavior of the entire freeze-dryer.

A model was developed by Schoen (1993) and Schoen and Jefferis (1993) which accounts for the coupled heat and mass transfer relationship governing the primary drying phase of a freeze-drying cycle. Mass transfer is assumed to be gov-

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* Corresponding author.

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erned by simple diffusion, and heat transfer is assumed to be driven primarily through conduction from the shelf. The combined processes form a nonlinear fourth-order system of differential equations.

The primary purpose of the present study was to adapt the model developed by Schoen and Jefferis (1993) to fit experimental data from product vials processed using a development scale freeze-dryer. The model was evaluated to ascertain the degree to which it simulated the primary drying time and temperature conditions for product vials during the primary drying phase of the cycle. The simulation results are presented as well as the corresponding parameters used to fit the data.

2. Theory

The schematic diagram in Fig. 1 depicts the sublimation process occurring at the interface, which is located at a distance x from the vial bottom. During sublimation the interface moves in a negative x direction, while the product height remains constant. The sublimed water leaves the product through the already dried product layer.

The mass transfer of the water vapor can therefore be regarded as a transfer through fine pores (Ho and Roseman, 1979) and be described using Knudsen diffusion. The heat flow from the shelf to the vial consists of the heat conducted through the contact area between the vial and the shelf. Since the vials have concave bottoms heat is also conducted through the enclosed gas between the vial and the shelf. Energy inside the frozen product layer is lost due to the sublimated water and the conducted heat to the dried product layer. The heat flux from the chamber to the condenser depends on the thickness of the crystallized water at the condenser wall. The derived model is based on the following assumptions:

(1) The heat and mass flow are unidirectional and occur perpendicular to the interface (McCulloch and Sunderland, 1970; Hill, 1971).
(2) The sublimation of the unbound ice occurs at the interface of the dried product layer and the frozen product layer parallel to the shelf (McCulloch and Sunderland, 1970; Hill, 1971).
(3) The distribution of the unbound and bound water is uniform over the sample height.

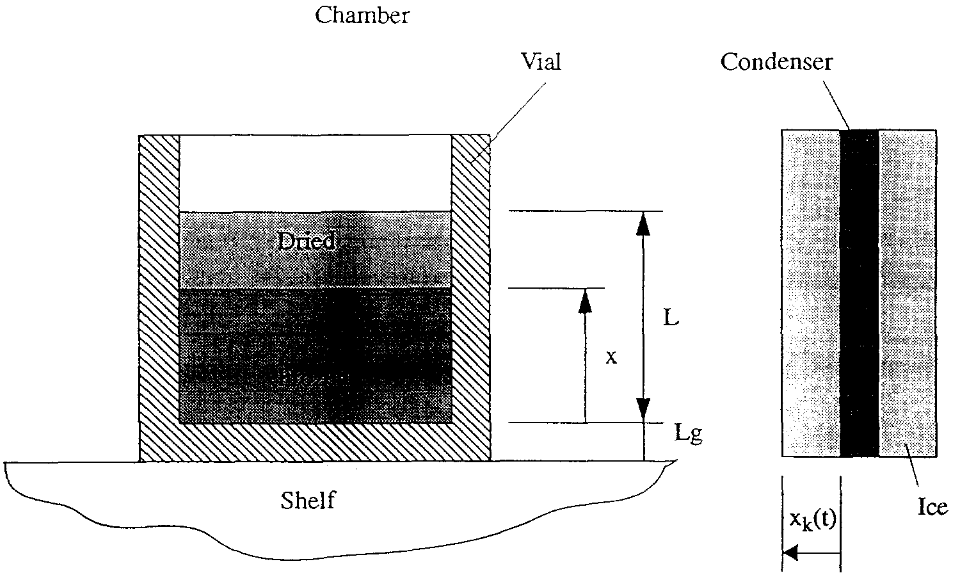

Fig. 1. A schematic diagram of the sublimation process in the vial and the condensation of the sublimed water at the condenser.

(4) The mass and heat transfer can be described with pseudo steady state equations (Hill, 1971).
(5) The temperature difference of the vapor between the product surface and condenser wall is considered negligible.
(6) The heat associated with the inlet of inert gas does not change the temperature of the chamber gas.
(7) The walls of the freeze-dryer chamber are perfectly insulated.
(8) The gas conduction occurs only between the heated shelf and the vial bottom, (Pikal et al., 1984).
(9) The subliming ice condenses only at the condenser coils. The water molecules removed from the system by the vacuum pump are considered negligible.

The partial pressure of water vapor in the model was calculated using a function developed by Jancso et al. (1970). The gas conduction term was derived from the theory described by Dushman (1962). The internal mass transfer coefficient was derived from the kinetic gas theory described by Kochs (1991). The resulting equations representing the mathematical model are described in Appendix A.

3. Materials and methods

The formulation was a 20 mg/ml solution of glycine in water adjusted to pH 3.0 with hydrochloric acid. The freeze-drying run used 50 vials containing 0.5 ml of formulation per vial. The vials were partially stoppered by hand and loaded on the same shelf in the freeze-dryer. Thermocouples were inserted into several vials to measure the temperature of the product during the cycle. These vials were positioned on the shelf to not be in physical contact with other vials. The surface temperature of the shelf near these vials was also measured using thermocouples.

The freeze-dryer used in the study was designed for small development scale batches. The polished interior of the freeze-dryer had a total volume of 0.35 m^3. The horizontally designed condenser had a total surface area of 1 m^2. The freeze-drying cycle was started by cooling the shelves from room temperature to 228 K. The total time for the freezing phase was 173 min under atmospheric pressure. Immediately before the start of the primary drying phase the total pressure in the chamber was decreased to 150 microns (20 Pa). After the pressure equilibrated at 150 microns the shelf temperature was in-

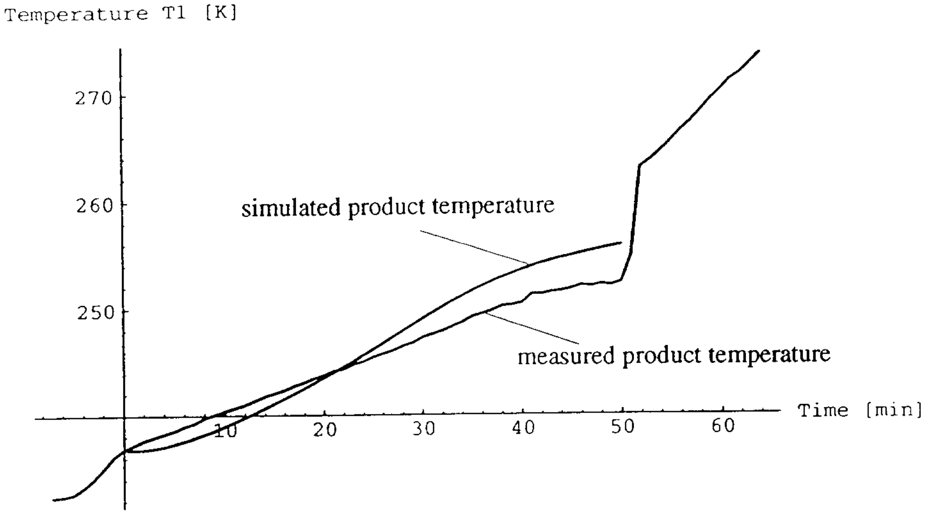

Fig. 2. The measured and simulated product temperature (K) for the product Vial #1 as a function of time (min).

creased from 228 to 298 K (requiring 43 min) and held at 298 K throughout primary drying. The primary drying phase was ended when the product temperature rose to a temperature above 273 K. A secondary drying phase was not included in the cycle. The condenser fluid input temperature throughout the run was 193 K. The total chamber pressure, condenser temperature and shelf fluid input temperature were measured using calibrated gauges in the freeze-dryer unit.

The model was simulated using Mathematica® (Version 2.2, Wolfram Research Inc., Champaign, IL, U.S.A.). Mathematica® is a general software system for solving mathematical problems, such as numerical integration. The simulation program is described in Appendix B.

The four differential equations solved are shown in Appendix B. The first, for Dgx, corresponds to Eq. 1 in Appendix A for the interface position. The second, for DgT1, corresponds to Eq. 2 of Appendix A for the temperature in the frozen region. The third, for DgT2, corresponds to Eq. 3 for the temperature in the dried product layer. The last, for DgTc, corresponds to Eq. 4 for the temperature of the gas in the freeze-dryer chamber. Mathematica® solves these four differential equations (heat and mass flow rates) internally by employing the well known Runge-Kutta method, which is a fourth-order approximation method.

4. Results and discussion

The temperature vs time profile for a representative vial is presented in Fig. 2. The primary drying phase for the cycle was started by increasing the shelf temperature from 228 to 298 K. During this heating period the product temperature cooled briefly but warmed with a slower rate of increase than the shelf temperature. The initial drop in the product temperature represents the sudden loss of heat due to sublimation and indicates the start of primary drying. After all of the unbound water has sublimed, the heat loss due to sublimation vanishes and the enthalpy input from the shelf causes a sharp elevation of the product temperature. This signals the end of primary drying for the product, which occurs at around 50 min in Fig. 2. The simulation results in Fig. 3 predict a product drying time of 51 min for this vial which is practically identical to the actual product drying time observed in Fig. 2.

The comparison in Fig. 2, between the simulation results for the product temperature and the measured product temperature, shows remark-

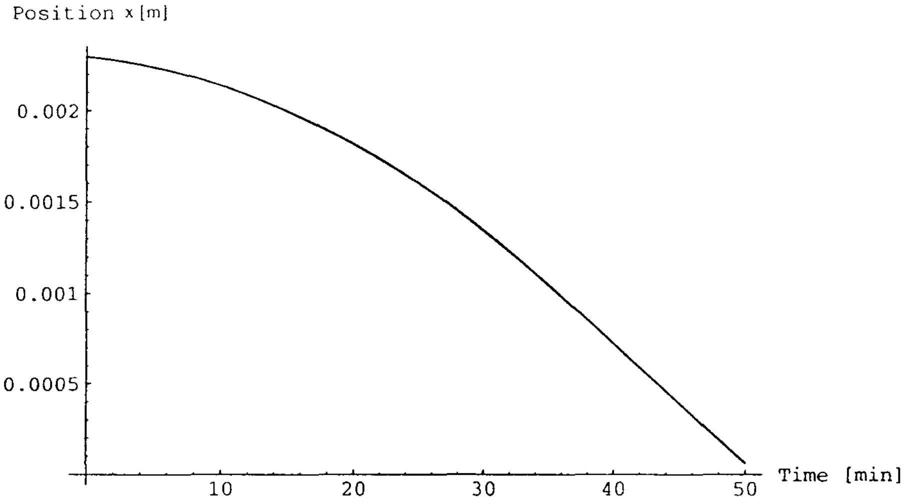

Fig. 3. The frozen-dried interface position (m) in the product as function of time (min.) for Vial #1. (Figs. 1–3 are submitted as hard copies only)

able agreement. The differences in product temperature are within the tolerance of the temperature measurements using thermocouples.

The model simulated in this study was derived from physical laws of heat and mass transfer and therefore requires the input of certain physical parameters. Some of these parameters, such as the thermal properties of the shelf, and the crystal structure of the frozen material, have random components that cannot be anticipated in the model. The model has coefficients that can be adjusted to fit such variations in the experimental data for individual vials in most cases. The set of coefficients resulting from the fit of the data will then vary from vial to vial because of the aforementioned random effects. The best simulation results for the vials of product evaluated in the cycle were determined by adjusting the factors that affect the heat (h_{ff}) and mass transfer (e_{ff}) coefficients. These factors are summarized in Table 1 for vials 1–3.

Other parameters that significantly affect the simulation results are condenser temperature (T_{km}) and condenser load, estimated pore radius (r_e) and the initial position of the interface front (x_0). The model was able to fit temperature data from all isolated (not clustered) vials on the shelf within ±3.5 K, ±2.5 K of which can be attributed to possible errors of temperature measurement. The fitted mass transfer coefficients and heat transfer coefficients were within the ranges of 1.09–1.40 and 0.73–0.91, respectively. When the heat and mass transfer coefficients determined for vial 1 were applied to vials 2 and 3, the predicted drying times varied ±12% from the measured values. This provided a measure of the ability of the model to predict results from conditions which have not been optimized.

Table 1
The heat (h_{ff}) and mass transfer (e_{ff}) coefficients used in the simulations for vials 1–3

Vial no.	h_{ff}	e_{ff}
1	0.73	1.33
2	0.81	1.09
3	0.91	1.40

The model appears to predict both temperatures and drying times within the practical limits imposed by temperature variation on the shelves.

5. Future work

The model will be evaluated using experimental data from a production scale freeze-dryer and modified if necessary to accommodate scaling factors. The primary goal of this study will be to develop a model to predict the lyophilization cycle profile in a large dryer from data generated in a smaller dryer. This would significantly improve the efficiency of cycle development and process transfer. Future research will also involve modifying the model to incorporate the nonlinear effects of shelf temperature and cake pore radius on the product drying times.

Appendix A

Differential equation for the moving interface:

$$\frac{d}{dt}x(t)=\frac{-A_1\left(40r_e e_{ff}\sqrt{\left(\frac{8\mathscr{R}T_c(t)}{\pi M_{H_2O}}\right)}\right)L}{m_{wi}\left(\frac{\frac{2r_e}{3}\sqrt{\left(\frac{8\mathscr{R}T_c(t)}{\pi M_{H_2O}}\right)}e_{ff}}{\sqrt{\frac{R_{res}T_c(t)}{12}}}+L\left(1-\frac{x(t)}{L}\right)\right)}\times\frac{\left(\Gamma_{15}10^{\Gamma_{14}}\right)\left(10^{-\frac{\Gamma_{13}}{T_2(t)}}-10^{-\frac{\Gamma_{13}}{T_c(t)}}\right)}{R_{H_2O}T_c(t)} \tag{1}$$

Glossary

Symbol	Definition	Units	Symbol	Definition	Units
A	cross-sectional area	(m^2)	Greek symbols		
c	thermal heat capacity	(J kg^{-1} K^{-1})	α	accommodation coefficient	(–)
Dia	internal diameter of vial	(m)	Γ	constant [a]	(–)
D_{in}	internal mass transfer coefficient	(m^2 s^{-1})	γ	specific heat ratio	(–)
D_{ex}	external mass transfer coefficient	(m s^{-1})	ζ	opening factor for valve	(–)
e_{ff}	heat transfer coefficient	(–)	Λ_o	free molecule heat conductivity at 0°C	(m K^{-1} min^{-1})
h_{ff}	heat transfer coefficient for gas conduction	(–)	λ	specific thermal conductivity	(W m^{-1} K^{-1})
ΔH	latent heat of sublimation	(J kg^{-1})	$\mathfrak{R}$	universal gas constant	(N m kg^{-1} K^{-1})
k	thermal conductivity	(W m^{-1} K^{-1})	μ	number of vials	(–)
L	thickness	(m)	ρ	density	(kg m^{-3})
M	molecular weight	(kg $kmol^{-1}$)	ϕ	diameter	(m)
m	mass	(kg)			
N_v	mass flux of vapor	(kg m^{-2} s^{-1})	Subscripts		
p	partial pressure	(N m^{-2})	c	chamber	
Q	heat flux	(W)	d	dryer	
R	gas constant	(N m kg^{-1} K^{-1})	g	vial	
r_e	effective radius	(m)	H_2O	water	
s_{ff}	heat transfer width for surface conduction	(m)	i	initial	
			k	condenser	
T	temperature	(K)	l	leakage	
t	time	(min)	N_2	nitrogen	
u	number of vials	(–)	p	product	
V	volume	(m^3)	s	shelf	
x	interface positions	(m)	t	total	
			w	water	
			0	single vial	
			1	frozen region	
			2	dried region	
			11...15	number for constants	

[a] Constants are given as: $\Gamma_{13} = 2668.726$, $\Gamma_{14} = 10.43113$ and $\Gamma_{15} = 133.333$.

Differential equation for the temperature in the frozen region:

$$\frac{\mathrm{d}}{\mathrm{d}t}T_1(t) = \frac{1}{\frac{x(t)}{L}\left((m_{wi}+m_p)c_1 + c_g m_{g0} u\right)}$$

$$\times \left(\left(\frac{k_g A_g (T_s - T_1(t))}{L_g}\right) + \frac{A_1}{5} h_{ff}\left(E_{oH_2O} + E_{N_2}\right) - \frac{k_1 A_1 (T_1(t) - T_2(t))}{x(t)} \right.$$

$$\left. - \frac{40 r_e e_{ff} \Delta H A_1 \dfrac{(p_{w1} - p_{wc})}{R_{H_2O} T_c(t)} \sqrt{\left(\dfrac{8 \mathscr{R} T_c(t)}{\pi M_{H_2O}} \right)}}{\dfrac{\dfrac{2 r_e}{3} e_{ff} \sqrt{\left(\dfrac{8 \mathscr{R} T_c(t)}{\pi M_{H_2O}} \right)}}{\sqrt{\dfrac{T_c(t) R_{res}}{12}}} + L\left(1 - \dfrac{x(t)}{L}\right)} \right) \tag{2}$$

where

$$E_{oH_2O} = \alpha \Lambda_{oH_2O} p_{wc} \left(\frac{273.2}{T_1(t)} \right)^{1/2} (T_s - T_1(t)) \qquad E_{oN_2} = \alpha \Lambda_{oN_2} p_{N_2} \left(\frac{273.2}{T_1(t)} \right)^{1/2} (T_s - T_1(t)) \tag{2a,b}$$

$$T_k = \exp((-0.016t)29.7) + 205 \tag{2c}$$

$$m_{c_{H_2O}} = \frac{V_d p_{wc}}{R_{H_2O} T_c(t)}; \qquad m_{c_{N2}} = \frac{V_d p_{N_2}}{R_{N_2} T_c(t)}; \qquad A_g = (\text{Dia} - 0.002) \pi \times u \times s_{ff}$$

$$R_{res} = \frac{1}{m_c} \left(m_{c_{H_2O}} R_{H_2O} + m_{cN_2} R_{N_2} \right) \tag{2d–g}$$

$$\lambda_{oH_2O} = \frac{1}{2} \left(\frac{\gamma_{H_2O} + 1}{\gamma_{H_2O} - 1} \right) \left(\frac{\mathscr{R}}{2\pi} \right)^{1/2} \frac{1}{\sqrt{(M_{H_2O} \times 273.2)}}$$

$$\lambda_{oN_2} = \frac{1}{2} \left(\frac{\gamma_{N_2} + 1}{\gamma_{N_2} - 1} \right) \left(\frac{\mathscr{R}}{2\pi} \right)^{1/2} \frac{1}{\sqrt{(M_{N_2} \times 273.2)}} \tag{2h,i}$$

and the enthalpy is defined as:

$$\Delta H = \Gamma_{11}(T_c(t) - T_1(t)) + \Gamma_{12} \tag{2j}$$

The partial pressures are given as:

$$p_{wc} = \Gamma_{15} 10^{\Gamma_{14}} 10^{-\frac{\Gamma_{13}}{T_c(t)}} \qquad p_{w1} = \Gamma_{15} 10^{\Gamma_{14}} 10^{-\frac{\Gamma_{13}}{T_2(t)}} \qquad p_{N_2} = p_t - \Gamma_{15} 10^{\Gamma_{14}} 10^{-\frac{\Gamma_{13}}{T_k(t)}} \tag{2k–m}$$

Differential equation for the temperature in the dried product layer:

$$\frac{d}{dt} T_2(t) = \frac{k_1 A_1}{x(t) \dfrac{(L - x(t))}{L} (m_p c_2 + m_{g0} c_g u)} (T_1(t) - T_2(t)) \tag{3}$$

Differential equation for the gas inside the freeze-drying chamber:

$$\frac{d}{dt} T_c(t) = \left\{ Q_1 + \left(\frac{40 r_e \sqrt{\left(\dfrac{8 \mathscr{R} T_c(t)}{\pi M_{H_2O}} \right)} e_{ff}}{\dfrac{\dfrac{2 r_e}{3} e_{ff} \sqrt{\left(\dfrac{8 \mathscr{R} T_c(t)}{\pi M_{H_2O}} \right)}}{\sqrt{\dfrac{T_c(t) R_{res}}{12}}} + L\left(1 - \dfrac{x(t)}{L}\right)} \times \frac{(\Gamma_{15} 10^{\Gamma_{14}}) \left(10^{-\frac{\Gamma_{13}}{T_2(t)}} - 10^{-\frac{\Gamma_{13}}{T_c(t)}} \right)}{R_{H_2O} T_c} \right) (\Gamma_{11}(T_c(t) + T_1(t)) + \Gamma_{12}) A_1 \right.$$

$$\left. - \frac{A_c \zeta}{\dfrac{1}{k_{kc}} + \dfrac{m_{wi}\left(1 - \dfrac{x(t)}{L}\right)}{A_k \rho_k \lambda_k}} (T_c(t) - T_k) \right\} \right) \Bigg/ \left\{ \left(\frac{m_{cH_2O} c_w}{m_c} + \frac{m_{cN_2} c_{N_2}}{m_c} \right) (m_{cH_2O} + m_{N_2}) \right\} \qquad (4)$$

Appendix B

```
(* SIMULATION PROGRAM FOR VIAL #1 *)

(* DETERMINATION OF THE SHELF TEMPERATURE FUNCTION *)

(* Input of shelf temperature data *)
(* Shelf # 14*)
  real = {{...}},t]
  pl = ListPlot[real, PlotJoined → True, PlotRange → All,
    AxesLabel → {"Time [min]","Temperature [K]"}]
  Interpolating Polynomial[{{...}},t]
  p = Plot[%,{t, – 5,100}, PlotRange → All]
  p2 = Show[p,pl]

(* SIMULATION PROGRAM *)

(* GEOMETRICAL CONSTANTS *)

u   = 50          (* number of vials *)
Dia = 0.01650     (* internal diameter of vial *)
Ac  = 1.00000     (* condenser area *)
ac  = 0.9         (* accommodation coefficient *)
l   = 0.00300     (* fill depth of vial *)
lg  = 0.00070     (* thickness of the bottom of the vial *)
lk  = 0.00159     (* thickness of the condenser wall *)
cc6 = 0           (* constant for the heat leakage into the system *)
Vd  = 0.3512      (* total freeze-dryer volume *)

(* PRODUCT PROPERTIES *)

re   = 50 × 10^(–7)   (* pore radius *)
roh1 = 928.6          (* density of the frozen product *)
roh2 = 20             (* density of the dried product *)
rohk = 920            (* ice density at the condenser *)
k1   = 2.10000        (* thermal conductivity of frozen product layer *)
k2   = 0.06           (* thermal conductivity of dried product layer *)
```

```
(* GENERAL ASSUMED CONSTANTS *)

eff     = 1.33              (* mass transfer coefficient *)
hff     = 0.73              (* heat transfer coefficient with gas conduction *)
sff     = 10^(-5)           (* heat transfer width for surface conduction *)
kg      = 0.81000           (* thermal conductivity of the vial *)
ksteel  = 35                (* thermal conductivity of steel (condenser wall) *)
kval    = 1.0               (* opening coeff. for valve *)
lamk    = 2.33000           (* specific thermal conductivity of ice *)
yH2O    = 7.656             (* specific heat ratio for water *)
yN2O    = 5.850             (* specific heat ratio for nitrogen *)
RH2O    = 46143*10^(-2)     (* gas constant for water *)
RN2     = 29682*10^(-2)     (* gas constant for nitrogen *)
MH2O    = 18.02             (* molecular weight for water *)
MN2     = 28.01             (* molecular weight for nitrogen *)
mgo     = 0.01              (* mass of one vial *)
cc3     = 2668726*10^(-3)   (* constant for the calculation of the w. v. pressure *)
cc4     = 1043112*10^(-5)   (* constant for the calculation of the w. v. pressure *)
cc5     = 1333333*10^(-4)   (* constant for the calculation of the w. v. pressure *)

(* CONTROL VARIABLES SETTINGS *)

Ts   = 229.45 + (108 + t)*(0.001666666666667046 +          (* shelf temperature *)
        (78 + t)*(0.0000277777777777683 +                    (* input polynomial *)
        (48 + t)*(6.172839506173543 × 10^ -7 +               (* derived from measurements *)
        (33 + t) × (-(2.057613168723111*10^ -8) +
        (18 + t)*(6.930165760194446*10^ -10 +
                 (7 + t)*
                 (6.241917038760171*10^ -9 +
                 (-(5.31703067770468*10^ -10) +
        (2.143829362834031*10^ -11 +
        (-(5.688766925658474*10^ -13) +
        (1.138007516407706*10^ -14 +
        (-(1.85909860117205 10 - 16) +
        (2.675106989970661*10^ -18 +
        (-(3.680124578211225*10^ -20) +
        (5.133508524788276*10^ -22 +
        (-(7.247588239911952*10^ -24) +
        (9.90615388661772*10 - 26 +
        (-(1.258507141852272*10^
        -27) +
        1.54895461198922*10^ -29*
        (-104 + t))*(-94 + t))*(-84 + t))*
        (-74 + t))*(-64 + t))*(-54 + t))*
        (-44 + t))*(-34 + t))*(-24 + t))*
        (-14 + t))*(-5 + t))*t))))))
Tkm = ((Exp[-0.016*(t)])*29.7) + 205                        (* condenser fluid temperature *)
pN2 = 20-cc5*(10^cc4)*(10^(-cc3/Tkm))                        (* average nitrogen pressure *)
        (* p(air) + p(n2) for Tc = Tkm and Po = 20 N/m2 *)  (* in the chamber *)
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(* GENERAL CALCULATED CONSTANTS *)

Al     = (Dia^2)*Pi/4*u                 (* total product cross sectional area *)
Ag     = (Dia-0.002)*Pi*u*sff           (* contact area between vial and shelf *)
As     = (Dia^2)*Pi/20*u                (* shelf contact area *)
Vprod  = Al*l                           (* total product volume *)
kk     = ksteel/lk                      (* thermal conductivity of the ice at the condenser *)
alfa   = ac*((273.2/Tc[t])^.5)/(2-ac)   (* effective accommodation coefficient *)

(* Model for t in min *)

AoH2O = 88.08*((yH2O + 1)/(yH2O – 1))/(MH2O^.5)   (* free molecular *)
AoN2   = 88.08*((yN2 + 1)/(yN2 – 1))/(MN2^.5)     (* heat conductivity *)
Rres   = mcH2O*RH2O/mc + mcN2*RN2/mc              (* resulting gas constant *)
Din    = 2*re*((8*RH2O*Tc[t]/Pi)^.5)*60/3*eff     (*internal mass transfer coefficient *)
Dex    = ((3*Rres*Tc[t])^(.5))*60/6               (* external mass transfer coefficient *)
cc1    = 34.9166                                  (* constant for the calculation of the enthalpy
  *)
cc2    = 47207.33                                 (* constant for the calculation of the enthalpy
  *)
c1     = 32.7966                                  (* thermal heat capacity of frozen product *)
c2     = 49.000                                   (* thermal heat capacity of dried product *)
cg     = 14.000                                   (* thermal heat capacity of the vial *)
cw     = 27.91167                                 (* thermal heat capacity of water vapor *)
cn     = 17.31667                                 (* thermal heat capacity of nitrogen *)
cc     = mcH2O*cw/mc + mcN2*cn/mc                 (* thermal heat capacity of chamber *)

(* Calculated masses *)

mp     = Vprod*roh2                 (* product mass after primary drying *)
mtotal = Vprod*rohl                 (* product mass before primary drying *)
mwi    = mtotal-mp                  (* initial water mass inside the product *)
mcH2O = Vd*pcw/(RH2O*Tc[t])         (* mass of water vapor inside the chamber *)
mcN2   = Vd*pN2/(RN2*Tc[t])         (* mass of nitrogen inside the chamber *)
mc     = mcH2O + mcN2               (* total gas mass inside chamber *)
m1     = x[t]*(mwi + mp)/l          (* mass of frozen product layer *)
m2     = (l – x[t] + 0.0001)*mp/l   (* mass of dried product layer *)
mg     = u*mgo                      (* total mass of empty vials *)

(* Heat and Mass equations *)

pfw  = cc5*(10^(cc4))*(10^(–cc3/T2[t]))                 (* partial water vapor pressures for *)
pcw  = cc5*(10^(cc4))*(10^(–cc3/Tc[t]))                 (* the interface front and chamber *)
b1   = (Din/Dex) + l*(l – (x[t]/l))                     (* coeff. for the mass transport *)
kc1  = l/((l/kk) + (mwi*(l – x[t]/l)/(Ac*rohk*lamk)))   (* therm. cond. at condenser *)
Mdot= Din*(pfw-pcw)/(RH2O*Tc[t]*b1)                     (* mass flux of water *)
DH   = ccl*(Tc[t] – Tl [t]) + cc2                       (* enthalpy of ice at the condenser *)
Es1  = alfa*AoH20*pcw*((273.2/Tl[t])^.5)*(Ts-Tl[t])     (* energy passed through –*)
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Es2  = alfa*AoN2* pN2*((273.2/T1 [t])^.5)*(Ts-Tl [t])   (* – the gas *)
Q1   = kl*Al*(Tl[t] – T2[t])/x[t]                        (* heat flux between frozen and dried region *)

Qg = (Es1 + Es2)*As* hff          (* heat flux due to gas conduction *)
Qs = kg*Ag*(Ts-Tl[t])/lg + Qg     (* heat flux between shelf and vial *)
Ql  = cc6                          (* heat leakage into the chamber *)
Qv = Ac* kcl* kval*(Tc[t]-Tkm)     (* heat flux at the condenser *)

(* Differential equations *)

Dgx  = – Mdot*Al*1/mwi                                    (* interface position x *)
DgTl = (Qs-Ql-Mdot* DH*Al)/(ml*cl + mg*cg* x[t]/l)        (* temperature Tl *)
DgT2= Ql/(m2*c2 + mg*cg*(1 – x[t])/l)                     (* temperature T2 *)
DgTc= Ql/(mc*cc) + Mdot* DH*Al/(mc*cc) – Qv/(mc*cc)       (* chamber temperature Tc *)

(* Solving Differential equations by Runge-Kutta and Mathematica *)

NDSolve[{x′[t] = = Dgx, Tl′[t] = = DgTl, T2′[t] = = DgT2, Tc′[t] = = DgTc, x[0] = = 2.3*10 (-3),
    Tl[0] = = 236.9,T2[0] = = 236.9,Tc[0] = = 234.71}, {x,Tl,T2,Tc},{t,0,50}]
    Plot[Evaluate[x[t]/.%],{t,0,50},AxesLabel → {“Time [min]”,“Position [m]”}]
    pl = Plot[Evaluate[Tl[t]/.%%],{t,0,50},PlotRange → All, AxesLabel →
    {“Time [min]”,“Temperature T1 [K]”}]
    Plot[Evaluate[Tl [t]/.%%%], {t,0,5},PlotRange → All,AxesLabel →
    {“Time [min]”,“Temperature Tl [K]”}]
    Plot[Evaluate[T2[t]/.%%%%],{t,0,50},PlotRange → All,AxesLabel →
    {“Time [min]”,“Temperature T2 [K]”}]
    Plot[Evaluate[T2[t]/.%%%%%],{t,0,5},PlotRange → All,AxesLabel →
    {“Time [min]”,“Temperature T2 [K]”}]
    Plot[Evaluate[Tc[t]/.%%%%%%], {t,0,50},PlotRange → All,AxesLabel →
    {“Time [min]”,“Temperature Tc [K]”}]
    Plot[Evaluate[Tc[t]/.%%%%%%%], {t,0,5},PlotRange → All,AxesLabel →
    {“Time [min]”,“Temperature Tc [K]”}]
    Plot[Ts, {t,0,50},PlotRange → All,AxesLabel →
    {“Time [min]”,“Temperature Ts [K]”}]
    reall = {{ – 7,232.4},{ – 6,232.5},{ – 5,232.7},{ – 4,233.3},{ – 3,234.1},{ – 2,235.1},
    { – 1,236.2},{0,236.9},{1,237.3},{2,237.7},{3,238},{4,238.3},{5,238.6},{6,239},{7,239.3},
    {8,239.8},{9,240.1},{10,240.4},{11,240.7},{12,241},{13,241.4}, {14,241.8},{15,242.1},
    {16,242.4},{17,242.8},{18,243.1},{
    19,243.5},{20,243.8},{21,244.2},{22,244.4},{23,244.8},{24,245.1
    },{25,245.5},{26,245.8},{27,246.1},{28,246.5},{29,246.8},{30,247.3},
    {31,247.6},{32,247.9},{33,248.3},{34,248.7},{35,249.2},{36,249.5},{37,249.8},{38,250.2}
    ,{39,250.3},{40,250.5},{41,251.3},{42,251.3},{43,251.5},{44,251.6},{45,251.8},
    {46,252.1},{47,252},{48,252.2},{49,252.1},{50,252.4},{51,254.8},{52,263},{53,263.7},
    {54,264.5},{55,265.4},{56,266.4},{57,267.2},{58,268.2},{59,269.3},{60,270.2},{61,271.2}
    ,{62,271.8},{63,272.7},{64,273.6}}
    p2 = ListPlot[reall, PlotJoined → True, PlotRange → All,
        AxesLabel → {“Time [min]”,“Temperature [K]”}]
    p3 = Show[pl,p2]
```

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