



## Analysis of heat and mass transfer mechanism of vacuum freeze-drying in the primary drying

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### Abstract:

The freeze-drying process is a complex heat and mass transfer process virtually. The drying process of freeze-drying is not only the key stage which decides the success of freeze-drying, but also the most difficult stage to control. There are lots of papers about heat and mass transfer in vacuum freeze drying at home and abroad. The present status of research on heat and mass transfer during vacuum freeze drying in the primary drying is summed up and analyzed, the trend of research in this field is discussed in this paper.

**Keywords:** vacuum freeze-drying; heat and mass transfer; mathematical model; primary drying

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## Introduction

Vacuum freeze-drying technology, is also called lyophilization. In the freeze-drying process, the fresh materials or wet materials preprocessed in some way, are cooled until their temperature is lower than the the eutectic point and the internal moisture of the materials is fully frozen, forming solid ice. Then, the air is extracted out of the drying chamber appropriately until the vacuum degree is up to a certain value. The hot plate is heated to a proper temperature, and the ice is sublimated into water vapor directly. Then the vapor is condensated by water catcher of vacuum system or vapour condenser of refrigerating system and the dry product is made finally <sup>[1]</sup>. The drying process of freeze-drying is the process of internal moisture changing its physical state and moving gradually. Because the change and move is under the condition of low temperature and low pressure, the basic principle of vacuum freeze-drying technology is heat and mass transfer mechanism at low temperature and low pressure <sup>[2]</sup>.

In order to lower the moisture content in materials to be suitable for preservation, drying process is divided into the primary drying and the secondary drying. During the primary drying, which is also called sublimation drying, the material is heated at relatively low temperature, to sublimate the free water into vapor. The secondary drying, also called desorption drying, is aimed at removing part of combined water. As the combined water molecules are bound by large intermolecular forces, they are needed to be provided lots of energy to keep the process of secondary drying. Therefore, the temperature of secondary drying is always higher than that of primary drying. In the secondary drying, the combined water in material firstly desorbs into liquid water which is at free stage, and then absorbs heat to sublimate into water vapor. The energy provided in the secondary drying consists of the energy for desorption and the energy for evaporation, so it is generally called desorption heat.

## 1. Research status at home and abroad

The vacuum freeze drying is a heat and mass coupled process, which belongs to the dynamics research category of continuously moving heat and mass transfer of the phase boundary between gas and solid at low temperature and low press <sup>[3]</sup>. In the process of freeze-drying, sublimation interface is the separatrix of solid and gas, on which the continuously moving change between gas and solid will occurs. Under the condition of radiation heating, the boundary condition is also nonlinear. Therefore, the mathematical model has strong nonlinear characteristic, and so we need to use finite difference method or finite element method to calculate and get the approximate solution in general, while we can get the analytic solution only under some special conditions <sup>[3,4]</sup>. Many scholars at home and abroad have made a lot of beneficial exploration on the mechanism of vacuum freeze-drying process.

At present, the relatively mature freeze-drying theory studied by people is the uniformly retreating ice front model (URIF), which was presented by Sandall and King <sup>[5]</sup>. In the URIF model, Sandall and King thought that the water vapor sublimation from the ice interface went through the porous dried layer and diffused to the surface of the condenser. The energy of the water vapor was not changed when it diffused through the porous dried layer, and the energy into the material imported by heating system was all used to sublimate water. The ice interface was retreated evenly to the frozen layer, and then the porous dried layer came up behind it. This model can accurately describe the parameter change and sublimation drying stage, during which almost all free water sublimates, accounting for 75% - 90% of all water. However, it can't describe the drying process and parameter change of the desorption drying. Subsequently, Dyre and Sunderland proposed the quasi-steady model in 1968 <sup>[6]</sup>. Lifchid and Liapis proposed the desorption-sublimation model in 1979 <sup>[7]</sup>. In the desorption-sublimation model, Lifchid and Liapis thought that the ice sublimation in the frozen layer was simultaneous with the combined water desorption in the dried layer, and both the mass and the energy of water vapor were unchanged when through the porous dried layer. This model improved the URIF model.



In recent years, the theory study of the drying process in vacuum freeze-drying goes forward slowly. The new models are based on URIF model, and make some supplements to the URIF model, the quasi-steady model and the desorption-sublimation model, but there are no breakthroughs in them. Most of the new models only make some changes, in consideration of some specific situations. In 1979, Lichtfield made deep research on the optimization of freeze-drying process, and established the unsteady heat transfer mathematical model under the condition of radiation heating <sup>[8]</sup>. He analyzed the vacuum freeze-drying by this model. The results showed that the maximum heat-flux density and pressure in freeze-drying chamber should be adopted in the beginning of freeze-drying, and when the interface temperature is close to the limit, the pressure should be lowed down to make the temperature at the limit value. In this way, the time of freeze-drying is shortest. M. J. Pikal and M. L. Roy studied the heat and mass transfer of bottled medicine in freeze-drying process <sup>[9]</sup>. In 1985, Millman and Liapis established unsteady heat and mass transfer model based on the energy balance and mass balance of frozen layer and the porous dried layer, and solve the one-dimensional desorption- sublimation model by a numerical method<sup>[10]</sup>. Compared with experimental value, this model can describe the freeze-drying process relatively well. In 1991, Kumagai made analysis with the freeze-drying rate in URIF model and modified URIF model <sup>[11,12]</sup>. In 1997, Mascarenhas put forward the two-dimensional axisymmetric desorption-sublimation model, which ignored the effect of heat-flux and radiation of vial wall under the condition of boundary conditions being simplified <sup>[13]</sup>. In 1998, Sheehan and Liapis proposed dynamic multidimensional model which can describe the dynamic behavior of primary drying and secondary drying in freeze-drying process which had the advantage that it can provide the distribution of concentration and temperature dynamic behavior of combined water in vial <sup>[14]</sup>. In 2004, based on thermal physics, Boss established a mathematical model which is suitable for real-time control, and optimized the drying process <sup>[15]</sup>. Suling Zhai put forward two-dimensional axisymmetric unsteady model in which the effect of curve of vial bottom is considered <sup>[16]</sup>. This model can predict and describe the movement of ice interface, freezing point curve and the effect of drying time and drying pressure, and can help to understand the heat and mass transfer in primary drying. Therefore, it can optimize the lyophilization process. In 2005, Gan proposed multi-dimensional unsteady model <sup>[17]</sup>, and he also considered the effect of the drying chamber wall and the lateral wall of tray. In 2006, R.Chakraborty proposed dynamic model of parameter sensitivity of modeling the primary drying process of food <sup>[18]</sup>, by changing the radiator temperature and the combustor pressure. In 2008, A.I.Liapis and R.Bruttini studied the freeze-drying energy analysis of pharmaceutical in trays and in vials on tray, and established mathematical model to describe the primary drying and secondary drying <sup>[19,20]</sup>. In 2009, J. F. Nastaj and K. Witkiewicz proposed mathematical modeling of the primary and secondary drying vacuum freeze drying of random solids at microwave heating <sup>[21,22]</sup>. In 2011, Cristian analyzed the effect of drying room pressure, tray temperature, vial shape, initial solution temperature, nucleation temperature and phase transition on the heat transfer and temperature distribution of sample <sup>[23]</sup>.

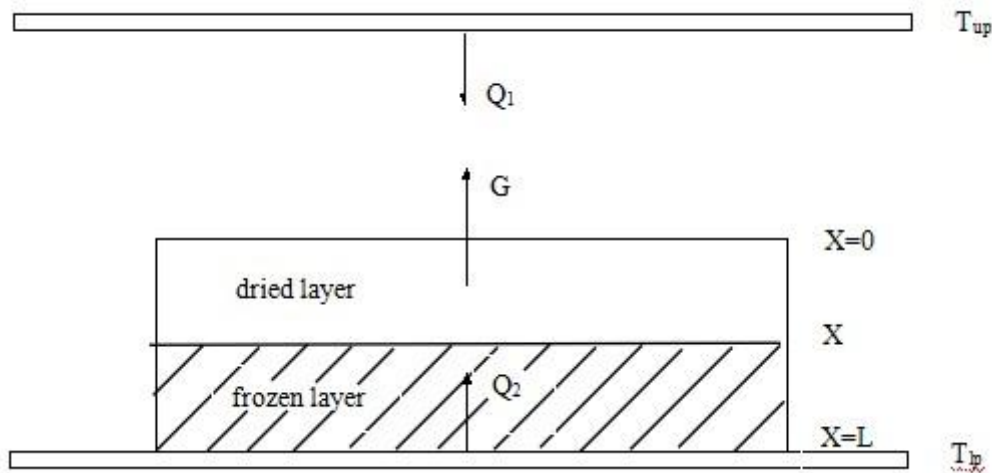
In China, the research on freeze-drying is relatively few, which are mainly focused on the technology of freeze-drying. But in recent years, the research moves towards the basic theory and mechanism of freeze-drying from its simple application gradually. In 2004, Huifen Zou established two-dimensional unsteady model of the heat and mass transfer of freeze-drying process, and carried on the simulation and calculation about freeze-drying process of cornea by finite element software <sup>[24]</sup>. The results showed that when the temperature of freeze-drying chamber is about -10°C and the pressure is about 50 Pa, the single side freeze-drying time of cornea is 230 min, and the double side time of cornea is 170 min. Based on the simplified unsteady model of vacuum freeze-drying, Zhihua Yao and Jieping Chen established quasi steady mathematical model in 2007 <sup>[25]</sup>. The comparison of theoretical calculation and experimental result showed that the quasi steady model can describe the primary drying well, but there is large deviation when used in desorption drying. In 2009, Ruiming Luo in Ningxia university made deep research on the dynamic simulation of desorption drying of frozen beef, and got the optimal operation condition of desorption drying <sup>[26]</sup>. Water and temperature changed over time in this model, which can simulate and predict the desorption drying. In 2012, the doctor Shuguo Guo in Shenyang agricultural university

summarized the existed results of freeze-drying, and made deep analysis on the characteristic of vacuum freeze-drying<sup>[27]</sup>. Then he put forward a new two-dimensional model of freeze-drying, in which comprehensive factors were taken into consideration and the theoretical calculation is closer to the actual process. This model provided the theoretical reference for mechanism analysis and thermal control of freeze-drying.

## 2 Mathematical model of primary drying

### 2.1 The energy equation and mass equations of primary drying

In the primary drying, materials are heated at vacuum and low temperature, to make the frozen ice sublimate which belongs to free water. The sublimation of material is mainly decided by the pressure of water vapor in the drying chamber, and most of heat is used for sublimation of frozen ice, while a little of heat is used by a small amount of combined water evaporation which is not at frozen state. Studies have shown that, in the primary drying, the evaporated combined water is so little that it can be ignored. The primary drying of materials in tray is shown as follows.



**Fig. 1 Sketch of primary drying of materials in tray**

It can be seen from the sketch above that, materials are in the tray which is heated by the lower separator plate with conduction heating, and the upper separator plate with radiation heating. Then, there are some assumed conditions as followings.

(1) The heating mode of materials is mixing heating.

(2) The heat transfer process is unidimensional, and its direction is Perpendicular to the dried layer surface and the sublimation surface.

(3) Sublimation only occurs on the interface between the frozen layer and the dried layer. The interface is infinitely thin, and the distribution of concentration and temperature is uniform. There is no sublimation in dried layer.

So, the energy equation in the dried layer is shown as follows.

$$\frac{\partial T_d}{\partial t} = a_{de} \frac{\partial^2 T_d}{\partial x^2} - \frac{C_{pg}}{\rho_{de} C_{pde}} \frac{\partial(GT_d)}{\partial x} + \frac{\Delta H_v \rho_d}{\rho_{de} C_{pde}} \frac{\partial m_{sw}}{\partial t}, t > 0; 0 \leq x \leq X \quad (2-1a)$$

$T_d$  -temperature of dried layer;

$t$  -time;



$k_{de}$  -effective thermal conductivity of dried layer;  $C_{pg}$  -thermal capacity of gas in dried layer;

$\rho_{de}$  -density of dried layer;  $C_{pde}$  -effective thermal capacity of dried layer;

$a_{de} = \frac{k_{de}}{\rho_{de}C_{pde}}$  -effective thermal diffusivity of dried layer;

$\Delta H_V$  -heat of desorption of combined water

$G_t = G_w + G_i$  -total flow rate of the gas extracted from the material;

$G_w$  -flow rate of water vapor;  $G_{in}$  -flow rate of non-condensable gas;  $\rho_d$  -density of dried layer during primary drying;  $m_{sw}$  -flow rate of desorbed combined water.

The left term in the above equation means the internal energy added. The first one on the right of equal sign means the energy imported to dried layer from the environment, the second means the working to the gas in the dried layer from pressure, and the third one means the desorption energy during the primary drying.

The mass equation of water vapor in the dried layer is:

$$\frac{1}{R} \frac{\partial}{\partial t} \left( \frac{p_{dw}}{T_d} \right) = - \frac{1}{M_w \varepsilon} \frac{\partial G_w}{\partial x} - \frac{\rho_d}{M_w \varepsilon} \frac{\partial m_{sw}}{\partial t}, t > 0; 0 \leq x \leq X \quad (2-2a)$$

The mass equation of non-condensable gas in the dried layer is:

$$\frac{1}{R} \frac{\partial}{\partial t} \left( \frac{p_{in}}{T_d} \right) = - \frac{1}{M_{in} \varepsilon} \frac{\partial G_{in}}{\partial x}, t > 0; 0 \leq x \leq X \quad (2-3)$$

The energy equation of frozen layer is:

$$\frac{\partial T_f}{\partial t} = a_f \frac{\partial^2 T_f}{\partial x^2}, t > 0; 0 \leq x \leq X \quad (2-4)$$

There is no mass transfer in frozen layer. Therefore, there is no mass transfer equation in frozen layer.

$p_{dw}$  -pressure of water vapor in dried layer;  $M_w$  -molecular weight of water;

$\varepsilon$  -porosity;  $R = 8.314 \text{ KJ}/(\text{kmol} \cdot \text{K})$ ;

$T_f$  -temperature of frozen layer;  $p_{in}$  -pressure of non-condensable gas in dried layer;

$a_f$  -thermal diffusivity of frozen layer.



In the equations above,  $G_w$  and  $G_{in}$  are closely related to the structure of dried layer. Based on the dusty-gas model<sup>[28]</sup>,  $G_w$  and  $G_{in}$  can be expressed as follows<sup>[29]</sup>.

$$G_w = -\frac{M_w}{RT_d} \left[ K_1 \frac{\partial p_w}{\partial x} + K_2 p_w \left( \frac{\partial p_w}{\partial x} + \frac{\partial p_{in}}{\partial x} \right) \right] \quad (2-5)$$

$$G_{in} = -\frac{M_{in}}{RT_d} \left[ K_3 \frac{\partial p_{in}}{\partial x} + K_4 p_{in} \left( \frac{\partial p_w}{\partial x} + \frac{\partial p_{in}}{\partial x} \right) \right] \quad (2-6)$$

So we can find the complex effects of structure and other factors by  $K_1, K_2, K_3$  and  $K_4$ <sup>[30]</sup>. And the mass balance partial differential equations about  $p_w$  and  $p_{in}$  are shown as follows.

$$\varepsilon \frac{\partial}{\partial t} \left( \frac{p_w}{T_d} \right) = \frac{\partial}{\partial x} \left\{ \frac{1}{T_d} \left[ K_1 \frac{\partial p_w}{\partial x} + K_2 p_w \left( \frac{\partial p_w}{\partial x} + \frac{\partial p_{in}}{\partial x} \right) \right] \right\}, 0 \leq x \leq X \quad (2-7)$$

$$\varepsilon \frac{\partial}{\partial t} \left( \frac{p_{in}}{T_d} \right) = \frac{\partial}{\partial x} \left\{ \frac{1}{T_d} \left[ K_3 \frac{\partial p_{in}}{\partial x} + K_4 p_{in} \left( \frac{\partial p_w}{\partial x} + \frac{\partial p_{in}}{\partial x} \right) \right] \right\}, 0 \leq x \leq X \quad (2-8)$$

## 2.2 Simplification of energy equation and mass equation of primary drying

### 2.2.1 Simplification of energy equation and mass equation of primary drying when the desorption is ignored

All of the equations from (2-1a) to (2-4) describe the desorption-sublimation model, in which ice sublimation in frozen layer is simultaneous with combined water desorption in dried layer and both mass and energy of water vapor change when moving through the porous dried layer. Simplify the equations above to solve the actual problem in application.

In the equation (2-1a), the last term represents the desorption phenomenon in primary drying. Research shows the effect of the term on primary drying is so little that it can be ignored. Therefore, the energy equation in dried layer can be simplified as follows.

$$\frac{\partial T_d}{\partial t} = a_{de} \frac{\partial^2 T_d}{\partial x^2} - \frac{C_{pg}}{\rho_{de} C_{pde}} \frac{\partial(G T_d)}{\partial x}, t > 0; 0 \leq x \leq X \quad (2-1b)$$

In the equation (2-2a), the last term represents the desorption phenomenon in primary drying. Research shows the effect of the term on primary drying is so little that it can be ignored. Therefore, the mass equation of water mass can be simplified as follows.

$$\frac{1}{R} \frac{\partial}{\partial t} \left( \frac{p_{dw}}{T_d} \right) = -\frac{1}{M_w \varepsilon} \frac{\partial G_w}{\partial x}, t > 0; 0 \leq x \leq X \quad (2-2b)$$



The equations (2-3) and (2-4) have nothing to do with desorption, so they can't be simplified when the desorption is ignored. Therefore, the equations (2-1b), (2-2b), (2-3) and (2-4) are the mass equations and energy equations during primary drying when the desorption is ignored.

### 2.2.2 The uniformly retreating ice front (URIF) model

In the URIF model, it was thought that the water vapor sublimation from the ice interface went through the porous dried layer and diffused to the surface of the condenser. The energy of the water vapor was not changed when it diffused through the porous dried layer, and the energy into the material imported by heating system was all used to sublimate water. The ice interface was retreated evenly to the frozen layer, and then the porous dried layer came up behind it.

$$\frac{\partial T_d}{\partial t} = a_{de} \frac{\partial^2 T_d}{\partial x^2}, t > 0; 0 \leq x \leq X \quad (2-1c)$$

## 3 Analysis of the heat and mass transfer of the primary freeze-drying process and its research prospect

The models above are unidimensional models, which are simpler than two-dimensional and multidimensional models. For the possibility of actual calculation, in both unidimensional steady model and multidimensional unsteady model of freeze-drying, macro parameters are studied, such as effects of pressure, temperature and macro-size on heat and mass transfer of freeze-drying, while the effects of material microstructure and micro supernormal heat and mass transfer are not considered. It is assumed that interior is homogeneous, and thermal conductivity, diffusivity, density and specific heat are the same everywhere. Even though the research is very difficult and there are many complicated description and calculation, more and more scientific researchers are interested in the frontier of freeze-drying. For example, people's researches moves from macro parameters to micro mesoscopic size, from conventional heat and mass transfer to supernormal heat and mass transfer of porous material which is studied with fractal method, from traditional steady models to unsteady models which accord with actual situation, from single effect of divided factor to synergism of multi-factors<sup>[31]</sup>. The vacuum freeze-drying, is a new comprehensive technology which is combination of vacuum science, cryoengineering, fluid technology, control engineering, heat and mass transfer and power engineering. It will become more perfect and more precise, and be widely used in food, pharmaceutical, biological products and other fields.

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