

Georg-Wilhelm Oetjen, Peter Haseley

Freeze-Drying

Second, Completely Revised and Extended Edition



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Georg-Wilhelm Oetjen, Peter Haseley

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Cover Illustration

The cover illustration shows the course of a main drying observed with a cryomicroscope. The photographs are taken after 1.5, 3.0, 4.5, and 6 minutes, respectively. Courtesy of M. Kochs, Ch. Körber, B. Nummer and I. Heschel, Int. J. Heat Mass Transfer 34 (1991) 2395 – 2408.

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Preface

Drying of food and herbs is one of the oldest preservation methods of humanity. Freeze-drying was first carried out, as K. H. Neumann wrote in his book *Grundriß der Gefriertrocknung*, 1954, by Altmann, who freeze-dried parts of organs in 1890. In 1932, Gersh designed an effective vacuum plant for freeze-drying of histological preparations with the help of the diffusion pump just invented by Gaede at that time. Sawyer, Lloyd and Kitchen successfully freeze-dried yellow fever viruses in 1929. Industrial freeze-drying began, as E. W. Flösdorf shows in his book *Freeze-Drying*, 1949, with the production of preserved blood plasma and penicillin.

Vacuum technology and penicillin were also my own first encounter with freeze-drying. After my studies of physics at the university in Göttingen, I worked in the development department of E. Leybold's Nachf. where I had to build a freeze-drying plant for penicillin. Since that time I was engaged in vacuum process technology for almost 25 years, from 1952 on as managing director of Leybold Hochvakuum Anlagen GmbH. From this time I know Peter Haseley, whom I employed for the freeze-drying department. Later, as 'Geschäftsführer' of Steris GmbH, he was actively involved with engineering modern freeze-drying plants with all their complex requirements of documentation and qualification. Together we have developed an old idea of mine to control the freeze-drying process not by predetermined time, pressure and temperature data, but by the data measured during the process. Therefore I was very happy when Peter Haseley agreed to rewrite the chapters *Installation and Equipment Technique* and *Trouble-shooting and Regulatory Issues* for this second edition.

Freeze-drying has always fascinated me as the most complex vacuum process. Mechanical and chemical engineering, chemistry and biology, sterility and regulatory issues are all part of the freeze-drying process.

After my retirement from the managing board of Drägerwerke AG, I had the time to write the German edition of this book, *Gefriertrocknen*, published in 1997, and the first English edition in 1999. This year, a translation into Japanese has been published.

When I started to write the German edition, Mr. Wolfgang Suwelack, managing partner of Dr. Otto Suwelack Nachf. GmbH & Co., asked me to work for him as consultant in freeze-drying, and I have to thank him for the permission to use some of the results achieved in the last years. This activity was the new start of my work in freeze-drying, and I would therefore like to dedicate this book to Mr. Wolfgang Suwelack out of gratitude for a harmonic cooperation lasting for over a decade.

Several companies and publishing houses have granted permission to use drawings and photographs to which they own the copyright. Mr. Haseley and I are grateful to all of them because they have thus made it possible to present freeze-drying under many aspects.

We have tried to show the interconnection between the properties of the product, the goal to make it stable and the necessary processes to achieve this. The problems of the different process steps are discussed with examples and the parameters influencing each step are described. We have avoided to follow the many theoretical attempts to describe one or more of the freeze-drying steps, but have restricted ourselves to a few equations which permit calculating process and product data with sufficient accuracy, or to at least allow an estimate based on measuring some of the data.

The freezing of a product is a very important step. The structure in the frozen product decides whether the product can be freeze-dried at all, and under which conditions it can be done. Therefore, the consequences of freezing rate, layer thickness of the product and excipients are discussed in some detail. The second main point is the measurement and control of the two drying phases, the main and secondary drying, and the third point concentrates on the residual moisture content, its measurement and the consequences during storage of the dry product. There will be critical opinions that some of the processes are unilaterally represented. I have tried to show the limits and advantages of certain procedures to enable the reader to decide for himself whether the ideas of the quoted authors or my own can be applied best to his particular task.

The approximately 270 literature references in the 1999 edition have been in part replaced and furthermore supplemented to a new total of 370.

Preface to the First Edition

This book is dedicated to my esteemed teacher, the late Prof. Dr. K. H. Hellwege, from whom I learned to tackle a problem from as many sides as I could imagine, with wide open curiosity.

One of humanity's oldest methods of preservation is the drying of food and herbs. Freeze-drying was first carried out by Altmann, who freeze-dried organ pieces in 1890, as Dr. K. H. Neumann wrote in his book 'Grundriß der Gefriertrocknung' in 1954. In 1932 Gersh designed an effective vacuum plant for the freeze-drying of histological preparations with the help of the diffusion pump, just invented by Gaede at that time.

Sawyer, Lloyd and Kitchen successfully freeze-dried yellow fever viruses in 1929.

Industrial freeze-drying began with the production of preserved blood plasma and penicillin, as shown by E. W. Flosdorf in his book 'Freeze-drying' in 1949.

Vacuum technology and penicillin were also my introduction to freeze-drying. After my studies of physics at the university in Göttingen, I worked in the development department of F. Leybold's Nachf. where I had to build a freeze-drying plant for penicillin. From then on, I was engaged in vacuum process technology for almost 25 years, including the time from 1952 as Managing Director of Leybold Hochvakuum Anlagen GmbH. Freeze-drying has always fascinated me as being the most complex vacuum process. Mechanical and chemical engineering, chemistry and biology, sterility and regulatory issues are all part of the freeze-drying process.

I intended to write this book many years ago, but only after my retirement as a member of the managing board of Drägerwerke AG did I have the time to do so.

It was at this time that Mr. Wolfgang Suwelack, Managing Partner of Dr. Otto Suwelack Nachf. GmbH & Co., asked me to work for him as a consultant in freeze-drying and I have to thank him for the permission to use some of the results achieved in the last years.

Furthermore, I am grateful to Dipl.-Ing. P. Haseley, Managing Director of AMSCO Finn-Aqua GmbH, now Steris GmbH, for the permission to use results, drawings and photographs of his company. Several companies and publishing houses have granted permission to use drawings and photographs to which they own the © copyright. I am grateful to all of them, because they have made it possible to present freeze-drying under many aspects.

I have tried to show the interconnection between the property of the product, the goal to make it stable and the necessary processes to achieve this. The problems of

the different process steps are discussed with examples and the parameters are described which influence each step. I have avoided following the many theoretical attempts describing one or more of the freeze-drying steps, but have restricted myself to a few equations which permit the calculation of process and product data with sufficient accuracy, or at least, allow an estimate, if some data is mentioned.

The freezing of a product is a very important step. The structure in the frozen product decides whether the product can be freeze-dried at all and under which conditions it can be done. For this reason, the consequences of the freezing rate, layer thickness of the product and excipients are discussed in some detail. The second main point is the measurement and control of the two drying phases; the main and secondary drying and the third concentrates on the residual moisture content, its measurement and the consequences during storage of the dry product. There will be critical opinions that some of the processes are unilaterally represented. My aim was to show the limits and the advantages of certain procedures to enable the reader to decide whether the ideas of the quoted authors, or my own can be applied to his tasks.

The approx. 220 references in the 1997 (German) edition are supplemented by approx. 50 new ones.

1

Foundations and Process Engineering

Freeze-drying or lyophilization is a drying process in which the solvent and/or the suspension medium is crystallized at low temperatures and thereafter sublimed from the solid state directly into the vapor phase.

Freeze-drying is mostly done with water as solvent. Figure 1.1 shows the phase diagram of water and the area in which this transfer from solid to vapor is possible. This step is relatively straightforward for pure water. If the product contains two or more components in true solutions or suspensions, the situation can become so complicated that simplified model substances have to be used to make the process more understandable. Such complex systems occur ubiquitously in biological substances.

The drying transforms the ice or water in an amorphous phase into vapor. Owing to the low vapor pressure of the ice, the vapor volumes become large, as can be seen in Figure 1.2. During the second step of the drying, the water adsorbed on the solids is desorbed.

The goal of freeze-drying is to produce a substance with good shelf stability and which is unchanged after reconstitution with water, although this depends also very much on the last step of the process: the packing and conditions of storage.

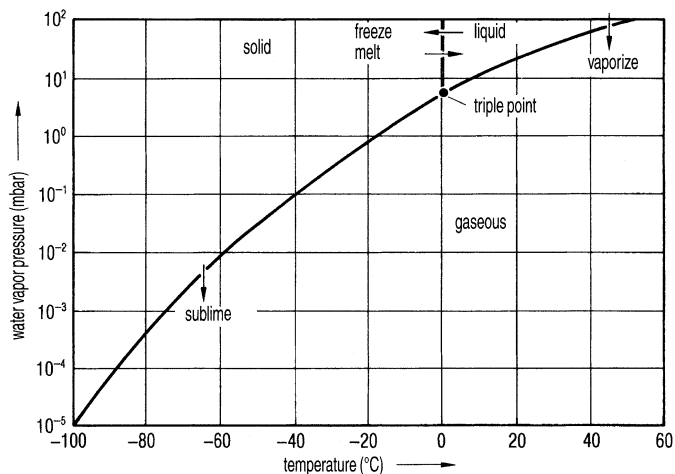


Fig. 1.1. Phase diagram of water

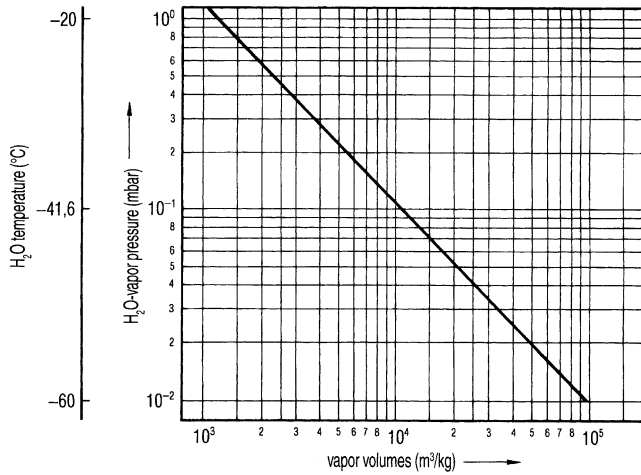


Fig. 1.2. Specific volume of water vapor as a function of the water vapor pressure. The temperature of the vapor in this diagram is that of ice

The advantages of freeze-drying can be summarized as follows:

- The drying at low temperatures reduces degradation of heat-sensitive products.
- The liquid product can be accurately dosed.
- The moisture content of the final product can be controlled during the process.
- The dry product can have an appealing physical form.
- The dry product with a high specific surface area is rapidly reconstituted.

The disadvantages are as follows:

- The high investment, operating and maintenance costs.
- The complexity of the process and the equipment requires a team of skilled and permanently trained collaborators.

1.1

Freezing

To freeze a substance it must be cooled to a temperature at which the water and the solids are fully crystallized or at which areas of crystallized ice and solids are enclosed in zones in which amorphous concentrated solids and water remain in a mechanically solid state (see Section 1.1.2). In the zone of freezing, the ice crystals are first growing, thus concentrating the remaining solution, which can vary the pH value. In many substances a eutectic temperature can be determined, but in many others this value does not exist. The crystallization depends on several factors which influence each other: cooling rate, initial concentration, end temperature of cooling and the

time at this temperature. In several products no crystallization takes place and the product remains in an amorphous, glass-like phase or a mixture of both occurs.

1.1.1

Amount of Heat, Heat Conductivity, Heat Transfer and Cooling Rate

For pure water, the melting heat to be withdrawn for freezing (Q_{tot}) can be calculated by Eq. (1), if the starting and the desired final temperatures are known:

$$Q_{\text{tot}} = c_w(T_1 - T_0) + Q_e + c_e(T_0 - T_2) \text{ (kJ/kg)} \quad (1)$$

where

c_w = specific heat capacity of water;

Q_e = melting heat of ice;

c_e = specific heat capacity of ice;

T_0 = freezing temperature of ice;

T_1 = initial temperature of water;

T_2 = final temperature of ice.

The temperature dependences of c_w between +20 and 0 °C and c_e between 0 and -50 °C have to be adopted as average values.

For solutions and suspensions the solid content has to be recognized. This is reflected in Eq. (2):

$$Q_{\text{tot}} = [(c_w x_w + c_f x_f)(T_1 - T_0)] + x_w Q_e + [(c_e x_w + c_f x_w)(T_0 - T_2)] \quad (2)$$

where

x_w = part of water above 0 °C;

c_f = specific heat of solids, for example:

for animal products $\approx 1.47 \text{ kJ/kg } ^\circ\text{C}$

for plant products $\approx 1.34 \text{ kJ/kg } ^\circ\text{C}$

for some solids:

carbohydrates $\approx 1.42 \text{ kJ/kg } ^\circ\text{C}$

proteins $\approx 1.55 \text{ kJ/kg } ^\circ\text{C}$

fats $\approx 1.7 \text{ kJ/kg } ^\circ\text{C}$

salts $\approx 0.8 \text{ kJ/kg } ^\circ\text{C}$;

x_f = part of solids;

x_w = part of ice, which freezes until temperature T_2 is reached. If not all water is frozen at T_2 , an additional term has to be introduced, which reflects the cooling of the unfrozen water.

Table 1.1.1 shows the unfreezable water (UFW) in various foods. The reasons and the consequences are described in Sections 1.1.3 and 1.1.4. In comparing these data with other publications, e.g. [1.3], smaller values may be found. This can depend not only on the different raw materials and the history of the probe until measurement, but also on the methods of measurement.

Table 1.1.1 Percentage of water frozen out at various temperatures for some foods (part of Table 1 in [1.1] and [1.2])

Product	Frozen out water at °C (% of the total water)				UFW (% of total water)
	–10	–15	–20	–30	
Lean beef	82	85	87	88	12
Haddock	84	87	89	91	9
Whole eggs, liquid	89	91	92	93	7
Yolk	85	86	87	87	13
Egg white	91	93	94		6
Yeast	80	85	88	89	11
Fruit juice	85	90	93	96	(3)
Peas	80	86	89	92	(7)

For meat with less than 4% fat content, Riedel [1.1] has published an enthalpy diagram (shown in Figure 1.3). For some other foods Table 1.2 shows enthalpy data at various temperatures. At -40 °C the enthalpy is set at 0 kJ/kg .

In Table 1.1.2 the UFW data for products used in pharmaceuticals are listed [3.6].

The transport of the calculated energy from the freezing zone of the product to the cooling medium can be described in a simplified way by the following steps: the product is an infinite plate, which is cooled from one site only, and the energy flows only perpendicular to its infinite expansion. The crystallization energy flows from the crystallization zone, through the already frozen ice, through the container bottom to a shelf and into the cooling brine.

The freezing time (t_e) is approximately given by Eq. (3) [1.4]:

$$t_e = \Delta J / \Delta T \rho_g (d^2 / 2\lambda_g + d / K_{su}) \quad (3)$$

$$t_e = \Delta J / \Delta T \rho_g (w + u) \quad (3a)$$

where

t_e = freezing time;

ΔJ = enthalpy difference between the the initial freezing point and the final temperature;

ΔT = difference of temperature between the freezing point and the cooling medium;

d = thickness of the product parallel to direction of prevailing heat transfer;

ρ_g = density of the frozen product;

λ_g = thermal conductivity of the frozen product;

K_{su} = surface heat transfer coefficient between cooling medium and the freezing zone.

Table 1.1.2 Percentage of unfrozen water (UFW), which cannot be frozen by lower temperature (see Figure 1.15.)

Excipient	UFW (%)
Trehalose	16.7
Sorbitol	18.7
Maltose	20
Glycerine	27
Glucose	29.1
Sucrose	35.9
Lactose	40.8
Glycerol	45.9
Fructose	49.0

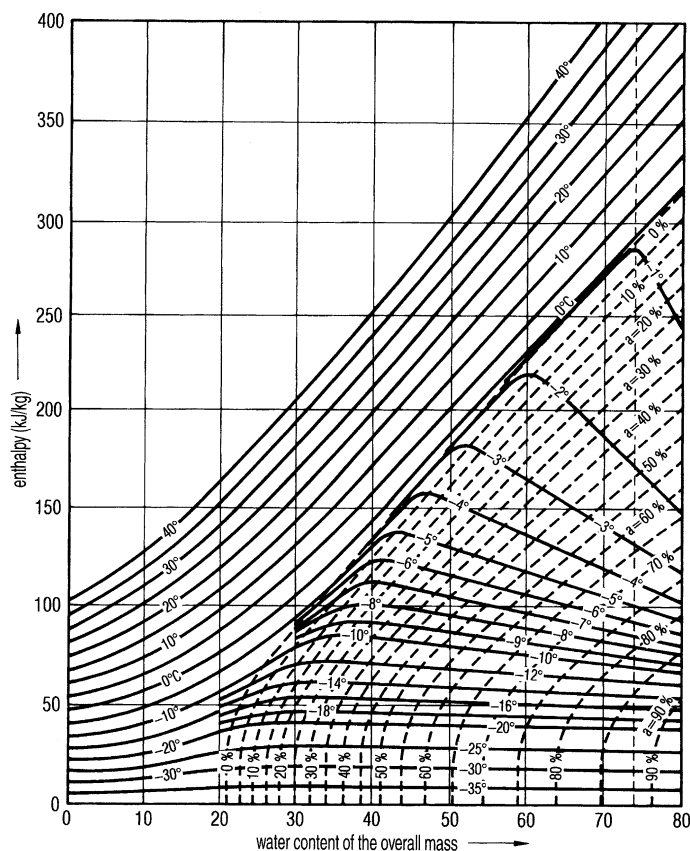


Fig. 1.3. Enthalpy of lean beef meat as a function of its water content (0 kJ/kg at -40°C). The temperatures at the beginning of cooling the and the desired end temperatures for freezing are plotted as parameters. The dotted lines indicate the percentage of water frozen at the end

temperatures (Fig. 1 from [1.1] and [1.2]). *Example:* Beef meat has 74% water. At $+10^{\circ}\text{C}$ the enthalpy is ~ 325 kJ/kg and at -20°C ~ 40 kJ/kg; therefore, 285 kJ/kg have to be removed and 83% of the water frozen. The maximum possible (88%) (see Table 1.1) is reached at $\approx 30^{\circ}\text{C}$

Table 1.2 Enthalpy of meat, fish and egg products (part of Table 3 in [1.1] and [1.2])

Product	Water content (weight %)	Enthalpy (kJ/kg) at a temperature of °C					
		–30	–20	–10	0	+5	+20
Beef, 8% fat	74.0	19.2	41.5	72.4	298.5	314.8	368.4
Cod	80.3	20.1	41.9	74.1	322.8	341.2	381.0
Egg white	86.5	18.4	38.5	64.5	351.3	370.5	427.1
Whole egg	74.0	18.4	38.9	66.2	308.1	328.2	386.9

The thermal conductivity of ice and of dried products is relatively well known, but the surface heat transfer coefficient K_{su} during freezing and the total heat transfer coefficient K_{tot} during freeze-drying vary largely as described in the various chapters. Table 1.3 gives a survey of some data of interest in freeze-drying.

The influence of the variables in Eq. (3) can be studied by an example. A slice of lean beef with a thickness which is small compared with its horizontal dimensions is to be frozen to -20 °C. The influences of the border of the slice are neglected. The thickness of the slice is $d = 2$ cm. As can be seen in Figure 1.3, the enthalpy difference for beef with 74% water is approximately 240 kJ/kg. If the freezing process starts between 0 and -3 °C and is mostly finished at -20 °C, the cooling medium has a tem-

Table 1.3 Surface heat transfer coefficient, total heat transfer coefficient and thermal conductivity

K_{su}	from gases to a solid surface (kJ/m ² h °C): free convection	17–21
	Laminar flow 2 m/s	50
	Laminar flow 5 m/s	100
K_{su}	between the shelf of a freeze-drying plant and a product in vials or trays during freezing (kJ/m ² h °C)	200–400
K_{su}	between a liquid and a solid surface (kJ/m ² h °C): oil in tubes, laminar	160–250
	LN ₂ by drops on the product ¹	900
	From liquids similar to water ²	1600
	From water at 1 bar, Temperature difference < 7 °C ³	3600
K_{tot}	between the shelf of a freeze-drying plant and the sublimationfront in the product contained in vials or trays under vacuum ⁴ (kJ/m ² h °C)	60–130
λ	thermal conductivity (kJ/m ² h °C)	
λ_{g}	frozen product (ice) ⁵	5.9–6.3
λ_{tr}	dry product ⁶	0.059–0.29

1 Reinsert, A.P.: Factors affecting the erythrocyte during rapid freezing and thawing. Ann. N. Y. Acade. Sci. **85**, 576–594, 1960.

2 [1.2].

3 From VDI- = Wärmeetlas 5. Auflage, Bild 38, P. A 26, VDI-Verlag, Düsseldorf, 1988.

4 Figures 1.74 and 1.75.

5 From [1.2].

6 From [1.50], [1.54], [1.55] and [1.56].

perature of $-43\text{ }^{\circ}\text{C}$ and an average $\lambda = 1.38 \times 10^{-2} \text{ J/}^{\circ}\text{C cm s}$ is used when the slice is in contact with a liquid, having a similar behavior to water at $20\text{ }^{\circ}\text{C}$, $K_{\text{su}} = 4.61 \times 10^{-2} \text{ J/}^{\circ}\text{C cm}^2 \text{ s}$ can be used for the calculation. The freezing time is

$$t_{\text{e}}^{\text{fl}}_{\text{d20}} = 5.4(0.725 \times 10^2 + 0.43 \times 10^2) \approx 12 \text{ min} \quad (4)$$

As shown in Eqs. (3) and (3a), the thickness d has a major influence if the conductivity term w , which includes d^2 , is large compared with the transfer term u , which includes only d .

In Eq. (4), $w:u = 1.7:1$, showing that the influence of the conductivity is almost double that of the transfer. Assuming that d is only 0.2 cm , the freezing time falls to

$$t_{\text{e}}^{\text{fl}}_{\text{d2}} = 5.4(0.725 + 4.35) \approx 28 \text{ s} \quad (5)$$

In this case $w:u = 1:6$ and the transfer term is overwhelming. The freezing time is neither reduced by d^2 nor by d , since the importance of w and u has changed. An increase in d by a factor of 3, to 6 cm , prolongs the freezing time:

$$t_{\text{e}}^{\text{fl}}_{\text{d60}} \approx 70 \text{ min} \quad (6)$$

Here $w:u = 5:1$, and the freezing time depends mostly on the heat conductivity of the material.

The freezing of a slice of beef in direct contact with a model liquid has been used to demonstrate the influence of the two terms w and u . To freeze a product for freeze-drying, two methods are mainly used: (i) freezing of the product in trays or in vials on cooled surfaces; or (ii) in a flow of cold air. If these methods do not result in a sufficient freezing rate, liquid nitrogen (LN_2) in direct contact with the vials is used (see Figures 2.2.1 and 2.2.2) or droplets of the product are sprayed into LN_2 (see Section 2.1.4).

The heat transfer coefficient K_{su} in air varies strongly with the gas velocity, surface conditions of the product and the geometry of the installation. In practical operations it will be difficult to achieve K_{su} values of $1.7\text{--}2.5 \times 10^{-3} \text{ J/cm}^2 \text{ s }^{\circ}\text{C}$ or $\sim 75 \text{ kJ/m}^2 \text{ h }^{\circ}\text{C}$ and in many applications only half of this value (or less) may be possible. However, even with this high K_{su} the above-discussed slice of beef (2 cm thick) has a freezing time

$$t_{\text{e}}^{\text{lu}}_{\text{d20}} = 5.4(0.72 \times 10^2 + 9.5 \times 10^2) \approx 92 \text{ min} \quad (7)$$

compared with 12 min when cooled by a liquid, since the K_{su} of a gas is $\leq 10\%$ that of a liquid.

The time to reach a desired temperature level can be expressed as freezing rate v_{f} , the change in temperature per unit time, e.g. $^{\circ}\text{C/min}$. Thus the results of Eqs. (4)–(7) are approximately as follows:

$$(4) \ v_{\text{f}} = 1.7\text{ }^{\circ}\text{C/min} \quad (5) \ v_{\text{f}} = 43\text{ }^{\circ}\text{C/min}$$

$$(6) \ v_{\text{f}} = 0.3\text{ }^{\circ}\text{C/min} \quad (7) \ v_{\text{f}} = 0.2\text{ }^{\circ}\text{C/min}$$

These data are calculated by using $0\text{ }^{\circ}\text{C}$ as the start and $-20\text{ }^{\circ}\text{C}$ as the end temperature to show the relative data. The exact calculation requires more information, as given below.

Figure 1.4.1 is the cooling curve of vials filled with a solution of 4% solid content and 27 mm filling height. From the curve, v_f can be estimated:

0 to -10°C	$\sim 0.15^{\circ}\text{C}/\text{min}$
0 to -14°C	$\sim 0.18^{\circ}\text{C}/\text{min}$
-14 to -30°C	$\sim 0.73^{\circ}\text{C}/\text{min}$
0 to -30°C	$\sim 0.3^{\circ}\text{C}/\text{min}$

During the freezing of the main part of the water v_T is only 25% compared with the value after most of the water is crystallized. Taking the average value between 0 and -30°C can therefore be misleading: The intention to freeze at a rate of $0.3^{\circ}\text{C}/\text{min}$ has not occurred during an important part of the operation. The difference between 0.15 and $0.7^{\circ}\text{C}/\text{min}$ influences the structure of the product. How important the change is has to be checked from case to case, but the difference between 0.15 and $0.7^{\circ}\text{C}/\text{min}$ is most likely important.

With Eq. (3), it is also possible to estimate K_{su} . The uncertainties are the differences between the freezing of the product around the temperature sensor and in the undisturbed product, the position of the sensors, the correlation between time and temperature and occasionally also the actual amount of frozen water. From Figure 1.4.1, the estimated K_{su} is approximately $480 \text{ kJ}/\text{m}^2 \text{ h } ^{\circ}\text{C}$ with a possible error of $\pm 10\%$ and maximum error of $\pm 20\%$. Such high values can only be expected if the vials are carefully selected for their uniformity, especially with respect to a very even and flat bottom. Otherwise, the K_{su} can be much smaller, e.g. $230 \text{ kJ}/\text{m}^2 \text{ h } ^{\circ}\text{C}$ as calculated from data shown in Table 1.4.1.

If the vials are placed in trays and these are loaded on the shelves, K_{su} will be reduced, very likely to $< 100 \text{ kJ}/\text{m}^2 \text{ h } ^{\circ}\text{C}$, with the consequence that the freezing time is twice or three times longer and freezing rates of $1^{\circ}\text{C}/\text{min}$ cannot be achieved.

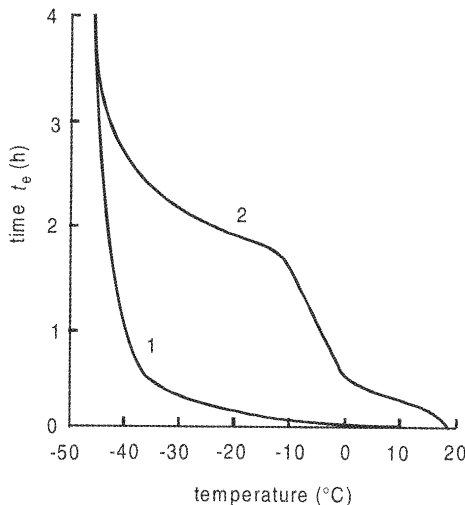


Fig. 1.4.1. Temperatures during freezing as a function of time. 1 = Shelf temperature; 2 = product temperatures in a product with $d = 2.7 \text{ cm}$, solid content $\sim 4\%$ (from [97])

Table 1.4.1 Cooling time and freezing rate as a function of layer thickness for well manufactured vials, not selected for the flatness of the bottom

Layer (mm)	Time from 0 °C to -10 °C (min)	Cooling rate (°C/min)	Time from -10 °C to -30 °C (min) ¹	Cooling rate (°C/min)	Cooling rate from 0 °C to -30 °C (°C/min)
6	14	0.71	9.3	2.1	1.29
12	32	0.31	12.9	1.6	0.67
20	60	0.17	19.0	1.1	0.38
30	105	0.095	28.3	0.7	0.23

¹ In this time the cooling of the glass of the vials from 0 °C to -30 °C is included.

Eq. (3) can be used to estimate the influence of the variation of the layer thickness and the shelf temperature, if the K_{su} values are measured for the type of vials used.

As shown, e.g., in Figures 1.4.2–1.4.4, the temperature as a function of time can vary. Therefore, the calculation of freezing rates and the resulting K_{su} contain a certain error. Table 1.4.2 shows a comparison of cooling rates [1.5]. Run 1 is from Figure 1.4.2, run 3 from Figure 1.4.3 and run 5 from Figure 1.4.4. The percentage indicates the maximum differences between the measurements with three temperature sensors in three vials.

To increase v_f , the following possibilities can be used: (i) reducing d ; (ii) reducing the shelf temperature; (iii) precooling of the vials, e.g. to -80 °C, and filling the pre-cooled product, e.g. +4 °C, into the cold vials; (iv) cooling of the vials directly with LN_2 ; and (v) dropping the product into LN_2 . With pre-cooled vials v_f can be of the order of 10–20 °C/min, and with direct cooling by LN_2 40–60 °C/min and more is possible. With droplet freezing up to 1000 °C/min can be achieved.

For laboratory work, different cooling liquids can be used as shown in Table 1.5. However, these substances are not easy to use, they boil and are partially explosive. The cooling method shown in Figure 1.5 can be helpful. LN_2 is evaporated under vacuum, freezing part of the N_2 as a solid. In this mixture the solid melts, if energy is

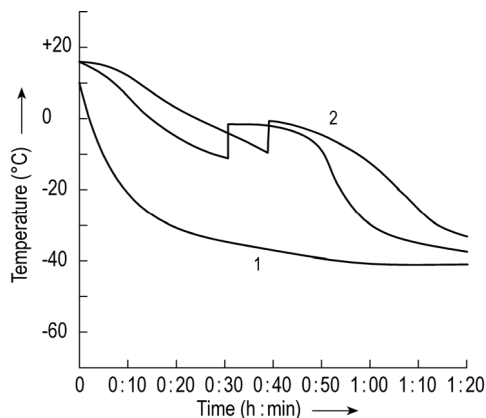


Fig. 1.4.2. Temperatures during freezing as a function of time for two different runs in the same plant, with the same product, T_{sh} cooled as quickly as possible. 1. Shelf temperature; 2, product temperature

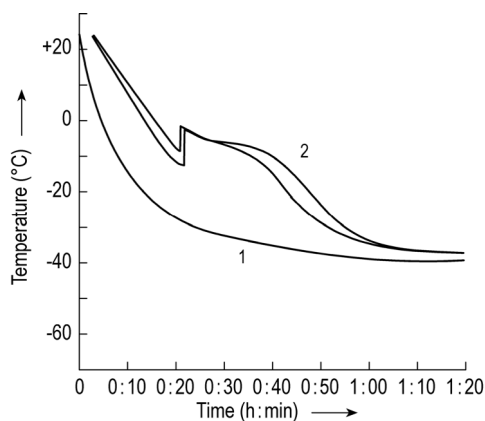
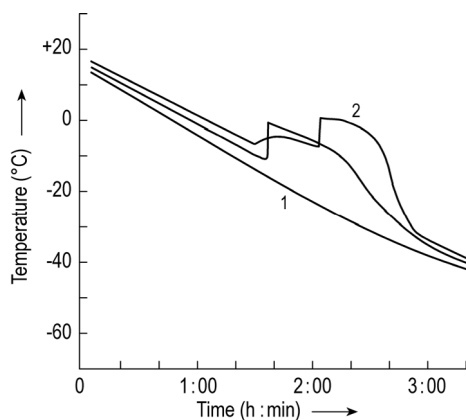


Fig. 1.4.3. See Figure 1.4.2

Fig. 1.4.4. As Figure 1.4.2, but T_{sh} cooled controlled (from [1.5])Table 1.4.2 Comparison of cooling rates, measured in the same installation, with comparable vials and comparable d

Run	Time from 0 °C to -10 °C (min)	Cooling rate (°C/min)	Time from -10 °C to -30 °C (min)	Cooling rate (°C/min)
1	34 ± 5	$0.29 \pm 15\%$	13 ± 5	$1.5 \pm 38\%$
2	25	0.4	17	1.2
3	23 ± 1.5	$0.4 \pm 6\%$	15 ± 2	$1.3 \pm 13\%$
4 ¹	19 ± 2.5	$0.5 \pm 13\%$	21 ± 3.5	$0.95 \pm 17\%$
5 ²	79 ± 7	$0.13 \pm 9\%$	38 ± 5	$0.5 \pm 13\%$

1 During the cooling phase -10 to -30 °C $\Delta T \approx 13$ °C instead of ≈ 20 °C in run 1-3; taking this into account, the value of 0.95 corresponds to 1.4 in run 1-3.

2 The shelf temperature was constantly lowered at ≈ 10 °C/30 min. Therefore, ΔT is only ≈ 8 °C

during the freezing phase, compared with ≈ 30 °C in run 1-3. 0.13 °C/min therefore corresponds to ≈ 0.48 °C/min. The same applies to the 0.5 °C/min during the cooling phase, making it comparable to 1.3 °C/min.

Table 1.5 Physical data of cooling liquids

Medium	Boiling point, T_s (°C)	c_p of liquid at T_s (kJ/kg °C)	λ of liquid at T_s (kJ/mh °C)	Heat of vaporization at T_s (kJ/kg)
Helium (He ⁴)	-268.9	4.41	0.098	20.5
Nitrogen	-195.8	2.05	0.506	197.6
Propane	-42.3	2.19		426.2
n-Pentane	+36.1	2.2		234.1

(Figure 2 from [1.98])

produced from cooling and crystallization. Thereby the formation of gaseous N₂ is greatly reduced, which otherwise limits the heat transfer. Figure 1.6 shows the relative cooling rates for different forms of N₂.

Riehle [1.6] has calculated the theoretically possible cooling velocities for small objects between 1 and 10⁻³ mm as shown in Figure 1.7. These calculations are made for a substance consisting of water only and K_{su} is assumed to be infinitely large for the geometric dimensions shown in (a) a sphere, (b) a square cylinder of infinite length

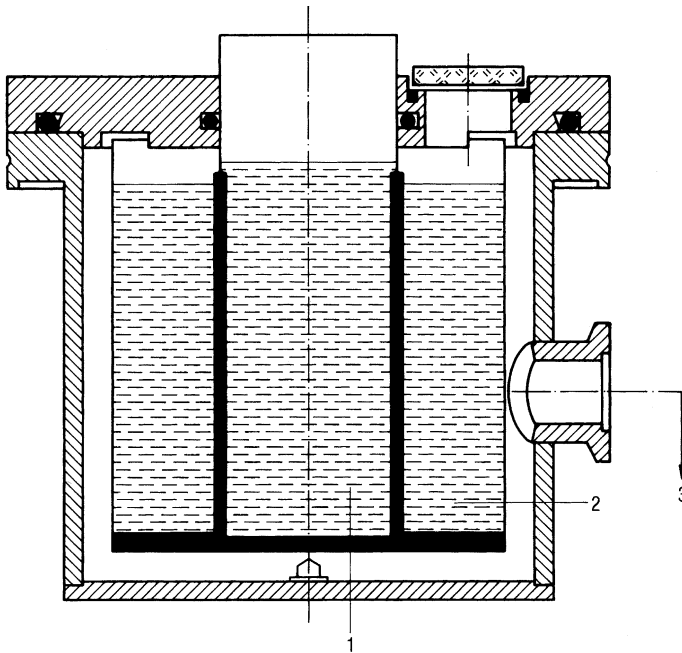


Fig. 1.5. Apparatus to produce a mixture of liquid and solid nitrogen. 1, Inner container with LN₂; 2, external container with LN₂ connected to a vacuum pump; 3, the container 2 is evacuated to ~124 mbar and kept at that

pressure. The evaporating nitrogen reduces the temperature in 2 and thereby also in 1, since the two containers are in close thermal contact. A temperature of -210 °C is reached in container 1 after ~5 min (from [1.99])

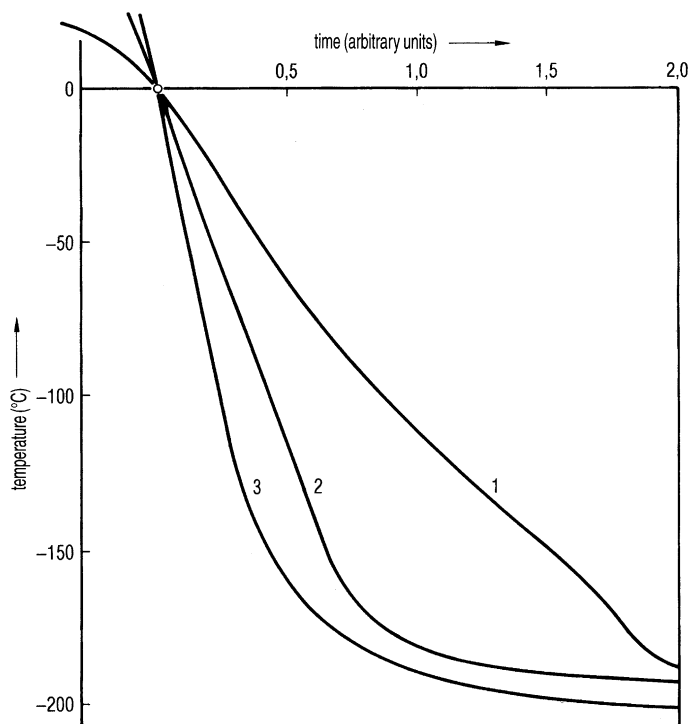


Fig. 1.6. Relative cooling rate of a small sample in different forms of N_2 . (The plot for LN_2 depends mostly on the successful removal of the nitrogen gas.) Melting solid nitrogen reduces the formation of gaseous N_2 , since the crystallization energy melts the solid

nitrogen and does not evaporate the liquid. (Note: Theoretically cooling in solid N_2 would be the fastest method, but liquid N_2 will be formed and the heat transfer is not stable.) 1, LN_2 ; 2, LN_2 + solid N_2 ; 3, melting of solid N_2 (from [1.100])

and (c) a plate of infinite length and the thickness X , cooled only from one side. For the plate (c), v_f is also calculated for three limited K_{su} : 10^3 , 10^4 and 10^5 $W/m^2 s$ (Chain lines). The purpose of this calculation is to show that freezing rates of 10^3 – 10^4 $^\circ C/s$ (6×10^4 – 6×10^5 $^\circ C/min$) cannot be achieved. However, these rates are necessary to reduce the velocity of crystal growth in pure water sufficiently to obtain water in a glass-like phase with irregular particle size $<10^{-8}$ m.

Riehle showed that such freezing rates can only be reached for layers of <0.1 mm under a pressure of 1.5–2.5 kbar.

A different way of obtaining short cooling and freezing times is to evaporate part of the water in the product under vacuum. The evaporation energy of water at $0^\circ C$ is approximately 2.5×10^3 kJ/kg. To cool 1 kg of beef from 0 to $-20^\circ C$, 240 kJ have to be removed, which corresponds to ~ 0.1 kg of water to be evaporated or 15% of the water in the beef. This quick evaporation will produce foam or bubbles in the product. This is unacceptable in most cases, since the original structure is changed and that part of

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