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Review Article

Recent Development of Optimization of Lyophilization Process

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The objective of this review is to survey the development of the optimization of lyophilization. The optimization study of the lyophilizer has been roughly developing by the order of (i) trial-and-error approach, (ii) process modeling using mathematical models, (iii) scalability, and (iv) quality-by-design. From the conventional lyophilization studies based on the trial-and-error, the key parameters to optimize the operation of lyophilization were found out, i.e., critical material attributes (CMAs), critical process parameters (CPPs), and critical quality attributes (CQAs). The mathematical models using the key parameters mentioned above have been constructed from the viewpoints of the heat and mass transfer natures. In many cases, it is revealed that the control of the primary drying stage determines the outcome of the lyophilization of products, as compared with the freezing stage and the secondary drying stage. Thus, the understanding of the lyophilization process has proceeded. For the further improvement of the time and economical cost, the design space is a promising method to give the possible operation range for optimizing the lyophilization operation. This method is to search the optimized condition by reducing the number of key parameters of CMAs, CPPs, and CQAs. Alternatively, the transfer of lyophilization recipe among the lab-, pilot-, and production-scale lyophilizers (scale-up) has been examined. Notably, the scale-up of lyophilization requires the preservation of lyophilization dynamics between the two scales, i.e., the operation of lab- or pilot-scale lyophilizer under HEPA-filtrated airflow condition. The design space determined by focusing on the primary drying stage is large and involves the undesired variations in the quality of final products due to the heterogeneous size distribution of ice crystals. Accordingly, the control of the formation of the ice crystal with large size gave impact on the product quality and the productivity although the large water content in the final product should be improved. Therefore, the lyophilization should take into account the quality by design (QbD). The monitoring method of the quality of the product in lyophilization process is termed the "process analytical technology (PAT)." Recent PAT tools can reveal the lyophilization dynamics to some extent. A combination of PAT tools with a model/scale-up theory is expected to result in the QbD, i.e., a quality/risk management and an *in situ* optimization of lyophilization operation.

1. Introduction

A shelf time of drug products and foods has been demanded to extend a period of time. It is also of importance to maintain their storage characteristics. The most key factor to deteriorate the product quality is water included in drug products and foods. Therefore, an appropriate drying method should be used to remove water from the drug products and foods. Well-known drying technologies are the lyophilization [1, 2], spray drying [3], and reduced-pressure drying [4]. In the manufacturing of pharmaceutical drug products such as unstable chemicals and sterile products, the lyophilization (or freeze drying) has been widely used as an effective means [1, 2, 5]. Meanwhile, lyophilization that is not optimized could take days or even weeks to terminate, which is a time- and energy-intensive process [6–10].

A failure of lyophilization gives a serious cost impact. This is because vials of several thousand scales are lyophilized at a time in the commercial scale production of the pharmaceutical drug. The same was true for the lyophilization of foods. In the earlier studies, a scale-up of the laboratory-scale lyophilization and a transfer of lyophilization recipe into other types of instruments has been studied in a manner of the trial-and-error method [11, 12].

Some researchers have suggested the practical advice for the design of lyophilization processes for pharmaceuticals [13] and foods [14–16]. Nevertheless, the design based on trial-and-error experiments often causes an instability in product quality. This results in an increase of manufacturing costs. Therefore, the existing scale-up theory is far from being sufficient. And so, a control method for the production-scale lyophilization needs to be amended. Such a problem has been claimed specifically in the area of pharmaceutical and food engineering.

1.1. Pharmaceuticals. In 2002, the Food and Drug Administration (FDA) announced a significant new initiative, Pharmaceutical Current Good Manufacturing Practices (CGMPs), for the 21st Century. In additional, guidance on process analytical technology (PAT) to meet the 21st-century challenges was represented by the FDA in 2004. In 2009, based on the agreement in the International Council for Harmonization, Technical Requirements for Pharmaceuticals for Human Use (ICH) Q8 (R2) Pharmaceutical Development was updated and the principle of quality by design (QbD) was described [17]. QbD means a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

The critical elements of QbD are the *Design Space* and *Process Analytical Technology* (PAT) [18]. According to "ICH Q8 Pharmaceutical Development Guidance" [17], a design space is the multidimensional combination of input variables and process parameters that have been demonstrated to provide assurance of quality. In order to proceed with the pharmaceutical development using a QbD approach, three key philosophies of *Critical Quality Attributes* (CQAs), *Critical Process Parameters* (CPPs), and *Critical Material Attributes* (CMAs) have been guided in the pharmaceutical industry. CQAs are physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CPPs are process parameters whose variability has an impact on a CQA and therefore should be monitored or controlled to insure the process produces the desired quality. CMAs are attributes of input materials whose variability has an impact on a CQA and therefore should be monitored or controlled to insure the process produces the desired quality. CQAs, CPPs, and CMAs should be clarified to develop based on a QbD approach. These attributes that include variables accepted so far are listed in Table 1. In accordance with the principles of ICH Q9, a risk assessment to identify and rank process parameters that may impact CQAs based on scientific knowledge and experiments will be conducted and effective control strategies will be developed to minimize the risks to acceptable levels. On the other hand, the PAT is an integral part of QbD, because the paradigm relies on the use of real-time process monitoring and control as a part of an overall control strategy [18]. To design robust control strategies, the design space and PAT are useful. In other words, the optimization of the lyophilization process should be provided by means of CQAs, CPPs, and CMAs, along the design space and PAT. For this purpose, the relationship between the three parameters and the two methods should be described.

1.2. Food Engineering. The lyophilization is of capital importance in the area of food engineering. This technique is often used in the case of the production of dried foods of noodle, pasta, fruits, vegetables, shrimps, meats, and fishes. The main reason is that foods mentioned above are perishable and difficult to preserve as fresh products. These dried products can be easily stored, transported at relatively low cost, and have reduced packing costs, and their low water content delays microbial spoilage. Thus, the variety of lyophilization techniques have been built up, i.e., the air-, freeze-, microwave- and sun-drying methods [14, 15]. The quality of the final product is of importance in every technique, which is the same as QbD in drugs.

For extending the shelf life of final products, the encapsulation technique has been recently and widely studied [19]. The bioactive compounds are encapsulated by the wall materials by the lyophilization [14, 19–21]. Typical bioactive compounds are vitamin E, anthocyanins, fish oil, catechin, and α-tocopherol [19]. The encapsulation permits to improve the stability, extend the shelf-life, minimize the environmental stress, and increase the retention percentage. Also, the influence of the wall materials to the core materials have been widely examined [19]. Meanwhile, the encapsulation recipe obtained by the lab-scale lyophilizer is uneasy to be transferred into the production scale lyophilizer. Therefore, the encapsulation process is practically fine-tuned in the production scale. A difficulty in the optimization of lyophilization process is thus involved in the food engineering.

As overviewed in the field of the pharmaceutical and food engineering, the robust strategy for optimizing the lyophilization process is amended. In this review, we survey the recent strategy to optimize the lyophilization process. First, the lyophilization is overviewed in the viewpoints of physicochemical and operation of lyophilizers, in order to discuss by which parameters the operation can be optimized. The optimization of the lyophilization is discussed on a basis of the trial-and-error approach and the mathematical modeling approach. The scale-up theory based on the model is also compared. Finally, we discuss the future perspectives to break through the present lyophilization.

2. Overview on Lyophilization

The lyophilization process of the food engineering is in general the same as that in pharmaceutical field. Accordingly, the lyophilization process of the pharmaceutical field will be explained in this section. This process normally consists of three stages: (1) freezing stage, (2) primary drying stage, and (3) secondary drying stage, as schematically depicted in Figure 1(a).

Table 1: Potential critical material attributes, critical process parameters, and critical quality attributes.

Critical material attributes (CMAs)	Critical process parameters (CPPs)	Critical quality attributes (CQAs)
(i) Glass transition temperature	(i) Freezing temperature	(i) Related substances
(ii) Eutectic temperature	(ii) Freezing rate	(ii) Appearance
(iii) Cake collapse temperature	(iii) Annealing temperature/time	(iii) Water content
(iv) Product temperature	(iv) Primary drying temperature/pressure/time	(iv) Reconstitution time
(v) Water vapor transfer resistance of the dried layer (R_p)	(v) Secondary drying temperature/pressure/time	

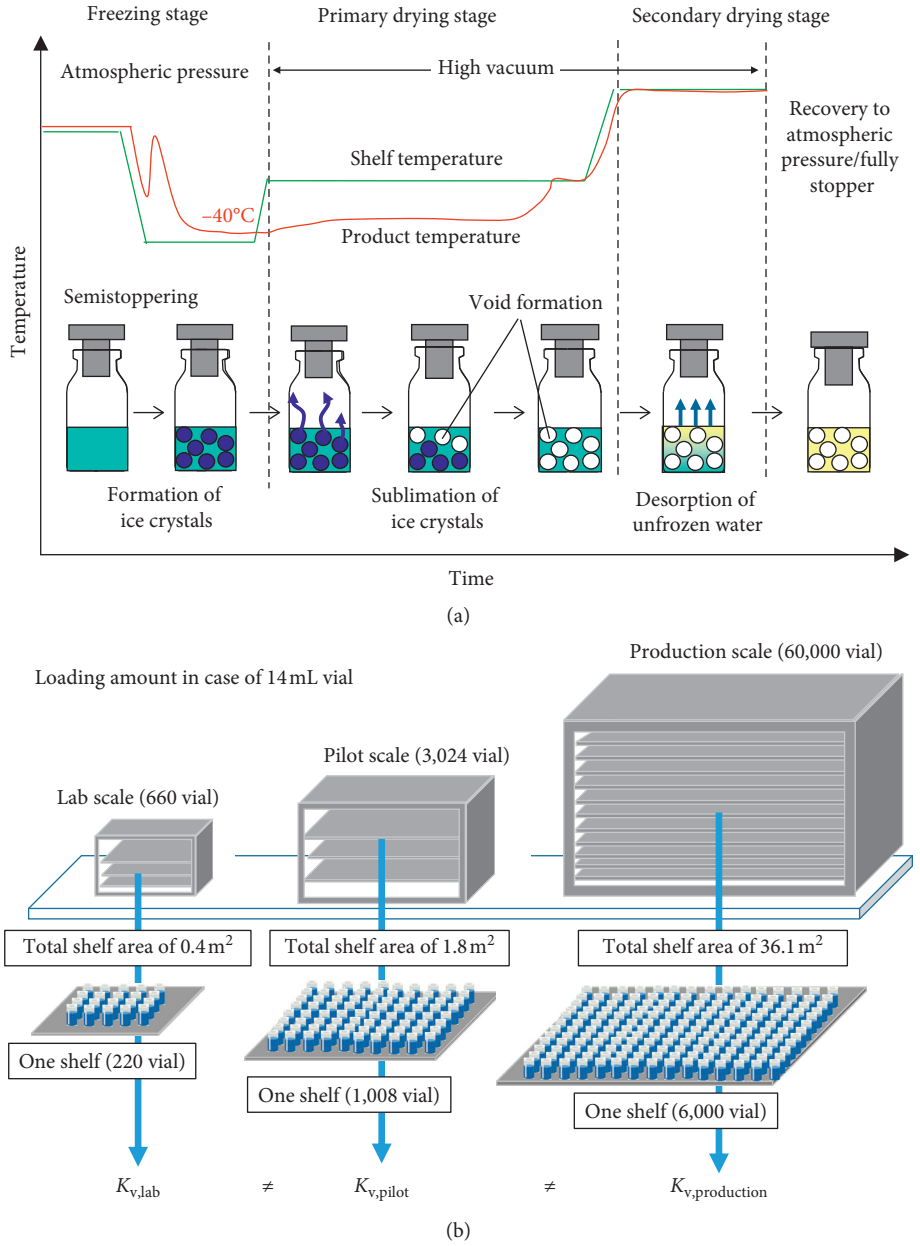

Figure 1: (a) Schematic illustration of lyophilization process. Green and red curves represent the shelf temperature and product temperature, respectively. (b) Comparison of lab, pilot, and production lyophilizers.

The freezing stage is the first stage of freeze drying. Water is a target of the freezing stage in the pharmaceutical and food engineering fields. Accordingly, we focus on water in this review. The freezing operation alters water into ice to separate from other solute components. In this process, the incontinuous temperature change is often observed as shown in Figure 1, which is termed "supercooling." The supercooling often occurs depending on the freezing rate.

The freezing is normally finished within a few hours [22, 23].

The primary drying stage is also called as a sublimation drying stage. In this stage, the chamber pressure is reduced below the equilibrium vapor pressure of ice. The shelf temperature is stepwise elevated, followed by a heat transfer from the shelf surface into the product. This heat transfer induces the sublimation of ice in vials. Thereafter, the sublimated vapor is transferred to the condenser and then turns into ice once more. The heat lost from the product as a latent heat of sublimation will be supplied again from the shelf [24]. As shown in Figure 1(a), the stage requiring the longest time among three stages in the lyophilization process is the primary drying stage, i.e., the primary drying stage needs the heavy economical cost. Therefore, the optimization and shortening of the time for the primary drying stage have been widely studied [25–30].

The secondary drying stage is the step where the product temperature elevates higher temperature than the primary drying stage (Figure 1(a)). There is water that did not turn into ice during the freezing phase and was captured inside the solute components as nonfreezing water. It is this step where a diffusion and desorption of remaining water occur in the product. The objective of secondary drying is to reduce the final residual water content to an acceptable level. Although this stage is usually completed within a few hours, it is an indispensable step in the lyophilization because the remaining water deteriorates the quality of products.

Next, three types of lyophilizers are introduced. Figure 1(b) is a schematic illustration of the lyophilizers of the lab-, pilot-, and production scales. A lab-scale lyophilizer can accommodate up to 660 vials by three shelves. This scale has been widely applied to obtain CPPs and optimize the lyophilization process. Later, the pilot scale is applied to bridge between the pilot- and production-scale lyophilizers. This pilot-scale lyophilizer can accommodate 3,024 vials by three shelves. Lastly, the operational optimization of parameters depicted in Figure 1(a) scales up to the production-scale lyophilizer. The production-scale lyophilizer can accommodate up to 60,000 vials by ten shelves. A final goal is to elucidate and optimize the operational conditions for the production-scale lyophilizer. The sort of investigation for the purpose is summarized in Table 2 and Figure 2. The optimization of operational conditions is surveyed from the following section.

3. Development from Trial-and-Error Approach to Scientific Approach

In general, the lyophilizer has the different heat transfer nature depending on the types of lyophilizers and their scale. Accordingly, to determine the optimal operating condition required the trial-and-error approach in the earlier studies. As stated in the last section, the primary drying stage takes the longest time in any scale lyophilizer. Therefore, the shortening of the primary drying stage is always an issue in terms of economic cost of a production scale. Inevitably, the accomplishment of lyophilization process is likely to be not a considerable level in the trial-and-error approach (Figure 2).

In the beginning, the freeze-drying process was, in a manner of trial-and-error, examined under the various conditions to find out the critical parameters. An improper freeze drying of the product occurs in the case where the product temperature largely rises during the drying stage, which is termed a "collapse" [30]. By continuously reducing the temperature of a bulk solution under the atmospheric pressure, the solution indicates a supercooled state below the freezing temperature (Figure 1(a)), followed by the elevation of the temperature up to around the equilibrium freezing point. This is because of the heat of crystallization caused by the ice nucleation. Thereafter, the continuous removal of heat results in the growth of ice crystals. Moreover, in the case where water is captured in solute components, the solution will be transferred to the ice with exclusion of the nonfreezing water [68]. This is because water is separated from solute components at the eutectic temperature (T_e). Then, the solute components are considerably concentrated. For examples, it is well known that mannitol, glycine, sodium chloride, and phosphate buffer are crystallized during the freezing process at a certain concentration [45]. In the case of drugs or excipients used as injection products bearing a high affinity to water, they rarely form eutectic crystals during the freezing process. The concentrated effect of the solute below the glass-transition temperature (T_g') forms the amorphous solids with the low molecular mobility, which is termed "glass transition." As the empirical determination of T_g' value, the low-temperature differential scanning calorimetry (DSC) is a promising method. The large elevation of the product temperature at the primary drying stage is subject to induce a collapse of the product [35]. The collapse temperature (T_c) can be determined by the freeze-drying microscopy. T_c is the temperature above which the lyophilized product loses its macroscopic structure and cake collapses during the primary drying process. It is well known that T_c is higher than T_g' by approximately 2°C [69]. The proper primary drying at the temperature lower than T_c allows us to obtain an acceptable lyophilized product. Thus, T_g', T_e, and T_c are CMA (see Table 2).

Alternatively, the transfer resistance of dried layers to water vapor flow can improve the drying process. The primary drying stage is controlled by the heat and mass transfer, as illustrated schematically in Figure 1(a). First, we will clarify the heat transfer in the lyophilizer. The heat medium yields the heat to the shelf surface, followed by the heat transfers to the bottom of the vial through three routes: (i) a heat transfer mediated by the gas (mainly vapor) that is present at the space between the shelf surface and the vial; (ii) a heat transfer at the contact area of bottom surface of the vial with the shelf; and (iii) the third route is the radiant heat from the walls of the lyophilizer. As stated in Section 6, the factor (iii) cannot be negligible [55]. Generally, the heat from the bottom of the vial is supplied to the sublimation interface via the frost layer. This heat is consumed as the latent heat of sublimation. Consequently, ice turns to vapor by these heat transfers, followed by the formation of the dried layer to play a role for the resistor against the sublimation. The formation of the dried layer suppresses the sublimation rate. Therefore, the drying resistance due to the dried layer

Table 2: Summary of the optimization of lyophilization.

	Target variables	Notes	Ref.
Trial-and-error without mathematical model	CQAs, CPPs, CMAs	Optimization of freezing process	[13, 31, 32, 33]
		Optimization of primary drying process	[12]
		Optimization of secondary drying process	[34]
Use of mathematical model	CMAs (T_b, R_p, and so on) and CPPs (T_s, P_c, the drying time, and so on)	A partial differential equation (PDE)	[31, 34–44]
		A model predictive control (MPC)	[29, 42, 45, 46]
		A computational fluid dynamics (CFD)	[15, 47, 48]
		K_v-based modeling	[49]
Designs space	P_c-dm/dt plane (Figure 4)	Control of primary drying process	[13, 17, 18, 50–52]
		Control of freezing process	[53]
Scale-up	K_v, P_c	Vial-position dependency of K_v	[12, 54]
		A use of empty vials at the edge of the shelf	[17]
		Equivalent resistance model under the dust-free condition using HEPA-filtered airflow (without empty vials)	[55]
Process analytical technology (PAT)	K_v, R_p, T_b, and P_c, dm/dt	In-line optimization	[56–67]

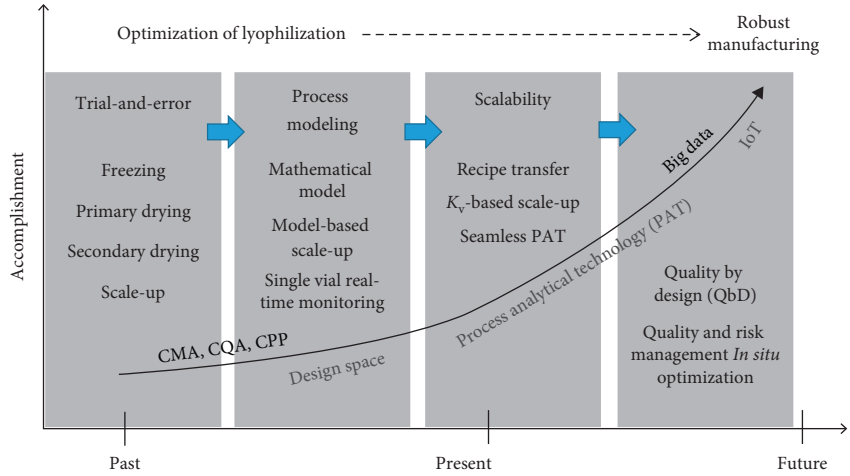

Figure 2: Possible technological transition and sublimation of lyophilization strategy for QbD in the pharmaceutical field. CQA: critical quality attribute; CPP: critical process parameter; CMA: critical material attribute; IoT: Internet of things.

has been quantified as the water vapor transfer resistance of the dried layer R_p [55]. A control of R_p enables the control of the heat input to the product, and the primary drying temperature will be optimized. Based on the R_p, the endpoint of primary drying as the CPP can be estimated. Thus, throughout the trial-and-error approaches, important variables have been found out.

According to the review by Tang and Pikal, the design of freeze-drying processes is quite difficult without further attempts at optimization [13]. The design based on the trial-and-error gives the information on CQAs, CPPs, and CMAs that are required in the optimization of the lyophilization recipe.

4. Process Modeling

Throughout enormous investigations with an approach of trial-and-error, the important CQAs, CPPs, and CMAs have been found out (Tables 1 and 2). In order to minimize the trial-and-error experiments, the mathematical model for the prediction of the optimized T_b value based on CQAs, CPPs, and CMAs has been thereafter developed [31, 34–44], as shown in Table 2. Owing to this, the accomplishment of lyophilization process is improved to some extent (Figure 2).

Modeling for the primary drying stage has been conducted based on the heat and mass transfer model, rather than a modeling with respect to the freezing [31] and secondary drying stages [34]. The initial modeling of the primary drying stage [35, 36, 37] took into account all the contributions to mass transfer resistance, e.g., the dried layer, the stopper, and the chamber. The model based on the partial differential equation (PDE) [38–41] and model predictive control (MPC) [42, 45, 46] has been developed and modified. Previous works regarding PDE and MPC were the numerical study. Notably, Hottot and his coworkers have developed and modified the model to fit the experimental data [70, 71]. Fissore and Barresi have described the multidimensional models and their main

drawback: their equations involve a lot of parameters, whose value cannot be easily obtained by means of experiments with a small uncertainty and calculation cost becomes high [27]. In the latest research, a computational fluid dynamics (CFD) has been attempting to deeply understand the mass and heat transfer in the drying chamber and condenser of the lyophilizer [47, 48]. Using CFD to a pilot-scale lyophilizer with four shelves, the heterogeneous velocity field, pressure distribution, and temperature distribution could be observed. The flow of water vapor could be also visualized: the vapor sublimated from vials is forced to flow towards the edge of the shelf and go to the duct on the wall to be collected in the condenser. Therefore, a numerical study can come to impart not only the qualitative confirmation of experimental solutions but also the validation of prediction by means of PDE and MPC.

In contrast, some of the recent modeling has become simpler than that covered by the literatures [27]. To our best knowledge, the heat and mass transfer model presented by Pikal et al. [49] is the earliest simplified model to focus on the role of the vial. Their simplified model that is based on the mass and heat transfer phenomena in the vial on the shelf is schematically illustrated in Figure 3(a). The mass loss over time (dm/dt) after the lyophilization is experimentally obtained to determine the amount of water used for the sublimation of ice. Ultimately, the vial heat transfer coefficient (K_v) is calculated from the shelf surface temperature (T_s), the product temperature (T_b), latent heat of ice (ΔH_s), cross-sectional area of vial calculated from its outer diameter (A_v), and dm/dt, according to the following equation:.

$$K_v = \frac{\Delta H_s (dm/dt)}{A_v (T_s - T_b)}. \quad (1)$$

As shown in Figure 3(a), the heat transfer into the vial consists of three hear transfers: (i) the contact heat transfer; (ii) gas heat transfer; and (iii) radiant heat transfer. Their heat transfer coefficients were defined as K_c, K_g, and K_r, respectively. According to the previous reports [5, 22], K_c and K_r do not depend on the chamber pressure (P_c) and the K_g value depends on P_c as is described as a function of $K_g = bP_c/(1 + cP_c)$ (b and c are the positive constants). In the case where the three heat transfers mentioned above are driven by the same temperature difference, K_v will obey the relationship of $K_v = K_c + K_g + K_r$. Accordingly, the following equation can be elucidated:

$$K_v = a + \frac{bP_c}{1 + cP_c}. \quad (2)$$

This relationship between K_v and P_c has been often used in the operational design of lyophilization [23, 54, 72].

As shown in Figure 1, T_s, T_b, and P_c are monitored during the lyophilization. The point at which T_b increases sharply toward the setting T_s value was determined as the drying endpoint for analysis. From T_s, T_b, and pressure profile of the equilibrium vapor pressure of ice (P_{ice}) on the sublimation interface and the vacuum pressure (defined as P_c) in the lyophilizer, the R_p value of dried layers with a cross-sectional area (A_p) was calculated according to the following equation:

$$R_p = \frac{A_p (P_{ice} - P_c)}{(dm/dt)}. \quad (3)$$

Equation (3) also yields the drying time. In the optimization of the primary drying stage, this equation is of great importance. The drying time calculated by equation (3) strongly depends on the architecture of lyophilization instrument, dimension of the shelf, arrangement of vials on the shelf, and environmental conditions.

Thus, the process modeling based on the mathematical model has been developed by taking into account (i) CMAs (T_b, R_p, and so on) and (ii) CPPs (T_s, P_c, the drying time, and so on).

5. Design Space

To construct the efficient operation recipe requires the adequate variables. It was plausible that one of the CPPs is the primary drying stage from the viewpoint of economical cost or operational time.

In the earlier studies, it has been clarified that the lyophilization process in the lab-, pilot-, production-scale lyophilizer depends on the position of vials on the shelf. Fissore and Barresi categorized three types of vials in terms of the overall heat transfer nature (Figure 3(a)) [27]. For example, vials of the group 1 are placed in the central part of the shelf. They are not affected by radiation from chamber wall. Vials of groups 2 and 3 are placed in the second and the first rows on each side of the shelf. Then, they are affected in different ways by radiation from the chamber walls. The sublimation behavior depended on the position of vials as shown in Figure 3(b) [55]. Thus, the position dependency of overall heat transfer nature of vials made it complex to elucidate and transfer the recipe from one to another instrument. Therefore, the same recipe obtained in the lab-scale equipment cannot generally be used without modifications to freeze-dry the product in a pilot- or production-scale lyophilizer (Figure 1(b)).

In the report from Chang and Fischer, they have already presented the graph similar to Figure 4, although not the point of the article [50]. Lyophilization process depends on the plural variables. Therefore, the optimization of lyophilization process as a whole can be considered as the multidimensional analysis. To indicate the typical optimized operational conditions, let us imagine the plane of P_c-dm/dt as shown in Figure 4. A lyophilizer has a desired operational condition where P_c cannot be controlled in a highly vacuumed condition or at an accelerated sublimation rate (i.e., a choked flow limit). Once both the K_v and R_p values are determined, both the sublimation interface temperature and the drying time (sublimation rate) during the primary drying stage can be predicted from equations (1)–(3) [13, 17, 18]. The upper and lower limit of product temperature was set to draw the solid line with a negative slope at the constant R_p. Also, the dashed curves of dm/dt as a function of P_c can be drawn at the constant T_s value, by combining equations (1) and (2). Varying T_s from −20 to

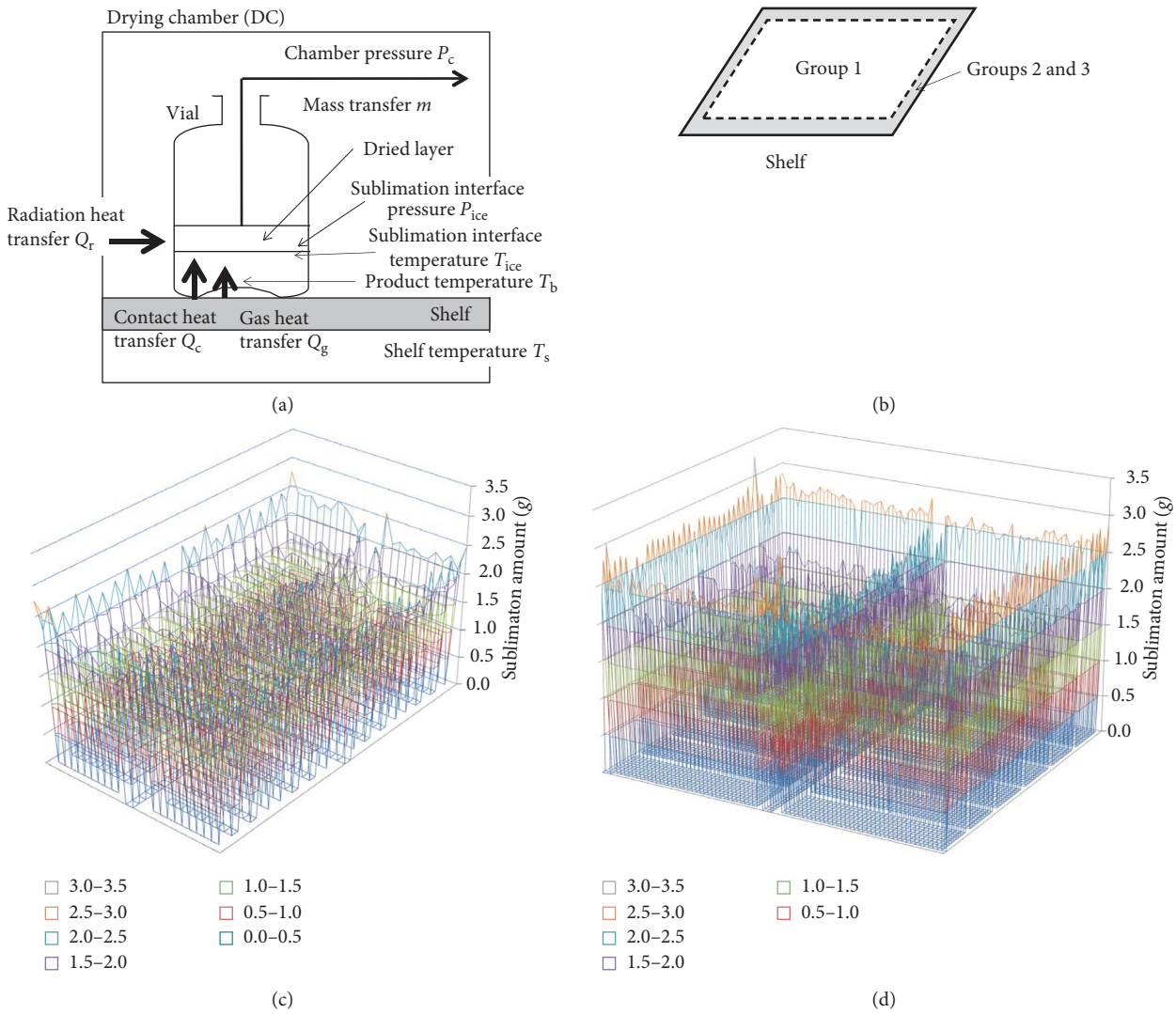

Figure 3: (a) Heat and mass transfer model for lyophilization. (b) Categorization of vials on the shelf. Group 1: vials are placed in the central part of the shelf; Groups 2 and 3: vials are placed in the second and the first rows on each side of the shelf, respectively. This categorization is based on the literature [27]. Distribution of sublimed amount of ice from the vials on the shelf. (c) 1,008 vials, (d) 6,000 vials. Data were redrawn based on [55].

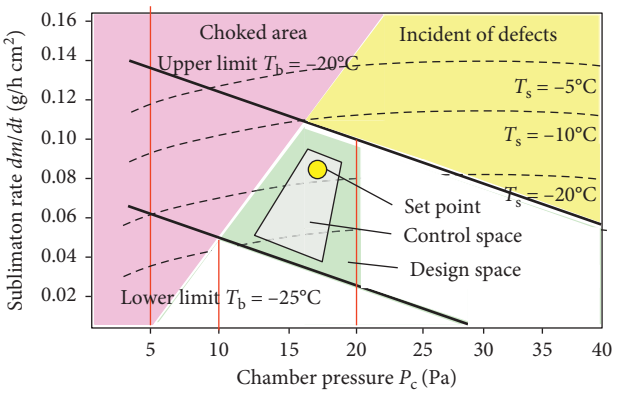

Figure 4: Example of design space. Typical determination method of design space is described in Section 5.

–5°C, the dashed curve shifts to the positive direction of dm/dt axis. In order to avoid the reduction of dm/dt, the P_c should be maintained to the lower pressure below 20 Pa. When the line $P_c = 20$ is drowning, the trapezoid region is formed, which is termed *Design space*. In line with this, the region where the product quality is not damaged and at the same time, where stable manufacturing can be performed is expected to be established [51, 52]. However, the stable operation has been performed in a practical level to tolerate the quality variations that occur in the freezing stage. Accordingly, a larger design space has been used to afford the excess safety factors. The set of wide range of both sublimation interface temperature and the drying time (sublimation rate) often comes to be a cause of the variations in the size of ice crystals. Thus, a design space is an optimized

operation method based on the equipment capability, K_v, and R_p (Table 2), which can improve the accomplishment of lyophilization process (Figure 2). At present, it looks like the design space obtained in the lab-scale lyophilizer, without any change, has not been applied to the pilot- or production-scale lyophilizers yet.

6. Scale-Up Theory

As stated in the last section, the lyophilization recipe such as the design space was limited to the target lyophilizer and could not be transferred to other equipments. As the understanding of the lyophilization process has progressed, the mathematical models based on parameters that dominate the lyophilization process have been developed [24–29]. In some studies, the higher temperature of products and reduction of resistance of the frost layer to vapor flow results in the improvement of the primary drying efficiency [27–29]. Accordingly, the key parameters are selected to construct the scale-up theory by focusing on the primary drying stage.

In the practical equipment, the excess heat input often causes the deviation from the operation after its optimization of the lab-scale equipment. The radiation from the shelf and from chamber walls is a main reason for the excess heat transfer to the product as stated in Section 5 (Figure 3(a)) [27]. The K_v value definitely depends on the position of vials on the shelf [27, 28, 55], which possibly becomes the obstacle to establish the scale-up theory for the production lyophilizer. In actual, the sublimated amount of ice at the position in the shelf was influenced by the radiation heat transfer from the wall of the machine (1,008 vials) (Figure 3(c)) [55]. The radiation effect of the wall in the case of 6,000 vials was significant as compared with the case of 1,008 vials. The K_v values at the edge were higher than those in the center positions in the shelf [17, 55]. Notably, the K_v values were dependent on the P_c. In the scale-up, the selection of the treatment of K_v at the edge and center positions is a key factor because the production lyophilization at large scale possesses the high portion of vials at the edge position to the ones in the central position than the lab-scale lyophilization. Previously [54], the scalable application of equation (2) was demonstrated in all scales of lyophilizers, in other words, a kind of the scale-up of K_v. Since the position dependency of K_v is still adopted, Fissore and Barresi have proposed to place the empty vial at the edge of the shelf [17]. Due to this idea, this recipe could improve the defect of products, although the reduction of productivity corresponding to the number of empty vials is there (Table 2).

In contrary, the scale-up theory without using empty vials has also been demanded from the viewpoint of the cost impact. Alternatively, the latest scale-up theory, termed *the equivalent resistance model* by Kawasaki et al. [55], is introduced in this paragraph. Generally, the dynamics in the lyophilization remains in all scales of lyophilizers to succeed in the scale-up, i.e., the R_p values of lab- and production-scale are equivalent [27]. Meanwhile, the operating condition where the R_P values at the lab and production scale are equivalent has been still unclear. Kawasaki et al. focused on the result that the production-scale lyophilization is performed under HEPA-filtered airflow condition. The R_p value determined by the pilot lyophilizer (1,008 vials) under HEPA-filtrated airflow condition should be able to be extended to the production-scale lyophilizer. Based on this idea, the lyophilization of 60,000-vial scale based on the R_p obtained at the pilot scale has achieved the yield of 99% or more without the use of empty vial placed as groups 2 and 3 (Figure 5) [55]. That is why a use of the dust-free condition using a HEPA-filtrated airflow is an indispensable condition for the preservation of R_p value between lab and production scale. Thus, the equivalent resistance model bridges the gap between the laboratory and production scale.

Therefore, the K_v and R_p values are key parameters to construct the scale-up theory (Figure 2). Specifically, it is likely that the equivalent resistance model permits to use the same design space among the lab-, pilot-, and production-scale lyophilizers, which would enable us to perform an efficient and robust process design using the design space (Table 2).

7. Control of Freezing Process

The freezing stage determines the degree of variations in the productivity as well as the product quality. Then, this stage is one of the most critical stages in the lyophilization process, as shown in Figure 1. One of the CPPs is the freezing stage. Since water does not voluntarily freeze and maintains its supercooled state, the freezing temperature cannot be directly controlled. We first focus on the effect of the freezing temperature. The higher freezing temperature (lower degree of supercooling) results in the formation of the larger size of the ice crystals, as shown in Figure 6. The larger the size of the ice crystals is, the higher the primary drying efficiency achieved. In earlier studies [73], it has been reported that the vials loading the product temperature sensors possibly indicate a bit of high freezing temperature, as compared with those without sensors. It is natural that their sublimation rate will be accelerated enough to alter the drying endpoint. Apart from this, an elevation of the freezing temperature by 1°C can shorten the primary drying time by 3% [74]. On the other hand, the size of the ice crystals determines their specific surface area. The size of the specific surface area determines the diffusion and desorption rate in the secondary drying stage [13, 74]. A high freezing temperature results in the formation of large size of the ice, which reduces the specific surface area. A study reported that this caused the secondary drying efficiency to decrease, increasing the moisture residue in the finished product [22]. Accordingly, it is expected that the control of the freezing temperature during the freezing stage might contribute to design a robust drying process.

An annealing is usually used to control the freezing temperature during the freezing stage [13]. The annealing is a simple holding of the product under the temperature condition above the final freezing temperature for a defined period to crystallize the components. This technique allows the crystallization with improved crystallinity [13]. Annealing above T_g' causes growth of ice crystals, inducing

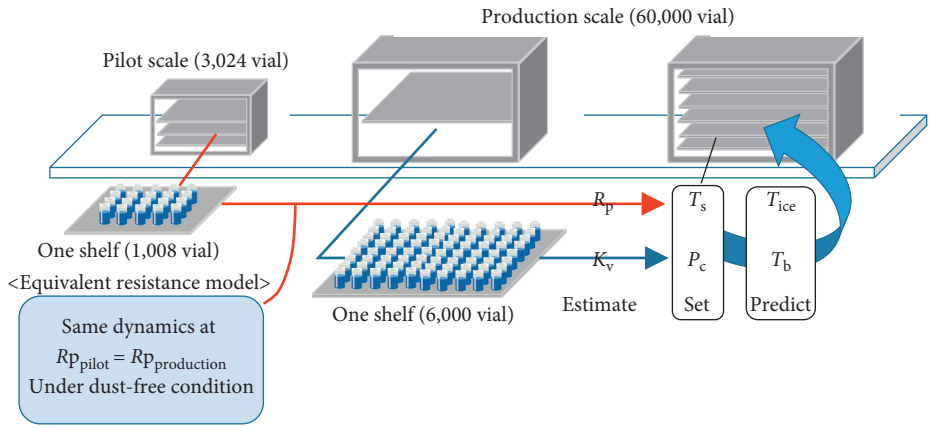

Figure 5: Scale-up theory based on the equivalent resistance model [55]. In this illustration, the equipment of the pilot scale can accommodate the three shelves. The equipment of the production scale accommodates ten shelves.

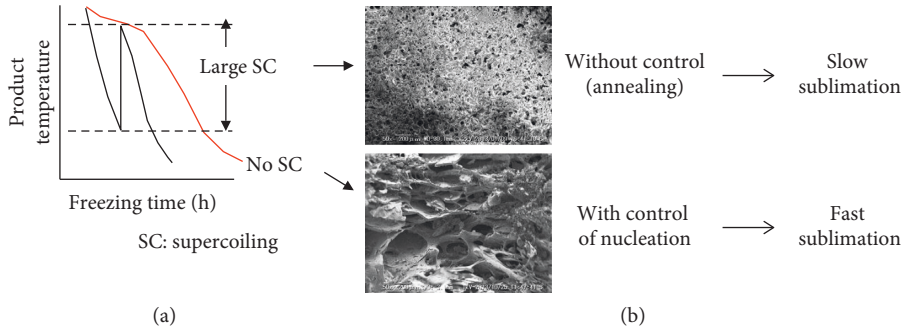

Figure 6: Schematic illustrations on controlled nucleation of ice [53]. (a) Time course of product temperature at a different freezing rate. (b) Scanning electron microscopy of lyophilized samples with and without control of nucleation of ice.

the reduction of R_p value of the product to shorten the primary drying time [32, 33].

Recently, the advantages and disadvantages concerning the ice nucleation techniques have been reported [75, 76]. The pressurization and depressurization technique was a powerful approach to control the ice nucleation behavior. For examples, the pressure inside the lyophilizer is elevated to 0.28~0.29 MPa by using nitrogen or argon gas and quickly decreased to 0.11 MPa (within 3 s). Due to this, the ice nuclei can be formed on the surface of the liquid in the vials [77]. Possible main driving forces for the ice nucleation are considered to be (i) the vibrational disturbance caused by the sudden depressurization, (ii) the cooling of liquid surface of cold gas contacting, or (iii) the local evaporation of liquid surface during the sudden depressurization [78].

Kawasaki et al. have demonstrated the ice crystal size has an impact on the product quality and the productivity [53]. In order to inhibit the supercooling of the solution and to control the size of ices formed in the drug product during the freezing stage, the (de)pressurization technique was combined with the control of freezing rate. This approach enabled us to reduce the R_p value during the primary drying stage. Accordingly, this approach was termed the ice nucleation control. Its beneficial point is shortening the primary drying time. The reduced R_p made it possible to set the robust design space for the primary drying stage. For example, the control space could be set instead of the design space as shown in Figure 4, and a compactification of the trapezoid region could be achieved [53], which can avoid the trial-and-error for searching optimized operational conditions. Selecting the *set point* in the trapezoid region in Figure 4 could achieve the uniform products with higher productivity (no collapsed cake in 726 vials) [53]. However, the method by Kawasaki et al. has the drawback that the increase in residual water content in lyophilized cake may affect the solid stability and burden the primary and secondary drying stages (imagine the large ice crystal in a vial in Figures 1 and 6). Thus, the determination of the maximum allowable water content in the product that is one of the CQAs would be required.

8. Process Analytical Technology

As shown in Figure 2, the selection of critical parameters to well operate the lyophilization gives the motivation to develop an *in situ* optimization technology. The monitoring data of temperature and pressure in the equipment could give much information so that not only the practitioner but also the academia could get the plausible interpretation regarding the deeper understanding of lyophilization principle. Thus, a technology to aim the abovementioned goal is termed process analytical technology (PAT). Relating PAT tools for the monitoring of the primary drying stage are summarized in Table 3. The PAT tools have been developed

Table 3: Process analytical technology (PAT) methods in the lyophilization.

Target	PAT method	Measurement parameter	Ref.
Single vial	Thermocouple (TC)	T_b	M^*
	Resistance thermal detectors (RTD)	T_b	[60]
	Temperature remote interrogation system (TEMPRIS)	T_b	[60]
Batch	Pirani vs capacitance manometer	P_c	[61]
	Mass spectrometer	Partial pressure of gas	[63]
	Tunable diode laser absorption spectroscopy (TDLAS)	Water vapor concentration	[63, 64]
	Manometric temperature measurement (MTM)	T_b, T_{ice}	[51, 55, 65]
	Valveless monitoring system (VMS)	T_b	[66]
	Temperature measurement by sublimation rate (TMbySR)	T_b	[67]

*Many researchers have used this method to measure the product temperature. Therefore, specific literature cannot be exemplified.

for the monitoring of a single vial and batch operation. There are some scientific reports that evaluated the (dis)advantages of these techniques [56–59].

A wire thermocouple (TC), resistance thermal detectors (RTDs), and temperature remote interrogation system (TEMPRIS) are representatives of PAT tools for single vial. TC is a popular technology to monitor the temperature at the tip of the detector. However, the wire thermocouples are difficult to be adjusted at the center bottom position in the vials (group 3 in Figure 3(b)), and the T_b-profile mapping in the pilot or production lyophilizer is often not available. In addition, the biased measurement of temperature relative to vials without sensors is problematic. The same was true for RTD [60]. In order to solve these problems, TEMPRIS as a wireless temperature sensor can be remarked as an effective means. TEMPRIS is always available to be adjusted at the center bottom in the vials, and therefore, narrow variations in the T_b-profile intrabatch and interbatch are expected, and also the endpoint of primary drying is expected to be monitored correctly. In addition, the possibility to use the same sensors in the laboratory, pilot, and production lyophilizer helps us to perform scale-up experiments easily and rapidly. A TEMPRIS system for application in freeze drying is well evaluated in the previous report [60]. In the development phase of lyophilization cycle, a single vial monitoring as a PAT tool is useful since the T_b-profile mapping that includes the difference in the temperature profile of the vials placed at the center and edge position in the lyophilizer should be understood to optimize the lyophilization cycle. As discussed above, TEMPRIS is a powerful PAT method to monitor the single vial.

Batch monitoring as a PAT method is effective to monitor the designed lyophilization cycle, deepen the cycle, and perform continuous cycle improvement. Pirani gauge is usually used in the lyophilizer. This principle is to measure the thermal conductivity of the gas in the drying chamber, and nitrogen gas is used as a calibration gas [61]. It is not nitrogen gas but water vapors that are produced during the primary drying stage. For the reason, the Pirani gauge often reads approximately 60% higher than a capacitance manometer, due to approximately 1.6 times thermal conductivity of nitrogen to water vapor [62]. In addition, Pirani is then dependent on the gas composition in the chamber [61]. From the above nature, the Pirani pressure could indicate the primary drying endpoint with a sharper pressure decrease toward the capacitance manometer pressure. The mass spectrometer is a candidate PAT tool to determine the endpoint of primary drying and secondary drying. Some potential applications to pharmaceutical lyophilization are reported [63]. Tunable diode laser absorption spectroscopy (TDLAS) that can directly measure the water vapor concentration in the duct connecting the chamber and the condenser allows in-line monitoring of the dm/dt value [64]. Therefore, TDLAS is also an effective tool to estimate the K_v and R_p values in equations (1) and (3). Meanwhile, TDLAS is still now an expensive technique which is not a standard accessory with lyophilizer. Manometric temperature measure (MTM), that is a well-known technology to monitor the primary drying stage [51, 55, 65], is a technique to measure the T_b value during primary drying by isolating the valve between the chamber and the condenser within approximately 30 s to analyze the pressure rise. Notably, MTM can yield both T_{ice} and R_p. The problem in MTM is that most production-scale lyophilizers have the difficulty in isolation of the valve between the chamber and the condenser within 30 s. Besides, T_b changes cannot be monitored during the later stage of primary drying and the period of transition from primary drying to secondary drying, due to no or little pressure rise originated from the completion of the sublimation of ice.

In contrast to the difficulty in the valve operation within 30 s as claimed in the MTM system, the valveless monitoring method (VMS) has been developed [66]. The VMS is the monitoring system without a valve operation for a lab-scale lyophilizer. The dm/dt should be estimated from the variation of P_c because the sublimation of ice is followed by the release of water vapor to the interior of the equipment. From equations (1)–(3), the parameters, e.g., K_v, R_p, and T_b, are obtainable from the dm/dt. Therefore, VMS makes it possible to monitor the parameters in a noninvasive manner. Furthermore, Kawasaki and his coworkers have reported the method to determine the endpoint of the primary drying stage, based on the T_b obtainable from the dm/dt, which termed the "temperature measurement by sublimation rate (TMbySR)" [67]. The TMbySR as well as VMS is the method to monitor the T_b without a valve operation. Limited to the

lab-scale lyophilizer, TMbySR could be applicable independent of vial numbers [67].

Thus, the representative PAT tools were introduced in this section. The monitoring of specific parameters has clarified the dynamics of lyophilization to some extent. For more sophisticated monitoring, the PAT tool should be combined with the mathematical model describing the dynamics of lyophilization. In such a sense, the model-based PAT tool would be helpful for a quality management in pharmaceuticals freeze-drying, e.g., the application of these PAT tools for in-line process optimization is promising by combining with the MPC (see Section 4). Besides, the highly QbD is expected to be achieved thorough the offline calculation of the design space of the process [59].

9. Possible Innovation Required to Breakthrough

Several aspects to advance the technology in the pharmaceutical lyophilization are considered: new elemental technology, although conducted at small scale or attempted in the field other than the pharmaceutical field. For examples, a microwave-assisted freeze-drying (MFD) has been proposed in the food engineering field [79]. Freeze-drying coupled with a microwave heat source can speed up the drying rate and improve the product quality [79]. Few experiments are required to be extended from the lab-to production-scale lyophilizer; the knowledge or experiments are separated between different scales. With the goal to effectively scale-up the promising method at a lab scale, the seamless scale-up procedure would be required.

The position-dependent model based on the thermodynamics in K_v has been improved previously [54]. As long as one of the operation conditions to achieve the same dynamics of R_p between pilot- and production-scale lyophilizer, the methodology that the K_v value obtained at lab scale is transferred to the production scale should be investigated to clarify the requisite condition for using the same K_v value after scale-up procedure. The further development of scale-up theory is expected to achieve the seamless use of K_v from the lab scale to the production scale.

Reduction of the cost impact at the primary drying stage can be in principle designed based on equations (1)–(3). As evidently seen in these equations, the sublimation of ice is the important phenomena and its rate dm/dt is the most essential CPP in the primary drying stage. If not only K_v and R_p but also T_b can be calculated from dm/dt at the production scale, the operation system would be more robust. This motivation is identical to both the VMS and TMbySR in PAT tool. At present, an attempt using VMS and TMbySR has been limited to the lab scale [66, 67]. The possibility of scalable application of both methods would be required for the seamless use of K_v and R_p from the lab scale; e.g., the influence of vial number on shelves among lab, pilot, and production scales (Figure 1(b)). As stated before, the ice nucleation control based on the freezing temperature makes it possible to control the dm/dt. Therefore, the application of the above technology would afford a seamless and rapid decision-making over the freezing and drying stages. This is one of the promising operation systems for the lyophilization because the quality of products is no longer tested into them, i.e., quality-by-design.

During these years, a risk analysis for a pilot-scale freeze dryer has been reported for the construction of the basis for the risk-based decision-making in plant and process design of a freeze-dryer [80]. In the future, the PAT tool might contribute to the risk management of each scale freeze dryer. Furthermore, the PAT tool would obtain the enormous big data from the equipment at each scale [81]. Important principle might be hidden behind the big data. For effective analysis, the use of the Internet of things (IoT) together with big data from PAT tool and the models including CFD would bring the rapid decision-making well fused with the practitioner's experiences [81–84]. The author expects that the operational research based on IoT and big data will be developed to improve the accomplishment of the lyophilization, as shown in Figure 2.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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