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REVIEW ARTICLE

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Innovations, energy efficiency quantification and equipment design of advanced liquid freeze-drying processes

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ABSTRACT

Freeze-drying (FD) serves as a crucial and highly effective technique in sectors including food and medicine. Nevertheless, conventional production approaches encounter challenges such as excessive energy usage, prolonged production periods, and obstacles to large-scale continuous manufacturing, thereby elevating the processing expenses for drugs and premium food items. The objective of this article is to investigate solutions to these efficiency and cost challenges *via* advancements in equipment and processing techniques. The article reviews several promising new technologies in this field, focusing on processes such as spray freeze-drying and spin freeze-drying. By modifying the product morphology, these methods significantly increase the material heat transfer area. Typical strategies include atomizing liquid feedstocks into microdroplets for spray freeze-drying and forming uniform thin films on container walls through centrifugal spinning for spin freeze-drying. Spin freeze-drying achieves a 10-fold reduction in total drying time, while carrier particle-assisted spray freeze-drying (SFD-CP) realizes a 37% faster drying rate. Both technologies exhibit remarkable improvements in energy efficiency. Furthermore, the article explores the application of advanced monitoring tools such as infrared thermal imaging to enable real-time monitoring of manufacturing operations, guaranteeing product quality uniformity and reliability. Overall, contemporary studies in freeze-drying suggest that the technology is undergoing a shift from low-efficiency batch-wise operations to high-efficiency, energy-conserving continuous manufacturing. The conclusions drawn from this review are broadly applicable to both pharmaceutical and high-value food liquid freeze-drying applications, Such progress is anticipated to substantially lower production expenses, drive sustainable manufacturing, and encourage the future proliferation and utilization of superior-quality, storage-friendly dried goods.

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1. Introduction

Freeze-drying is a modern technology with a long history,[1–3] which removes moisture through sublimation based on the principle of water sublimation at its triple point.[4] Freeze-drying's cryogenic conditions serve as the optimal approach for compounds susceptible to thermal degradation or oxidation, ensuring retention of nutritional and flavor profiles alongside extended shelf life for solid or powdered products.[5,6] Following the freezing and sublimation stages, solutes are retained in the crystalline framework, yielding a highly porous powder characterized by superior dissolvability and reconstitution capacity.[7,8] Thus, freeze-drying represents a renowned method for manufacturing premium solid and powder products, with broad contemporary applications spanning pharmaceutical, biological, and food sectors.[9,10] Nevertheless, inherent and interrelated limitations of conventional batch freeze-drying have severely impeded its commercial viability and industrial scalability. That is, its energy demand is frequently several times that of standard drying techniques, slow drying rates, and high vacuum requirements leading to extremely low productivity, and intense mass transfer resistance during sublimation further extends processing times—all of which collectively result in poor cost-effectiveness.[11] Shifting from high-energy batch modes to

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energy-efficient continuous processes is a pivotal research and engineering goal under global sustainability initiatives. Resolving the inherent conflict between product quality preservation and process inefficiency has become the core focus of contemporary freeze-drying research.[12]

Conventional batch lyophilization at the water triple point is technically mature. However, its inherent drawbacks have become increasingly evident. These include slow freezing rates that lead to solute segregation, edge effects caused by insufficient heat and mass transfer, and inconsistent product quality between batches. These shortcomings can no longer meet modern industrial requirements for process standardization, aseptic operation, and particulate control.[12,13] Furthermore, constrained by limited mass transfer driving forces during sublimation, extends processing times to multiple days in conventional lyophilization, with products typically forming cake-like blocks, that require post-processing milling for powder conversion, introducing additional operational hazards and expenses.[9] Consequently, the research focus of freeze-drying technology have transitioned from basic parametric refinement to exploring novel drying mechanisms and continuous equipment design, targeting transformative reinvention *via* radical technological innovation.

The shift to continuous, high-efficiency operations has catalyzed numerous innovative process developments. To overcome mass transfer resistance caused by ice crystal growth in conventional freeze-drying, researchers have developed diverse novel pretreatment and drying technologies. For instance, Spray Freeze-Drying (SFD) integrates the advantages of atomization and lyophilization, facilitating high-yield generation of micro-/nanoparticles via enhanced surface-to-volume ratio, with notable applications in inhaled therapeutics and modified-release systems.[13] Spin Freeze-Drying employs centrifugal action to create uniform thin-film frozen structures on container surfaces, effectively resolving heat transfer heterogeneity and substantially reducing drying duration.[14] Significantly, under the Industry 4.0 paradigm, Process Analytical Technology (PAT) has emerged as a critical nexus between technological advancement and quality assurance. Real-time surveillance *via* nonintrusive tools—such as pulsed microwave freezing,[15] NIR, thermal imaging, and computational models,[16] allows continuous tracking of thermal gradients and moisture dynamics, which is vital for QbD implementation in continuous manufacturing.

Despite significant lab-scale progress, major challenges remain. These include scaling up, system integration, and controlling complex multiphase flow dynamics. Most concepts are still at the conceptual or laboratory stage. Current literature mainly explains the basic principles of individual techniques.[17–19] Few studies systematically compare different continuous lyophilization methods. There is also a lack of in-depth analysis on how pretreatment technologies affect heat and mass transfer efficiency.

This review aims to comprehensively survey recent energy-efficient technologies and equipment innovations in freeze-drying, with critical analysis of operational mechanisms, advantages, and limitations of advanced processes including spray freeze-drying, spin freeze-drying, atmospheric freeze-drying, and agitated freeze-drying. Concurrently, it examines the current application status of Process Analytical Technology (PAT) in continuous lyophilization and proposes strategies for accelerating drying through parameter optimization and auxiliary technologies, thereby synthesizing diverse research perspectives.[20,21]

2. Progression of drying methods and transition to continuous freeze-drying

Freeze-drying techniques operate on the core principle of sublimation where a solid-vapor phase transition occurs when the kinetic energy of water molecules in the ice phase exceeds the lattice binding energy threshold.[22] Critical process control requires sustaining triple-point parameters ($T \leq 273.16$ K, $P \leq 611.657$ Pa). The typical lyophilization sequence involves three essential stages, namely freezing, primary drying (sublimation), and secondary drying (desorption).

Although these principles have long been validated, conventional batch processing has critical limitations in modern industry. These limitations are driving the transition to continuous manufacturing.

2.1. Constraints and technical hurdles in batch lyophilization

In conventional batch lyophilization processes, materials are typically maintained in a stationary configuration within trays or vials. This operational mode exhibits inherent deficiencies in heat/mass transfer efficiency and product quality uniformity. Primarily, static freezing of bulk materials frequently results in suboptimal freezing rates promotes significant solute segregation,[23,24] Nonuniform freezing creates

intricate stress distributions and temperature differentials, resulting in marked microstructural nonuniformity.[25,26] Secondly, drying dynamics rely on conductive heat transfer from shelves, convective gas flow, and radiative heat supply as the energy source for sublimation. However, this hybrid heat transfer mechanism proves challenging to precisely regulate, causing substantial thermal flux variations between shelves/products and among differentially positioned vials.[27–31] Notably, the 'edge effect' phenomenon manifests as accelerated drying in perimeter vials receiving excess radiative heat,[32–35] while central samples demonstrate delayed drying. Such variation critically undermines batch consistency. Furthermore, pressure gradients within the chamber also cause sublimation kinetics and product temperature instabilities.[36,37] These phenomena extend processing times with thick monolithic products often needing multi-day drying,[38,39] while complicating scale-up endeavors.[40] More critically, prolonged sublimation elevates the risk of high-volatility flavor compounds co-removal with vapor (e.g., coffee aromatics[25]). With final products typically forming monolithic cakes, post-process pulverization to generate powders. This additional step increases energy consumption and introducing particulate contamination and sterility concerns.

2.2. Classification and mechanism innovations in continuous freeze-drying

To overcome these limitations, multiple continuous lyophilization systems were engineered. As illustrated in Figure 2, demonstrates five freeze-drying approaches namely Agitated freeze-dryers,[42] Continuous freeze dryers,[41] Spin freeze-drying systems, Corver belt-fed industrial systems,[43] Spray freeze dryers.[44] Based on variations in pretreatment methods and final product morphology. These innovations are primarily classifiable as particulate-based fluidization technologies and container-based dynamic processing approaches. Its fundamental architecture retains standard lyophilization components, including a drying chamber, cryogenic subsystem, vacuum assembly, and thermoregulated shelves. satisfying core thermodynamic criteria for freeze-drying mass/energy transport.[45,46] After material loading, the products are sealed in the drying chamber, and the refrigeration system supplies cold energy to the cavity to create a low-temperature environment ensuring product $T < T_g$(glass transition temperature, the critical temperature at which amorphous materials transition from a rigid glassy state to a viscous rubbery state). Subsequently, vacuum pumps activate to achieve required pressure parameters. Regulated shelves operate at programmed intervals to facilitate adsorbed water removal[47].

2.2.1. Agitated freeze-drying for surface scraping and crystal restructuring

Concerning mass transfer barriers caused by directionally heterogeneous pores formed under mechanical stress and uncontrolled ice crystallization in traditional lyophilization,[48,49] Agitated freeze-drying (AFD) incorporates a mechanical intervention mechanism. Through continuous mechanical stirring in the drying cavity, shear forces progressively detach the desiccated matrix surface, thereby substantially reducing vapor migration pathlength.[42] To further optimize pore architecture, an annealing strategy was established. Reinforcing pore boundaries *via* localized molecular chain reorganization in glassy materials.[50,51] Additionally, Capozzi et al.[41] engineered a modular continuous lyophilization system, enabling crystal nucleation *via* accurate supercooling control in vacuum-induced nucleation module, followed by radiative heating for drying. This approach yields samples with larger and more homogeneous pore size distributions than conventional lyophilization, effectively diminishing mass transfer resistance.[41,52] AFD technology is suitable for the freeze-drying of high-viscosity liquid food materials with suspended solid particles, such as probiotic suspension,[42] fruit and vegetable pulp liquid, and protein emulsion. The mechanical stirring and scraping mechanism of AFD can effectively prevent the agglomeration of suspended particles in high-viscosity liquid,[53] and the obtained dried powder has a uniform particle size distribution, which is suitable for the production of functional food powders with probiotics or plant active ingredients.

2.2.2. Spray freeze-drying for surface area maximization

Spray freeze-drying (SFD) represents a distinct technological pathway. Atomization intrinsically links drying duration to particle size squared[54] (derived from Planck's equation). Through liquid feedstock atomization and instantaneous freezing in cryogenic media, SFD generates microspheres exhibiting elevated specific surface area. dramatically improving desiccation rates. This technique demonstrates unique advantages in fabricating inhalable formulations and controlled-release microspheres with high sphericity, porosity, and superior aerodynamic

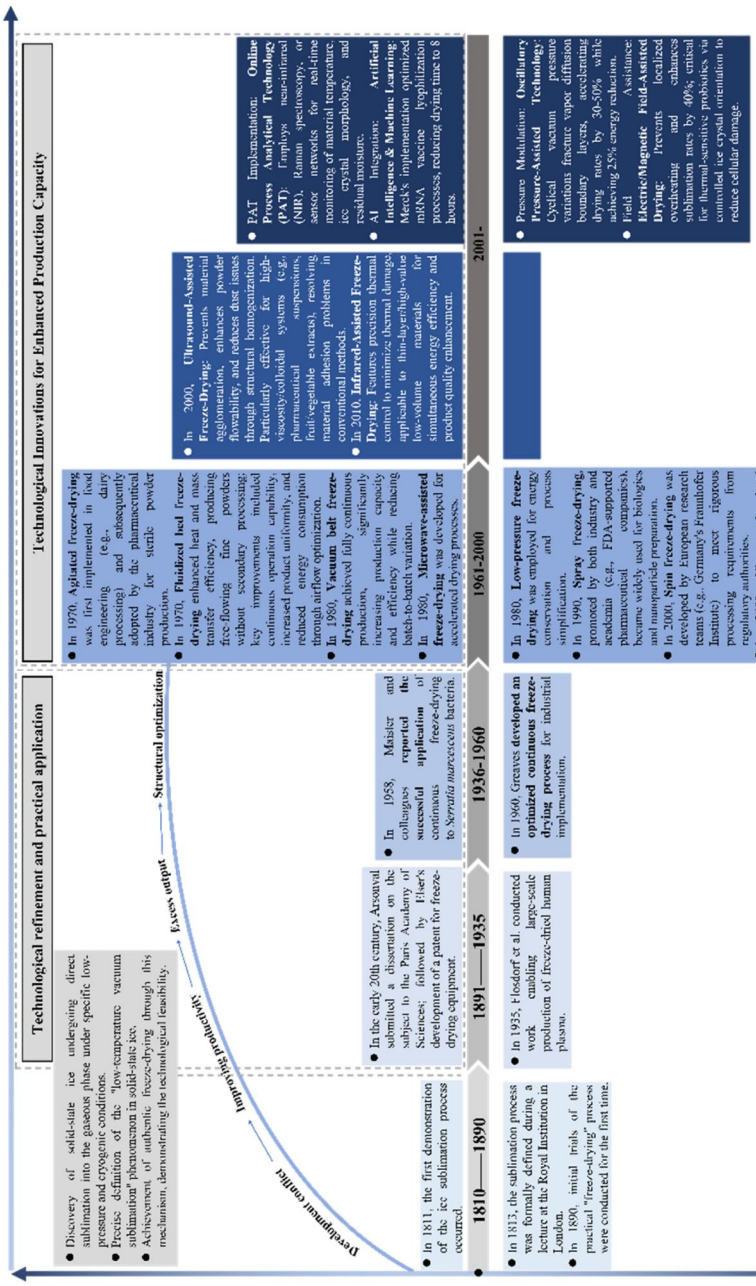


Figure 1. Historical Development of Lyophilization.

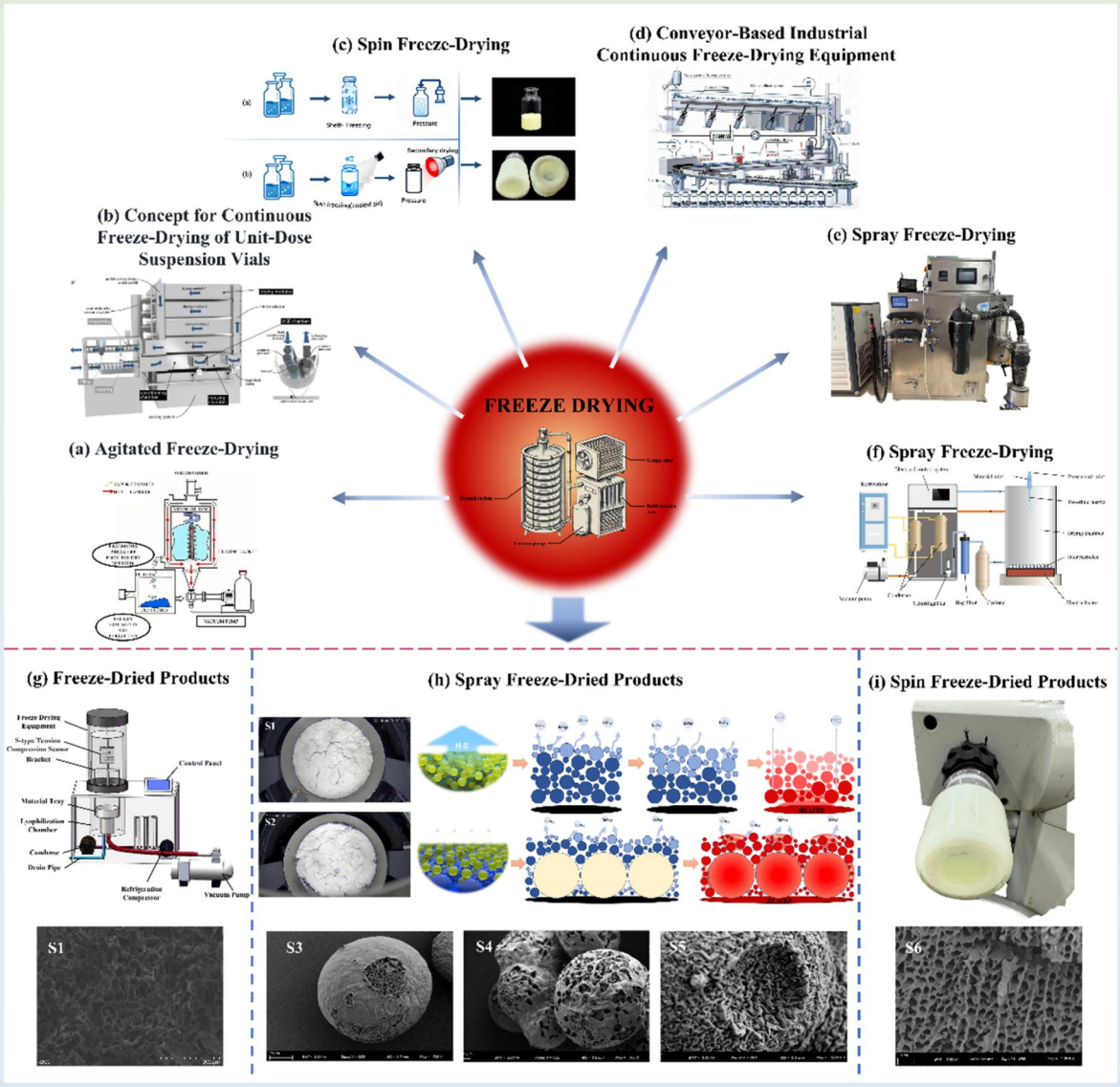


Figure 2. Comparative drying methods and final product morphologies (a) agitated freeze-drying; (b) concept for continuous freeze-drying of unit-dose suspension vials [41]; (c) spin freeze-drying; (d) conveyor-based industrial continuous freeze-drying equipment; (e) spray freeze-drying; (f) spray freeze-drying; (g) freeze-dried products; (h) spray freeze-dried products; (i) spin freeze-dried products.

performance.[13,55–58] Unlocking fresh potential across pulmonary drug delivery, modulated-release vehicles, and parenteral dosage forms, nozzle innovations encompass four-fluid coaxial systems,[59] ultrasonic vibrators,[60] electrostatically-driven inkjet devices,[61] EHD nebulizers.[62] Such sprayer advancements produce finer and more uniform particulates. However, industrial-scale continuous SFD encounters significant hurdles. Current SFD research remains lab-scale with limited throughput typically less than 5 mL/min.[61,63,64] For industrial continuous production, Rey et al.[43] proposed a conveyor-based continuous SFD concept, utilizing IR radiation for primary drying energy. Nevertheless, direct conveyor transport still confronts issues of fine powder agglomeration (<1 mm), dust dispersion, and sterility control. Addressing these, Xu et al.[65] simulated freezing dynamics of droplets impacting cryogenic surfaces, employing high-speed videography to document droplet spreading on diverse-material balls. Revealing enhanced droplet spreading on cryogenic surfaces, with transient spreading-retraction phases post-impact with spreading timescale substantially less than freezing period. Droplets freeze faster on

stainless steel than PTFE surfaces and achieve larger spreading diameters. Thus in SFD practice, higher surface temperatures induce minor residue formation *via* droplet recoil. Wall material critically influences post-freezing droplet stacking behavior. Subsequently, Li et al.[66] and Zhang et al.[67–69] developed Carrier Particle-assisted SFD (SFD-CP). Designing the carrier particle drying apparatus shown in Figure 2(i). SFD-CP utilizes fluidized cryo-inert particles as deposition substrates, ensuring instantaneous droplet spreading and solidification on carriers. Research confirms cryogenic carrier surfaces substantially reduce nucleation time, prevent solute segregation, and induce better-interconnected porous matrices (Figure 2(h)-S1). Specifically, Using 5-mm SS spheres achieved 37% faster drying than standard SFD. Producing powders with tighter size distribution and reduced D50 $\approx 35\mu$m. SEM confirmed SFD-CP powders exhibit higher porosity (Figure 2(h)-S1), since chilled carriers facilitate rapid solidification. granting impacting droplets shorter nucleation and complete freezing times forming ice with finer crystalline structures, which desiccates into well-connected porous frameworks, thereby eliminating phase separation and enhancing drying dynamics. SFD and SFD-CP are the most widely used continuous liquid freeze-drying technologies in the food field, suitable for the freeze-drying of low-to-medium viscosity liquid food materials with high added value.[70,71] Laboratory-scale SFD is mainly used for the preparation of micro-/nano-powder of high-value food active ingredients, such as plant polyphenol extract liquid,[72] natural pigment extract liquid (e.g., curcumin, anthocyanin), and vitamin microemulsion. Carrier-assisted SFD (SFD-CP) solves the agglomeration problem of SFD and is suitable for industrial pilot production of bulk food powder, including fruit and vegetable juice powder (e.g., kiwi juice, orange juice),[67] dairy liquid powder (e.g., goat milk powder, human milk powder),[73] and probiotic fermentation liquid.[74] In particular, SFD-CP can retain the activity of heat-sensitive probiotics by 90% above,[72] which is significantly better than traditional batch freeze-drying.

However, industrial-scale continuous SFD still faces scalability challenges that restrict its widespread practical application, though some previously reported limitations have been alleviated with technological advancements. These challenges include the following three aspects. 1) Lab-to-pilot throughput scalability constraints. Laboratory-scale SFD typically exhibits a feed rate of 10–15 mL/min,[75] and pilot-scale scaling up can achieve a feed rate of 200–400 L/h—representing a throughput increase of 1,500–3,000 times. Nevertheless, large-scale industrialization (feed rate > 1,000 L/h) still requires optimization of multi-nozzle coordination and gas-liquid distribution uniformity[70]; 2) Fine powder agglomeration and dust dispersion issues. SFD produces micro-powders with a particle size of 5–50 μm, and while high surface energy tends to cause mild agglomeration, this problem can be effectively mitigated by introducing inert carrier particles (SFD-CP) or optimizing process parameters. The resulting agglomerates are typically $<100\,\mu$m (no large clusters >1 mm), and the powder yield can reach 90%,[67] with only a 5–10% yield reduction in extreme cases; 3) Aseptic control and material loss challenges. Modern continuous SFD adopts a closed atomization-freezing-integration design, combined with nitrogen purging and in-line sterilization modules, which effectively addresses aseptic control difficulties for pharmaceutical applications.[68] The high-speed airflow in the drying chamber causes a material loss rate of 5–8%, mainly due to filter retention and pipeline residual, which can be further reduced by optimizing pipeline length and filter structure.

2.2.3. Spin freeze-drying for thin-film drying

As an innovative continuous solution for vial formulations, spin freeze-drying (SFD) was developed by Corver's team.[14] By rotating vials at high speed along their longitudinal axis, liquid formulations into uniform thin layers on vial walls for freezing. This thin-film structure dramatically enhances sublimation interface area and concurrently diminishes product thermal resistance, resulting in over 10-fold reduction in total process duration compared to conventional lyophilization.[14,76] Microstructurally, Spin FD-generated pore architectures exhibit highly hierarchical order (Figure 2(i)-S1). This is distinctly different from the disordered pore networks formed in conventional lyophilization. This ordered pore structure creates interconnected, directionally aligned vapor diffusion channels with diameters of 1–5 μm. Such a structure reduces vapor diffusion tortuosity from 3–5 (batch FD) to 1.2–1.5 (Spin FD). This reduction shortens the water vapor migration path and eliminates isolated closed pores, thus significantly improving mass transfer efficiency.[77] Moreover, the Spin FD system uses a continuous conveying mechanism. Vials are automatically and sequentially transported through freezing, primary drying, and secondary drying modules *via* a precision conveyor belt. Each vial experiences the same residence time, temperature, pressure, and radiative heating conditions in every module. This

Table 1. Comparison of innovation types and core performances of continuous freeze-drying technologies.

Technology type	Innovation classification	Core equipment feature	Drying rate improvement	Industrialization stage	References
AFD	Transformative advance	Stirring drying cavity with scraping device	2–3 times	Pilot scale	[42,82]
Spray FD	Transformative advance	Laboratory-scale atomization and cryogenic freezing chamber	3–4 times	Laboratory scale	[65,83]
SFD-CP	Hybrid innovation	Inert carrier fluidized bed and atomization nozzle	4-5 times vs (batch) 37% (vs SFD)	Pilot scale	[70,84]
Spin FD	Transformative advance	Centrifugal rotation module and radiative heating	>10 times	Lab-pilot transition	[80,85]

mechanism eradicates the thermal edge effects characteristic of batch production by ensuring uniform process conditions across all vials and enables real-time quality monitoring *via* PAT tools such as NIR spectroscopy[78] and infrared thermography[79] permitting in-process surveillance of CQAs.

In summary, spanning agitated annealing to spray freezing and spin freezing, these continuous technologies fundamentally reconfigure material freezing behavior and heat and mass transfer pathways. Progressively addressing the critical limitations of conventional lyophilization, namely high energy consumption and low efficiency, establishing a robust foundation for efficient, uniform, and scalable industrial production. Although Spin FD is currently mainly used for pharmaceutical unit dose liquid formulations,[80] it has potential application value in the freeze-drying of small-dose high-value liquid food for personalized nutrition. The thin-film freeze-drying of Spin FD can ensure the uniform drying of small-dose liquid food, and retain the flavor and active ingredients to the maximum extent.[81]

2.3. Summary of continuous freeze-drying technology innovation

The above continuous FD technologies have different innovation types, core equipment characteristics, and energy performance, and all of them have made significant progress compared with traditional batch FD (Table 1). AFD is a transformative advance based on mechanical intervention, with moderate energy efficiency improvement and limited industrial application due to sterility problems. SFD and Spin FD are typical transformative advances, with significant improvement in energy efficiency, but the former is limited by low throughput and particle agglomeration, and the latter has poor formulation adaptability. SFD-CP is a hybrid innovation, which makes up for the defects of SFD and further improves the energy efficiency and product performance. In general, the core of continuous FD technology innovation is to optimize the heat and mass transfer path by changing the material form or process mode, and the key to realizing industrialization is to solve the problems of equipment integration, scale-up and performance optimization.

3. Technology-assisted process optimization and quality control

Beyond instrumental PAT tools, mathematical modeling approaches constitute equally vital components in continuous FD system development and optimization. By modeling pressure transients caused by vapor flux changes during sublimation, researchers can deduce key critical process parameters (CPPs), including product temperature, vapor transport resistance, residual moisture content, and ice sublimation rate. For spin freeze-drying as an emerging continuous FD technology, researchers have developed mechanistic models based on heat and mass transfer governing equations, which can determine the optimal thermal and pressure parameters throughout the primary drying stage and achieve targeted optimization of processing conditions.

3.1. Mathematical modeling

Beyond instrumental PAT tools, mathematical approaches constitute equally vital components in system development. Modeling pressure transients caused by vapor flux changes allows deduction of critical process parameters, including temperature, vapor transport resistance, residual moisture, and ice sublimation rates.[86,87] For spin freeze-drying as an emerging technology, researchers have developed mechanistic models based on heat and mass transfer governing equations to determine ideal thermal and pressure

parameters throughout primary drying, achieving optimized processing conditions. Leys et al.[85] constructed a model incorporating product layer resistance (Rp) and heat input parameters as core inputs. This model Enabling accurate forecasting of thermal profiles and drying completion in Spin-FD processes. Model analysis revealed that the thin-layer structure formed by spin freezing substantially reduces Rp values, which allows the application of elevated thermal energy while avoiding collapse phenomena thereby drastically curtailing primary drying time.

Lammens[88] refined the mathematical formulation of drying resistance, demonstrating that Rp typically exhibits linear proportionality to dried layer thickness. This linear relationship is applied for real-time thermal power optimization *via* computational algorithms. Specifically, the algorithm continuously calculates the real-time dried layer thickness based on online monitored Rp values, and dynamically adjusts the shelf/radiative heating power to match the sublimation rate—ensuring maximum heat input without exceeding the product collapse temperature, and maintaining a constant and efficient sublimation rate throughout the primary drying stage. Regarding the critical heat transfer coefficient (Kv), Pikal et al.'s foundational theory[32] identified Kv as pressure-dependent with significant contributions from shelf conduction and vial contact heat transfer. Continuous processing equipment exhibits significant Kv variability attributable to dimensional disparities in vial configuration and base curvature. Rambhatla et al.[89] developed methodologies for determining stable drying pressures and maximum sustainable sublimation rates in lyophilizers. These three elements enable computer-aided modeling of process dynamics. Significantly, the advent of micro-computed tomography (μCT) now provides high-fidelity microstructural data for modeling (Figure 3), μCT-derived pore morphologies permit accurate geometric parameterization in simulation frameworks. Mitigating simulation errors induced by structural oversimplification, thereby substantially enhancing model predictive accuracy for complex material drying behaviors.

Computational fluid dynamics (CFD) has emerged as a methodology for resolving complex multiphase flow behaviors in spray freezing applications. Droplet freezing, being a complex process involving multiphase heat/mass transfer, is effectively investigated through CFD simulation approaches. As referenced, Zhao et al.[90] employed numerical simulations to quantify how droplet size, gas velocity, and cryogenic temperature govern freezing dynamics, providing mechanistic understanding for plate-impact freezing in SFD processes. Key metrics including phase-change progression and temperature fields elude direct measurement, necessitating analysis *via* droplet hydrodynamics and heat transfer to isolate parametric effects on single-droplet solidification. Gunjal et al.[91] constructed droplet impact models *via* the Volume of Fluid (VOF) approach. This model systematically investigates the evolution of droplet spreading diameter and height under the combined effects of droplet size, viscosity, surface tension, and impact velocity, and the study also incorporates a detailed sensitivity analysis of computational domain size and boundary condition settings. Yao et al.[92] implemented multiphysics-coupled level-set simulations in COMSOL to simulate the spreading and phase change of low-viscosity droplets on cold substrates, resolving regional temperature gradients and solidification rates throughout the entire droplet freezing process. Building on these simulation results, frost-prevention strategies for spray freeze-drying (SFD) chamber walls are proposed. Specifically, CFD-guided equipment design optimizes wall temperature distribution (−10–0 °C) to effectively inhibit droplet condensation and frost nucleation, while refined operational parameters maintain droplet impact velocities within the 1–3 m/s range—minimizing wall-directed rebound and splashing as well as subsequent liquid adhesion to suppress frost propagation.

3.2. Process analytical technology (PAT)

Process analytical technology (PAT) constitutes a real-time monitoring system integrating detection tools and programmatic control strategies for manufacturing processes to achieve process visualization, dynamic diagnostics, and operational refinement.[93] Lyophilization processes demand high-accuracy monitoring instruments due to extreme conditions (cryogenic temperatures, high vacuum, aseptic requirements), and commonly used PAT tools in lyophilization include near-infrared (NIR) spectroscopy, manometric temperature measurement (MTM), infrared (IR) thermal imaging, Fiber Bragg Gratings (FBGs), and microwave resonance spectroscopy. Under this regulatory mandate, FDA's 2004 PAT Framework requires PAT integration in pharmaceutical manufacturing design and execution. Consequently, research focus has increasingly shifted toward lyophilization process analysis techniques.[94]

3.2.1. Spectroscopic and thermographic techniques

Near-infrared (NIR) spectroscopy constitutes a molecular vibration-based analytical technique. Its high sensitivity to moisture and molecular structures renders it a powerful tool for monitoring drying kinetics. PCA-assisted NIR data processing yields more

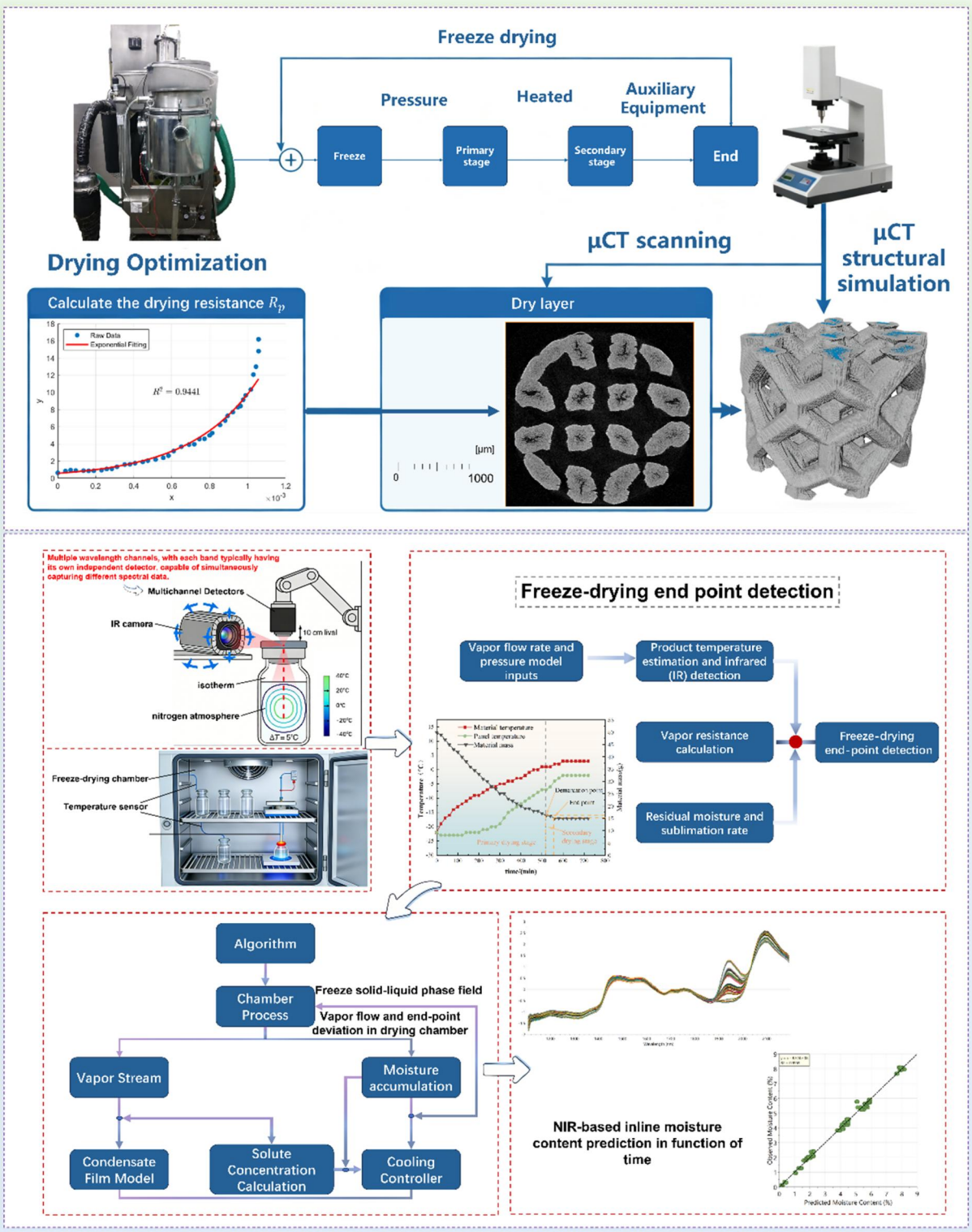


Figure 3. Implementation of micro-CT and computational fluid dynamics in process analytical technology [19].

statistically significant process signatures (Figure 4). For noncontact heat transfer systems, Bockstal et al.[14] implemented NIR in infrared-heated continuous spin freeze-drying. Results showed NIR concurrently quantifies dehydration kinetics and deciphers nonlinear correlations of IR emitter power and sample proximity to sublimation yield. The study revealed that chamber pressure's impact on

sublimation rate is substantially diminished under radiative heat transfer dominance. Such insight proves crucial for implementing independent parameter control strategies.

As an advanced visualization tool, IR thermography enables comprehensive mapping of thermal distribution profiles. IR imagers provide areal temperature mapping at 0.5-mm resolution, surpassing conventional thermocouple limitations. Haken et al.[95] achieved continuous surface temperature monitoring *via* germanium-viewport mounted IR cameras on lyophilizer ceilings. This configuration substantially enhanced temperature monitoring coverage. However, such top-down approaches lack depth penetration, precluding assessment of core thermal profiles. To address this, Lietta's group[94] developed an innovative in-chamber infrared (IR) thermographic system, integrated with nitrogen purging and thermal insulation encapsulation to mitigate interference from the vacuum cryogenic environment of freeze-dryers. Experiments confirmed the system's capability to capture temperature distributions across vial batches, and the IR camera itself acts as a physical shield that modifies the thermal environment of the vials directly in front of it—eliminating the need for an additional cylindrical insulation shield. This shielding effect arises from the camera blocking radiant heat from the freeze-dryer chamber walls, which aligns with the thermal conditions experienced by central vials typically shielded from wall radiation by surrounding vials, rather than edge vials exposed to excess wall radiation. This shielding-induced alignment with central vial dynamics was validated experimentally. Specifically, when monitoring vials in front of the IR camera, their weight loss (a proxy for sublimation flux) averaged 1.17 g (standard deviation 3.0%), which is only 7% higher than the mean weight loss of central vials (1.09 g) and far closer to central vial behavior than the 30% deviation observed in unshielded edge vials. Additionally, temperature measurements from the IR system showed excellent agreement with thermocouple data, with deviations within the thermocouple's inherent uncertainty range (±1 K) when comparing product temperatures at the vial bottom. Beyond temperature monitoring, the IR system demonstrated comparable performance to traditional methods in critical process assessments. Specifically, it accurately identified the endpoint of primary drying (consistent with the Pirani-Baratron pressure ratio method) and reliably estimated key process parameters (overall heat transfer coefficient Kv and dried product resistance Rp), with results matching those derived from thermocouple measurements.

3.2.2. Pressure-Flow based endpoint detection

Precise determination of sublimation endpoint during primary drying is critical for preventing energy waste and product overheating[96–98]。 Parvis et al.[99] devised sputter-coated glass-embedded thermocouples, while Kasper et al.[100] integrated Fiber Bragg Gratings (FBGs) into shelves. Despite meeting functional requirements, their implementation in standard equipment faces integration challenges. Beyond thermocouple monitoring, pressure-based feedback methods demonstrate superior stability. The Pirani-Baratron pressure ratio method remains the most reliable endpoint detection technique.[101] However, vapor flow parameters are susceptible to process conditions, product load, and equipment configuration. Under continuous processing, continuous flow conditions amplify vapor flux fluctuations, introducing substantial uncertainty in full-sublimation detection. Consequently, Pisano et al.[102] engineered a novel End-Point Detection (EPD) system. Its core algorithm employs temporal integration of solvent flow rate, continuously estimates the percentage of sublimated ice mass. Primary drying termination is automatically triggered when exceeding a preset threshold (e.g., 99%) with total vapor flux below critical value. Such methodology provides batch-wide noninvasive endpoint monitoring. Thereby establishing framework for autonomous operation in continuous lyophilization.

Collectively, convergence of computational modeling and process analytics is converting freeze-drying into a precisely engineered unit operation. Advancements in ML algorithms and sensing technology will facilitate development of self-optimizing freeze-drying platforms. Ultimately improving operational reliability and economic viability for industrial deployment.

4. Energy efficiency evaluation of advanced freeze-drying technologies

Energy efficiency is the core index to evaluate the performance of FD technology, and the key to realizing the sustainable development of FD is to reduce energy consumption and improve energy efficiency.[81,103] This chapter defines the core evaluation indexes of FD energy efficiency, quantifies and compares the energy performance of different FD technologies, analyzes the key factors affecting energy efficiency, and discusses the life cycle energy (LCE) of FD technology, so as to provide a comprehensive energy efficiency evaluation system for FD technology research and industrial application.

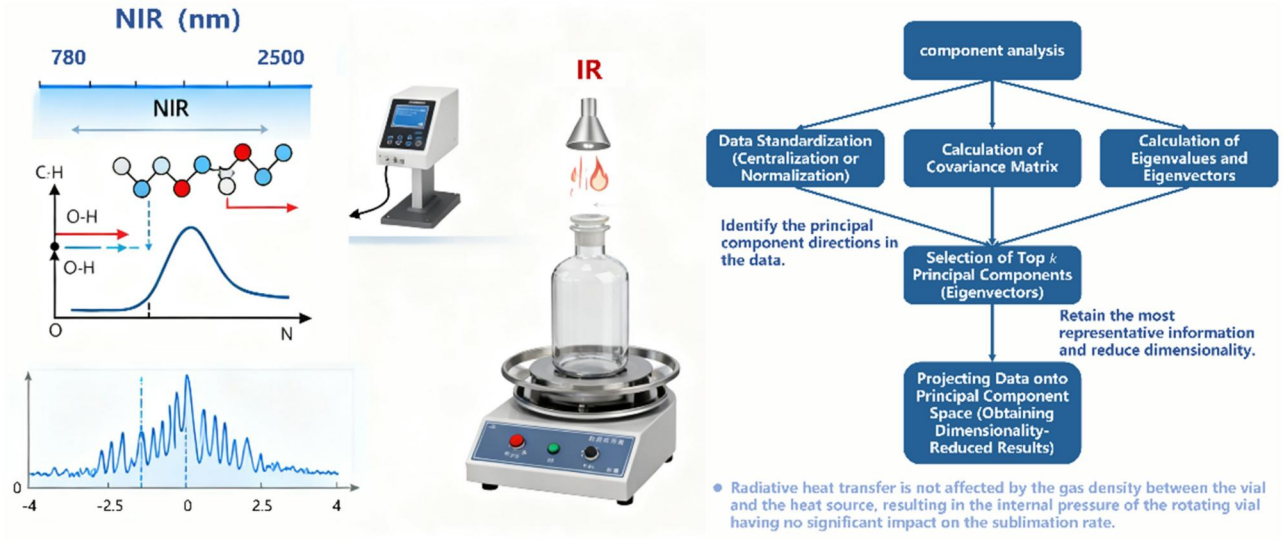


Figure 4. Thermal imaging for freeze-drying process monitoring.

4.1. Core evaluation indexes of freeze-drying energy efficiency

To accurately evaluate the energy efficiency of FD technology, it is necessary to unify the core evaluation indexes and calculation methods.[104,105] Combined with the characteristics of FD process and industrial application requirements, the core evaluation indexes of FD energy efficiency are defined as follows.

(1) Specific Energy Consumption (SEC)

SEC refers to the total energy consumed by removing unit mass of water or producing unit mass of dried product in the FD process, with the units of kJ/kg H_2O (preferred for process comparison) and kJ/kg product (preferred for industrial production). The calculation formula is.

$$\mathrm{SEC} = \frac{E_{\mathrm{total}}}{m_w}$$

where E_{total} is the total input energy of the FD process (including refrigeration energy, vacuum energy, heating energy and auxiliary equipment energy), and m_w is the mass of water removed in the FD process. SEC is the most direct index to reflect the energy consumption of FD technology, and the smaller the value, the better the energy efficiency.

(2) Drying Efficiency (DE)

DE refers to the ratio of the energy effectively used for water sublimation in the FD process to the total input energy, with the unit of %. The calculation formula is.

$$\mathrm{DE} = \frac{E_{\mathrm{sublimation}}}{E_{\mathrm{total}}} \times 100\%$$

Where $E_{\mathrm{sublimation}}$ is the energy required for water sublimation (calculated according to the sublimation latent heat of water, that is, 2834 kJ/kg[104]). DE reflects the energy utilization rate of FD technology, and the larger the value, the higher the energy utilization rate.[106]

(3) Drying Rate (DR)

DR refers to the mass of water removed per unit area and per unit time in the FD process, with the unit of kg $H_2O/(m^2 \cdot h)$. DR is an indirect index to reflect the energy efficiency of FD technology. A higher DR means a shorter processing time, which can reduce the comprehensive energy consumption of the FD process (such as vacuum and refrigeration energy consumption).

(4) Energy Payback Period (EPP)

EPP refers to the time required for the energy cost saved by the advanced FD technology compared with the traditional batch FD technology to recover the additional equipment investment cost, with the unit of years. EPP is an index for evaluating the economic benefits of energy efficiency improvement of FD technology in industrial application, and the smaller the value, the higher the economic benefit.[107]

4.2. Quantitative comparison of energy efficiency of different freeze-drying technologies

Based on the above evaluation indexes, combined with the published experimental data and research

Table 2. Summary of food product adaptability of liquid freeze-drying technologies.

Liquid freeze-drying technology	Applicable food category	Food material form	Product application	Advantages for food processing	Limitation for food industry	References
AFD	Probiotic food, plant pulp food, protein emulsion food	High-viscosity liquid (solid content: 10%-30%)	Functional food powder, probiotic powder	Prevent particle agglomeration, uniform powder	High equipment cost, low throughput	[53]
SFD (Lab-scale)	Plant active ingredient food, natural pigment food, vitamin food	Low-viscosity extract liquid (solid content: <5%)	Micro/nano functional food powder, food additive powder	High specific surface area, good solubility	Severe agglomeration, high production cost	[70,71]
SFD-CP (Pilot-scale)	Fruit and vegetable juice food, dairy food, probiotic fermentation food	Low-to-medium viscosity liquid (solid content: 5%-20%)	Bulk fruit and vegetable powder, milk powder, probiotic food powder	High drying rate, good powder flowability, high active ingredient retention	Carrier separation cost, complex process	[68,84]
Spin FD	Personalized nutrition food, royal jelly food, functional peptide food	Small-dose liquid (volume: <5 mL/unit)	Mini-dose food powder, oral instant powder	Uniform drying, high flavor/active retention	Low throughput, only small-dose application	[45,80]
Atmospheric Liquid FD	Low-moisture fruit and vegetable food, cereal liquid food	Low-viscosity liquid (solid content: 10%-25%)	Bulk food powder, snack food powder	Low equipment cost, short payback period	Low active ingredient retention	[22,63]

results,[10,14,16,17,22,39] the energy efficiency of different FD technologies (traditional batch FD, AFD, SFD, SFD-CP, Spin FD, atmospheric FD) is quantified and compared (Table 2). The data in the table are the average values of the published research results, and the specific values are affected by the material properties, process parameters and equipment configuration.

It can be seen from Table 3 that the continuous FD technologies (AFD, SFD, SFD-CP, Spin FD) have significant energy efficiency advantages compared with the traditional batch FD, with SEC reduced by 30%–60% and DE increased by 0–20 percentage points. Among them, Spin FD has the best energy performance, with SEC as low as 6,000–7,500 kJ/kg H_2O and DE more than 50%, which is due to the thin-film structure formed by centrifugal action, which fundamentally optimizes the heat and mass transfer path.[88] SFD-CP has the second best energy performance, with DE reaching 45–50%, which is due to the inert carrier particles solving the agglomeration problem of SFD and further improving the drying rate.[68] Atmospheric FD has moderate energy efficiency, but its EPP is only 1–2 years, which has significant economic benefits in the industrial application of food powder.

In addition, the energy efficiency of FD technology is also affected by the material properties. For example, the SEC of high solid content materials is 30% lower than that of low solid content materials,[81] because the high solid content materials have a shorter sublimation time and lower refrigeration and vacuum energy consumption. The SEC of heat-sensitive materials is 15%–20% higher than that of nonheat-sensitive materials,[108] because the heat-sensitive materials need a lower freezing temperature and a slower heating rate, which increases the process energy consumption.

4.3. Key factors affecting the energy efficiency of freeze-drying technology

4.3.1. Process factors

The freezing process and sublimation process are the core process factors affecting the energy efficiency of FD.[109,110] The freezing rate directly affects the ice crystal structure. Specifically, the rapid freezing rate (freezing rate >10 K/min) forms fine and uniform ice crystals, which have a small sublimation resistance and a high drying rate, thus reducing the SEC by 15%–20%.[69] The annealing process can optimize the ice crystal structure, reduce the sublimation resistance, and improve the DE by about 5%.[51] In the sublimation process, the control of shelf temperature and vacuum pressure is the key. Specifically, the appropriate shelf temperature (close to the collapse temperature of the material[36]) can improve the sublimation rate without product collapse, and the optimal vacuum pressure 10–50 Pa can reduce the heat transfer loss and improve the DE by about 8%.[47]

4.3.2. Equipment factors

The heat transfer mode and equipment structure are the core equipment factors affecting the energy efficiency of FD.[29,30,33] The heat transfer mode of FD

Table 3. Quantitative comparison of energy efficiency among different freeze-drying technologies.

FD technology type	SEC (kJ/kg H_2O)	DE (%)	DR (kg H_2O/(m^2·h))	EPP (years)	References
Traditional batch FD	15,000–20,000	<30	0.02–0.05	–	[85]
Agitated FD (AFD)	10,000–12,000	~35%	0.04–0.15	3–4	[53]
Spray FD (SFD)	7,500–9,000	~40%	0.10–0.40	–	[68]
Carrier-assisted SFD (SFD-CP)	6,750–8,000	35%-45%	0.15–0.50	2–3	[67]
Spin FD	6,000–7,500	>50%	0.20–0.60	3–5	[14]
Atmospheric FD	8,000–10,000	35–40	0.08–0.30	1–2	[63]

mainly includes contact heating, radiative heating and microwave heating. Specifically, the DE of contact heating is about 25%–30%,[34] the DE of radiative heating is about 35%–45%, and the DE of microwave heating can reach more than 45%.[15] However, microwave heating has the problem of local overheating, which limits its application in pharmaceutical products. The equipment structure directly affects the heat and mass transfer efficiency. Specifically, the continuous FD equipment with optimized structure (e.g., Spin FD with thin-film structure, SFD-CP with fluidized bed structure) can reduce the heat and mass transfer resistance and improve the energy efficiency.

4.3.3. Material factors

The solid content, initial moisture content, and glass transition temperature (T_g) of the material are the core material factors affecting the energy efficiency of FD.[23] The initial moisture content affects the total sublimation energy consumption. Specifically, the higher the initial moisture content, the higher the total sublimation energy consumption, but the DE is basically unchanged. The T_g of the material affects the process parameters. Specifically, the material with low T_g (e.g., biological products) needs a lower shelf temperature in the sublimation process, which increases the SEC by 15%–20%.

5. Future perspectives and conclusions

The freeze-drying sector is undergoing a paradigm shift from discontinuous batch operations toward integrated continuous production systems. The core of this transformation is the transformative advance of FD technology and the optimization of equipment design, and the key goal is to realize the industrialization of continuous FD technology.

Among continuous approaches, mechanically-scraped agitated freeze-drying has demonstrated progress in particulate containment. However, spin-based and spray-based freeze-drying offers the most promising scalability and innovation impact. Spin freeze-drying establishes thin-film configurations *via* centrifugal force, fundamentally resolving heat transfer heterogeneity in conventional lyophilization. This enables integrated production of premium unit-dose parenteral products. The future equipment design of Spin FD should focus on the modular design of centrifugal rotation module and expansion of formulation adaptability, developing a multi-functional Spin FD equipment suitable for both vial and nonvial formulations. Meanwhile, spray freeze-drying combines liquid dispersion with ultra-rapid freezing. The large surface-to-volume ratio of fine particles dramatically improves thermal and mass transfer kinetics. Imparting superior powder flowability and dissolution characteristics to products. Although SFD has achieved laboratory-scale success with certain high-value pharmaceuticals, its industrial translation remains constrained by limited throughput and formulation dependency (e.g., uncertainties in eutectic point T_e and glass transition temperature T_g). To overcome these bottlenecks, future research should focus on equipment integration, continuous flow design, and carrier-assisted strategies. Building on Rey's continuous model,[43] researchers should develop enclosed conveyor-based continuous SFD systems with high throughput. Commonly used inert carrier particles for SFD include 3–5 mm stainless steel spheres, polytetrafluoroethylene spheres, edible starch microspheres, and silica gel particles[66–69]; introducing these carrier particles enhances mass transfer dynamics by providing a large, cryogenic freezing surface area. Within fluidized or conveyor systems, carriers offer substantial freezing interfaces that promote rapid ice nucleation, while functioning as structural scaffolds to prevent product agglomeration. Implementing residence time control in aseptic enclosures coupled with IR or microwave heating instead of contact conduction. This approach may resolve static carrier sedimentation issues, enabling continuous droplet-to-powder conversion.

Collectively, freeze-drying evolution is shifting focus from cake morphology to granular products, continuous operation, and smart technologies. Ambient-pressure drying lowers equipment costs, novel spin/spray methods reinvent thermal pathways, while PAT enables real-time parameter monitoring. Future integration of mathematical modeling and engineering design may eliminate freeze-drying's high-cost perception, positioning it as an efficient,

green, and specialized dehydration solution for pharmaceutical liquid formulations and high-value food liquids (e.g., probiotic suspensions, fruit juice concentrates, and functional peptide emulsions). This optimized liquid freeze-drying technology will provide robust technical support for the large-scale production of nanomedicine carriers and high-value functional foods, and drive the sustainable development of the pharmaceutical and high-value food processing industries.

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Disclosure of statement

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Data availability

Data will be made available on request.

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