



## Drying of Biopharmaceuticals: Recent Developments, New Technologies and Future Direction

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The dehydration of biopharmaceutical products through drying provides numerous benefits, including ease of handling and storage, reduction in transportation costs, and improved stability. Typically, the drying of biotherapeutics is accomplished through freeze-drying, however, the removal of water by lyophilization possesses several drawbacks, including lengthy drying times, low energy efficiency, and the high cost of purchasing and maintaining the equipment. Furthermore, freeze-drying is a batch process which may be challenging to adapt and implement with the recent push for continuous manufacturing. These limitations have led to the search for next-generation drying technologies that can be applied to the manufacture of biotherapeutic products. Several alternative drying methods to freeze-drying have been developed and implemented in industries outside of pharmaceuticals, such as food and agriculture, and some are at an advanced state. With the aim of applying lessons learned from technologies in various industries, herein, we review several processing technologies with particular emphasis on the advantages and disadvantages of each in comparison to lyophilization and their potential to be adapted and utilized for drying biotherapeutic compounds.

**Keywords:** Biotherapeutics, freeze-drying, spray drying, stability, continuous manufacture

### 1. Introduction

Biopharmaceuticals or biologics, distinct from small molecule pharmaceuticals, include a wide variety of therapeutic products derived from living organisms or produced using biotechnology, *e.g.*, recombinant proteins, vaccines, blood components, cellular therapies, and gene therapies. Following the advent of recombinant DNA technology in the 1970s, the pharmaceutical industry observed a shift in pipeline development from predominantly chemically synthesized drugs towards biologics. The FDA approved the first protein-based biologic (recombinant insulin, Humulin) in 1982 and the first monoclonal antibody (–OKT-3) in 1986 (later withdrawn). Thereafter, there has been continual growth in the number of biopharmaceuticals on the market. The US and EU have seen a combined average of more than 10 new approvals every year since the mid-1990s [1], which is in stark contrast to the total number of approv-

als prior to 1990, which was 9.

As the number of biopharmaceutical approvals and those in development continues to grow, the complexity has also increased. In the late 90's, recombinant proteins and monoclonal antibodies (mAbs) were at the frontline of innovation, offering many challenges associated with stabilizing their highly labile structures. Currently, the industry is faced with manufacturing antibody drug conjugates (ADCs), multi-valent polysaccharide-conjugate vaccines, and gene therapies, to name a few. The challenges associated with manufacturing these compounds are considerably greater, with the formulation scientist and process engineer having to extrapolate his/her basic knowledge of stabilization approaches for proteins to these novel modalities.

Removal of water through drying provides numerous benefits in addition to improved stability, including ease of handling/storage and reduction in transportation costs. These factors are critical in products for which: 1) bulk drug substance (DS) is not converted into drug product (DP) immediately and/or 2) formulation/fill-finish activities and DS manufacture take place at different

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sites. Currently, these challenges are being met by freezing the bulk DS, however this necessitates implementing a robust system (*i.e.*, facility, equipment, validation, etc.) for maintaining the integrity and stability of the DS at low temperature during storage and transport.

All drying techniques share a common objective (*i.e.*, removal of water), however conceptually they are different and may require modifications based on the properties of the compound. The need to preserve high product quality of labile biomolecules and maintain aseptic processing has limited the number of process technology employed in the biopharmaceutical industry. Lyophilization is the most widely acceptable technique for improving the stability of biopharmaceutical compounds and several commercially approved products are available [2]. As such, lyophilization represents the gold standard to which alternative drying methods must be compared.

## 2. Next Generation Drying Technologies

The choice of drying method depends on several factors including the physical properties of the product, application of the product, container closure system, type of energy source available, and scalability requirements. The temperature at which the product is dried is one of the key parameters influencing the quality of the dried product. Typically, higher temperatures will have a negative impact on product quality while decreasing the drying time. Lower drying temperatures, on the other hand, maintain product quality, but require a lengthy drying process. Thus, optimization of the drying temperature and processing time is the most common challenge encountered in developing an efficient drying process. Depending on the energy source and the configuration of the drying system, the parameters to be optimized will differ, as will be described below for select processing techniques. Energy consumption, quality, process yield (recovery), and shelf-life of the dried product are critical parameters assessed during the evaluation of a novel drying technology. The different techniques introduce varying stresses, which may compromise stability [3]. In addition, lessons learned and advances in drying technologies from more mature industries, such as food science, may be adapted to address the unique challenges encountered by the biopharmaceutical industry.

### 2.1 Spray Drying

Several spray dried food powders are commercially

available in the market today, including powdered milk, whey, and egg products. The spray drying process is conceptually simple; a solution is fed through an atomizer to create a spray, which is exposed to a heated gas stream to promote rapid evaporation. When sufficient liquid mass has evaporated, the remaining solid material in the droplet forms particles which are then separated from the gas stream using a filter or a cyclone. Particle formation time is a function of the initial liquid droplet size, the composition of the droplet, and evaporation rate. The rate of particle formation is a key parameter that dictates the required residence time and hence the scale of equipment and processing parameters required to produce the desired particle size at the target production rate. The concept has been implemented over a range of equipment scales from bench units to large multistory commercial drying towers. Exubera® (Nektar/Pfizer) was the first inhaled therapeutic to be successfully manufactured by spray drying [4].

In addition to its ability to control powder properties, the key advantages of spray drying compared to conventional freeze-drying include: (1) shorter process cycle time (*i.e.*, more batches per unit time), (2) scalability (*i.e.*, large batch size per unit, requiring fewer production units), and (3) the ability to process at atmospheric pressure.

Figure 1 shows the drastic difference in the structure and shape of freeze-dried and spray dried mango powders [5]. The spray dried preparations possessed a spherical shape and smooth surface whereas the freeze-dried preparations possessed a skeletal-like structure and were highly porous. The color of the spray dried mango powder was lighter compared to freeze-dried powder, which was due to an additional excipient (maltodextrin) used in the spray dried formulation. Both powders exhibited amorphous properties (*i.e.* no crystalline peak in the X-ray diffraction pattern) with no significant difference in the  $T_g$ . The drying residence time of a few seconds for the spray dried process was significantly shorter than the drying time of the freeze-dried product (>30 hours).

Similar to lyophilization, protein denaturation has been reported during spray drying due to desiccation- and surface-associated stresses, often necessitating the use of excipients for stabilization. Even though the drying gas temperature may exceed 100°C in a typical spray drying condition, thermal denaturation of proteins is commonly not observed, mainly because the temperature of the droplet barely exceeds the wet bulb temperature of

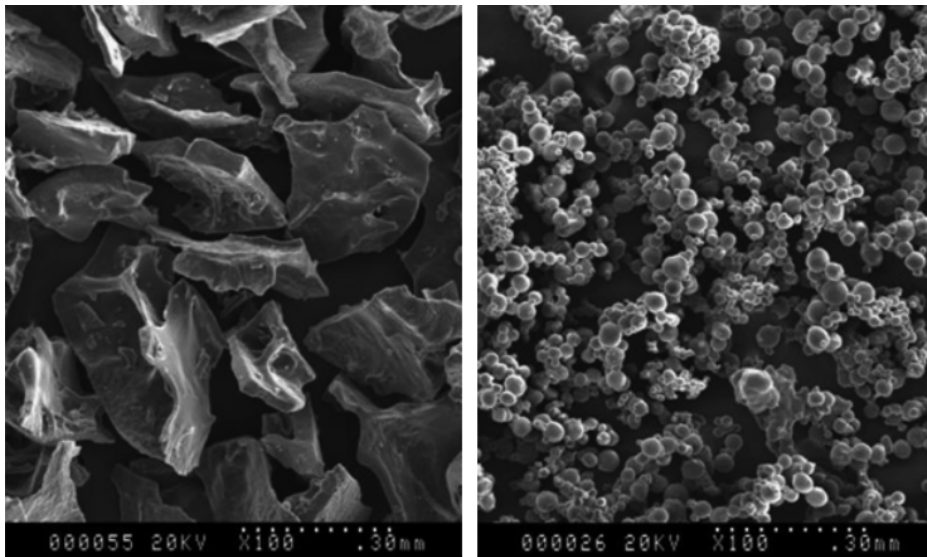


Fig. 1 Scanning electron micrographs (SEM) of freeze-dried (left) and spray dried (right) mango powders (magnification of 100x). Figure from Caparino [5].

water ( $\sim 40^\circ\text{C}$ ). Additionally, the protein denaturation temperature is a function of water content, increasing sharply with decreasing water content. Although one must keep in consideration the risk of prolonged particle exposure to drying gas in the collector vessel, dry proteins are relatively stable, demonstrating denaturation temperatures typically exceeding  $100^\circ\text{C}$  [6].

Feasibility to spray dry sucrose-based mAb formulation was assessed using lab-scale MS-35 (SPX Flow Inc., Elkridge, MD, USA) and bench-top B290 (Büchi, New Castle, DE, USA) spray drying units. Sucrose was maintained at 50 mg/mL and protein concentration was varied between 12.5 to 83 mg/mL for two mAbs, mAb 1 and mAb 2. Process parameters were initially optimized using a placebo formulation and then adjusted throughout the production runs to maintain the desired target outlet temperature. For both mAbs, recovery decreased with increasing sucrose-to-mAb ratio ( $R_{sm}$ ), which may be explained by the decrease in protein surface accumulation and  $T_g$ ; in the case of mAb 1, recovery decreased from 90% to 53% upon increasing  $R_{sm}$  from 0.6 to 4. For reference, the recovery from the bench-top B290 (Büchi) was 62% at 0.6  $R_{sm}$  with much lower throughput (*i.e.*,  $\sim 5$ x lower). Recovery in the absence of a surfactant was greater than that in its presence for both mAbs. In terms of storage stability, no change in % monomer was observed by size-exclusion chromatography (SEC) irrespective of  $R_{sm}$  for mAb 1, mAb 2 formulated at 0.6  $R_{sm}$  did not demonstrate any change in % monomer upon storage at 2–8 $^\circ\text{C}$  for 12 mo. At higher  $R_{sm}$  values, how-

ever,  $\sim 20\%$  decrease in % monomer was observed.

Bowen *et al.* [7] evaluated the feasibility of spray drying several mAbs in a trehalose-based formulation using similar dryers. In the initial study,  $>95\%$  recovery was reported for mAbs processed using MS-35. Similar to the observations for the sucrose-based formulations provided above, much lower recovery ( $\sim 50\%$ ) was achieved using the various bench-top spray drying units. The authors attributed the enhanced recovery for the MS-35 unit to longer residence time (*i.e.*, longer drying time) and greater compatibility with respect to the material of construction (stainless steel vs. glass). In regards to the impact of formulation composition, decrease in recovery was reported as the trehalose-to-mAb ratio ( $R_{tm}$ ) was increased, similarly to the trend observed for the sucrose-based formulations. Comparable change in % monomer was reported for mAb powders immediately following spray drying to those obtained following freeze-drying. Difference was observed upon storage at  $40^\circ\text{C}$ ; the spray dried mAbs demonstrated lower decrease in % monomer compared to the freeze-dried mAbs, although the residual water content was higher for the former. This is a good counter example to the currently-accepted mantra of drier product leads to improved stability. The observation was more substantial at  $R_{tm}$  of 2 than at 0.5. Work by Greiff [8] also suggests the existence of optimal residual water content for influenza virus (1–2%), for which the lowest water content (0.4%) resulted in the worst stability.

In the follow-up study, Gikanga *et al.* [9] evaluated the

feasibility to manufacture the spray dried mAb using a pilot-scale unit (MS-150, SPX Flow Inc.), which is approximately 4 times larger than MS-35. With a throughput of ~50 mL/min, the powder yield was similar to that previously reported (>95%). Increased aggregation (<1% HMWS) was reported following spray drying. Upon storing the powdered mAb at 25°C and 40°C for 6 months and 3 months, respectively, differing stability behavior was reported for the two mAbs, mAb A and mAb B, in comparison to that in their liquid form; liquid formulation of mAb A aggregated faster than the powder counterpart, while the reverse trend was observed for mAb B, providing further evidence that proteins possess different sensitivity to drying stress. Interestingly, when liquid formulations reconstituted from the spray dried powders were compared to the liquid formulations prior to spray drying, their tendency to aggregate/fragment was reported to be similar. It should be noted that all powders were completely dissolved within 3 min at 25 mg/mL protein target. Dani *et al.* [10] also used spray drying to prepare a high-dose human IgG formulation intended for subcutaneous injection. Analyses demonstrated maintenance of the mAb's secondary structure post-processing, and the dry powder mAb was successfully reconstituted at 200 mg/mL without loss of protein monomer content. The powders were reported to reconstitute within a few minutes although the authors noted the solutions to be more turbid than the respective liquid formulations prior to spray drying, which may suggest the presence of insoluble protein aggregates. Furthermore, the activity of mAb formulations post-spray drying was reported to be comparable to those prior to spray drying using an *in vitro* potency assay.

While the examples provided above have been limited to proteins, spray drying has been utilized to successfully prepare a number of dry vaccines, including measles vaccine [11] and tuberculosis vaccine [12]. Spray drying represents the most mature alternative drying technology to lyophilization. The process provides an opportunity to engineer particle size and shape, which can enable delivery methods that are infeasible using other drying techniques. Spray drying can also be accomplished more quickly than lyophilization in most cases. It allows for the processing of material under atmospheric pressure, offering energy savings. Spray drying does come with some unique caveats. Aseptic processing for spray drying is more challenging than it is for lyophilization. Additionally, a secondary drying method may be required if very low residual water content is

desired in the final product, which may reduce the time and energy savings for spray drying as compared to lyophilization. Furthermore, there may be difficulties associated with handling hygroscopic and/or electrostatically charged powders. The fact that material recovery is <100% is also an issue when considering its implementation for high-cost therapeutics. Still, proper process design can overcome many of these limitations, highlighting the great potential of spray drying as an alternative to lyophilization that may enable continuous manufacturing.

## 2.2 Spray Freeze-Drying

Spray freeze-drying (SFD) is a drying process that involves elements of spray drying and freeze-drying. SFD technology has been applied to a range of food products such as whey protein, maltodextrin, coffee, and milk powder [13]. However, applications may be limited to valuable food and pharmaceutical products due to the high fixed and operating costs of the freeze-drying process. The process steps involved in SFD include atomization, rapid freezing, primary drying, and secondary drying. As in spray drying, atomization involves spraying of the liquid drug product. Instead of atomizing into a heated gaseous medium, the liquid feed is atomized directly into a cryogenic medium, in which rapid freezing of droplets takes place to form ice particles. The suspended frozen droplets are collected by sieves, or are collected following evaporation of cryogen. The frozen particles are then transferred to pre-chilled shelves of a lyophilizer for subsequent drying. The principle of drying by ice sublimation for this phase is identical to primary drying in a conventional freeze-drying process. One advantage of SFD is that sublimation and secondary drying of the frozen particles are more rapid than those encountered in conventional freeze-drying due to the increased surface area of the frozen starting material. To date, SFD has been utilized to produce several vaccines [14, 15], solid dispersions [16], and nanoparticles [17]. One particular area in which SFD has demonstrated superiority over spray drying and freeze-drying is in the preparation of dry Alum-containing vaccines [18].

In addition to the usual stresses experienced during freezing and drying, SFD presents additional stresses including those resulting from: 1) the shear forces experienced during atomization and 2) the exposure to the air-water interface, at which potential adsorption, unfolding, and aggregation of proteins may occur [19]. The inclusion of surfactants and lyoprotectants has been

reported to reduce the impact of processing-induced stresses on the stability of several therapeutic SFD proteins similar to conventional freeze-drying. Webb *et al.* [20] evaluated the level of excess recombinant human interferon- $\gamma$  (rhIFN- $\gamma$ ) on the surface of SFD particles using X-ray photoelectron spectroscopy and found the level to decrease 10-fold from 34% to 3.4% upon the inclusion of surfactant (0.12 % Polysorbate 20).

As the use of SFD results in the formation of powders possessing high specific surface area, the technology has also been utilized to promote rapid wetting and faster dissolution of poorly water soluble drugs [21]. Spray freeze-dried skim milk powders were reported to be highly porous and wetted three times faster in comparison to their spray dried counterparts [22]. Several mAb formulations were processed using the spray freeze-dryer at Meridion Technologies (Müllheim, Germany). mAb formulation containing sucrose at 5:2 weight ratio (mAb-to-sucrose) resulted in a free-flowing pellet that was easy to aliquot and re-suspend; very short reconstitution time was achieved (<7 min) even at the target concentration of >200 mg/mL. The impact of annealing on the reconstitution behavior was also investigated by Webb *et al.* [23]; while the annealed lyophilized cakes exhibited slower dissolution compared to the un-annealed cakes (1.3 to 17.7-fold slower, depending on formulation composition), the annealed SFD samples exhibited an increase in dissolution rate compared to the corresponding un-annealed material (1.7 to 4.9-fold higher, depending on formulation composition). For the latter, the authors proposed the annealing-induced decrease in the internal surface area of the porous particles to lead to an increase in their density, thus accelerating powder submersion and dissolution.

Overall, SFD offers several advantages over lyophilization including faster drying times, lower energy consumption during drying, and flexibility during scaling. Difficulties inherent to spray-based processes, as described above for spray drying, will need to be overcome.

### 2.3 Foam Drying

Foam drying is a desiccation process, whereby the solution is converted to a dried foam structure in a single step [24]. The overall method involves boiling, or foaming, of the solution under reduced vapor pressure followed by rapid evaporation, leaving a solidified foam structure. The product appearance is analogous to that for a formulation that has undergone extensive gross/

macro-collapse during freeze-drying [3]. The temperature is carefully controlled to avoid freezing due to evaporative cooling. Excellent vacuum control is crucial for foam drying. In addition to the processing variables, the formulation composition has been reported to affect the foaming efficiency and the subsequent storage stability of the biotherapeutics.

Benefits of foam drying include: 1) the ability to operate at near-ambient temperature, 2) the removal of water at a moderate rate, as the process is completed within hours to days, and 3) the avoidance of ice formation, which has been reported to lead to protein aggregation. Additionally, foam dried materials typically possess lower specific surface areas in comparison to lyophilized materials, which may lead to stability enhancement.

Three recent examples demonstrate the utility of the foam drying method on vaccines that currently require lyophilization to obtain adequate shelf-life. Foam dried Ty21a vaccine was reported to demonstrate stability for longer than 4 and 42 weeks at 37 and 25°C, respectively [25], while Vivotif<sup>TM</sup> (freeze-dried, commercial vaccine) demonstrated stability for 12h and 2 weeks at 37°C and 25°C, respectively [26]. Foam dried *Francisella tularensis* was reported to demonstrate less than 1 log<sub>10</sub> decrease in titer following 12 weeks of storage at 25°C [27] and no loss in activity for at least 12 weeks at 2–8°C. In comparison, lyophilized *F. tularensis* LVS demonstrated >3 log<sub>10</sub> decrease in titer following 12 week of storage under ambient condition [24]. For live attenuated influenza vaccine (LAIV), several stabilization approaches have been attempted, including freeze-drying, spray drying, and foam drying [28]. Storage stability of live attenuated Type-A H1N1 and B-strain influenza vaccines was assessed at 4, 25, and 37°C using a TCID<sub>50</sub> potency assay. Foam dried preparations demonstrated significant improvement in stability compared to those processed by spray drying or freeze-drying (Table 1), while exhibiting low process loss and full retention of immunogenicity.

Abdul-Fattah *et al.* [29] evaluated the stability of a genetically engineered bivalent live attenuated virus vaccine (Medi 534). The loss of viral potency of Medi 534 following various drying processes and subsequent storage stability at 25°C for up to 20 weeks and 37°C for 1 to 2 weeks was reported (Table 2). Freeze-drying Medi 534 resulted in an initial loss in activity of 1.4 log<sub>10</sub> TCID<sub>50</sub>/mL, whereas spray drying and foam drying resulted in an initial loss of 0.8 log<sub>10</sub>. The increased process loss from freeze-drying was associated with greater susceptibility of the vaccine to the ice-water interface (during

Table 1 Comparison of storage stability of H1N1 LAIV processed using freeze-drying, spray drying, and foam drying. Table adapted from Lovalenti *et al.* [28].

Process	Process loss <sup>a</sup>	Rate of titer loss <sup>b</sup>	
		4°C	37°C
Freeze-drying	0.5±0.2	0.028±0.006	0.66±0.12
Spray drying	0.3±0.2	0.014±0.003	0.72±0.09
Foam drying	0.4±0.4	0.006±0.002	0.055±0.011

<sup>a</sup> log TCID<sub>50</sub>/mL<sup>b</sup> log TCID<sub>50</sub>/mL/wkTable 2 Recovery of vaccine after drying and rate of loss of viral potency for storage stability at 25 and 37°C for dried formulations of Medi 534. Table adapted from Abdul-Fattah *et al.* [29].

Process	Process loss <sup>a</sup>	Rate of loss of potency ( <i>k</i> ) <sup>b</sup>	
		25°C	37°C
Freeze-drying	1.4	1.09±0.08	2.65±0.30 <sup>c</sup>
Spray drying	0.8	1.04±0.06	2.76±0.19
Foam drying	0.8	0.73±0.05	2.31±0.19

<sup>a</sup> log TCID<sub>50</sub>/mL<sup>b</sup> log TCID<sub>50</sub>/mL/wk<sup>0.5</sup><sup>c</sup> *k* value was determined from only two time points: initial and 1 week. Beyond 1 week, viral potency in freeze dried preparations dropped below detection limits of the assay.

freezing) compared to the air-water interface encountered during foam drying and spray drying. Foam dried Medi 534 was reported to have a rate of loss of potency of 0.73 log<sub>10</sub> TCID<sub>50</sub>/mL/week<sup>0.5</sup> at 25°C, whereas spray dried and freeze-dried exhibited rates >1 log<sub>10</sub> TCID<sub>50</sub>/mL/week<sup>0.5</sup>. The improved storage stability of foam dried preparations was associated with decreased specific surface area and vaccine surface exposure.

Additional mechanistic understanding of the stabilization effects employed by foam drying has been reported by Abdul-Fattah *et al.* [30]. Foam dried IgG1 mAb preparation with varying levels of sucrose resulted in increased storage stability in comparison to freeze-dried and spray dried preparations. The increased storage stability of the foam dried 1:4 mAb:sucrose formulation was attributed to the significant reduction in specific surface area and total protein surface accumulation. In addition, the foam dried material resulted in the lowest molecular mobility (from global motions and fast dynamics). A reduction in high frequency, local mobility, *i.e.* β-relaxations, had previously been reported to play a key role in protein stability [31]. The increased stability in the 1:4 mAb:sucrose formulation was observed even though it possessed the greatest perturbation in secondary structure. This work highlights the correlation between the stabilization effects of foam drying to surface area and molecular mobility. It is noteworthy that in protein-rich

formulations (4:1 and 2:1 mAb:sucrose), freeze-drying resulted in the poorest storage stability.

Foam drying does introduce its own unique set of stresses not encountered in lyophilization, namely the surface tension stress associated with cavitation. In addition, the rate of water desorption is expected to be slower for foam dried material compared to a similar formulation processed by freeze-drying. Thus, a longer secondary drying process may be required to reduce the residual water content to similar levels as that achieved by freeze-drying, which may potentially negate the energy and time savings associated with foam drying. While decreased secondary drying times can be achieved by increasing the drying temperature, the compound being processed should be kept in mind; for example, cell and virus viability has been reported to be reduced by greater than 90% with the utilization of high temperature secondary drying conditions [32]. Previous examples [29, 32] highlight that increased drying kinetics and reduced residual water content are not always preferred from a product stability standpoint. Foam drying cycle optimization requires an understanding of the effect of drying kinetics and residual water content, as well as distribution, on product stability.

Although much research has been conducted recently on understanding the nature of foaming materials, additional challenges will need to be overcome before foam

drying becomes a robust and scalable drug product process. Even when operating at near-ambient temperatures (15–25°C), evaporative cooling can lead to freezing of the solution and thus product damage. The potential for boil over could also negatively impact container closure, leading to sterility concerns. Additionally, the appearance of foam dried materials is inherently more heterogeneous than that of lyophilized cakes, which may make product characterization and quality control difficult, let alone acceptance by patients and health care professionals. Despite these challenges, its utilization for processing and storage of drug substance intermediate may be a possibility if scalability can be demonstrated.

#### 2.4 Microwave-Assisted Drying

Microwaves are commonplace in everyday use for heating food, however their application at the industrial scale may be unfamiliar to most. Microwave drying is based on the absorption of microwave radiation by water molecules leading to vaporization [33]. One of the main advantages of microwave-assisted drying is the reduction of drying time. This is in part attributed to its unique supply of energy. In microwave drying, heat is supplied volumetrically by high frequency polarization of dipole molecules, in comparison to infrared and convective drying for which energy is supplied to the surface of material. Other notable advantages include efficient energy conversion, improved and more rapid process control, and uniform heating (assuming a uniform distribution of the microwave field) [34]. In recent years, microwave drying has been combined with vacuum- and freeze-drying to obtain food and pharmaceutical products of acceptable quality [35, 36].

Microwave-assisted vacuum drying (MVD) combines the rapid heating, high efficiency, and control of microwave drying with improved efficiency from the lowering of the boiling point of water under vacuum [37]. Figure 2 illustrates the residual water content (% wet basis)-versus-time curves of edamame dried by freeze-drying (FD), hot air drying (AD), MVD, and combined air and microwave vacuum drying (AD + MVD) [38]. The drying time of FD was much longer (greater than 17 hr) than the drying time of MVD. There was not a significant change in the color of MVD samples compared to fresh edamame samples. Compared to fresh samples, a volume change of 82, 71, 68, and 49% was observed after FD, MVD, AD+MVD, and AD, respectively. The rehydration ratio, which is often related to product quality, was the best for FD samples (2.29) followed by MVD (2.14), AD+MVD (2.09), and AD (1.94). A

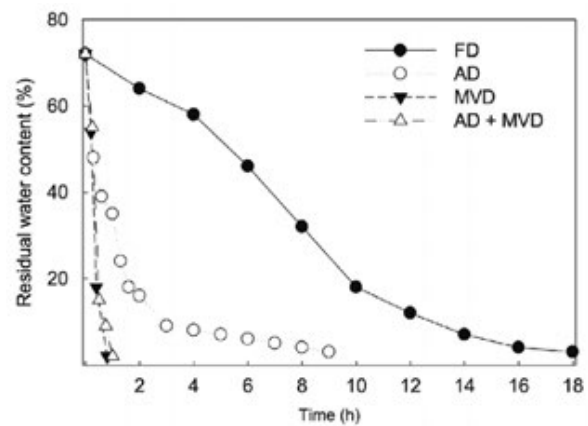


Fig. 2 Drying curves of edamame that has been processed by freeze-drying (FD), air drying (AD), microwave vacuum drying (MVD), and combined air and microwave vacuum drying (AD + MVD). Figure adapted from Qing-guo *et al.* [38].

reduction in the vitamin C and chlorophyll content of the MVD edamame preparations was observed compared to FD preparations. These data demonstrate that drying method can have a significant impact on structure and product quality. Other work has reported that drying under a pulsed microwave vacuum is suitable for the drying of temperature-sensitive products, such as enzymes and proteins [39–41].

Microwave-assisted freeze-drying (MFD) utilizes microwaves as the heat source to enable sublimation in the freeze-drying process [42]. Compared to conventional freeze-drying, MFD has a much greater drying efficiency and reduced energy consumption. The freeze-drying process time of cabbage has been reduced by half utilizing MFD while maintaining similar product quality [43]. Durance *et al.* [44] reported the feasibility to dry a 10% lysozyme solution to 2–5% residual water content with a dehydration time of 27 minutes using MFD. There was no change in the lysozyme enzymatic activity before and after dehydration.

For heat-sensitive products, such as labile biopharmaceuticals, the exposure to microwave radiation may need to be limited. While microwave-assisted drying technologies can provide substantial benefit to reducing drying times, their ability to stabilize biopharmaceuticals without microwave-induced product damage will need to be demonstrated. In addition, significant changes in drying kinetics, as well as potential alterations in the distribution of water, may impact product quality and stability.

### 3. Conclusion

Traditional methods of commercial drying are limited either by their high production costs or significant quality loss due to their exposure to various process-related stresses. Although freeze-drying remains the gold standard for the drying technology used in the pharmaceutical industry, novel technologies are continuously being evaluated. Some of the notable techniques that have been examined include spray drying, spray freeze-drying, foam drying, and microwave-assisted drying. In addition, there are a great number of drying technologies that are available, if not already in use, in the food, agriculture, and textile industries. In addition to microwaves, other alternative energy sources have been utilized, such as infrared radiation [45] and acoustic waves [46]. As the sensitivity of pharmaceuticals is unique to the given compound, the selected drying technique may not be universally applicable. By understanding the drying mechanisms and the unique stresses involved, the drying techniques can be and should be tailored for use (*e.g.*, hybrid drying). Furthermore, for comparing various technologies, it is important to keep in consideration the final water content and the material used; if the % H<sub>2</sub>O values and material properties differ significantly, comparison becomes difficult. For implementation, technical evaluation should include the scalability of the process, energy efficiency, as well as the capability to implement the technique in a GMP environment. Furthermore, financial evaluation, including net present value (NPV), needs to be conducted to fully vet the benefit of implementing the novel technology. There are several unexplored areas for further research, which if addressed appropriately, may dictate the focus and investment strategy for the next-generation drying technology suitable for the pharmaceutical industry.

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### NOMENCLATURE

DP	: Drug product
DS	: Drug substance
$T_g$	: Glass transition temperature, °C
HMWS	: High molecular weight species
TCID <sub>50</sub>	: 50% tissue culture infectious dose
IgG	: Immunoglobulin G
mAb	: Monoclonal antibody
ADC	: Antibody drug conjugate
$R_{sm}$	: Sucrose-to-mAb ratio
$R_{tm}$	: Trehalose-to-mAb ratio
SEC	: Size-exclusion chromatography
SFD	: Spray freeze-drying
rhIFN- $\gamma$	: Recombinant human interferon-gamma
Ty21a	: <i>Salmonella typhi</i> Ty21a
LAIV	: Live attenuated influenza vaccine
MVD	: Microwave-assisted vacuum drying
FD	: Freeze-drying
AD	: Hot air drying
MFD	: Microwave-assisted freeze-drying
GMP	: Good manufacturing practice
NPV	: Net present value

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◇◇◇◇ 和文要約 ◇◇◇◇

## バイオ医薬品の乾燥：近年の進歩および新技術開発と今後の展望

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ほとんどのバイオ医薬品は水分を多く含み、その量が 80%w/w を超えるものも少なくない。そのため乾燥プロセスを用いた水の除去は、製品の取り扱いを容易するだけでなく、運送コストの低減、保存安定性の向上など、数々の利点をもたらす。一般的に、バイオ医薬品の生産工程での乾燥は、ほとんどが凍結乾燥法で行われているが、この方法には生産コスト高、乾燥時間が長い、エネルギー効率が低いなどの欠点がある。バイオ医薬品の乾燥技術としては、現在も凍結乾燥が

信頼性の高い標準法であるが、凍結乾燥がもつ課題を克服するための、代替となる新しい乾燥技術の開発と評価が進んでいる。これらの乾燥技術には共通の目的（脱水和）があるものの、エネルギー効率や乾燥対象物に与える影響が異なるため、その特性に合わせた選択と最適化が必要となる。この総説では、種々の新しい乾燥法の長所と欠点を凍結乾燥法と比較して考察し、これらの技術をバイオ医薬品の乾燥に応用する可能性を論じた。

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