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REVIEW

Next-Generation Drying Technologies for Pharmaceutical Applications

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ABSTRACT: Drying is a commonly used technique for improving the product stability of biotherapeutics. Typically, drying is accomplished through freeze-drying, as evidenced by the availability of several lyophilized products on the market. There are, however, a number of drawbacks to lyophilization, including the lengthy process time required for drying, low energy efficiency, high cost of purchasing and maintaining the equipment, and sensitivity of the product to freezing and various other processing-related stresses. These limitations have led to the search for next-generation drying methods that can be applied to biotherapeutics. Several alternative drying methods are reviewed herein, with particular emphasis on methods that are commonly employed outside of the biopharmaceutical industry including spray drying, convective drying, vacuum drying, microwave drying, and combinations thereof. Although some of the technologies have already been implemented for processing biotherapeutics, others are still at an early stage of feasibility assessment. An overview of each method is presented, detailing the comparison to lyophilization, examining the advantages and disadvantages of each technology, and evaluating the potential of each to be utilized for drying biotherapeutic products. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: drying; dehydration; freeze-drying; hybrid drying; spray drying; foam drying; processing; supercritical fluids; microwave; proteins

INTRODUCTION

Most biological materials contain high water content (typically ≥80%, w/w). Removal of water through drying provides numerous benefits, including ease of handling and storage, reduction in transportation costs, and improved stability, to name a few. Although all drying techniques share a common objective (i.e., dehydration), conceptually they are different and require modification/adaptation based on the properties of the compound.

Prior to discussing the various drying technologies, the process of drying will be described in general terms. In order to convert a solution or suspension into a dry powder or cake, water must be removed. Applying heat during drying through conduction, convection, and/or radiation are the basic techniques utilized to vaporize water (Fig. 1). In addition, forced air or vacuum may be applied to enhance the rate of dehydration. The choice of drying method depends on several factors including the physical properties of the product, application of the product, type of energy source available, container closure system, and scalability of the equipment. For high value products, as is often the case with pharmaceuticals, the cost of the raw ingredient may be the primary driver that dictates the selection of the processing method, as low yield or product recovery less than 100% may not be acceptable. Energy consumption, quality, and shelf-life of the dried product are also critical parameters assessed during the evaluation of a novel drying technology. The different techniques introduce varying stresses, which may compromise stability. Furthermore, the techniques can produce dry materials possessing significantly different characteristics.[1,2]

Freeze-drying, or lyophilization, is the most widely used technique for improving the stability of biopharmaceutical compounds. In the book by Rey and May,[3] a primitive form of lyophilization is described as having been employed centuries ago by the Inca to dry frozen meat through the application of heat (radiation from the sun) and low pressure (high altitude of the Altiplano). For a detailed description of the lyophilization process, the reader is referred to the following reviews.[4–6] Several commercially approved products are manufactured by freeze-drying.[7] As such, lyophilization represents the gold standard to which alternative drying methods must be compared. Lyophilization, however, suffers from a number of shortcomings that limit its utility. Such limitations can be addressed through modification of the process or equipment setup, as will be discussed below, or through the use of alternative drying methods.

The majority of pharmaceutical compounds are susceptible to stresses that develop during freezing and drying. A combination of rational formulation design and process development can reduce degradation during lyophilization.[5,6] Even with proper design, freeze-drying processing times can be lengthy (on the order of days),[5] and in the case of poorly designed formulations and processes, the cycle durations can be unusually long (weeks). Rational formulation and cycle design, in

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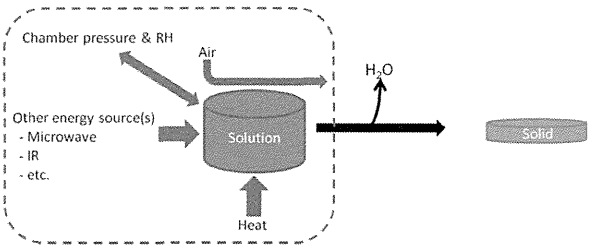

Figure 1. Illustration of a generic drying process. The energy supplied to the solution or suspension can come in a variety of forms (heat, microwave, IR, etc.); other environmental conditions can also be imposed (i.e., convection, vacuum, lowered RH, etc.) to enhance the drying process.

place of traditionally employed empirical approaches, can be utilized to design a lyophilization process of suitable duration. Still, freeze-drying remains a complex problem of coupled heat and mass transfer. Typically, the primary drying stage is the longest step of lyophilization; an analysis of the energy balance for lyophilization in vials demonstrated that most of the energy losses were associated with the primary drying step followed by losses associated with the condenser and the vacuum system.[8] Ultimately, energy losses lead to reduced efficiency. Alexeenko[9] determined that the efficiency of fully loaded laboratory and production-scale lyophilizers ranged from 1.5% to 2%, for which efficiency is defined as the ratio of the product of the sublimation enthalpy and rate, to the power input into a lyophilization process. In addition, it should be noted that the fundamental design of a lyophilizer has not evolved significantly[10] even though there have been several key advancements in the development of tools to monitor the freeze-drying process.[11] The design of the drying chamber and the configuration and geometry of the duct, which connects the drying chamber to the condenser of the lyophilizer, influence the vapor flow during the drying process.[10] Formulations undergoing freeze-drying can be sensitive to deviations in temperature and chamber pressure, which may be exacerbated in a lyophilizer with poor temperature and chamber pressure control, thereby leading to additional losses in process efficiency as well as poor product appearance and quality attributes. Furthermore, the high costs of purchasing and maintaining a freeze-drying equipment contribute to the final cost of a freeze-dried product.

NEXT-GENERATION DRYING TECHNOLOGIES

Traditional methods of commercial drying are limited either by their high production costs (e.g., dehydration by sublimation under vacuum) or high quality loss due to the long exposure time of the product to high temperature (e.g., solar drying or drying by hot air). The temperature at which a 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. In addition, the greater the deviation of the processing temperature from ambient, the greater the energy consumption. Thus, finding the optimum drying temperature is the most common problem

Table 1. Summary Table of Various Drying Technologies with Applications and References

Drying technique	Applications
Foam drying	Monoclonal antibodies,[1] vaccines[13–19]
Supercritical fluid drying	Proteins,[20–24] metal composite,[25] aerogel,[26,27] polymers[28]
Convective drying	Yeast,[29] probiotics,[30] proteins,[31,32] antibodies,[33] enzymes,[34] platelets,[35] fish,[36] fruit[37]
Vacuum drying	Probiotics,[38–40] food,[41–44] enzymes[45,46]
Microwave drying[a]	Food,[47–51] enzymes,[52] yeast,[53] pharmaceuticals,[54–56] biopharmaceuticals,[57] polymers[58]
Acoustic drying	Food,[59–62] lumber,[63] coal,[64] waste treatment[65]
Infrared drying	Food,[66–69] polymer film[70]
Osmotic drying	Food[71–75]
Ohmic heating	Food,[76–78] waste treatment[79]
Spouted bed drying	Food,[80,81] blood plasma,[82] yeast,[83] pharmaceutical powders,[84] probiotics[85]
Fluidized bed drying	Yeast,[86] food,[87] sludge waste,[88] chemicals,[89] microspheres,[90] pharmaceutical tablets[91,92]

[a]Includes microwave drying, microwave vacuum drying, and microwave freeze-drying (both atmospheric and vacuum).

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.

The focus of the current review is drying methods that offer an alternative to lyophilization. First, modifications to a typical freeze-drying process (e.g., bulk freeze-drying and foam drying) will be described. Next, spray drying will be reviewed, with the theory behind the process, its application, and recent developments examined in detail. Spray drying is currently used for the production of dry powder across a wide range of applications in the food, chemical, and pharmaceutical industries,[12] and as such represents the most mature alternative technology to lyophilization. Following the description of spray drying, supercritical fluid (SCF) drying technologies will be reviewed as these drying methods have been tested with biologics. Finally, other methods of drying, such as vacuum, osmotic, fluidized bed, ohmic, microwave, and combinations thereof will be reviewed. These drying methods are common in other industries (Table 1), but currently of limited use with biopharmaceuticals. Advantages and disadvantages of each drying method will be presented, with emphasis on how the techniques compare to lyophilization and potential barriers to their implementation in the pharmaceutical industry.

MODIFICATIONS TO FREEZE-DRYING

There has been an increased emphasis on replacing the traditional trial-and-error-based approaches with rational formulation and process design for lyophilized pharmaceuticals.[4] In addition, the technologies to control and characterize the freeze-drying process have advanced significantly. The characteristics of the frozen matrix (number and size of ice crystals) depend on the ice nucleation temperature, or the degree of supercooling, an attribute which, until recently, could not be controlled adequately due to the stochastic nature of the freezing process.[93] Since ice nucleation occurs at different

temperatures within the vials undergoing freezing, heterogeneity in drying is unavoidable. In a Class 100, Good Manufacturing Practices (GMP) production environment, the degree of supercooling is higher (i.e., the ice nucleation temperatures are lower) in comparison to freezing conducted at laboratory scale in a typical non-GMP environment.[5] Consequently, the ice crystals are smaller, which leads to higher product (i.e., cake) resistances during drying and a longer primary drying process during manufacturing. The inclusion of an annealing step (post freezing and prior to initiating drying) promotes growth of ice crystals through Ostwald ripening and could reduce intervial heterogeneity during primary drying.[94] Unfortunately, annealing can also facilitate the crystallization of buffer components and phase separation in polymer solutions or protein–sugar systems, which can lead to instability during freeze-drying. A suitable alternative to annealing during lyophilization is the use of controlled ice nucleation-based approaches. Several methods to induce and control ice nucleation have been developed and refined in the past decade. These include the use of agitation,[95] electric current,[96] ice fog,[97,98] pressurization–depressurization,[99] ultrasound,[100–102] and vacuum.[103,104] Both ice fog- and pressurization–depressurization-induced freezing systems are available for use in laboratory and commercial lyophilizers, and appear to be the most promising methods in comparison to the other approaches proposed for ice nucleation. Key advantages of controlled ice nucleation include: formation of larger ice crystals during freezing that facilitate faster ice sublimation, larger pores within the cake, and more homogeneous drying behavior. Recently, Geidobler et al.[105] observed a reduction in the reconstitution time from 15 to 5 min of cakes containing a highly concentrated freeze-dried monoclonal antibody (161.2 mg/mL) and trehalose (10%, w/v). They suggested the role of improved wetting and displacement of gas from the larger pores in cakes, generated using controlled ice nucleation, as the main cause. There have also been efforts to increase the ice sublimation rates by drying at higher temperatures, either close to or above the temperature of collapse (T_c).[106,107] At temperatures slightly above the T_c, the pore structure may remain intact, but is accompanied by the appearance of small holes in the walls of the pores as a consequence of limited viscous flow of the formulation. In this scenario, described as micro-collapse, the tortuosity of the path decreases, enabling a greater mass transport, and thus faster sublimation. Several reports document lyophilization accompanied by micro-collapse at temperatures up to 15°C greater than the T_g' of protein formulations (>20 mg/mL).[106,108–110] It is proposed that the freeze-concentrate of protein formulations is highly viscous and thereby has only limited mobility, which avoids visible collapse even if drying is performed at temperatures above the T_g'. Such aggressive drying cycles have been effectively employed to reduce the drying time by a factor of two in comparison to the conservative drying conducted at temperatures below the T_c.[106,110] There appeared to be no significant impact on protein stability as long as the residual water content in the product remained low, thus proving the usefulness of this strategy.

Several reports have described approaches and technologies to improve the drying rate and production quality of freeze-drying. Recently, Ganguly et al.[10] presented a simulation framework that enabled quantification of the impact of lyophilizer design at the commercial scale on drying rates and product temperature. Upon modifying the design of the dryer to include a combined valve–baffle system (instead of only a valve as in a traditionally designed dryer), the vapor flow rate was reported to increase by a factor of 2.2. Additional minor modifications, including the relocation of the baffle further downstream into the condenser, increased the vapor flow rate by 54%. The work demonstrated that changes in the dryer design could increase drying rates, decrease cycle duration, and enhance efficiency. Furthermore, a combination of computational fluid dynamics with system-level, non-steady-state heat and mass transfer model enabled the prediction of dynamic process parameters for dryers of different configurations.[10] In another report, Xu et al.[111] investigated the ultrasound pretreatment on edamame prior to freeze-drying and have reported the formation of finer ice crystals and reduction of crystallization time. Woo and Mujumdar[112] provided a review on the application of electric or magnetic field to affect the freezing characteristics of water; application of DC and AC fields were reported to confer opposite effects on inducing nucleation (enhancement and delay, respectively), whereas the application of magnetic field has been reported to result in the generation of smaller ice crystal size distribution and delayed nucleation. Although the application of ultrasound, electric, and magnetic fields may be useful in controlling the freezing process, their effects on the stability of labile biologicals have not yet been thoroughly examined. Cui et al.[113] reported on the application of microwave during freeze-drying process of carrot and apple crisps and demonstrated reduction in processing time by nearly 50% of that required for lyophilization to produce samples of comparable quality and residual water content. Several combination drying techniques with examples of their application will be reviewed below.

Bulk Freeze-Drying

Pharmaceutical freeze-drying is performed within a confined container (cartridge, syringe, or vial), which ensures sterility of the final dried product, but limits the amount of material that can be processed. Bulk freeze-drying is typically employed when either large amounts of material are needed or the dried material is subjected to additional processing steps following completion of drying; for example, the production of process intermediates that are not required to be sterile. Bulk drying can be performed in open metal trays (fabricated from stainless steel, aluminum, anodized aluminum, or alloys), although this does present risks of contamination of the equipment and product flyoff during processing, in addition to the potential increase in the cleaning time post-drying.[114] The LYOGUARD® Freeze-Dry tray is an alternative to drying using open metal trays. The tray comprises a polypropylene frame sealed at the bottom with a thin, transparent, flexible polypropylene film and closed at the top with a semipermeable GORE-TEX®-expanded polytetrafluoroethylene laminate specifically developed for lyophilization. The top of the tray is equipped with a fill port and a liquid-tight, screw-tight cap to enable filling, sealing, and unloading of the tray. Although water uptake can be of concern with materials dried in open trays, the inclusion of a semipermeable membrane and a screw-tight cap in LYOGUARD® presents a barrier and holds the dried material in a confined environment.

Several reports describe the combination of spray freezing with dynamic bulk freeze-drying at atmospheric[115] or reduced pressure.[116] Droplets of the formulation to be dried are generated by spraying or atomizing the liquid, directly into a

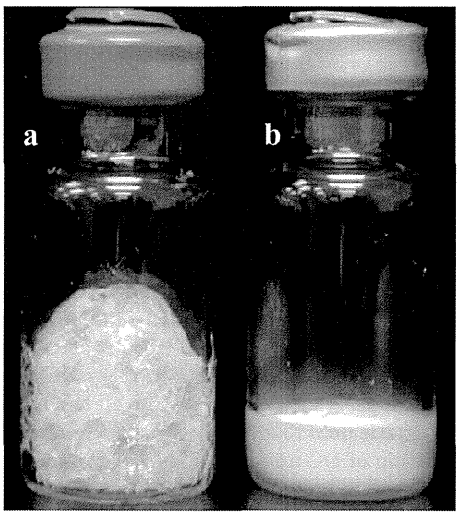

Figure 2. Appearance comparison of a (a) foam dried sample to (b) freeze-dried sample. Sample consists of Ty21a in 25% sucrose and 25 mM potassium phosphate. Figure adapted from Ohtake et al.[17]

cryogenic medium (liquid nitrogen) to freeze the droplets. Freezing in liquid nitrogen results in a high degree of supercooling and formation of smaller ice crystals. The frozen pellets are then transferred to either prechilled shelves of a lyophilizer (for drying in trays) or to a rotating vacuum lyophilizer (continuous process). In the latter case, ice sublimation occurs via heat transfer through radiation and temperature-controlled surfaces. The rotational movement ensures uniform heat and mass transfer, thereby improving product homogeneity and increasing the drying rates in comparison to those achievable by conventional freeze-drying. Coupling between atomization and rapid freezing significantly influences the morphology of the dried product. Typically, non-hollow spherical particles with high internal porosity[117] and high specific surface area[118] are generated from a spray freeze-drying (SFD) process (see more in section *Spray Freeze-Drying*).

Foam Drying

Foam drying is a desiccation process, whereby the solution is converted to a dried foam structure in a single step. The overall method involves boiling, or foaming, of the solution under reduced vapor pressure followed by rapid evaporation, leaving a solidified foam structure (Fig. 2). The temperature is carefully controlled to avoid freezing due to evaporative cooling. The process can be thought of as a freeze-drying method conducted under a cake collapse condition.

Excellent vacuum control is crucial for foam drying.[16,17] For processing methods in which the system pressure is decreased too quickly, the solution has a greater tendency to freeze and will not foam effectively. Conversely, foaming will be inhibited by decreasing the pressure too slowly, as the concentration and viscosity of the remaining solution will increase. By decreasing the chamber pressure stepwise, while allowing for a short equilibration period, the process-associated loss can be minimized significantly.[17] In addition to the processing variables, the formulation composition has been reported to affect the foaming efficiency and the subsequent storage stability of the labile biological. Effective formulation composition is similar to that used in freeze-drying, including sugars, polyols, polymers, and surfactants, as can be inferred from the references pertaining to the following examples.

For parainfluenza virus stored at 25°C for 20 weeks, foam drying outperformed spray drying and freeze-drying by demonstrating 0.73 log/week$^{0.5}$ loss in titer, whereas the other two processes demonstrated greater than 1 log/week$^{0.5}$ decrease in titer.[15] The foam dried *Francisella tularensis* was reported to demonstrate less than 1 $\log_{10}$ decrease in titer following 12 weeks of storage at 25°C,[16] and no loss in activity for at least 12 weeks under refrigerated condition (2–8°C). In comparison, lyophilized *F. tularensis* LVS demonstrated >3 $\log_{10}$ decrease in titer following 12 weeks of storage under ambient condition.[119] The foam dried Ty21a vaccine was reported to demonstrate stability for longer than 4 and 42 weeks, at 37°C and 25°C, respectively.[17] In comparison, Vivotif™ (freeze-dried, commercial vaccine) demonstrated stability for 12 h at 37°C and 2 weeks at 25°C.[120,121] Scalability of the process is yet to be demonstrated, but the reported stability of the foam dried material is remarkable.

Benefits of foam drying include the ability to operate at near-ambient temperature (i.e., 15–25°C).[1,15] This reduces energy consumption compared to the processes that require either low or high temperature for drying, allowing for a more economical process and reduced stress on the material. In addition, foam drying removes water at a moderate rate, as the process is completed within hours to days. Foam drying avoids the formation of ice, which may lead to protein aggregation.[16] Additionally, foam dried materials typically possess lower specific surface areas in comparison to lyophilized materials, which may lead to stability enhancement.[16] With respect to aseptic processing, the challenges encountered in foam drying are similar to those in freeze-drying. 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 with a similar formulation processed by freeze-drying, due to the lower specific surface area of the former.[15] 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. Furthermore, vacuum levels must be optimized so that foaming is effective. Freezing of the solution or rapid boiling, which may cause material to escape from the vial, must be avoided through the choice of appropriate vacuum conditions that may be challenging at scale. The potential for boil over could also negatively impact container closure, leading to sterility concerns. Although much research has been conducted recently on understanding the nature of foaming materials,[122,123] significant process development is still required to ensure a robust process. Additionally, the appearance of foam dried materials is inherently more heterogeneous than that of lyophilized cakes (Fig. 2), which may make product characterization and quality control difficult, let alone acceptance by patients and health care professionals. Hence, foam drying faces a number of significant barriers that may be difficult to overcome prior to its implementation for manufacturing a drug product. Its utilization for processing and storage of drug substance intermediate, however, may be a possibility if scalability can be demonstrated.

SPRAY DRYING

Introduction

Spray drying provides control of particle properties such as crystallinity, particle size, residual water content, bulk density, and morphology.[124] In the pharmaceutical industry, the process was first applied as an intermediate processing step for the production of solid dosage forms. Exubera® (Nektar/Pfizer) is the first inhaled therapeutic that has been successfully manufactured by spray drying.[125] Spray drying is also being evaluated as an alternative to freeze-drying for stabilization of biotherapeutics.[126] Similar to freeze-drying, spray drying involves the exposure of pharmaceutical material to various stresses, which will be described in more detail below. Despite these stresses, if an appropriate formulation is selected and processing conditions are optimized, a stable pharmaceutical powder can be produced.[127,128]

Theory

The spray drying process is conceptually simple; a solution is fed through an atomizer to create a spray, which is exposed to a suitable gas stream to promote rapid evaporation. When sufficient liquid mass has evaporated, the remaining solid material in the droplet forms an individual particle, which is 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 evaporation rate is dependent upon the heat and mass transfer of the system. 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. Powder production rates for a typical bench spray dryer are on the order of grams/hour, whereas commercial systems process tons/year. Regardless of the size of the equipment, three fundamental subprocesses occur for a spray drying operation: (1) atomization, (2) droplet drying/particle formation, and (3) particle collection. Each of these will be described in more detail next.

Atomization

The atomization stage produces a spray of droplets possessing a high surface-to-mass ratio. Atomization results from an energy source acting on liquid bulk, and the minimum energy for atomization is that required to create a new liquid–air surface. Resultant forces build up to a point at which liquid breakup occurs and individual spray droplets are created. Insufficient energy transfer during atomization is a problem that is common to all atomization techniques. A key performance parameter for nozzle design is the resulting liquid droplet size distribution. Ideally, a narrow droplet size distribution should be targeted to enable a more uniform drying event and to prevent product loss to the sidewalls of the drying chamber. Droplets of a spray evaporate quickly,[129] and low droplet temperatures are maintained during the drying phase due to evaporative cooling. The final product particle size is controlled predominantly by the initial liquid droplet size and to a lesser extent by the feedstock concentration and the solution-to-particle density ratio. For applications requiring tight control of the final product distribution, this process must start with the appropriate design or selection of an atomizer nozzle.

The impact of nozzle selection propagates into the drying environment by influencing the initial droplet size and trajectory. These initial conditions set the stage for the evaporation process within the drying chamber. Therefore, atomizer design and performance parameters should be considered during the development of a spray drying process to ensure the achievement of target powder properties such as size and density, while minimizing thermal exposure of the active ingredient. Atomizer performance, as a function of solution properties and operating conditions, has been described elsewhere.[12] Of the various types of atomizers available,[12] rotary atomizers and twin-fluid nozzles are the most commonly provided nozzles by commercial spray drying manufacturers for pharmaceutical applications. In rotary atomization, the liquid feed is centrifugally accelerated to high velocity before being discharged into the drying chamber. The atomization energy is provided by the rotational speed of the wheel, and the droplet size decreases with increasing rotational speed. Twin-fluid nozzles utilize a high speed gas stream, typically air, to blast the liquid into droplets. A variety of twin-fluid designs exist with the distinction being the geometry, which controls the gas and liquid interaction, and subsequent droplet size distribution. Twin-fluid nozzles produce smaller droplets with a broader distribution in comparison to rotary atomizers, and are therefore preferred for applications targeting smaller particle size. During the selection process of a nozzle from the various types of atomizers available, consideration must be given to the design that economically produces the most favorable spray characteristics as well as throughput for a given set of operational conditions.

Particle Formation

The evaporation of volatiles (usually water) from a spray involves simultaneous heat and mass transfer, the rate of which depends on temperature, humidity, and transport properties of the gas surrounding each droplet. It is also a function of droplet diameter and relative velocity between droplet and gas. For single droplet evaporation, the evaporation rate (κ) can be approximated as

$$\kappa = 8D_g \frac{\rho_g}{\rho_l}(Y_s(T_e) - Y) \quad (1)$$

where D_g is the diffusion coefficient of the gas phase, ρ_g and ρ_l are the density of the gas and liquid phases, respectively, Y_s is the mass fraction of solvent at the surface of the droplet, which is a function of T_e, the equilibrium temperature of the droplet, and Y_∞ is the mass fraction of solvent far from the surface. For a more detailed description of the evaporation rate, the reader is referred to the work of Vehring.[124]

The particle formation process involves the conversion of the atomized spray droplets into solid particles. First, the droplets must adjust to the temperature of the environment near the nozzle. The type of atomizer will have an impact on the droplet temperature profile, as described above. The next stage involves the constant rate drying period of the carrier solvent, during which the evaporation rate will be driven by the net balance between the heat transfer to the droplet and the energy removed due to evaporative cooling.[12] During the constant rate period, the liquid droplet will experience a temperature close to the thermodynamic wet bulb value, which will be significantly

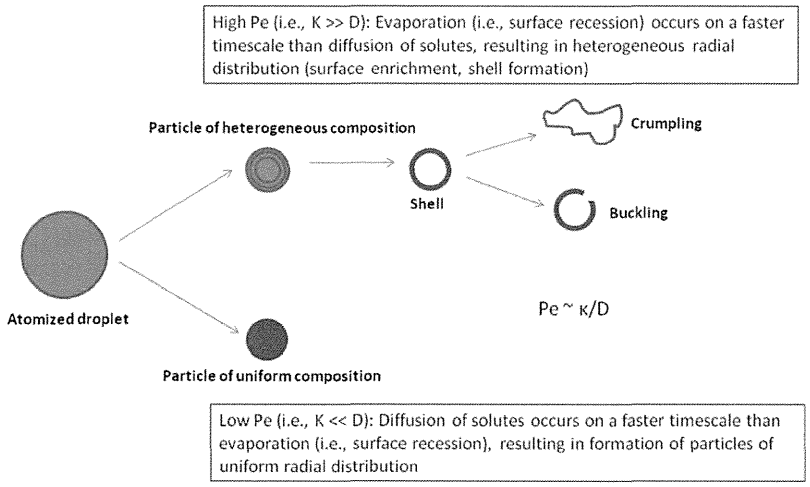

Figure 3. Illustration of particle formation process and impact of Peclet number (*Pe*). Figure adapted from Vehring.[125]

below the local drying gas temperature.[130] The final stage of particle formation occurs following the evaporation of a portion of the solvent carrier. The solid content within the droplet influences the evaporation rate of the solvent into the gas medium. Typically, this reduces the mass transfer rate for the remaining solvent, and thus this stage is commonly referred to as the "falling rate period."[12] At this point, as the solute concentration reaches its solubility, the droplet surface starts to solidify, resulting in shell formation (Fig. 3). This creates an internal droplet diffusion-controlled mass transfer process, which slows the rate of solvent escape from the inner core to the surface prior to evaporation.[131,132]

For products in which low residual water content is critical, the outlet relative humidity (RH) will effectively determine the powder production rate for a given dryer outlet temperature. The manner in which the spray combines with the drying gas dictates the rate and extent of drying. Drying chamber and gas disperser design must create a flow pattern that prevents the deposition of partially dried product on the wall. Retention of product on the chamber wall is undesirable, as it affects product quality, reduces product yield, and contributes to more frequent shutdown of the dryer for cleaning.

Particle Collection

Completion of the particle formation process in the spray dryer creates a dispersed particulate aerosol, from which the solid material needs to be separated from the process gas stream. One of two different methods is typically used for product capture in a pharmaceutical spray drying process; cyclone separation or baghouse filtration. Each approach offers distinct advantages for efficient recovery of high-value pharmaceuticals.

The cyclone, or inertial separation method, is the most commonly used industrial approach for segregating a dispersed phase from a continuous medium. The principal of separation is based upon the density difference between particle and gas. Cyclone separation efficiency is dependent upon the cyclone design, operating conditions, and the particle size distribution of the incoming material, to name a few. The nature of inertial separation-based technologies impose the limitation that larger and more dense particles will be readily separated from the gas phase, and thus obtain higher collection yields compared with smaller, less dense particles. Therefore, this method of particle collection can alter the resulting particle size distribution.

Baghouse filtration utilizes filters to collect dried particles while allowing the drying gas to pass through. The selection of an appropriate filter is critical as baghouse filtration has the capability to collect very fine particles that cannot be recovered using an inertial separator. The composition of the filter must be compatible with the application and robust enough to withstand the temperatures and humidity levels employed in spray drying.[133] Although cake formation on the filter surface is beneficial in many baghouse separations, it does not always have a positive impact on spray drying applications. Should a problem arise during processing, moist particles could agglomerate on the cake at the filter surface causing increased backpressure and requiring extensive cleaning.[133] Additionally, prolonged contact with the filter surface may lead to extended exposure of the product to high temperatures, which could negatively impact product quality.[133]

Application

The basic theory of spray drying is well understood and enables excellent control of the critical parameters that affect product attributes. Judging by the number of publications, one can conclude that spray drying is a process that meets the demand of sophisticated pharmaceutical systems through an efficient, one-step process that may enable continuous manufacturing. Spray drying has seen increasing utilization as a process to stabilize biologics, as will be described below. In addition to its ability to control powder properties (e.g., particle size, particle morphology, powder density, and surface composition), the key advantages of spray drying as compared with conventional freeze-drying are: (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. As can be inferred from the following examples, the application of spray drying to the various aspects of pharmaceutical product development is expected to continue its growth, although there are certain areas that still require further development. Table 2 lists areas of current interest and new applications.

Table 2. Various Applications of the Spray Drying Process in the Pharmaceutical Industry

Application	Reference
Vaccines	128,134–141
Antibodies	142–147
Inhalation therapeutics	125,148–153
Spray freeze-drying	154–162
Particle engineering	163–168
Coating and encapsulation	169–176

Particle Engineering

Many particle parameters affect powder dispersibility; frequently mentioned are size distribution, density, morphology, surface roughness, and surface hydrophobicity. The traditional approach to improving the dispersibility of cohesive powders is to blend them with carrier particles that modify the interparticle forces. Various amino acids and chitosan have been suggested for this purpose.[177,178] For example, spray dried leucine and tri-leucine have been reported to form hollow, low density particles[163,164] (Fig. 4a). In fact, this particle design concept has been utilized to improve the dispersibility of, or encapsulate a variety of, active pharmaceutical ingredients and vaccines, including disodium cromoglycate[165] and bacillus Calmette-Guerin vaccine.[134]

Shell formation will occur if one of the formulation components reaches its solubility and precipitates (Fig. 3). Low aqueous solubility components have the tendency to precipitate early in the drying process as their solubility is reached quickly, resulting in the formation of corrugated particles. In contrast, highly water-soluble components remain in solution as the liquid droplet dries, resulting in the formation of smooth, spherical particles. In addition, surface activity may lead to preferential adsorption of components on the droplet surface, causing a diffusional flux toward the surface. On the other hand, as the evaporating droplet shrinks, its receding droplet surface leads to increasing solute concentrations at the surface. This causes a diffusional flux away from the surface. Slowly diffusing components can become enriched at the particle surface if recession of the air–liquid interface of the droplet is faster than the diffusion of the component from the surface. The Peclet number, *Pe*, provides a measure of the evaporation rate relative to diffusive motion. It is defined as

$$Pe = \frac{\kappa}{8D} \tag{2}$$

where D is the diffusion coefficient of the solute. As each solute component has a distinct diffusion coefficient, each component has a distinct Peclet number for a given evaporation rate. Large values of *Pe* indicate the component diffuses slower than the recession of droplet surface, whereas small values of *Pe* indicate the component diffuses faster than the recession of the droplet surface (Fig. 3).

Quite often, the shell is likely to be deformed by stress due to the pressure differential and changes in material properties caused by desiccation and/or phase transformations.[179] This period of the particle formation process determines whether a dry particle remains a hollow sphere, forms dimples, or folds on itself, and is a critical area of focus in particle engineering (Fig. 3). The key to successful particle engineering is the control of mechanisms that determine the radial distribution of components during the drying process. Early shell formation can be intentionally forced by selecting high initial saturation, high Peclet number, or a combination of both for the shell forming component (Fig. 4b). Which shell former dominates the particle formation process depends on their characteristic times to

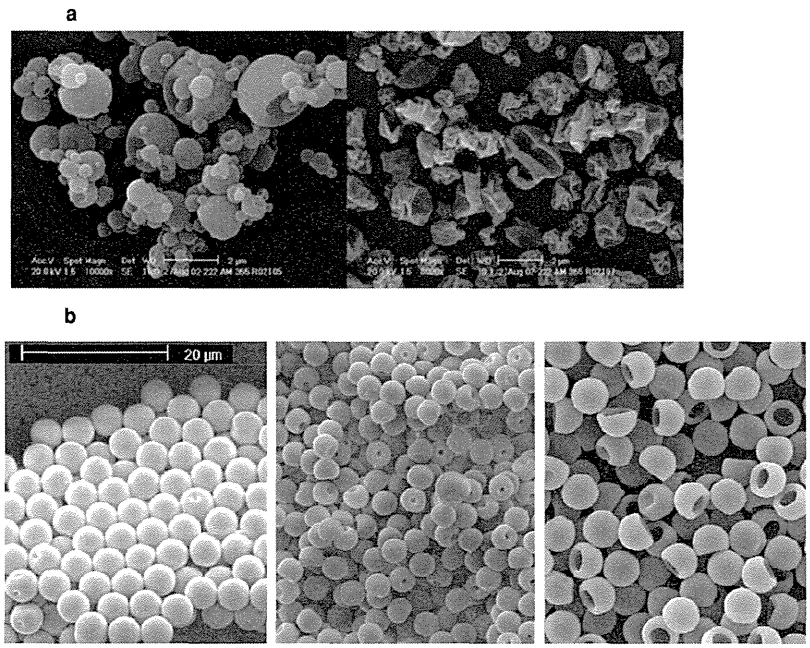

Figure 4. SEM images of various types of particles formed by spray drying. (a) Gentamicin without (left panel) and with 15% trileucine (right panel),[164] (b) glycoprotein particles produced at *Pe* numbers of 2.7, 5.6, and 16.8 (left to right panel).[125] Figures adapted from the references provided.

reach a critical surface concentration and their interactions. For a detailed consideration of Peclet number in particle engineering, the reader is referred to the work by Vehring.[179]

Spray Dried Powders for Inhalation

Systemic drug delivery using the pulmonary approach must target the deep lung region, which requires the use of very small particles ranging in aerodynamic size from 1 to 3 μm. If the particles are too large, they will deposit in the upper airway at which absorption is poor. If they are too small, they will stay suspended in air and be exhaled. Therefore, control of the particle size distribution is critical to achieve an efficient and reproducible pulmonary deposition.[180]

The first pharmaceutical product targeting systemic treatment through the pulmonary route was inhaled insulin, Exubera®.[125] It contains 60% recombinant human insulin formulated with sodium citrate, glycine, and mannitol.[181] This dry powder-based delivery system utilized spray drying to create homogeneous particles that were engineered to disperse using a handheld delivery device. Numerous physicochemical attributes were optimized to manufacture the powder for inhalation, including particle size, stability (both physical and chemical), and aerosol dispersibility. In pharmaceutical dry powder applications, the ability to disperse the powder into individual particles is critical. In general, as particle size is reduced, dispersion becomes difficult as a result of shift in balance between interparticle cohesive forces and drag forces.[182] Residual water content can also affect powder dispersion and powder flow characteristics,[183] highlighting the importance of achieving the targeted residual water content as well as the use of an effective container closure system to eliminate water uptake.

Stabilization of Biologics

Similar to lyophilization, protein denaturation has been observed during spray drying due to the dehydration-associated stress, often necessitating the use of excipients for stabilization.[184,185] Even though the drying gas temperature may exceed 100°C in normal spray drying conditions, thermal denaturation of proteins is typically not observed, mainly because the temperature of the droplet barely exceeds the wet bulb temperature of water (~40°C). Additionally, the protein denaturation temperature is a function of water content, increasing sharply with decreasing water content. Although one must keep in mind the risk of prolonged particle exposure to drying gas in the collector vessel,[186] dry proteins are relatively stable, demonstrating denaturation temperatures typically exceeding 100°C.[187] The components in a particle may separate, due to the differences in diffusion rates and solubilities, and lead to heterogeneous distribution within the particle. Rapid droplet evaporation tends to produce dry particles in which the composition is a function of the radius. Hence, the glass transition temperature is also expected to be different for the core and the shell of a layered particle.[188] Denaturation may occur if the stabilizers separate from the molecule they are designed to stabilize.

Besides the stress caused by thermal dehydration, the protein is subjected to shear stress and exposed to increased air–liquid interface during atomization. Although proteins have been reported to withstand shear rates on the order of magnitude encountered during atomization, significant instability can result if shear stress is combined with the rapid formation of air–liquid interface.[189] For this purpose, surfactants are typically included to stabilize and prevent the formation of insoluble aggregates. The type and amount of surfactant must be carefully selected, as it may unintentionally produce a coat on the particle surface with low glass transition temperature. Such a coat can cause unacceptably high cohesive forces between the particles.[1]

The surface activity of the protein is an important determinant for stability at the air–liquid interface. Proteins may enrich the particle surface as a result of slow diffusivity if the other formulation components are low-molecular-weight (LMW) compounds with high solubility in water. Alternatively, LMW excipients with low aqueous solubility (e.g., leucine, trileucine, etc.), or larger molecular-weight excipients, can be used to control the surface composition/enrichment. Using this concept, spray drying has been employed to engineer particles possessing variable radial composition to effectively "coat" protein particles and to reduce or prevent surface-induced conformational changes of the protein during spray drying.[164,171] Several examples of spray drying applications for mAbs are reported in the literature. Costantino et al.[142] have produced a stable, dry powder recombinant human anti-IgE mAb (rhuMAbE25) formulated using mannitol and various levels of sodium phosphate. Kaye et al.[143,144] have demonstrated the feasibility of spray drying a model antibody intended for nasal and pulmonary delivery. In one case,[144] the antibody was formulated using lactose, poly(lactic-co-glycolic acid) (PLGA), and Dipalmitoylphosphatidylcholine (DPPC), and then spray dried, resulting in nanoparticles that exhibited continuous release of the encapsulated antibody over a 35-day period. The released antibody was demonstrated to be stable and active.

Spray drying can also be used to prepare a high-dose mAb formulation by reconstitution using low diluent volume. Dani et al.[145] demonstrated the use of spray drying in preparing 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.

The majority of commercially available vaccines are stored under refrigerated conditions, if not frozen. Although significant focus and progress have been made to develop new vaccines demonstrating improved safety and efficacy, progress toward the development of thermally stable vaccines appears incremental. In contrast, a review of recent publications reveals a number of promising approaches. Spray drying has been utilized to successfully prepare a number of dry vaccines, including measles vaccine,[128] tuberculosis vaccine,[135] live Newcastle disease vaccine,[136] and hepatitis B antigen,[137] to name a few. The dry powder vaccines can be utilized directly for pulmonary delivery or for mass production to allow for bulk storage. The complexity of vaccines range from proteins, or their fragments, to live attenuated viruses. Further exploration of spray drying methods to prepare stable vaccines is expected.

Spray Freeze-Drying

Spray freeze-drying (SFD) is a drying process that involves elements of spray drying and freeze-drying. The process steps involved in SFD include atomization, rapid freezing, primary drying, and secondary drying. As in spray drying, atomization

involves spraying of a feedstock. 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 after the cryogen has boiled off. The frozen particles are then transferred to prechilled shelves (typically −40°C) of a lyophilizer for subsequent drying. The principle of drying by ice sublimation for this phase of the drying process 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. Key areas of application of spray freeze-dried materials in biopharmaceuticals include microencapsulation in biodegradable polymers, pulmonary delivery, and delivery to the skin via epidermal powder immunization.[190] In addition, SFD has been utilized to produce several vaccines, including anthrax vaccine[156] and influenza whole inactivated virus vaccine,[158] microspheres,[155] solid dispersions,[157] and nanoparticles.[159] One particular area in which SFD has demonstrated superiority over spray drying and freeze-drying is in the preparation of dry Alum-containing vaccines.[160]

Maa et al.[118] observed the formation of larger, porous particles using SFD in comparison to the smaller and denser particles produced by spray drying. Costantino et al.[191] investigated the effect of atomization variables on the size and stability of spray freeze-dried bovine serum albumin particles. An increase in the mass flow ratio (i.e., ratio of the mass of atomization nitrogen gas to the mass of liquid feed) resulted in the formation of more friable (e.g., easy to disintegrate) particles. In addition to the usual stresses experienced during freezing and drying, SFD presents additional stresses to protein-containing formulations. These stresses result from the shear forces experienced during atomization and from the exposure to the air–water interface at which potential adsorption, unfolding, and aggregation of proteins may occur.[190] The inclusion of surfactants and lyoprotectants has been demonstrated to reduce the impact of processing-induced stresses on the stability of several therapeutic spray freeze-dried proteins similar to conventional freeze-drying. Although the inclusion of trehalose (at a protein:sugar ratio of 60:40) has been reported to decrease aggregation during freeze-drying and SFD of rhDNase and rhMAb, the inclusion of polysorbate 20 conferred additional stabilization in comparison with the surfactant-free powders.[192,193] Further, annealing of spray frozen particles at −15°C for 1 h prior to the initiation of drying was reported to decrease the specific surface area and the extent of protein aggregation.[192] An increase in the annealing temperature from −15°C to −5°C was also reported to minimize surface area and reduce protein aggregation. Webb et al.[194] determined the excess protein molecules on the surface of spray freeze-dried recombinant human interferon-gamma (rhIFN-γ) and trehalose powders using X-ray photoelectron spectroscopy. The inclusion of 0.12% polysorbate 20 was reported to reduce the amount of excess protein molecules on the surface to 3.4%, in comparison with 34% excess observed in the absence of surfactant.

As the use of SFD results in the formation of powders prossessing high specific surface area, the technology has also been utilized to promote rapid wetting and faster dissolution of poorly water soluble drugs formulated with polyvinyl alcohol, polyvinylpyrrolidone, poloxamer, and other polymers.[195–197] Hu et al.[198] observed enhancement in wetting (from contact angle measurements) and dissolution rates of spray freeze-dried danazol–poloxamer 407 and carbamazepine–sodium lauryl sulfate particles in comparison to the lyophilized samples or their physical mixtures. Spray freeze-dried skim milk powders were reported to be highly porous and wetted three times faster than their spray dried counterparts.[199] Time-lapse photography demonstrated that the dissolution of the spray freeze-dried particles was accompanied by rapid distintegration into smaller particles upon the entry of water into the pores. In contrast, Webb et al.[200] observed a 55-fold increase in the dissolution rates of lyophilized and unannealed rhIFN-γ, sucrose, and hydroxethyl starch cakes in comparison to the spray freeze-dried and unannealed particles. The impact of annealing on the reconsititution behavior was also investigated. While the annealed lyophilized cakes exhibited slower dissolution compared to the unannealed cakes, the annealed spray freeze-dried samples exhibited a 1.7-fold increase in dissolution rate compared to the corresponding unannealed material. The authors proposed a mechanism operating via a reduction in the surface area of the annealed lyophilized cakes to explain the 18-fold decrease in the dissolution rate in comparison with the unannealed material. In the case of the spray freeze-dried samples, the authors proposed that an annealing-induced decrease in the internal surface area of the porous particles led to an increase in their density, thus accelerating powder submersion and dissolution. In addition, the authors suggested that different mechanisms may be governing the reconstitution of annealed and unannealed lyophilized cakes in comparison to the spray lyophilized particles.

Due to the requirement of freezing the material, protein degradation caused by exposure to ice surfaces is a possibility during SFD. Significant amounts of liquid nitrogen may be required for the process if it is used to freeze the samples. Additionally, aseptic processing of material can be challenging. Overall, SFD offers some advantages over lyophilization including faster drying times, lower energy consumption during drying, and flexibility during scaling. However, some of these advantages appear to be offset by energy consumption during freezing and difficulties inherent to spray-based processes.

Spray Drying Summary

Spray drying represents the most mature alternative drying technology to lyophilization. The process provides an opportunity to engineer particle size and shape (including morphology, surface area, and surface composition), 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 as well. Aseptic processing for spray drying is more challenging than it is for lyophilization. Material is exposed to significant shear stress during atomization, and the large surface to mass ratio in droplets results in significant air–water interfaces at which proteins can denature. Although the temperature in the evaporating droplet barely exceeds the wet bulb temperature, dried material can be exposed to high temperatures for prolonged periods of time in the collection vessel. Additionally, a secondary drying method may be required if very low residual water content is needed 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 of 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.[146]

SUPERCRITICAL DRYING

Supercritical fluid (SCF) technology has been investigated with focus on the production of high purity, micron-sized particles with controlled morphology and tailored properties. Supercritical CO_2 is the most widely used SCF in pharmaceutical processing due to its low critical temperature (T_c = 31.1°C) and environmental friendliness.

Several techniques employing SCF have been investigated. In SCF-assisted nebulization drying, protein formulation is sprayed into SCF.[24] The setup is similar to that employed for a typical spray drying process, with SCF being used in place of a drying gas. Desiccation is driven by the precipitation of solute in the droplet, which subsequently loses solvent power. The supersaturated protein solution precipitates as the water is extracted to the SCF and the protein is then vitrified in an amorphous matrix.

In another process, supercritical antisolvent (SAS) process, the protein solution is mixed with the SCF prior to atomization and then sprayed under atmospheric condition.[201] Here, SCF is used as an antisolvent that causes precipitation of the protein. Several examples of nano- and micro-particles have been reported, including insulin[20] and α-chymotrypsin,[21] although varying degrees of stability have been reported. SAS processes have also been considered for the production of protein-loaded microparticles by co-precipitation of the biodegradable polymer and the protein from an organic cosolvent.[22] In this study, the reported protein loading was rather low.

In CO_2-assisted nebulization, the process involves the mixing and dissolution of CO_2 within the aqueous protein solution under supercritical pressure and temperature (typically 8–10 MPa and 20–50°C).[202,203] The solution is then sprayed and expanded through a flow restrictor to atmospheric pressure, resulting in the generation of dense aerosols. When CO_2 expands during spraying, drops are broken down to finer droplets, which are then dried rapidly by gas flow to yield micron-size particles. In this process, CO_2 is not used as an antisolvent to precipitate the protein, but rather as an aerosolization aid (dispersing agent) that permits droplet drying at a lower temperature than that used in conventional spray drying. Thus, this technique may be useful for processing thermally unstable materials.[204]

Other processes, leveraging the unique properties of SCF, include solution-enhanced dispersion supercritical fluid,[205] rapid expansion of supercritical solutions,[206] particle from gas saturated solutions,[207] and coating.[208] These processes will not be described here, thus the interested reader is referred to the references provided.

Supercritical fluid drying offers many advantages, including safety and low cost of materials. Using CO_2 in SCF drying allows operation at moderate temperatures and leaves no toxic residues as it reverts to gas phase upon exposure to ambient condition. Ice formation is avoided, as is exposure of the material to extreme temperatures. Additionally, sterilization of microorganisms and viral inactivation can be achieved during the SCF drying process,[209] alleviating some concerns about aseptic processing. As the atomization process is similar to spray drying, particle engineering efforts for alternative delivery methods are also achievable.[210] However, only a limited number of studies have addressed the effect of SCF drying on protein structure and stability. In addition to the unique stresses of SCF drying, other stresses common to freeze-drying and spray drying also exist (e.g., adsorption and denaturation at the fluid–fluid interface). The high pressure requirement for SCF may impact protein structure/stability and the dissolution of CO_2 may result in pH decrease if the solution is not buffered appropriately. Furthermore, the use of organic solvents in protein solution (to enhance protein solubility in SCF) may result in aggregation[211] and instability caused by residual solvent or impurities introduced by the parent solvent. Process scale-up may be an issue with several of the above described SCF processes; specialized and expensive equipment, able to withstand elevated pressures, is required and compression costs can be significant.[212] For a thorough review on SCF-based technologies, the reader is referred to the work by Sheth et al.[213] Overall, SCF-based drying methods offer a number of advantages over other drying methods; however, the technology is less mature than spray drying and requires the use of high pressure that may impact protein stability, potentially hindering its use for the production of biotherapeutics.

CONVECTIVE DRYING

Convective drying is perhaps the simplest of all drying techniques. The solution/suspension is dried upon exposure to air (which can be heated or at ambient temperature), while controlling the RH of the environment. A wide range of biologicals has been processed by convective drying, including yeast,[29] probiotics,[30] human platelets,[35] antibodies,[33] restriction enzymes,[34] and fish.[36] Of the various processing parameters that can be controlled, the rate of drying has been reported to significantly impact recovery.[214]

Lemetais et al.[215] investigated the stability of baker's yeast, *Saccharomyces cerevisiae*, to air drying stress and reported a survival rate of 40%. The loss in viability was attributed to plasma membrane (PM) reorganization, which was confirmed by the lower survival rate of a mutant strain with an osmotically fragile PM. Brinkhous and Read[35] reported the successful drying of human platelets by exposing the samples to a stream of air at 23–25°C; integrity of the platelet aggregating factor/von Willebrand factor (PAF/vWF) platelet receptor was maintained following drying. In addition, the aggregation rate with PAF/vWF was reported to be rapid and essentially unchanged from that observed with the control platelet preparation. These results were comparable to those reported for platelets preserved by freezing or freeze-drying. Fellowes[33] compared the storage stability of the virus-neutralizing antibody of foot-and-mouth disease that had been air dried on paper or freeze-dried in bottles. Air drying was accomplished by exposing the antiserum to 23°C and 30% RH for 18 h. Remarkably, the antiserum remained stable for up to 28 weeks upon storage at 37°C, and was found to be more stable than the freeze-dried preparation.

Champagne et al.[30] examined the stability of various probiotic cultures, including *Lactobacillus rhamnosus*

(*L. rhamnosus*) and *Lactobacillus plantarum* (*L. plantarum*) upon air drying. Samples were exposed to dehumidified air (<5% RH) at 90 L/h and dried for 24 h at room temperature in the presence of supersaturated solution of lithium chloride to control water activity. Optimum survival of *L. plantarum* and *L. rhamnosus* was reported to be 78% and 70%, respectively, which are both within the range of survival levels observed with freeze-drying.[216]

The main benefit of convective drying is its simplicity, especially compared with freeze-drying. However, a number of issues make its use difficult for the drying of biologics. Convective drying requires excessively long drying times at ambient temperature or exposure of material to elevated temperatures, which may degrade product quality. Additionally, scalability of the process is poor, as convective drying requires small volumes spread over large surface areas. Paucity of data in regard to the final residual water content achievable is also a concern. Given the high initial water content in many biologics, convective drying alone may not be a viable or economical option for processing of biotherapeutics products.

VACUUM DRYING

Vacuum drying utilizes the application of low pressure to enhance the rate of dehydration. Vacuum drying differs from foam drying as the latter relies on the intentional creation of a foam structure while vacuum drying does not. Presently, vacuum drying has been applied to various food materials as an alternative to freeze-drying, with the aim of lowering the manufacturing cost.[38,41,42] Foerst et al.[39] examined the storage stability of dried probiotic, *Lactobacillus paracasei* (*L. paracasei*) F19, produced by vacuum drying. The drying was conducted for 22 h at 15°C and 15 mbar chamber pressure. Vacuum dried *L. paracasei* was reported to be highly stable during storage at 4°C, and no significant inactivation was reported following 3 months of storage. This result is in accordance with studies on storage of freeze-dried lactic acid bacteria.[217,218] Comparatively, the inactivation rate constants of cells dried by vacuum drying were lower than those of the same strain dried by freeze-drying. Conrad et al.[219] examined the effect of vacuum drying on the stability of *Lactobacillus acidophilus* (*L. acidophilus*). Drying was carried out at room temperature at 85 mTorr for 4 days. *L. acidophilus* on its own demonstrated 19% recovery, whereas the addition of trehalose improved the recovery to 38%. Rossi et al.[45] reported the stabilization of a restriction enzyme, *Eco*RI, by vacuum drying in various formulations. In trehalose, no loss was observed upon storage at 6°C for up to 35 days, and up to 12 days at 45°C. Similarly, Uritani et al.[46] reported the ability to stabilize restriction endonucleases, including *Hin*dIII, *Eco*RI, and *Bam*HI, using vacuum drying in the presence of trehalose.

Vacuum drying possesses distinct characteristics, including high drying rate and low drying temperature, which may lead to improved quality of dried products. The reduction in pressure (50–100 mbar) causes the expansion of water molecules to vapor phase. Low temperature can be used under vacuum, making it ideal for heat-sensitive material. Additionally, the lack of ice formation in vacuum drying eliminates the potential for protein denaturation that can occur at the ice–water interface. Temperature control/monitoring is required to avoid freezing caused by evaporative cooling, and pressure needs to be carefully adjusted to prevent boiling over for material with low solids content. Food materials and cells are able to be vacuum dried as the high solids content (and the presence of membrane) provides structure to the product. On the other hand, vacuum drying of biotherapeutics, containing high water content, is expected to transition into foam drying at the pressures utilized for processing. Thus, it may be more appropriate to consider foam drying, discussed earlier, for processing of biotherapeutics.

MICROWAVE DRYING

Drying with microwaves is different from conventional drying. When using conventional dryers with hot air or vacuum, the speed of drying is limited by the rate at which water or solvent diffuses from the interior of the material to its surface, at which evaporation occurs. The rate of drying is enhanced by raising the temperature (or applying vacuum), which increases the evaporation rate of water from the surface. Still, drying may be limited by the rate at which the interior water diffuses to the surface. For example, fast drying may result in the overdyring of surface, thus hindering the transport of water to and away from the surface. Also, as drying progresses, the path for diffusion of interior water becomes longer and more difficult, resulting in the reduction of drying rate (as is observed for lyophilization).

Microwaves themselves do not generate heat, but rather the absorbed energy is converted to heat inside the product; heating by microwave energy is accomplished by the absorption of microwave energy by dipolar water molecules and ionic components, if present. The carrier, or substrate, is heated primarily and slowly by conduction. Microwaves are part of the electromagnetic spectrum, and are located between 300 MHz and 300 GHz. The preferred frequency for drying processes is reported to be 2.45 GHz. At this level, microwaves cause the molecules of suitable materials/size to vibrate, and this vibration creates intermolecular heat that results in evaporation.

Examples of industrial microwave dryers include: Linn High Therm GmbH,[220] Thermex Thermatron,[221] EnWave,[222] and Industrial Microwave Systems.[223] Products that are processed using various microwave-assisted drying technologies include pasta, dried milk, grains, fruit, coffee, and shrimp.[224] Promising results have been reported for drying chicken pieces[48] and potato slices[47] by a combination of cool air and low-power microwave; quality and ability to reconstitute have been reported to be comparable to those for freeze-dried foods. In addition, microwave drying has been used to process yeast,[53] enzymes,[52] small molecule pharmaceuticals,[55,225] and various biopharmaceuticals.[57]

The main advantage of microwave drying is the shortening of drying time. It is possible to accomplish in seconds-to-minutes what could take minutes-to-hours using conventional heating methods (Fig. 5). It is not, however, economical to use microwave heating for the complete drying of highly hydrated foods. Rather, it should be used as a complement to conventional heating to enhance the drying at the later stages of the process (see *Hybrid Drying* section below). The on–off nature of microwave application and the ability to change the degree of heating (by controlling the output power of the generator) enables fast, efficient, and accurate control of the process. Although uniform heating can be realized in theory, the key problem lies in the inherent nonuniform distribution of the

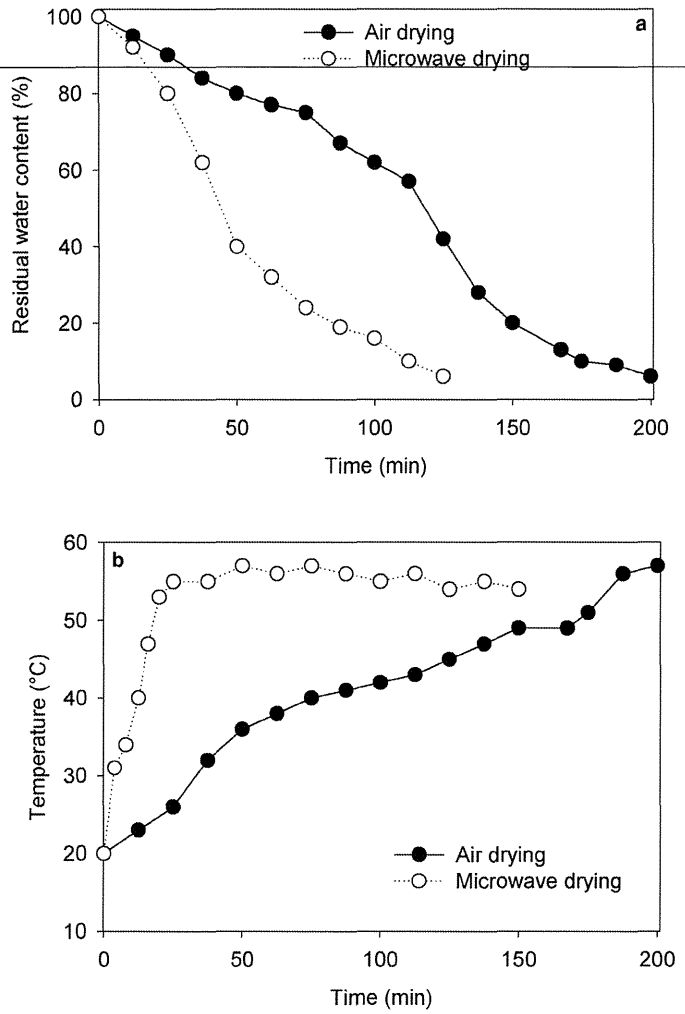

Figure 5. Comparison of (a) drying time and (b) sample temperature for convective drying (air drying) with microwave drying. Figure adapted from Li and Ramaswamy.[224]

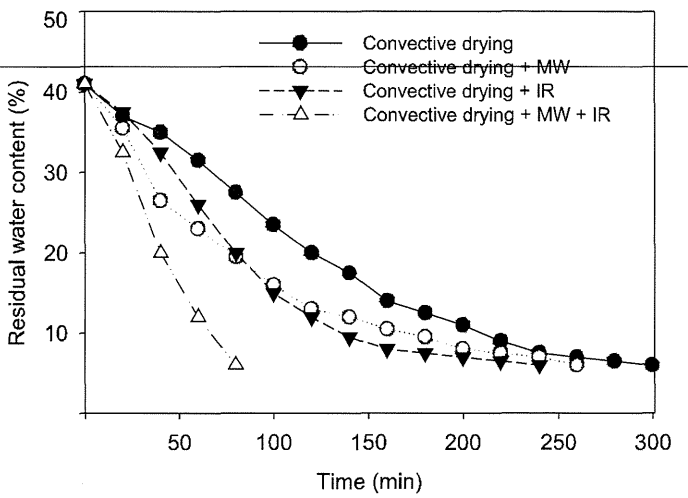

Figure 6. Drying curves of granulated kaolin (initial water content of 0.4 $kg/kg_{dry\ basis}$) processed by (1) convective drying, (2) convective drying enhanced with microwave (MW), (3) convective drying enhanced with infrared radiation (IR) in the constant drying rate period, and (4) convective drying enhanced with MW and IR through the first 70 min of drying. Drying was completed upon reaching the final residual water content (0.06 kg/kg). Figure adapted from Kowalski and Rajewska.[227]

microwave field, which can lead to uneven temperature distribution within the drying material.[226] The use of certain excipients may also be precluded due to their polar/ionic nature, which could cause the temperature of the solution to increase excessively without careful control of the microwave condition. This will be an issue if reformulation is not an option, although this challenge may be circumvented with further advancement in microwave technology. In addition, a thorough analysis of the effect of microwave application on protein mobility, structure, and stability is yet to be reported. Thus, the usefulness of microwave drying may be restricted for biotherapeutics; however, its coupling to another drying technology may be a possibility, as will be described below.

HYBRID DRYING

Introduction

Hybrid drying techniques are becoming more common as they receive a combination of the benefits of individual processes.[227] As mentioned in *Introduction*, there are many drying technologies available, thus a large number of possible combinations. Suitable application (or compatibility) of the individual drying methods and reasonable partitioning of the energy sources are necessary.

For example, convective, microwave, and infrared drying differ from each other in energy supply and area of impact. In convective drying, energy is supplied through the surface of material using air. In microwave drying, heat is supplied volumetrically by high frequency polarization of dipole molecules. In infrared drying, energy is supplied to the body through surface radiation, which can be absorbed, reflected, or permeated through the body. Figure 6 compares the drying time of various combinations of these drying techniques on granulated kaolin.[227] The greatest reduction in drying time was achieved through the use of convective drying enhanced with microwave and infrared radiation. In comparison, similar residual water content (0.06 $kg/kg_{dry\ basis}$, or 6%) was achieved in 5 h using pure convective drying (3.8-times longer). The advantage of applying microwave heating in the early stage of drying is that a significant amount of water is pushed out to the surface of the material rapidly through increase in pore pressure, thermo-diffusion, reduction of liquid viscosity at higher temperature, etc. In other examples, Garcia and Bueno[228] examined the efficiency of combined convective-microwave drying on agar gel and *Gelidium* seaweeds under several operating conditions. Goluannec et al.[229] and Salagnac et al.[230] presented the kinetics of drying, achieved by the combination of convection with infrared and microwave radiation. Several successful cases of hybrid drying technologies will be described below.

Microwave-Assisted Vacuum Drying

In recent years, microwave vacuum drying (MVD) has been investigated to obtain products of acceptable quality, including foods and pharmaceutical products.[54,231] Microwave-assisted vacuum drying is a technology that not only possesses the

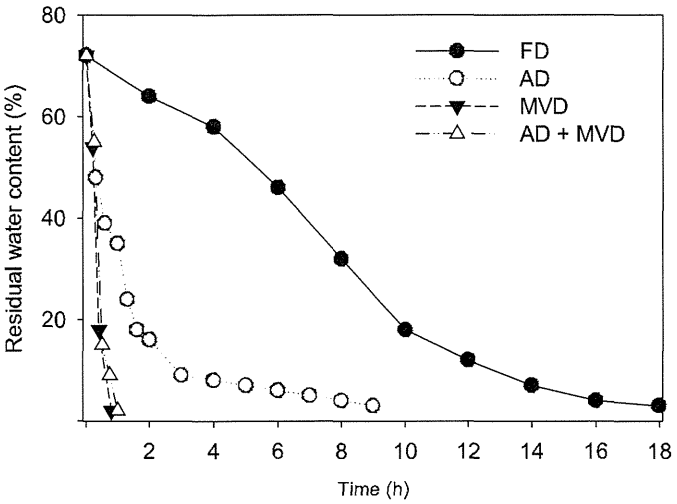

Figure 7. Drying curves of freeze-dried (FD), air dried (AD), microwave vacuum dried (MVD), and combined air and microwave vacuum dried (AD + MVD) edamame. Figure adapted from Zhang et al.[238]

advantages of microwave heating (i.e., rapid heating, high efficiency, good control, etc.) but also improves the energy efficiency of the process by lowering the boiling point of water through application of vacuum.[232] For example, MVD of fingerroot (*Boesenbergia pandurata*) was compared with hot air drying at 60–70°C, and a 90% reduction in drying time was reported.[233] MVD has been utilized in the processing of various foods, including banana slices[231] and potato slices.[234] Studies have demonstrated that drying under a pulsed microwave vacuum is suitable for the drying of temperature-sensitive products, such as enzymes and proteins.[235,236]

In another example, drying of edamame using various techniques was compared.[237] Figure 7 illustrates the residual water content-versus-time curves of edamame dried by: (1) freeze-drying, (2) air drying, (3) MVD, and (4) combined air and MVD.[238] MVD was more efficient in reducing the water content than air drying or freeze-drying at any point. Although MVD required 40 min to reach the target water content (~3%), air drying required 9 h. Drying time for freeze-drying was 18 h, far longer than the other methods examined. MVD was also used in the drying of α-amylase bacterial enzyme.[52] For all of the conditions examined, 200 s was necessary to reduce the residual water content to near-zero value, except at high power, for which drying was completed within 120 s. Applying a higher pressure gradient helped lower the evaporating temperature and enhance the drying process. The best results were obtained for processes using lower powers (200 and 300 W). Although high vacuum normally yields improved quality, the equipment and operating costs increase and this may be prohibitive for low profit margin products.[239]

Microwave vacuum drying processes retain the benefits of vacuum drying while further decreasing drying time and increasing energy efficiency by using microwaves as an additional energy source. Employment of microwaves for drying processes results in the transfer of energy throughout the drying volume, but within the penetration depth of the microwaves.[240] This results in the formation of porous structures which can keep resistance low during the drying process and allow for quick rehydration of microwave vacuum-dried materials in comparison to materials dried using other methods.[233] Tight control over vacuum levels is still necessary to prevent unwanted freezing of the product. Additionally, MVD has been reported to cause color changes in some products, such as Saskatoon berries[241] and fingerroot,[233] with the degree of color change dependent upon vacuum level, microwave power, and the composition of the material being dried. As noted earlier, vacuum drying of biologics at the pressure levels to be employed is expected to transition into the realm of foam drying. Application of MVD to such a process for high value biologics would require extensive optimization of process variables through a rationally designed experiment to eliminate, or at least reduce, the impact of microwave radiation on product quality.

Microwave-Assisted Freeze-Drying

In microwave freeze-drying (MFD), the microwave field is used as the heat source to enable sublimation in the freeze-drying process.[242] MFD requires much less drying time and energy consumption compared to a conventional freeze-drying method. MFD has been applied to a variety of products, including fruits, vegetables, and solid soup.[50,243,244] Temperature-sensitive material should only be exposed to microwave radiation for a limited duration. Duan et al.[245] demonstrated that the process time for freeze-drying of cabbage can be halved through the application of microwave without affecting the product quality significantly. In another example, Duan et al.[244] examined MFD of sea cucumber and reported a reduction in drying time by about half of that required for conventional freeze-drying, while providing similar product quality. Wang et al.[246] studied the effects of MFD on the microstructure and quality of potato slices and reported methods to avoid changes in shape during processing. Additionally, sterilization effect through the use of microwave has been reported.[247]

Microwave can be applied to convective drying,[248] thus its application to atmospheric freeze-drying (AFD) seems logical. AFD is based on the sublimation of ice driven by the pressure gradient (convective drying).[249] The most important application of AFD is convective drying performed at temperatures below the freezing point of the product. Compared with freeze-drying, the temperature is higher, typically in the range of −3°C to −10°C. This is due to the physical properties of humid air, as lower air temperature reduces the ability to remove moisture. Drying at temperatures around −10°C has proven to be a viable trade-off between quality and costs when a fast process is required. AFD is controlled by internal resistance to heat and mass transfer (due to lower vapor diffusivity at atmospheric pressure), which unfortunately increases drying time. Because the process is slow in general, microwave radiation can be applied in order to increase sublimation in both fluid and fixed bed conditions. For example, with the application of microwave, the drying time of green peas was reduced by approximately 50%.[49] The first industrial AFD system for vegetables, based on a heat pump to condition and circulate the drying air, was built in Hungary in 2005.[250] Several industrial MFD units are currently available for processing various products.[222,251]

The advantages of MFD processes include shorter drying time compared with lyophilization, energy savings, improved product quality, and flexibility in producing a wide array of dried products.[240] Sublimation can occur throughout the volume of the drying material which is within the penetration depth of microwaves, and penetration depths are increased if

Table 3. Heat Transfer Coefficients for Convective Drying (h) and Acoustic-Assisted Convective Drying (h_{ac}) of Carrots at Various Slice Thickness and Air Velocity

	Air Velocity (2.2 m/s)			Air Velocity (2.8 m/s)		
	d = 0.5 cm	d = 1.0 cm	d = 1.5 cm	d = 0.5 cm	d = 1.0 cm	d = 1.5 cm
h (J/s m^2 K)	73.3	57.2	50.2	95.1	85.3	62.5
h_{ac} (J/s m^2 K)	95.7	64.0	59.5	135.5	108.7	89.8

Table adapted from Aversa et al.[61].

water is frozen below −5 °C,[252] further increasing the efficiency of MFD processes. Material dried by MFD may be susceptible to degradation and color change as noted for material dried by MVD. Color changes can occur due to the development of hot spots caused by localized melting of ice crystals,[253] or in more extreme cases due to the formation of plasma in the drying chamber.[254] The degree to which energy efficiency can be enhanced through the application of microwave to a lyophilization cycle is yet to be determined, as is the effect of modified drying kinetics on the stability of biopharmaceuticals. In addition, scalability is unknown. Residual water content is expected to be as low or lower than that achievable by lyophilization, given the ability to apply secondary drying to MFD-processed material. Ultimately, MFD may be suitable for the production of biotherapeutics if it can be demonstrated that the application of microwave does not negatively impact product quality.

Acoustic Energy-Assisted Drying

The utilization of acoustic waves in the food industry is becoming increasingly widespread.[59] The first attempt at using sound waves to intensify drying process at low temperature dates back to the 1970s. The expression "acoustic drying" typically denotes the removal of water from material under the combined influence of hot air and high-intensity ultrasonic waves propagating in air.[59] Patist and Bates[60] reported improved performance of acoustic drying compared with convective process in removing water from various food products. For example, ultrasound was reported to enhance the drying rate of cylindrical carrot samples, in comparison to that dried using a traditional convective process.[61] In addition, acoustic drying makes use of lower temperatures than that employed in typical convective drying processes. Acoustic drying has also been used for processing lumber,[63] coal,[64] and in waste treatment.[65]

The mechanism of acoustic-assisted convective drying has not yet been thoroughly explained; it is somewhat ascribed to a combination of different effects impacting both internal and external transport phenomena. Several authors reported that acoustic stirring reduced the resistance to mass and heat transfer developing in air, close to the surface of wet material.[59,255] Moreover, the sonic waves were hypothesized to produce a series of rapid compressions and expansions of the material. Finally, the better performance of acoustic-assisted drying was attributed to cavitation, which promotes the growth of small bubbles.[59] The application of an efficient power ultrasound has been reported to produce mechanical effects on both the gas-solid interface and the material being dried; ultrasound may intensify water removal without introducing a high amount of thermal energy during drying.[256] Thus, the use of ultrasound either to dry heat-sensitive materials or for application in low-temperature drying appears to possess great potential. Furthermore, Moy and DiMarco[257,258] tested ultrasonic application in both vacuum and non-vacuum freeze-drying.

When ultrasound was used to dry carrots, the heat transfer coefficient and the corresponding mass transfer coefficient were higher than those for convective drying (Table 3).[61] Data shown in Table 3 confirm the correlation between air velocity, sample diameter, and heat transfer, as predicted by the semi-empirical correlations available in the literature.[259] Drying enhancement mainly occurred at the beginning of the process, that is, when external transfer was the controlling step, which indicates that ultrasound is responsible for a significant increase in external heat and mass transfer coefficients. As hypothesized by Garcia-Perez et al.,[260] this effect is ascribed to the reduction, as promoted by sound waves, of the boundary layer thickness at the material–air interface. In another example, the effect of ultrasound application was found to be similar for low- (carrot), medium- (apple), and high- (eggplant) porosity products,[261] with the drying time on average being shortened by 65–70%.[62]

Benefits of applying ultrasound in drying processes include reduced drying times and energy consumption. Ultrasound may allow the use of lower temperatures in drying processes, decreasing the risk of product degradation. Drawbacks to the use of ultrasound to improve drying processes include the requirement to purchase specialized equipment and the potential for cavitation stress. Sonication of proteins has been reported to produce amyloid-like aggregates,[262] or rather to induce aggregation,[263] so the impact of high powered ultrasound on protein structure and stability would need to be assessed further. The lowest residual water content achievable, energy efficiency, and scalability are also unknown. At this moment, the use of ultrasound is not expected to be of benefit for drying samples containing high water content. It could, however, be employed as a complement to secondary drying during lyophilization once a solid structure has been formed.

Additional Technologies

In addition to those described above, there are several other drying techniques being utilized in various industries outside of the pharmaceutical industry. These include osmotic drying,[71–75] infrared drying,[66–68,70] ohmic heating,[76–79] spouted bed drying,[80–85,116] fluidized bed drying,[86–89,91,116] centrifugal drying,[264] and impingement jet drying,[265] to name a few (Table 1). In the case of impingement jet drying, stable probiotic bacteria (*L. acidophilus*) have been produced[266]; residual water content of 10% was obtained following 3 h of operation, in comparison with 13% after 19 h of freeze-drying. Lin et al.[267] examined the effect of far-infrared radiation on freeze-drying of sweet potato. As far-infrared radiation creates internal heating, it was selected as a complementary technology to shorten the processing time of freeze-drying. For a sweet potato cube with 10 mm length, the drying time was reduced from >12 to

Table 4. Summary of Challenges Encountered by Drying Technologies as an Alternative to Lyophilization. Examples of Equipment Manufacturers at Laboratory- and Commercial-Scale are Provided.

Drying Technique	Challenges Encountered from Equipment Design, Processing, and Product Quality Perspectives	Examples of Laboratory-Scale Equipment Manufacturer	Examples of Commercial-Scale Equipment Manufacturer
Freeze-drying	(i) Heterogeneity in drying (ii) Use of conservative cycles resulting in long processing times (iii) Low process efficiency[a] (iv) Lack of evolution in equipment design, leading to limited heat and mass transfer	GEA Lyophil, IMA Life, Millrock Technologies, SP Scientific	GEA Lyophil, IMA Life, OPTIMA Pharma Klee Klee Optima Group, KYOWAC, SP Scientific
Foam drying	(i) Rapid boiling/boil over, freezing during foaming (ii) Inability to control higher chamber pressures during foam formation (iii) Heterogeneity in product appearance (iv) Long duration of drying to reduce water content	Currently laboratory-scale freeze-dryers are employed for feasibility assessment	
Spray drying	(i) Significant shear stress during atomization (ii) Aseptic processing may be challenging (iii) Exposure of dried material to high temperatures in the collection vessel (iv) Material recovery is <100%; could be increased by modification in equipment design (v) Higher water contents in comparison to freeze-drying	BUCHI, GEA Niro, Ohkawara Kakohki Company, Ltd., SPX Anhydro	GEA Niro, Ohkawara Kakohki Company, Ltd., SPX Anhydro
Spray freeze-drying	(i) Significant shear stress during atomization and freezing (ii) Aseptic processing (iii) Material recovery can be <100%	Meridion Technologies GmbH, PowderPro AB	Meridion Technologies GmbH (in development), PowderPro AB
Supercritical fluid drying	(i) Impact of shear, CO_2 pressure, and organic cosolvents (during processing and residual levels post processing) on protein stability; impact of CO_2 dissolution on pH (ii) Aseptic processing (iii) Material recovery can be <100% (iv) Equipment costs (v) Scalability	Separex, Apeks Supercritical, NATEX	Separex, NATEX
Convective drying	(i) Long drying times at ambient temperatures (ii) Potential for product instability at higher processing temperatures (iii) Poor process scalability (iv) Very limited data exist on the achievable water content in dried materials	Binder, G.U.N.T. Gerätebau GmbH	Ingetecsa

[a]Efficiency is defined as the ratio of the product of the sublimation enthalpy and rate, to the power input into a lyophilization process (Ref. 8).

Table 4. Continued

Drying Technique	Challenges Encountered from Equipment Design, Processing, and Product Quality Perspectives	Examples of Laboratory-Scale Equipment Manufacturer	Examples of Commercial-Scale Equipment Manufacturer
Vacuum drying	(i) Risk of freezing during evaporative cooling (ii) Risk of boiling and transition into foam drying (iii) Long duration of drying (iv) Scalability	Binder, Memmert, Hosokawa Micron B.V., Paul O. Abbe	Hosokawa Micron B.V., Paul O. Abbe
Microwave drying	(i) Uneconomical for complete drying of highly hydrated materials (ii) Nonuniform temperature distribution within material (iii) Unsuitable for materials with low water content or polar/ionic excipients (iv) Effect on pharmaceutical stability is unknown	EnWave, Püschner, Sairem	EnWave, Industrial microwave Systems, Linn High Therm GmbH, Püschner, Sairem, Thermex Thermatron
Microwave-assisted vacuum drying	(i) Control of chamber pressure to prevent freezing (ii) Alterations in the physical appearance (color) of materials during drying (iii) Effect of processing variable (microwave power, exposure time, chamber pressure, etc.) on product quality (stability)	EnWave, Püschner, Sairem	EnWave, Püschner, Sairem
Microwave-assisted freeze-drying	(i) Heterogeneity in temperature can lead to generation of "hot spots" as a consequence of ice melting or plasma formation, leading to changes in physical appearance (color) (ii) Potential for degradation during processing (iii) Alterations in the physical appearance (color) of materials (iv) Effect of processing variable (microwave power, exposure time, chamber pressure, etc.) on product quality (stability) (v) Scalability	EnWave, Püschner	EnWave, Püschner
Acoustic energy-assisted drying	(i) Impact of cavitation resulting from sonication and other processing variables on stability (aggregation) and other product quality attributes (appearance and water content) (ii) Need for specialized equipment (iii) Scalability	Pusonics, Heat Technologies, Inc.	None

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5 h, upon the application of 200 W power with a wavelength in the range of 4–50 μm. In another example, Pham[268] examined the use of a spouted-bed dryer for the production of dried bovine blood, whereas Feng and Tang[81] examined the application of microwave heating during spouted bed drying of diced apples. Electrohydrodynamic drying (EHD) was used by Hashinaga et al.[269] to dry apple slices for which 4.5-fold enhancement in drying rate to that achieved by ambient air drying was reported. This technique utilizes an electric wind (corona wind) to enhance the mass transfer between the material and ambient air. EHD was first reported by Asakawa,[270] who demonstrated an enhancement of water vaporization rate by up to 40–50 times at 12°C.

Despite the abundance of drying technologies available, in their current state, the vast majority of these techniques are not directly applicable for the processing of biopharmaceutical materials for many reasons, including (1) unknown effect of energy source on structure/stability of the biopharmaceutical, (2) energy efficiency, (3) scalability, and (4) inability to achieve low residual water content. These may be a consequence of the fact that the above described processes have been optimized for drying products possessing a solid structure and containing much lower water content than those typically found in liquid pharmaceutical products. However, it should be noted that the drying technologies currently employed in the pharmaceutical industry (i.e., lyophilization[271] and spray drying[12]) first began in the food industry and were adopted only after many years of development and demonstrated success. This may well be the case with microwave drying and other hybrid drying technologies described in this review. A summary of challenges currently faced by these technologies as well as scales of equipment available are provided in Table 4.

SUMMARY

Traditional methods of commercial drying are limited either by their high production costs (e.g., lyophilization) 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, SFD, and foam drying. Furthermore, there are a great number of drying technologies that are available, if not already in use, in the food, agriculture, and textile industries. These employ alternative energy sources, such as microwave, ultrasonic wave, infrared radiation, etc. As the sensitivity of pharmaceuticals is unique to the given compound, the selected drying technique may not be universally applicable. By understanding the drying mechanism and the stresses involved, the drying techniques can 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_2O 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 technology implementation. As discussed throughout the review, there are many 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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