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RECENT ADVANCES AND EMERGING APPLICATIONS OF SPRAY DRYING IN DRUG DELIVERY AND BIOPHARMACEUTICAL FORMULATION

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ABSTRACT

More than a century after the first patent describing a rudimentary atomization and drying apparatus, spray drying remains an indispensable technology in the pharmaceutical industry. Recent advances have transformed spray drying from a simple particle-generation process into a sophisticated platform capable of producing powders from solutions, suspensions, and emulsions while enabling precise control over particle size, morphology, and physicochemical properties. Since its early adoption in the dairy industry, spray drying has evolved to support a wide range of pharmaceutical applications owing to its advantages as a single-step, continuous, cost-effective, and scalable manufacturing process. Initially employed primarily for the production of microparticles, modern spray-drying technologies now facilitate the precise engineering of nanoparticles and other advanced drug delivery systems. Furthermore, technological innovations have expanded its applicability to heat-sensitive materials, including proteins, peptides, and other biologics, without compromising their stability or functionality. Spray drying also enables versatile particle surface modifications, allowing targeted delivery to specific tissues and organs. Consequently, spray-dried formulations have been investigated for administration through multiple routes, including local, intravenous, and pulmonary delivery. Rather than providing an exhaustive overview of all pharmaceutical applications of spray drying, this review highlights recent technological advances and emerging applications that are redefining its role in modern drug development and manufacturing. By examining current trends and innovations, the review aims to provide insights into the expanding potential of spray drying as a versatile platform for pharmaceutical product design and delivery.

Keywords: Spray Drying; Solid Nanoparticles; Powdered Peptides and Proteins; Vaccines; Oligonucleotides; Long Acting Injectables

1 INTRODUCTION

The history of spray drying dates back to 1872, when Samuel Percy was granted the first U.S. patent, entitled *"Improvement in Drying and Concentrating Liquid Substances by Atomizing"* [1] In this pioneering work, Percy described the simultaneous atomization and drying of liquids and solid-containing fluids, a process that later became known as spray drying. His primitive spray dryer allowed a liquid feed to pass through a tube, where it encountered a stream of air upon exiting, causing the liquid to disperse into fine droplets. Exposure of these droplets to heated air resulted in rapid solvent evaporation, producing dry powder particles that could be collected [1]. Remarkably, the fundamental principle underlying Percy's invention remains the basis of modern spray-drying technology. Although the concept was introduced in the late nineteenth century, widespread industrial adoption of spray drying did not occur until the mid-twentieth century. The technology gained significant momentum during World War II, when the dairy industry employed spray drying to manufacture milk powder for military supplies, demonstrating its practicality, efficiency, and scalability. Since then, continuous technological innovations have refined the process, enabling greater control over particle formation, improved energy efficiency, and enhanced product quality. Today, spray drying is recognized as a versatile and robust manufacturing platform across numerous industries, including food, pharmaceuticals, cosmetics, and materials science. Its popularity stems from several key advantages, including its ability to convert liquid formulations into dry powders in a single-step, continuous, scalable, and cost-effective process. These attributes have established spray drying as an indispensable technology for the production and engineering of a wide variety of functional materials and advanced pharmaceutical dosage forms.

In simple terms, spray drying is a single-step process used to convert a liquid feed into dry solid particles. The feed material may exist in various forms, including solutions, suspensions, emulsions, pastes, or even molten materials. Owing to its rapid, continuous, cost-effective, and scalable nature, spray drying has become one of the most widely employed techniques for the production of dry powders [2]. For ease of understanding, the spray-drying process can be divided into three fundamental stages: atomization, drying, and particle collection. The process begins with atomization, during which the feed slurry is introduced into an atomizer and dispersed into fine droplets. These droplets are then conveyed into the drying chamber, where they come into contact with a stream of heated drying gas. The large surface area of the atomized droplets facilitates rapid solvent evaporation, resulting in the formation of solid particles. In the final stage, the dried particles are separated from the drying gas and collected in a designated chamber or cyclone separator as free-flowing powders. The quality and physicochemical characteristics of the resulting particles are strongly influenced by several critical process parameters, including inlet and outlet temperatures, feed rate, atomization conditions, drying gas flow rate, and chamber pressure. Careful optimization of these variables is essential, as they directly affect particle size, morphology, density, moisture content, encapsulation efficiency, and overall product performance. Consequently, precise control of spray-drying conditions is crucial for producing powders that meet the desired quality attributes and application-specific requirements.

A wide variety of spray dryers are available, and the selection of an appropriate system depends on both the physicochemical properties of the formulation and the desired attributes of the final product. Processing capacity is a key consideration, as spray dryers are available across a broad range of scales, from laboratory units capable of handling feed volumes as low as a few milliliters to large industrial systems designed to process several liters, or even thousands of liters, per hour. Consequently, the intended production scale plays a major role in determining the most suitable spray-drying platform. Beyond processing capacity, the choice of atomization system is one of the most critical factors in spray dryer design and operation. Atomization governs droplet formation and size distribution, which in turn strongly influences particle size, morphology, drying kinetics, and overall product performance. Several atomization technologies are commonly employed in spray drying, including pressure (single-fluid or hydraulic), pneumatic (two-fluid), rotary (centrifugal), and ultrasonic nozzles. Pressure nozzles generate droplets by forcing the liquid feed through a small orifice under high pressure. This method generally produces relatively uniform droplets and is often preferred when a narrow particle size distribution is desired [3]. In contrast, pneumatic or two-fluid nozzles utilize a high-velocity gas stream, typically compressed air or an inert gas such as nitrogen, to atomize the liquid feed. These nozzles commonly produce droplets in the 10-100 μm size range and are among the most widely used atomization systems in laboratory-scale spray dryers. Furthermore, modified atomization configurations, such as three-fluid and four-fluid nozzles, have been developed to facilitate the fabrication of composite, core-shell, and multilayered microparticles, thereby expanding the versatility of spray drying for advanced drug delivery applications [4-6]. Rotary atomizers operate through a different mechanism, relying on centrifugal forces generated by a rapidly rotating disc or wheel to disperse the feed into fine droplets. These systems typically produce droplets over a broader size range (approximately 10-500 μm) and are particularly advantageous for processing high-viscosity formulations and large feed volumes [3]. Ultrasonic atomizers, on the other hand, employ high-frequency electrical signals to excite piezoelectric transducers, generating controlled vibrations that produce fine droplets with a relatively narrow size distribution [7]. Overall, the selection of an atomization system is primarily dictated by the properties of the feed material, particularly viscosity, as well as the energy and mechanism available for droplet generation. These factors collectively determine the characteristics of the resulting droplets and, ultimately, the size, morphology, and functional performance of the dried particles [8]. Although

a comprehensive discussion of the engineering principles and physicochemical phenomena governing spray drying is beyond the scope of this review, an understanding of the major atomization technologies and their respective capabilities provides important context for appreciating the growing role of spray drying in modern pharmaceutical manufacturing and drug delivery.

2 ADVANTAGES OF SPRAY-DRYING

Since its introduction in the 1870s, spray drying has undergone continuous technological refinement and has evolved into a versatile manufacturing platform used across a broad range of industries. Today, the technique plays a critical role in sectors such as food, pharmaceuticals, cosmetics, chemicals, and materials science, largely because of its numerous operational and product-related advantages (Figure 1) [9]. As a highly automated and continuous process, spray drying minimizes labor requirements while enabling efficient large-scale production. The continuous mode of operation also promotes uniform processing conditions, contributing to the production of particles with consistent and reproducible size distributions. The technique has attracted considerable interest in both academic and industrial settings owing to its scalability, operational simplicity, and economic feasibility. One of the most significant advantages of spray drying is its ability to rapidly transform liquid formulations into dry powders in a single processing step. Compared with conventional drying methods, particularly freeze-drying, spray drying is generally faster and more cost-effective. Unlike freeze-drying, which requires energy-intensive freezing and sublimation cycles, spray drying relies on rapid solvent evaporation and therefore consumes less time and energy [10]. As a result, many researchers have proposed spray drying as a practical alternative to freeze-drying for the preparation of a variety of pharmaceutical and biopharmaceutical products [11-13].

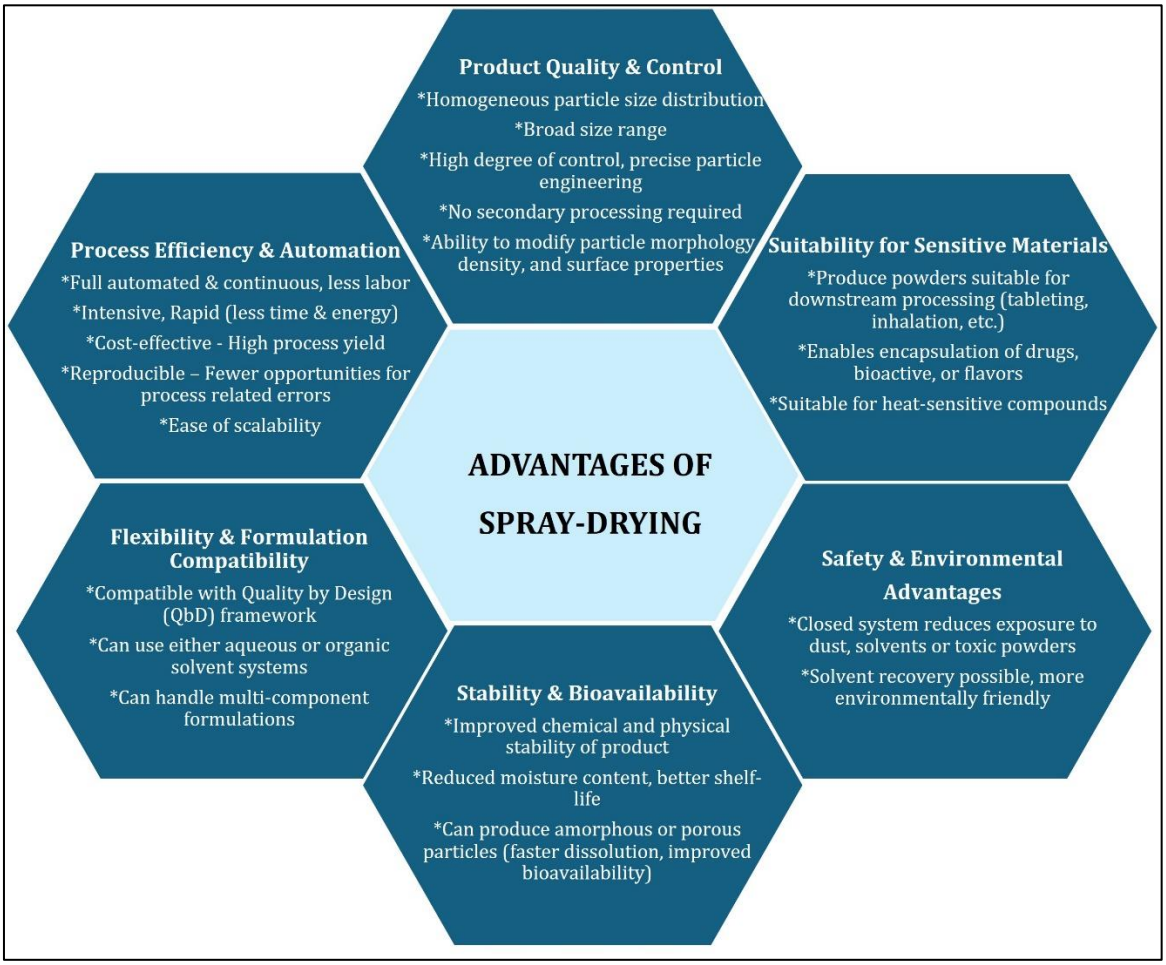

Figure 1: Advantages of spray drying

The quality and performance of spray-dried products are highly dependent on process parameters, which also represent one of the technology's greatest strengths. Key variables, including inlet and outlet temperatures, feed rate, atomization conditions, drying gas flow rate, and feed composition, can be precisely controlled to tailor critical particle attributes such as size distribution, morphology, density, porosity, and residual moisture content. This high degree of process flexibility enables the rational design of particles with properties optimized for specific therapeutic and

manufacturing requirements. Furthermore, once process conditions have been optimized and maintained within a defined operating window, spray drying offers excellent reproducibility and batch-to-batch consistency. Such robustness is particularly valuable in pharmaceutical manufacturing, where stringent quality requirements demand precise control over product attributes and process performance. The ability to engineer particle characteristics while maintaining consistent product quality has established spray drying as a powerful and reliable platform for the development and manufacture of advanced pharmaceutical formulations.

In addition to its numerous operational advantages, spray drying is inherently well suited to the principles of the Quality by Design (QbD) paradigm and has consequently emerged as a robust, scalable, and regulatory-compliant manufacturing platform in the pharmaceutical industry. As outlined in the International Council for Harmonization (ICH) Q8 guideline, QbD advocates a systematic, science-based, and risk-driven approach to pharmaceutical development in which product quality is designed into the formulation and manufacturing process rather than assessed solely through end-product testing. This framework emphasizes a thorough understanding of the relationship between material attributes, process parameters, and product performance to ensure consistent quality throughout the product lifecycle. A fundamental aspect of QbD is the identification and control of Critical Quality Attributes (CQAs), such as particle size distribution, particle morphology, residual moisture content, bulk density, aerodynamic behavior, and solid-state characteristics, including amorphous or crystalline forms. Equally important is the determination of Critical Process Parameters (CPPs) that influence these attributes. In spray drying, CPPs commonly include inlet and outlet temperatures, feed concentration and feed rate, atomization pressure or gas flow rate, droplet size distribution, solvent composition, and drying gas flow rate. These variables directly affect heat and mass transfer, solvent evaporation kinetics, supersaturation behavior, particle formation, and solidification mechanisms during the drying process.

The highly controllable nature of spray drying makes it particularly amenable to systematic process optimization using Design of Experiments (DoE), risk-assessment methodologies, and multivariate statistical tools. Such approaches facilitate the establishment of a design space, defined as the multidimensional combination of material attributes and process parameters that consistently produces a product meeting predefined quality criteria. Developing this level of process understanding enables manufacturers to predict and control the impact of process variability on final product attributes, thereby enhancing process robustness and reducing development risk. Importantly, the integration of QbD principles with spray-drying technology provides unparalleled flexibility for particle engineering. Through precise control of formulation and process variables, spray drying can be used to produce particles with tailored physicochemical properties, including amorphous solid dispersions for improved bioavailability, porous low-density particles for pulmonary delivery, targeted drug carriers, and controlled-release matrices. This capability to rationally design particle characteristics while maintaining consistent product quality underscores the value of spray drying as both a manufacturing and formulation platform.

Consequently, spray drying not only aligns closely with contemporary regulatory expectations but also offers a powerful framework for implementing QbD-driven pharmaceutical development. Its combination of process understanding, operational flexibility, scalability, and reproducibility has established spray drying as a cornerstone technology for the development and manufacture of advanced pharmaceutical products.

Beyond its strong alignment with the Quality by Design (QbD) paradigm, spray drying offers several practical and operational advantages that further enhance its utility in pharmaceutical manufacturing. One important consideration is process yield, which is closely influenced by the scale of operation. At the industrial scale, product losses are generally minimal relative to the total production volume, allowing for highly efficient manufacturing processes [14]. In contrast, laboratory-scale spray dryers often exhibit lower product recovery, typically ranging from 20% to 70%, owing largely to equipment geometry, limited cyclone efficiency, and powder deposition on chamber walls and collection surfaces [15, 16]. Furthermore, as a single-step and continuous process, spray drying provides superior reproducibility compared with multi-step manufacturing methods, reducing process complexity and minimizing opportunities for operator- or process-related variability [17-19]. Spray drying also offers considerable formulation flexibility. The process can accommodate a wide variety of feed systems, including aqueous and organic solvent-based formulations, and may be operated in open- or closed-loop configurations to ensure the safe processing of volatile and flammable solvents [20, 21]. In addition, spray-dried products often exhibit improved storage stability due to their low residual moisture content and reduced water activity, both of which help mitigate degradation pathways and enhance product shelf life [22].

Another major advantage of spray drying is its exceptional capability for particle engineering across a broad size range, spanning from nanometer-scale particles to micrometer-sized powders. Through appropriate formulation design and process optimization, particle size, morphology, density, porosity, and surface characteristics can be precisely tailored to meet specific application requirements. In many cases, the resulting powders can be used directly without the need for additional downstream processing, facilitating their incorporation into dosage forms such as capsules, tablets, inhalation products, and injectable formulations [23]. Depending on the selected process conditions, spray drying can produce free-flowing powders, granules, agglomerates, or highly porous particulate systems with well-defined

physicochemical properties and performance characteristics [24]. Importantly, despite the use of elevated inlet temperatures, spray drying is often suitable for thermally sensitive compounds. The rapid evaporation of solvent and the extremely short residence time of droplets within the drying chamber substantially limit thermal exposure, thereby reducing the risk of heat-induced degradation. This feature has enabled the successful processing of a diverse range of sensitive materials, including proteins, peptides, vaccines, and other biopharmaceuticals. Collectively, these advantages highlight the versatility, efficiency, and robustness of spray drying as a pharmaceutical manufacturing platform. Its combination of scalability, reproducibility, formulation flexibility, particle-engineering capability, and suitability for heat-sensitive materials has positioned spray drying as a cornerstone technology for the development of advanced drug delivery systems and innovative pharmaceutical products. These attributes provide the foundation for the diverse and emerging applications discussed in the following sections.

3 APPLICATIONS OF SPRAY DRYING IN BIOPHARMACEUTICAL FORMULATION

Spray drying, first developed in the late nineteenth century, was initially adopted by the food and chemical industries, where advances in atomization, pumping systems, and particle-collection technologies facilitated its large-scale implementation [25]. The application of spray drying to pharmaceutical manufacturing emerged several decades later. One of the earliest reports was published by Riegelman and co-workers in 1950, who demonstrated the utility of spray drying for modifying the physical and pharmaceutical properties of drug substances, including sulfanilamide and sulfadiazine [26]. Early pharmaceutical applications also included the production of dried medicinal extracts from natural products, where spray drying was valued for its ability to rapidly generate homogeneous powders from highly thermosensitive materials while minimizing degradation [20, 27]. These advantages soon established spray drying as a preferred technique for manufacturing dry extracts and other pharmaceutical intermediates. Over subsequent decades, continued advances in formulation science, polymer chemistry, and particle-engineering technologies greatly expanded the scope of spray drying within the pharmaceutical sector. By the 1990s, spray drying had become a key enabling technology for improving the solubility and bioavailability of poorly water-soluble drugs, particularly through the preparation of amorphous solid dispersions. As pharmaceutical research increasingly focused on complex drug delivery systems, spray drying evolved beyond its traditional role as a drying process and became an essential platform for particle design and formulation development [28]. Today, spray drying is recognized as one of the most versatile and widely utilized particle-engineering technologies in the pharmaceutical industry. Its ability to produce fine, homogeneous, and physically stable powders in a rapid, scalable, and reproducible manner has led to widespread adoption across numerous industrial sectors [29, 30].

Over the past two decades in particular, spray drying has undergone a remarkable transformation, evolving from a conventional drying operation into a sophisticated platform for pharmaceutical particle engineering and advanced drug delivery (Figure 2). One of the most significant applications of spray drying is the production of amorphous solid dispersions of poorly water-soluble drugs. By incorporating active pharmaceutical ingredients into polymeric or other stabilizing matrices, spray drying can enhance dissolution rates, improve oral bioavailability, and maintain the physical stability of amorphous drug forms. The technology has also become indispensable in pulmonary drug delivery, enabling the manufacture of dry powder inhalers with optimized aerodynamic properties for the delivery of small molecules, proteins, peptides, vaccines, nucleic acids, and oligonucleotide-based therapeutics.

Table 1: Classification of spray drying applications in biopharmaceutical industry

Based on Formulation Objectives	Based on Route of Administration	Based on Type of Molecules
Solubility & Dissolution Enhancement	**Oral Delivery**	**Small Molecules**
Amorphous solid Dispersions	ASDs for poorly soluble drugs	Poorly water-soluble APIs
Solid state transformations	Immediate-release powders	Heat-sensitive small drugs
Particle size reduction	Controlled-release oral microparticles	Highly potent compounds
co-precipitated drug-polymer system	Sachet formulations	Combination drug products
Supersaturating drug delivery systems	Reconstitute oral suspensions	
Nanocomposite particles		**Proteins**
	Pulmonary Delivery	Monoclonal antibodies
Stability Enhancements	Dry Powder Inhalers (DPIs)	Enzymes
Protection of moisture-sensitive drugs	Inhalable biologics	Growth factors
Oxidation protection	Inhalable vaccines	Therapeutic proteins
Thermal stabilization of labile molecules	Inhaled anti-infectives	
Stabilization of biologics		**Peptides**

Dry vaccine stabilization Prevention of polymorphic transitions Improved long-term storage stability **Taste Masking & Patient Acceptability** Polymer encapsulation of bitter drugs Orodispersible powder formulations Pediatric-friendly dry formulations **Controlled & Modified Release** Sustained release microparticles Delayed-release systems Polymer-encapsulated depot systems Matrix-based release control Long-acting injectable formulations Site-specific release formulations **Particle Engineering & Performance Optimization** Aerodynamic optimization for inhalation Density and morphology modification Flow property enhancement Directly compressible powders Improved downstream processability	Pulmonary gene delivery systems Systemic delivery via lungs **Parenteral / Injectable** Powders for reconstitution Long-acting injectable depots Biologic stabilization for injection Lyophilization alternative for injectables **Nasal Delivery** Intranasal vaccines Nose-to-brain delivery systems Peptide nasal powders **Buccal & Sublingual** Fast-dissolving powders Systemic absorption via mucosa **Topical & Transdermal** Spray-dried microparticles in creams/gels Wound healing powders Dermal sustained-release systems	Hormonal peptides Antimicrobial peptides Pulmonary-delivered peptides **Nucleic Acid-Based Therapeutics** mRNA siRNA DNA plasmids Oligonucleotides Gene delivery systems **Vaccines** Live attenuated vaccines Subunit vaccines mRNA vaccines Viral vector formulations Thermostable vaccine powders **Nanocarriers & Advanced Systems** Polymeric nanoparticles Lipid-based systems Solid lipid nanoparticles Hybrid nano–micro systems Drug–polymer composites

The versatility of spray drying extends beyond oral and inhalation products. In parenteral drug delivery, spray drying has been employed to produce powders for reconstitution, sustained-release depot systems, and stabilized biologic formulations, offering attractive alternatives to conventional lyophilization. Furthermore, advances in nanoengineering have enabled the fabrication of nanoparticles, nanocomposites, and multifunctional carrier systems with precisely controlled size, morphology, porosity, and surface characteristics. These capabilities have facilitated the development of targeted delivery platforms, combination therapies, and next-generation pharmaceutical products.

More recently, the integration of spray drying with Quality by Design (QbD) principles, Design of Experiments (DoE), process analytical technologies (PAT), and advanced process-monitoring tools has further enhanced process understanding, reproducibility, scalability, and regulatory compliance. Consequently, spray drying has evolved into a highly controllable and scientifically driven manufacturing platform that supports the development of a broad spectrum of modern drug products. Its unique combination of formulation flexibility, particle-engineering capability, and industrial scalability has firmly established spray drying as a cornerstone technology in contemporary pharmaceutical development and manufacturing.

This rapid technological evolution has coincided with an increasing global demand for complex therapeutic modalities, particularly biologics and other advanced pharmaceutical products. The growing prevalence of chronic and life-threatening diseases, including cancer, diabetes, cardiovascular disorders, and chronic respiratory diseases, has intensified the need for effective, stable, and scalable drug delivery platforms [31]. In response, substantial research efforts have focused on the development of protein- and peptide-based therapeutics, as well as other sensitive biological products that require sophisticated formulation and processing strategies. Despite their therapeutic potential, the formulation and manufacture of biologics present significant challenges due to their inherent sensitivity to environmental stresses, including heat, moisture, interfacial interactions, and mechanical forces. Consequently, the application of conventional spray-drying technologies to such molecules has historically been limited by concerns regarding product stability, process yield, and preservation of biological activity [20]. However, recent advances in spray-drying equipment, process control, atomization technologies, and formulation design have substantially overcome many of these limitations, greatly expanding the utility of spray drying for biologic drug products. Modern, next-generation spray dryers are capable of producing particles with tighter size distributions, enhanced control over

morphology, and improved product recovery, even when processing small quantities of valuable or early-stage materials [32]. These systems incorporate sophisticated process controls and optimized drying configurations that enable efficient handling of heat-sensitive compounds while maintaining their structural integrity and biological functionality. As a result, spray drying has increasingly transitioned from a laboratory-scale research tool to a clinically and commercially relevant manufacturing platform. Numerous spray-dried formulations, including biologics, inhalable therapies, and advanced drug delivery systems, have successfully progressed from proof-of-concept studies to clinical development and commercial application. These advances underscore the growing importance of spray drying as a versatile and enabling technology for the next generation of pharmaceutical products.

Earlier generations of spray dryers were viewed primarily as drying devices designed to convert liquid feedstocks into stable powders. However, advances in spray-drying technology over the past two decades have significantly expanded their role beyond conventional drying applications. Modern spray dryers have evolved into sophisticated particle-engineering platforms capable of producing particles across a wide size range, including nanoparticles specifically designed for drug delivery applications, bioavailability enhancement, and the controlled delivery of biologically active compounds [20]. A major milestone in this evolution was the introduction of the Büchi Nano Spray Dryer B-90 HP, which enabled the production of particles in the nanometer range with unprecedented efficiency. This laboratory-scale system can process extremely small sample volumes (<2 mL) while generating particles as small as approximately 200 nm, making it particularly valuable for early-stage formulation development and the evaluation of expensive or limited-availability compounds [33]. Such technological innovations have expanded the capabilities of spray drying far beyond traditional powder manufacture, allowing precise control over particle size, morphology, porosity, and surface characteristics. As a result, spray drying is now widely employed in the preparation of amorphous solid dispersions, nanoparticulate drug delivery systems, and a broad range of biopharmaceutical products, including vaccines, peptides, proteins, hormones, and nucleic acid-based therapeutics. Furthermore, the technology has become an important tool for the fabrication of micro- and nano-carriers capable of encapsulating active pharmaceutical ingredients, protecting labile molecules from degradation, and facilitating targeted or controlled drug release.

To better appreciate the breadth of contemporary pharmaceutical applications, spray-drying technologies can be viewed from three complementary perspectives: (i) the type of therapeutic entity being processed, including small molecules, peptides, proteins, nucleic acids, vaccines, and other biologics; (ii) the intended route of administration, such as oral, pulmonary, parenteral, transdermal, or other delivery pathways; and (iii) the specific formulation objectives being addressed, including solubility enhancement, stabilization of sensitive drugs, controlled release, taste masking, targeted delivery, and bioavailability improvement. Although spray drying has been utilized across a diverse range of pharmaceutical applications for several decades, the focus of this review is not to provide a comprehensive historical account of all reported uses. Instead, emphasis is placed on recent advances and emerging applications that exemplify the current state of the technology and its growing importance in addressing contemporary formulation challenges and evolving therapeutic needs. These developments highlight the transformation of spray drying from a conventional drying operation into a versatile and enabling platform for modern pharmaceutical product development.

3.1 Vaccines

Vaccine wastage remains a significant global challenge, with losses frequently attributed to failures in cold-chain management, transportation, storage, and inventory control [34, 35]. Many currently available vaccines require stringent refrigerated storage conditions to maintain their potency and efficacy, creating significant logistical and economic challenges, particularly in low- and middle-income countries where cold-chain infrastructure may be limited or unreliable. Consequently, ensuring vaccine stability throughout manufacturing, distribution, and storage remains a critical public health priority. The COVID-19 pandemic further highlighted the urgent need for vaccine technologies that can be manufactured rapidly, remain stable under less restrictive storage conditions, and be distributed efficiently on a global scale. These challenges have intensified interest in formulation strategies capable of enhancing vaccine stability while simultaneously improving manufacturing flexibility and accessibility.

In this regard, spray drying has emerged as a promising platform for vaccine stabilization and delivery. By converting liquid vaccine formulations into dry powder products, spray drying can significantly improve physicochemical stability, reduce degradation during storage, and extend shelf life. The resulting powders often exhibit reduced dependence on continuous refrigeration, thereby mitigating one of the major barriers to vaccine distribution in resource-limited settings [36]. In addition, spray drying is a continuous and scalable manufacturing process, enabling rapid production and facilitating large-scale deployment during public health emergencies. Beyond improved stability and manufacturability, spray-dried vaccine formulations offer additional advantages, including reduced transportation costs, simplified storage requirements, and the potential for alternative routes of administration such as pulmonary or mucosal delivery. Collectively, these benefits position spray-dried vaccines as a transformative approach to vaccine development and distribution. By addressing key limitations associated with conventional liquid formulations and cold-chain dependence, spray-drying technology has the potential to enhance global immunization programs, improve vaccine accessibility, and strengthen preparedness for future infectious disease outbreaks and emerging health threats.

The exploration of spray-dried vaccine formulations began in the early 1990s, motivated by the need to develop stable, controlled-release vaccine delivery systems capable of reducing reliance on multiple immunizations. Early investigations demonstrated that vaccine antigens could be successfully encapsulated within biodegradable polymeric microspheres while maintaining their immunogenicity. Among the pioneering studies, Gander and co-workers reported that tetanus toxoid encapsulated in poly(lactic-co-glycolic acid) (PLGA) microspheres exhibited a pulsed-release profile and elicited strong immune responses in mice following a single administration [37]. These findings provided an important proof of concept for the development of single-dose vaccination strategies. Subsequent work by Men et al. [38] further validated the potential of microencapsulated vaccine systems, demonstrating that PLGA-based microsphere formulations could induce both cellular and humoral immune responses comparable to those achieved with conventional aluminum-adjuvanted vaccines. Around the same period, Aubran and colleagues [39] emphasized the critical role of formulation composition, showing that the incorporation of appropriate stabilizing excipients was essential for preserving antigen integrity and biological activity during microencapsulation and storage [39]. These studies highlighted the importance of both carrier design and antigen stabilization in the successful development of particulate vaccine formulations.

By the late 1990s, advances in spray-drying technology had enabled the efficient encapsulation of vaccine antigens into polymeric microparticles. Baras et al.[19] demonstrated that conserved antigens could be successfully entrapped within polyester-based microparticles using spray drying while retaining their biological activity and immunogenic potential. Importantly, these formulations induced sustained antibody responses, further highlighting the advantages of particulate vaccine delivery systems for prolonged immune stimulation. Collectively, these pioneering studies established spray drying as a promising platform for vaccine formulation and delivery. They demonstrated the feasibility of combining antigen stabilization, controlled release, and immune enhancement within a single particulate system, thereby laying the foundation for subsequent advances in spray-dried vaccines. Since these early investigations, continuous improvements in spray-drying technology, excipient selection, and particle engineering have expanded the scope of vaccine applications, positioning spray drying as an increasingly important tool for the development of next-generation immunization strategies.

In recent years, interest in spray-dried vaccine formulations has grown substantially, driven by the global need for thermostable, easily deployable vaccines that can reduce dependence on cold-chain infrastructure. Advances in particle engineering, formulation science, and excipient design have enabled the development of spray-dried vaccine powders with enhanced antigen stability, improved immunogenicity, and controlled-release characteristics. A variety of stabilizing excipients, including sugars, amino acids, and polymer-based systems, have been successfully employed to protect sensitive proteins, viral particles, and other biologically active components from stresses associated with atomization and drying. These developments have facilitated the production of dry powder formulations capable of maintaining biological activity and structural integrity over prolonged storage periods [36, 40, 41]. In parallel, growing evidence from preclinical studies has demonstrated that spray-dried vaccine formulations can elicit robust systemic and mucosal immune responses, highlighting their potential for alternative, needle-free routes of administration such as pulmonary and intranasal delivery [42, 43]. Such approaches not only improve patient compliance but also offer the possibility of inducing localized immunity at mucosal surfaces, which represent the primary entry point for many pathogens. More recently, research efforts have focused on applying spray-drying technology to the development of vaccines against emerging and re-emerging infectious diseases, while simultaneously exploring scalable manufacturing strategies capable of supporting rapid deployment during public health emergencies [44]. Although no spray-dried vaccine has yet reached commercial approval, these developments underscore the growing potential of spray drying as a transformative approach in next-generation vaccine formulation and delivery. Although no spray-dried vaccine has yet achieved full commercial approval, the substantial progress made in formulation design, stability enhancement, and manufacturing scalability underscores the growing potential of spray drying as a transformative platform for next-generation vaccine development and delivery. The technology offers a unique combination of thermostability, scalability, and formulation flexibility, making it particularly attractive for improving vaccine accessibility in resource-limited settings and strengthening global pandemic preparedness.

Several recent studies have further demonstrated the advantages of spray drying for vaccine stabilization. For example, Gomez et al. [45, 46] developed a spray-dried tuberculosis vaccine powder containing trehalose and L-leucine with the objective of improving thermostability and enabling pulmonary administration. The formulation retained excellent aerosolization performance after one year of storage and exhibited remarkable thermal stability. Notably, approximately 45% of the antigen remained intact after storage at 50°C for one year, whereas the corresponding liquid control formulation underwent complete antigen degradation within seven months at 40°C. These findings highlight the potential of spray drying to substantially enhance vaccine shelf life under challenging storage conditions. Similarly, LeClair et al. [47] investigated the spray-drying of a herpes simplex virus (HSV) vaccine candidate as a strategy to reduce cold-chain requirements. By incorporating protective disaccharides such as trehalose and sucrose, the researchers were able to preserve antigen stability during spray drying and subsequent storage. The study demonstrated the effectiveness of excipient-based stabilization approaches in maintaining vaccine integrity and immunogenic potential, further supporting the use of spray drying as a viable platform for the development of thermostable vaccines. Thus,

these advances illustrate the growing maturity of spray-drying technology in the vaccine field. By enabling the production of stable, highly dispersible, and temperature-resistant formulations, spray drying addresses several major limitations associated with conventional liquid vaccines.

Another study further highlights the feasibility of spray drying as a strategy for the development and manufacture of thermostable vaccines. In this investigation, a replicon-nanostructured lipid carrier (NLC) vaccine targeting the highly pathogenic H5N1 avian influenza A virus was successfully converted into a dry powder using spray drying, resulting in substantially improved thermal stability [48]. The spray-dried formulation remained chemically stable for at least one month at 40°C, while its immunogenicity was preserved for at least three months when stored at 4°C and subsequently administered intramuscularly to C57BL/6 mice following reconstitution. Notably, the researchers demonstrated precise control over the aerodynamic particle size of the spray-dried powder, enabling the production of particles theoretically suitable for direct nasal or pulmonary administration without the need for reconstitution. The replicon-NLC platform is composed of readily available materials and can be manufactured rapidly at scale, making it particularly attractive for stockpiling and emergency deployment. Collectively, these findings demonstrate that spray drying can be successfully integrated with advanced RNA-based vaccine technologies to generate thermostable, scalable, and versatile vaccine products capable of supporting rapid responses to future pandemics and infectious disease outbreaks.

Similarly, spray drying has shown considerable promise in the development of thermostable vaccines against COVID-19. A spray-dried intranasal COVID-19 vaccine candidate incorporating a nanoliposomal adjuvant system and SARS-CoV-2 spike protein antigen demonstrated excellent physicochemical stability and aerosolization performance [42]. The formulation, which utilized trehalose and L-leucine as stabilizing excipients, maintained antigen integrity, adjuvant content, particle morphology, and aerodynamic properties after storage for up to 10 months at both 25°C and 40°C. Importantly, the dry powder exhibited characteristics suitable for nasal administration, offering the potential for a needle-free vaccination strategy while eliminating many of the logistical challenges associated with refrigerated storage and transport [42]. These results further underscore the value of spray drying as a platform for the production of thermostable vaccines that can be distributed independently of cold-chain infrastructure, thereby improving vaccine accessibility and facilitating rapid deployment during global public health emergencies. Together, these studies exemplify how advances in spray-drying technology are addressing some of the most significant barriers in vaccine development and distribution. By enabling the production of stable, highly dispersible, and temperature-resistant formulations, spray drying not only enhances vaccine shelf life and manufacturability but also expands the possibilities for alternative routes of administration, including intranasal and pulmonary delivery. As next-generation vaccine platforms continue to emerge, spray drying is poised to play an increasingly important role in improving global vaccine accessibility, strengthening pandemic preparedness, and supporting equitable immunization efforts worldwide.

Diseases such as cholera remain endemic in many regions of Asia, Africa, South America, and Central America, where inadequate sanitation, limited access to clean water, and poor hygiene practices contribute to recurrent outbreaks. In these resource-constrained settings, effective vaccination programs represent one of the most important public health interventions for disease prevention and control. However, the successful implementation of immunization campaigns is often hindered by challenges associated with vaccine storage, transportation, and cold-chain maintenance. Consequently, the development of thermostable vaccine formulations has attracted considerable interest as a means of improving vaccine accessibility and coverage in underserved populations. In this context, Año and colleagues [49] investigated the use of spray drying for the microencapsulation of inactivated *Vibrio cholerae* utilizing the methacrylic acid copolymers Eudragit® L30D-55 and Eudragit® FS30D. The study demonstrated the feasibility of producing spray-dried oral vaccine formulations capable of protecting the encapsulated bacteria and providing controlled release within the gastrointestinal tract. Such an approach offers a promising strategy for improving vaccine stability while enabling alternative routes of administration that are particularly well suited for large-scale immunization programs in regions where healthcare resources are limited. Another noteworthy application of spray drying in vaccine formulation was reported by Ohtake and co-workers [50], who developed a heat-stable measles vaccine powder through the careful selection of stabilizing excipients combined with optimized, mild spray-drying conditions. The resulting formulation exhibited exceptional thermal stability, remaining viable for up to eight weeks under elevated temperature conditions, substantially exceeding the World Health Organization's minimum requirement of one week of stability. These findings demonstrated the potential of spray drying to overcome one of the major limitations of conventional live-attenuated vaccines and highlighted its value as a platform for developing thermostable vaccines suitable for deployment in regions where refrigeration is unreliable or unavailable.

Together, these studies illustrate the significant potential of spray-drying technology to address critical challenges in global vaccination efforts. By enabling the development of stable, orally administrable, and heat-resistant vaccine formulations, spray drying can reduce dependence on cold-chain infrastructure, improve vaccine accessibility in remote and resource-limited settings, and ultimately contribute to the prevention and control of infectious diseases such as cholera and measles. As advances in formulation science and particle engineering continue, spray drying is expected to play an increasingly important role in expanding the reach and effectiveness of global immunization programs.

3.2 Inhalation Powders

In recent years, pulmonary drug delivery has attracted considerable interest owing to several inherent advantages, including its noninvasive nature, avoidance of first-pass hepatic metabolism, relatively low enzymatic activity in the lungs, large absorptive surface area, rapid onset of action, and potential for both local and systemic drug delivery. Consequently, pulmonary administration has emerged as a well-established and extensively studied route for a wide range of therapeutic agents. However, conventional manufacturing approaches often struggle to meet the formulation requirements of modern therapies, particularly those involving poorly water-soluble compounds, biologics, high-dose medicines, and advanced delivery systems. These challenges have fueled growing interest in spray drying as a versatile platform for pulmonary drug delivery. Spray drying offers unique advantages for the production of inhalable powders because it enables precise control over particle size, morphology, density, porosity, and surface properties through the optimization of formulation composition and processing conditions. Such control is critical for pulmonary and nasal delivery, where particle characteristics directly influence aerosolization performance, deposition behavior, drug dissolution, and ultimately the rate and extent of drug absorption. As a result, spray drying has become one of the leading particle-engineering technologies for the development of dry powder inhalation products.

A notable example reported in the literature includes Marasini et al. [51], who developed an excipient-free co-spray-dried formulation comprising tobramycin and diclofenac using both two-fluid and three-fluid nozzle systems. The resulting powder exhibited excellent aerosolization performance and demonstrated considerable potential as a combination therapy for cystic fibrosis, simultaneously addressing pulmonary infection and inflammation. In another study, Wang et al. successfully encapsulated cryptotanshinone into inhalable L-leucine-based swellable microparticles designed for the treatment of cystic fibrosis [52]. A similar approach was employed in the development of inhalable spray-dried microparticles containing N-acetylcysteine, a mucolytic agent widely used in cystic fibrosis management [53]. The formulation combined N-acetylcysteine with mannitol, while both excipient selection and process parameters were systematically optimized to generate particles suitable for deep lung deposition. Although the incorporation of neutralizing agents such as sodium hydroxide or glass-transition modifiers including dextran, maltodextrin, and chitosan yielded spherical primary particles prone to agglomeration, the addition of L-leucine (20-25%) proved particularly effective in reducing particle adhesion. The optimized formulation exhibited favorable aerodynamic characteristics, including a mass median aerodynamic diameter (MMAD) of 5.95 ± 1.53 μm and a fine particle fraction of 33.06%. Furthermore, the encapsulated N-acetylcysteine retained sustained mucolytic activity in vitro, demonstrating the potential of spray-dried microparticles as an attractive alternative to conventional liquid formulations.

Several other spray-dried inhalation products have also been investigated for the management of respiratory diseases. One notable example is Exubera®, the first inhalable insulin dry powder approved by the U.S. Food and Drug Administration and manufactured using spray-drying technology [54]. Although the product demonstrated clinical efficacy, it was ultimately withdrawn from the market because of commercial factors, including its high cost and the cumbersome nature of the inhalation device, rather than limitations related to the spray-dried formulation itself. Nevertheless, Exubera® provided a landmark demonstration of the commercial feasibility of spray-dried pulmonary drug delivery systems. The versatility of spray drying has also been demonstrated in oncology applications. A spray-dried inhalable formulation of 5-azacytidine was shown to significantly reduce both tumor burden and systemic exposure, suggesting potential utility in the treatment of metastatic lung cancer [55]. Importantly, the study demonstrated successful spray drying of materials with glass transition temperatures below room temperature, while still achieving high production yields. These findings challenge the long-standing perception that such thermally sensitive materials are unsuitable for spray-drying processes and further expand the scope of inhalable anticancer formulations.

Beyond small molecules, spray drying has emerged as a promising platform for pulmonary delivery of biological therapeutics. In one notable study, researchers successfully developed spray-dried inhalable microparticles co-encapsulating bacteriophages targeting *Pseudomonas aeruginosa* and the antibiotic aztreonam [56]. Using mannitol, leucine, and trehalose as excipients, the formulation produced particles with aerodynamic properties suitable for deep lung deposition and a rapid burst-release profile to achieve immediate antimicrobial action. Aztreonam was encapsulated with high efficiency (97.87 ± 0.91%), while phage viability was maintained during both spray drying and subsequent storage for up to 28 days at 4°C and −20°C. The formulation achieved a 99.90% reduction in biofilm-associated bacterial load within 24 hours and demonstrated excellent in vitro biocompatibility, underscoring the translational potential of spray-dried phage-antibiotic combination therapies for the treatment of chronic pulmonary infections.

The flexibility of spray drying in tailoring the physicochemical properties of inhalable formulations was further illustrated by Foley et al. [57], who investigated the production of respirable guaifenesin particles using a methanol-water co-solvent system. The study systematically evaluated the effects of solvent composition, atomization gas flow rate, and excipient incorporation on process yield, particle size distribution, and particle density. Through process

optimization, the researchers successfully engineered particles with characteristics suitable for pulmonary administration, demonstrating the applicability of spray drying to a broad range of small-molecule therapeutics.

More recently, spray drying has been explored as a means of formulating inhalable cannabinoid-based therapies. One such study investigated anandamide, an endogenous cannabinoid with potential therapeutic utility in asthma management. Anandamide represents an attractive alternative to conventional β_2-adrenoceptor agonists, which may be associated with systemic side effects and receptor desensitization following prolonged use [58]. However, its clinical translation is challenged by poor aqueous solubility and susceptibility to degradation by heat and light. To overcome these limitations, researchers developed a spray-dried nano-in-microparticle system consisting of anandamide-loaded amphiphilic cyclodextrin nanoparticles co-spray-dried with mannitol. This approach combined the protective benefits of nanoparticle encapsulation with the favorable aerosolization properties of microparticles, resulting in a formulation suitable for targeted bronchial delivery. By enhancing drug stability while maintaining pulmonary delivery performance, the study further demonstrated the value of spray drying for the formulation of labile and structurally sensitive therapeutic agents.

Collectively, these studies highlight the transformative role of spray drying in pulmonary drug delivery. Through its ability to precisely engineer particle characteristics, stabilize sensitive molecules, and accommodate a wide range of therapeutic modalities, spray drying has emerged as a cornerstone technology for the development of next-generation inhalation therapies. As advances in particle engineering, biologics formulation, and inhalation-device technologies continue, spray drying is expected to play an increasingly important role in expanding the therapeutic possibilities of pulmonary drug delivery.

3.3 Encapsulation of Oligonucleotides

Antisense oligonucleotides (ASOs) have emerged as a promising class of therapeutics for the treatment of a wide range of diseases. Their therapeutic activity is achieved by selectively modulating gene expression, either through steric inhibition of messenger RNA (mRNA) translation or by promoting targeted mRNA degradation, thereby preventing the synthesis of disease-associated proteins. The successful clinical translation of ASO-based therapies, however, depends on the development of suitable delivery systems capable of protecting these molecules from degradation and facilitating their efficient transport to target tissues. Spray drying has increasingly been explored as a versatile platform for the formulation and delivery of oligonucleotide-based therapeutics and vaccines. In a notable study, Matilla et al. [59], investigated the efficacy of a spray-dried microparticulate vaccine targeting sperm protein 17 (SP17), a cancer-testis antigen aberrantly expressed in ovarian cancer. The formulation incorporated both the SP17 peptide antigen and the immunostimulatory Toll-like receptor 9 (TLR9) agonist CpG oligonucleotide. To enhance oral delivery and immune activation, the microparticles were prepared using enteric and sustained-release polymers and functionalized with *Aleuria aurantia* lectin to target microfold (M) cells within gut-associated lymphoid tissue. Oral administration of the vaccine in mice resulted in a significant reduction in ascites formation and tumor progression after four weeks compared with placebo-treated controls, highlighting the potential of spray-dried particulate systems for oral cancer immunotherapy.

The utility of spray drying for antisense oligonucleotide delivery has also been demonstrated in cardiovascular applications. Patel et al. [60] developed albumin-based microspheres encapsulating antisense oligonucleotides directed against nuclear factor kappa B (NF-κB) for the treatment of congestive heart failure. The microspheres were produced using spray-drying technology and evaluated in a rat model of cardiac remodeling. Treatment with the ASO-loaded microspheres led to significantly lower NF-κB activation and reduced tumor necrosis factor-alpha (TNF-α) release compared with control groups. Importantly, the formulation effectively attenuated ventricular remodeling, demonstrating the therapeutic potential of targeted gene-silencing approaches for cardiovascular disease management. Albumin represents an attractive carrier for ASO delivery because of its biocompatibility, biodegradability, and ability to protect encapsulated oligonucleotides from nuclease-mediated degradation, thereby enhancing their stability and therapeutic efficacy.

Beyond systemic administration, spray drying has also shown considerable promise for the pulmonary delivery of nucleic acid therapeutics. The lungs provide an attractive route for local and systemic delivery owing to their large surface area, extensive vascularization, and relatively low enzymatic activity. In this context, Munir et al. [61] investigated the development of inhalable nucleic acid formulations by spray drying nanoparticles composed of the cationic peptide RALA complexed with plasmid DNA. The study focused on optimizing spray-drying parameters to produce stable dry powder formulations suitable for inhalation. The resulting particles retained nanoparticle integrity following reconstitution and exhibited physicochemical characteristics compatible with pulmonary administration. These findings demonstrate the feasibility of employing spray drying for the manufacture of inhalable gene delivery systems and highlight its potential for the development of advanced nucleic acid-based therapies. Collectively, these studies underscore the growing importance of spray drying in the formulation of oligonucleotide therapeutics, genetic vaccines, and gene-delivery platforms. By enabling the encapsulation, stabilization, and targeted delivery of sensitive

nucleic acid molecules, spray drying offers a scalable and versatile manufacturing strategy for next-generation pharmaceutical products. As interest in RNA- and DNA-based therapeutics continues to expand, spray-drying technologies are expected to play an increasingly important role in overcoming formulation and delivery challenges, thereby facilitating the translation of these innovative therapies into clinical practice.

3.4 Protein-based Therapeutics

Protein-based therapeutics have become one of the most important classes of pharmaceutical products, accounting for a substantial and continuously growing share of the global pharmaceutical market. Over the past several decades, proteins have transformed the treatment of numerous diseases, including diabetes (insulin), anemia (erythropoietin), autoimmune disorders, and various cancers, exemplified by monoclonal antibodies such as rituximab. Owing to their high specificity, potent biological activity, and favorable therapeutic profiles, protein-based drugs continue to attract significant research and commercial interest, driving the development of increasingly sophisticated biologic therapies. Despite their remarkable therapeutic potential, proteins present unique challenges in formulation, delivery, and long-term storage. Proteins are inherently complex macromolecules whose biological activity depends on the preservation of their three-dimensional structure. They are susceptible to a wide range of degradation pathways, including denaturation, aggregation, deamidation, oxidation, hydrolysis, and adsorption to surfaces. Furthermore, proteins are readily degraded by enzymatic activity within the gastrointestinal tract and often exhibit poor permeability across intestinal epithelia, resulting in extremely limited oral bioavailability [15, 62]. Consequently, most therapeutic proteins are administered via parenteral routes, particularly intravenous, subcutaneous, or intramuscular injection. However, the need for frequent injections can compromise patient compliance and quality of life, motivating extensive efforts to develop noninvasive delivery strategies.

Another major challenge associated with protein therapeutics is maintaining their stability throughout manufacturing, storage, transportation, and administration. Protein degradation can lead not only to loss of biological activity but also to the formation of aggregates that may trigger unwanted immunogenic responses. For this reason, considerable attention has been devoted to developing solid-state formulations, which generally exhibit superior stability compared with liquid formulations. Dehydration reduces molecular mobility and limits degradation reactions, thereby extending shelf life and improving storage stability. Traditionally, lyophilization has been the most widely used method for producing solid protein formulations. This technique is well established and has been successfully employed for numerous injectable biologics that are reconstituted prior to administration. However, lyophilization possesses several limitations, including long processing times, high energy consumption, and limited control over particle characteristics. Moreover, lyophilized products are typically obtained as cakes rather than free-flowing powders, often requiring additional processing before further formulation. Unlike particle-engineering technologies, lyophilization also provides limited flexibility in tailoring particle size, morphology, and aerodynamic properties.

Against this backdrop, spray drying has emerged as a powerful alternative platform for the formulation of protein therapeutics. Over the last 25 years, interest in applying spray-drying technology to sensitive biologics has increased dramatically. One of the earliest studies in this field was reported by Labrude and colleagues in 1989, who successfully spray-dried oxyhemoglobin, a metalloprotein, thereby demonstrating the feasibility of processing biologically active proteins using this technique [63]. Since then, spray drying has evolved into an important tool for producing stable protein powders for a variety of pharmaceutical applications.

The attractiveness of spray drying stems from its ability to convert protein solutions into dry powders in a single, continuous, and scalable process. Nevertheless, the technology also presents significant challenges when applied to proteins. During spray drying, proteins may be exposed to thermal, mechanical, dehydration, and interfacial stresses that can result in structural perturbations, aggregation, or loss of biological activity. Among these, dehydration-induced conformational changes and exposure to air-liquid interfaces during atomization are often considered more critical than heat exposure itself. Importantly, although spray drying typically employs elevated inlet temperatures, the actual thermal exposure experienced by protein molecules is limited because droplets remain within the drying chamber for only a few seconds. This short residence time substantially reduces the likelihood of temperature-induced degradation and enables the successful processing of many heat-sensitive biomolecules.

A key strategy for preserving protein stability during spray drying is the incorporation of appropriate excipients. These stabilizing agents protect proteins both during processing and throughout storage by minimizing structural alterations and inhibiting aggregation. In their pioneering work, Labrude et al. [63] demonstrated that the addition of sucrose significantly improved the stability of oxyhemoglobin during spray drying. Since then, numerous studies have highlighted the importance of formulation design in producing stable spray-dried protein products. Commonly employed excipients include disaccharides such as trehalose and sucrose, polyols such as mannitol, amino acids such as leucine and glycine, and surfactants that reduce interfacial stress. Together, these excipients can preserve protein conformation, reduce aggregation, improve powder dispersibility, and enhance long-term storage stability.

More recently, advanced stabilization approaches have been investigated to further improve the performance of spray-dried biologics. For example, a recent study evaluated the use of 2-hydroxypropyl-β-cyclodextrin (HPβCD) in combination with trehalose for stabilizing a model monoclonal antibody (mAb1) in spray-dried formulations [64]. The authors demonstrated that HPβCD effectively inhibited or delayed the recrystallization of trehalose, thereby maintaining the amorphous matrix required to preserve protein integrity during storage. This strategy significantly enhanced the physical stability of the monoclonal antibody in the dried state and highlighted the growing sophistication of excipient-based stabilization technologies. Beyond stabilization, spray drying also enables the production of protein-loaded micro- and nanoparticles that offer significant therapeutic advantages. Encapsulation within particulate carriers protects proteins from enzymatic degradation, prolongs circulation time, and can enhance bioavailability by reducing premature clearance from the body. Moreover, nanoparticulate systems provide opportunities for controlled release and targeted delivery to specific tissues or cell populations, thereby improving therapeutic efficacy while reducing systemic side effects. The ability of spray drying to simultaneously engineer particle properties and preserve protein stability has therefore made it a valuable platform for the development of next-generation biologics, including monoclonal antibodies, therapeutic enzymes, growth factors, peptides, vaccines, and nucleic acid-based medicines. Through careful optimization of process parameters and excipient selection, spray drying can overcome many of the stability and delivery challenges traditionally associated with biologics. As demand for protein-based medicines continues to expand, spray drying is poised to play an increasingly important role in enabling the development of stable, scalable, and patient-friendly therapeutic products.

3.5 Long Acting Injectables

Chronic diseases continue to represent a major global health burden and frequently require lifelong pharmacotherapy to achieve sustained disease management. However, many treatment regimens depend on frequent dosing schedules, which can adversely affect patient adherence and ultimately compromise therapeutic outcomes. Poor adherence is particularly problematic in conditions that require the maintenance of consistent drug concentrations over extended periods. In psychiatric disorders, for example, medication nonadherence is common and is strongly associated with symptom relapse, hospitalization, and treatment discontinuation. Likewise, interruptions in therapy for chronic conditions such as HIV infection and diabetes can result in treatment failure, disease progression, and, in some cases, the emergence of drug resistance. Consequently, poor adherence imposes a substantial clinical, social, and economic burden on patients, caregivers, and healthcare systems worldwide [65, 66].

To address these challenges, long-acting injectables (LAIs) have emerged as an effective therapeutic strategy that provides sustained drug release following a single administration, thereby maintaining therapeutic drug levels for weeks or even months while significantly reducing dosing frequency. In addition to improving patient adherence, LAIs reduce fluctuations in plasma drug concentrations, minimize peak-related adverse effects, and enhance overall treatment efficacy. As a result, they have become an increasingly important component of treatment strategies for a wide range of chronic diseases, including psychiatric disorders, HIV infection, diabetes, cancer, and chronic inflammatory diseases [67, 68]. The rapid advancement of LAI technologies over the past two decades has been driven by innovations in biodegradable polymers, lipid-based delivery systems, and formulation science, as well as significant improvements in pharmaceutical manufacturing technologies [69, 70]. Traditionally, LAI formulations, particularly polymeric microspheres, have been manufactured using emulsion-solvent evaporation or solvent-extraction techniques. While these methods have successfully enabled the commercialization of numerous LAI products, they typically involve multiple processing steps, including emulsification, solvent removal, washing, and drying. Such complex manufacturing processes can increase production time, result in drug loss, contribute to batch-to-batch variability, and create challenges during scale-up. Moreover, prolonged exposure of therapeutic agents to aqueous-organic interfaces during emulsification can adversely affect the stability of sensitive compounds, particularly peptides, proteins, and nucleic acids.

To overcome these limitations, spray drying has emerged as a highly versatile particle-engineering platform for the development of long-acting injectable formulations. Unlike conventional emulsion-based manufacturing processes, spray drying is a single-step, continuous operation that rapidly converts drug-containing solutions, suspensions, or emulsions into dry particulate systems through solvent evaporation. The rapid and controlled nature of the process enables precise manipulation of critical particle attributes, including particle size, morphology, density, porosity, and drug distribution within the particle matrix. These characteristics are fundamental determinants of injectability, depot formation, drug-loading efficiency, and sustained-release performance. In addition, spray drying is readily scalable and compatible with a broad spectrum of materials, including biodegradable polymers, lipids, proteins, and emerging biomaterials, as well as a diverse range of therapeutic agents. These advantages make spray drying particularly attractive for the development of next-generation LAIs, especially as the field expands beyond conventional small-molecule drugs to encompass complex biologics and nucleic acid-based therapeutics.

The clinical relevance of spray drying as a manufacturing technology for LAIs is exemplified by its application in the development of several poly(lactic-co-glycolic acid) (PLGA)-based depot formulations. The successful clinical

translation of spray-dried long-acting injectable technologies is exemplified by marketed PLGA-based depot products such as Trelstar® [71] while numerous studies have further demonstrated the ability of spray drying to generate biodegradable microspheres with physicochemical characteristics suitable for sustained drug delivery [72] over weeks to months. For example, spray-dried PLGA microspheres encapsulating the peptide drug leuprolide were engineered to closely mimic the composition and release characteristics of the commercially available product Lupron Depot® [73]. Through careful optimization of spray-drying parameters, the resulting microspheres achieved sustained peptide release for approximately one month, exhibiting release profiles comparable to, and in some cases superior to, those of the reference product. These findings demonstrate the ability of spray drying to generate clinically relevant controlled-release formulations with predictable performance. Similar success has been reported for spray-dried PLGA microparticles containing bovine serum albumin (BSA) as a model protein. Detailed characterization studies revealed that the initial burst release was governed primarily by protein localization near the particle surface rather than by particle morphology alone. Such findings provide valuable mechanistic insights into the factors controlling drug release from spray-dried depot systems and underscore the importance of engineering particle architecture during formulation development.

The versatility of spray drying has also been demonstrated in the formulation of anti-infective depot therapies. In one notable study [74] , biodegradable spray-dried microparticles containing capreomycin oleate for the treatment of multidrug-resistant tuberculosis achieved encapsulation efficiencies approaching 92%, substantially higher than those obtained using conventional solvent evaporation methods (approximately 56%). Furthermore, the formulation exhibited controlled drug release both in vitro and in vivo while demonstrating favorable local tissue compatibility following intramuscular administration. These results highlight the potential of spray drying to enhance drug loading, improve manufacturing efficiency, and maintain desirable release characteristics in long-acting injectable systems.

Collectively, these studies demonstrate that spray drying is far more than a scalable powder-production technology. Rather, it represents a sophisticated particle-engineering platform capable of producing long-acting injectable formulations with high encapsulation efficiency, controlled and predictable release profiles, excellent biocompatibility, and robust manufacturing reproducibility. As therapeutic pipelines increasingly incorporate peptides, proteins, monoclonal antibodies, and nucleic acid-based therapeutics, the formulation flexibility and scalability offered by spray drying are likely to establish it as a key enabling technology in the next generation of long-acting drug delivery systems.

4 CONCLUSION

Over the past decade, spray drying has evolved from a conventional drying operation into a highly sophisticated particle-engineering technology that plays a central role in modern pharmaceutical development. Advances in formulation science, process optimization, and spray-drying equipment have significantly expanded its capabilities, enabling the successful manufacture of complex drug delivery systems, including inhalable dry powders, thermostable vaccines, long-acting injectables, protein therapeutics, nucleic acid-based medicines, and nanoparticle formulations. These developments highlight the unique versatility of spray drying in generating particles with precisely tailored physicochemical and biopharmaceutical properties while accommodating a wide range of therapeutic agents and delivery platforms. Beyond its well-established utility for improving drug stability, solubility, and bioavailability, spray drying offers several important advantages that are increasingly valued in pharmaceutical manufacturing. As a single-step, continuous, scalable, and cost-effective process, it provides high manufacturing efficiency, excellent reproducibility, and precise control over critical quality attributes. Its strong compatibility with Quality by Design (QbD) principles and modern process-control strategies further enhances its suitability for robust product development and commercial-scale production. Importantly, the role of spray drying has expanded far beyond simple powder production. It has emerged as a powerful platform for particle design, enabling the engineering of micro- and nanoscale delivery systems with controlled morphology, aerodynamic performance, release behavior, and targeting capabilities. These capabilities have facilitated the development of innovative therapies across multiple routes of administration, including oral, pulmonary, parenteral, and mucosal delivery, while also supporting the stabilization and delivery of increasingly complex biologics and genetic medicines. As the pharmaceutical landscape continues to shift toward biologics, nucleic acid therapeutics, personalized medicines, and advanced drug delivery systems, the demand for flexible manufacturing technologies capable of preserving the integrity of sensitive molecules while enabling precise control of therapeutic performance will continue to grow. Future advances in spray drying are likely to be driven by the integration of novel biomaterials, advanced excipient systems, continuous manufacturing technologies, process analytical technologies (PAT), and data-driven optimization tools, including artificial intelligence and machine learning. Together, these innovations are expected to further enhance process understanding, product quality, and manufacturing efficiency. In conclusion, spray drying has transformed into a versatile and enabling technology that bridges formulation science, particle engineering, and pharmaceutical manufacturing. Its unique combination of scalability, controllability, and adaptability positions it as a cornerstone platform for the development and production of next-generation pharmaceutical products. As research and technological innovation continue to advance, spray drying is poised to play an increasingly important role in shaping the future of precision drug delivery and pharmaceutical manufacturing.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

The authors declare no conflicts of interest.

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