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REVIEW ARTICLE



Spray drying: A promising approach for microencapsulation in controlled drug delivery

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ABSTRACT

Spray drying has emerged as one of the most versatile and scalable microencapsulation techniques for developing controlled and targeted drug delivery systems. Its ability to convert liquid formulations into stable particulate systems in a single step has made it widely applicable for improving the stability, bioavailability, and release characteristics of therapeutic agents. This review critically examines the role of spray-dried microencapsulation in controlled drug delivery, with particular emphasis on formulation design, particle engineering, process optimization, and recent technological advancements. The review highlights that the performance of spray-dried microcapsules is primarily governed by the interplay between formulation composition and drying conditions. Appropriate selection of polymers, stabilizers, and processing parameters enables the production of particles with tailored size, morphology, encapsulation efficiency, and drug-release behavior. Recent innovations, including nano-spray drying, hybrid carrier systems, and stimuli-responsive polymers, have expanded the applicability of spray-dried formulations across oral, pulmonary, nasal, transdermal, and parenteral delivery routes while improving the protection and delivery of sensitive bioactive compounds. Despite these advances, several challenges continue to limit industrial translation, including thermal degradation of labile compounds, variability in particle formation, scale-up complexities, and regulatory constraints. Emerging approaches, such as QbD, advanced process modeling, AI-assisted optimization, and smart polymeric systems offer promising solutions to enhance reproducibility and therapeutic performance. Overall, spray-dried microencapsulation represents a robust and evolving platform for controlled and site-specific drug delivery. Continued integration of formulation science, process engineering, and advanced materials is expected to facilitate the development of next-generation drug delivery systems with improved efficacy, safety, and scalability.

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1. Introduction

Microencapsulation is an advanced formulation strategy that plays a critical role in improving drug stability, bioavailability, and controlled release behavior. Among the various encapsulation techniques, spray drying has emerged as a highly efficient and scalable method owing its ability to convert liquid formulations into dry, stable microcapsules in a single step. The significance of spray drying lies in its capability to engineer particle size, morphology, and internal structure, which directly influences drug release kinetics and targeting efficiency. Unlike conventional

encapsulation methods, spray drying offers advantages, such as continuous processing, cost-effectiveness, and compatibility with a wide range of polymers and bioactive compounds. In controlled and targeted drug delivery systems, spray-dried microcapsules enable the protection of sensitive drugs, modulation of release profiles, and improved site-specific delivery when combined with appropriate formulation strategies. Therefore, understanding the interplay between the formulation components and spray drying process parameters is essential for the rational design of advanced drug delivery systems.

1.1. Summary of controlled and targeted drug delivery

Controlled and targeted drug delivery systems are designed to optimize therapeutic outcomes by maintaining drug concentration within the therapeutic window while minimizing systemic side effects.^[1] The modern drug delivery systems are targeted and controlled, and would greatly benefit from new advances in nanotechnology and nanomaterials that enhance pharmacokinetic and pharmacodynamic efficiency.^[2,3] Controlled drug delivery systems maintain drug levels within therapeutic ranges, and have the benefit of reduced toxicity, enhanced bioavailability, and enhanced patient compliance. In contrast targeted drug delivery, limits exposure to normal tissues by targeting specific cells or organs with therapeutic agents, and is especially effective in therapies such as cancer. Such targeting techniques are passive, which takes advantage of the physiological characteristics of diseased tissues, and active, which involves the modification of drug carriers to provide increased receptor interaction.^[4] The strategies will enable better localization and efficacy of the drugs in addition to reducing side effects.^[5]

1.2. Why microencapsulation important?

Microencapsulation is a major method for the enclosure of liquid droplets and tiny solid particles, usually ranging between 1 and 1000 nm, in a fine film of biocompatible polymer to produce targeted delivery mechanisms.^[6] The microcapsules, microspheres, micro-particles, and micro-emulsions can be distinguished by their size, composition, structure, and functional behavior. The use of microencapsulation has gained importance as its application has increased dramatically in the various scientific and industrial applications, an occurrence that was triggered by the pharmaceutical industry to regulate drug release profiles.^[7]

Microencapsulation has one of its main benefits in the form of protection which is instrumental in protecting sensitive bioactive compounds against environmental stressors. This technology is efficient in forming a protective layer that reduces chemical degradation, oxidation, and contamination to improve the stability, bioavailability, and controlled release of bioactive molecules.^[8] In addition, hygroscopic compounds can be encapsulated, resulting in better flow characteristics, stability, and shelf life. The physicochemical properties and solubility of core materials determine the choice of encapsulating materials and

solvent systems which can eventually influence the release kinetics and functional performance of the core materials.^[9]

Microencapsulation has widespread applicability in different sectors of the economy, including pharmaceuticals, food, agriculture, cosmetics, skincare, and aquaculture, among others, making it an important product performance enhancer. Microencapsulation in the food sector has proven useful in fortifying food products such as biscuits, drinks, rice, wheat, fermented milk, and enriched yoghurt with bioactive components such as fat-soluble vitamins, curcumin, and catechin among others without affecting the flavor and stability of the foods. This method also enables the introduction of flavoring substances to food, promoting the usefulness and health-related advantages of foods.^[10]

Microencapsulation in pharmaceutical formulations is also used to achieve controlled and sustained drug release and, improve therapeutic efficacy and patient compliance whereas in food systems, it is used to optimize nutrient delivery, stability, and sensory properties of functional ingredients.^[11] In addition, microencapsulation greatly enhances the manipulation and treatment of active ingredients by boosting their stability and safety. For example, it inhibits eutectic formation and liquefaction that may occur in the case of direct contact between incompatible components and enables successful separation and microencapsulation before mixing. This method also reduces the volatility of active compounds thereby allowing them to be stored for a longer time without significant evaporation or any substantial loss of action. Furthermore, microencapsulation is effective in addressing safety issues associated with the use of hazardous substances such as fumigants, herbicides, insecticides, and pesticides that are not easily handled, due to their toxicity.^[12]

2. Spray drying: mechanistic basis and relevance in microencapsulation

Spray drying is a formulation-driven particle engineering technology widely used for pharmaceutical microencapsulation and controlled drug delivery. The process converts liquid feeds into dry particles through atomization and rapid solvent evaporation, enabling simultaneous particle formation, and drying in a single continuous step.^[13–15] Unlike conventional drying methods, spray drying provides precise control over particle size, morphology, encapsulation efficiency, and drug-release characteristics, making it particularly valuable for designing advanced drug delivery

systems. Particle formation is governed by coupled heat- and mass-transfer phenomena. Following atomization, solvent evaporation increases solute concentration, leading to precipitation, vitrification, or shell formation depending on formulation composition. The balance between solvent evaporation and solute diffusion determines particle architecture, with rapid surface solidification producing hollow or porous particles and slower solidification yielding dense matrices.^[13–15] These structural attributes directly influence drug loading, stability, dissolution, aerodynamic behavior, and release kinetics. The functional performance of spray-dried systems is primarily dictated by formulation design rather than the drying process itself. Polymers such as PLGA, chitosan, alginate, and cellulose derivatives regulate drug release through diffusion-, swelling-, and erosion-controlled mechanisms. Spray drying also enhances the stability of poorly soluble drugs, peptides, proteins, and other sensitive bioactives by entrapping them within protective matrices.^[13–15]

Previous studies have highlighted the importance of mechanistic particle engineering in spray-dried formulations. Ré demonstrated that rapid matrix solidification improves encapsulation and protects bioactives from environmental degradation.^[16] Vehring emphasized the role of particle morphology and aerodynamic properties in pharmaceutical performance.^[17] Similarly, Deshmukh et al. reported that understanding droplet drying and particle solidification is essential for developing reproducible micro- and nanoparticulate drug delivery systems with controlled release characteristics.^[18] Collectively, these findings establish spray drying as a robust platform for the rational design of microencapsulated drug delivery systems.

2.1. Process overview

Spray drying converts liquid formulations (solutions, suspensions, or emulsions) into dry particles through

atomization and rapid solvent evaporation in a heated gas stream.^[14,19] The high surface-area-to-volume ratio of atomized droplets enables rapid drying within seconds, facilitating the production of stable particulate systems. During the early drying stage, evaporative cooling limits thermal stress on encapsulated compounds; however, increasing particle temperature at later stages may affect heat-sensitive actives.^[20,21] Owing to its continuous, scalable nature and ability to engineer particle properties, spray drying is extensively used for the preparation of amorphous solid dispersions, inhalable powders, and microencapsulated drug delivery systems (Figure 1).^[15,19,22,23]

2.2. Particle formation mechanism

Particle formation is governed by solvent evaporation, solute diffusion, and matrix solidification.^[24,25] As solvent evaporates, increasing solute concentration induces precipitation, vitrification, or shell formation. The balance between evaporation kinetics and solute mobility determines particle morphology: rapid surface solidification produces hollow or porous particles, whereas uniform solute redistribution yields dense matrices.^[26–28] Feed composition further influences particle structure, with polymers typically forming amorphous matrices that stabilize encapsulated drugs.^[29–31] These microstructural characteristics directly affect encapsulation efficiency, aerodynamic behavior, dissolution, and drug-release kinetics.^[17,18,32–35] Mechanistic studies by Ré, Vehring, and Deshmukh et al. demonstrated that understanding droplet drying and particle solidification is critical for establishing structure–property relationships in spray-dried pharmaceutical systems (Figure 2).^[16–18]

2.3. Equipment design and process parameters

A spray dryer typically comprises a feed delivery system, atomizer, drying chamber, and particle collection

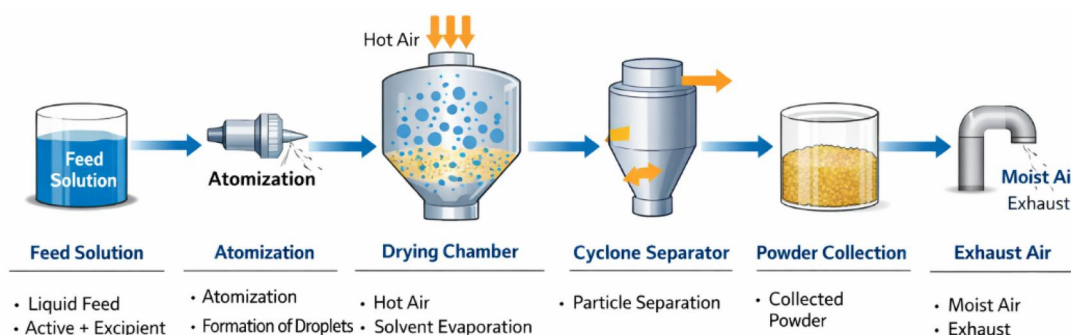


Figure 1. General process flow diagram of spray drying.

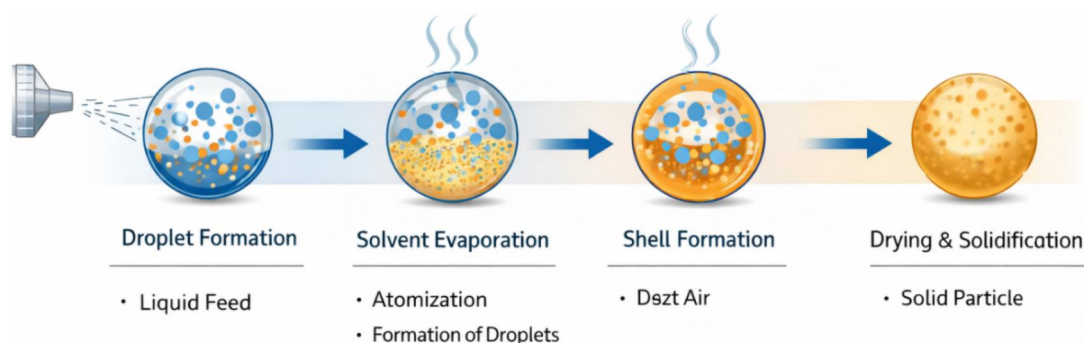


Figure 2. Droplet-to-particle transformation mechanism.

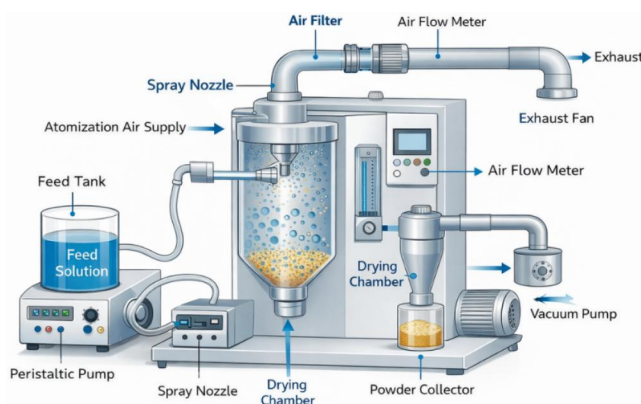


Figure 3. Schematic layout of a laboratory spray dryer.

unit.^[36,37] Critical process parameters include inlet/outlet temperatures, feed rate, atomization conditions, airflow, and humidity, which collectively influence drying kinetics, particle size, morphology, residual moisture, and encapsulation efficiency.^[38–48] During scale-up, variations in airflow patterns, heat transfer, and residence time may alter product characteristics, necessitating mechanistic process control.^[15,22] Consequently, Quality by Design (QbD) approaches and computational modeling are increasingly employed to establish robust and reproducible operating conditions for pharmaceutical manufacturing (Figure 3).^[49–53]

3. Materials used in spray-dried microcapsule formulation

The performance of spray-dried microcapsules is largely determined by the selection of core materials, wall polymers, and stabilizing excipients. These components collectively influence encapsulation efficiency, particle morphology, release kinetics, and storage stability. Recent studies have demonstrated that rational material selection is critical for achieving targeted delivery, improved bioavailability, and protection of sensitive bioactives.^[14]

3.1. Core materials (drugs and actives)

Core materials constitute the therapeutic or functional payload of spray-dried microcapsules and include small-molecule drugs, peptides, proteins, vaccines, probiotics, essential oils, and nutraceuticals.^[54–56] In pharmaceutical applications, spray drying is frequently employed to improve the dissolution and bioavailability of poorly soluble drugs through amorphous solid dispersions.^[57–59] For example, Vehring et al. demonstrated that spray-dried inhalable formulations enable precise aerodynamic control for pulmonary delivery, while Sipos et al. reported enhanced nasal permeability and rapid drug release from spray-dried vinpocetine-loaded systems.^[17] In food and nutraceutical applications, encapsulation of polyphenols, carotenoids, probiotics, and essential oils improves oxidative stability, masks undesirable sensory properties, and extends shelf life.^[60–65]

3.2. Polymers and wall materials

Wall materials form the protective matrix surrounding the active ingredient and govern drug release and particle stability.^[66,67] Pharmaceutical formulations commonly utilize PLGA, chitosan, alginate, and cellulose

derivatives owing to their biodegradability and ability to modulate release behavior.^[49,68,69] For instance, PLGA-based spray-dried particles have demonstrated sustained ocular drug delivery and enhanced corneal retention. In food and nutraceutical formulations, maltodextrin and gum Arabic remain the most widely used carriers because of their excellent drying characteristics and regulatory acceptance.^[70–72] Polymer blending is often employed to combine structural stability with emulsification efficiency, thereby improving encapsulation performance and storage stability.^[73,74]

3.3. Role of solvents and stabilizers

Solvents and stabilizers play a critical role in feed preparation and particle formation.^[18,75,76] Water is the preferred solvent; however, hydroalcoholic systems are often required for poorly soluble compounds.^[77–79] Stabilizers such as surfactants, emulsifiers, antioxidants, and plasticizers improve emulsion stability, reduce interfacial stress, and protect sensitive bioactives during drying.^[80–88] For biologics, excipients including trehalose, mannitol, and leucine have been shown to preserve structural integrity and improve powder stability during storage. Collectively,

the interactions among core materials, polymers, solvents, and stabilizers determine the physicochemical and functional performance of spray-dried microcapsules.^[89–91] Figure 4 and Table 1 which describe the relationship between formulation materials (core, wall, solvent, and additives) and spray-drying equipment, in which preparation of the feed, atomization, drying, and particle collection jointly determine microcapsule formation, structure, and performance.

Overall, successful spray-dried microencapsulation relies on the balanced integration of core materials, wall polymers, and stabilizing systems. A formulation-driven approach, supported by mechanistic understanding and systematic optimization, is essential for achieving the desired structural and functional performance in pharmaceutical, nutraceutical, and food applications.^[92–94]

4. Formulation optimization of spray-dried microcapsules

Spray-dried microencapsulation is widely employed to enhance the stability, protection, and controlled release of bioactive compounds. However, successful industrial translation remains challenging because

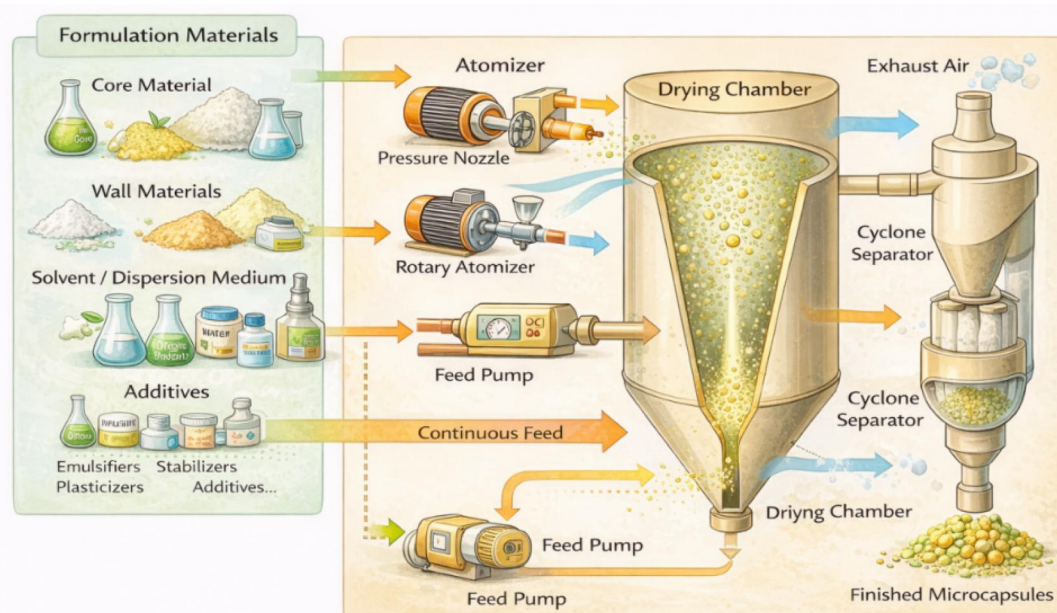


Figure 4. Relation between formulation materials and spray-drying equipment.

Table 1. The key components and their functional contributions to drug delivery systems.

Component type	Examples	Functional role	Impact on drug delivery
Core material	Curcumin, Insulin, Peptides	Active drug	Bioavailability, stability
Polymers	PLGA, Chitosan, Alginate	Encapsulation matrix	Controlled/sustained release
Stabilizers	Lecithin, Tween, PEG	Emulsion stability	Encapsulation efficiency, uniformity

particle characteristics optimized at the laboratory scale are often difficult to reproduce during scale-up owing to differences in equipment design, airflow patterns, heat and mass transfer, and residence time.^[95–98] Therefore, a mechanistic understanding of both formulation and process variables is essential for robust product development.

The physicochemical properties of active ingredients and wall materials play a central role in determining encapsulation efficiency, particle morphology, and release behavior. Common wall materials include maltodextrin, gum Arabic, cyclodextrins, modified starches, whey protein, gelatin, alginate, and chitosan, which are selected based on their film-forming ability, compatibility with the active compound, and stabilization capacity.^[99] Studies have shown that formulation composition and carrier selection significantly influence drying behavior, particle formation, and long-term stability.^[100] Critical process parameters include feed solids content, viscosity, emulsion stability, atomization conditions, inlet and outlet temperatures, and drying airflow.^[101–103] These variables govern droplet formation, solvent evaporation, shell development, residual moisture content, and particle size distribution, ultimately influencing product quality and performance.^[104,105] Furthermore, the physicochemical properties of carrier systems, particularly proteins and polysaccharides, can affect encapsulation efficiency, process robustness, and particle stability during manufacturing and storage.^[106,107]

The encapsulation of highly sensitive bioactives remains a major challenge because oxidation, moisture uptake, and thermal degradation can compromise product quality.^[108,109] At industrial scale, issues, such as nozzle clogging, non-uniform atomization, wall deposition, and batch-to-batch variability may further affect process reproducibility.^[110]

Recent investigations have demonstrated that the performance of spray-dried microcapsules is governed by the interplay between formulation composition, drying kinetics, and particle microstructure. For example, spray-dried *Spirulina* (*Arthrospira platensis*) protein formulations revealed that evaporation-driven shell formation influences protein localization within particles, a phenomenon described by the Peclet number (Pe).^[100] Similarly, spray-dried formulations containing bioactives from *Eruca sativa*, *Raphanus sativus*, and *Brassica oleracea* showed improved antioxidant retention when carbohydrate–protein carrier systems were employed because of enhanced film-forming properties and higher glass transition temperatures.^[111]

Overall, the successful development of spray-dried microcapsules depends on the integrated optimization of formulation composition, process parameters, and particle engineering principles. Such an approach is essential for improving encapsulation efficiency, product stability, scalability, and therapeutic performance.

5. Characterization of spray-dried microcapsules

Spray-dried microcapsules are characterized to evaluate the influence of formulation composition and drying conditions on particle properties, encapsulation performance, and storage stability. Critical quality attributes include particle size, morphology, encapsulation efficiency, release behavior, and thermal stability, which collectively determine the functionality of spray-dried powders.^[17,112–116]

5.1. Particle size and morphology

Particle size distribution (PSD) is a key parameter affecting powder flowability, dispersibility, and dissolution behavior of spray-dried microcapsules. PSD is commonly determined by laser diffraction and reported as volume mean diameter (D_{4,3}) and median diameter (D_{v50}).^[112,117] Process variables such as feed solids concentration, atomization pressure, and drying temperature significantly influence particle size.^[118]

Particle morphology is typically examined using scanning electron microscopy (SEM). Spray-dried particles generally exhibit spherical structures with smooth, wrinkled, hollow, or porous surfaces depending on drying kinetics and formulation composition.^[119–122] Rapid solvent evaporation promotes hollow or porous particle formation, whereas slower drying results in denser particles with reduced porosity and improved encapsulation performance.^[123–126]

5.2. Encapsulation efficiency and surface characteristics

Encapsulation efficiency (EE) is one of the most important indicators of spray-drying performance and reflects the ability of the wall material to retain the core compound during drying.^[127,128] EE is affected by feed composition, wall material properties, and drying conditions. Higher solid content and appropriate carrier selection generally improve matrix formation and reduce active compound migration to the particle surface.^[112,129]

Surface-associated active compounds are commonly quantified to assess encapsulation quality. Excessive surface deposition may increase oxidation susceptibility, stickiness, and particle agglomeration during storage.^[130,131] Studies using maltodextrin–gum Arabic carrier systems have demonstrated improved retention of sensitive bioactives due to enhanced emulsion stability and rapid matrix formation during spray drying.^[132]

5.3. *In vitro* release characteristics

Drug release from spray-dried microcapsules is primarily governed by carrier solubility, particle structure, and matrix permeability.^[133] Hydrophilic carriers generally produce rapid release profiles, whereas polymeric matrices can provide sustained release through diffusion-controlled mechanisms.^[130,134]

Release kinetics are commonly evaluated using mathematical models such as zero-order, first-order, and Higuchi equations to identify the dominant release mechanism.^[135] For pH-responsive spray-dried systems, release studies are often performed under simulated gastrointestinal conditions to assess site-specific delivery and polymer responsiveness.^[136]

5.4. Thermal and storage stability

Thermal and storage stability are essential quality attributes of spray-dried microcapsules. Residual moisture content and glass transition temperature (T_g) strongly influence powder stability, caking tendency, and active compound retention.^[137,138] The stability of encapsulated compounds is commonly monitored through active compound retention, moisture uptake, and physicochemical changes during storage.^[139–141] Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) are routinely used to evaluate thermal transitions and degradation behavior of spray-dried formulations.^[142,143] High- T_g carrier materials, such as maltodextrin, gum Arabic, and modified starch improve the stability of spray-dried powders by maintaining the matrix in a glassy state and reducing molecular mobility.^[144–152] Structural changes and interactions between core and wall materials are further assessed using FTIR and X-ray diffraction (XRD) analyses.^[153]

Overall, characterization of spray-dried microcapsules provides essential information regarding particle formation, encapsulation performance, release behavior, and stability, facilitating optimization of spray-drying processes and formulation development.^[154]

6. Applications of spray-dried microcapsules in drug delivery

Spray drying is a unique method for creating particles. It can convert a liquid feed, such as a solution, suspension, or emulsion, into a dry powder composed of microcapsules or microspheres. This process plays an important role in pharmaceutical science by ensuring controlled release and targeted drug delivery.^[155]

Spray drying can easily modify the properties of the final product. These modifications may affect the size, shape, and drug release pattern of the products. These changes can be achieved by consciously selecting formulation parameters such as temperature and feed rate, as well as formulation components such as wall materials.^[156] By controlling these parameters, spray drying enables the custom design of microcapsules targeted to different body parts and routes of administration, as listed below:

6.1. Delivery via mouth

Microcapsules for oral drug delivery can be prepared using spray drying technology. This method effectively encapsulates active pharmaceutical ingredients (API) within the protective polymer matrix. The challenges of oral drug delivery that spray-dried microcapsules can easily address are listed in Table 2.

6.2. Delivery through the lungs and nose

Spray-dried microcapsules constitute a highly promising platform for achieving both local and systemic drug delivery *via* the respiratory system, utilizing Dry Powder Inhalers (DPIs) to enable Pulmonary and Intranasal Drug Delivery Systems. These noninvasive routes offer important benefits for biopharmaceuticals. They allow drugs to bypass hepatic first-pass metabolism, reduce drug breakdown by avoiding the harsh enzymes in the gastrointestinal tract, and achieve high concentrations for local treatment.^[162] Using spray-dried microparticles through these routes is a better alternative to traditional oral drug delivery systems. These systems often face challenges such as low target-site doses and unwanted systemic effects from first-pass metabolism.^[163]

To targeting the central nervous system through the nasal tract is easy. In cases where an instant effect is needed, the drug can be delivered through the nasal tract and absorbed quickly owing to the high blood supply in the nasal tract and by bypassing the blood–brain barrier.^[164] The challenges of delivering drugs through the lungs and nose can be effectively

Table 2. Challenges in oral drug delivery and their solution with spray-dried microcapsules.

Physiological challenge	Mechanism of limitation	Spray-dried microcapsule solution	Reference
Degradation and instability	Harsh acidic/enzymatic environment of the stomach; Exposure to external factors (heat, light, and oxidation) during storage.	Encapsulation within a protective polymer matrix shields sensitive APIs from the GI environment and external stress, extending formulation shelf life.	[157]
Non-specific action/dosing frequency	Immediate, non-targeted release; Need for frequent dosing to maintain therapeutic levels.	Modulation of release kinetics via specific wall polymers for sustained drug delivery. pH-sensitive polymers enable enteric-coated microcapsules for targeted intestinal release (pH > 5.5)	[158,159]
Low bioavailability	Poor water-solubility and low dissolution rate of crystalline APIs limit absorption.	Dispersing the API in an amorphous state within the core matrix enhances surface area and saturation solubility, directly leading to improved oral bioavailability	[160]
Poor patient compliance	Obnoxious taste and odor of the API make the drug unpalatable, especially for pediatric and geriatric patients.	Encapsulation effectively masks the taste and odor of the API, thereby enhancing the formulation's palatability and patient adherence	[159]
Limited dosage form options	Inflexibility of traditional dosage forms; difficulty swallowing for certain patient populations.	Production of a stable, free-flowing powder enabling versatile processing into diverse dosage formats (conventional tablets/capsules, oral disintegrating tablets [ODTs] or sachets) to accommodate patient needs	[161]

addressed using spray-dried microcapsules, as explained in the following points in Table 3.

The particle engineering skills of spray drying allow us to create microcapsules with better size, shape, and surface chemistries. These features help the microcapsules bypass natural defense mechanisms, achieve targeted delivery, and ensure steady release. Consequently, they significantly enhance the availability and effectiveness of inhaled and intranasal drugs.

6.3. Systems for transdermal and parenteral use

A Spray-on Film-Forming System (SFFS) can be easily developed using a spray drying technique for transdermal drug delivery. Compared to traditional topical dosage forms such as creams and gels – which mainly depend on passive drug diffusion – spray drying offers several clear advantages in terms of drug delivery efficiency and patient convenience.

6.3.1. Application and mechanism

The primary goal of spray drying in SFFS is to transform a solution or suspension containing the drug and film-forming polymers into a formulation that can be easily sprayed onto the skin surface. Once applied, the volatile solvent evaporates quickly, leaving behind a thin, uniform, and adhesive polymer film on the skin. The film adheres well to the skin and provides consistent drug coverage.

One of the key benefits of this process is the improved drug permeation. As the volatile solvent

evaporates, it temporarily increases the thermodynamic activity of the drug, helping it to cross the stratum corneum, the main barrier to drug penetration through the skin.

Another important advantage is the controlled drug release. After forming the film, the polymer layer behaves as a reservoir, through which the drug, whether it is in the form of a small molecule, peptide, or protein, diffuses slowly out of the matrix in a controlled manner over an extended period. Similar to transdermal patches, this mechanism is more flexible, easy to apply, and offers greater patient compliance.^[170]

Spray drying directly tackles major issues in transdermal delivery as listed in Table 4:

Spray drying is also a good technique for producing stable drug powders for injection. These drug powders are usually not injectable as such, but they need to be reconstituted in water for injection to make their solution or suspension before use. In their dried form, they usually protect and provide long-term stability to sensitive drugs and biopharmaceuticals, such as protein peptides and vaccines.

6.3.2. Mechanism and stability enhancement in parenteral formulations

Spray drying is used to convert heat-sensitive biopharmaceutical liquids, which are unstable in solution form, into a stable dried form. It helps stabilize proteins, peptides, and vaccines by removing water, which can destabilize them. Additionally, it removes

Table 3. Challenges in pulmonary drug delivery and their solution with spray-dried microcapsules.

Physiological challenge	Mechanism of limitation	Spray-dried microcapsule solution	Reference
Anatomical Filtration and Impaction	Larger particles mass median aerodynamic diameter (MMAD > 5 µm) are efficiently trapped by impaction in the upper airways (nose, throat) and fail to reach the deep lungs.	Engineered Aerodynamic Diameter: Production of microcapsules with a (MMAD) precisely tuned to 1–5 µm, which is the optimal range for deep alveolar penetration.	[165]
Alveolar Macrophage Clearance	Macrophages in the deep alveolar region engulf and clear fine particles (MMAD 1–5 µm) rapidly reducing drug residence time.	Controlled Morphology (Low-Density Porous Particles): Creating microcapsules with a large geometric size (about 5–30 µm) and low density. These “Large Porous Particles” maintain the low MMAD needed for deep penetration while preventing quick phagocytosis because of their larger size. This design helps to prolong therapeutic residence time.	[166]
Mucociliary Clearance (MCC)	The mucus layer and cilia continuously transport deposited particles out of the airways, often within minutes or hours.	Improved Mucus Penetration and Mucoadhesion: Nanoparticles, which can be included in larger microcapsules, are designed with hydrophilic, neutral surfaces through PEGylation to effectively penetrate the mucus barrier. Alternatively, specialized polymer surfaces can be used to enhance mucoadhesion, which increases residence time.	[167]
Chemical Degradation and Stability	Sensitive APIs (e.g. peptides) are vulnerable to local enzymatic degradation (proteases) and instability due to moisture, heat, or oxidation in liquid formulations.	Enhanced Chemical Stability: Spray drying generates a dry powder formulation, dramatically improving the chemical and physical stability of the API compared to liquid solutions, thereby extending shelf life and preserving efficacy.	[168]
Inconsistent dosing (DPIs)	Poor powder flowability, inter-particle cohesion, and electrostatic charges lead to poor aerosolization efficiency from Dry Powder Inhalers (DPIs), resulting in inconsistent dosing.	Improved flow and dispersibility come from specific excipients, like leucine, and surface engineering that creates a wrinkled or textured surface. These methods reduce forces between particles, which results in better flow properties and more effective aerosolization.	[169]

the requirement for cold chain storage, thereby maintaining their stability as they become more stable and have a longer shelf life.

Although dry microcapsules are usually not injected directly because of the risk of embolism, spray drying plays a key role in preparing the carrier systems used in controlled-release injectable formulations.^[156]

During spray drying, drugs can be encapsulated within biodegradable polymers, such as PLGA or chitosan to form micro- or nanoparticles. These carefully engineered carriers are then dispersed in a suitable liquid to form injectable suspensions. Once administered, they release the drug slowly and in a controlled manner over an extended period inside the body, helping maintain therapeutic drug levels and reduce dosing frequency.^[172]

Current advancements have also led to the development of aseptic spray-drying techniques, which are utilized in large-scale parenteral manufacturing. In addition to sterility, spray drying produces amorphous

solid dispersions of drugs with poor aqueous solubility. When these amorphous spray-dried powders are reconstituted before use, they produce injectable solutions or suspensions with better solubility and improved bioavailability than their crystalline form.

Spray drying resolves the following issues in parenteral delivery as listed in Table 5.

7. New developments and case studies

7.1. Nano-spray drying and hybrid systems

Nano-spray drying is a sophisticated technique which uses spray drying to generate ultrafine, submicron particles (nanoparticles) from liquid solutions, overcoming the limitation of conventional techniques.^[175,176] It helps generate particles that are of equal size, having greater surface area, with the possibility of greater bioavailability for poorly soluble actives. The advantage of greater yield, coupled with

Table 4. Spray drying's role in overcoming transdermal drug delivery system challenges.

Challenge addressed	Spray drying mechanism/benefit	Reference
Limited permeation and bioavailability	Enables the creation of amorphous solid dispersions or nanocrystals, which have enhanced surface area and solubility, improving dissolution rates and absorption. The final excipient-drug powder has been shown to improve efficacy.	[25]
Drug stability	By transforming a liquid formulation into a dry powder, spray drying helps protect sensitive substances – such as lipids, proteins, and peptides – from heat damage and oxidation. This improved stability makes it easier to incorporate these delicate compounds into the final film formulation without loss of activity.	[171]
Dose control and esthetics	This approach allows precise control over particle size and shape, often at the nanoscale, while forming a smooth, non-greasy film that feels comfortable on the skin. As a result, it improves patient acceptance, offers better cosmetic appeal, and provides greater dosing flexibility compared to conventional transdermal patches.	[170]

Table 5. Spray drying in overcoming challenges in parenteral drug delivery.

Physiological/formulation challenge	Mechanism of limitation in parenteral delivery	Spray-dried microcapsule solution	Reference
Drug instability	Sensitive biopharmaceuticals (proteins, vaccines) rapidly degrade in aqueous solutions, necessitating expensive cold chain storage.	Converts the API into a stable, anhydrous solid powder, dramatically extending shelf life and eliminating the need for cold chain management.	[173]
Sterility requirements	Stringent regulatory requirements mandate the absolute sterility of all injectable products.	Development of Aseptic Spray Drying techniques and protocols ensures the maintenance of a sterile environment throughout the encapsulation and powder collection process.	[173]
Low solubility/dosing volume	Poorly water-soluble drugs cannot be formulated at high concentrations, limiting the injectable dose volume.	Creation of Amorphous Solid Dispersions (ASDs) enhances the solubility and dissolution rate, allowing for the formulation of concentrated, therapeutically effective injectable suspensions.	[174]
Inconsistent therapeutic levels	Conventional injectable solutions result in a rapid 'burst' followed by swift clearance, requiring frequent injections.	Fabrication of polymeric micro- and nanoparticles (e.g., using PLGA) encapsulates the drug, providing controlled and sustained release <i>in vivo</i> after injection.	[172]
Particle denaturation	Sensitive APIs (e.g., proteins) can be damaged by shear stress during atomization or thermal stress during drying.	Optimization of process parameters (low inlet temperature, low shear nozzles) and the use of cryoprotectants/stabilizers to mitigate shear and thermal stress, preserving API integrity.	[173]

the applicability for the development of delivery systems at the nano-scale, holds promises in the areas of targeted or controlled release systems. This technique increases the bioavailability, drug stability, and the possibility of target release for sensitive biologics.^[177,178]

According to a new study, according to B Sipos et al, to increase mucoadhesion, drug release, and permeability in nasal drug delivery, hyaluronic acid-coated polymeric micelles containing vinpocetin was developed through nano-spray drying. Hyaluronic acid-coated polymeric micelles exhibited a concentration-dependent activity, and an optimized formulation exhibited more than 80% yield, with uniform particles of 4 µm in size and a hydrated particle size of 107 nm, with more than 80% encapsulation efficiency, more than 70% drug release in 15 min, and higher permeability in the nasal route than free drug, which was

analyzed through solid-state analysis (XRD and laser diffraction analysis), and dispersion analysis. Spherical and monodisperse particles exhibited fast kinetic and good mucous affinity and hold great potential for applications in nasal nanomedicines.^[179] Table 6 shows an overview of nano-spray-dried encapsulation for specific delivery routes.

Pioglitazone-loaded PLGA-PEG NPs were prepared using nano spray drying (B-90) for ocular inflammation therapy, retaining biological activity and corneal safety. Physicochemical analyses confirmed that the NPs were suitable for ocular therapy, releasing the drug for up to 46 h after drying. Ex-vivo studies showed higher corneal retention and permeability than scleral permeability, yielding equal results for *in-vivo* bioavailability. Synchrotron X-ray scattering analyses showed unaltered corneal collagen distribution in both pre-dried and post-dried corneas compared to

Table 6. Overview of nano-spray dried encapsulation for specific delivery routes.

Polymers	Drug	Delivery route	Reference
Hyaluronic acid	Vinpocetine	Nasal Delivery	[179]
PLGA, PEG	Pioglitazone	Ocular Delivery	[178]
Hydroxyl propyl methyl cellulose	Levocetirizine Dihydrochloride	Topical Delivery	[180]
Sulfobutylether- β -cyclodextrin (SBECD)	Ibuprofen	Pulmonary	[181]
Beta-cyclodextrin (β -CD), methylated-beta-cyclodextrin (RAMEB), sulfobutylated-beta-cyclodextrin sodium salt (SBECD) (hydroxypropyl)-beta-cyclodextrin (HPBCD)	Levocetirizine Dihydrochloride	Nasal Delivery	[182]
Hydroxypropyl methylcellulose (Methocel E5, HPMC), polyvinyl-pyrrolidone			
Cremophor-EL, Pluronic F-127, cyclodextrin and inulin	lysozyme and BSA	Inhalation and injections	[183]

the control groups. Storage at 4 °C ensured stability, confirming that nano spray drying is an effective method for drying NPs while retaining their biological activity and tissue integrity.^[178]

A nanospray-dried formulation of Levocetirizine Dihydrochloride was produced with the use of a carrier substance of HPMC, which formed 2.6-micron amorphous microparticles (51–53% drug loaded) for topical anti-edema gels. The microparticles were mixed with Miglyol 812 oleo-gels (5–10% microparticle loading) with an optional addition of a menthol enhancer (0.05%). Confocal Raman microscopy of human skin sections, revealed skin epidermal/dermal accumulation, which was further enhanced by menthol. When applied to croton oil-induced edema in the ears of mice, the non-menthol formulation delivered results equivalent to those of Fenistil gel.^[180]

Cyclodextrins (SBECD, QABCD) complexed with ibuprofen were nano spray-dried alongside mannitol/leucine excipients for pulmonary delivery in cystic fibrosis treatment, enhancing solubility while minimizing doses and side effects. The Particle size (Mastersizer), morphology (SEM), crystallinity (XRPD, DSC), and interactions (FT-IR) confirmed the formation of amorphous complexes with optimal aerosol properties. Andersen Cascade Impactor showed ~50% fine particle fraction for leading formulations. *In vitro* dissolution demonstrated rapid ibuprofen release from all samples. QABCD-based powders exhibited reduced membrane diffusion compared to SBECD owing to electrostatic interactions, balancing rapid release with controlled permeation for sustained lung deposition.^[181]

Ibuprofen was nano spray-dried with SBECD and QABCD cyclodextrin complexes for improved solubility and reduced dosing and toxicity for delivery in cystic fibrosis. Size (Mastersizer), shape (SEM), crystallinity (XRPD, DSC), and inter/actions (FT-IR) analyses revealed optimal amorphous nanoscale ibuprofen complexes for aerosol delivery. Andersen Cascade

Impactor analysis revealed an approximate 50% Fine Particle Fraction of leading ibuprofen candidates. A rapid ibuprofen release was observed *in vitro* for all samples. The permeation rates of QABCD powders through membranes are reduced relative to those of SBECD powders owing to their electrostatic properties, which balanced fast and controlled drug release for sustained delivery into the lungs.^[182]

7.2. Biopharmaceutical encapsulation

Formulations for nano spray drying biopharmaceuticals facilitate the gentle drying of biologics, proteins, peptides, vaccines, and mRNA lipid nanoparticles (LNPs), forming stable submicron-size powders that maintain bioactivity and enhance storage and bio-delivery.^[177] The Büchi B-90 system processes feedstocks in milligram quantities to produce homogeneous biologic particles (nanoscale, 300 nm to 5 μ m) through piezoelectric mesh atomization with an electrostatic deposition mechanism, which is most appropriate for initial R&D biologics encapsulation in PLGA, chitosan, or PVP formulations. Typical applications include DPIs for pulmonary biologics to eliminate cold chain requirement and controlled-release formulations for insulin and monoclonal antibodies with yields above 85%.^[176] Supporting excipients for biologic reformulation include manitol, leucine, and/or cyclodextrins for improved aerosol and stability; research has revealed fast reconstitution and sustained.

The main challenges in the biopharmaceutical encapsulation process are denaturation and activity loss from shear (atomization), adsorption (to mesh/interfaces), thermal (even at low 50–100 °C inlet), and dehydration stresses during droplet formation and drying. The high surface-to-volume ratios of submicron droplets further amplify interfacial unfolding. To mitigate protein unfolding, stabilizers, such as trehalose, mannitol, and leucine may be used. Low solids

content of 0.1–1% w/v required for fine droplets limits throughput and escalates excipients needs; viscous feeds, for example, due to polymeric stabilizers, clog piezoelectric meshes. Amorphous powders risk recrystallization during storage without humidity control. Lab-scale yields, which are within 85–90% for electrostatic collection, do not translate easily into production. For pilot or commercial scale production, B-90 versions do not exist yet, hindering the GMP manufacturing of respirable biologics.^[183]

7.3. Working with other ways to give drugs

Current trends in targeted and controlled drug delivery have been driven by nanotechnology and intelligent robotics. These have been followed by nanocomposite drug carriers and intelligent drug-delivery robots that facilitate site-specific drug delivery using pH and temperature stimuli or magnetic fields. The biological drug sector, which uses drugs such as biologics and RNA-targeted drugs is also likely to see substantial growth in controlled drug delivery methods.^[184,185]

7.4. Case studies/new developments

Recent experimental studies further validate the importance of formulation-driven design, such as spray drying of *Spirulina* proteins, which demonstrated stabilization *via* hydrogen bonding and matrix immobilization, preventing denaturation. Royal jelly encapsulation confirmed that binary carrier systems outperform single polymers due to complementary physicochemical properties and essential oil microcapsules showed that release kinetics can be tuned through shell thickness and porosity, enabling applications beyond drug delivery such as food preservation. Collectively, these findings indicate that the encapsulation performance is governed by both thermodynamic and kinetic factors.

8. Challenges and future perspectives in spray-dried microencapsulation

8.1. Technological and regulatory challenges

Despite significant progress, the advancement of spray-dried microencapsulation systems is constrained by technological complexities and evolving regulatory frameworks. One of the primary challenges is the limited standardization of process parameters and regulatory guidelines, particularly for novel polymeric carriers and multifunctional delivery systems, which

often delays clinical translation and industrial adoption.^[186]

From a technological standpoint, issues such as process variability, scale-up inconsistencies, and the thermal degradation of sensitive bioactives remain critical barriers to reproducibility and product stability.^[187] In addition, the growing incorporation of artificial intelligence (AI)-driven formulation design and process optimization introduces new regulatory concerns, particularly regarding the validation, transparency, and integrity of models.^[187] Therefore, ensuring compliance with emerging frameworks such as AI-based risk and quality management systems is essential for future implementation. Furthermore, the increasing complexity of spray-dried systems, including nano-enabled carriers and hybrid formulations, complicates their safety evaluation, characterization, and regulatory approval processes. The absence of clear, harmonized regulatory pathways for such advanced systems underscores the need for adaptive and science-based regulatory strategies that can keep pace with technological innovation without compromising safety and efficacy.^[188]

8.2. Emerging trends and future opportunities

Future developments in spray-dried microencapsulation are expected to be driven by innovations in material science, process engineering, and digital technologies. The design of stimuli-responsive and smart polymeric carriers is gaining attention for enabling site-specific and controlled drug release, thereby improving the therapeutic outcomes.^[189] The integration of AI and machine learning (ML) into formulation development is anticipated to accelerate optimization processes through predictive modeling and data-driven QbD approaches, enhancing efficiency and reproducibility.^[189] Similarly, advancements in microfluidic-assisted atomization and nano-spray drying technologies are expected to provide better control over droplet formation, resulting in uniform particle size distribution and improved encapsulation efficiency.^[190] Sustainability is also emerging as a critical consideration, with increasing emphasis on green spray drying processes, energy-efficient systems, and environmentally compatible carrier materials aimed at reducing environmental impact.^[190] Additionally, the development of biopharmaceutical formulations, including proteins, peptides, and nucleic acids, represents a promising area in which spray drying can improve stability and reduce reliance on cold-chain storage.^[187] Overall, bridging the gap between rapid technological

innovation and regulatory adaptation is essential to fully realize the potential of spray-dried microencapsulation as a robust platform for next-generation drug delivery systems.^[191]

9. Conclusion

Spray-dried microencapsulation has emerged as a versatile and scalable platform for the development of controlled and site-specific drug delivery systems. Its significance lies in its ability to integrate formulation design with particle engineering, enabling precise control over particle size, morphology, encapsulation efficiency, and drug release kinetics. These attributes make spray drying particularly suitable for improving the stability, solubility, and bioavailability of a wide range of bioactive compounds. However, the performance and reliability of spray-dried systems remain strongly dependent on the complex interplay between formulation variables and process parameters. Key challenges – including thermal degradation of sensitive compounds, variability in particle formation, nozzle clogging, and batch-to-batch inconsistency – continue to limit reproducibility and large-scale industrial translation. In addition, concerns related to polymer safety, regulatory acceptance, and the practical implementation of QbD frameworks highlight the need for more standardized and mechanistically driven approaches. Despite these limitations, ongoing advancements in material science and process engineering are rapidly expanding the capabilities of spray-dried microencapsulation. Emerging strategies such as the development of smart and stimuli-responsive polymers, nano-enabled hybrid carrier systems, microfluidic-assisted atomization, and AI-guided process optimization offer promising solutions to current technological constraints. These innovations are expected to enhance formulation precision, improve scalability, and enable more predictable performance of microencapsulated systems. Looking forward, spray drying is poised to play a critical role in the evolution of next-generation drug delivery, particularly in the context of personalized and targeted therapies. Future research should focus on strengthening structure–property–performance correlations, improving long-term stability, and developing robust scale-up strategies to bridge the gap between laboratory research and clinical application. Overall, spray-dried microencapsulation represents a dynamic and evolving technology with substantial potential to advance the design of efficient, safe, and patient-centric drug delivery systems.

10. Future prospects

Spray-dried microencapsulation is expected to play an increasingly important role in the advancement of next-generation drug delivery systems, particularly in the context of personalized and targeted therapies. One of the most promising directions lies in the development of stimuli-responsive and smart polymeric carriers, which can modulate drug release in response to environmental triggers, such as pH, temperature, enzymes, or redox conditions. These systems have the potential to significantly enhance site-specific delivery and therapeutic efficacy. The integration of nanotechnology with spray drying, including nano–micro hybrid systems, is another emerging area that enables improved control over particle architecture, enhanced bioavailability of poorly soluble drugs, and more efficient cellular uptake. In parallel, advancements in nano-spray drying and microfluidic-assisted atomization are expected to provide superior control over droplet formation, resulting in highly uniform particle size distributions and improved reproducibility. A major future direction involves the application of AI and ML in formulation design and process optimization. These tools can facilitate predictive modeling of spray drying parameters, enabling faster development cycles, reduced experimental burden, and improved robustness through data-driven QbD approaches. Additionally, increasing emphasis on green and sustainable manufacturing is driving the development of energy-efficient spray drying systems, solvent-free formulations, and eco-friendly carrier materials. These approaches are expected to improve environmental compatibility while maintaining product performance. The growing demand for biopharmaceutical delivery systems, including proteins, peptides, vaccines, and nucleic acid-based therapeutics, further highlights the relevance of spray drying as a platform for stabilizing sensitive biomolecules in dry powder form. This is particularly important for improving storage stability and reducing dependence on cold-chain logistics.

11. Limitations

Despite its significant potential, spray-dried microencapsulation faces several critical limitations that must be addressed to ensure successful industrial and clinical translation of the technology. One of the primary challenges is the thermal sensitivity of bioactive compounds, as exposure to elevated temperatures during drying may lead to their degradation, denaturation, or loss of biological activity. Although rapid drying can

mitigate some of the thermal effects, optimization remains formulation-specific and complex. Another limitation is the variability in particle formation, which arises from the dynamic interplay between the formulation properties and process parameters. This often leads to inconsistencies in the particle size distribution, morphology, and encapsulation efficiency, ultimately affecting product performance and reproducibility. Scale-up and industrial translation remain challenging because of the differences in heat and mass transfer, airflow dynamics, and residence time between laboratory and commercial-scale equipment. Maintaining consistent product quality across scales requires a deeper mechanistic understanding and robust process control strategies. Powder instability, particularly related to moisture uptake and glass transition temperature (T_g), also presents a significant challenge. Particles stored near or above T_g may undergo structural collapse, stickiness, or accelerated degradation, affecting their shelf life and handling properties. From a regulatory perspective, the lack of standardized guidelines for spray-dried microencapsulation systems, especially for novel polymers and complex formulations, complicates product approval and commercialization processes. Additionally, concerns regarding polymer safety, biocompatibility, and long-term toxicity must be thoroughly evaluated. Finally, practical challenges, such as nozzle clogging, wall deposition, and batch-to-batch variability continue to affect process efficiency and scalability, highlighting the need for improved equipment design and real-time monitoring technologies.

Author contributions

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