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Carboxymethyl Cellulose-Based Spray-Dried Microspheres: Recent Advances and Applications in Targeted Drug Delivery Systems

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Abstract

Microspheres are spherical particles ranging from 1 to 1000 µm, made from natural or synthetic polymers and inorganic materials. Their structure allows precise drug delivery, improving targeted release and minimizing off-target effects. Natural polymers such as starch, chitosan, and alginate are favored for their biodegradability, adhesion, and compatibility, enhancing mucosal interaction and residence time. Microspheres are widely used in site-specific drug delivery, gene therapy, and vaccine administration, improving immunogenicity, extending drug release, and increasing safety. This review addresses gaps in previous literature, particularly in natural polymer-based delivery and gene therapy applications. It highlights recent advancements and evolving technologies, providing an updated analysis of microspheres in targeted and sustained drug delivery systems. The article focuses on Carboxymethyl Cellulose (CMC)--based spray-dried microspheres, emphasizing spray drying and exploring CMC's chemical structure, substitution level, and physicochemical properties. Key process variables like atomization, feed rate, drying gases, and their influence on particle morphology and size distribution are discussed. The review also addresses drug-polymer interactions, stabilizers, cross-linkers, and parameters like drug loading, entrapment efficiency, surface charge, swelling, porosity, and in-vitro release kinetics. Analytical techniques such as FTIR and density determination are presented, assessing the stability and pharmaceutical applications of CMC-based microspheres. The review aims to offer a comprehensive, updated analysis of recent advancements, integrating emerging trends and novel therapeutic approaches to bridge previous gaps and respond to evolving clinical needs and technological progress in drug delivery systems.

Keywords: Microspheres, drug delivery, carboxymethyl cellulose (CMC), spray drying, targeted release gene therapy

INTRODUCTION

Microspheres are small spherical objects that measure from 1 to 1000 µm in size (or even 50 nm to 2 mm). These structures, which are frequently called microparticles, may be created from a range of synthetic and natural polymers and inorganic materials like ceramics. With the variety of manufacturing techniques available for microspheres, medication delivery characteristics may be precisely controlled, improving targeted release and reducing dissemination to non-target areas. The active pharmaceutical component is protected and performs at its best before and after delivery. The effectiveness of microparticulate delivery systems as carriers for site-specific medication delivery is now well acknowledged. Because they are biodegradable, biocompatible, and bioadhesive, natural polymers like starch are particularly prized. Due to their high swelling capacity in aqueous

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conditions, these polymers can interact with mucosal membranes efficiently, resulting in gel formation and a longer residence period. Controlled-release techniques have evolved from time-release coatings on tablets or medication particles to microparticulate delivery systems for site-specific medication delivery. Natural polymers like starch are highly prized for their biodegradability, biocompatibility, and bioadhesive properties. Polymer-based microspheres, such as chitosan, alginate, and gelatin, have potential biological traits and are ideal for drug delivery systems in the eyes [1]. They are also used in gene therapy applications, such as DNA plasmids and insulin administration. Biodegradable microspheres offer vaccine distribution, providing enhanced immunogenicity and prolonged release. They are commonly used in nasal medication delivery systems and pre-transplant interventions for hepatocellular carcinoma. Microspheres offer a viable substitute for traditional vaccinations, improving safety profiles and delivery efficiency while boosting immune response. Microsphere-based systems offer a safe and efficient delivery of genetic material, as vaccines require a response to a specific pathogen.

The Significance of Spray Drying for Medication Administration

Spray drying is frequently used to extract moisture or solvents from liquid materials, providing a productive way to create dry materials with certain properties appropriate for use in pharmaceutical applications [2]. This method was first used in the pharmaceutical industry to create dry extracts from plant raw materials. It became well-liked because heat-sensitive liquid extracts can be dried without losing their active ingredients. Spray drying is the most common technique for producing dry plant extracts on an industrial scale. It produces consistent, fine powders with improved physical qualities, which is preferable to conventional drying methods. The final product's particle size and surface shape are greatly influenced by critical factors such as feed rate, solution concentration, and input and output temperatures [3]. In contrast to lyophilization, which frequently produces hygroscopic materials that easily absorb moisture from the air, spray drying produces powders that flow freely and have good handling qualities and a narrow particle size distribution. However, even within the same production batch, traditional spray-dried goods usually show great variation in particle properties. Researchers have developed a microfluidic spray drying method that precisely controls size and properties while producing incredibly uniform micro particles. This low-waste and scalable approach enables the systematic investigation of how formulation and drying conditions affect particle behavior. More effective and economical manufacturing techniques may be possible with a better understanding of the connection between formulation parameters, process parameters, and particle formation.

Carboxymethyl Cellulose's (CMC) Microspheres

Because of its superior biocompatibility, biodegradability, and non-toxicity, CMC, an anionic, water-soluble cellulose derivative, is frequently used to create microspheres. CMC functions as a matrix-forming agent in microsphere systems, enhancing the stability and structural integrity of the drug delivery system. Adjusting drug diffusion and degradation rates improves drug encapsulation efficiency and permits regulated and prolonged release of therapeutic substances [4]. Recent developments in microsphere formulation have investigated CMC in combination with other natural and synthetic polymers like chitosan, alginate, and gelatin to enhance bioadhesive properties and develop pH-responsive systems. Its hydrophilic nature also supports swelling behavior, crucial for controlled drug release in various physiological environments. In mucosal and gastrointestinal drug administration, where site-specific release is essential, these combinations are especially advantageous. To create polyelectrolyte complexes with enhanced mechanical strength, swelling behavior, and drug entrapment effectiveness, these combinations use the ionic interactions between the carboxyl groups of CMC and the amino groups of polymers such as chitosan [5]. Strong mucoadhesion demonstrated by CMC-chitosan microspheres enables an extended residence period at mucosal surfaces, essential for improving medication absorption through the nasal or gastrointestinal tract. CMC-alginate blends create hydrogel microspheres perfect for colon-targeted drug administration since they expand and release their payload in neutral to basic conditions while remaining stable in acidic settings]. In the case of CMC-gelatin systems, the hydrophilic and ionically active structure of CMC is complemented by the

thermosensitive and biodegradable nature of gelatin, resulting in microspheres that can effectively encapsulate proteins and peptides while maintaining biocompatibility [6]. Mixing CMC with synthetic polymers like polyvinyl alcohol (PVA) or Eudragit has enabled adjustment of release kinetics, mechanical durability, and surface charge to accommodate different administration routes, such as parenteral, ocular, and oral. Because of their increased surface area and functional ability, nanocellulose-based CMC microspheres have demonstrated promise in cutting-edge biomedical applications such as tissue engineering, wound healing, and targeted cancer treatment Furthermore, because CMC can be derived from renewable biomass and processed in moderate settings, it is becoming more widely acknowledged for its role in environmentally friendly and sustainable medication delivery, consistent with eco-friendly pharmaceutical practices.

CMC Characteristics

Carboxymethyl Cellulose (CMC) is an anionic, water-soluble derivative of cellulose obtained by the chemical modification of natural cellulose, where some hydroxyl groups are substituted with carboxymethyl groups (-CH_2COOH). This substitution introduces negative charges along the cellulose backbone, enhancing its solubility, swelling behavior, and interaction with biological environments.

The chemical structure of CMC contributes significantly to its performance in drug delivery systems. The hydrophilic and ionically active carboxymethyl groups allow for strong water absorption and swelling, facilitating controlled drug release through matrix diffusion. Moreover, the anionic nature of CMC enables electrostatic interactions with cationic drugs or polymers such as chitosan, forming polyelectrolyte complexes that improve drug entrapment, stability, and mucoadhesion.

The degree of substitution (DS), typically ranging from 0.4 to 1.2, influences key properties such as viscosity, solubility, and gel formation, which are crucial for modulating drug release kinetics. CMC's biocompatibility, biodegradability, and capacity to form hydrogels and microspheres make it a suitable candidate for oral, nasal, ocular, and parenteral drug delivery systems. Its compatibility with spray drying allows the production of microspheres with controlled particle size and morphology, enhancing drug stability and targeting efficiency.

Parameters Influencing Particle Size, Morphology, and Surface Characteristics

The particle size, morphology, and surface characteristics of spray-dried CMC microspheres are governed by multiple interdependent process and formulation variables. Key parameters include the feed concentration, atomizer type and gas flow rate, inlet and outlet temperatures, feed rate, and solvent properties. Higher feed concentrations typically produce larger particles due to increased solute availability, while higher atomization pressures result in smaller droplets and finer particles. The morphology—such as smoothness, porosity, or surface wrinkling—is strongly influenced by the solvent evaporation rate, drying chamber temperature, and solute diffusion. Rapid drying can cause surface skin formation and hollow or crumpled particles, while slower drying may yield more spherical and denser microspheres. The surface charge (zeta potential), influenced by CMC's anionic nature and the pH of the feed solution, affects microsphere stability and aggregation. Thus, optimizing spray-drying parameters is critical for controlling particle characteristics that determine drug release, dispersibility, and bioavailability.

Derivatization and chemical structure

Cellulose is a naturally occurring linear polysaccharide composed of anhydroglucose units joined by β-1,4-glycosidic linkages. CMC is an anionic, water-soluble derivative of cellulose. The primary structural distinction between CMC and natural cellulose is that some of the hydroxyl groups present in cellulose are replaced by carboxymethyl groups (-CH2COOH) in CMC [7]. Wood and other cellulose-rich plant sources have historically provided the cellulose needed to produce CMC. More recent research, however, has found several plant-based materials to be good substitutes. CMC and its hybrid derivatives are widely used in many industries, such as biomedicine, pharmaceuticals, textiles, construction, food packaging, plastics, cosmetics, paper manufacturing, and petroleum. CMC is widely

used in absorbent nonwoven fabrics and tissue and bone engineering in biomedical applications. The success of CMC in various applications is influenced by its purity, degree of polymerization (DP), degree of substitution (DS), and structural uniformity. These elements influence particle size, viscosity, and solubility.

Level of substitution

The reactive groups of cellulose are important markers of its chemical reactivity in cellulose chemistry. The average number of substituent groups bonded to the reactive hydroxyl groups on the anhydroglucose units in cellulose is known as the degree of substitution (DS). The DS typically ranges from 0 to 3. The DS value is essential for evaluating the properties of cellulose derivatives, especially CMC [8]. When CMC is synthesized from cellulose, the DS indicates how many carboxymethyl groups are bound to each anhydroglucose unit. The solubility of CMC is highly dependent on its DS; it is only swellable below a DS value of 0.4, at which point it becomes soluble. In addition to improving solubility, raising the DS increases substitution uniformity along the polymer chain, affecting viscosity. According to research, the best concentration of NaOH for creating CMC with high DS values is 30%. Moreover, changes in the kinds and concentrations of solvents used during etherification, such as ethanol or isobutanol, impacted DS values.

Etherification process temperature

The degree of substitution (DS), degree of polymerization (DP), and other final product characteristics, including viscosity, swelling behavior, and thixotropy, are all greatly influenced by the temperature during the etherification process. Discovered that a reaction temperature of 45°C produced their products with the greatest DS (0.821) [9]. Significant drops in DS levels were seen both at and below this temperature. As the temperature increased from 30°C to 70°C, the DS for carboxymethylation of cellulose obtained from cashew tree gum dropped significantly from 0.75 to 0.16. Under the same circumstances, however, the response yield rose from 32% to 57%. On the other hand, the ideal temperature for carboxymethylation utilizing different non-biological waste materials was higher than 70°C.

Physicochemical characteristics of CMC microspheres

Properties of rheology materials' flow properties, such as behaviors like thixotropy, pseudoplasticity, viscoelasticity, and stress-strain response, may be generally understood by rheological study. The structure of polymer systems, which is impacted by several elements like structure, particle size, concentration, shape, and surface properties, is highly related to these qualities. For instance, under stress-strain circumstances, CMC displays intricate flow characteristics that substantially impact its uses in coating, filmmaking, and food packaging. CMC's thixotropic, pseudoplastic, and viscoelastic properties are essential for its application in various sectors, including paints, adhesives, suspension injections, food processing, and cosmetics. However, CMC could exhibit viscous flow properties at lesser concentrations and operate like a Newtonian fluid. The investigation found that CMC behaves Newtonianly at concentrations of around 1% and changes to non-Newtonian behavior at 2% to 5%. For all concentrations (1–5%), the study's shear stress-shear rate curves were almost linear, as shown in the supplemental materials. On the other hand, viscosity-shear rate curves showed a declining linear trend (above 1%, up to 5%) or were almost horizontal (at or below 1%) [10]. Shear-thinning behavior (STB) is strongly connected to properties like thixotropy, pseudoplasticity, and viscoelasticity. The ability of CMC to display both viscous and elastic properties is known as viscoelasticity. CMC exhibits this behavior because of its long chain structure, entanglement characteristics, and lengthy relaxation period. Tests such as creep-recovery and dynamic tests are used to examine the viscoelastic behavior of CMC. Values like creep compliance and elastic recovery index are computed in the creep-recovery test to assess the viscoelastic behavior of the material. Thixotropy is when a shear-thinning system changes from a high-consistency gel to a low-consistency solution. After resting, the solution gradually returns to its gel-like state. The up curve represents the high viscosity of CMC, which shows that the shear rate will rise in relation to stress until the target value is attained. The viscosity then drops as the shear rate stabilizes, as shown by the hysteresis loop's downward slope. CMC's degree of substitution (DS) or

concentration also affects its thixotropic properties. In addition to synthesis parameters like temperature, pH, and NaOH concentration, the viscosity of CMC is also influenced by cellulose particle size, molecular weight, and degree of substitution (DS). Because of its viscosity qualities, CMC is used in various food industry applications; high-viscosity kinds are used as gelling agents, while low-viscosity forms are used as moisture binders.

Because of its anionic nature and carboxyl groups, CMC has pH-sensitive characteristics when in its hydrogel state]. Because of this feature, there is now more interest in employing hydrogel carriers based on CMC for various biological applications. Their swelling behavior, which is affected by pH, composition, temperature, ionic strength, and the degree of crosslinking within the polymer network, has been one of the main obstacles in using these hydrogels. The network expands due to electrostatic repulsion between polymer chains caused by the negatively charged carboxyl groups in CMC hydrogels, particularly at pH values higher than the material's pKa. Biodegradable and biocompatible microspheres made of CMC are attractive for drug delivery due to their ability to create specific release patterns. These systems offer regulated and sustained medication release over long periods. Depending on the formulation procedure, drugs can produce nanocapsules or nanospheres within the polymer matrix.

Spray drying for microspheres

Spray drying is frequently employed in the industry to microencapsulate volatiles, probiotics, and live cells. Despite the apparent disadvantages (low yield, high loss), this process is quite common because of its varied advantages (uniform particle size, use of organic solvents, ability to encapsulate heat-sensitive components, and all operations performed in a single device). Wu et al. investigated using spray-drying to create solid lipid microparticles with protein medications, using insulin as a model protein [11]. They found lower burst release and longer-lasting release of insulin. Momin et al. improved co-spray drying of kanamycin with rifampicin, creating inhalable powders with amorphous particle sizes. Konjac glucomannan (KGM) microparticles containing rifabutin and isoniazid were created for TB treatment.

The polydispersity of microparticles in traditional spray drying is due to the large size variety and uneven droplet trajectories. To enhance the homogeneity of spray-dried microparticles, atomizers that generate droplets with constrained size distributions and predictable trajectories were used. MDGs generate a continuous stream of droplets with a vertical trajectory, minimizing wall collisions and improving droplet-drying air interaction [12]. Droplets are created when the weight of the liquid is greater than the force of surface tension. Continuous mode generates droplets faster than DOD mode but requires more energy and a larger volume of working fluid. The liquid is heated by the THDG (thermo-hydrodynamic droplet generator) using thermal energy, generating pressure impulses that cause droplets to form. The liquid in the nozzle is warmed by a heating device (such as thin film resistors) that may generate heat pulses. A smaller amount of the liquid evaporates when heated, which causes gas bubbles to form inside the nozzle. After migrating to the region of somewhat colder liquid, the gas bubble bursts upon condensation. Monodisperse droplets form due to gas bubbles' continuous formation and implosion, which produce pressure waves.

Process variables of spray drying

A cyclone, drying chamber, atomizer nozzle, pump, and feed solution are all involved. Determining drying conditions and variables such as input concentration and flow rate may regulate powder particle size. The choice of lipids, surfactants, and active ingredients affects the loading capacity of nanolipid powders. To preserve the integrity of the lipid structure and avoid encapsulation breakdown, the drying conditions must be carefully selected. Spray drying increases the solubility and bioavailability of hydrophobic substances by facilitating their effective encapsulation [13]. The liquid input is atomized into droplets, particles are formed, and the dry product is separated. Product characteristics and the solubility of active ingredients dictate the feedstock's composition. There are several varieties of spray dryers for use in commercial pharmaceutical settings. The difference between the solvent's partial pressure in the gas phase and its vapor pressure inside the droplet drives the solvent removal process

during droplet evaporation, which is a combined heat and mass transfer phenomenon. When the solvent evaporates from the droplet surface, the diameter uniformly decreases, marking the start of the constant-rate period. The crucial moisture level marks the start of the falling-rate phase. High-pressure homogenization and spray drying to create dispersible, porous nanocrystalline agglomerates of tobramycin encased in an amorphous clarithromycin matrix [14]. Pharmaceutical engineering uses supercritical fluids, such as supercritical carbon dioxide (sc-CO2), because of its non-toxic properties, low cost, and recyclable nature. Equipment design, process variables, and fluid feed factors can all affect the quality of spray-dried powder. Atomizer shape influences particle size; greater nozzle diameters result in larger particles. Even with modest sample amounts, the Bnano spray-dryer, a novel piece of laboratory equipment that enhances conventional models, can create fine powders with particle sizes ranging from 300 nm to 5 μm.

Atomization

Atomization is a crucial stage in spray-drying that creates droplets with the required size distribution and shape [15]. The atomization process particle size, drying chamber residence time, and product form. Regardless of the kind of atomizer, the atomization process is influenced by several interdependent elements, including surface tension, droplet viscosity, shearing and inertial forces, and droplet size distribution. Each of these variables influences the angle and velocity of the atomized spray. The internal geometry of the atomizer has a significant impact on the final powder qualities.

Particle Formation

Control of particle size and shape is essential regardless of the application. The efficacy of a medicine is significantly influenced by its physical and chemical characteristics, particularly its dissolving rate, flowability, compressibility, aerodynamic qualities, and particle size distribution [16]. Surface activity and evaporation rate are two of the most crucial variables in determining the radial distribution of individual components. Surface activity may lead components to align preferentially on the surface, whereas evaporation increases component concentrations and produces a concentration gradient away from the surface. Therefore, it is crucial to realize that evaporation involves the simultaneous movement of heat and mass.

Inactive Ingredients

Amorphous solid dispersions (ASDs) can be created by spray drying. A monophasic system with all of the active medicinal ingredient molecules fully integrated with the carrier molecules is the ideal ASD. Using characteristics such as melting point, enthalpy, thermal stability, ionization constant, hydrogen bond donating/accepting qualities, solubility parameters, interaction metrics, and partition coefficients, the best less soluble candidates for ASD formulations may be chosen. The primary components of an ASD solution are the excipient, solvent, and active medicine. Consequently, combining these elements determines the spray drying process parameters needed for certain end powder characteristics. Selecting excipients for spray drying requires that the active pharmaceutical component and excipients have significant solubility and chemical stability in the solution state in a typical volatile solvent or a solvent combination. Water absorption in amorphous solids is mostly influenced by mass, whereas the available surface area determines water adsorption in crystalline materials. Water reduces molecular hydrogen bonding and raises the free volume of amorphous solid dispersions (ASDs). The production of hollow spray-dried particles exhibits enhanced porosity and decreased bulk density at higher feed concentrations.

Feeding Rate

In the spray-drying process, the feed rate is represented as the mass of powder transferred per unit of time. It regulates how much liquid and solid material gets into the drying chamber. Therefore, physicochemical characteristics, including density, shape, particle size, and solvent evaporation rate, may be altered by varying the feeding rate. Previous studies have shown that increased feed rates increase moisture content in the final particles. Moreover, lower feed rates were associated with better yields. When the feedstock feeding rate is increased while the atomizing gas flow rate stays constant, less atomization results in larger droplets.

Inlet and Outlet Temperatures

The entrance temperature directly impacts heat and mass transport during the droplet drying. The impact of intake temperature on the final properties of amorphous solid dispersions has been studied by Singh et al [17]. Because of the faster rate of solvent evaporation, elevated intake temperatures impact the particle formation process. This procedure may produce a pressure differential within and outside the droplet, affecting the powder's final shape and surface roughness. When the inlet temperature is high, a solid skin quickly forms outside the droplet, encasing the solvent vapors.

Drying Gases and Atomization

For drying and atomization, the choice of gas type and flow rate is crucial in establishing droplet size, density, velocity, and final particle properties [18]. Previous spray drying methods have used a variety of atomization gases, including carbon dioxide, nitrogen, and compressed air. The final properties of spray-dried powders are largely determined by the atomization gas's properties, such as density and specific heat capacity. Langrish and others 35 have studied the impact of atomization and drying gas type on crystallization. The drying and atomizing gases affected the final spray-dried lactose's crystallinity from greatest to lowest crystallinity.

Equipment for Atomization

One-fluid nozzles can create larger particles than other atomizers, allowing direct tablet pressing without granulation [19]. Nevertheless, high-viscosity non-Newtonian feedstocks cannot be employed with these nozzles. The most popular atomizer for creating and researching amorphous solid dispersions is the two-fluid nozzle. Since the final particle size distribution is mostly determined by the atomizing gas and solution input rate, precise control over the atomization process is possible. Combining lower input rates with higher gas flow rates frequently results in smaller particle sizes.

Table 1. Spray drying process parameters and their classifications.

Process parameter	Description	Process parameter type
Atomizer gas flow rate	Controls droplet formation during atomization	Atomization
Solid content	Refers to feedstock concentration affecting particle formation	Feed concentration
Aspiration rate	Regulates the airflow in the drying chamber	Atomization and drying gas
Feedstock feeding rate	Controls the amount of solution entering the drying chamber	Feed rate
Inlet temperature	Temperature of drying air at the inlet	Inlet/outlet temperature
Outlet temperature	Temperature at the exit of the drying chamber	Inlet/outlet temperature
API/excipient ratio	The ratio between active pharmaceutical ingredients and excipients	Excipients
Composition of solvents	Solvent system used for particle formation	Particle formation
Atomizing air flow rate	Determines the efficiency of the atomization process	Atomization and drying gas
Atomization device	Equipment used to atomize the liquid (e.g., nozzle or rotary atomizer)	Atomization device
pH	Affects the solubility and stability of the feed solution	Excipients
Particle size (e.g., MMAD, GSD)	Indicates average size and distribution of particles	Particle size distribution
Morphology (e.g., SEM imaging)	Refers to shape, surface, and structural attributes of particles	Morphology
Crystallinity	Degree of structural order in particles	Morphology
Dissolution rate	The rate at which the drug dissolves from the dried particles	Particle formation
Yield	Total powder recovered after drying	General output
Drug loading/encapsulation efficiency	Amount of drug successfully loaded or encapsulated in particles	Excipients/Particle formation

Particle Size Distribution

When creating powders, the distribution of particle sizes is highly important, especially when pulmonary administration is involved, Baldinger and associates. It is recognized that an aerodynamic particle size distribution of 1–5 μm is optimal for pulmonary delivery [20]. Using near-infrared spectroscopy (NIR), Maltesen et al. examined the effects of several formulation and processing parameters on the final aerodynamic particle size distribution, including solid content, aspirator capacity, intake gas temperature, nozzle gas flow rate, and feed flow rate.

Influence on Microparticle Morphology

For biopharmaceutical applications of oral inhalation administration, the spray-dried product's shape is very critical [21]. The final morphology of the particles is significantly influenced by formulation factors, such as the pace at which the solvent evaporates and the rate at which the solute diffuses from the inner core to the outside crust of the particles. Two-fluid nozzles' smaller nozzle tips and lower solid content provide finer end particles due to their smaller droplets. A unique categorization scheme for the morphology of spray-dried biomolecules was reported. Particles in this system were classified as spherical or irregular, and their surfaces were categorized as crumpled or smooth (Table 1) [22]. The large contact area between the particles is improved by the flat surface, which raises the cohesive forces between them.

Advantages of Spray Drying

Spray drying's adaptability, scalability, and affordability make it one of the most popular microencapsulation methods in the food and pharmaceutical sectors. One of its main benefits is its rapid and continuous processing, enabling heat-sensitive substances to be encapsulated with less degradation due to the incredibly fast drying time (milliseconds to seconds). Spray drying is simple, rapid, and more cost-effective than concertation, solvent evaporation, or freeze-drying methods, especially for large-scale manufacturing. Modifying the variables such as feed concentration, inlet temperature, and atomization pressure provides exact control over particle size and shape. This control makes the creation of homogeneous, spherical microspheres with customized release profiles possible. Spray drying usually yields good encapsulation efficiency, and the procedure may be readily modified for volatile chemicals, probiotics, and thermally stable APIs. It appeals to contemporary pharmaceutical development due to its interoperability with continuous production systems. Spray drying outperforms conventional encapsulation techniques by combining speed, efficiency, and flexibility.

Spray-Dried CMC Microspheres

Cellulose is a substrate to create spherical beads, microparticles, and nanoparticles with millimetric, micrometric, and nanometric scale diameters. Druel et al. produced cellulose aerogel microparticles with diameters varying from 5.4 ± 1.8 μm to 20.9 ± 8.9 μm using the emulsion-coagulation technique [23]. Utilizing biopolymers derived from microbial, plant, or animal sources is advantageous; non-biodegradable and biodegradable synthetic polymers and semi-synthetic cellulose derivatives are also utilized. In addition to lipids and waxes, proteins or polysaccharides are commonly utilized in formulations. $CaCl_2$, glutaraldehyde, and poly-l-lysine are examples of non-polymer excipients that aid in cross-linking polymer chains, forming and fortifying the polymer network of drug delivery systems. Numerous studies demonstrate that copolymerizing synthetic and natural polymers (such as agarose-Carbopol® and hyaluronic acid-polyethyleneglycol) enhances cell survival and biocompatibility. Hydrophobic excipients (poly-"-caprolactone) may alter the release of low-solubility drugs from alginate and produce sustained release by forming hydrophobic contacts with the drug molecule.

Interactions Between Drugs and Polymers

Because of its hydrophilicity, anionic nature, and biocompatibility, CMC is frequently employed in microencapsulation to alter drug release patterns and enhance stability. Drug-polymer interactions and spray drying process significantly influence the encapsulation efficiency, drug loading, and release kinetics of CMC-based microspheres. With different medications, CMC creates van der Waals forces, hydrogen bonds, and electrostatic interactions that can stabilize the encapsulated substances and control their release. CMC has demonstrated potent ionic interactions with cationic medications like

doxorubicin and chitosan-bound actives to improve mucoadhesion and prolonged release. Hydrogen bonding between the hydroxyl and carboxymethyl groups of CMC and the medication might decrease burst release and extend drug availability in formulations that contain non-steroidal anti-inflammatory medications (NSAIDs), such as ibuprofen [24]. CMC works with other polymers like gelatin or alginate to create polyelectrolyte complexes that more effectively encapsulate hydrophobic medications by enhancing matrix integrity and reducing drug diffusion. Furthermore, by creating a gel barrier that limits environmental exposure, CMC can protect delicate medications like peptides or antioxidants from deterioration [25].

Use of Stabilizers and Cross-Linkers

By crosslinking CMC chemically or physically, the microspheres are stabilized, and the polymer network is strengthened. Networks of homopolymers or copolymers can be created by chemical or physical cross-linking, which makes them water-resistant. CMC has been combined with various artificial and natural polymers, such as polyvinyl alcohol, chitosan, alginate, starch, and polyvinylpyrrolidone, to create superabsorbent polymers. Because of its hydrophilic properties, a higher concentration of CMC increases diffusion constants and solvent front velocities. Both the size of the hydrodynamic free volume and the presence of hydrophilic functional groups that promote hydrogen bonding with water determine the swelling capacity of hydrogels. A greater CMC concentration in the polymer matrix with cross-linkers causes an enhanced swelling rate due to its highly hydrophilic properties. Cross-linking creates a three-dimensional network and reduces the mobility of polymer segments. Carboxymethylation modifies drug release and increases gums' hydrophilicity and swelling in dissolving fluids. Cross-linking reduces gum swelling because the drug may escape before it reaches the absorption site.

The durability of cross-linked polymers is higher than that of natural polymers. When cross-linkers come into contact with functional groups (-OH, -COOH, and -NH2), cross-linking takes place. Silva et al. used epichlorohydrin to create cross-linked and carboxymethylated cashew gum (CM-CSG) [26]. When epichlorohydrin and polysaccharide react, sodium hydroxide produces polysaccharide alkoxide. A new epoxy macromolecule is created when epichlorohydrin cleaves the epoxy ring. Cross-linking produces a three-dimensional network and decreases the mobility of polymer segments. Carboxymethylation and cross-linking caused a 23% rise in edema. The polysaccharide backbones of carboxymethylated tragacanth gum (CM-TG) were cross-linked with glutaraldehyde (GA) to produce CM-TG-GA hydrogels. Guo-Qing Huang et al. investigated the pH-sensitive delivery vehicle genipin-cross-linked O-CM-CH-GAR (O-carboxymethyl chitosan–gum Arabic).

Drug loading Capacity and Encapsulation Efficiency

Because CMC's anionic, hydrophilic nature facilitates the trapping of hydrophilic and moderately hydrophobic pharmaceuticals, spray-dried microspheres based on CMC have excellent drug encapsulation efficiencies. The drug's composition, the ratio of the drug to the polymer, and the processing conditions are some of the formulation characteristics that affect the microencapsulation efficiency (Table 2). Several variables affect drug load into CMC-based microspheres, such as the drug's characteristics, the kind of polymer employed, and the microencapsulation technique. Hydrophilic or mildly hydrophobic drugs can be effectively encapsulated in CMC due to their anionic and hydrophilic characteristics [27]. Drug–polymer interactions, concentration, and encapsulation techniques, including concertation, solvent evaporation, and spray drying, all have a major role in the drug loading capacity. The benefits of spray drying include scalable processing, rapid solvent evaporation, and regulated particle size, all of which contribute to uniform encapsulation. However, optimizing polymer concentration is essential since too much CMC can reduce loading efficiency by increasing solution viscosity and interfering with droplet formation. CMC stabilizes drug molecules within the matrix by forming ionic contacts and hydrogen bonds with them; CMC-based microspheres have excellent drug-loading efficiency for various medicines. CMC creates a stable network that enables high encapsulation efficiency while preserving drug stability in the case of hydrophilic medications such as acetaminophen or ibuprofen. Greater drug loadings often result in rapid release rates because there is more drug accessible for diffusion, the drug loading efficiency also affects the drug release profile.

Table 2. Formulation aspects of microspheres.

Formulation aspect	Description
Selection of polymer concentration	Determines microsphere size, mechanical strength, and release characteristics.
Drug-polymer interactions	Affects drug stability, release rate, and compatibility.
Use of cross-linkers and stabilizers	Enhances structural integrity and stability of the microspheres.
Encapsulation efficiency and drug loading capacity	Critical for achieving desired therapeutic efficacy and minimizing waste.

CMC-Based Spray-Dried Microspheres

Shape and distribution of particle sizes

Microparticles larger than 3 μm in diameter are often examined for particle size using a Coulter counter or the laser light diffraction (LD) technique. The distribution in LD represents the span value, whereas d0.1, d0.5, and d0.9 are parameters used to compare results. The size distribution within the microparticles' lower size range is reflected in the polydispersity index (PDI), which is determined via dynamic laser light scattering. Double-walled microsphere coating characteristics may be controlled using light microscopy (LM). Before and after coating, the microsphere forms may be seen, and the changes can be measured under a microscope [28]. Scanning electron microscopy (SEM) makes examining the surfaces of spray-dried microspheres easier and may be used to study double-walled systems once particles have been cross-sectioned. Optimizing spray drying parameters helps minimize aggregation and improve sphericity [29]. Controlled particle size enhances performance in pharmaceutical and biomedical applications, including targeted drug delivery and controlled release systems.

AFM (Atomic forced microscopy) uses surface profiling to provide information on the nanoscale surface properties of microparticles. The high-resolution imaging AFM offers comprehensive information on the nanoscale surface properties of spray-dried microparticles. In contrast to traditional microscopy techniques, AFM creates a three-dimensional topographical map by moving a pointed probe, or tip, across the particle surface (Figure 1). AFM provides a strong tool for comprehending how process variables like intake temperature, feed rate, and atomization pressure impact the surface architecture and fineness of the final particles in the context of spray drying, where these factors substantially impact particle formation. AFM is critically used when examining particles in the sub-micron to nanometer region, where conventional particle size methods might not be accurate. It counts and detects specific particles suspended in an electrolyte solution as they move through a tiny aperture using the electrical sensing zone (impedance-based measurement) approach. This technique is especially important when evaluating spray-dried microparticles intended for intravenous (IV) administration, where exact control of particle size and uniformity is necessary to prevent adverse effects like embolism or capillary blockage. Each particle displaces its electrolyte volume, resulting in a change in electrical resistance proportionate to its size. Regulatory bodies such as the FDA and EMA must strictly adhere to particle size requirements in parenteral formulations, particularly those incorporating microspheres, liposomes, or emulsions. By providing real-time, quantitative data on particle counts across many size bins, the Coulter counter is essential for tracking and adjusting these parameters. This is particularly crucial for intravenous drug administration, where stringent particle size control (usually less than 10 μm) is necessary to avoid immunological responses, vascular blockage, and biodistribution variability. It is perfect for evaluating microspheres used in targeted medicine administration since it can detect particles from 0.4 μm to several hundred micrometers. The Coulter counter helps identify large or clumped particles that might compromise safety and guarantees batch uniformity for spray-dried microspheres made with polymers like CMC or polylactic acid (PLGA). It provides a clear benefit over optical sizing techniques like laser diffraction by providing actual volumetric particle counts. This is especially useful for low-concentration samples or polydisperse systems of these spray-dried microparticles, which are frequently seen in spray-dried goods.

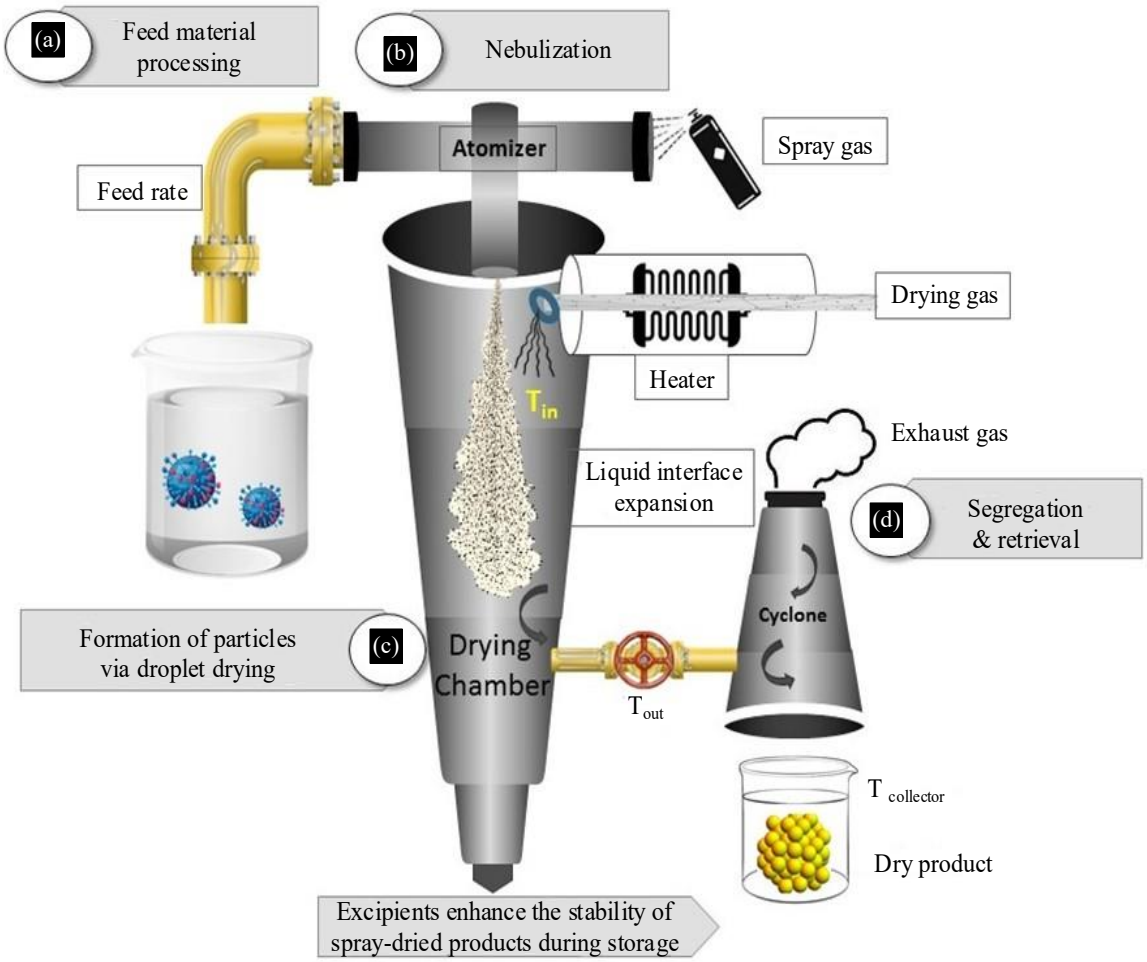

Figure 1. Schematic representation of the spray drying process showing key stages: (A) feed material preparation, (B) atomization via nebulization, (C) droplet drying in the drying chamber, and (D) particle separation and collection.

FTIR for spray-dried CMC microparticles

The degradation of the polymeric matrix inside the carrier system is evaluated using FT-IR. Attenuated total reflectance (ATR) measurements analyze the microspheres' surface. The ATRFT-IR provides information about the microspheres' surface composition based on production circumstances and procedures. It is a critical analytical tool used to characterize spray-dried microparticles, providing insights into chemical integrity, functional group interactions, and possible structural modifications during drying. In spray-dried formulations, FTIR helps confirm the presence of characteristic polymer and drug peaks and can detect potential interactions such as hydrogen bonding, esterification, or complexation between drug and carrier matrix [30]. FTIR spectra typically exhibit strong absorption bands around 1600–1650 cm^{-1} (asymmetric stretching of $–COO^-$ groups), 1410–1450 cm^{-1} (symmetric stretching), and a broad peak near 3200–3500 cm^{-1} associated with –OH stretching vibrations [31] (Figure 2). These peaks serve as reference markers for assessing the chemical stability of CMC after spray drying. Shifts or changes in the intensity of these bands in drug-loaded microparticles may indicate intermolecular interactions, such as hydrogen bonding between the CMC polymer matrix and active pharmaceutical ingredients (API) [32]. TIR helps verify drug encapsulation and can be used to detect residual solvents or unreacted excipients. This ensures that spray drying has not induced unwanted degradation or altered the material's chemical profile. When combined with other characterization tools like DSC or XRD, FTIR offers a robust approach to evaluating formulation stability and molecular dispersion in microparticulate drug delivery systems [33].

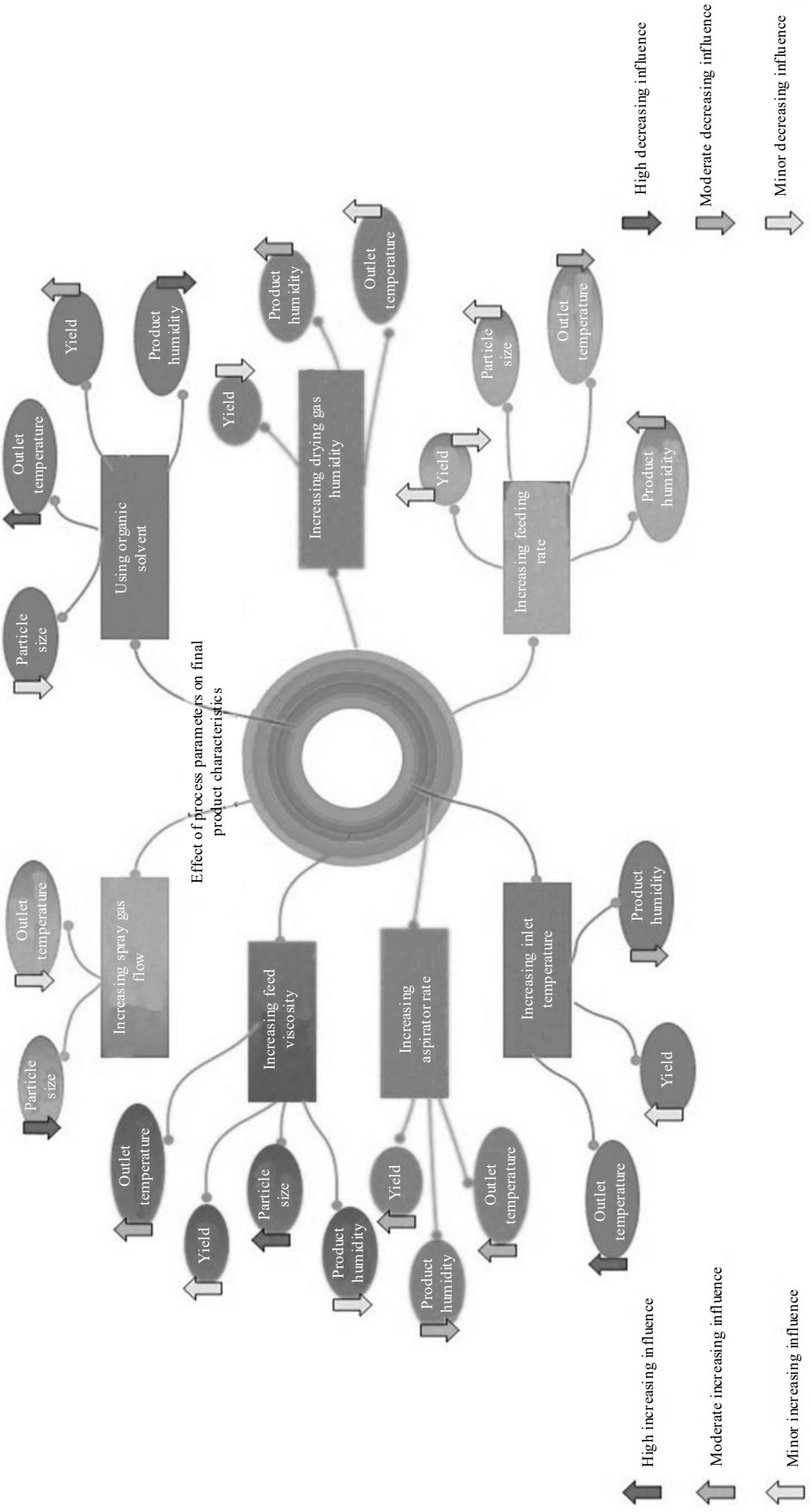

Figure 2. Impact of process parameters on spray-dried product characteristics.

Density determination

Spray drying often produces low-density, porous microparticles due to rapid solvent evaporation, especially at high inlet temperatures. The feed composition, atomization rate, and polymer properties influence this. CMC-based microparticles exhibit lower bulk densities due to their hydrophilic and polymeric nature, which encourages internal pore formation during drying [34]. Adjustments in crosslinking or blending with higher-density excipients can modify these characteristics. Studies have shown CMC microparticles to have true densities ranging from 1.2 to 1.5 g/cm³, with bulk densities significantly lower (~0.3–0.6 g/cm³), depending on spray-drying conditions [35]. Understanding and controlling density parameters enables the design of microparticles with optimal handling, dispersibility, and release characteristics, especially in inhalable or oral dosage forms.

Efficiency of entrapment (EE)

High EE ensures optimal therapeutic payload, reduced dosage frequency, and controlled release. The EE of spray-dried microparticles is influenced by polymer type, drug-polymer interaction, the solubility of the drug in the feed solution, spray drying conditions (inlet/outlet temperature, feed rate), and drying kinetics [36]. Typically, EE is determined by dissolving a known quantity of microparticles in an appropriate solvent to extract the drug, followed by quantification using UV–Vis spectroscopy, HPLC, or fluorometry [37]. Carboxymethyl cellulose (CMC)--based spray-dried microparticles have shown moderate to high EE depending on formulation variables. Due to its hydrophilicity and gel-forming properties, CMC can effectively entrap both hydrophilic and some hydrophobic drugs when crosslinked or blended with other polymers [38]. However, the high aqueous solubility of CMC may lead to drug leakage during atomization if not optimized. Blending CMC with hydrophobic polymers or using crosslinkers like calcium ions can improve EE and sustain drug release [39].

Surface Charge

Their surface charge significantly influences spray-dried CMC microspheres' stability, mucoadhesion, and biocompatibility. As an anionic polysaccharide, CMC gives microspheres a negative surface charge, affecting their behavior in aqueous and biological settings. This charge enhances the formulation's dispersion and stability over time [40] by preventing particle aggregation through electrostatic repulsion. Particles' surface charge significantly influences their biological function and physical characteristics, such as their ability to aggregate. Chitosan and poly-l-lysine are examples of positively charged microparticles that are mucoadhesive and hemocompatible. Quantifying zeta potential and particle size is possible using photon correlation spectroscopy. The Brownian motion of the particles is essential for measuring dynamic light scattering. Zeta potential measurements provide crucial information about the aggregation potential of surface-charged microparticles in suspension (particles with a zeta potential above 30 mV are stable due to repulsive forces) as well as whether the surface-charged molecule is encapsulated or adsorbed onto the surface [41].

Swelling and Porosity

Spray-dried CMC microspheres' ability to swell and porosity is essential to their use in regulated medication delivery systems. Because of its hydrophilic and anionic properties, CMC effectively absorbs water, which causes the microsphere matrix to swell and permits long-term drug transport across the enlarged polymer network. Critical physicochemical characteristics of CMC-based microspheres that affect mucoadhesion, drug release patterns, and bioavailability include their swelling behavior and porosity. The matrix expansion caused by CMC's easy absorption of water as a hydrophilic, anionic polymer facilitates the regulated diffusion of encapsulated medications. The degree of substitution (DS), crosslinking density, polymer concentration, and environmental pH all affect the swelling capacity of CMC microspheres; a higher DS or polymer concentration generally results in greater water uptake, whereas extensive crosslinking can limit swelling by limiting the mobility of the polymer chain [42]. The interior empty area in microspheres is referred to as porosity, and it directly impacts the rate of drug diffusion, water penetration, and degradation. While less porous methods provide continuous delivery, highly porous microspheres show quicker initial drug release (sometimes known as "burst release"). By altering the spray drying settings, changing the polymer mixes (such as

CMC with gelatin or alginate), or adding porogens during formulation, the porosity may be customized [43]. Kinetics, swelling, and porosity must be balanced to achieve the desired drug release. While porosity controls the accessibility of the release medium and the microspheres' effective surface area, swelling enables regulated release by diffusion or erosion. An equilibrium swelling study can be used to examine how dry particles behave under different circumstances. The original particle diameter (di) before reconstitution and the swollen particle diameter (ds) are used to compute the swelling index (S%)

Analysis of Temperature

Thermogravimetry (TG) and differential scanning calorimetry (DSC) offer crucial insights into the spray-dried polymer's thermal characteristics in microparticles. Measuring the glass transition temperature is essential in the production and release processes. Tensile strength, shear strength, peel-off, and in vitro wash-off tests may be performed on mucoadhesive systems. Two crucial methods for assessing the thermal stability and phase transitions of spray-dried CMC microspheres are thermogravimetric analysis (TGA) and DSC. TGA provides information on moisture content, thermal degradation, and the existence of residual solvent by measuring a sample's mass change when heated. Thermal analysis techniques methodically assess these changes using predetermined specimen atmospheres and pressures and preprogrammed temperature variations for heating and cooling. Minor variations in gas evolution, thermal expansion or contraction, weight fluctuations, Young's modulus, and changes in heat and enthalpy are the most often observed phenomena [44]. TGA to determine the cellulose material's mass fluctuation as a function of temperature, as well as its volatile component proportion and thermal stability. Lignin, hemicellulose, and cellulose in CMC have different chemical structures; thus, they degrade at different temperatures. Lignin breaks down thermally extremely slowly at temperatures ranging from 200°C to 700°C. However, because acetyl groups are present, hemicellulose undergoes very little thermal degradation, starting at temperatures between 220 and 315 degrees Celsius. The temperature range at which cellulose thermally degrades is 315 °C to 400 °C. As a result, fibrous material has limited thermal stability because hemicellulose breaks down before cellulose and lignin.

Factors Determining the Drug Release Profile

The release profile of drugs from CMC microspheres—whether immediate, sustained, or delayed—is influenced by a range of formulation and process-related factors. Key determinants include the degree of cross-linking, polymer concentration, drug-to-polymer ratio, and the physicochemical properties of both the drug and the polymer matrix. A lower cross-linking density and higher water solubility of the drug typically result in immediate release, whereas increased cross-linking and the inclusion of hydrophobic polymers or stabilizers can slow diffusion, leading to sustained or delayed release. The degree of substitution (DS) of CMC also plays a crucial role; higher DS enhances swelling and diffusion, influencing how quickly the drug is released. The microsphere size, porosity, and surface morphology—shaped by spray-drying parameters like feed rate, atomization pressure, and drying temperature—further modulate the release rate. Environmental conditions such as pH and ionic strength affect swelling behavior, particularly for pH-responsive systems, making these microspheres adaptable for site-specific or delayed drug delivery.

In-Vitro Release Kinetics

Diffusion, swelling, erosion, and osmotic pressure are some of the mechanisms that regulate the in vitro release kinetics of spray-dried CMC microspheres. Because CMC is hydrophilic, it promotes water absorption, which causes the pore networks to widen and the polymer matrix to swell. Drug diffusion is accelerated by this swelling, especially for drugs that are soluble in water [45]. Numerous elements, such as the drug's characteristics, formulation, and release medium, affect the drug release process of microparticulate. In spray-dried microparticulates, the polymer matrix containing the active medication component can either function as a membrane or dissolve in the media. The primary reason for the spread is the active ingredient's release. The microparticles are coated with a film-forming polymer that may function as a membrane or disintegrate in the liquid. One, two, or more triggers may be needed for disintegration in smart drug delivery microparticle systems, and feedback may be generated via start

and stop signals. The tracheobronchial tract collects inhaled particles according to their form [46]. Because the mucus layer, which serves as the site of medicine absorption, has a restricted volume, alternative dissolving procedures are employed throughout development. Drug dispersion between the two liquid phases prevents the dialysis bag technique and the USP 2 spinning paddle equipment from reproducing the air-liquid transition [47].

Spray-Dried CMC-Microsphere Stability

Spray drying produces dry, spherical particles with improved structural integrity, a narrow size distribution, and lower moisture content; these characteristics are essential for controlled medication release and long-term storage. Spray drying improves encapsulation efficiency and shelf life by reducing pore formation and locking the medication within the matrix by quick solvent evaporation [48]. The enhanced flowability and re-dispersibility of spray-dried CMC microspheres make them appropriate for oral or inhaled drug administration systems [49]. To improve the stability, functionality, and clinical viability of spray-dried CMC-based microspheres, chemical cross-linking, ionic gelation, and spray drying work in concert. The biocompatibility and biodegradability of CMC microspheres make them valuable for drug delivery applications. Glutaraldehyde is commonly used as a bifunctional aldehyde to cross-link CMC, resulting in decreased solubility chemically and enhanced mechanical strength. Ionic cross-linking with calcium ions is an effective and safer method for biomedical applications. The degree of cross-linking can be modulated by varying glutaraldehyde concentration, affecting drug release kinetics and microsphere stability. This non-toxic and eco-friendly method encapsulates sensitive biomolecules. Polyelectrolyte complexes combining CMC with stabilizing polymers like chitosan or alginate increase mechanical strength and resistance to pH fluctuations.

Scale-Up Challenges in Spray Drying

While spray drying is a widely adopted technique in pharmaceutical manufacturing, scaling up the production of CMC-based microspheres presents several challenges. Maintaining consistent particle size, morphology, and drug loading across larger batches is difficult due to variations in droplet formation, drying rates, and chamber dynamics. Uniform atomization and heat distribution become harder to control at scale, potentially affecting drug encapsulation efficiency and product homogeneity. High feed solution viscosity, common with CMC formulations, can lead to nozzle clogging or uneven atomization. Furthermore, process parameters such as inlet temperature, feed rate, and airflow must be precisely optimized for each formulation, and even minor deviations can result in batch-to-batch variability. Equipment limitations, high energy consumption, and difficulties in recovering low-yield microspheres also impact scalability. Regulatory compliance, reproducibility, and cost-effectiveness further complicate the transition from lab-scale to commercial-scale spray drying for CMC-based drug delivery systems.

Current Developments and Prospects

Spray-dried CMC microspheres have advanced recently, emphasizing the creation of novel alterations to improve their efficacy in drug delivery applications. Using composite microspheres, in which CMC is mixed with other polymers like chitosan, alginate, or poly (lactic-co-glycolic acid) (PLGA), is one approach that shows promise. These composite systems provide synergistic benefits, including increased stability, controlled release, and drug encapsulation efficiency. Another new concept is creating smart hydrogels based on CMC for responsive drug delivery. For instance, mixing CMC with chitosan might enhance mucoadhesive qualities, resulting in extended drug retention at target areas. These hydrogels may alter morphologically when exposed to environmental stimuli like pH, temperature, or ionic strength. CMC-based hydrogels are made to respond to the intestine's neutral pH or the stomach's acidic pH by swelling and releasing the medication, providing tailored drug release. Future studies will likely focus on adding nanomaterials, such as nanoparticles or nanostructured carriers, to CMC microspheres to improve drug delivery accuracy and therapeutic efficacy further. These developments should enhance site-specific delivery, lessen adverse effects, and provide more individualized therapy choices. The combination of smart materials and multipurpose composites has the potential to transform drug delivery systems based on CMC completely. Future research is

anticipated to be driven by sustainability and green chemistry, emphasizing using ecologically benign and biocompatible solvents for spray drying. Drug delivery methods may have a much less environmental impact if biodegradable and non-toxic excipients are developed to formulate CMC microspheres. Personalized medicine will advance CMC microsphere formulations by allowing customized drug release patterns based on patient-specific characteristics, including genetic composition and medical problems, resulting in more potent therapies.

CONCLUSION

Spray drying emerges as a pivotal technique in formulating carboxymethyl cellulose (CMC) microspheres, contributing to enhancing drug delivery systems. Through careful manipulation of process variables, such as atomization, particle formation, and temperature control, CMC microspheres exhibit optimized physicochemical characteristics, including drug loading capacity, encapsulation efficiency, and stable particle morphology. Using stabilizers and cross-linkers further improves drug stability and controlled release, ensuring consistent therapeutic efficacy. In-vitro release kinetics and FTIR analysis provide valuable insights into the microspheres' behavior while incorporating mucoadhesive properties that enhance targeted drug delivery. This review highlights the significant potential of CMC-based spray-dried microspheres in pharmaceutical applications, emphasizing their role in regulated drug release and targeted therapy. Future advancements in spray drying techniques and CMC formulations hold promise for more efficient and personalized medication administration, making this approach a crucial area for continued research and development.

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