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Review

A Practical Guide to Microparticle Fabrication: An Illustrated Review of Sixteen Methods

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Abstract

Selecting a microparticle fabrication method requires an understanding of payload compatibility, particle formation, and manufacturing constraints. This review summarizes these considerations and provides guidance on method selection. PubMed, Scopus, and Web of Science databases were searched up to February 2026, supplemented by Google Scholar searches. This structured narrative review compares 16 microparticle fabrication methods, examining their mechanisms, key formulation and process variables, material compatibility, particle properties, release behavior, scalability, and limitations. Representative patented methods are also listed to provide an additional informative technological context. Among the analyzed methods, interfacial dynamics, heat and mass transfer, payload partitioning, and carrier solidification help explain how processing conditions influence particle properties and release. Spray drying and coating are relatively well-established industrial processes. Droplet microfluidics and electrospraying enable precise control over particle size and architecture, though throughput and scale-up remain challenges. Whereas mild aqueous processing may help preserve the integrity of labile biomacromolecules, solvent- and melt-based techniques require careful control of residual solvents and thermal exposure. For long-acting delivery, particular attention must be paid to matrix tortuosity, the changing contributions of diffusion and degradation, and initial burst release. However, direct comparisons are difficult due to differences in formulation parameters and testing conditions. Method selection remains application-dependent. Payload stability, desired particle structure and release profiles, manufacturing constraints, and production scale must all be comprehensively considered. More consistent reporting and direct comparisons under relevant industrial conditions would provide stronger support for these decisions.

Keywords: microparticles; method of preparation; solvent evaporation; solvent extraction; spray drying; electrospraying; single emulsion; double emulsion; pan coating

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1. Introduction

The process of forming microparticles—including microspheres, microcapsules, and microbeads—with 1–999 μm size represents an essential feature of modern drug delivery

systems and functional material development [1]. The multiparticulate drug delivery system has several advantages, especially with regard to the controlled release of active pharmaceutical ingredients (APIs) and the improvement of the bioavailability of poorly soluble APIs [2]. In addition, the system is effective in masking undesirable tastes and providing API protection from early degradation by the environmental factors [3]. An important difference in the release of microspheres and microcapsules is generally attributed to the internal structure of these microparticles. The microsphere is a matrix system, while the microcapsule is a reservoir system with a well-defined core–shell structure [4]. Here, "microparticle" is the umbrella term; "microbead" refers to gel-based particles, and "micropellet" refers to small, preformed pellets used as coating substrates, provided their size falls within the micrometer range. However, the drug release behavior cannot be determined solely by the internal structure. In the polymer particle system, the drug release is also influenced by the chemical properties of the polymer, hydrophilicity, molecular weight, chain length, end group functions, crystallinity, and the degradation or dissolution rate of the polymer matrix [5]. In the lipid-based system, the most important influencing factors include lipid composition, hydrophobicity, melting behavior, polymorphism, crystallinity, drug–lipid miscibility and distribution, surfactant content, and the lipid digestion or matrix dissolution process [6]. Generally, these factors interact together to affect the water permeability, drug diffusion, matrix remodeling, and initial release rate of the system.

The preparation method is one of the factors influencing the final physicochemical properties of particulate drug delivery systems (Figure 1). Particle size and porosity are determined jointly by formulation components and process parameters, while surface charge mainly depends on the nature of the formulation components and their specific surface area distribution. The choice of a microparticle fabrication method generally depends on the properties of the payload and the desired product attributes. Relevant factors include solubility, chemical and thermal stability, phase behavior, viscosity, interfacial tension, heat and mass transfer, the solidification mechanism, and the expected production scale. Lipophilic and hydrophilic payloads often differ in their partitioning behavior and processing requirements. Protein formulations may be sensitive to heat, dehydration, shear, and interfacial exposure during spray drying. Suitable excipients and careful control of inlet and outlet temperatures and residence time may mitigatesome of these effects. Nitrogen may also be used as the drying gas when oxidative degradation is a concern. When organic solvents are required, their compatibility with the payload and the residual solvent levels should be assessed [7,8]. Microfluidic systems provide fine control over particle size and morphology, although higher throughput usually requires the parallelization of multiple microchannels. Spray drying can usually be scaled more readily for industrial production [9]. Herein, we evaluate sixteen microencapsulation techniques, comparing their underlying physical mechanisms, critical process parameters (CPPs), critical quality attributes (CQAs), and scale-up feasibility. This comparative framework aims to help select the appropriate preparation method based on the physicochemical properties of the active pharmaceutical ingredient and the desired product characteristics.

Existing reviews typically focus on individual preparation techniques or specific materials and applications, limiting direct comparisons of fundamental mechanisms, process variables, and scale-up limitations among different methods. To address this gap, this review evaluates sixteen different particulate preparation methods within a unified framework that links physicochemical mechanisms and key process parameters to the properties and performance of the particles. Its principal contribution is an integrated comparison linking fabrication mechanisms, critical process parameters, particle attributes, payload compatibility, and scale-up considerations, supported by diagrams and quantitative examples.

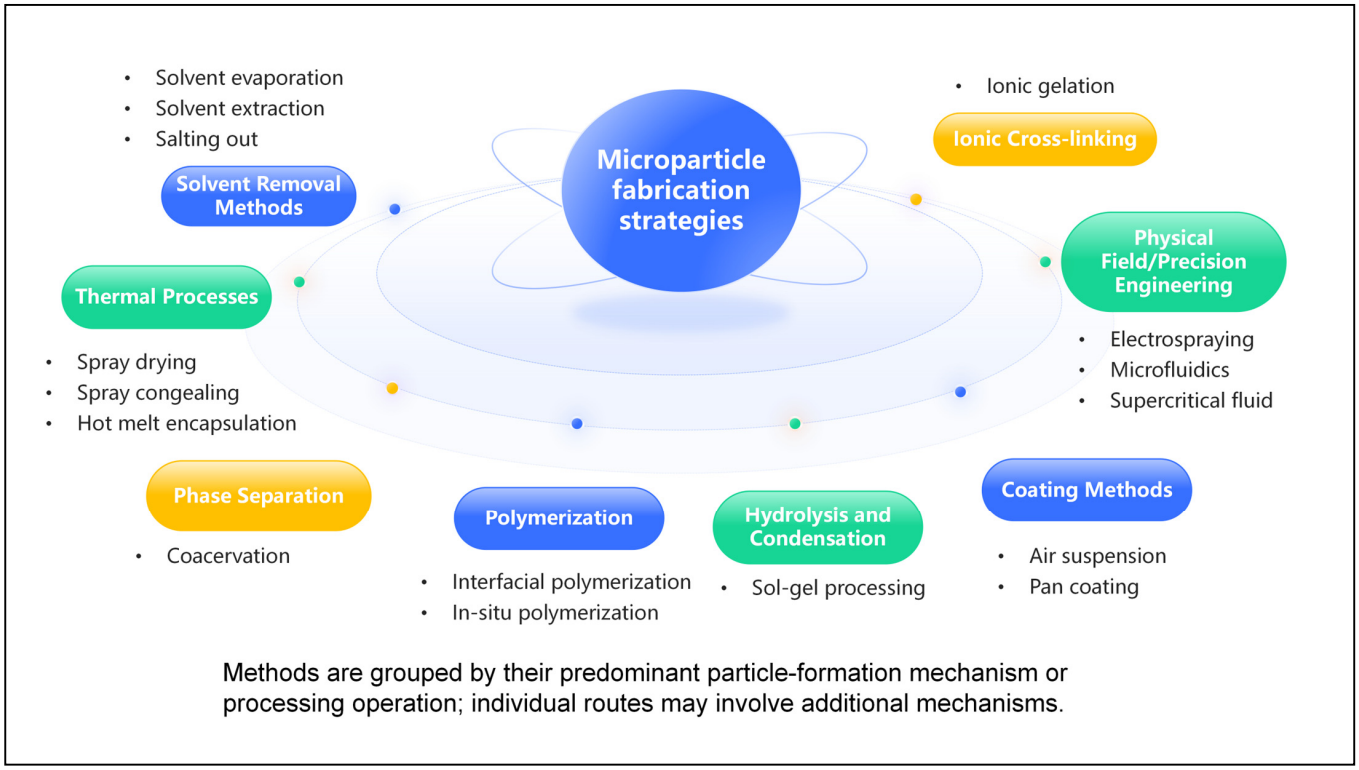


Figure 1. Classification and mechanisms of microparticle fabrication methods.

1.1. Common Physicochemical Determinants of Microparticle Formation

Although equipment and processes differ, the production of microparticle formulations is influenced by many common physicochemical factors. The final particle size, morphology, internal structure, solid-state properties, encapsulation efficiency, and release behavior reflect the interactions among formulation composition, interfacial phenomena, transport processes, and solidification conditions. Manufacturing processes can affect these properties, but these effects are not independent of the payload, carrier, solvent system, and operating parameters.

The formation of droplets depends on the balance among inertial, viscous, and interfacial forces. This balance can be described by the Weber number, Capillary number, Reynolds number, and viscosity ratio:

$$\mathrm{We} = \frac{\rho U^2 L}{\gamma},\ \mathrm{Ca} = \frac{\mu U}{\gamma},\ \mathrm{Re} = \frac{\rho U L}{\mu},\ \lambda = \frac{\mu_d}{\mu_c}$$

where ρ and μ are the density and dynamic viscosity of the continuous phase, U is the characteristic relative velocity, L is the characteristic length, γ is the interfacial tension, and μ_d and μ_c are the viscosities of the dispersed and continuous phases, respectively. The Weber number is particularly relevant when inertial forces contribute substantially to droplet breakup, while the capillary number is commonly used for low-Reynolds-number flows, such as those in microchannels. Greater shear or lower interfacial tension generally promotes droplet deformation and size reduction. A high dispersed-phase viscosity may resist breakup, producing larger or less uniform droplets. Surfactants can lower interfacial tension and limit coalescence, although excessive concentrations may increase continuous-phase viscosity or alter the particle surface [10–18]. Wetting also affects whether a liquid

phase spreads over a solid core or previously formed particles. The capillary pressure across a curved interface is described by the following:

$$\Delta P = \gamma\left(\frac{1}{R_1} + \frac{1}{R_2}\right)$$

where R_1 and R_2 are the principal radii of curvature [19]. Changes in interfacial tension, curvature, and wettability can therefore affect droplet stability, coating deposition, and shell formation.

Heat and mass transfer govern the conversion of liquid droplets or precursor phases into solid microparticles. Solvent transport is driven by differences in chemical potential and can often be approximated using Fick's law:

$$J = -D\nabla C$$

where J is the solvent flux, D is the diffusion coefficient, and ∇C is the concentration gradient. For a spherical droplet, the surface-area-to-volume ratio is 3/R, where R is the droplet radius. Smaller droplets therefore tend to exchange heat and mass more rapidly and have shorter internal diffusion distances. Solvent volatility and water miscibility, external-phase volume, temperature, pressure, gas flow, humidity, residence time, and dilution rate can all influence solvent removal. Rapid solvent loss may produce an early surface layer that restricts subsequent transport and promotes pores, cavities, or particle collapse. Slower removal can allow more extensive polymer rearrangement and may produce a denser internal structure [20–31]. In sol–gel systems, capillary pressure generated during ambient drying can also cause network shrinkage or cracking, while supercritical drying can reduce this stress [32,33].

Carrier properties and solid-state transitions further influence particle formation and stability. Polymer concentration and molecular weight affect solution viscosity, chain entanglement, droplet breakup, and molecular mobility. The glass transition temperature, T_g, describes the transition of amorphous polymer regions from a glassy state to a more mobile rubbery state. Residual solvents, absorbed water, plasticizers, and some payloads may increase free volume and lower T_g. When the processing or storage temperature approaches T_g, greater chain mobility may promote particle adhesion, pore collapse, payload diffusion, or physical instability [25,26,34–39]. Drug–carrier miscibility and the rates of cooling, drying, and precipitation influence whether the payload remains molecularly dispersed or forms amorphous or crystalline domains. Rapid cooling or precipitation may retain a metastable structure, whereas subsequent recrystallization or lipid polymorphic transitions can redistribute the payload and change its release behavior [40–45]. In melt-based processes, carrier melting range, melt viscosity, and cooling rate also affect droplet breakup, particle sphericity, and the thermal exposure of the payload.

Payload retention depends partly on its solubility and partitioning among the phases present during fabrication. Lipophilic payloads generally show greater retention in an organic or hydrophobic carrier phase, while hydrophilic payloads may migrate into the external aqueous phase, reducing encapsulation efficiency. Double emulsions and core–shell structures can limit this loss, but additional interfaces may increase leakage or expose sensitive biomolecules to interfacial stress [46–48]. Differences in osmotic pressure between the internal and external aqueous phases can drive water transport and cause droplet swelling, internal cavities, or membrane disruption. Electrolytes may alter water activity, ionic strength, solvent–water miscibility, and interactions between the payload and carrier. Their type and concentration require careful adjustment because excessive ionic strength may precipitate sensitive payloads or modify particle structure and release

kinetics [30,49–57]. Ion-specific effects associated with the Hofmeister series are discussed separately in Section 2.16.

Some fabrication methods introduce pressure or electrical energy as additional process variables. In supercritical fluid processing, pressure and temperature determine carbon dioxide density, phase behavior, and solvent strength. Rapid depressurization or antisolvent mixing can generate supersaturation and nucleation, while dissolved carbon dioxide may plasticize polymer matrices and reduce their glass transition temperature and viscosity [39,58–62]. In electrospraying, particle formation depends on solution conductivity, solvent volatility, humidity, feed rate, and droplet residence time [63–70]. These variables influence whether the process produces discrete particles, satellite droplets, wet deposits, or fibrous structures.

The final release profile reflects the combined effects of matrix porosity, pore connectivity, tortuosity, particle size, payload distribution, and interactions between the payload and carrier. Greater connected porosity usually facilitates water penetration and diffusion, whereas greater tortuosity lengthens the transport pathway and reduces effective diffusivity. The relative contributions of water uptake, diffusion, matrix relaxation, erosion, and polymer degradation can change during the release period [71,72]. Payload located near the surface and rapid pore formation may increase initial burst release. An excessively dense matrix can instead produce a long lag phase or incomplete release. Method selection should therefore consider payload stability, target particle structure, release requirements, solvent and thermal exposure, and the intended production scale.

1.2. Literature Search Strategy

This structured narrative review searched PubMed, Scopus, and Web of Science from database inception to 9 February 2026. Recent studies published within the preceding five years were prioritized for representative applications and technological developments, while earlier foundational studies were retained when necessary to describe established principles and mechanisms. The search terms were "(microparticles or microspheres or microcapsules) and (preparation or encapsulation)", combined with the names of the sixteen methods described in later sections. Google Scholar and reference lists were also consulted to identify additional studies. After removing duplicates, titles, abstracts, and full texts were reviewed. Stage-specific record counts are not reported because they cannot be reliably reconstructed from the available search records. Peer-reviewed journal articles form the primary evidentiary basis. Established principles are supported by citations of seminal works and relevant sections, while the patent literature is used solely to provide representative technical background. Priority was given to recent examples with originality, while foundational studies elucidating established principles were retained. The comparative discussion focuses on micron-scale particle systems. Studies encompassing both submicron and micron dimensions are included, with the reported size ranges explicitly specified, rather than treating all particles indiscriminately as micron-sized.

2. Method of Microparticle Preparation

2.1. Solvent Evaporation

The solvent evaporation technique remains a foundational, highly scalable approach for the fabrication of biodegradable polymeric microparticles within industrial pharmacy. At its core, the methodology relies on a multiphase system where a preformed polymer and an active pharmaceutical ingredient are dissolved in a volatile organic solvent (the dispersed phase) and subsequently emulsified into discrete droplets within an immiscible continuous phase (dispersion medium). The transition of the liquid droplet to a solid matrix structure is regulated by a coupled mass transport phenomenon whereby the organic solvent diffuses

into the continuous phase before being eevaporating into the ambient air at the gas–liquid interface [8]. This stage-wise transition is illustrated in Figure 2.

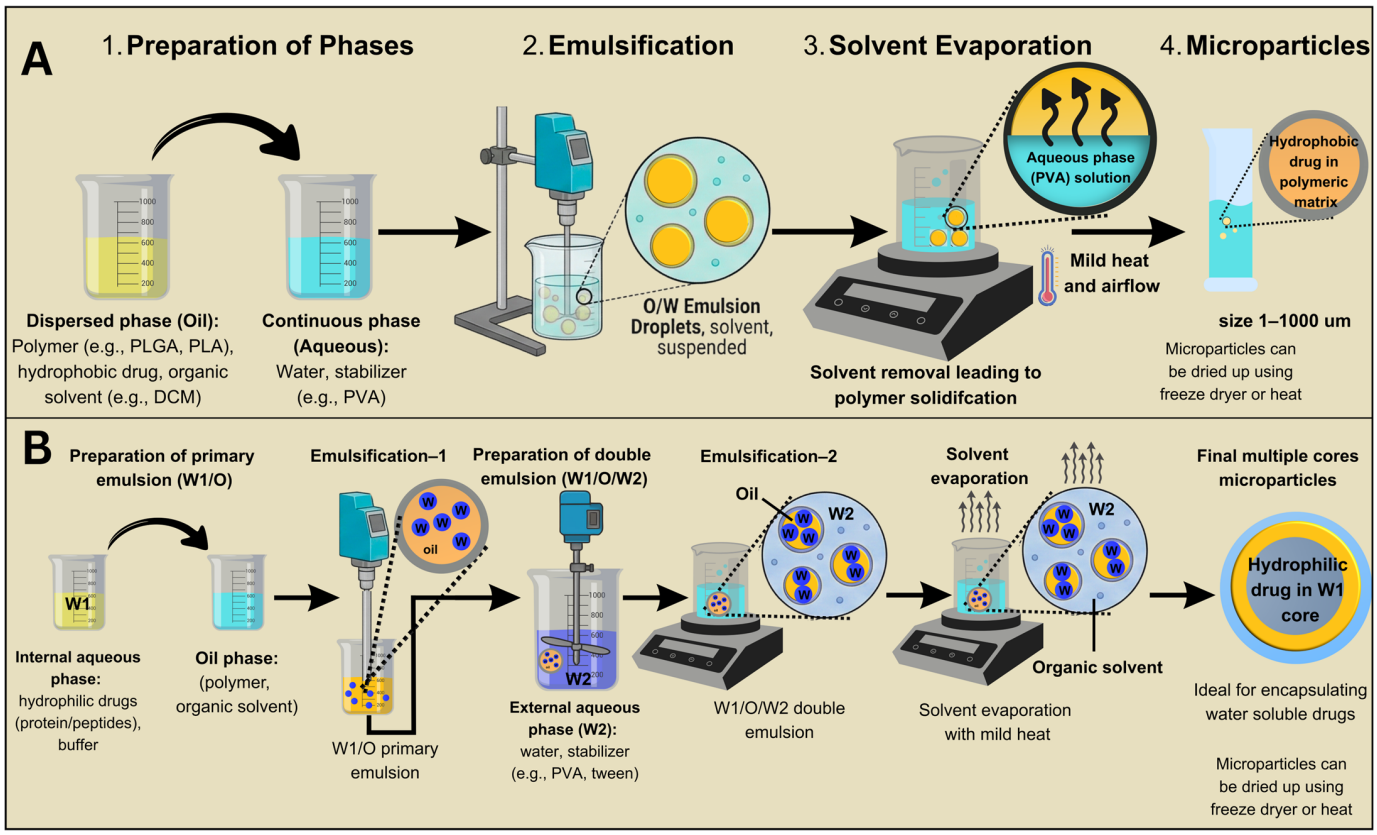


Figure 2. Illustration and practical steps for the preparation of microparticles using the solvent evaporation method. (**A**) Single emulsion evaporation method. (**B**) Double emulsion evaporation method.

2.1.1. Fluid Dynamics and Interfacial Mechanics of Emulsification

The emulsification process determines the initial droplet size distribution, which in turn significantly affects the final particle size. As shown in Figure 2, the polymer (e.g., poly(lactic-co-glycolic acid)) and the active ingredient are dissolved in an organic solvent, typically dichloromethane [31]. The organic phase is then introduced into an aqueous phase containing a stabilizer (e.g., poly(vinyl alcohol)) and emulsified by high-shear homogenization or ultrasonic cavitation [73]. Generally, higher shear rates and lower interfacial tension during solvent evaporation favor the formation of smaller emulsion droplets, resulting in smaller particles [10].

2.1.2. Solvent Transport and Kinetics of Solidification

During solvent evaporation, as the organic solvent partitions from the polymer-rich phase and is removed from the continuous phase, the dispersed droplets gradually solidify. The solvent removal rate directly influencesthe morphology and internal porosity of the particles. Rapid removal can lead to premature surface vitrification and the formation of internal voids or irregular pores. Slower removal may allow greater polymer chain rearrangement and favor a denser matrix, depending on the formulation and processing conditions [20,74]. These trends do not predict release kinetics by themselves, which also depends on residual-solvent plasticization and the associated changes in glass transition temperature, pore connectivity, and payload distribution.

2.1.3. Formulation Modulation Based on Drug Lipophilicity

As shown in Figure 2, the technique can be fine-tuned using chemical modification based on the logP value of the medicinal compound:

- Single Emulsion (O/W) Approach: This process works well with lipophilic drugs, where the hydrophobic drug preferentially partitions into the organic polymer phase due to thermodynamic affinity, hence giving very high encapsulation efficiencies [46].
- Double Emulsion (W/O/W) Technique: In the case of hydrophilic substances—such as proteins, peptides, or highly soluble small molecules—a water-in-oil (W1/O) primary emulsion must first be created, which is then dispersed in a secondary water phase (W2). The water droplets act as isolated cores for the hydrophilic cargo molecules. However, this technique poses several technical difficulties. Osmotic and mass transport phenomena can promote coalescence between the internal and external aqueous phases, leading to leakage of the drug and low efficiency of entrapment. Emulsification may also expose sensitive proteins to oil–water interfaces, which can induce interfacial shear and protein denaturation or aggregation [75].

2.1.4. Influence of Polymer Molecular Weight on Matrix Formation and Drug Release

Polymer molecular weight influences dispersed-phase viscosity and chain entanglement. However, its effects on particle formation and release kinetics depend on polymer chemistry, polymer concentration, solvent composition, and processing conditions. At comparable polymer concentrations, a higher molecular weight generally increases solution viscosity and can hinder droplet breakup during emulsification. This does not necessarily produce a denser matrix or slower drug release, as porosity, payload distribution, water uptake, and degradation also contribute to the observed profile [74,76]. End-group chemistry also modifies these effects. For polymers sharing the same backbone, a lower molecular weight corresponds to a greater concentration of chain ends per unit mass; whether this increases hydrophilicity depends on the nature of those end groups. Acid-terminated and ester-capped polyesters (such as PLGA) therefore should not be assumed to behave identically [5]. Residual solvents and some payloads may plasticize the polymer matrix and depressits glass transition temperature (T_g). The extent of plasticization depends on their concentration and thermodynamic miscibility with the polymer, with potential consequences for particle stability depending on formulation composition and processing or storage temperature [34–37].

2.1.5. Interfacial Stabilization and Residual Surfactant Effects

Surfactant concentration is a key variable in the solvent evaporation process. Poly(vinyl alcohol) (PVA) adsorbs at the oil–water interface, thereby lowering interfacial tension and suppressing droplet coalescence during solvent removal. Within a certain range, increasing the PVA concentration can reduce particle size; however, excessive PVA increases the continuous-phase viscosity and leads to irreversibleadsorption of surfactants on the particle surface [11,12]. Residual PVA can affect zeta potential, surface wettability, and initial burst release kinetics. Washing can reduce the amount of stabilizer adsorbed on the particle surface; however, excessive washing can induce shear-mediated particle damage or promote payload leaching [13].

2.1.6. Recent Experimental Application of Solvent Evaporation Method

Alvarez et al. used a double-emulsion solvent evaporation method to compare the use of dichloromethane and ethyl lactate in the preparation of gemcitabine-loaded PLGA microparticles [77]. Gemcitabine was encapsulated in an inner aqueous phase, and a primary emulsion was first prepared using a high-speed homogenizer at speeds of 5600 to

12,000 rpm, which was then dispersed in a 1% (*w*/*v*) Poly(vinyl alcohol) solution. Higher homogenization speeds resulted in smaller droplets. The high water solubility of ethyl lactate also accelerated solvent mass transfer into the continuous phase, directly influencing phase separation and particle agglomeration [77].

2.2. Solvent Extraction

Solvent extraction solidifies emulsion droplets by transferring an organic solvent from a dispersed polymer phase into a large external extraction medium. Solvent extraction and evaporation may both contribute to solvent removal; the terms distinguish the predominant removal route rather than mutually exclusive mechanisms [78,79]. As the solvent diffuses from the droplet, the polymer reaches supersaturation and precipitates, forming solid particles, Figure 3. The extraction rate affects the particle morphology, internal porosity, and residual solvent levels [21,22,80].

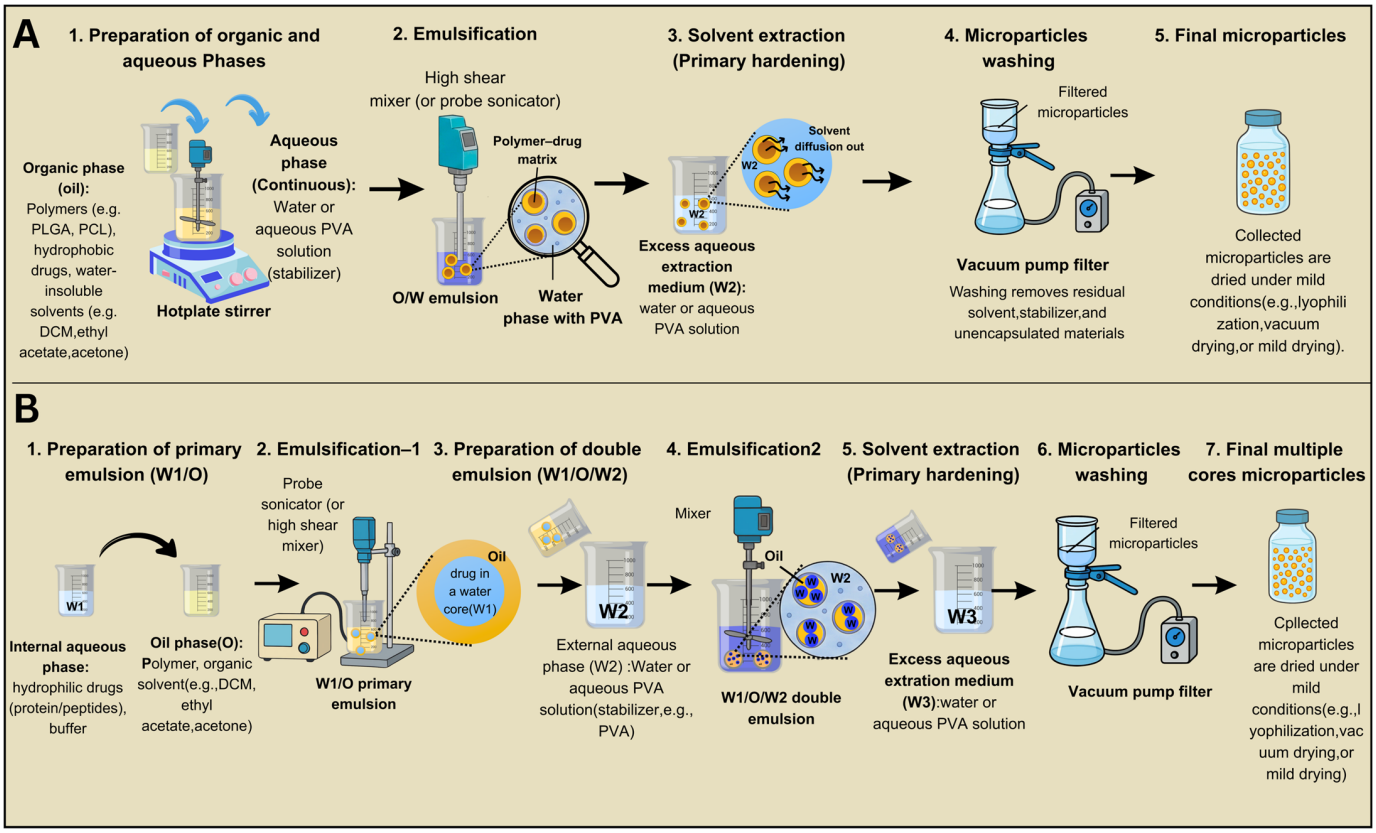


Figure 3. Illustration and practical steps for the preparation of microparticles using the solvent extraction method. (**A**) Single emulsion solvent extraction method (O/W) for hydrophobic drugs. (**B**) Double emulsion extraction method (W1/O/W2) for hydrophilic drugs, peptides, or proteins.

2.2.1. Solvent Partitioning and Particle Hardening

The solvent partitioningbetween the organic droplet and the surrounding aqueous phase determines the hardening rate of the particles. Solvent transfer from the droplets into the aqueous phase depends on solvent–water miscibility and the concentration gradient; rapid transfer may promote early polymer precipitation at the droplet surface [23]. If the solvent diffusion rate exceeds the relaxation rate of the polymer chains, the outer regions may vitrify before the interior is fully depleted of solvent. This can result in irregular porosity and elevated residual solvent levels [24]. The initial droplet size also affects extraction, with smaller droplets resulting in a larger specific surface area per unit volume.

Therefore, phase viscosity and emulsification conditions indirectly affect solvent transport by determining the initial droplet size distribution [14,15,21].

2.2.2. Effect of Extraction Medium Volume Ratio

The effect of the extraction-medium volume depends on solvent–water miscibility and the stage of particle formation. In an ethyl acetate–PLGA system, the initial organic-to-aqueous phase ratio is selected to permit droplet formation while avoiding premature polymer precipitation; subsequent dilution promotes microsphere solidification [81]. Thus, the volume ratio and timing of dilution must be optimized concurrently. Resulting changes in surface morphology and internal pore structure should be established empirically for the specific polymer–solvent system. Table 1 summarizes these formulation-specific considerations.

Table 1. Formulation-specific considerations for solvent extraction.

Parameter	Consideration	Evidence Boundary
Solvent removal	Consider external-phase capacity, dilution timing, and diffusion within the matrix.	Initial particle formation and final residual-solvent removal can be controlled by different factors.
Polymer solidification	Avoid premature precipitation before stable droplets form.	Demonstrated for the ethyl acetate–PLGA system; no universal volume-ratio threshold is established.
Particle morphology	Assess surface morphology and internal structure for the selected formulation.	A general higher-ratio versus moderate-ratio ranking is not established.
Payload retention	Measure drug loading and release together with residual-solvent content.	Volume ratio alone does not establish retention or burst release.

Note: These are formulation-development considerations, not universal directional predictions.

2.2.3. Osmotic Balance and Electrolyte Effects

Hydrophilic payloads may partition into the external aqueous phase during solvent extraction, thereby reducing encapsulation efficiency. Electrolytes can limit this loss by altering water activity and osmotic balance [49]. In double-emulsion systems, the osmotic pressure difference between the inner and outer aqueous phases can lead to droplet swelling, internal cavity formation, or membrane rupture. Careful adjustment of the type and concentration of electrolytes can improve structural stability, but excessively high ionic strength may cause sensitive payloads to precipitate or alter subsequent drug release kinetics [50–52].

2.2.4. Recent Experimental Application of Solvent Extraction Method

A 2024 study explored methods for removing residual solvent from blank and drug-loaded PLGA microspheres prepared by oil-in-water (O/W) solvent extraction/evaporation [81]. The microspheres solidified while still retaining approximately 5–10% (*w*/*w*) dichloromethane. Subsequent wet extraction with low concentrations of aqueous methanol or ethanol improved the removal of dichloromethane, likely because the alcohols plasticizedthe PLGA matrix and increased polymer chain mobility. Excessive alcohol concentrations or process temperatures reduced the retention of dexamethasone and risperidone. Therefore, the relationship between residual solvent removal and drug loss appears to depend on formulation and process conditions [81].

2.3. Coacervation (Phase Separation)

Coacervation is a liquid–liquid phase separation process in which a polymer solution separates into into a polymer-rich condensed phase and a polymer-poor equilibrium phase (dilute phase) [82]. The preparation of microparticles typically involves four sequential steps: (1) dispersing the core material in the polymer solution; (2) inducing phase separation; (3) depositing the coacervate droplets around the core; and (4) solidifying the deposited layer to form a stable shell [83].

2.3.1. Simple and Complex Coacervation

Simple coacervation occurs in single-polymer solutions and is typically induced by the addition of non-solvents, miscible alcohols, electrolytes, or other desolvating agents. This reduces polymer–solvent interactions, leading to a decrease in polymer solubility and the separationof a polymer-rich liquid phase [84,85]. In contrast, complex coacervation involves the associative phase separation of two or more oppositely charged polyelectrolytes (typically proteins and polysaccharides). Electrostatic attraction, coupled with the entropic gain driven by the release of counterions and bound water, promotes phase separation [86,87].

2.3.2. Fluid Mechanics and Interfacial Adsorption Parameters

Effective shell formation requires a liquid coacervate layer to wet the core material surface. This tendency can be described by the spreading factor:

$$S = \gamma_{cs} - (\gamma_{cc} + \gamma_{sc})$$

where γ_{cs} is the interfacial tension between the continuous phase and the core, γ_{cc} is the interfacial tension between the continuous phase and the coacervate, and γ_{sc} is the interfacial tension between the solid core and the coacervate. Spontaneous encapsulation requires a positive spreading coefficient ($S > 0$), which causes the liquid coacervate phase to wrap uniformly around the core material during the deposition stage shown in Figure 4 [88].

These three interfacial tensions correspond to the interfaces between the continuous phase and the core, the continuous phase and the coacervate phase, and the core and the coacervate phase, respectively. A positive spreading coefficient promotes the wetting and spreading of the coacervate phase over the core surface and the formation of a continuous coating. Controlled stirring can improve the contact between the core and the coacervate phase while limiting droplet coalescence [16].

2.3.3. Shell Hardening and Crosslinker Selection

The deposited coacervate layeris initially liquid and may require chemical or enzymatic crosslinkingto form a stable shell (Figure 4). Glutaraldehyde reacts rapidly with primary amines, but this can cause cytotoxicity and residual crosslinker issues [82,89]. Depending on the shell material, charge stability, and required processing time, other crosslinking systems—such as genipin, transglutaminase, and EDC/NHS coupling—can be selected [90–93]. EDC/NHS-mediated coupling promotes amide-bond formation between carboxyl and primary amine groups without introducing a spacer into the linkage; its efficiency depends on pH and competes with hydrolysis of the activated intermediates.

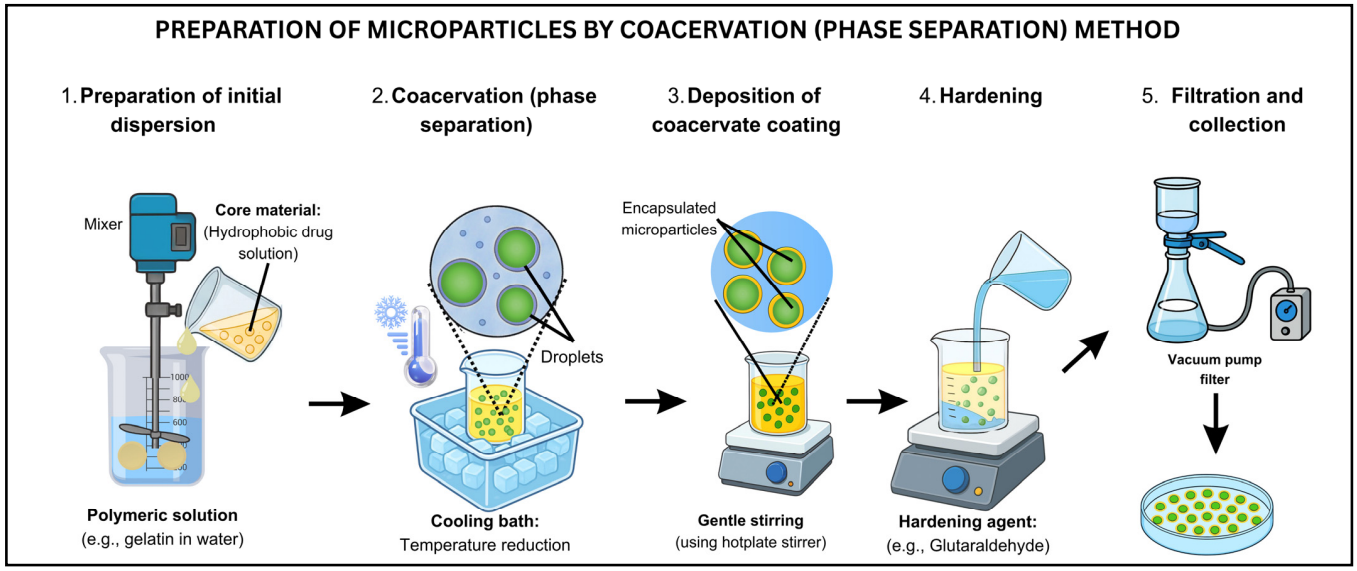


Figure 4. Illustration and practical steps for microparticle preparation by coacervation.

2.3.4. Ionic Strength and Electrostatic Screening

Complex coacervation is highly sensitive to ionic strength because dissolved ions screen the electrostatic attraction between oppositely charged macromolecules. Coacervation can occur within a suitable range of ionic strength; however, excessively high electrolyte concentrations can weaken polymer association and suppress coacervate phase separation [94,95]. The influence of ionic strength depends on pH, polymer charge density and mixing ratio, and electrolyte composition, including ion identity and valence; no single ionic-strength or Debye-length range applies to all coacervating systems.

2.3.5. Timing of Electrolyte Addition

The timing of electrolyte addition affects shell hydration, porosity, and payload release kinetics. Adding electrolyte during coacervate deposition may disrupt compact polymer association, resulting in a more hydrated shell, while treatment after coating may promote shell dehydration and densification [86,96]. These effects depend on the polymer composition and are the specific electrolyte conditions.

2.3.6. Recent Experimental Application of Coacervation Method

In one study, a combination of complex coacervation and spray drying was used to encapsulate propolis extract using chia seed mucilage and gelatin as shell materials [97]. Turbidity and zeta potential measurements showed that pH 3.5 was optimal for coacervate formation. The selected formulation contained 3.13% (w/v) propolis extract, and the resulting particles had a total phenolic content of 15.36 mg gallic acid equivalents per gram and exhibited high thermal stability under the reported test conditions [97].

2.4. Spray Drying

Spray drying is a continuous process in which a liquid feed is atomized into droplets, dried in a heated drying stream, and then collected as a dry powder. Particle formation typically involves three sequential stages: atomization; solvent evaporation and droplet solidification; and separation of the dried particles from the exhaust gas (Figure 5) [98].

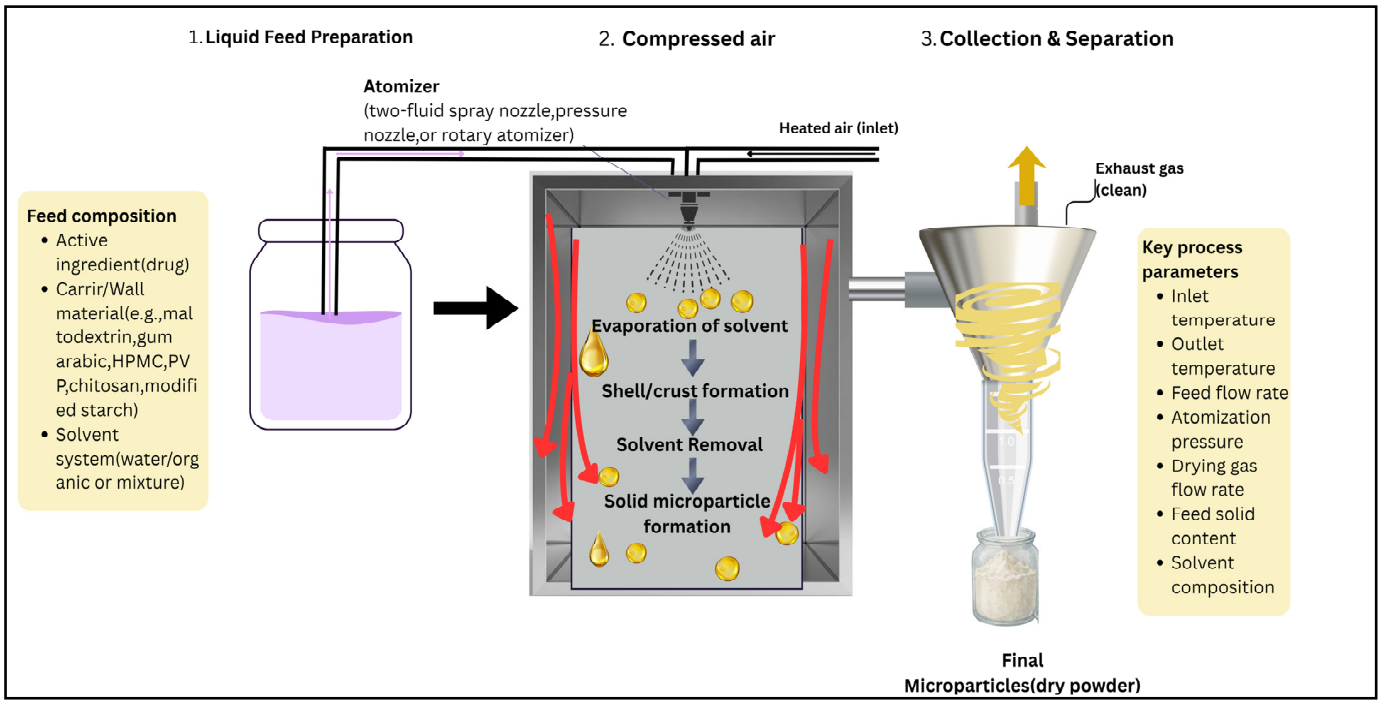


Figure 5. Illustration and practical steps for microparticle preparation by spray drying.

2.4.1. Atomization and Droplet Formation

Atomization dispersesthe liquid feed into fine droplets, thereby increasing the specific surface area available for solvent evaporation. Droplet size and size distribution depend on atomizer geometry, feed viscosity, surface tension, feed rate, and atomization pressure. Rotary atomizers, two-fluid nozzles, and multi-fluid nozzles impose distinctshear regimes, which govern the resulting initial droplet size distributions [40,99].

2.4.2. Solute Migration and Particle Morphology

During the early constant-rate drying period, solvent evaporation keeps the droplet temperature near the wet-bulb temperature of the drying gas, thus limiting thermal exposure [100,101]. The competition between surface recession and solute diffusion can be expressed by the Péclet number:

$$Pe = (R \times E)/D$$

where R is the droplet radius, E is the surface recession rate, and D is the solute diffusion coefficient. At a low Péclet number, solutes can redistribute within the droplet, forming a relatively uniform matrix. At a high Péclet number, the surface recession rate is faster than the solute diffusion rate, which may promote surface enrichment, shell formation, porosity, or the formation of hollow particles [102–105]. These outcomes also depend on solute concentration, solubility, and surface activity.

2.4.3. Drying, Solidification, and Thermal Stress

As drying continues, a crust forms due to solute enrichment at the droplet surface, after which internal solvent diffusion becomes rate-limiting. Reducing evaporative cooling during this falling-rate drying period can bring the particle temperature close to the outlet gas temperature. Product temperature relative to the formulation's glass transition temperature (*Tg*) remains an operational constraint, as soft or sticky particles may adhere to the chamber wall or agglomerate [25,26]. Labile macromolecules, despite short residence times, are affected by thermal stress, dehydration stress, shear stress, and interfacial adsorption stress [27–29]. Rapid solvent removal may kinetically trap poorly soluble active

pharmaceutical ingredients as an amorphous solid dispersion within the polymer matrix, significantly enhancing their dissolution rate [106].

2.4.4. Recent Experimental Application of Spray Drying Method

A 2024 study used a two-fluid nozzle to investigate the distribution and initial release kinetics of bovine serum albumin from spray-dried PLGA microspheres [107]. Surface-sensitive analyses showed that the protein accumulated near the particle surface, with approximately 85% released during the initial burst phase. The authors attributed this phenomenon to the rapid surface recession relative to protein diffusion during particle formation. Subsequently, hydration and pore formation in the outer PLGA matrix provided short diffusion pathways for surface-enriched proteins [107].

2.5. Spray Congealing (Spray Cooling)

Spray congealing, also known as spray cooling, is a solvent-free process in which a molten matrix containing dissolved or dispersed payloads is atomized into a cooled chamber. As the droplet temperature falls below the melting or crystallization range of the carrier, the droplets solidify intolipid- or wax-based microparticles (Figure 6) [108]. This process eliminates solvent removal requirements but is restricted to carriers and active ingredients that can withstand the melting temperature.

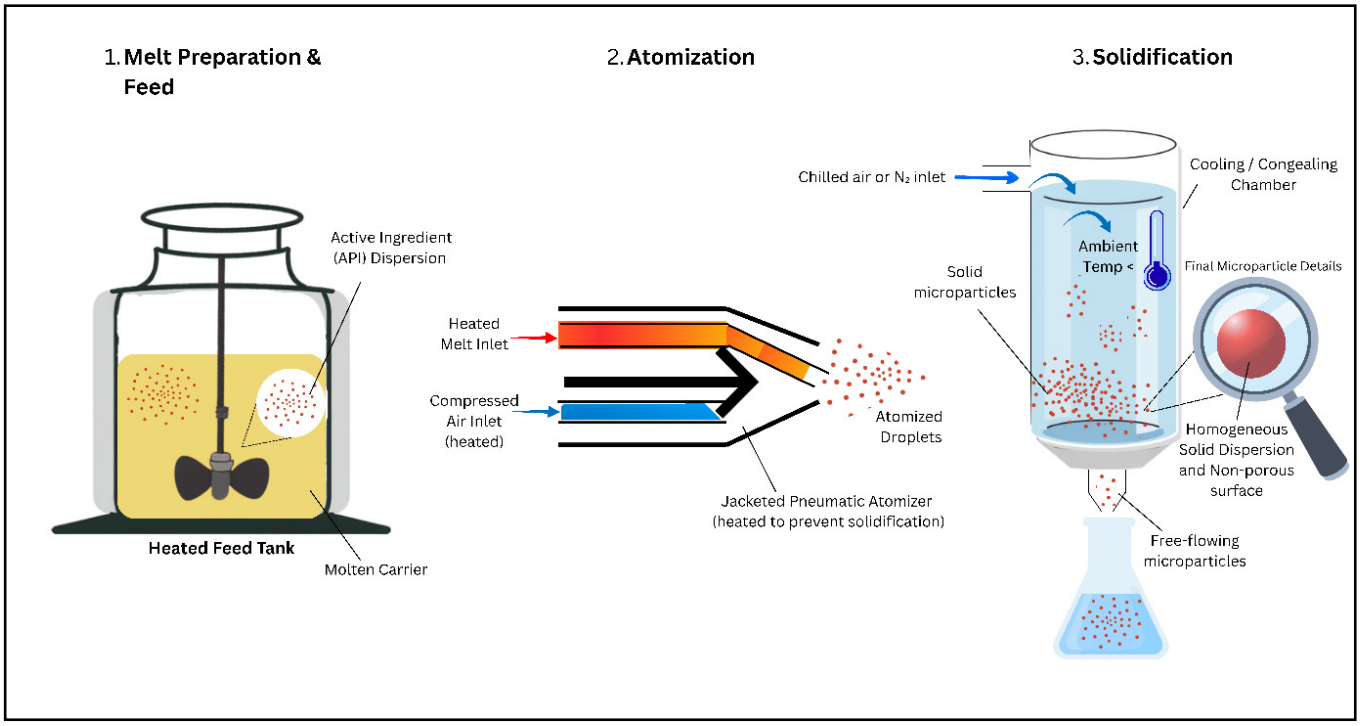


Figure 6. Illustration and practical steps for microparticle preparation by spray congealing.

2.5.1. Carrier Selection and Payload Compatibility

The composition and melting behavior of the carrier govern droplet solidification, payload distribution, and drug release kinetics. Commonly used carriers include carnauba wax, beeswax, stearic acid, and acylglycerols(e.g., glycerol dibehenate), which can be used in combination with hydrophilic excipients (e.g., low molecular weight poly(ethylene glycol)) [109,110]. Lipophilic payloads typically dissolve in molten carriers, whereashydrophilic compounds are dispersed as solid microparticles or incorporated through emulsion-based feed systems. Solid payload micronization improves disper-

sion homogeneity in suspension feeds, though it is unnecessary for fully solubilized systems [41,108].

2.5.2. Lipid Polymorphism and Payload Redistribution

Depending on lipid composition and cooling kinetics, rapid cooling can generate metastable polymorphic forms. In triacylglycerol systems, these predominantly include α and β' polymorphs that may subsequently undergo polymorphic transition toward the thermodynamically stable β form, but this sequence is not universal. Sub-cell recrystallization or polymorphic transitions compress the crystalline lattice, which can trigger payload expulsion to the particle surface and accelerate release kinetics. Crystalline habit modifiers, such as lecithin and sorbitan esters, can kinetically retard these polymorphic transitions, but their efficacydepends on matrix composition and storage temperature [41,111].

2.5.3. Cooling Rate, Annealing, and Solid-State Stability

The cooling rate governs the crystalline organization of lipid microparticles. Rapid thermal quenching promotes the kinetic trapping of metastable polymorphs, whereas controlled slower cooling rates or post-process thermal annealing drive transformation into thermodynamically stable crystalline forms. To prevent interparticle sintering and plastic deformation, the annealing temperature must remain below the onset of the carrier melting endotherm [109,110]. The resulting lipid polymorphic forms and phase transitions are standardly characterized using differential scanning calorimetry (DSC) and X-ray diffraction (PXRD) [109,111].

2.5.4. Recent Experimental Application of Spray Congealing Method

In a 2023 study, researchers prepared biphasic polymer–lipid microparticles using a spray congealing method. Compritol 888 ATO constituted the continuous lipid phase, and poly(ethylene glycol) 400 constituted the hydrophilic internal phase [112]. Fluconazole, tolbutamide, and nimesulide were selected as model active pharmaceutical ingredients spanning distinct aqueous solubilities. For the hybrid biphasic microparticles (b-MPs) investigated in this study, encapsulation efficiencies ranged from 90.5% to 99.6% across fluconazole, tolbutamide, and nimesulide, and the distinct poly(ethylene glycol)-rich and Compritol-rich microdomains clearly resolved. Drug release kinetics were modulated by adjusting the polymer-to-lipid ratio, thereby obtaining a variety of release profiles ranging from rapid release to near-zero-order release kinetics [112].

2.6. Ionic Gelation

Ionic gelation is an aqueous particle-forming method in which charged macromolecules undergo physical crosslinking with oppositely charged multivalent counterions or polyelectrolytes to establish a three-dimensional hydrogel network. The process typically involves preparation of the polymer feed, droplet formation, and ionic crosslinking in a gelling bath, as illustrated in Figure 7. The mild processing conditions make the technique suitable for heat- and solvent-sensitive payloads, although final critical quality attributes depend on polymer molecular weight, pH, ionic strength, counterion valency, and crosslinking kinetics [113].

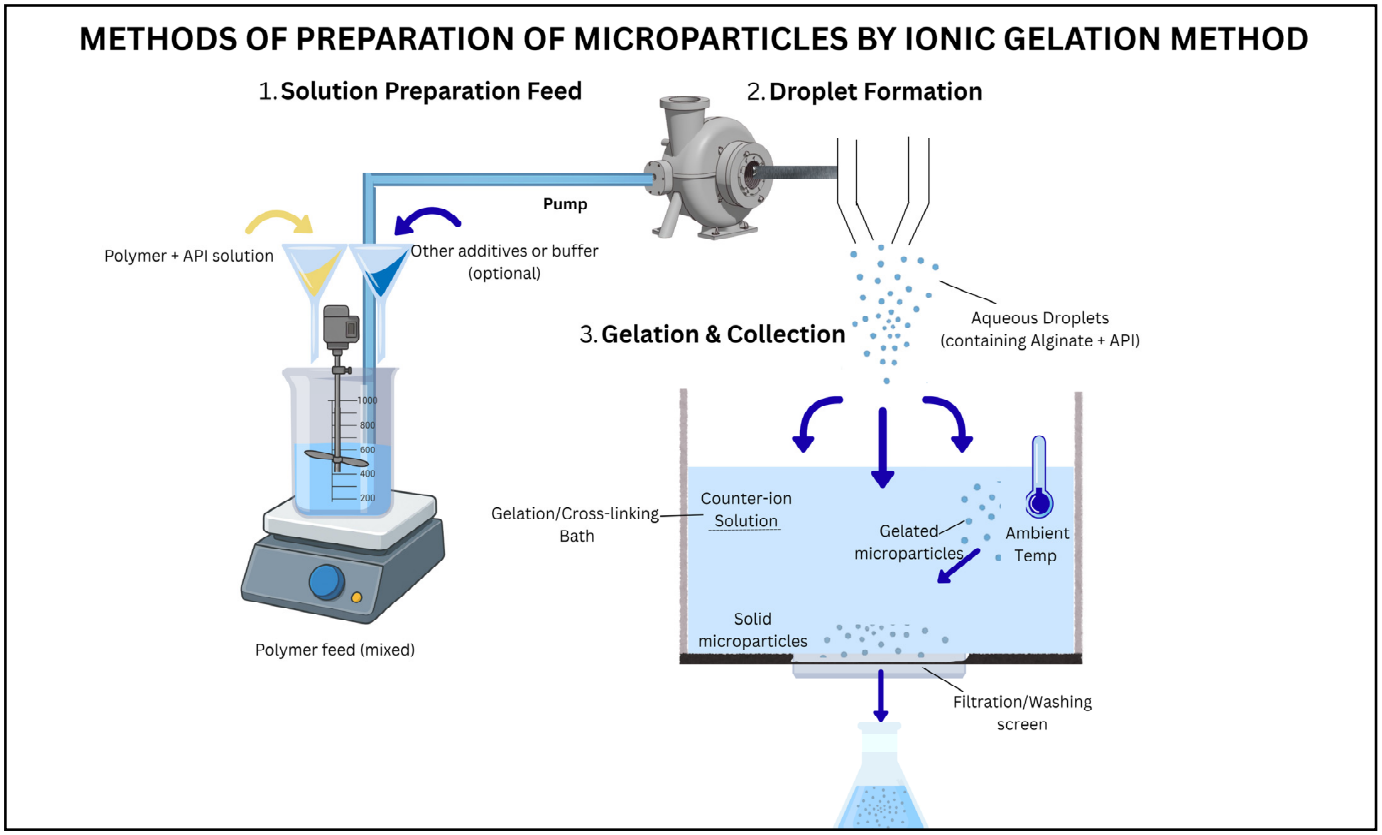


Figure 7. Illustration and practical steps for microparticle preparation by ionic gelation.

2.6.1. Alginate Coordination and Network Formation

In alginate systems, divalent cations such as Ca^{2+} coordinatespecifically with contiguous α-L-guluronic acid blocks to form an ionically crosslinked hydrogel network, commonly described by the egg-box model [113,114]. These ambient aqueous processing conditions are suitable for encapsulating labile biomacromolecules. However, the high mesh size of the hydrated hydrogel network permits rapid out-diffusion of small hydrophilic payloads, while phosphate, citrate, and other calcium-binding species can weaken the gel by removing crosslinking ions [114].

2.6.2. Surface Coating and Charge Complementarity

Surface coating with an oppositely charged polyelectrolyte reduces effective mesh size and modulates payload release kinetics For example, negatively charged alginate microparticles can be coated with poly(L-lysine) or chitosan via layer-by-layer electrostatic deposition to form an interfacial polyelectrolyte complex membrane [113]. Depending on polymer charge, ionic gelation may involve anionic polymers crosslinked with multivalent cations, or cationic polymers crosslinked with polyanions such as tripolyphosphate [114,115]. Polymer concentration, crosslinker valency and concentration, and curing residence time govern hydrogel crosslink density, mechanical rigidity, and release kinetics, whereas hydrophobic payloads necessitate incorporation via pre-emulsified internal phases [113,116].

2.6.3. External and Internal Gelation

In external gelation, polymer droplets are introduced into a bath containing crosslinking ions. Inward diffusion of counterions from the continuous phase toward the droplet interior produces a radial crosslinking gradient, resulting in a dense outer shell and a less crosslinked core [114]. In internal gelation, a sparingly soluble ion source, such as calcium carbonate, is dispersed within the feed, and calcium ions are released through gradual

acidification, often using glucono-δ-lactone. The resulting hydrogel network exhibits a homogeneous matrix structure governed by ion-release kinetics, droplet dimensions, and precursor stoichiometry [116,117].

2.6.4. Recent Experimental Application of Ionic Gelation Method

A 2024 study prepared insulin-loaded sodium alginate microparticles by ionic gelation and investigated the effects of nonionic surfactants [118]. The encapsulation efficiency exceeded 80% across the tested formulations. The sodium alginate matrix limited insulin release under acidic conditions and showed greater swelling and release at higher pH. After 120 min in simulated intestinal fluid, approximately 66% of the insulin remained, suggesting that enzymatic degradation remained a practical limitation [118].

2.7. Interfacial Polymerization

Interfacial polymerization forms core–shell microcapsules through a polycondensation between complementary monomers partitioned into two immiscible liquid phases. An oil-soluble monomer, such as a diisocyanate or diacid chloride, is dissolved in the dispersed organic core phase, while a water-soluble nucleophile, commonly a diamine, or polyamine, is dissolved in the continuous aqueous phase. Their reaction at the oil–water droplet interface yields a crosslinked polyurea or polyamide shell encapsulating the core, as illustrated in Figure 8 [119].

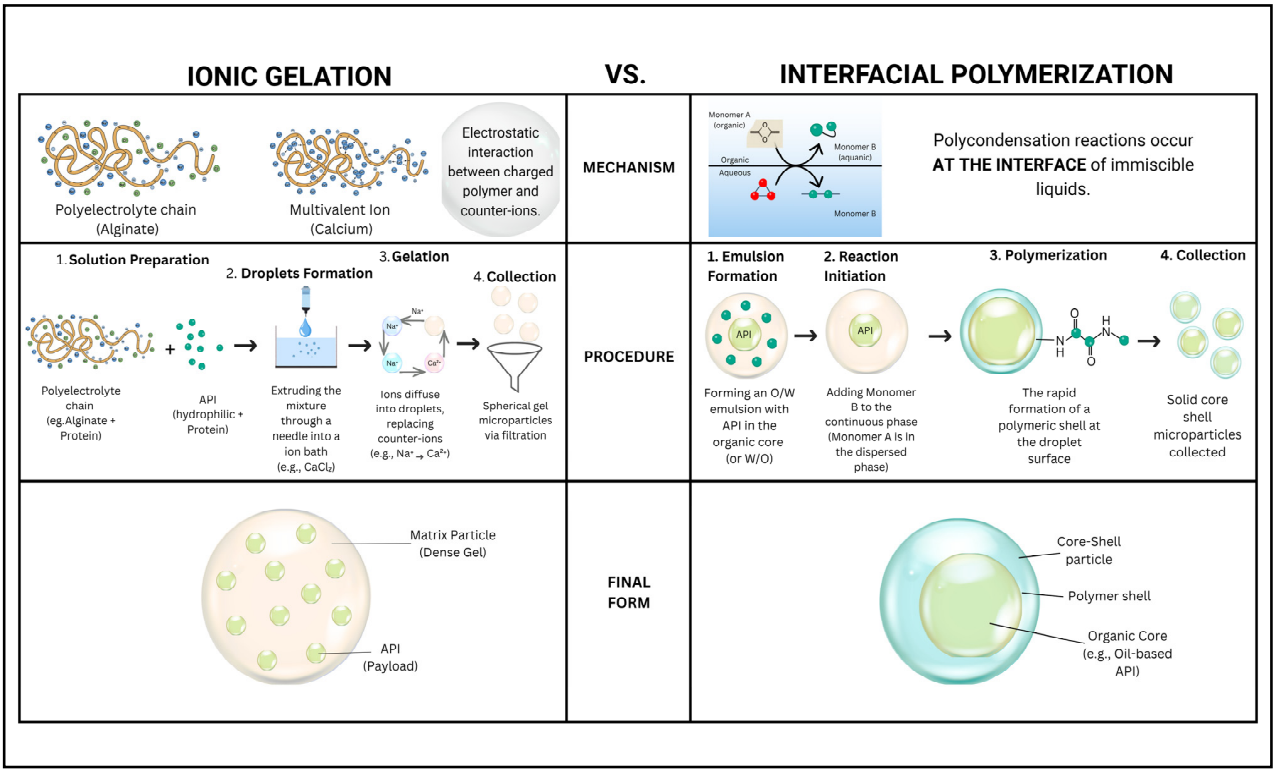


Figure 8. Comparison of microparticle preparation by interfacial polymerization and ionic gelation.

2.7.1. Interfacial Reaction and Diffusion-Limited Shell Growth

Once the monomers contact each other at the liquid–liquid interface, an incipient polymeric membrane forms rapidly around each droplet. Subsequent shell growth becomes increasingly limited by monomer permeationthrough the developing shell layer. As the shell thickens and its crosslink density increases, the diffusional resistance rises, attenuating the rate of polymerization. Monomer diffusivity, partition coefficients, reaction kinetics,

and specific interfacial area govern the final shell thickness, crosslinking profile, and shell uniformity [120].

2.7.2. Residual Monomer Risk and Stoichiometric Control

Residual unreacted monomers represent a primary safety and biocompatibility concern, particularly in systems based on diisocyanates or diacidchlorides. Rigorous downstream purification and analytical quantification of residual monomer levels are therefore mandatory when the resulting microcapsules are intended for biomedical applications. Sensitive payloads may also react with the monomers or be affected by the local reaction conditions. Monomer stoichiometry critically governs shell integrity; an off-stoichiometric molar ratio can leave unreacted functional groups or result in defective, incomplete shell architectures [119,121].

2.7.3. Recent Experimental Application of Interfacial Polymerization Method

A 2024 study prepared IPDI- or HDI-containing polyurea microcapsules in a PVA-stabilized O/W emulsion, using MDI and DETA as the shell-forming monomers [121]. Increasing the homogenization speedreduced the capsule size from approximately 100 μm at 600 rpm to 10–20 μm at 4000 rpm, and about 1 μm at 10,000 rpm. The authors selected 4000 rpm for subsequent characterization. Shell formation also depended on the MDI/DETA ratio, which was adjusted to allow complete reaction of the available amine groups [121].

2.8. Air Suspension (Wurster Coating)

Wurster coating is a bottom-spray fluidized-bed process used to deposit polymer films on solid cores, such as drug crystals, granules, pellets, and nonpareils. Fluidizing air carries the particles upward through a central draft tube, where they encounter atomized coating droplets. The particles then enter the expansion chamber, descend through the surrounding annular region, and return to the spray zone for repeated coating and drying cycles [122].

2.8.1. Particle Circulation in the Wurster Column

Particle circulation results from differences in gas velocity and pressure between the central draft tube and the surrounding annular region. Gas flow transports the particles upward through the draft tube, while expansion of the gas stream above the draft tube reduces the gas velocity and allows them to descend. Airflow rate, partition gap, bed mass, core size, and core density can influence particle circulation and coating uniformity [123,124].

2.8.2. Droplet Deposition and Film Formation

In the bottom-spray zone, particles and atomized coating droplets move upward in the same direction. This arrangement promotes droplet deposition before extensive drying. Film formation then depends on droplet impact, spreading, and solvent evaporation. The droplet-to-particle size ratio and the coating-liquid viscosity affect deposition, while the polymer, solvent system, and plasticizer content influence the continuity and mechanical properties of the film [38,125,126].

2.8.3. Spray–Drying Balance and Agglomeration Control

Stable coating requires the liquid spray rate to remain compatible with the drying capacity of the fluidizing air. Excessive liquid application causes overwetting and capillary bridging, which may lead to particle agglomeration. Excessive drying or atomizing air can dry droplets before adequate spreading, increasing spray loss and producing discontinuous or porous films, Table 2 [38,126].

Table 2. Comparison of top-spray, bottom-spray (Wurster), and tangential-spray fluidized-bed processes.

Feature	Top Spray	Bottom Spray (Wurster)	Tangential Spray
Typical application	Granulation and general coating	Film coating of particles and pellets	Pelletization, powder layering, and coating
Spray and particle movement	Mainly counter-current	Mainly co-current through the draft tube	Tangential spray onto a rotating particle bed
Film uniformity	Moderate and process-dependent	Often high when circulation is well controlled	Often high for regular and sufficiently dense pellets
Agglomeration tendency	Moderate to high during wet granulation	Low to moderate, but increases with overwetting	Moderate and dependent on bed moisture
Drying behavior	Relatively rapid	Controlled cyclic wetting and drying	Moderate
Typical substrate	Powders and granules	Fine particles, granules, and pellets	Pellets and relatively dense granules

2.8.4. Recent Experimental Application of Air Suspension Method

A 2023 study examined how seed-particle properties affect coating using an aqueous sodium benzoate and HPMC formulation in a Wurster fluidized bed, Figure 9 [124]. Larger or denser seed particles generally produced coating shells with lower porosity. Seed size, density, and bed mass also affected particle circulation, while unsuitable operating combinations reduced coating uniformity by disrupting movement near the partition gap [124].

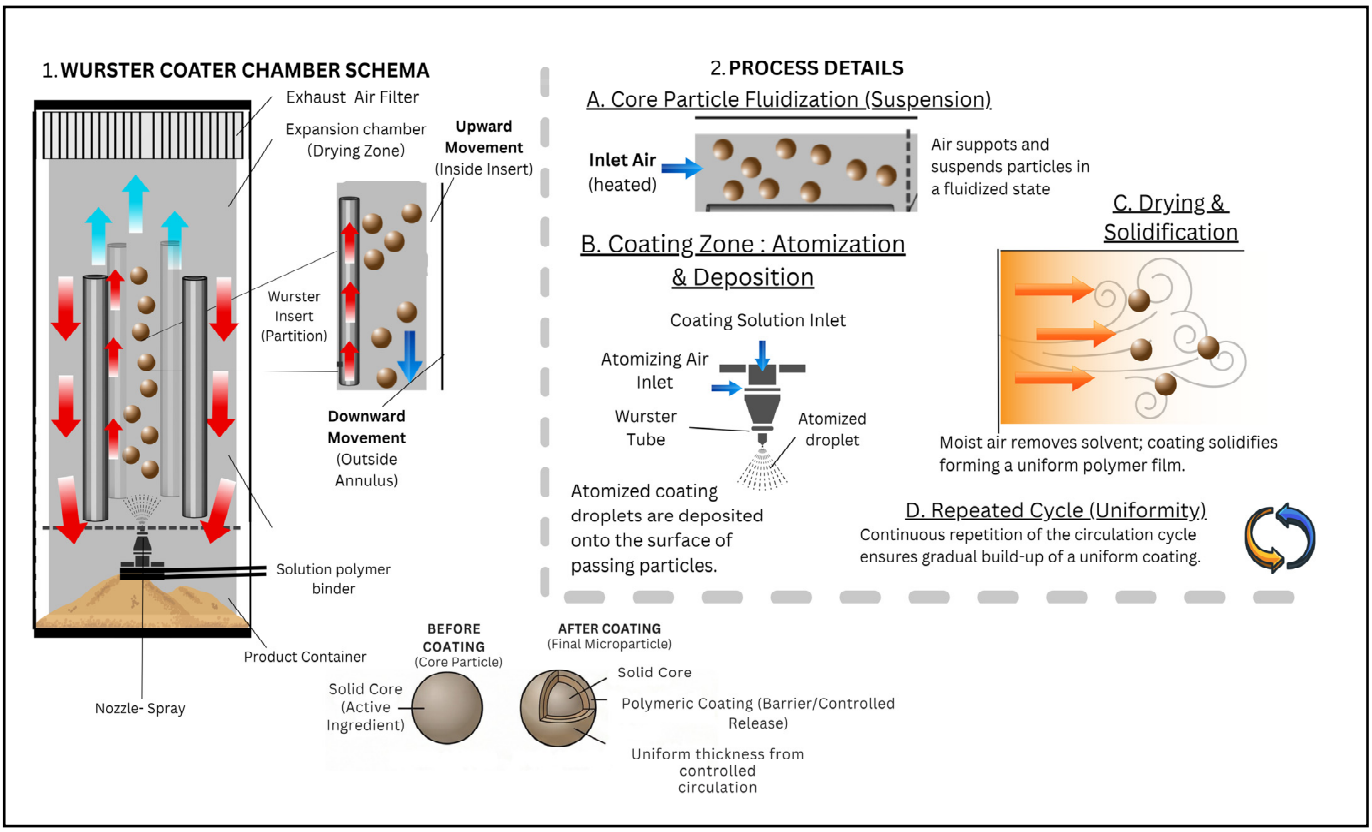


Figure 9. Process steps for microparticle coating in a Wurster fluidized bed.

2.9. Pan Coating

Pan coating is a batch process in which a coating solution is sprayed onto a moving bed while tablets, granules, or pellets are agitated in a rotating drum and then dried with hot air. A film is formed on the substrate surface through repeated wetting, spreading, and drying. This process is typically used for substrates with high mechanical strength, but its applicability decreases as particle size becomes smaller [127]. Pan coating is included here as a method for applying functional films to preformed particulate substrates, rather than for generating microparticles from liquid precursors, Figure 10.

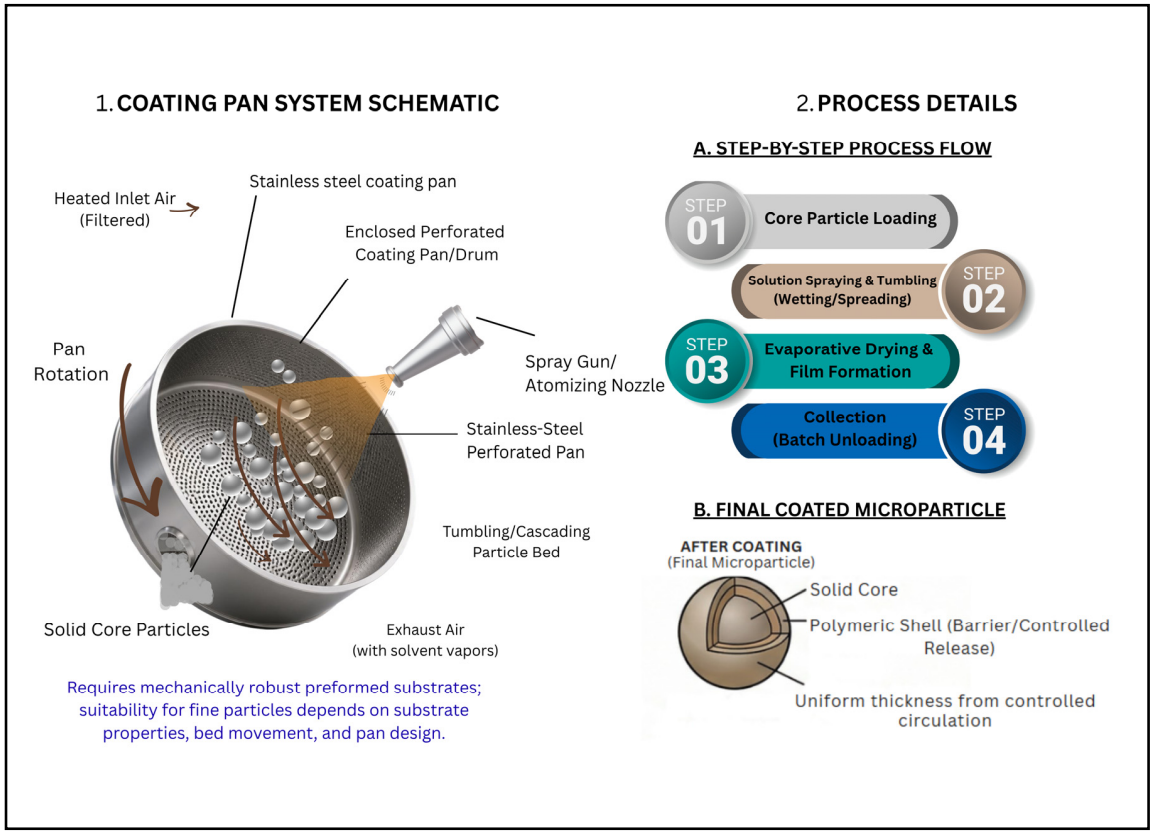


Figure 10. Process steps for film coating of solid substrates in a rotating pan.

2.9.1. Particle-Size and Mechanical Limitations

Conventional pan coating becomes more difficult as substrate size decreases because cohesion and liquid bridging can impair bed movement and promote agglomeration. Its practical applicability depends on substrate properties, coating conditions, and pan design rather than on a universal particle-size threshold. As particle size decreases, cohesive and liquid-capillary forces overcome gravity, thereby reducing stable cascading and promoting particle agglomeration. In addition, since the substrate must withstand repeated impacts and abrasions, mechanically robust granules or pellets are generally preferred over fine API powders [127,128].

2.9.2. Film-Forming Materials and Drying Requirements

Commonly used film-forming materials are cellulose derivatives and methacrylic acid copolymers, the choice of which depends on the desired protective, enteric, or sustained-release function [127]. The quality of the film depends on the properties of the coating solution and the balance between spraying rate, bed temperature, and drying-air capacity. Insufficient drying may result in residual moisture, while overdrying may affect droplet spreading and film continuity [127,129].

2.9.3. Rotation, Atomization, and Coating Defects

Pan speed and atomization conditions affect bed mixing, droplet deposition, and coating defects. Insufficient speed increases the contact area between wet substrates, potentially leading to twinning. Conversely, excessive speed can cause chipping and abrasion. Insufficient atomization pressure produces large, unevenly dispersed droplets, while excessive pressure produces small droplets that dry before reaching the substrate. If the coating adhesion is too strong, anti-tacking agents can be used [129,130].

2.9.4. Conventional and Perforated Pans

Compared with conventional solid pans, perforated pans allow drying air to pass through a moving bed, thereby improving heat and mass transfer and accelerating the aqueous coating process [129,130].

2.9.5. Representative Experimental Comparison

A factorial study compared partially perforated and fully perforated pan coaters using aqueous or organic hypromellose-based coatings for placebo tablets [131]. Pan design and solvent type significantly affected process time and energy consumption, but neither of these factors significantly affected final tablet weight or process yield. Among the combinations tested, the aqueous coating process on a partially perforated pan had the shortest process time and lowest energy consumption [131].

2.10. In Situ Polymerization

In situ polymerization forms core–shell microcapsules by polymerizing monomers or prepolymers mainly within the continuous phase of an emulsion. As the polymer chains grow, their solubility in the continuous phase decreases, leading to phase separation and deposition at the surface of the dispersed core droplets, Figure 11. Afterwards, further polymerization and crosslinking consolidate the deposited material into a shell [132]. In interfacial polymerization, complementary monomers usually exist in separate immiscible phases, as shown in Table 3.

Table 3. Comparison of interfacial and in situ polymerization for microencapsulation.

Parameter	Interfacial Polymerization	In Situ Polymerization
Initial location of reactive species	Complementary monomers usually located in separate immiscible phases	Monomers or prepolymers located mainly in the continuous phase
Shell formation	Polymerization localized at the droplet interface	Polymerization followed by phase separation and deposition at the interface
Shell characteristics	Thinner, potentially more porous	Denser, smoother, more rigid
Typical shell materials	Polyurea, polyamide, or polyurethane	Urea–formaldehyde, melamine–formaldehyde, or related amino resins
Key controlling factors	Monomer diffusion, stoichiometry, and interfacial area	pH, temperature, emulsifier concentration, and prepolymer solubility
Main limitations	Residual reactive monomers and payload compatibility	Residual formaldehyde and exposure to acidic or heated conditions
Representative applications	Core–shell encapsulation in formulation and functional-material systems	Encapsulation of oils, fragrances, phase-change materials, and self-healing agents

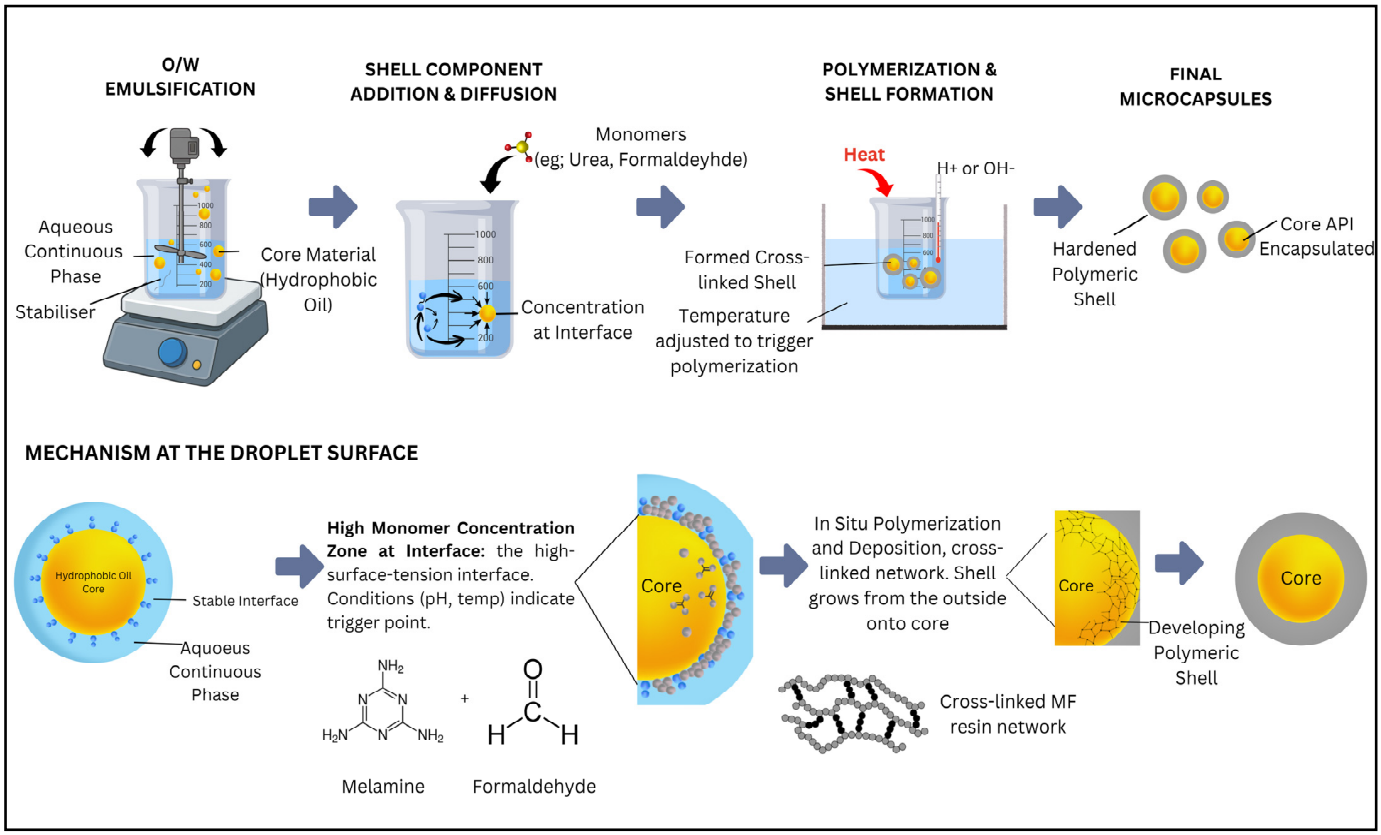


Figure 11. Process steps for microcapsule formation by in situ polymerization.

2.10.1. Polymerization, Phase Separation, and Shell Deposition

Urea–formaldehyde and melamine–formaldehyde shells are typically prepared from water-soluble amino-resin prepolymers. After core emulsion formation, adjustment of pH and temperature promotes polymerization. As chain growth reduces polymer solubility, the polymer separates from the aqueous phase, deposits at the oil–water interface, and undergoes further crosslinking to form the shell [133–136]. The required pH and temperature depend on the resin chemistry and formulation conditions.

2.10.2. Emulsifier Effects and Shell Thickness

Emulsifier concentration affects droplet size, interfacial area, prepolymer deposition, and final shell thickness. Excessive interfacial coverage can hinder prepolymer deposition, while anionic stabilizers—such as poly(ethylene-alt-maleic anhydride) (EMA)—can promote the adsorption of protonated amino-resin species through electrostatic interactions. Therefore, the monomer-to-core ratio should be adjusted according to the emulsifier system and the target droplet size [132,135,137].

2.10.3. Residual Formaldehyde and Payload Compatibility

Residual formaldehyde and exposure to acidic or high-temperature environments may limit the application of conventional amino-resin shells in pharmaceutical and biomedical formulations. Furthermore, reactive resin components may interact with sensitive payloads, thus requiring formulation compatibility and residual-monomer testing. Formaldehyde-free melamine systems are currently being investigated as alternatives, but their suitability depends on the intended application. In situ polymerization using formaldehyde-based resins is included for completeness as a functional-material encapsulation method, but both formaldehyde-based and formaldehyde-free systems require application-specific assessment of residual reactive species and safety [135,138].

2.10.4. Recent Experimental Application of in Situ Polymerization Method

In a 2024 study, researchers used factorial design and response surface analysis to optimize poly(urea–formaldehyde) microcapsules containing 5-ethylidene-2-norbornene for self-healing applications [139]. A formulation prepared at a rotation speed of 700 rpm and pH 3.0, with an EMA amount of 0.425 g, fell within the optimized region. Under these conditions, microcapsules with good morphology, a yield of 52%, and an encapsulation efficiency of 80% were obtained [139].

2.11. Supercritical Fluid Technologies (RESS, SAS, GAS, and PGSS)

Supercritical fluid processing utilizes fluids with temperatures and pressures above their critical points to control solvation, mass transfer, and particle precipitation. Carbon dioxide is often used as a supercritical fluid because its critical conditions (approximately 31.1 °C and 7.38 MPa) are relatively easy to achieve, and its density and solvent properties can be adjusted by pressure and temperature [58]. In microparticle fabrication, supercritical carbon dioxide can be used as a solvent in the RESS process, an antisolvent in the SAS and GAS processes, and a plasticizing and expansion agent in the PGSS process, Figure 12.

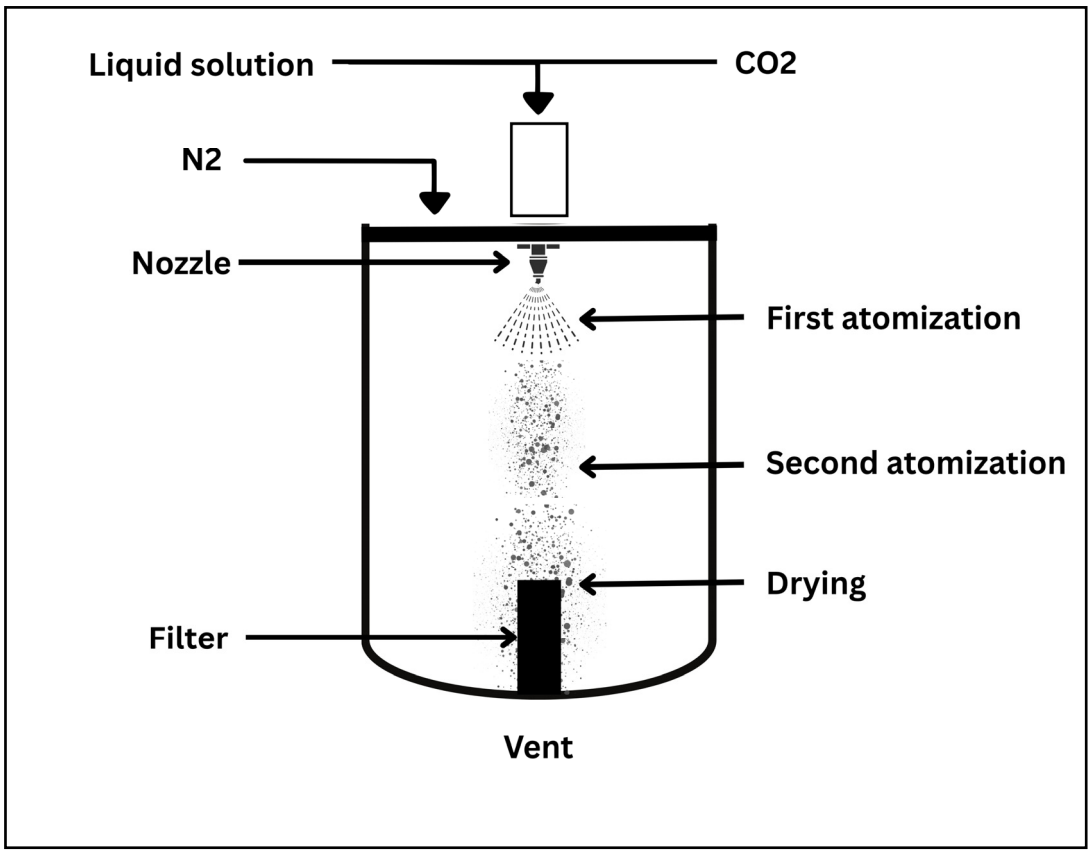


Figure 12. Illustration and practical steps for the supercritical fluid technologies (RESS, SAS, GAS) in microparticle fabrication.

2.11.1. Rapid Expansion of Supercritical Solutions

In RESS, the formulation components are first dissolved in supercritical CO_2, and the resulting solution is then rapidly expanded through a nozzle. Depressurization sharply reduces the density and solvent power of CO_2, producing supersaturation and promoting rapid particle nucleation [59]. The process can minimize organic solvent residues, although its application is limited to compounds with sufficient solubility in supercritical CO_2. Many polar compounds and polymers show limited solubility under these conditions [60].

2.11.2. Supercritical and Gas Antisolvent Processing

In SAS and GAS processing, the solute is dissolved in an organic solvent, and CO_2 is used as an antisolvent. SAS generally introduces the liquid feed into a continuous supercritical CO_2 phase, whereas GAS introduces compressed CO_2 into a batch solution. Mutual diffusion between CO_2 and the organic solvent reduces the solvent strength of the liquid phase and promotes solute precipitation [58,59]. Pressure, temperature, feed composition, mixing conditions, and nozzle design may affect particle size and morphology [61]. Polar modifiers may alter solute interactions and precipitation behavior, although their effects depend on the formulation and operating conditions [58].

2.11.3. Particles from Gas-Saturated Solutions

In PGSS, compressed CO_2 dissolves in a molten or softened carrier and acts as a plasticizer, reducing melt viscosity and often lowering the required processing temperature. Expansion through a nozzle releases CO_2 and cools the mixture, promoting droplet formation and solidification. PGSS does not require the carrier to dissolve in supercritical CO_2, but it requires a melt-processable formulation and careful evaluation of payload stability under the selected pressure and temperature conditions [39,62,140].

2.11.4. Recent Experimental Application of Supercritical Fluid Technologies

A 2024 study used the SAS process to prepare luteolin and naringenin microparticles with polyvinylpyrrolidone or β-cyclodextrin as carriers [141]. The compounds were precipitated separately from dimethyl sulfoxide using supercritical CO_2 as the antisolvent, while pressure, solution concentration, and the active compound-to-carrier molar ratio were varied. Under the optimized conditions, spherical microparticles with mean diameters of 2.7 ± 0.9 µm for luteolin and 5.5 ± 1.9 µm for naringenin were obtained. The β-cyclodextrin formulations also showed faster dissolution than the corresponding unprocessed compounds [141].

2.12. Electrospraying

Electrospraying, also termed electrohydrodynamic atomization, uses an electric field to deform a liquid meniscus and generate charged droplets from a polymer solution or dispersion. Solvent evaporation during droplet flight produces solid micro- or nanoparticles, often under near-ambient thermal conditions, Figure 13 [63,64]. This creates a highly controlled method of transporting a liquid material by first charging it, accelerating it, and then breaking it up into microdroplets [63].

2.12.1. Electrohydrodynamics and Taylor Cone Mechanics

An applied electric potential generates electrical stress at the liquid–air interface. When this stress balances the surface tension, the liquid meniscus forms a Taylor cone, and a thin jet emerges from its apex. Stable cone–jet operation depends on the applied voltage, flow rate, nozzle geometry, surface tension, viscosity, and electrical conductivity. The jet subsequently breaks into charged droplets that shrink as the solvent evaporates [63].

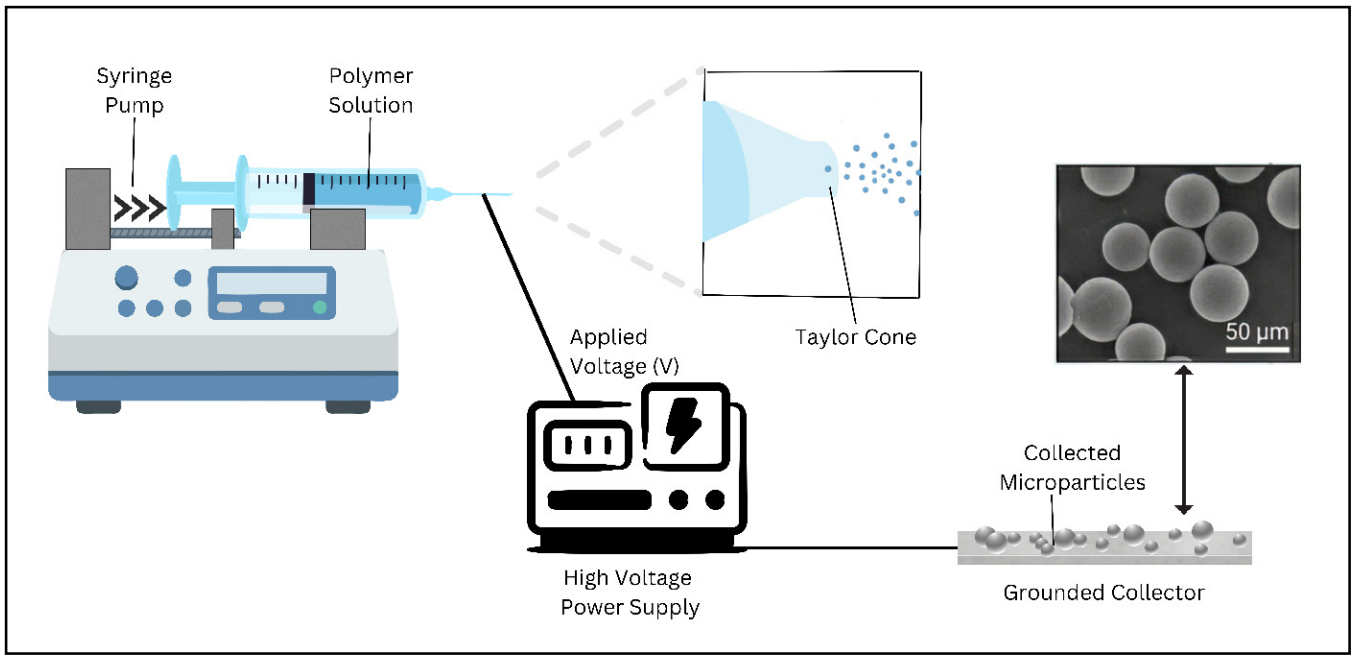


Figure 13. Schematic illustration of the electrospraying process for microparticle fabrication.

2.12.2. Fluid Mechanics: Viscosity Ratios and the Electrospinning Boundary

Solution viscosity and polymer-chain entanglement largely determine whether the charged jet breaks into droplets or elongates into fibers. Below the chain-entanglement threshold, capillary and electrostatic instabilities generally promote droplet formation. Increasing polymer concentration or molecular weight can suppress jet breakup, producing bead-on-string structures and eventually continuous fibers [64,67]. Conductivity and surface tension also influence this transition, so the boundary between electrospraying and electrospinning depends on both formulation and operating conditions. Near-ambient processing may benefit thermally sensitive payloads [67], but mild thermal conditions alone do not establish the suitability of electrospraying for sensitive biological materials. For living-cell applications, cell viability may depend on electrical exposure and other processing conditions, including the spraying and collection configuration, and should therefore be evaluated for the specific system [142].

2.12.3. Multi-Fluid Nozzle Architectures and Production Throughput Limits

Coaxial and multi-fluid electrospraying can produce core–shell or Janus particles by supplying separate formulations through concentric or adjacent channels. In a coaxial system, the fluids form a compound Taylor cone and jet, followed by solvent removal and solidification of the resulting droplets [65,68]. A surrounding shell may reduce surface exposure of hydrophilic payloads and modify burst release, although the outcome depends on fluid compatibility and interfacial stability. Table 4 compares the principal features of single-fluid and coaxial electrospraying.

Industrial scale-up of electrospraying is mainly constrained by the low throughput of a single nozzle. Multiplexed nozzle arrays and needleless configurations can increase production capacity, although interactions between adjacent electric fields may affect jet stability and product uniformity [66]. Common morphological defects and possible corrective actions are summarized in Table 5.

Table 4. Comparison of single-fluid and coaxial electrospraying.

Feature	Single-Fluid Electrospraying	Coaxial Electrospraying
Particle structure	Homogeneous or dispersed matrix	Core–shell reservoir structure
Payload distribution	Payload distributed throughout the matrix	Payload separated between the core and shell
Burst release	Depends on surface loading and matrix properties	May be reduced by an external shell
Equipment	One feed line and one nozzle	Separate feed lines and a concentric nozzle
Scale-up	Multiplexed or needleless systems	Coaxial multi-nozzle arrays with greater operational complexity

Table 5. Common electrospraying defects, probable causes, and possible corrective actions.

Observed Defect	Probable Cause	Possible Corrective Action
Fiber formation	Excessive polymer concentration, viscosity, or chain entanglement	Reduce polymer concentration or molecular weight and adjust solvent composition
Bead-on-string structures	Intermediate chain entanglement or unstable jet stretching	Optimize polymer concentration, applied voltage, and feed flow rate
Broad size distribution or multiple jets	Unstable cone–jet caused by excessive voltage or flow rate	Adjust voltage and flow rate within the stable cone–jet range
Wet deposition or coalescence	Incomplete solvent evaporation before collection	Increase collection distance, reduce flow rate or humidity, and adjust solvent volatility
Dripping or poor atomization	Insufficient electrical stress to overcome surface tension	Increase voltage within the stable range, reduce flow rate, or adjust solution conductivity

2.12.4. Droplet Flight, Coulomb Fission, and Process Stability

The tip-to-collector distance determines the time available for solvent evaporation before the droplets reach the collector. Too short a distance can lead to wet deposition or coalescence, while too long a distance reduces collection efficiency [64,68]. During solvent evaporation, the droplet charge approaches the Rayleigh limit:

$$q_R = 8\pi\sqrt{\epsilon_0 \gamma r^3}$$

where q_R is the maximum stable charge, ϵ_0 is the vacuum permittivity, γ is the liquid surface tension, and r is the droplet radius [143]. If the electrostatic repulsion exceeds the stabilizing surface tension, the droplet will split due to Coulomb fission [69]. Feed rate, applied voltage, solution conductivity, and relative humidity all have a combined effect on cone–jet stability and particle morphology. High flow rates can increase particle size and produce pulsating or multijet modes, while excessively high electric field strength can lead to discharge-related instability [63,64,70].

2.12.5. Recent Experimental Application of Electrospraying Method

A 2024 conference study reported that minocycline-loaded and temozolomide-loaded PLGA microparticles as separate formulations were prepared using vertical electrospraying for potential local treatment of glioblastoma [144]. Lower chamber humidity and shorter spraying durations resulted in microparticles that were more spherical and less aggregated.

The addition of polyethylene glycol increased minocycline loading from 3.23 ± 0.29% to 4.02 ± 0.34%, and the loading efficiency from 49.40 ± 4.49% to 64.30 ± 5.47%. For temozolomide, the use of acetonitrile instead of dichloromethane increased the drug loading to 4.72 ± 0.76% and the loading efficiency to 70.77 ± 11.43%. Minocycline release reached 65.46% during the first hour, indicating a pronounced burst effect [144].

2.13. Droplet Microfluidics

Droplet microfluidics typically utilizes T-junction or flow-focusing geometries to generate emulsion templates within defined microchannels. Compared with bulk emulsification, controlled flow conditions generally result in narrower droplet-size distributions. Droplets can be transformed into microparticles through methods such as solvent removal, polymerization, gelation, or thermal solidification [145–147]. Despite this level of control, limited throughput and scale-up complexity remain constraints in practical applications, Figure 14.

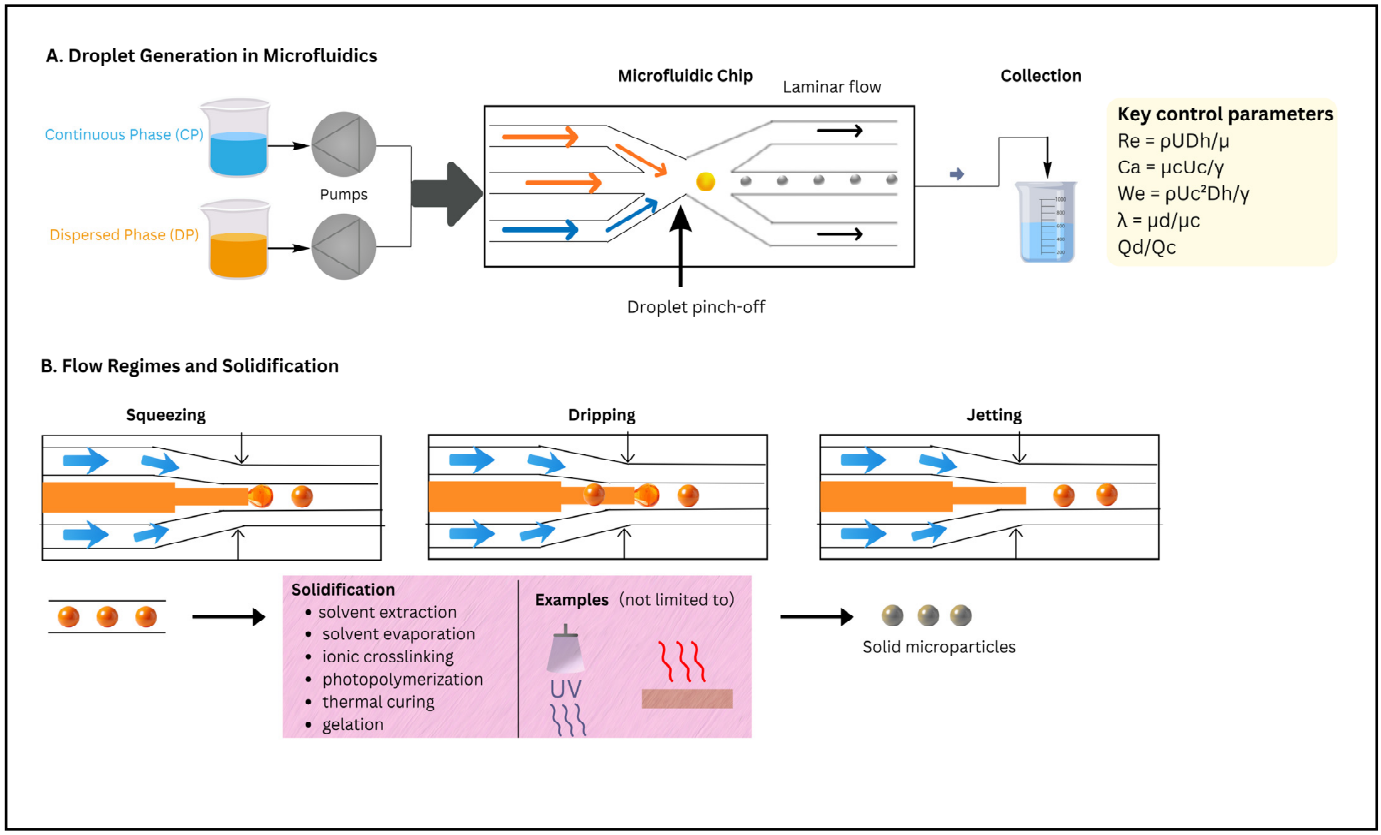


Figure 14. Schematic illustration of droplet-based microfluidic preparation of microparticles.

2.13.1. Fluid Dynamics and Dimensionless Scaling Parameters

Droplet formation within microchannels typically occurs under low-Reynolds-number laminar flow and is influenced by the capillary number, viscosity ratio, channel wettability, geometry, and phase flow-rate ratio [9,18]. These parameters define the relative contributions of viscous, interfacial, and pressure forces to droplet deformation and breakup.

2.13.2. Squeezing, Dripping, and Jetting Regimes

Depending on the capillary number and the phase flow-rate ratio (Qr = Qc/Qd), droplets can form in squeezing, dripping, or jetting regimes. Qc and Qd represent the flow rates of the continuous and dispersed phases, respectively. At low capillary numbers, the dispersed phase may obstruct the channels, and the resulting upstream pressure can

promote pinch-off in the squeezing regime. Jetting can increase throughput, but it typically results in a wider droplet size distribution and a larger number of satellite droplets [9,18].

2.13.3. Viscosity Ratio and Multicompartment Particle Formation

The viscosity ratio ($\lambda = \mu_d/\mu_c$) affects droplet deformation and breakup, where μ_d and μ_c represent the viscosities of the dispersed and continuous phases, respectively. Higher dispersed-phase viscosity delays pinch-off and facilitates the formation of elongated droplets and liquid threads. Coaxial and sequential microfluidic geometries also favor the formation of core–shell, multicompartment, or Janus-structured particles [18,148]. The formation of these structures depends on flow-rate ratios, wettability, interfacial tension, viscosity, and fluid compatibility. While these structures facilitate the isolation of sensitive payloads, mild flow conditions alone cannot guarantee their biological stability.

2.13.4. Throughput Scaling by Numbering-Up

Since the throughput of a single microfluidic junction is typically limited, scale-up often relies on the parallelization, or numbering-up, of multiple droplet generators [9,149,150]. Symmetric channel networks and balanced hydraulic resistance are necessary for uniform fluid distribution across parallel units. While numbering-up can improve production capacity, fabrication tolerances, channel blockage, pressure imbalances, and interactions between parallel units can all affect droplet uniformity at larger scales.

2.13.5. Recent Experimental Application of Droplet Microfluidics Method

In a 2024 study, researchers used a flow-focusing polydimethylsiloxane microfluidic device to prepare monodisperse PLGA-b-PEG/PLGA microspheres from oil-in-water emulsion templates [151]. The dispersed phase contained the polymers in a dimethyl carbonate and dichloromethane solvent mixture, while the continuous phase contained 3% (w/v) poly(vinyl alcohol). Continuous- and dispersed-phase flow rates of 0.020 and 0.005 mL/min, respectively, supported droplet formation in the dripping regime. Variations in polymer composition and processing conditions resulted in microspheres with lace-like, fish-tail-like, and sponge-like surface structures, which were correlated with different drug-release behavior [151].

2.14. Sol–Gel Process

The sol–gel process forms inorganic or organic–inorganic hybrid particles through the hydrolysis and condensation of molecular precursors. In silica systems, tetraethyl orthosilicate or tetramethyl orthosilicate hydrolyzes to generate silanol groups, which subsequently condense to form a siloxane network [152,153]. Payloads can be introduced during network formation or loaded into the pores after drying [154]. Precursor composition, pH, water-to-alkoxide ratio, catalyst, aging, and drying conditions all affect the resulting particle structure [154]. While relatively mild temperatures can be used, processing pH, alcohol by-products, and unreacted precursors can affect sensitive payloads, Figure 15 [155].

The properties of sol–gel particles depend on precursor chemistry, catalyst conditions, aging, and drying. Ambient evaporation produces xerogels, which shrink or crack due to capillary pressure. Supercritical drying reduces the liquid–vapor interfacial stress, preserving a more porous aerogel structure [32,33,156]. Alcohol by-products and residual precursors must be removed before biomedical applications [157]. Organic modification can be used to adjust matrix flexibility, hydrophobicity, and interactions with the payload. Table 6 summarizes the main differences between xerogels and aerogels.

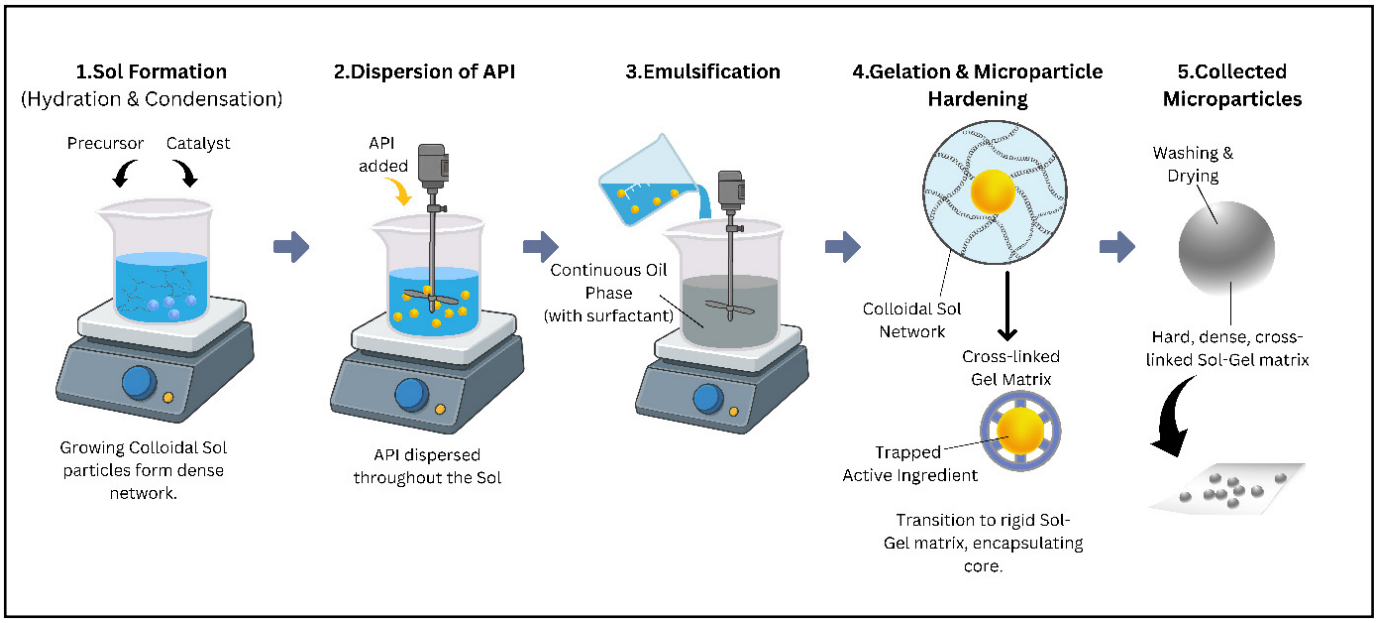


Figure 15. Schematic illustration of microparticle formation through hydrolysis, condensation, gelation, and drying in the sol–gel process.

Table 6. Comparison of xerogels and aerogels produced from sol–gel systems.

Property	Xerogel	Aerogel
Drying approach	Evaporation under ambient or reduced pressure	Supercritical or other low-capillary-stress drying
Capillary stress	Present during solvent evaporation	Substantially reduced
Structural change	Greater shrinkage and possible cracking	Better preservation of the gel pore network
Porosity and surface area	Generally lower and formulation-dependent	Generally higher and formulation-dependent
Processing requirements	Relatively simple drying equipment	Specialized pressure equipment may be required
Potential implication	Denser matrices may restrict molecular diffusion	Higher pore volume may increase loading and mass transfer

Catalyst conditions alter the relative rates of hydrolysis and condensation, thereby affecting network structure, pore characteristics, and drying behavior, as summarized in Table 7 [158–162].

Organically modified silicates contain non-hydrolyzable organic groups within the silica network, which can modulate its flexibility, hydrophobicity, pore environment, and interactions with the payload [163,164]. Alkyl groups can reduce water uptake, while bulkier organic groups can affect network packing and porosity. Since these effects depend on precursor composition and condensation conditions, organic modification does not necessarily prevent cracking or burst release.

Surface functionalization with redox-, pH-, or enzyme-responsive groups can enable triggered release from silica-based carriers, the performance of which depends on functional-group density, accessibility, and stability under physiological conditions [165–169].

Table 7. Influence of catalyst conditions on silica network formation.

Catalyst Condition	Predominant Reaction Tendency	Typical Network Characteristics	Drying Behavior	Main Limitation
Acidic, such as HCl	Hydrolysis is generally favored relative to condensation	Polymeric, weakly branched networks with relatively small pores	Greater shrinkage may occur during drying	Brittle structures may form after extensive densification
Basic, such as NH_3	Deprotonation of silanols promotes condensation	Branched or particulate networks with relatively larger pores	Shrinkage may be lower than in strongly acid-catalyzed systems	Rapid aggregation may increase structural heterogeneity
Nucleophilic, such as F^-	Nucleophilic catalysis accelerates hydrolysis and condensation	Rapid network formation with formulation-dependent porosity	Shorter gelation time	The processing window and residual-ion content require control

Recent Experimental Application of Sol–Gel Method

A 2023 study demonstrated that mesoporous silica microspheres can be prepared in porous polymeric hard templates via sol–gel reactions [170]. Researchers developed 15 formulations by varying the water-to-precursor ratio and ammonia concentration. The resulting particle sizes ranged from less than 1 μm to several micrometers, with relatively narrow size distributions. Therefore, this study encompasses submicron and micron-sized particles and is included here due to its relevance to the preparation of micron-sized silica supports. Response surface methodology related these processing variables to particle size, pore size, pore volume, and specific surface area. Subsequently, researchers surface-functionalized larger-scale batches of particles and evaluated them as stationary phases for the chromatographic separation of proteins and amino acids [170].

2.15. Hot-Melt Encapsulation

Hot-melt encapsulation prepares microparticles by dispersing or dissolving the payload in a molten polymer, lipid, or wax carrier. The molten formulation is divided into droplets in an immiscible continuous phase and then cooled to solidify the matrix, Figure 16 [171]. Depending on payload–carrier compatibility and the cooling conditions, the payload in the final product may be in the form of a molecular dispersion or discrete suspended domains [42]. This process reduces reliance on volatile organic solvents and their associated solvent-removal steps, although some variants require the use of an external liquid phase. Thermal exposure and melt viscosity remain important limiting factors, especially for heat-sensitive payloads [171].

2.15.1. Carrier Selection and Release Behavior

Release behavior should be assessed for the specific carrier and payload loading. For example, polyanhydride microspheres prepared by hot-melt microencapsulation showed heterogeneous degradation at low loadings of a hydrophilic drug [171]. General considerations concerning payload–carrier compatibility and solid-state behavior are discussed in Section 1.1.

2.15.2. Melt Viscosity and Particle Formation

For melt dispersion, the effects of melt viscosity, interfacial stabilization, mixing, and cooling should be evaluated for each formulation.

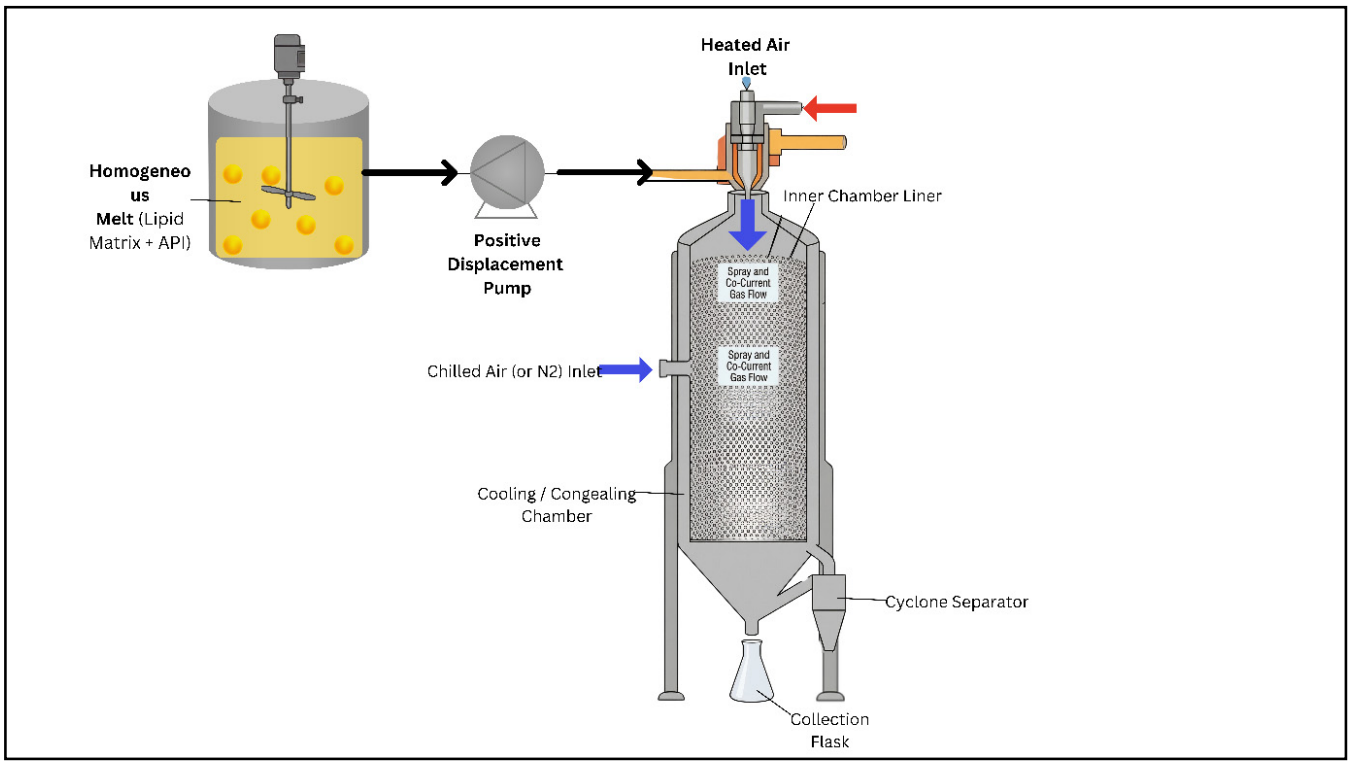


Figure 16. Illustration and practical steps for the hot-melt encapsulation (HME) method in microparticle fabrication.

2.15.3. Recent Experimental Application of Hot-Melt Encapsulation Method

In a 2025 study, researchers used a melt dispersion method to prepare wax microspheres containing L-carvone or hexyl salicylate, using carnauba wax, candelilla wax, and beeswax as carriers [172]. The mean diameter of the unloaded wax microspheres was approximately 22 µm. For L-carvone-loaded carnauba wax microspheres, the mean diameter decreased from 22.3 ± 0.3 µm to 15.3 ± 0.2 µm when the oil-to-wax ratio increased from 1:10 to 1:1. The type of wax and the oil loading also affected the surface morphology and mechanical properties of the microspheres, indicating that the choice of carrier material affects particle formation and subsequent handling [172].

2.16. Salting-Out

Salting-out is a modified emulsification–solvent-diffusion method that utilizes electrolytes in the aqueous phase to temporarily reduce the miscibility between water and water-miscible organic solvents, Figure 17. The resulting miscibility gap allows the polymer solution containing the payload to form stable droplets. Subsequent dilution restores the miscibility between the solvent and water, promotes solvent diffusion, and precipitates the polymer matrix [30,53,54]. This method is most commonly used to prepare nanoparticles and submicron particles, but micrometer-scale particles can also be prepared by adjusting droplet formation and solvent-transfer conditions [173].

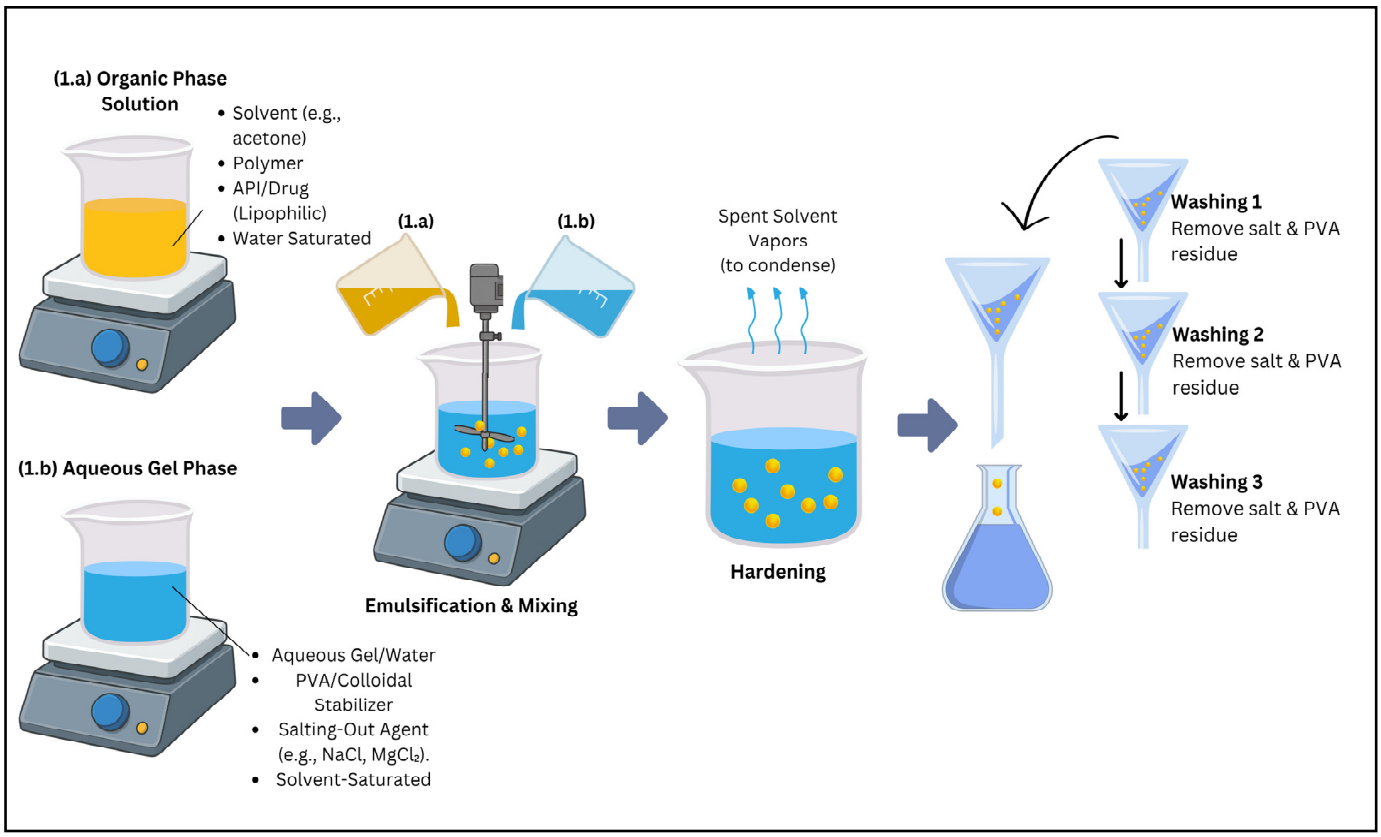


Figure 17. Illustration and practical steps for the salting-out method in microparticle fabrication.

2.16.1. Reversible Solvent Demixing and Polymer Precipitation

A polymer solution containing the payload is emulsified in an aqueous phase containing a salting-out agent and a colloidal stabilizer. The electrolyte significantly reduces solvent–water miscibility, thereby maintaining the droplets during emulsification. Water is then added to reduce the electrolyte concentration, restore solvent–water miscibility, and allow the organic solvent to diffuse into the continuous phase, precipitating the polymer matrix. Polymer concentration, salt concentration, phase volume ratio, stirring, and dilution rate all affect speed, particle size, and solidification [30,53,54].

2.16.2. Processing Advantages and Limitations

Salting-out can typically be performed at or near room temperature using nonhalogenated solvents such as acetone, thereby reducing thermal exposure and reliance on chlorinated solvents. However, hybrid formulations may require a co-solvent that is immiscible with water. Scale-up is constrained by the large dilution volume, saline wastewater, and the need for repeated washing or cross-flow filtration to remove residual electrolytes and stabilizers. Furthermore, hydrophilic payloads may partition into the external aqueous phase unless an appropriate double-emulsion or retention strategy is employed [55,56].

2.16.3. Electrolyte Selection and Hofmeister Effects

The Hofmeister series provides qualitative guidance on ion-specific effects on solvent–water demixing. Strongly hydrated ions (often described as kosmotropic) can enhance salting-out and reduce the dilution required for polymer precipitation. However, the magnitude of this effect depends on the solvent, polymer, payload, and salt concentration. Electrolyte selection should therefore balance phase separation against payload stability and downstream removal requirements [54,57].

2.16.4. Representative Experimental Application of Salting-Out Method

In a representative study, ovalbumin-loaded Eudragit S100 microparticles were prepared by combining salting-out with double-emulsion solvent evaporation. To control solvent diffusion, an acetone/isopropanol/chloroform organic phase (3:0.5:1.5) and an aqueous magnesium chloride solution were used. The resulting microparticles were smooth and spherical with a mean diameter of 26.3 μm, a polydispersity index of 0.36, and an encapsulation efficiency of 56.5 ± 0.5% [174]. These microparticles released ovalbumin rapidly under alkaline conditions [174].

3. Engineering Considerations for Long-Acting Injectable Microparticles

Long-acting injectable microparticles are designed to extend drug release over weeks or months after a single administration. Their performance depends on particle structure, payload distribution, polymer properties, and the relative contributions of diffusion and matrix degradation [71]. A narrow particle-size distribution reduces size-related variability but does not ensure identical degradation rates, which also depend on polymer composition, porosity, hydration, drug distribution, the local environment, and, in degradable polyesters, the extent of autocatalysis [175,176]. Method selection should also consider initial burst release, incomplete release, payload stability, and manufacturing reproducibility [176,177].

4. Key Engineering Strategies for Long-Term Release

Long-acting performance is governed by the combined effects of factors such as matrix architecture, water uptake, drug diffusion, and polymer degradation. These factors interact throughout the release period and may produce an initial burst, a lag phase, incomplete release, or a sustained release profile. The following sections discuss three engineering considerations that apply across different microparticle fabrication methods [71,72].

4.1. Controlling Matrix Tortuosity

Matrix tortuosity describes the length and complexity of diffusion pathways relative to a direct path through the carrier material. Greater tortuosity and lower pore connectivity generally reduce the effective diffusion rate, although the observed release profile also depends on porosity, water uptake, drug solubility, and polymer relaxation or erosion [72]. Processing conditions that produce dense and continuous matrices may prolong release, while excessive densification can contribute to a long lag phase or incomplete drug release. Tortuosity should therefore be considered together with pore structure and degradation behavior.

4.2. Synchronizing Degradation and Diffusion

Drug release from degradable microparticles often reflects overlapping contributions from water uptake, drug diffusion, pore formation, and polymer degradation. The relative importance of these processes may change during the dosing period and depends on polymer composition, molecular weight, particle size, payload distribution, and interactions between the drug and polymer [71,72]. Slow degradation may produce a lag phase or incomplete release, whereas rapid water uptake and pore formation can increase early drug release. Formulation design should balance these processes across the intended release period.

4.3. Minimizing the "Initial Burst"

Initial burst release refers to the rapid liberation of a substantial fraction of the payload soon after administration or contact with the release medium. It is commonly associated with drug located near the particle surface, interconnected pores, rapid water uptake, or

incomplete barrier formation [72,178]. Changes in payload distribution, solidification conditions, particle size, and surface or shell structure may reduce the burst effect. Additional coating can provide a diffusion barrier, although it may also increase processing complexity or delay subsequent drug release.

4.4. Conditional Comparison of Fabrication Routes

Table 8 compares the physicochemical suitability of the reviewed fabrication methods, while Table 9 summarizes their scalability and principal manufacturing constraints. The approaches include droplet-generation platforms, solidification mechanisms, and coating operations that may be combined within a complete manufacturing route.

Table 8. Comparison of particle architectures, carrier materials, and formulation requirements across microparticle fabrication methods.

Method	Typical Architecture	Representative Carrier Materials	Payload Compatibility and Critical Processing Conditions
Solvent evaporation	Matrix microspheres; porous or internally compartmentalized particles	PLGA, PLA	Lipophilic payloads can be incorporated through O/W emulsions; hydrophilic payloads may require W/O/W systems. Phase partitioning, emulsification stress, polymer concentration, and solvent removal govern retention and structure.
Solvent extraction	Solidified polymeric microspheres with formulation-dependent porosity	Preformed polymers, including PLGA	Payload retention depends on partitioning into the extraction medium. Solvent–water affinity, external-phase volume, temperature, and extraction rate require joint control.
Coacervation	Core–shell microcapsules or coacervate particles	Gelatin, polysaccharides, and protein–polysaccharide combinations	Compatibility depends on payload–polymer interactions and the hardening step. Important variables include pH, polymer ratio, charge density, electrolyte composition, and mixing.
Spray drying	Dense, porous, or hollow matrix particles	PLGA, carbohydrates, proteins, and other film-forming carriers	Dissolved or dispersed payloads can be processed if the feed remains stable. Atomization, feed composition, product temperature, residence time, and dehydration stress affect product quality.
Spray congealing	Solid lipid or wax matrix particles; multiphase particles with suitable feeds	Waxes, acylglycerides, and lipid–hydrophilic excipient blends	Payloads must tolerate the melting step. Melt viscosity, payload solubility or dispersion, atomization, cooling rate, and lipid crystallization are important.
Ionic gelation	Hydrogel beads or microspheres; coated gel particles	Alginate, chitosan, and other ionically crosslinkable polymers	Aqueous processing may suit sensitive payloads, but small hydrophilic compounds can diffuse out. Polymer concentration, pH, crosslinker concentration, and gelation time control the network.
Interfacial polymerization	Core–shell microcapsules	Polyurea, polyamide, and related interfacially formed polymers	Payloads must be compatible with reactive monomers. Emulsification, monomer stoichiometry, interfacial reaction, and residual-monomer removal control capsule quality.
Air-suspension coating	Films deposited on preformed solid cores	Cellulose derivatives and other film-forming polymers	Suitable for cores that can be fluidized without excessive attrition. Core size and density, airflow, partition gap, spray rate, and drying capacity determine coating performance.

Table 8. *Cont.*

Method	Typical Architecture	Representative Carrier Materials	Payload Compatibility and Critical Processing Conditions
Pan coating	Films deposited on preformed granules or pellets	Cellulose derivatives and methacrylic acid copolymers	Requires mechanically robust substrates and stable bed movement. Pan design, rotation, atomization, wetting, and drying determine uniformity and agglomeration.
In situ polymerization	Core–shell microcapsules	Urea–formaldehyde, melamine–formaldehyde, and related resins	Conventional systems require payload tolerance to reactive components and acidic or heated conditions. pH, temperature, emulsifier, and shell-former-to-core ratio affect shell formation.
Supercritical-fluid processing	Precipitated particles or carrier matrices, depending on the process	PVP, β-cyclodextrin, and suitable polymers or lipids	RESS requires solubility in supercritical CO_2; SAS/GAS requires suitable solvent–antisolvent phase behavior; PGSS requires a melt-processable or softened carrier. Pressure, temperature, and expansion or mixing conditions are critical.
Electrospraying	Matrix particles; core–shell or Janus structures with suitable nozzle configurations	Solution-processable polymers, including PLGA	Payload compatibility depends on the solvent, electrical exposure, drying, and collection conditions. Conductivity, viscosity, voltage, feed rate, humidity, and collection distance govern stable particle formation.
Droplet microfluidics	Matrix, core–shell, or multicompartment particles	PLGA-based polymers, hydrogels, and other carriers compatible with downstream solidification	Payload compatibility depends on both the emulsion and the solidification route. Channel geometry, wettability, phase flow-rate ratio, viscosity, and interfacial tension control droplet formation.
Sol–gel processing	Porous inorganic or organic–inorganic hybrid particles	Silica and organically modified silicates	Sensitive payloads require compatibility with precursors, catalysts, pH, and solvent by-products. Hydrolysis, condensation, aging, and drying control network and pore structure.
Hot-melt encapsulation	Solidified matrix microspheres	Melt-processable polymers, lipids, and waxes	Payloads must tolerate the processing temperature and time. Melt dispersion, viscosity, interfacial stabilization, and cooling determine size and payload distribution.
Salting-out	Precipitated polymeric matrix particles	Solvent-soluble polymers, including Eudragit S100	Payloads must tolerate the electrolyte and solvent system. Salt concentration, phase ratio, dilution rate, payload partitioning, and washing requirements are important.

For thermally sensitive proteins, low-temperature emulsion–solvent evaporation may be preferable when thermal exposure cannot be controlled, provided that the protein tolerates the solvent interface and subsequent processing. Van de Weert et al. observed incomplete aqueous-phase recovery and interfacial aggregation of lysozyme after emulsification with dichloromethane [75]. Conversely, Bürki et al. retained full β-galactosidase activity after optimized spray drying with trehalose [179]. Spray drying therefore remains an option when an aqueous feed and controlled drying can provide a powder with retained activity. These studies used different proteins and carriers and do not establish a head-to-head ranking; the protein–sugar result should not be extrapolated directly to PLGA depot microspheres. Selection should consider retained activity, aggregation, residual solvent, product recovery, and release requirements.

Table 9. Practical advantages, implementation context, and scale-up constraints of microparticle fabrication methods.

Method	Main Practical Advantage	Implementation Context and Scale-Up Position	Principal Limitations and Downstream Requirements
Solvent evaporation	Flexible formulation of biodegradable polymeric microspheres	Established route in polymeric microparticle preparation; scale-up requires control of emulsification and solvent removal	Mixing and tank geometry; residual solvents; payload leakage; particle recovery and washing
Solvent extraction	Particle hardening can be adjusted through solvent transfer into an external phase	Applicable to polymeric microsphere processing; extraction and purification capacity influence production scale	Large external-phase volumes; solvent recovery; payload loss during extraction; residual-solvent removal
Coacervation	Shell formation around dispersed cores using a range of carrier combinations	Used in encapsulation applications across food and formulation research; scale-up is sensitive to phase-separation and hardening conditions	Batch variability; pH and electrolyte control; agglomeration; crosslinker residues where applicable
Spray drying	Continuous conversion of liquid feeds into collectable powders	Established industrial operation; applicability to a specific pharmaceutical product remains formulation-dependent	Thermal and dehydration stress; wall deposition; powder recovery; solvent handling and energy demand
Spray congealing	Particle formation without a solvent-removal step	Uses melt atomization and cooling; manufacturing performance depends on carrier behavior and cooling capacity	Thermal exposure; melt viscosity; atomization; polymorphic changes during cooling and storage
Ionic gelation	Aqueous formation of crosslinked carrier networks	Production capacity depends on the droplet-generation route; limitations of dripping do not apply to every configuration	Gelation uniformity; payload leakage; mechanical strength; washing, separation, and drying
Interfacial polymerization	Direct formation of a shell at the droplet interface	Industrial relevance includes non-pharmaceutical encapsulation; this does not establish suitability for drug delivery	Reactive-monomer compatibility; reaction heat; residual monomers; purification and shell reproducibility
Air-suspension coating	Functional films can be deposited through repeated coating and drying cycles	Established fluidized-bed coating operation; coating fine microparticles requires control of cohesion and circulation	Agglomeration and attrition; airflow distribution; moisture balance; coating uniformity and spray losses
Pan coating	Functional coating of mechanically robust preformed substrates	Established for tablets and suitable granules or pellets; applicability is more restricted for fine microparticles	Unstable bed movement at small sizes; agglomeration; drying efficiency; coating variability and abrasion
In situ polymerization	Shell formation by polymerization and deposition around dispersed cores	Established relevance in non-pharmaceutical encapsulation, including functional materials; biomedical use requires separate assessment	Reaction time; acidic or heated conditions; residual formaldehyde or other reactive species
Supercritical-fluid processing	Tunable phase behavior provides alternative precipitation or solidification routes	Specialized high-pressure processing; implementation differs substantially among RESS, SAS/GAS, and PGSS	Equipment cost; phase compatibility; mixing or expansion control; yield, recovery, and process-specific solvent removal
Electrospraying	Fine control of particle formation and access to multiple architectures	The reviewed examples mainly demonstrate research-scale processing; increased capacity requires suitable multiplexed or alternative emitter designs	Low single-emitter throughput; electrical interactions; nozzle stability; drying and collection efficiency

Table 9. *Cont.*

Method	Main Practical Advantage	Implementation Context and Scale-Up Position	Principal Limitations and Downstream Requirements
Droplet microfluidics	Controlled droplet templates support narrow size distributions and compartmentalized structures	Parallelization provides a route to increased production; research demonstrations should be distinguished from validated manufacturing	Flow maldistribution; channel blockage; fabrication tolerances; integration with solidification, recovery, and purification
Sol–gel processing	Porous inorganic and hybrid networks can be tailored through reaction and drying conditions	Established materials-processing chemistry; the reviewed particle examples include specialized applications such as chromatography	Aging time; drying shrinkage or cracking; precursor and by-product removal; particle recovery
Hot-melt encapsulation	Avoids volatile organic solvents in the carrier phase	Melt-dispersion studies demonstrate feasibility; the reviewed examples do not establish a uniform level of industrial maturity	Thermal stability; melt viscosity; mixing at scale; cooling and crystallization; removal of the external phase where used
Salting-out	Polymer precipitation can be triggered by controlled dilution, often near ambient temperature	A formulation-specific emulsification–diffusion route; the reviewed examples do not establish broad industrial deployment	Large dilution volumes; salt-containing wastewater; removal of electrolytes and stabilizers; payload loss and product recovery

Droplet microfluidics and electrospraying both offer particle control, but their scale-up constraints differ. Microfluidics may be preferable for emulsion-templated structures when channel wetting, phase compatibility, and subsequent solidification remain controlled across parallel generators. Nisisako and Torii demonstrated 256 droplet-formation units producing acrylate droplets at 320 mL/h with a diameter coefficient of variation of 1.3% [150]. Electrospraying is an alternative when the formulation supports stable cone–jets and suitable drying and collection, but multiplexing requires uniform feed distribution and control of electric-field interactions. Deng et al. enabled all 91 nozzles to operate using a modified feed configuration, with greater variation in mean droplet size between jets than in a 37-nozzle configuration [66]. These different materials and configurations do not support a throughput ranking. Selection should instead assess whether the target size and architecture remain reproducible at the required rate of recovered, specification-compliant particles.

The entries summarize the formulation and process considerations discussed in Sections 2.1–2.16. Particle-size values are reported in their study-specific context in the corresponding sections. Payload compatibility depends on the complete formulation and processing route; no universal suitability ranking is intended.

Industrial context refers to the application sector and manufacturing evidence described in the cited sources. Established use in one sector does not establish suitability for pharmaceutical manufacturing. Scale-up constraints depend on equipment configuration, formulation, product specifications, and downstream processing requirements. The qualitative comparisons reflect the process characteristics and manufacturing constraints discussed in the cited literature; patent publication or grant status was not used as a criterion for scalability or industrial maturity. Reported feed throughput should be distinguished from the rate of recovered particles meeting the target specifications, because solidification, collection, and purification may become limiting steps.

5. Future Prospects and "Smart" Microparticles

The present development of microparticle preparation involves creating environmentally friendly methods that produce more sustainable processes with improved control over particle attributes. Scientists actively work to replace hazardous chlorinated solvents—including dichloromethane, which traditional solvent evaporation uses—through alternative processes that may reduce reliance on chlorinated solvents, including supercritical carbon dioxide extraction and solvent-free hot-melt techniques [180]. Solvent selection should consider safety, environmental impact, and process requirements [181]. FDA guidance on process analytical technology and continuous manufacturing supports process understanding and control, while implementation remains product- and process-dependent [182,183]. Translation of microfluidics and electrospraying to pharmaceutical manufacturing requires reproducible scale-up and downstream processing. Coaxial electrospraying can generate core–shell structures [65], while microfluidic designs can produce Janus droplets [150].

The evolution of microencapsulation technology has moved away from the basic concept of matrix entrapment toward the development of complex and multifunctional constructs that can respond dynamically to the surrounding physiological environment. This evolution is based on the understanding that the choice of preparation technology is no longer seen as a simple technological choice but as a strategic compromise between the unique physicochemical profile of the drug and the unique biological requirements of the target site. Ionic gelation forms polymer networks in aqueous media, while Wurster coating deposits functional films on preformed particles. Hybrid approaches combine complementary fabrication methods to address specific processing limitations. For instance, monodisperse calcium alginate microcapsules with hollow or core–shell structures can be prepared using a microfluidic double-emulsion templating method combined with internal ionic gelation; this demonstrates how particle architecture can be controlled by integrating droplet formation with network solidification processes [184]. After spray drying, fluidized-bed coating can be applied to add a protective outer layer. For example, coating spray-dried β-carotene powders with hydroxypropyl cellulose has demonstrated the potential of this sequential approach to protect sensitive ingredients, with performance depending on the coating conditions [185]. Compared with bulk emulsification, droplet microfluidics can provide narrower droplet-size distributions and greater control over particle architecture. These advantages do not, however, guarantee high encapsulation efficiency or a predictable release profile. Both outcomes depend on payload partitioning, carrier composition, interfacial stability, and the subsequent solidification process. Intelligent microparticles are increasingly being engineered to respond to local biological stimuli—such as unique pH gradients, temperature cues, and enzyme signatures—of diseased tissues [186,187]. Future trends in the development of microencapsulation technology indicate the development of more personalized medicine with on-demand manufacturing using 3D microparticle printing technology and lab-on-a-chip fabrication technology [188–190]. However, the development of next-generation microparticles depends on the capacity to precisely control the fabrication environment in response to the unique molecular requirements of the therapeutic payload, whether the therapeutic payload is a fragile mRNA molecule or a robust lipophilic molecule. Success in this area depends on the synergistic integration of structural integrity, process control, and biocompatibility to ensure that the microparticles are not only safe but also effective in delivering the desired therapeutic outcome. Table 10 lists representative patent examples associated with the fabrication methods reviewed.

Table 10. Representative patent publications associated with microparticle fabrication methods.

Fabrication Method	Representative Patent Publication Number
Solvent Evaporation	US5650173A
Solvent Extraction	US6379703B1
Coacervation	US20060105038A1
Spray Drying	US6451349B1
Spray Congealing	US6264987B1
Ionic Gelation	US10085948B2
Interfacial Polymerization	EP0399911B1
Air Suspension	US2648609A
Pan Coating	US5958458A
In Situ Polymerization	US4626471A
Supercritical Fluid	US6063910A
Electrospraying	US12433849B2
Microfluidics	US20110268803A1
Sol–Gel Process	WO2022040751A1
Hot-Melt Encapsulation	US20160015703A1
Salting-Out	US8852644B2

The listed patent publications are illustrative examples, not a systematic patent landscape or an assessment of current legal status. Their inclusion does not establish commercial implementation, industrial maturity, or scalability.

6. Limitations of the Review and Available Evidence

This review has several limitations. The included studies differ substantially in payload type, carrier material, equipment configuration, processing conditions, and outcome definitions. These differences limit direct comparisons among fabrication methods, particularly because head-to-head studies are uncommon and industrial-scale data remain limited for several emerging technologies. Reporting practices also vary across studies, especially for particle-size distributions, encapsulation efficiency, process yield, residual solvents, and release testing. The comparative assessments presented in Tables 8 and 9 are therefore qualitative and should be interpreted in relation to the formulation and production context. This structured narrative review did not include a meta-analysis; quantitative synthesis would be appropriate only where studies are sufficiently comparable. Study selection and qualitative interpretation may consequently remain subject to some author judgment.

7. Conclusions

Among the sixteen methods considered in this review, no single microparticle fabrication technique performs optimally across all formulation and manufacturing criteria. Method selection should consider payload stability, target particle structure, release requirements, solvent and thermal exposure, and the intended production scale. Spray drying, Wurster coating, and pan coating generally offer greater industrial maturity, while microfluidics and electrospraying allow finer control of particle size and architecture but continue to face throughput and scale-up challenges. Mild aqueous methods, including ionic gelation, may be suitable for sensitive payloads, whereas melt- and solvent-based processes require careful assessment of thermal stability, solvent compatibility, and residual solvent levels. Hybrid approaches may combine complementary process advantages, although they can

increase manufacturing complexity and validation requirements. Future studies would benefit from standardized reporting, direct comparisons among fabrication methods, and evaluation under industrially relevant conditions.

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References

1. Da Silva, R.Y.P.; De Menezes, D.L.B.; Oliveira, V.d.S.; Converti, A.; De Lima, Á.A.N. Microparticles in the development and improvement of pharmaceutical formulations: An analysis of in vitro and in vivo studies. *Int. J. Mol. Sci.* **2023**, *24*, 5441. [CrossRef] [PubMed]
2. Bertoni, S.; Albertini, B.; Passerini, N. Spray congealing: An emerging technology to prepare solid dispersions with enhanced oral bioavailability of poorly water soluble drugs. *Molecules* **2019**, *24*, 3471. [CrossRef] [PubMed]
3. Lengyel, M.; Kállai-Szabó, N.; Antal, V.; Laki, A.J.; Antal, I. Microparticles, Microspheres, and Microcapsules for Advanced Drug Delivery. *Sci. Pharm.* **2019**, *87*, 20. [CrossRef]
4. Siepmann, J.; Faisant, N.; Akiki, J.; Richard, J.; Benoit, J.P. Effect of the size of biodegradable microparticles on drug release: Experiment and theory. *J. Control. Release* **2004**, *96*, 123–134. [CrossRef] [PubMed]
5. Borrelli, M.A.; Warunek, J.J.P.; Ravikumar, T.; Balmert, S.C.; Little, S.R. End group chemistry modulates physical properties and biomolecule release from biodegradable polyesters. *J. Mater. Chem. B* **2025**, *13*, 10621–10634. [CrossRef] [PubMed]
6. Wolska, E.; Sadowska, K. Drug Release from Lipid Microparticles—Insights into Drug Incorporation and the Influence of Physiological Factors. *Pharmaceutics* **2024**, *16*, 545. [CrossRef] [PubMed]
7. Poozesh, S.; Connaughton, P.; Sides, S.; Lechuga-Ballesteros, D.; Patel, S.M.; Manikwar, P. Spray drying process challenges and considerations for inhaled biologics. *J. Pharm. Sci.* **2025**, *114*, 766–781. [CrossRef] [PubMed]
8. Rostinawati, T.; Muhaimin, M.; Chaerunisaa, A.Y.; Hazrina, A. Development of casticin-loaded ethyl cellulose microparticles by solvent evaporation method with single emulsion system. *Int. J. Appl. Pharm.* **2023**, *15*, 235–240. [CrossRef]
9. Ma, L.; Zhao, X.; Hou, J.; Huang, L.; Yao, Y.; Ding, Z.; Wei, J.; Hao, N. Droplet Microfluidic Devices: Working Principles, Fabrication Methods, and Scale-Up Applications. *Small Methods* **2024**, *8*, 2301406. [CrossRef] [PubMed]
10. Guo, Y.; Liu, Y.; Hou, T.; Zhang, X.; Gao, J.; He, J.; Wang, C.; Wang, J.; Zhao, Q.; Chan, Y.; et al. Oscillatory flow driven microdroplet breakup dynamics and microparticle formation in LMPA-water two phase flow system. *Eng. Appl. Comput. Fluid Mech.* **2024**, *18*, 2315972. [CrossRef]
11. Ortega-Oller, I.; Padial-Molina, M.; Galindo-Moreno, P.; O'Valle, F.; Jódar-Reyes, A.B.; Peula-García, J.M. Bone Regeneration from PLGA Micro-Nanoparticles. *BioMed Res. Int.* **2015**, *2015*, 415289. [CrossRef] [PubMed]
12. Khan, A.; Saikia, P.; Saxena, R.; Rakshit, D.; Saha, S. Microencapsulation of phase change material in water dispersible polymeric particles for thermoregulating rubber composites—A holistic approach. *Int. J. Energy Res.* **2020**, *44*, 1567–1579. [CrossRef]
13. Allison, S.D. Analysis of initial burst in PLGA microparticles. *Expert Opin. Drug Deliv.* **2008**, *5*, 615–628. [CrossRef] [PubMed]
14. Grace, H.P. Dispersion phenomena in high viscosity immiscible fluid systems and application of static mixers as dispersion devices in such systems. *Chem. Eng. Commun.* **1982**, *14*, 225–277. [CrossRef]
15. Freitas, S.; Rudolf, B.; Merkle, H.P.; Gander, B. Flow-through ultrasonic emulsification combined with static micromixing for aseptic production of microspheres by solvent extraction. *Eur. J. Pharm. Biopharm.* **2005**, *61*, 181–187. [CrossRef] [PubMed]
16. Thomasin, C.; Merkle, H.P.; Gander, B.A. Physico-chemical parameters governing protein microencapsulation into biodegradable polyesters by coacervation. *Int. J. Pharm.* **1997**, *147*, 173–186. [CrossRef]
17. Zhan, S.; Chen, S.; Chen, L.; Hou, W. Preparation and characterization of polyurea microencapsulated phase change material by interfacial polycondensation method. *Powder Technol.* **2016**, *292*, 217–222. [CrossRef]
18. Wang, J.; Li, Y.; Wang, X.; Wang, J.; Tian, H.; Zhao, P.; Tian, Y.; Gu, Y.; Wang, L.; Wang, C. Droplet Microfluidics for the Production of Microparticles and Nanoparticles. *Micromachines* **2017**, *8*, 22. [CrossRef]
19. de Gennes, P.G.; Brochard-Wyart, F.; Quéré, D. *Capillarity and Wetting Phenomena*; Springer: Berlin/Heidelberg, Germany, 2004.
20. Wang, Y.; Liu, S.; Yan, N.; Ma, T.; Zhu, Y. Recent advancements in the precise engineering of block copolymer microparticles via confined assembly in emulsion droplets. *Nanoscale* **2025**, *17*, 27667–27684. [CrossRef] [PubMed]
21. Li, M.; Rouaud, O.; Poncelet, D. Microencapsulation by solvent evaporation: State of the art for process engineering approaches. *Int. J. Pharm.* **2008**, *363*, 26–39. [CrossRef] [PubMed]

22. Li, W.I.; Anderson, K.W.; Mehta, R.C.; Deluca, P.P. Prediction of solvent removal profile and effect on properties for peptide-loaded PLGA microspheres prepared by solvent extraction/evaporation method. *J. Control. Release* **1995**, *37*, 199–214. [CrossRef]
23. Pu, M.; Liu, K.; Zhang, M.; Yuan, P.; Cai, J. Microparticles and Microcapsules from the Solvent Extraction of Deep Eutectic Solvent-Based Emulsion. *Ind. Eng. Chem. Res.* **2020**, *59*, 2892–2898. [CrossRef]
24. Baena-Aristizábal, C.M.; Fessi, H.; Elaissari, A.; Mora-Huertas, C.E. Biodegradable microparticles preparation by double emulsification—Solvent extraction method: A Systematic study. *Colloids Surf. A Physicochem. Eng. Asp.* **2016**, *492*, 213–229. [CrossRef]
25. Ziaee, A. Spray Drying of Pharmaceuticals and Biopharmaceuticals: Experimental Optimization of Process and Formulation. Doctoral Dissertation, University of Limerick, Limerick, Ireland, 2019. Available online: https://hdl.handle.net/10344/9959 (accessed on 7 January 2026).
26. Bhandari, B.R.; Howes, T. Implication of glass transition for the drying and stability of dried foods. *J. Food Eng.* **1999**, *40*, 71–79. [CrossRef]
27. Edwards, D.A.; Hanes, J.; Caponetti, G.; Hrkach, J.; Ben-Jebria, A.; Eskew, M.L.; Mintzes, J.; Deaver, D.; Lotan, N.; Langer, R. Large porous particles for pulmonary drug delivery. *Science* **1997**, *276*, 1868–1871. [CrossRef] [PubMed]
28. Abdul-Fattah, A.M.; Truong-Le, V.; Yee, L.; Nguyen, L.; Kalonia, D.S.; Cicerone, M.T.; Pikal, M.J. Drying-induced variations in physico-chemical properties of amorphous pharmaceuticals and their impact on stability (I): Stability of a monoclonal antibody. *J. Pharm. Sci.* **2007**, *96*, 1983–2008. [CrossRef] [PubMed]
29. Maa, Y.F.; Nguyen, P.A.; Sweeney, T.; Shire, S.J.; Hsu, C. Protein inhalation powders: Spray drying vs spray freeze drying. *Pharm. Res.* **1999**, *16*, 249–254. [CrossRef] [PubMed]
30. Allemann, E.; Gurny, R.; Doelker, E. Drug-loaded nanoparticles: Preparation methods and drug targeting issues. *Eur. J. Pharm. Biopharm.* **1993**, *39*, 173–191.
31. Mawazi, S.M.; Doolaanea, A.A.; Hadi, H.A.; Chatterjee, B. The impact of carbamazepine crystallinity on carbamazepine-loaded microparticle formulations. *Int. J. Pharm.* **2021**, *602*, 120638. [CrossRef] [PubMed]
32. Kirkbir, F.; Murata, H.; Meyers, D.; Ray Chaudhuri, S.; Sarkar, A. Drying and sintering of sol-gel derived large SiO_2 monoliths. *J. Sol.-Gel Sci. Technol.* **1996**, *6*, 203–217. [CrossRef]
33. Bin, R.A.; Shishir, S.I.; Mahfuz, M.A.; Hossain, M.T.; Hoque, M.E. Silica Aerogel: Synthesis, Characterization, Applications, and Recent Advancements. *Part. Part. Syst. Charact.* **2023**, *40*, 2200186. [CrossRef]
34. Makadia, H.K.; Siegel, S.J. Poly Lactic-co-Glycolic Acid (PLGA) as Biodegradable Controlled Drug Delivery Carrier. *Polymers* **2011**, *3*, 1377–1397. [CrossRef] [PubMed]
35. Park, T.G. Degradation of poly(lactic-co-glycolic acid) microspheres: Effect of copolymer composition. *Biomaterials* **1995**, *16*, 1123–1130. [CrossRef] [PubMed]
36. Liu, G.; McEnnis, K. Glass Transition Temperature of PLGA Particles and the Influence on Drug Delivery Applications. *Polymers* **2022**, *14*, 993. [CrossRef] [PubMed]
37. Otte, A.; Soh, B.K.; Park, K. The Impact of Post-Processing Temperature on PLGA Microparticle Properties. *Pharm. Res.* **2023**, *40*, 2677–2685. [CrossRef] [PubMed]
38. Christensen, F.N.; Bertelsen, P. Qualitative Description of the Wurster-Based Fluid-Bed Coating Process. *Drug Dev. Ind. Pharm.* **1997**, *23*, 451–463. [CrossRef]
39. Hao, J.; Whitaker, M.J.; Serhatkulu, G.; Shakesheff, K.M.; Howdle, S.M. Supercritical fluid assisted melting of poly(ethylene glycol): A new solvent-free route to microparticles. *J. Mater. Chem.* **2005**, *15*, 1148–1153. [CrossRef]
40. Lefebvre, A.H.; McDonell, V.G. *Atomization and Sprays*, 2nd ed.; CRC Press: Boca Raton, FL, USA, 2017.
41. Oh, C.M.; Guo, Q.; Wan Sia Heng, P.; Chan, L.W. Spray-congealed microparticles for drug delivery—An overview of factors influencing their production and characteristics. *Expert Opin. Drug Deliv.* **2014**, *11*, 1047–1060. [CrossRef] [PubMed]
42. Bordos, E.; Islam, M.T.; Florence, A.J.; Halbert, G.W.; Robertson, J. Use of Terahertz-Raman Spectroscopy to Determine Solubility of the Crystalline Active Pharmaceutical Ingredient in Polymeric Matrices during Hot Melt Extrusion. *Mol. Pharm.* **2019**, *16*, 4361. [CrossRef] [PubMed]
43. Patil, H.; Tiwari, R.V.; Repka, M.A. Hot-Melt Extrusion: From Theory to Application in Pharmaceutical Formulation. *AAPS PharmSciTech* **2015**, *17*, 20–42. [CrossRef] [PubMed]
44. Repka, M.A.; Majumdar, S.; Battu, S.K.; Srirangam, R.; Upadhye, S.B. Applications of hot-melt extrusion for drug delivery. *Expert Opin. Drug Deliv.* **2008**, *5*, 1357–1376. [CrossRef] [PubMed]
45. Miller, D.A.; McConville, J.T.; Yang, W.; Williams, R.O.; McGinity, J.W. Hot-melt extrusion for enhanced delivery of drug particles. *J. Pharm. Sci.* **2007**, *96*, 361–376. [CrossRef] [PubMed]
46. Lukova, P.; Katsarov, P.; Pilicheva, B. Application of Starch, Cellulose, and Their Derivatives in the Development of Microparticle Drug-Delivery Systems. *Polymers* **2023**, *15*, 3615. [CrossRef] [PubMed]

47. Muhaimin, M.; Chaerunisaa, A.Y.; Bodmeier, R. Polymer type effect on PLGA-based microparticles preparation by solvent evaporation method with single emulsion system using focussed beam reflectance measurement. *J. Microencapsul.* **2022**, *39*, 512–521. [CrossRef] [PubMed]
48. Sharma, Y.; Mahar, R.; Chakraborty, A.; Nainwal, N. Optimizing the formulation variables for encapsulation of linezolid into polycaprolactone inhalable microspheres using double emulsion solvent evaporation. *Tuberculosis* **2023**, *143*, 102417. [CrossRef] [PubMed]
49. Tabata, M.; Kumamoto, M.; Nishimoto, J. Chemical Properties of Water-Miscible Solvents Separated by Salting-out and Their Application to Solvent Extraction. *Anal. Sci.* **1994**, *10*, 383–388. [CrossRef]
50. Yang, Y.Y.; Chung, T.S.; Ping Ng, N. Morphology, drug distribution, and in vitro release profiles of biodegradable polymeric microspheres containing protein fabricated by double-emulsion solvent extraction/evaporation method. *Biomaterials* **2001**, *22*, 231–241. [CrossRef] [PubMed]
51. Li, X.; Wang, B.; Liu, Q.J.; Zhao, R.; Song, D.P.; Li, Y. Supersoft Elastic Bottlebrush Microspheres with Stimuli-Responsive Color-Changing Properties in Brine. *Langmuir* **2021**, *37*, 6744–6753. [CrossRef] [PubMed]
52. da Trindade, R.A.; de Araujo, P.S.; Helena Bueno-da-Costa, M. Hoffmeister Ion Series Protected Bee Venom Proteins from Damages Induced by Microencapsulation Process. *Drug Deliv. Lett.* **2012**, *2*, 54–59. [CrossRef]
53. Allémann, E.; Gurny, R.; Doelker, E. Preparation of aqueous polymeric nanodispersions by a reversible salting-out process: Influence of process parameters on particle size. *Int. J. Pharm.* **1992**, *87*, 247–253. [CrossRef]
54. Galindo-Rodriguez, S.; Allémann, E.; Fessi, H.; Doelker, E. Physicochemical parameters associated with nanoparticle formation in the salting-out, emulsification-diffusion, and nanoprecipitation methods. *Pharm. Res.* **2004**, *21*, 1428–1439. [CrossRef] [PubMed]
55. Pulingam, T.; Foroozandeh, P.; Chuah, J.A.; Sudesh, K. Exploring Various Techniques for the Chemical and Biological Synthesis of Polymeric Nanoparticles. *Nanomaterials* **2022**, *12*, 576. [CrossRef] [PubMed]
56. Mora-Huertas, C.E.; Fessi, H.; Elaissari, A. Polymer-based nanocapsules for drug delivery. *Int. J. Pharm.* **2010**, *385*, 113–142. [CrossRef] [PubMed]
57. Mendoza-Munoz, N.; Quintanar-Guerrero, D.; Allemann, E. The Impact of the Salting-Out Technique on the Preparation of Colloidal Particulate Systems for Pharmaceutical Applications. *Recent Pat. Drug Deliv. Formul.* **2012**, *6*, 236–249. [CrossRef] [PubMed]
58. Do, Y.S.; Kiran, E. Formation of polymer particles with supercritical fluids: A review. *J. Supercrit. Fluids* **2005**, *34*, 287–308. [CrossRef]
59. Debenedetti, P.G.; Tom, J.W.; Kwauk, X.; Yeo, S.D. Rapid expansion of supercritical solutions (ress): Fundamentals and applications. *Fluid Phase Equilib.* **1993**, *82*, 311–321. [CrossRef]
60. Cooper, A.I. Polymer synthesis and processing using supercritical carbon dioxide. *J. Mater. Chem.* **2000**, *10*, 207–234. [CrossRef]
61. Reverchon, E.; De Marco, I.; Torino, E. Nanoparticles production by supercritical antisolvent precipitation: A general interpretation. *J. Supercrit. Fluids* **2007**, *43*, 126–138. [CrossRef]
62. Franco, P.; De Marco, I. Nanoparticles and Nanocrystals by Supercritical CO_2-Assisted Techniques for Pharmaceutical Applications: A Review. *Appl. Sci.* **2021**, *11*, 1476. [CrossRef]
63. Jaworek, A.; Sobczyk, A.T. Electrospraying route to nanotechnology: An overview. *J. Electrost.* **2008**, *66*, 197–219. [CrossRef]
64. Bock, N.; Woodruff, M.A.; Hutmacher, D.W.; Dargaville, T.R. Electrospraying, a Reproducible Method for Production of Polymeric Microspheres for Biomedical Applications. *Polymers* **2011**, *3*, 131–149. [CrossRef]
65. Loscertales, I.G.; Barrero, A.; Guerrero, I.; Cortijo, R.; Marquez, M.; Gañán-Calvo, A.M. Micro/nano encapsulation via electrified coaxial liquid jets. *Science* **2002**, *295*, 1695–1698. [CrossRef] [PubMed]
66. Deng, W.; Klemic, J.F.; Li, X.; Reed, M.A.; Gomez, A. Increase of electrospray throughput using multiplexed microfabricated sources for the scalable generation of monodisperse droplets. *J. Aerosol Sci.* **2006**, *37*, 696–714. [CrossRef]
67. Enayati, M.; Ahmad, Z.; Stride, E.; Edirisinghe, M. One-step electrohydrodynamic production of drug-loaded micro- and nanoparticles. *J. R. Soc. Interface* **2009**, *7*, 667. [CrossRef] [PubMed]
68. Davoodi, P.; Feng, F.; Xu, Q.; Yan, W.C.; Tong, Y.W.; Srinivasan, M.P.; Sharma, V.K.; Wang, C.-H. Coaxial electrohydrodynamic atomization: Microparticles for drug delivery applications. *J. Control. Release* **2015**, *205*, 70–82. [CrossRef] [PubMed]
69. Hartman, R.P.A.; Brunner, D.J.; Camelot, D.M.A.; Marijnissen, J.C.M.; Scarlett, B. Electrohydrodynamic atomization in the cone–jet mode physical modeling of the liquid cone and jet. *J. Aerosol Sci.* **1999**, *30*, 823–849. [CrossRef]
70. Rosell-Llompart, J.; Fernández de la Mora, J. Generation of monodisperse droplets 0.3 to 4 μm in diameter from electrified cone-jets of highly conducting and viscous liquids. *J. Aerosol Sci.* **1994**, *25*, 1093–1119. [CrossRef]
71. Park, K. Controlled drug delivery systems: Past forward and future back. *J. Control. Release* **2014**, *190*, 3–8. [CrossRef] [PubMed]
72. Fu, Y.; Kao, W.J. Drug release kinetics and transport mechanisms of non-degradable and degradable polymeric delivery systems. *Expert Opin. Drug Deliv.* **2010**, *7*, 429–444. [CrossRef] [PubMed]

73. Mawazi, M.; Hadi, H.A.B.; Mohammed, S.; Al-Mahmood, A.; Doolaanea, A. Development and Validation of Uv-vis Spectroscopic Method of Assay of Carbamazepine in Microparticles. 2019. Available online: http://creativecommons.org/licenses/by/4.0/ (accessed on 7 January 2026).
74. Mawazi, S.M.; Al-Mahmood, S.M.A.; Chatterjee, B.; Hadi, H.A.B.; Doolaanea, A.A. Carbamazepine Gel Formulation as a Sustained Release Epilepsy Medication for Pediatric Use. *Pharmaceutics* **2019**, *11*, 488. [CrossRef] [PubMed]
75. Van De Weert, M.; Hoechstetter, J.; Hennink, W.E.; Crommelin, D.J.A. The effect of a water/organic solvent interface on the structural stability of lysozyme. *J. Control. Release* **2000**, *68*, 351–359. [CrossRef] [PubMed]
76. Quan, P.; Guo, W.; Yang, L.; Cun, D.; Yang, M. Donepezil accelerates the release of PLGA microparticles via catalyzing the polymer degradation regardless of the end groups and molecular weights. *Int. J. Pharm.* **2023**, *632*, 122566. [CrossRef] [PubMed]
77. Alvarez, I.; Gutiérrez, C.; Gracia, I.; Rodríguez, J.F.; García, M.T. Synthesis of Gemcitabine-Loaded PLGA Microparticles with Green Solvents. *ACS Omega* **2025**, *10*, 33946. [CrossRef] [PubMed]
78. Freitas, S.; Merkle, H.P.; Gander, B. Microencapsulation by solvent extraction/evaporation: Reviewing the state of the art of microsphere preparation process technology. *J. Control. Release* **2005**, *102*, 313–332. [CrossRef] [PubMed]
79. Katou, H.; Wandrey, A.J.; Gander, B. Kinetics of solvent extraction/evaporation process for PLGA microparticle fabrication. *Int. J. Pharm.* **2008**, *364*, 45–53. [CrossRef] [PubMed]
80. Bodmeier, R.; McGinity, J.W. Solvent selection in the preparation of poly(dl-lactide) microspheres prepared by the solvent evaporation method. *Int. J. Pharm.* **1988**, *43*, 179–186. [CrossRef]
81. Kias, F.; Bodmeier, R. Acceleration of Final Residual Solvent Extraction from Poly(lactide-co-glycolide) Microparticles. *Pharm. Res.* **2024**, *41*, 1869–1879. [CrossRef] [PubMed]
82. Kaş, H.S.; Öner, L. Microencapsulation Using Coacervation/Phase Separation: An Overview of the Technique and Applications. In *Handbook of Pharmaceutical Controlled Release Technology*; Chapter 15; Wise, D.L., Ed.; Marcel Dekker: New York, NY, USA, 2000.
83. Jameela, S.R.; Jayakrishnan, A. Glutaraldehyde cross-linked chitosan microspheres as a long acting biodegradable drug delivery vehicle: Studies on the in vitro release of mitoxantrone and in vivo degradation of microspheres in rat muscle. *Biomaterials* **1995**, *16*, 769–775. [CrossRef] [PubMed]
84. Burgess, D.J. Practical analysis of complex coacervate systems. *J. Colloid Interface Sci.* **1990**, *140*, 227–238. [CrossRef]
85. Mohanty, B.; Bohidar, H.B. Systematic of Alcohol-Induced Simple Coacervation in Aqueous Gelatin Solutions. *Biomacromolecules* **2003**, *4*, 1080–1086. [CrossRef] [PubMed]
86. De Kruif, C.G.; Weinbreck, F.; De Vries, R. Complex coacervation of proteins and anionic polysaccharides. *Curr. Opin. Colloid Interface Sci.* **2004**, *9*, 340–349. [CrossRef]
87. Burgess, D.J.; Carless, J.E. Microelectrophoretic studies of gelatin and acacia for the prediction of complex coacervation. *J. Colloid Interface Sci.* **1984**, *98*, 1–8. [CrossRef]
88. Torza, S.; Mason, S.G. Three-phase interactions in shear and electrical fields. *J. Colloid Interface Sci.* **1970**, *33*, 67–83. [CrossRef]
89. Rane, A.M.; Schwing, J.A.; Jonnalagadda, S. Coacervation and Phase Separation. In *Encyclopedia of Pharmaceutical Science and Technology*, 4th, ed.; CRC Press: Boca Raton, FL, USA, 2013; pp. 497–511. Available online: https://www.taylorfrancis.com/chapters/edit/10.1081/E-EPT4-120050215/coacervation-phase-separation-anuja-rane-james-schwing-sriramakamal-jonnalagadda (accessed on 11 July 2026).
90. Muzzarelli, R.A.A.; El Mehtedi, M.; Bottegoni, C.; Aquili, A.; Gigante, A. Genipin-Crosslinked Chitosan Gels and Scaffolds for Tissue Engineering and Regeneration of Cartilage and Bone. *Mar. Drugs* **2015**, *13*, 7314–7338. [CrossRef] [PubMed]
91. Merve Buldur, P. Encapsulation of food flavors via coacervation method. *Curr. Opin. Biotechnol.* **2011**, *22*, S96. [CrossRef]
92. Grabska-Zielińska, S. Cross-Linking Agents in Three-Component Materials Dedicated to Biomedical Applications: A Review. *Polymers* **2024**, *16*, 2679. [CrossRef] [PubMed]
93. D'Agostino, I. Design of Biopolymer Nanoparticles for Encapsulation and Delivery of Nutraceuticals. 7 April 2017. Available online: https://arts.units.it/handle/11368/2907989 (accessed on 11 July 2026).
94. Moulik, S.P.; Rakshit, A.K.; Pan, A.; Naskar, B. An Overview of Coacervates: The Special Disperse State of Amphiphilic and Polymeric Materials in Solution. *Colloids Interfaces* **2022**, *6*, 45. [CrossRef]
95. Soussi Hachfi, R.; Hamon, P.; Rousseau, F.; Famelart, M.H.; Bouhallab, S. Ionic Strength Dependence of the Complex Coacervation between Lactoferrin and β-Lactoglobulin. *Foods* **2023**, *12*, 1040. [CrossRef] [PubMed]
96. Timilsena, Y.P.; Wang, B.; Adhikari, R.; Adhikari, B. Preparation and characterization of chia seed protein isolate–chia seed gum complex coacervates. *Food Hydrocoll.* **2016**, *52*, 554–563. [CrossRef]
97. Ligarda-Samanez, C.A.; Choque-Quispe, D.; Palomino-Rincón, H.; Moscoso-Moscoso, E.; Guzmán Gutiérrez, R.J.; Banda Mozo, I. Microencapsulation of Propolis by Complex Coacervation with Chia Mucilage and Gelatin: Antioxidant Stability and Functional Potential. *Antioxidants* **2025**, *14*, 845. [CrossRef] [PubMed]
98. Sander, C.; Nielsen, H.S.; Sgøaard, S.R.; Stvøing, C.; Yang, M.; Jacobsen, J.; Rantanen, J. Process development for spray drying of sticky pharmaceuticals; case study of bioadhesive nicotine microparticles for compressed medicated chewing gum. *Int. J. Pharm.* **2013**, *452*, 434–437. [CrossRef] [PubMed]

99. Gharsallaoui, A.; Roudaut, G.; Chambin, O.; Voilley, A.; Saurel, R. Applications of spray-drying in microencapsulation of food ingredients: An overview. *Food Res. Int.* **2007**, *40*, 1107–1121. [CrossRef]
100. Liu, W.; Chen, X.D.; Selomulya, C. On the spray drying of uniform functional microparticles. *Particuology* **2015**, *22*, 1–12. [CrossRef]
101. Sansone, F.; Mencherini, T.; Picerno, P.; D'Amore, M.; Aquino, R.P.; Lauro, M.R. Maltodextrin/pectin microparticles by spray drying as carrier for nutraceutical extracts. *J. Food Eng.* **2011**, *105*, 468–476. [CrossRef]
102. Vehring, R. Pharmaceutical Particle Engineering via Spray Drying. *Pharm. Res.* **2007**, *25*, 999–1022. [CrossRef] [PubMed]
103. Vehring, R.; Foss, W.R.; Lechuga-Ballesteros, D. Particle formation in spray drying. *J. Aerosol Sci.* **2007**, *38*, 728–746. [CrossRef]
104. Sansone, F.; Esposito, T.; Lauro, M.R.; Picerno, P.; Mencherini, T.; Gasparri, F.; De Santis, S.; Chieppa, M.; Cirillo, C.; Aquino, R.P. Application of Spray Drying Particle Engineering to a High-Functionality/Low-Solubility Milk Thistle Extract: Powders Production and Characterization. *Molecules* **2018**, *23*, 1716. [CrossRef] [PubMed]
105. Sahoo, N.; Abbas, A.; Li, C. Micro/Nanoparticle Design and Fabrication for Pharmaceutical Drug Preparation and Delivery Applications. *Curr. Drug Ther.* **2008**, *3*, 78–97. [CrossRef]
106. Huang, Y.; Dai, W.G. Fundamental aspects of solid dispersion technology for poorly soluble drugs. *Acta Pharm. Sin. B* **2014**, *4*, 18–25. [CrossRef] [PubMed]
107. Michaelides, K.; Al Tahan, M.A.; Zhou, Y.; Trindade, G.F.; Cant, D.J.H.; Pei, Y.; Dulal, P.; Al-Khattawi, A. New Insights on the Burst Release Kinetics of Spray-Dried PLGA Microspheres. *Mol. Pharm.* **2024**, *21*, 6245. [CrossRef] [PubMed]
108. Candiani, A.; Milanesi, A.; Bonda, A.F.; Diana, G.; Bari, E.; Segale, L.; Torre, M.L.; Giovannelli, L. Solid Lipid Microparticles by Spray Congealing of Water/Oil Emulsion: An Effective/Versatile Loading Strategy for a Highly Soluble Drug. *Pharmaceutics* **2022**, *14*, 2805. [CrossRef] [PubMed]
109. Albertini, B.; Passerini, N.; Pattarino, F.; Rodriguez, L. New spray congealing atomizer for the microencapsulation of highly concentrated solid and liquid substances. *Eur. J. Pharm. Biopharm.* **2008**, *69*, 348–357. [CrossRef] [PubMed]
110. Passerini, N.; Perissutti, B.; Voinovich, D.; Albertini, B.; Franceschinis, E.; Rodriguez, L. Screening of the ultrasonic spray congealing process variables by factorial design [conference abstract]. In *Proceedings of the European Conference on Drug Delivery and Pharmaceutical Technology, Sevilla, Spain, 10–12 May 2004*; Universidad de Sevilla: Sevilla, Spain, 2004; p. 123.
111. Bunjes, H. Structural properties of solid lipid based colloidal drug delivery systems. *Curr. Opin. Colloid Interface Sci.* **2011**, *16*, 405–411. [CrossRef]
112. Bertoni, S.; Albertini, B.; Ronowicz-Pilarczyk, J.; Passerini, N. Tailoring the release of drugs having different water solubility by hybrid polymer-lipid microparticles with a biphasic structure. *Eur. J. Pharm. Biopharm.* **2023**, *190*, 171–183. [CrossRef] [PubMed]
113. Racoviţă, Ş.; Vasiliu, S.; Popa, M.; Luca, C. Polysaccharides based on micro-and nanoparticles obtained by ionic gelation and their applications as drug delivery systems. *Rev. Roum. Chim.* **2009**, *54*, 709–718.
114. Poncelet, D.; Lencki, R.; Beaulieu, C.; Halle, J.P.; Neufeld, R.J.; Fournier, A. Production of alginate beads by emulsification/internal gelation. I. Methodology. *Appl. Microbiol. Biotechnol.* **1992**, *38*, 39–45. [CrossRef] [PubMed]
115. Rajabimashhadi, Z.; Masi, A.; Bagheri, S.; Mele, C.; Colangelo, G.; Paladini, F.; Pollini, M. Development and Characterization of Chitosan Microparticles via Ionic Gelation for Drug Delivery. *Polymers* **2025**, *17*, 2603. [CrossRef] [PubMed]
116. Lin, D.; Kelly, A.L.; Miao, S. Alginate-based emulsion micro-gel particles produced by an external/internal O/W/O emulsion-gelation method: Formation, suspension rheology, digestion, and application to gel-in-gel beads. *Food Hydrocoll.* **2021**, *120*, 106926. [CrossRef]
117. Silva, C.M.; Ribeiro, A.J.; Figueiredo, I.V.; Gonçalves, A.R.; Veiga, F. Alginate microspheres prepared by internal gelation: Development and effect on insulin stability. *Int. J. Pharm.* **2006**, *311*, 1–10. [CrossRef] [PubMed]
118. Bácskay, I.; Papp, B.; Pártos, P.; Budai, I.; Pető, Á.; Fehér, P.; Ujhelyi, Z.; Kósa, D. Formulation and Evaluation of Insulin-Loaded Sodium-Alginate Microparticles for Oral Administration. *Pharmaceutics* **2023**, *16*, 46. [CrossRef] [PubMed]
119. Hıncal, A.A.; Kaş, H.S. Microencapsulation Technology: Interfacial Polymerization Method. In *Handbook of Pharmaceutical Controlled Release Technology*; Chapter 13; Wise, D.L., Ed.; Marcel Dekker: New York, NY, USA, 2000.
120. Song, Y.; Fan, J.B.; Wang, S. Recent progress in interfacial polymerization. *Mater. Chem. Front.* **2017**, *1*, 1028–1040. [CrossRef]
121. Avdeliodi, E.; Tsioli, A.; Bokias, G.; Kallitsis, J.K. Controlling the Synthesis of Polyurea Microcapsules and the Encapsulation of Active Diisocyanate Compounds. *Polymers* **2024**, *16*, 270. [CrossRef] [PubMed]
122. Farzi, G.; Gheysipour, M. Microencapsulation: Air suspension technique. *Princ. Biomater. Encapsulation* **2023**, *1*, 297–303. [CrossRef]
123. Mohylyuk, V.; Patel, K.; Scott, N.; Richardson, C.; Murnane, D.; Liu, F. Wurster Fluidised Bed Coating of Microparticles: Towards Scalable Production of Oral Sustained-Release Liquid Medicines for Patients with Swallowing Difficulties. *AAPS PharmSciTech* **2019**, *21*, 3. [CrossRef] [PubMed]
124. Liu, D.; Guo, J.; Ma, J.; Liang, C.; Chen, X. Effects of Seed Particle Properties on Coating in a Wurster Fluidized Bed. *Ind. Eng. Chem. Res.* **2023**, *62*, 15687–15698. [CrossRef]

125. Wurster, D.E. Preparation of compressed tablet granulations by the air-suspension technique II. *J. Am. Pharm. Assoc.* **1960**, *49*, 82–84. [CrossRef] [PubMed]
126. Jones, D.; Godek, E. Development, optimization, and scale-up of process parameters: Wurster coating. *Dev. Solid Oral Dos. Forms* **2026**, *2*, 1333–1356. [CrossRef]
127. Salawi, A. Pharmaceutical Coating and Its Different Approaches, a Review. *Polymers* **2022**, *14*, 3318. [CrossRef] [PubMed]
128. Garg, A.; Chhipa, K.; Kumar, L. Microencapsulation Techniques In Pharmaceutical Formulation. *Eur. J. Pharm. Med. Res.* **2018**, *5*, 199–206.
129. Aminahmadi, B.; Vaes, E.; Willemse, F.; Braile, D.; Gomez, L.N.; Andersen, S.K.; De Beer, T.; Kumar, A. Experimental and Modeling-Based Approaches for Mechanistic Understanding of Pan Coating Process—A Detailed Review. *Pharmaceutics* **2026**, *18*, 19. [CrossRef] [PubMed]
130. Porter, S.C. The role of high-solids coating systems in reducing process costs. *Tablets Capsul.* **2010**, *8*, 10–15.
131. de Melo, V.P.; Löbenberg, R.; Bou-Chacra, N.A. Statistical evaluation of tablet coating processes: Influence of pan design and solvent type. *Braz. J. Pharm. Sci.* **2010**, *46*, 657–664. [CrossRef]
132. Brown, E.N.; Kessler, M.R.; Sottos, N.R.; White, S.R. In situ poly(urea-formaldehyde) microencapsulation of dicyclopentadiene. *J. Microencapsul.* **2003**, *20*, 719–730. [CrossRef] [PubMed]
133. Li, W.; Zhu, X.; Zhao, N.; Jiang, Z. Preparation and Properties of Melamine Urea-Formaldehyde Microcapsules for Self-Healing of Cementitious Materials. *Materials* **2016**, *9*, 152. [CrossRef] [PubMed]
134. Alič, B.; Šebenik, U.; Krajnc, M. Applying pH Modulation to Improve the Thermal Stability of Melamine–Formaldehyde Microcapsules Containing Butyl Stearate as a Phase-Change Material. *Polymers* **2024**, *16*, 2463. [CrossRef] [PubMed]
135. Nguon, O.; Lagugné-Labarthet, F.; Brandys, F.A.; Li, J.; Gillies, E.R. Microencapsulation by in situ Polymerization of Amino Resins. *Polym. Rev.* **2018**, *58*, 326–375. [CrossRef]
136. Mustapha, A.N.; Zhang, Y.; Zhang, Z.; Ding, Y.; Li, Y. A systematic study on the reaction mechanisms for the microencapsulation of a volatile phase change material (PCM) via one-step in situ polymerisation. *Chem. Eng. Sci.* **2022**, *252*, 117497. [CrossRef]
137. Zhang, H.; Wang, X. Fabrication and performances of microencapsulated phase change materials based on n-octadecane core and resorcinol-modified melamine–formaldehyde shell. *Colloids Surf. A Physicochem. Eng. Asp.* **2009**, *332*, 129–138. [CrossRef]
138. León, G.; Paret, N.; Fankhauser, P.; Grenno, D.; Erni, P.; Ouali, L.; Berthier, D.L. Formaldehyde-free melamine microcapsules as core/shell delivery systems for encapsulation of volatile active ingredients. *RSC Adv.* **2017**, *7*, 18962–18975. [CrossRef]
139. de Carvalho Freire, M.P.; da Silva, G.A.; Pereira de Paula, Y.M.; Marini, J.; Melo, J.D.D.; Costa, M.C.B. Optimization of synthesis parameters of PUF/ENB microcapsules for self-healing applications using factorial design methodology. *J. Appl. Polym. Sci.* **2024**, *141*, e55508. [CrossRef]
140. Vezzù, K.; Campolmi, C.; Bertucco, A. Production of Lipid Microparticles Magnetically Active by a Supercritical Fluid-Based Process. *Int. J. Chem. Eng.* **2009**, *2009*, 781247. [CrossRef]
141. Mottola, S.; De Marco, I. Designing Microparticles of Luteolin and Naringenin in Different Carriers via Supercritical Antisolvent Process. *Polymers* **2024**, *16*, 3600. [CrossRef] [PubMed]
142. Nosoudi, N.; Hasanzadeh, A.; Hart, M.; Weaver, B. Advancements and Future Perspectives in Cell Electrospinning and Bio-Electrospraying. *Adv. Biol.* **2023**, *7*, 2300213. [CrossRef] [PubMed]
143. Frs, L. On the equilibrium of liquid conducting masses charged with electricity. *Lond. Edinb. Dublin Philos. Mag. J. Sci.* **1882**, *14*, 184–186. [CrossRef]
144. Rodriguez, A.; Quintanilla, J.; Amieva, J.; Arriaga, M.A.; Nievera, S.; Davila, I.; Martirosyan, K.S.; Chew, S.A. Abstract 5745: Electrosprayed minocycline and temozolomide-loaded PLGA microparticles for the treatment of glioblastoma. *Cancer Res.* **2024**, *84*, 5745. [CrossRef]
145. Moragues, T.; Arguijo, D.; Beneyton, T.; Modavi, C.; Simutis, K.; Abate, A.R.; Baret, J.-C.; deMello, A.J.; Densmore, D.; Griffiths, A.D. Droplet-based microfluidics. *Nat. Rev. Methods Primers* **2023**, *3*, 32. [CrossRef]
146. Anna, S.L.; Bontoux, N.; Stone, H.A. Formation of dispersions using "flow focusing" in microchannels. *Appl. Phys. Lett.* **2003**, *82*, 364–366. [CrossRef]
147. Dendukuri, D.; Doyle, P.S. The synthesis and assembly of polymeric microparticles using microfluidics. *Adv. Mater.* **2009**, *21*, 4071–4086. [CrossRef]
148. Duncanson, W.J.; Lin, T.; Abate, A.R.; Seiffert, S.; Shah, R.K.; Weitz, D.A. Microfluidic synthesis of advanced microparticles for encapsulation and controlled release. *Lab Chip* **2012**, *12*, 2135–2145. [CrossRef] [PubMed]
149. Vladisavljević, G.T.; Khalid, N.; Neves, M.A.; Kuroiwa, T.; Nakajima, M.; Uemura, K.; Ichikawa, S.; Kobayashi, I. Industrial lab-on-a-chip: Design, applications and scale-up for drug discovery and delivery. *Adv. Drug Deliv. Rev.* **2013**, *65*, 1626–1663. [CrossRef] [PubMed]
150. Nisisako, T.; Torii, T. Microfluidic large-scale integration on a chip for mass production of monodisperse droplets and particles. *Lab Chip* **2008**, *8*, 287–293. [CrossRef] [PubMed]

151. Chen, W.; Li, H.; Zhang, X.; Sang, Y.; Nie, Z. Microfluidic preparation of monodisperse PLGA-PEG/PLGA microspheres with controllable morphology for drug release. *Lab Chip* **2024**, *24*, 4623–4631. [CrossRef] [PubMed]
152. Barbé, C.; Bartlett, J.; Kong, L.; Finnie, K.; Lin, H.Q.; Larkin, M.; Calleja, S.; Bush, A.; Calleja, G. Silica particles: A novel drug-delivery system. *Adv. Mater.* **2004**, *16*, 1959–1966. [CrossRef]
153. Brinker, C.J.; Scherer, G.W. Sol-Gel Science: The Physics and Chemistry of Sol-Gel Processing. In *Sol-Gel Science: The Physics and Chemistry of Sol-Gel Processing*; Academic Press: San Diego, CA, USA, 2013; pp. 1–908.
154. Ciriminna, R.; Sciortino, M.; Alonzo, G.; De Schrijver, A.; Pagliaro, M. From Molecules to Systems: Sol−Gel Microencapsulation in Silica-Based Materials. *Chem. Rev.* **2011**, *111*, 765–789. [CrossRef] [PubMed]
155. Gupta, R.; Chaudhury, N.K. Entrapment of biomolecules in sol–gel matrix for applications in biosensors: Problems and future prospects. *Biosens. Bioelectron.* **2007**, *22*, 2387–2399. [CrossRef] [PubMed]
156. Wright, J.D.; Sommerdijk, N.A.J.M. *Sol-Gel Materials: Chemistry and Applications*; Advanced Chemistry Texts; Gordon and Breach Science Publishers: Amsterdam, The Netherlands, 2001; Volume 4.
157. Avnir, D.; Lev, O.; Livage, J. Recent bio-applications of sol–gel materials. *J. Mater. Chem.* **2006**, *16*, 1013–1030. [CrossRef]
158. Radin, S.; Chen, T.; Ducheyne, P. The controlled release of drugs from emulsified, sol gel processed silica microspheres. *Biomaterials* **2009**, *30*, 850–858. [CrossRef] [PubMed]
159. Ciriminna, R.; Fidalgo, A.; Pandarus, V.; Béland, F.; Ilharco, L.M.; Pagliaro, M. The Sol–Gel Route to Advanced Silica-Based Materials and Recent Applications. *Chem. Rev.* **2013**, *113*, 6592–6620. [CrossRef] [PubMed]
160. Klein, L.C. Sol-Gel Processing of Silicates. *Annu. Rev. Mater. Res.* **1985**, *15*, 227–248. [CrossRef]
161. Dilsiz, N.; Akovali, G. Study of sol–gel processing for fabrication of low density alumina microspheres. *Mater. Sci. Eng. A* **2002**, *332*, 91–96. [CrossRef]
162. Hench, L.L.; West, J.K. The sol-gel process. *Chem. Rev.* **1990**, *90*, 33–72. [CrossRef]
163. Pagliaro, M. *Silica-Based Materials for Advanced Chemical Applications*; Royal Society of Chemistry: Cambridge, UK, 2009. [CrossRef]
164. Sanchez, C.; Julián, B.; Belleville, P.; Popall, M. Applications of hybrid organic–inorganic nanocomposites. *J. Mater. Chem.* **2005**, *15*, 3559–3592. [CrossRef]
165. Corma, A.; Botella, P.; Rivero-Buceta, E. Silica-Based Stimuli-Responsive Systems for Antitumor Drug Delivery and Controlled Release. *Pharmaceutics* **2022**, *14*, 110. [CrossRef] [PubMed]
166. Zaidi, Z.S.; Teki, S.V.N.; Katti, D.S. Stimuli-Responsive Mesoporous Silica Nanoparticles for Cancer Therapy. In *Advances in Stimuli-Responsive Nanosystems for Cancer Therapy*; Springer Nature: Singapore, 2026; pp. 181–211. Available online: https://link.springer.com/chapter/10.1007/978-981-95-2744-1_8 (accessed on 5 September 2026).
167. Rosenholm, J.M.; Lindén, M. Towards establishing structure–activity relationships for mesoporous silica in drug delivery applications. *J. Control. Release* **2008**, *128*, 157–164. [CrossRef] [PubMed]
168. Cauda, V.; Schlossbauer, A.; Kecht, J.; Zürner, A.; Bein, T. Multiple Core-Shell Functionalized Colloidal Mesoporous Silica Nanoparticles. *J. Am. Chem. Soc.* **2009**, *131*, 11361–11370. [CrossRef] [PubMed]
169. Yang, P.; Gai, S.; Lin, J. Functionalized mesoporous silica materials for controlled drug delivery. *Chem. Soc. Rev.* **2012**, *41*, 3679–3698. [CrossRef] [PubMed]
170. Steinbach, J.C.; Fait, F.; Mayer, H.A.; Kandelbauer, A. Sol–Gel-Controlled Size and Morphology of Mesoporous Silica Microspheres Using Hard Templates. *ACS Omega* **2023**, *8*, 30273. [CrossRef] [PubMed]
171. Mathiowitz, E.; Langer, R. Polyanhydride microspheres as drug carriers I. Hot-melt microencapsulation. *J. Control. Release* **1987**, *5*, 13–22. [CrossRef]
172. Huang, Q.; Zhang, Z. Microencapsulation of L-carvone and hexyl salicylate in carnauba wax, candelilla wax and beeswax by melt dispersion method. *Polym. Test.* **2025**, *143*, 108728. [CrossRef]
173. Zhang, A.; Wei, Q.; Zheng, Y.; Ma, M.; Cao, T.; Zhan, Q.; Cao, P. Hydrogen Sulfide Delivery System Based on Salting-Out Effect for Enhancing Synergistic Photothermal and Photodynamic Cancer Therapies. *Adv. Healthc. Mater.* **2024**, *13*, 2400803. [CrossRef] [PubMed]
174. González Álvarez, E.; Castro Ríos, R.; Luna Olvera, H.A.; González Horta, A.; Galindo Rodríguez, S.A.; Chávez Montes, A. Polymeric microparticles containing protein prepared using a controllable combination of diffusion and emulsification steps as part of the salting out procedure. *Afr. J. Pharm. Pharmacol.* **2013**, *7*, 2849–2858. [CrossRef]
175. Klose, D.; Siepmann, F.; Elkharraz, K.; Krenzlin, S.; Siepmann, J. How porosity and size affect the drug release mechanisms from PLGA-based microparticles. *Int. J. Pharm.* **2006**, *314*, 198–206. [CrossRef] [PubMed]
176. Butreddy, A.; Gaddam, R.P.; Kommineni, N.; Dudhipala, N.; Voshavar, C. Plga/pla-based long-acting injectable depot microspheres in clinical use: Production and characterization overview for protein/peptide delivery. *Int. J. Mol. Sci.* **2021**, *22*, 8884. [CrossRef] [PubMed]
177. Park, K.; Otte, A.; Sharifi, F.; Garner, J.; Skidmore, S.; Park, H.; Jhon, Y.K.; Qin, B.; Wang, Y. Formulation composition, manufacturing process, and characterization of poly(lactide-co-glycolide) microparticles. *J. Control. Release* **2021**, *329*, 1150–1161. [CrossRef] [PubMed]

178. Kim, S.M.; Patel, M.; Patel, R. PLGA Core-Shell Nano/Microparticle Delivery System for Biomedical Application. *Polymers* **2021**, *13*, 3471. [CrossRef] [PubMed]
179. Bürki, K.; Jeon, I.; Arpagaus, C.; Betz, G. New insights into respirable protein powder preparation using a nano spray dryer. *Int. J. Pharm.* **2011**, *408*, 248–256. [CrossRef] [PubMed]
180. Soh, S.H.; Lee, L.Y. Microencapsulation and Nanoencapsulation Using Supercritical Fluid (SCF) Techniques. *Pharmaceutics* **2019**, *11*, 21. [CrossRef] [PubMed]
181. Byrne, F.P.; Jin, S.; Paggiola, G.; Petchey, T.H.M.; Clark, J.H.; Farmer, T.J.; Hunt, A.J.; McElroy, C.R.; Sherwood, J. Tools and techniques for solvent selection: Green solvent selection guides. *Sustain. Chem. Process.* **2016**, *4*, 7. [CrossRef]
182. Q13 Continuous Manufacturing of Drug Substances and Drug Products. Available online: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q13-continuous-manufacturing-drug-substances-and-drug-products (accessed on 5 September 2026).
183. U.S. Food and Drug Administration. Guidance for Industry: PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance. September 2004. Available online: https://www.fda.gov/media/71012/download (accessed on 5 September 2026).
184. Liu, L.; Wu, F.; Ju, X.J.; Xie, R.; Wang, W.; Niu, C.H.; Chu, L.-Y. Preparation of monodisperse calcium alginate microcapsules via internal gelation in microfluidic-generated double emulsions. *J. Colloid Interface Sci.* **2013**, *404*, 85–90. [CrossRef] [PubMed]
185. Coronel-Aguilera, C.P.; San Martín-González, M.F. Encapsulation of spray dried β-carotene emulsion by fluidized bed coating technology. *LWT-Food Sci. Technol.* **2015**, *62*, 187–193. [CrossRef]
186. Karimi, M.; Ghasemi, A.; Zangabad, P.S.; Rahighi, R.; Basri, S.M.M.; Mirshekari, H.; Amiri, M.; Pishabad, Z.S.; Aslani, A.; Bozorgomid, M.; et al. Smart micro/nanoparticles in stimulus-responsive drug/gene delivery systems. *Chem. Soc. Rev.* **2016**, *45*, 1457–1501. [CrossRef] [PubMed]
187. Lee, Y.J.; Kim, M.S. Advances in drug-loaded microspheres for targeted, controlled, and sustained drug delivery: Potential, applications, and future directions. *Biomed. Pharmacother.* **2025**, *189*, 118244. [CrossRef] [PubMed]
188. Eugster, R.; Ganguin, A.A.; Seidi, A.; Aleandri, S.; Luciani, P. 3D printing injectable microbeads using a composite liposomal ink for local treatment of peritoneal diseases. *Drug Deliv. Transl. Res.* **2023**, *14*, 1567–1581. [CrossRef] [PubMed]
189. Li, K.; Sun, J.; He, S.; Zhou, X.; Li, H.; Liu, Y. On-demand preparation of calcium alginate microspheres via piezoelectric microfluidics. *Sens. Actuators A Phys.* **2022**, *347*, 113925. [CrossRef]
190. Peeler, D.J.; Sun, R.; Kütahya, C.; Peschke, P.; Zhou, K.; Brachi, G.; Yeow, J.; Rifaie-Graham, O.; Wojciechowski, J.P.; Debets, T.F.F.F.; et al. Nanoscale Biodegradable Printing for Designed Tuneability of Vaccine Delivery Kinetics. *Adv. Mater.* **2025**, *37*, 2417290. [CrossRef] [PubMed]

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