Review

A Practical Guide to Microparticle Fabrication: A Comprehensive Illustrated and Updated Review

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Posted Date: 7 April 2026

doi: 10.20944/preprints202604.0403.v1

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 doi:10.20944/preprints202604.0403.v1

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A Practical Guide to Microparticle Fabrication: A Comprehensive Illustrated and Updated Review

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Abstract

Background: The domain of microencapsulation technology is considered to be at the level of an advanced scientific discipline that includes the fields of materials science, pharmaceutical engineering, and food technology in the formulation of very specific matrices of polymeric or lipid nature. **Method**: In this review, a comprehensive analysis of sixteen different techniques of microparticles preparation has been presented: Solvent Evaporation, Solvent Extraction, Coacervation, Spray Drying, Spray Congealing, Ionic Gelation, Interfacial Polymerization, Air Suspension, Pan Coating, In-situ Polymerization, Supercritical Fluid Technology, Electrospraying, Microfluidics, Sol-Gel Process, Hot Melt Encapsulation, and Salting Out. Each technique has been explained by describing the basic physical and chemical phenomena that govern the process of microparticles formation. **Results**: The review has been presented with a critical analysis of the operating parameters, along with the core and shell material, as well as the applications of the technique, which are of interest in the field of pharmaceuticals, cosmetics, food, and medicine. **Conclusion**: The types of drugs that are best suited for the particular technique, as per their physical and chemical properties, i.e., solubility in water, lipid solubility, acid–base properties, as well as their thermoreactive properties, have been discussed in the review. The possibility of scaling up the technique from the laboratory scale to the industrial scale has been evaluated by searching the patent database, as well as the grant status of the patents, presented in the review. The prospective industrial applications of the technique, as well as the current limitations that restrict the scaling up of the laboratory-scale protocol, have been discussed in the review.

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

1. Introduction

The process of forming microparticles, including microspheres, microcapsules, and microbeads with a size ranging from 1–1000 μm, represents an essential feature of modern drug delivery systems as well as the development of functional materials [1]. The multiparticulate drug delivery system has several advantages, especially with regard to the controlled release of active pharmaceutical ingredients (APIs) as well as the improvement of the bioavailability of poorly soluble APIs. In addition, the system is effective in the masking of undesirable tastes as well as the protection of APIs from early degradation by the environment. An important difference in the release of microspheres and microcapsules is generally attributed to the internal structure of these microparticles. The microparticles is a matrix system, while the microcapsule is a reservoir system with a well-defined

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core–shell structure [2]. The method of microparticle preparation is an important aspect that determines the final physicochemical properties of the drug delivery system (Figure 1), as it has a direct influence on the size, porosity, surface charge, and the efficiency of the drug delivery system. Although the conventional method of pan coating is appropriate for macroscopic particles, the requirement for precision in modern drug therapy, as well as food science, has prompted the pharmaceutical as well as the food industry to explore innovative approaches, including the application of microfluidics as well as supercritical fluids [3]. The modern approach utilizes various physicochemical phenomena, including coacervation, thermodynamic phase separation, as well as the application of supercritical fluids, which facilitate rapid mass transport [4]. The chemical structure and inherent properties of the drug compound play an important role in the viability of the particular approach for drug synthesis. Lipophilic compounds, as well as water-soluble peptides, differ markedly in terms of the processing environment required for drug synthesis. As an example, the high-temperature processing environment that is characteristic of the spray-drying approach is not suitable for proteins, as they are highly susceptible to thermal degradation. Furthermore, the organic solvent approach faces major challenges in terms of the denaturation of proteins and the formation of toxic residues [5]. Currently, the development in the industry faces an important challenge in terms of the scalability of the approach, as the precision that microfluidics affords in terms of the size and shape of the drug particles is not easily scalable, as it would require the development of solutions that would exceed the capacity of the spray-drying approach. The present review article offers an exhaustive review of the sixteen basic methods that are currently being adopted by researchers in the field of microparticulate drug delivery systems. The present review would be an important contribution to the field, as it would provide an understanding of the intricate relationships that exist in the development of drug delivery systems.

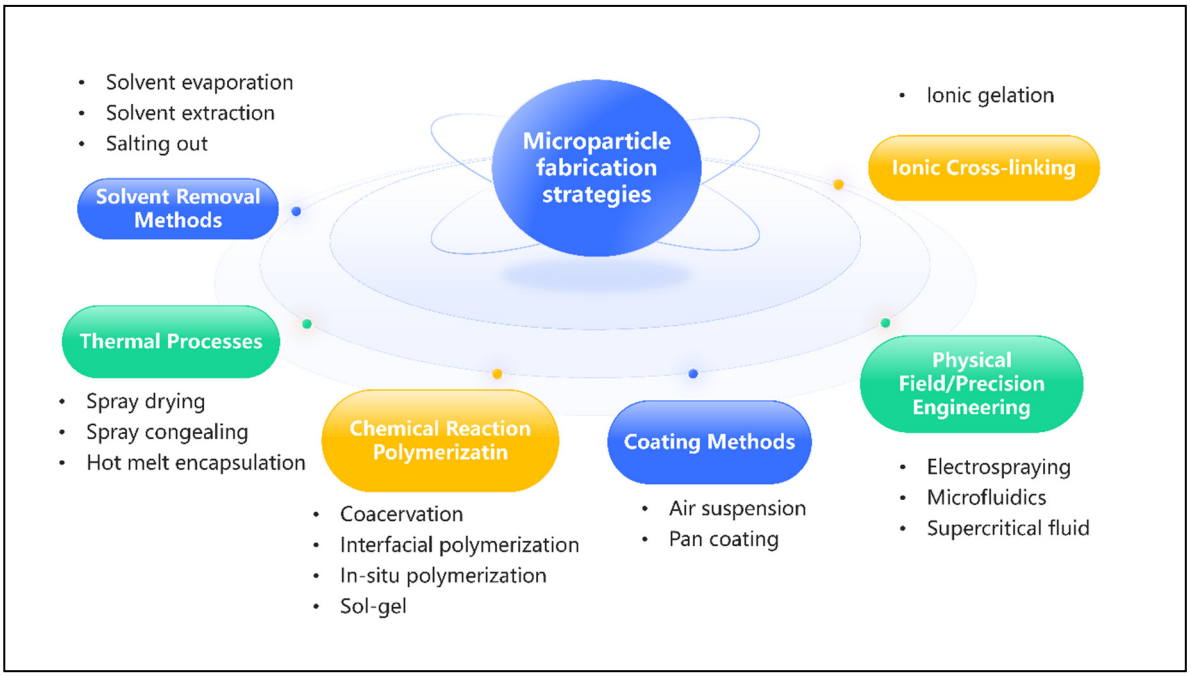

Figure 1. Classification and mechanisms of microparticle fabrication methods.

2. Method of Microparticle Preparation

2.1. Solvent Evaporation

The solvent evaporation method is the major technique used in the production of biodegradable polymeric microparticles in the pharmaceutical industry. The method involves emulsifying an organic solution of the polymer containing an active pharmaceutical ingredient into an immiscible

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continuous liquid phase (Figure 2). The evaporation of the solvent from the emulsion droplets results in the precipitation of the polymer, thereby entrapping the active ingredient in a solid form. The technique is an intricate combination of emulsification and mass transfer, which occurs in two different stages that are sequential in nature. The first step in the solvent evaporation method is the dissolution of the biodegradable polymer, usually poly(lactic-co-glycolic acid) [PLGA], along with the active pharmaceutical ingredient, in an organic solvent, which is usually dichloromethane [DCM] [6]. The solution is then emulsified into an aqueous solution that contains a stabilizer, usually polyvinyl alcohol, which helps in the formation of droplets of the solution [7]. The size of the particles is determined by the size of the droplets that are formed, which is controlled by emulsification shear forces as well as the reduction of interfacial tension by the addition of surfactants. The second step in the solvent evaporation method is the stabilization of the droplets into solid particles. The evaporation of the solvent occurs when the solution is stirred, causing the solvent to diffuse from the droplet surface into the aqueous solution, which is followed by evaporation at the air–water surface. The extent of evaporation determines the structure of the particles that are produced, with fast evaporation, usually at high temperatures and low pressures, causing the rapid formation of the skin of the particles, which is highly porous, while slow evaporation causes the chains of the polymer to relax, forming a dense structure [8]. The solvent evaporation technique has been demonstrated to have considerable versatility in the engineering of microparticles based on the solubility of the drug, with two different approaches: the single emulsion (O/W) and the double emulsion (W/O/W) methods. In the case of hydrophobic drug substances with LogP > 2, the single emulsion technique is still the most suitable method, where the drug dissolves in the organic solution and is carried in with a high efficiency of encapsulation [17]. The use of the double-emulsion technique is important for the encapsulation of hydrophilic bioactive agents, such as proteins and peptides, in which the drug is emulsified in oil and then encapsulated in an outer aqueous phase containing a polymer matrix. This flexibility is possible with a variety of polymers, such as polylactic acid, poly(lactic-co-glycolic) acid, polycaprolactone, and different types of ethyl cellulose, using volatile solvents with low water solubility, such as dichloromethane, chloroform, and ethyl acetate. However, there are certain drawbacks in the use of the double emulsion technique in the microencapsulation of drug substances, such as the unwanted incorporation of hydrophilic substances in the outer phase, which may result in low efficiency of encapsulation. In addition, though the evaporation process is carried out at low temperatures, which is beneficial in preserving bioactive agents, there is considerable denaturation of sensitive bioactive agents during the emulsification process [9,10].

The molecular weight of polymers plays an important role in defining their mechanical properties and degradation rate. This property of polymers also affects the release of drug particles. When the molecular weight of polymers is high, it means that the chain length of the polymer is also high. This results in a more compact matrix, and hence, the diffusion of drug particles through this matrix is low. This, in turn, results in a delayed erosion of the matrix. This is because more hydrolysis of the polymer's ester bond is required for erosion. On the other hand, low molecular weight polymers contain more terminal carboxylic acid groups. This results in an autocatalytic degradation of the polymer. In addition, more stabilizer molecules remain unreacted. This results in an increased burst release of drug particles. In practice, pharmaceutical scientists use different combinations of polymers of varying molecular weights. This results in bimodal release of drug particles. In this way, it is possible to predict the degradation rate of microparticles. This results in controlled erosion of the matrix [9,11–13].

The glass transition temperature (Tg), as a thermodynamic property, plays a significant role in determining the physical state of the polymer matrix, with this temperature marking the boundary beyond which the polymer is in a rubbery rather than a glassy state. In pharmaceutical microparticles, this temperature should be significantly greater than that at storage as well as 37°C, which is the physiological temperature. If storage temperature is close to or exceeds Tg, then polymer chains will possess sufficient kinetic energy to enable segmental motion, thereby leading to pore structure collapse as well as coalescence of individual particles. As a consequence, physical stability is

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compromised, with premature migration of the drug to the surface of individual particles, thereby affecting drug release kinetics. The molecular weight of the polymer is known to play a significant role in determining this temperature, with increased molecular weight being associated with increased values of Tg owing to reduced free volume as well as increased entanglements. In terms of formulation, as a general rule, solvents as well as stabilizers can act as plasticizers, effectively reducing Tg by increasing the distance between polymer chains as well as facilitating molecular mobility at temperatures below Tg. In this context, as lipophilic drugs are encapsulated within microparticles, they can act as plasticizers, thereby necessitating that the polymer be in a glassy state throughout the shelf life of the product to prevent "cold flow" as well as ensure that microparticles possess their desired morphology as well as degradation rate [14–16].

The concentration of the surfactant/stabilizer in the continuous phase of the aqueous solution is one of the main factors that can be controlled to modulate the final microparticles' characteristics in terms of their size and surface properties. In other words, the main role of the stabilizer, most often in the form of polyvinyl alcohol (PVA) and tweens, is to adsorb at the oil/water interface and thereby reduce the interfacial tension between two non-miscible liquids. This reduction in interfacial tension directly translates into a lower mechanical energy requirement to reduce the oil droplets in the solution to their final sizes. In other words, there is a direct correlation between the concentration of the surfactant and the reduction in the mean diameter of the microparticles, which continues until a critical point is reached. However, the main purpose of the presence of the surfactant is not only to reduce the microparticles' sizes but also to prevent their coalescence during the evaporation of the volatile solvent, which is essential to have a monodisperse population. However, the main challenge in the design of such drug delivery systems is that there is a plateau effect, which means that if the concentration of the surfactant is increased beyond a certain point, the solution may become more viscous, which may hinder the process and result in the formation of a thick film on the surface of the microparticles. This film is not only a result of the manufacturing process but is also an essential part of the microparticles' characteristics that can change their zeta potential and affect their degradation rate [17–19]. The degree and extent of the residual stabilizer also play an important role in the initial burst effect, wherein the rate of drug release tends to be much higher than desired, almost immediately after coming into contact with the medium in which it is intended to dissolve. If the amount of polyvinyl alcohol present as a residue on the surface of the drug particle is quite high, it may provide an interface that allows water molecules to penetrate the drug matrix quite readily, thus accelerating the rate of dissolution of the drug molecules present in the periphery of the drug particle. On the other hand, if the washing process is too vigorous, it may cause the drug microbead to fracture or even coalesce, thus compromising the integrity of the drug release interface, as the stabilizers that provide the structure to the drug matrix may be washed off in the process. From the point of view of designing drug delivery systems, it must be understood that the interaction of the stabilizer with the drug molecules plays an important role in the release characteristics, as it may either plasticize the drug matrix or provide an interface that prevents the migration of drug molecules, and hence, the importance of carefully designing the chemistry of the drug interface through the removal of the stabilizer must be understood as an important tool in the design of drug delivery systems that minimize the burst effect in drug release [20]. The removal of any trace stabilizers, such as PVA, is an important step in microparticulate engineering because it creates a persistent network with the polymer matrix on the surface of the microparticle. The removal of PVA is achieved by repeated washing cycles using deionized water or a buffer solution, which are then subjected to high-speed centrifugation or cross-flow filtration. When PVA is particularly embedded in the microparticle, chilled water or specific solvent/water mixtures are used, which can disrupt the hydrogen bonds that bind PVA to the surface of the microparticle. The presence of PVA in microparticles is not merely a chemical concern, as it has profound effects on the biological identity of the microparticle. The presence of a thick PVA layer on the surface of microparticles can have a "stealth" effect, potentially prolonging circulation time, but it can also inhibit cellular uptake by preventing direct contact between the polymer matrix and the cellular membrane. PVA presence has been known to inhibit

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microparticle uptake into negatively charged cellular membranes, as it tends to make the surface of the microparticle zeta neutral, thus reducing electrostatic attraction. When considering the toxicology of microparticle formulation, PVA is generally considered safe, but the presence of PVA can lead to unintended inflammatory or toxic reactions depending on the route of administration. Thus, it is a requisite step in the development of pharmaceutical microparticles to validate the removal of these trace stabilizers using X-ray Photoelectron Spectroscopy (XPS) or Fourier Transform Infrared Spectroscopy (FTIR) [21–23]. Accurate determinations of the exact amount of the residual stabilizer, specifically the PVA content, are best done with highly accurate analytical techniques due to the high tendency of the stabilizer to form a permanent film on the polymeric surface. The analytical technique used is the iodine-boric acid assay is the reaction between the PVA and iodine in the presence of boric acid to form a blue-colored complex. The concentration of the complex can then be determined spectrophotometrically at wavelengths between 650 and 690 nm, and the PVA content calculated from the calibration curve [24]. Even though this analytical technique is relatively simple and inexpensive, the total amount of the PVA content in the supernatant or extracted solution can be determined using this assay. To obtain more accurate determinations of the surface components of the microparticle, the surface components are analyzed using the X-ray Photoelectron Spectroscopy (XPS) technique to obtain the elemental composition of the surface of the microparticle, which is within the depth range of 1–10 nm from the surface [25]. Since the PVA contains only carbon, hydrogen, and oxygen as its surface components, the same components are also found in the surface components of the biodegradable polymer matrix, such as the Poly(lactic-co-glycolic acid), the short name is PLGA or the Polycaprolactone (PCL). The binding energy shifts are used to identify the hydroxyl groups of the PVA from the hydroxyl groups of the polymer matrix. Fourier Transform Infrared Spectroscopy (FTIR) can also be used to monitor the hydroxyl groups by observing the change in the intensity of the hydroxyl stretching vibration at approximately 3300 cm^{-1} as the level of the residual stabilizer content changes [26].

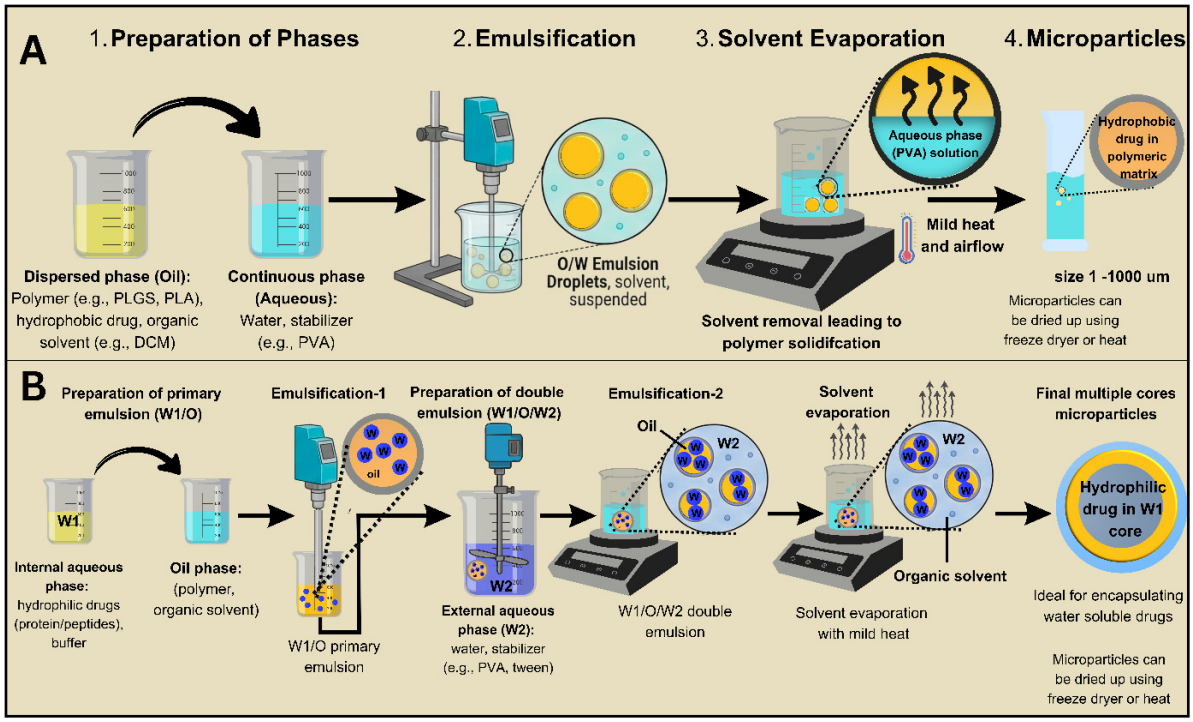

Figure 2. Illustration and practical steps for the preparation of microparticles using the solvent evaporation method. (A) single emulsion evaporation method, (B) double emulsion evaporation method.

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2.2. Solvent Extraction

Physico-chemical maturation of microparticles takes place mainly through two different mechanisms, namely solvent extraction and solvent evaporation. While solvent evaporation depends on the volatility of the solvent for it to be transformed from the liquid to the gaseous state, solvent extraction utilizes an extraction medium for the removal of the solvent from the dispersed droplets (Figure 3). The solvent extraction mechanism starts with the formation of an emulsion similar to that of solvent evaporation. However, instead of using vigorous stirring for solvent evaporation, the emulsion is added to an excess of an extraction medium. The choice of the solvent extraction medium is based on its ability to be miscible with the organic solvent and, at the same time, be immiscible with the polymer, thus creating a driving force for solidification. The rate of hardening of microparticles is controlled by the partition coefficient of the organic solvent. The solvent dissolves rapidly into the solvent extraction medium, resulting in an immediate supersaturation of polymers and their precipitation, thereby instantaneously forming the final microparticle structure [27,28]. This method has several advantages, especially when dealing with thermolabile compounds that may degrade at the temperatures that are often necessary for efficient evaporation. The rapid solidification of the microspheres is a much more efficient technique than the traditional methods, as the process is done within minutes as opposed to hours. However, this may cause some problems, as if the efflux of the solvent from the droplet is much faster than the rearrangement of the polymer chains, the material may become highly porous in structure. The most commonly used matrices in this technique are poly(lactic-co-glycolic) acid, polylactic acid, and polyhydroxybutyrate. In order to obtain the most efficient results, the solvents that are most commonly used have a moderate to high water solubility, such as isopropanol, acetone, and ethyl acetate, while the extraction medium is usually water, buffers, or a combination of water and alcohol. This technique is especially useful when dealing with highly unstable peptides and thermolabile drugs, as it minimizes the temperature exposure as well as the time of exposure to the organic solvent. Hydrophobic agents, in general, show considerable retention in the polymeric matrix, while hydrophilic agents may also be extracted into the extraction medium during the rapid mass transfer process, especially if they show some level of solubility in the washing solution [29,30]. The ratio of the volume of the extraction solution to the organic phase represents an important parameter that plays an important role in governing the kinetics of the process of solidification (Table 1). It plays an important role in the level of internal crystallinity and the surface texture of the formed microparticles. An excessively high ratio may induce the removal of the solvent in an almost instantaneous fashion, causing the polymer chains to precipitate in an irregular fashion, hence lowering the level of crystallinity, resulting in an amorphous structure. Though the amorphous structure may show an increased rate of solubility, it may also show an increased rate of degradation, hence an unpredictable drug-release profile. From the structural point of view, the ratio of the volume of the extraction solution to the organic phase represents an important parameter that determines the surface smoothness and the mechanical properties of the formed microparticles. If the rate of the process of extraction is too high, i.e., the ratio is too high, the outer layer of the droplet may be rendered rigid before the inner region of the droplet has sufficient time to shrink, hence buckling of the microparticles. However, the simultaneous rigidity of the outer and inner droplet regions, as controlled by the ratio, may allow the polymer chains sufficient time to relax, hence the formation of spherical particles with a smooth, non-porous surface [31,32]

Table 1. Comparison of extraction dynamics.

Parameter	High Extraction Ratio (Vext>>Vorg)	Moderate Extraction Ratio
Solidification Rate	Immediate / Quenched	Gradual / Controlled
Polymer State	Predominantly Amorphous	Increased Semi-crystallinity
Surface Morphology	Rough, Wrinkled, or Porous	Smooth and Spherical
Drug Retention	High risk of burst/leakage	Improved encapsulation for peptides

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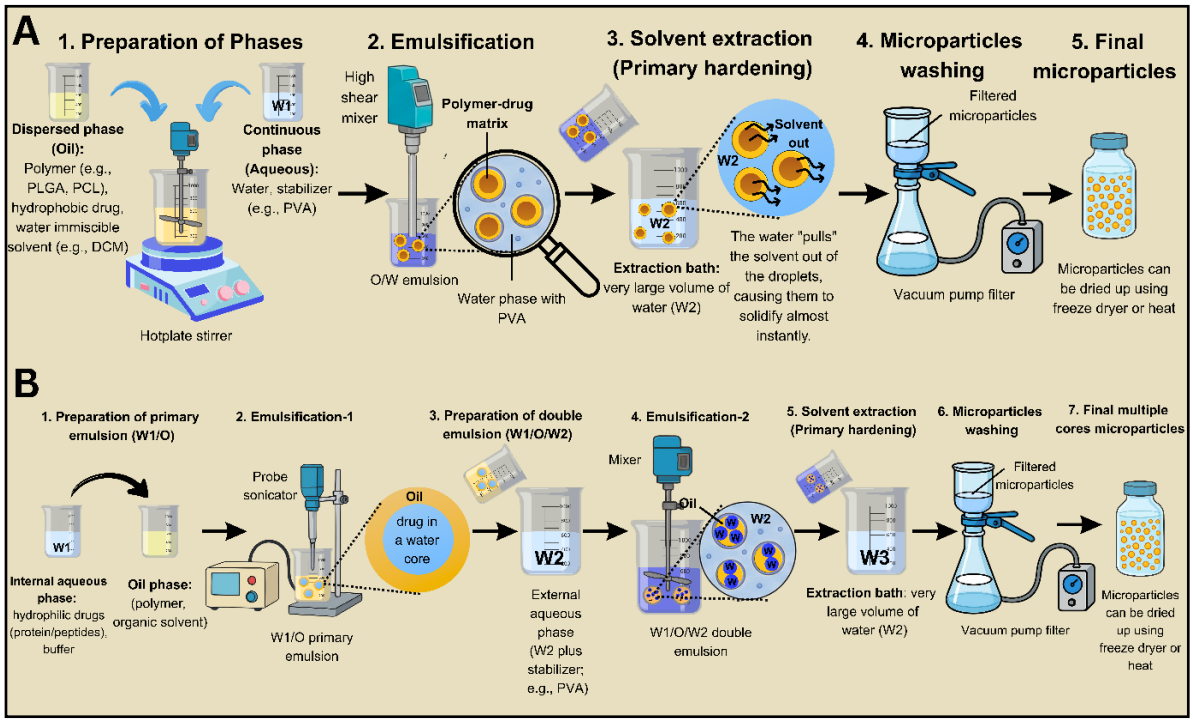

Figure 3. Illustration and practical steps for the preparation of microparticles using the solvent extraction method. (A) single emulsion extraction method, (B) double emulsion extraction method.

The optimization of this ratio is a fine balance between the speed of the process and the structural integrity of the particles. In the development of pharmaceuticals, the stepwise method of extraction is commonly used, whereby the emulsion is initially introduced into a smaller volume, which then starts the gentle hardening process, followed by the introduction of the larger volumes of the solution, which is used as an excess measure to complete the solvent removal process. This method ensures the spherical structure of the microparticles is maintained, while the final product is free of any traces of the organic solvent. With the optimization of the volumes of the solution, the microparticles may be designed with the specific surface area properties necessary for the delivery of the drugs [33,34].

The prevention of drug partitioning is a highly desirable goal in the extraction method; without intervention, hydrophilic drugs tend to partition into the external aqueous phase, leading to a significant reduction in encapsulation efficiency. The addition of specific types of salts, such as sodium chloride, magnesium sulfate, and ammonium sulfate, increases the ionic strength of the solution, causing the solubility of the organic solvent and the hydrophilic drugs in the water solution to decrease substantially. This is due to the interaction of the ions with the water molecules, forming hydration shells, which act as a squeezing effect on the drugs, causing them to go back into the organic polymer solution as the solvent is removed, thus increasing the efficiency of the extraction method, especially for the encapsulation of small peptides and hydrophilic drugs. In the case of the double emulsion system, the osmotic pressure can cause swelling and rupture of the internal aqueous droplets through the polymer shell, leading to loss of the payload. By balancing the osmotic pressure of the internal drug reservoir with the extraction medium, the stability of the emulsion can be achieved to prevent the rupture of the droplets. This is one of the key considerations in the design of the system to achieve the desired dense and non-porous shell to prevent the loss of the payload. Using these altered media, the pharmaceutical chemist can design microparticles with the advantage of rapid solvent extraction and high retention of the drug, as opposed to the slow processes of microparticle formation [35]. The choice of the electrolyte in the extraction medium is also a complex consideration that goes beyond the mere solubilization of the drug; this choice is largely dictated by the Hofmeister series (also called the lyotropic series), which ranks ions based on their capacity to stabilize or destabilize biological macromolecules. Kosmotropes are ions that are known to stabilize

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the hydrophobic effect and induce protein folding by improving the structure of water. On the contrary, chaotropic ions are undesirable, as they have the capacity for protein denaturation, which in turn results in molecular aggregations, thus affecting the efficiency of the microparticulate drug delivery system. While sodium chloride is commonly used for its biocompatibility and osmotic modulation, magnesium sulfate has been seen to show enhanced efficiency in double emulsions, as it counters the osmotic pressure, thus inhibiting the rupture of the microparticles. In terms of structural design, it has been observed that the concentrations of salts are critical, as, while a higher ionic strength has been seen to inhibit the partitioning of hydrophilic drugs into the external phase, excessive concentrations of salts can result in the precipitation of proteins or the alteration of the viscosity of the extraction media, thus affecting the surface topography of the microparticles. It has also been seen that these salts can result in alterations in the glass transition temperatures of the polymer matrices, thus necessitating a holistic formulation strategy in which the chemical environment of the extraction media is altered according to the requirements of the encapsulated biologic [36–38].

2.3. Coacervation (Phase Separation)

The colloidal mechanism of coacervation represents one of the most advanced phase separation techniques whereby a homogeneous solution of polymers separates into two distinct liquid phases, with one phase enriched with polymers and the other depleted of polymers. The process of coacervation typically involves three sequential steps initiated by the induction of phase separation through deliberate modifications of the equilibrium of the system. In the process of simple coacervation, the addition of a desolvating agent to the solution of polymers induces partial dehydration of the polymers, thus initiating phase separation of the polymers from the solvent (Figure 4) [35]. In complex coacervation, two or more polymers bearing opposite electrical charges to each other are used to induce phase separation by virtue of electrostatic attraction between them, as exemplified by the complex coacervation of gelatin and acacia gum [39]. From the perspective of designing a process based on the coacervation technique, the success of the process depends on the ability of the liquid coacervate phase to selectively adsorb onto the surface of the dispersed phase material. Since the adsorbed phase is liquid, the process of providing structural integrity to the adsorbed phase involves the crosslinking of the adsorbed phase to a solid form. Traditionally, glutaraldehyde has been used as the crosslinking agent of choice owing to its high reactivity and cost-effectiveness. However, the high level of cytotoxicity of glutaraldehyde and the need to adopt rigorous purification procedures to eliminate impurities in the reagent have prompted a strategic shift to biocompatible crosslinking reagents in modern pharmaceutical technology [40,41].

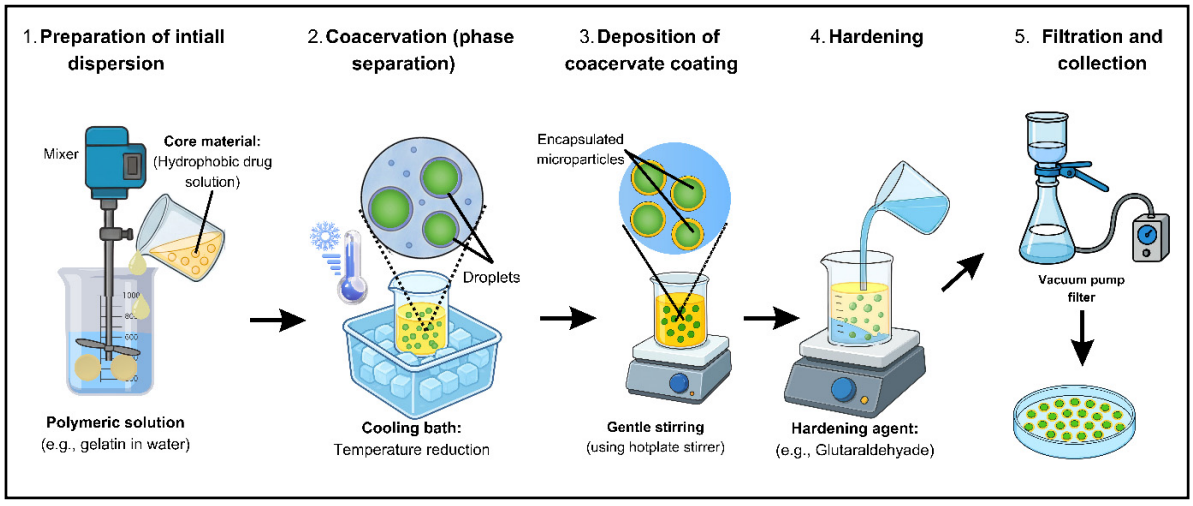

Figure 4. Illustration and practical steps for the preparation of microparticles using the coacervation method (separation method).

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Genipin, an iridoid glycoside found in Gardenia jasminoides, has been recognized as an important substitute that is claimed to be less cytotoxic than glutaraldehyde while retaining the structural integrity of protein matrices via nucleophilic attack of primary amine groups. However, the reaction is slower in nature and is typically required to be carried out over long periods of time [42,43]. Alternatively, microbial transglutaminase has been recognized as an important tool that is capable of providing excellent specificity via the formation of isopeptide bonds between glutamine and lysine residues at physiological conditions, thereby providing an important tool for the encapsulation of sensitive proteins and cells without the risk of chemical residue. In cases where pharmaceutical applications require mechanical strength without the risk of chemical residue in the matrix, the 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride and N-hydroxysuccinimide (EDC/NHS) system is recognized as an important tool that is capable of providing zero-length crosslinking reactions between carboxyl and amine functionalities. These developments have provided important solutions to the traditional drawbacks of the coacervation technique, which were based on the use of potentially toxic agents. However, the technique retains the unique ability to provide exceptional payloads, with coacervate structures often providing 90 percent core-to-wall ratios, which is substantially higher than that offered by emulsion-based methods [44,45]. By integrating these safer stabilization techniques, coacervation remains a premier methodology for the aqueous encapsulation of flavors, essential oils, and vitamins, as well as highly unstable peptides that require gentle processing conditions to avoid denaturation.

The ionic strength of the aqueous medium is considered to be one of the critical parameters in the design of the system that affects the thickness, density, and stability of the coacervate layer by controlling the Debye screening length between the charged polymer chains. As the electrostatic interactions are the driving force in the formation of the coacervate phase in the complex coacervation process, the addition of exogenous ions such as sodium or chloride can effectively attenuate the electrostatic attraction between the oppositely charged polymer chains. As a result of this screening effect at low to moderate values of the ionic strength, the coacervate phase can form more uniformly and flexibly due to the more gradual adsorption of the polymer droplets onto the core material [40]. However, at high values of the ionic strength beyond a critical limit, the electrostatic attraction between the polymer chains can be completely attenuated, resulting in the dissolution of the coacervate phase and the failure of the encapsulation process. The ionic strength also affects the degree of hydration of the polymers and hence the viscosity and surface tension of the coacervate droplets. It can result in the formation of a more “dilute” coacervate with increased water content at high values of the ionic strength, which can potentially result in the formation of a thinner and more porous shell by crosslinking the coacervate droplets. The accurate regulation of the concentration of the salts can facilitate the formation of a dense and highly protective shell that is essential for the sequestering of the volatile oils or vitamins. If the shell is not sufficiently crosslinked, the sudden change in the ionic environment can cause the microcapsules to swell or disintegrate prematurely. Therefore, the optimization of the ionic environment at the adsorption and crosslinking stages is considered to be the key factor in the development of microparticles with the necessary mechanical robustness to withstand the biological fluids [46]. The effectiveness of complex coacervation for microparticle fabrication is critically dependent on the precise control of the solution’s ionic strength, as it is a parameter that controls the Debye screening length, i.e., the range within which electrostatic attraction is operative. The ideal formation of microparticles of good quality, along with a stable shell, is typically achieved at an ionic strength within a range of 1-20 mM. At such low concentrations, the Debye screening length is relatively extended, i.e., within a range of 2-10 nm. This allows oppositely charged polymers to interact through the aqueous environment, resulting in the formation of a dense coacervate shell. On the other hand, increasing the concentration of ions results in increased screening, causing the Debye screening length to collapse into sub-nanometer dimensions. This attenuates the electrostatic interaction between polymers, hindering their separation and causing the dissolution of microparticles. Therefore, it is critical to maintain a low concentration of ions during fabrication to prevent droplet dissociation [47].

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The timing of the electrolyte addition during the course of the coacervation procedure represents a methodological parameter for controlling the porosity and diffusional properties of the microcapsule shells. The addition of a salt solution during the adsorption phase acts as a desolvating agent to disrupt the packing of the polymer chains, resulting in a coacervate phase with high hydration and a loose molecular structure. This leads to the formation of a porous structure for the shells, which is favorable for drug delivery applications where the drug needs to be released quickly or for the encapsulation of large molecules, where the drug needs to diffuse through the capsule walls within a specific timeframe. On the other hand, the maintenance of low ionic strength during the adsorption phase favors the formation of a dense polymer shell driven by electrostatic interactions. The subsequent addition of the electrolyte solution after the establishment of a liquid film around the core material triggers an 'ionic quenching' effect on the chemical potential, resulting in the rapid dehydration and contraction of the polymer network. This effectively collapses the existing void spaces and forms an extremely dense and nonporous shell. This method is favorable for the encapsulation of volatile compounds and small hydrophilic molecules, where a low burst effect and a high retention effect are required. By controlling the timing of the ionic strength variations, researchers can design the mesh size of the polymer network according to the specific requirements for drug delivery [48,49].

2.4. Spray Drying

As a highly efficient and continuous operation, spray drying can be used to transform the liquid feedstock directly into the desired dry powdered form by atomizing the liquid feedstock within the hot drying medium. The exact mechanisms of the operation are based on extremely rapid kinetics of heat and mass transfer, which occur almost instantaneously as the droplets of the liquid come into contact with the hot drying medium (Figure 5). The operation commences with the atomization step, whereby the liquid feedstock is converted to fine droplets by the action of the rotary atomizer or the special nozzle, thus creating the high surface area necessary to facilitate the rapid evaporation of the solvent. An essential safety measure in the operation is the wet bulb effect, which guarantees that the temperature within the droplet remains significantly lower than the hot air or the stream of nitrogen used in the operation. This phenomenon assumes particular importance with respect to the maintenance of the integrity of the core material, although the exit temperature should always be monitored as it may still be sufficiently high to affect sensitive biological structures [50,51].

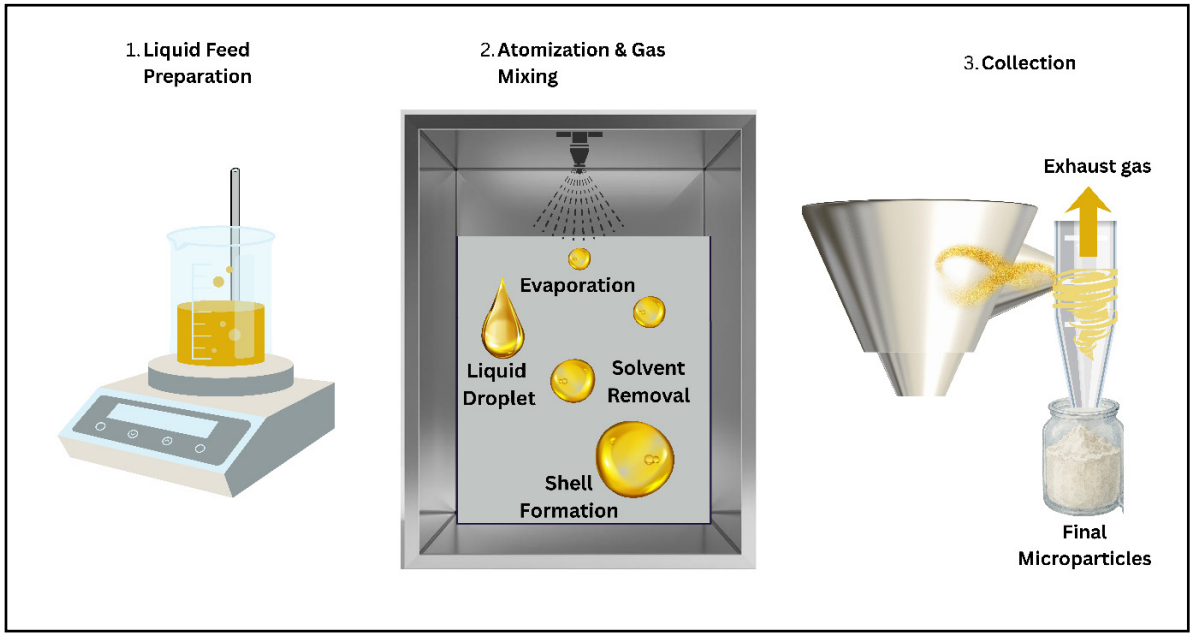

Figure 5. Illustration and practical steps for the preparation of microparticles using the spray drying method.

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From an engineering perspective, the one-step process of the spray drying system provides several advantages over batch processes, such as lyophilization, with respect to economic viability and industrial applicability. The system may be designed to produce particles of particular characteristics by controlling the critical process variables such as the temperature of the hot air supplied to the drying chamber, the exit temperature, the rate of flow of the feedstock, and the pressure of the compressed air used. By optimizing these variables in conjunction with the selection of the wall materials such as maltodextrin, gum arabic, modified starches, chitosan, and synthetic polymers such as hydroxypropyl methyl cellulose (HPMC) and polyvinyl pyrrolidone (PVP), the particles may be engineered to achieve particular density, moisture content, and aerodynamic diameter. One of the most important applications of this technique in modern pharmaceutics involves the formulation of drugs classified as BCS Class II by employing amorphous solid dispersions (ASDs), whereby the high rate of evaporation serves to “fix” the drug molecules in a polymer matrix, thus inhibiting recrystallization and maximizing the bioavailability of the drug by virtue of the high energy state of the amorphous form. In addition, the microparticle structure may be engineered by employing multi-fluid nozzles to achieve hollow particles [52,53]. The spray drying technique is a robust method for producing free-flowing microparticles. However, when this technique is employed in a laboratory setting, several issues are often encountered, including agglomeration of material on chamber walls, resulting in suboptimal product recovery. This is often related to the sticky point or Glass Transition Temperature (Tg) of excipients. When the temperature of the product is above the Glass Transition Temperature, it transforms from a glassy to a rubbery form, causing agglomeration on the inner walls of the dryer. Although the wet bulb effect provides a degree of thermal insulation for the droplet core, it is also possible for proteins of interest to be denatured due to mechanical stresses and shear forces, especially when using a high-pressure atomization system. Although spray drying is a more continuous and high-throughput method for protein delivery compared to lyophilization, which is currently regarded as the gold standard for thermolabile macromolecules, it is not capable of completely avoiding thermal stresses. This is because, unlike lyophilization, which sublimates at subzero temperatures under a vacuum, spray drying requires heating of the product. Although lyophilization results in a "cake" product, which requires additional processing to obtain the free-flow properties of spray-dried powders, it is currently regarded as the method of choice for thermostable macromolecules [54,55]. From a particle design point of view, spray drying allows for improved control over aerodynamic properties, thus enabling the design of "large porous particles" or hollow spheres. The design of such particles is particularly important for deep lung delivery, a feature that is difficult to achieve using the irregular and angular flakes obtained by milling freeze-dried cakes. In addition, regarding the issue of stability, it has been noted that spray-dried microparticles have a more continuous and dense crust compared to the surface of the product obtained by lyophilization, thus offering a more effective barrier against moisture and oxygen. Nevertheless, it must be noted that the high energy required by the spray drying method leads to a considerable shear stress, thus potentially denaturing macromolecules at the surface of the droplets. This issue is avoided by the static conditions of a freeze dryer. In conclusion, the choice of either of the two processes depends on the required particle design and the sensitivity of the active agent to energy [56–58].

2.5. Spray Congealing (Spray Cooling)

Spray congealing, also known as spray cooling, is an advanced hybrid process characterized by atomization and a process of solidification by thermal phase transition rather than solvent evaporation. This technique involves the dispersion of an active pharmaceutical ingredient in a molten matrix of lipids, waxes, and fatty acids. This molten mixture is then atomized into a cold gas chamber with a temperature below the melting point of the system. As a result of rapid solidification of droplets passing through the cold gas stream, an active pharmaceutical ingredient is encapsulated in a stable lipid matrix (Figure 6). From an environmental point of view, pray congealing is seen to be an example of green technology by avoiding the use of organic solvents and their recovery process.

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Additionally, spray congealing is an energy-efficient process due to the low latent heat of solidification of lipid-based systems compared to the latent heat of vaporization of aqueous and organic solvents. As a result of these two factors, spray congealing is seen to be a powerful and green alternative for pharmaceutical microparticles [59,60]. The key factor that influences the feasibility of the manufacturing process as well as the kinetics of drug release, is the choice of the lipidic or wax-based excipient. The excipients of choice are natural waves, including carnauba wax and beeswax, fatty acids, including stearic acid, as well as specific lipids, including glyceryl behenate, along with low-melting-point hydrophilic polymers, including polyethylene glycol (PEG). The choice of these naturally hydrophobic excipients offers excellent protection to the drug, as they form a robust barrier against environmental degradation of the drug substance, which is sensitive to moisture. Although this method is most suitable for lipophilic drugs that have excellent compatibility with the molten excipient, the method has also been useful for the encapsulation of hydrophilic drugs. The active ingredient, in this case, is processed to remain suspended in the molten excipient before atomization, resulting in a solid dispersion that is capable of controlling the release of the drug substance, which is soluble in water [61,62]. Although these systems offer a number of advantages, the complex nature of the polymorphism of lipids still represents a key factor in the development of these systems. When lipids initially solidify, they tend to form metastable crystalline structures, which can be in the form of the alpha (α) or beta-prime (β') polymorphs, which have a somewhat open molecular arrangement. However, over time or with increased temperature, these crystalline structures naturally convert to a thermodynamically stable beta (β) form, which can result in a contraction of the crystal structure, causing the drug to be expelled from the lipid particle, significantly changing the drug's dissolution profile and storage stability. In order to counteract this, crystal growth modifiers, which can be in the form of lecithin, sorbitan esters, or polyoxyethylene compounds, are added to the melt, which can help maintain metastable states and control the drug's release profile [63]. Additionally, while spray congealing represents a process that tends to be less stressful on the system in comparison with spray drying, the API must still be stable at the melting point of the carrier, which can be in the range of 40-90 degrees Celsius. In the case of highly thermostable biopharmaceuticals, the use of narrow-range, low-melting-point lipids in combination with surfactant stabilization must be used in order to maintain molecular integrity without compromising physical stability [62]. The cooling rate in the spray congealing chamber is a critical process parameter that plays a significant role in influencing the polymorphic character of the lipid matrix. The droplets are quenched when they come into contact with a substantial temperature gradient. This quenching action arrests the lipid chains in their metastable alpha polymorph. Although the alpha polymorph is known for accommodating higher levels of drugs, it facilitates accelerated release due to its lower packing density, it is also thermodynamically unstable and prone to unpredictable transformations during storage. On the other hand, a slower cooling rate allows time for lipid molecule arrangement into their more stable beta crystalline polymorph. The cooling rate is often optimized for attaining a stable polymorphic character before packaging, as it is of paramount importance. This is because, during the transition from alpha polymorphs, there is an increase in crystallinity, causing contraction of the lipid lattice, which physically displaces the drugs onto the surface, causing an unwanted burst release [63]. To address the inherent instabilities associated with metastable states of the crystal lattice structure formed as a result of rapid cooling, a routine tempering or annealing procedure is utilized as a critical post-manufacturing step of the spray congealing method. The procedure involves the maintenance of the temperature of the microparticles within a range of the alpha-to-beta transition temperature and the melting point of the carrier to provide the necessary activation energy to the lipid molecule to achieve a thermodynamically stable crystal lattice structure. By intentionally inducing this lattice structure transition, the pharmaceutical scientist is able to achieve the desirable effect of inhibiting the spontaneous expulsion of active pharmaceutical ingredients from the lipid matrix, a phenomenon referred to as syneresis, which is a common occurrence during storage. Furthermore, this controlled transition ensures the prevention of an unpredictable burst effect and ensures a consistent release kinetics profile along the shelf life of the product. The efficacy of the annealing procedure relies on a

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fine balance whereby the temperature must be sufficiently high to induce motion within the lipid chains while being well below the melting point of the carrier to avoid the possibility of fusion of the particles or loss of spherical shape. Hence, the incorporation of a dedicated annealing procedure, often in the presence of crystal growth modifiers such as surfactants, presents a viable approach to ensuring the physical and chemical stability of lipid-based drug delivery systems [64,65].

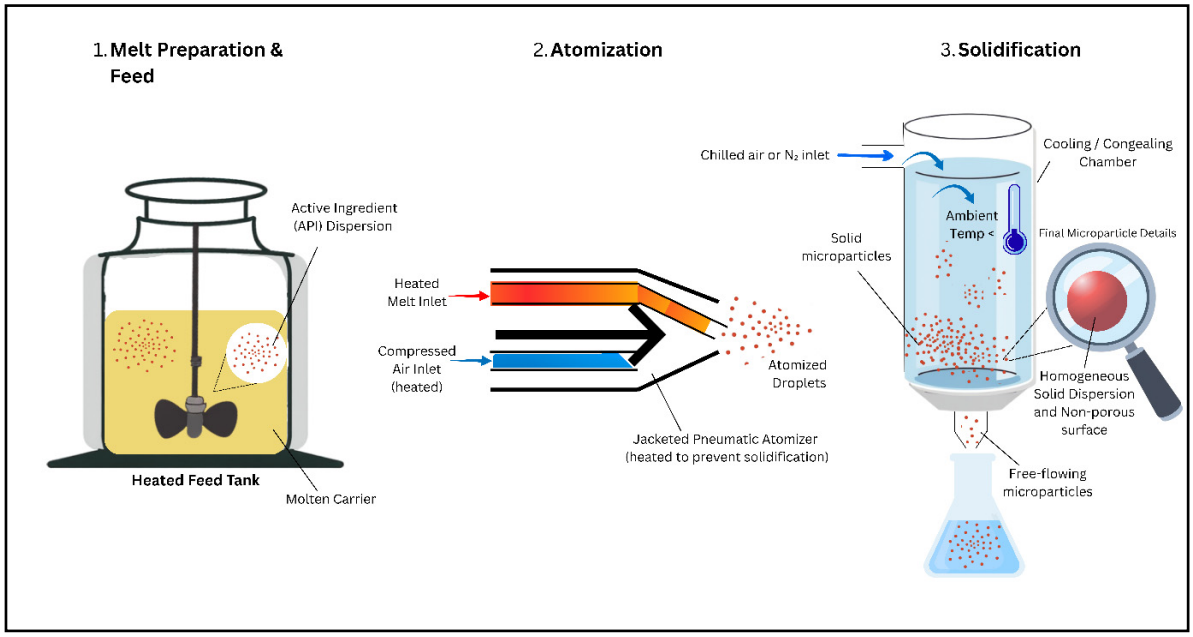

Figure 6. Illustration and practical steps for the preparation of microparticles using the spray congealing (spray cooling) method.

With precise control over the pressure of atomization and the temperature of the cooling gas, pharmaceutical scientists can design microparticles with a crystalline fingerprint, thereby ensuring a balance between process efficiency and product stability. A detailed understanding of the phenomenon of polymorphism in lipid-based microparticles is a must, with a growing emphasis on the combined use of Differential Scanning Calorimetry (DSC) and X-ray Diffraction (XRD) for the characterization of these materials. In the case of microparticles, DSC can be used to detect the heat flow in the process of phase change, thereby generating a thermogram where the peaks represent the melting points of different polymorphs of a drug substance. Since the metastable alpha form of a drug substance tends to have a lower melting point and enthalpy than the stable beta form, this technique can be used as a key tool for monitoring the changes in the crystals over a period of time. XRD, on the other hand, can be used for ascertaining the long-range molecular arrangement in a crystalline solid by measuring the scattering angle and intensity of X-rays, which in turn gives a fingerprint for the structure of a drug substance. For example, in the case of the metastable alpha form, a broad peak can be observed at a d-value of 4.2 Å, while in the case of the stable beta form, sharp, characteristic peaks are observed at 4.6 Å and 3.8 Å, respectively. With the use of Hot Stage Microscopy (HSM) or Fourier Transform Infrared Spectroscopy (FTIR) in combination with these techniques, a comprehensive understanding of the physical form of a drug substance can be achieved [63,66].

2.6. Ionic Gelation

The ionic gelation technique is a highly versatile and biocompatible approach to microparticle preparation, characterized by the creation of robust hydrogel networks through the electrostatic cross-linking of aqueous polyelectrolyte solutions in fully water-based environments. This technique is mainly based on the principle of the interaction of a polyelectrolyte with a multivalent counterion,

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thus avoiding the need for organic solvents and thermal activation. Sodium alginate is a typical example of this technique. As a linear polysaccharide composed of 1,4-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) blocks, sodium Alginate is known for its rapid phase transition when exposed to divalent cations [67]. The fundamental characteristics of the ionic gelation method for microparticle fabrication can be described based on the egg-box model, which explains the mechanism of interaction of calcium ions with the cavities formed by the cooperative alignment of G-blocks in alginate polymers. This results in a three-dimensional zone of stable interlocking of polymers. Due to the maintenance of physiologic conditions during cross-linking, this method is widely regarded as the gold standard for encapsulation of labile biological entities, including viable cells, drugs, and DNA. The physical characteristics of microparticles fabricated using this method are characterized by an inherent porous hydrogel matrix. Although this facilitates the easy diffusion of oxygen and nutrient requirements for encapsulated viable cells, it often leads to a significant burst effect of small, soluble drugs, which can easily diffuse through the hydrogel matrix (Figure 7). Furthermore, the stability of these microparticles is highly dependent on their chemical environment, as they can be destabilized in the presence of phosphate or citrate ions, which are known for their calcium-sequestering properties [68,69].

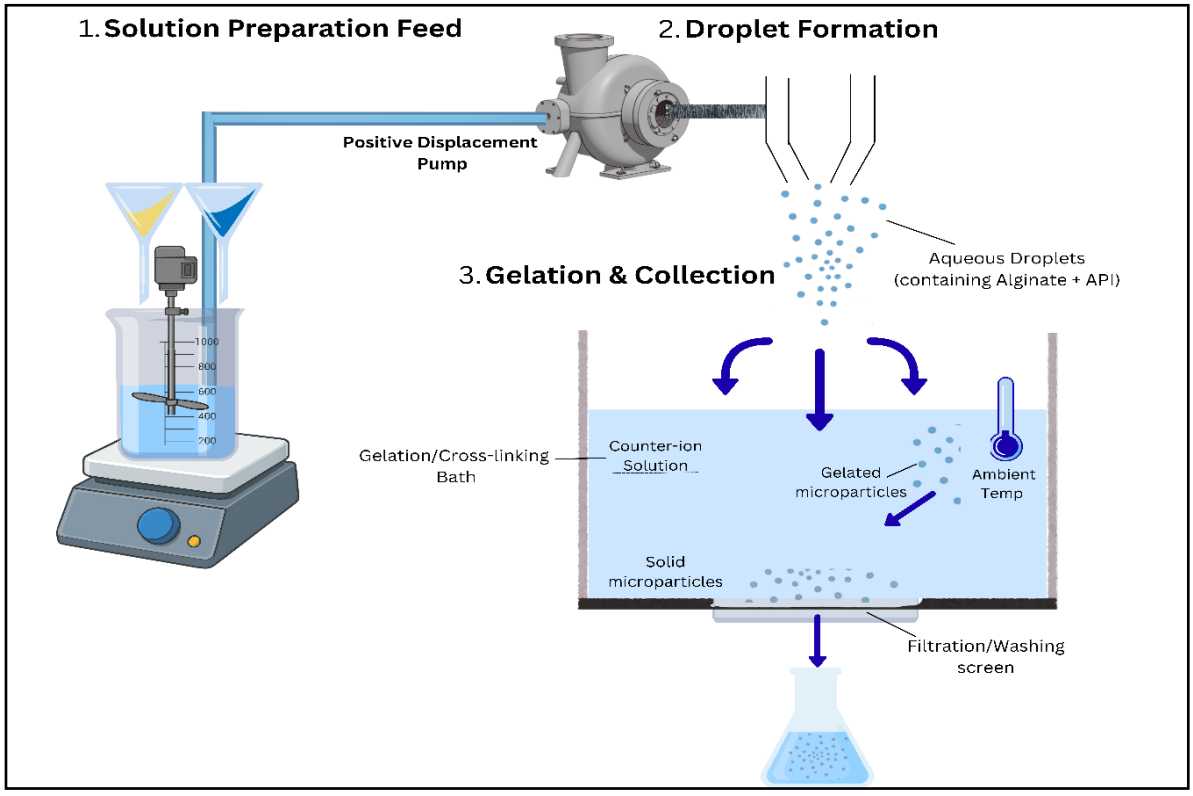

Figure 7. Illustration and practical steps for the preparation of microparticles using the ionic gelation method.

To circumvent the inherent disadvantages of the method, such as high porosity and burst release, a layer-by-layer (LbL) coating technique involving polycations such as poly-L-lysine or chitosan is often utilized. This technique leads to a semi-permeable polyelectrolyte complex membrane, which greatly improves the mechanical properties and decreases the mesh size of the gel network. The choice of polymers is mainly governed by the electrostatic properties of the drug-polymer complex [70]. Anionic polymers, such as alginate, pectin, and carboxymethylcellulose gel through a divalent cation such as calcium chloride, while cationic polymers, such as chitosan, are cross-linked by a polyanionic compound such as sodium tripolyphosphate (TPP). In this case, the charge of the active pharmaceutical ingredient plays a vital role. The method works well only for hydrophilic drugs, but can be extended to hydrophobic compounds by initially forming an oil-in-

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water (O/W) emulsion. The degradation rate and release characteristics of the formed micro-particles can be precisely controlled by varying the concentrations of polymers and cations, as well as the incubation time [71].

The choice between internal and external gelation represents one of the most important strategic decisions in the design of microparticles, particularly about the homogeneity of the gel network and the accuracy of the size distribution of the particles. For the case of the external gelation method, the droplets of the polyelectrolyte are generally added to the solution containing the cations that induce the gelation reaction. The reaction starts on the surface of the droplets and extends to the center, creating a heterogeneous core-shell structure with a greater density of cross-links on the surface of the particles. Although this method is simple, the droplets may be distorted during the process at high speeds, and bubbles may be trapped on the surface, causing heterogeneities in the structure [72]. Internal gelation, also known as in situ gelation, uses the aforementioned cations, now in the form of calcium carbonate, which are initially distributed in the solution of the polymers. The pH level of the solution is then reduced gradually, typically by the action of the slowly reacting acidifier glucono-delta-lactone, causing the cations to be released simultaneously throughout the volume of the solution. The result is the formation of a highly homogeneous internal structure with excellent sphericity. Internal gelation is generally preferred for the formation of micrometer-sized particles by the method of emulsification, whereas the external method is generally restricted to the formation of large-sized particles by the method of dripping. The homogeneity of the structure is particularly important for injectable systems to avoid clogging of the needles and to ensure the degradation rate of the drug is consistent. The slower rate of reaction also allows for the alignment of the polymer chains, thereby increasing the mechanical strength of the beads and creating a more efficient barrier against the burst release of the drugs [73,74].

2.7. Interfacial Polymerization

Interfacial Polymerization is a robust chemical method for microencapsulation, which facilitates the in situ formation of a polymeric membrane between two immiscible liquids. This chemical method is based on a polycondensation reaction between two bifunctional monomers in separate phases, usually an organic oil phase and a continuous aqueous phase (Figure 8). A typical example is a diisocyanate-based monomer in the oil phase and a diamine-based monomer in the aqueous phase. When they are mixed, they spontaneously travel to the interface, where they rapidly react to produce an insoluble polyurea or polyamide membrane. One of the most interesting aspects of this chemical method is that, due to the barrier effect of the membrane, the rate of monomers traveling towards the reaction interface is reduced, thereby providing precise control over the membrane thickness and uniformity. This chemical method is highly effective for protecting volatile liquids, such as oily drugs, essential oils, and pesticides, from degradation caused by environmental factors or oxidation. This is due to the exceptional mechanical strength and thermal stability of the resultant microcapsules [75]. Despite the engineering benefits that interfacial polymerization provides for the development of pharmaceutical formulations, the practical utility of this approach is greatly hampered by the toxicological profiles that are inherent to the isocyanate and acid chloride monomers that are used during the process. For the development of injectable or oral formulations that are safe for human use, a series of exhaustive washing cycles must be employed to remove any residual monomers that may have been left behind during the polymerization process. During this approach, the active pharmaceutical ingredient (API) that is encapsulated must remain completely inert to both monomers that are used during the polymerization process. Therefore, this approach is not considered to be particularly useful for the development of formulations that contain sensitive biological structures or protein-based carriers, due to the high likelihood that denaturation may occur during the course of the process. In order to ensure that the best possible therapeutic response is obtained, it is essential that the molar ratios of monomers that are used during the process are carefully calibrated to determine the interfacial tension that is required for the development of a particular particle size with a particular permeability characteristic [76,77].

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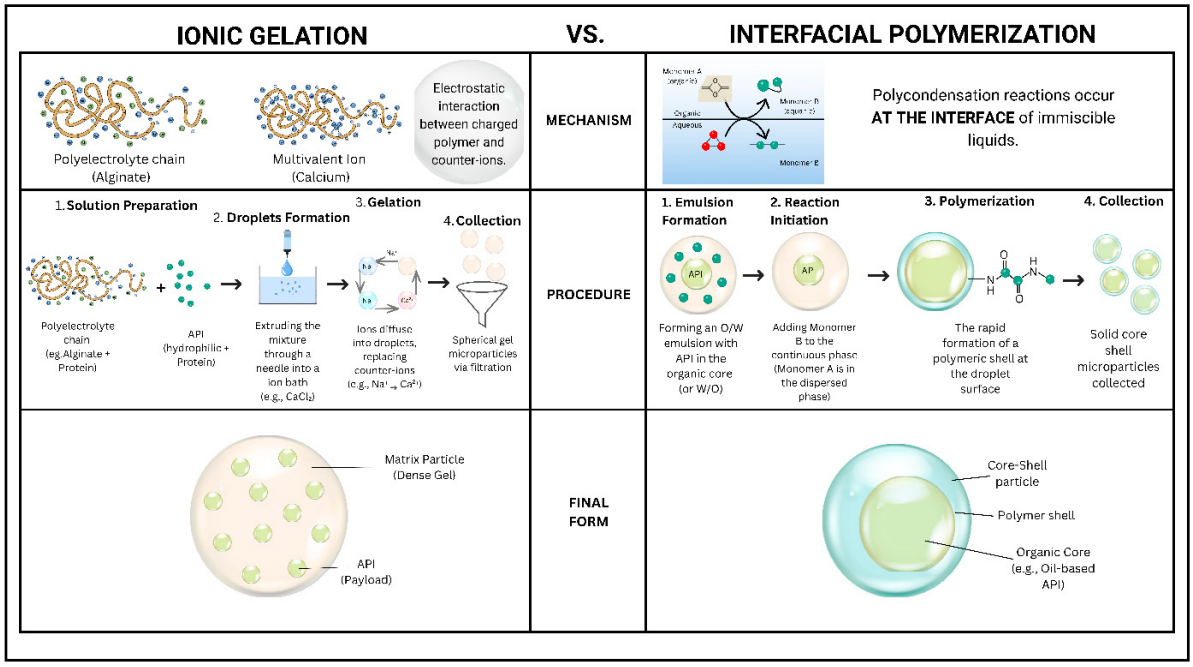

Figure 8. Illustration and practical steps for the difference of the microparticle preparation methods between interfacial polymerization and ionic gelation.

2.8. Air Suspension (Wurster Coating)

The air suspension technique, also known as the Wurster coating or the bottom spray fluidized bed coating, is one of the major techniques employed in the development of reservoir-type microparticulate systems as opposed to monolithic matrix-type systems. This advanced technology involves the suspension of the core particles in a high-velocity upward airstream, which generates a cyclic motion that exposes each and every particle to the coating substance uniformly [78]. The heart of the system is the Wurster insert, which is a partition that creates a high-energy upward air zone where the particles are accelerated and passed through the spray of the coating solution or suspension. As the particles exit the top of the insert, they are directed towards the expansion chamber where the air speed is low enough to allow the evaporation of the solvent and the solidification of the coating before the particles drop down to the base of the chamber to begin the process all over again. This uniform film coating is achieved with great accuracy by the air suspension technique, which is not possible with other techniques of encapsulation [79].

Air suspension coating, with special emphasis on the Wurster bottom spray technique, presents a highly precise methodology for the production of complex, multilayered microparticles through sequential application of functional polymers (Figure 9). Commonly used materials include methacrylic acid copolymers (Eudragit, etc.), ethyl cellulose, hydroxypropyl methylcellulose (HPMC), and shellac for the control of the release profile. By carefully controlling key process parameters, such as the pressure of the atomizing air, temperature of the fluidizing air, and spray rate, the porosity and mechanical properties of the applied polymer film can be accurately controlled. In order to maintain the integrity of the applied polymer film and prevent cracking during the evaporation process, plasticizers are often added to the polymer formulation in order to decrease the glass transition temperature of the polymer. Due to the physical nature of the process, a high degree of versatility can be achieved, making the process largely independent of the lipophilicity/hydrophilicity of the drug substance [80]. However, the success of the process also highly depends on the physical properties of the drug core, which must be present as a hard crystal, granule, or pellet, capable of withstanding the mechanical stress and high-energy collisions within the fluid bed process. Although primarily used for the production of microparticles from solids, liquid drug substances can also be processed, provided they are adsorbed onto mesoporous

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materials. Ultimately, the interplay between the mechanical robustness of the drug core and the interfacial properties of the polymer film enables the production of high-performance microparticles, specifically designed for a variety of applications, from targeted delivery systems to taste masking formulations [81]. The manner in which the spraying is carried out, i.e., top, bottom (Wurster), and tangential, has been identified as a key factor that influences the efficacy of the coating process, the quality of the resulting film, and the likelihood of agglomeration of the coated particles. Top-spray, although the most common method of granulation, has been noted to be less effective in the process of microencapsulation, as the downward motion of the spray in opposition to the upward motion of the hot air leads to spray drying, resulting in the formation of a porous and non-adherent membrane. On the other hand, the bottom-spray method, also known as the Wurster method, has been established as the gold standard in the process of micro-coating, as the spraying nozzle is placed at the bottom of the chamber, allowing the droplets to be sprayed concurrently with the direction of the fluidizing air, thereby greatly reducing the distance that the droplets have to travel before impact, which ensures that the liquid coating remains in the liquid state upon impact, thereby resulting in the formation of a dense and functional membrane (Table 2). However, this method requires that the rate of spray be carefully calibrated to prevent the formation of wet masses, which are non-functional agglomerations. The tangential spray method, also known as the rotary method, involves the use of the high shear force generated by the rotation of the disc at the bottom of the chamber, which is particularly useful in the coating of dense materials, as this method can counteract the adhesive forces that cause agglomeration in high-moisture environments [82].

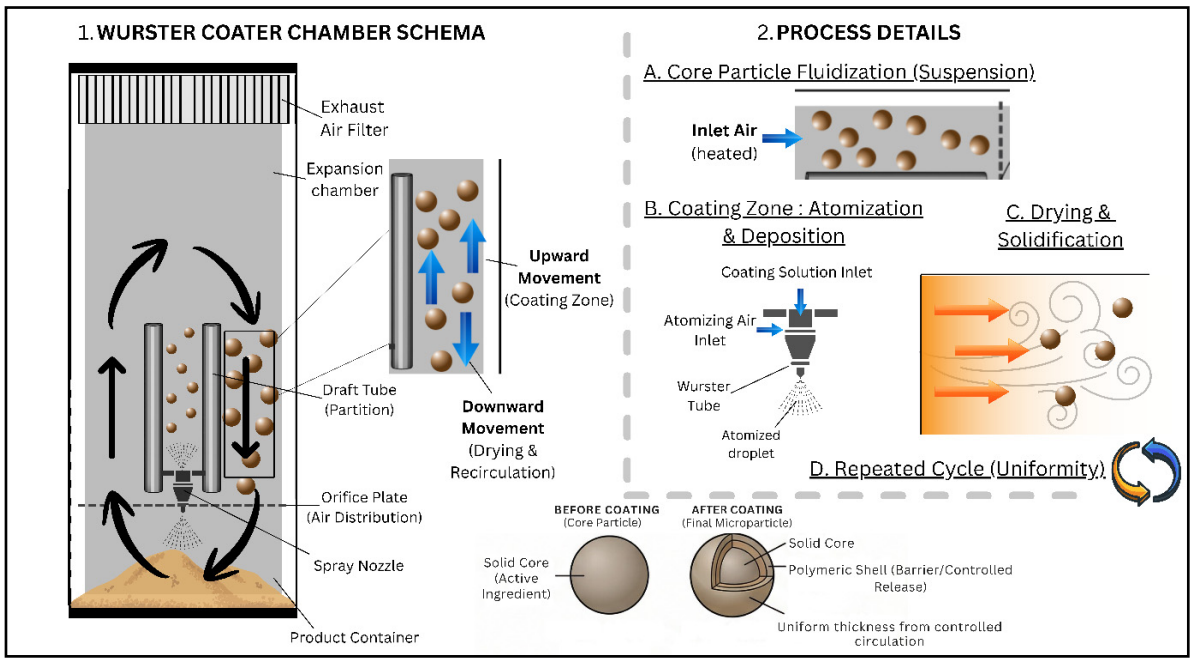

Figure 9. Illustration and practical steps for the preparation of microparticles using air suspension (Wurster coating).

Table 2. Comparison of Top Spray, Bottom Spray (Wurster), and Tangential Spray Methods in Fluid Bed Systems.

Feature	Top Spray	Bottom Spray (Wurster)	Tangential (Rotary)
Primary Application	Granulation / Hot Melt	Precision Micro-coating	Coating of Dense Pellets
Film Quality	Porous / Less Uniform	Dense / Highly Uniform	High Density / Uniform
Agglomeration Risk	Low	Moderate (Requires tuning)	Low (Due to high shear)
Drying Rate	Very High	Controlled	High
Particle Size Range	Medium to Large	Wide (Small to Large)	Large / Heavy Pellets

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2.9. Pan Coating

Pan coating is an established method for the application of a functional or cosmetic coat to larger substrates such as tablets, beads, and pellets. This method involves the rhythmic tumbling motion of the particles within a rotating vessel, which may be a conventional spinning pan or a perforated one. During this process, the substrates are subjected to a flow of atomized liquid droplets while a concurrent flow of hot air assists the evaporation of the solvent [83]. Although the pan coating method is preferred for its mechanical simplicity and high capacity for handling large quantities, it is subject to certain limitations from a physical point of view for the application in the field of microparticle engineering (Figure 10). This method is not applicable for substrates smaller than 500 micrometers in size owing to the high surface area to volume ratio of the substrates, which leads to a high degree of agglomeration upon the addition of a liquid binder. In addition, the material should have sufficient mechanical strength to withstand the high weight and the abrasive action of the substrates during the coating process. This method is therefore only applicable for the application of a functional coat to substrates such as granules and pellets, as the powders comprising the active pharmaceutical ingredient would not have sufficient strength to resist the forces of attrition and fragmentation [84].

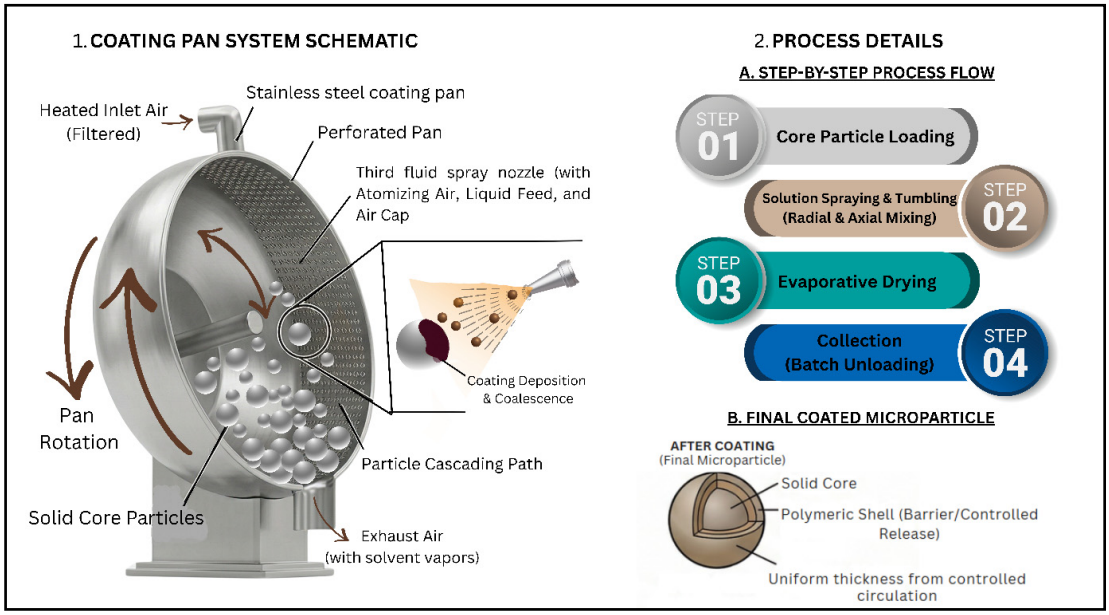

Figure 10. Illustration and practical steps for the preparation of microparticles using the pan coating method.

The development of coating media formulation techniques has grown from traditional sugar coating based on sucrose to modern-day film coating techniques using synthetic polymers like hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), and acrylic acid resins. Even though the pan coating technique offers flexibility with regard to the solubility of active ingredients, there is a lack of heat transfer efficiency with this method compared to air suspension coating. It is critical to control air temperature with regard to thermolabile active ingredients to avoid degradation. However, there is a heat-energy constraint with this method, leading to concerns about active ingredient stability due to residual moisture. To improve on these drawbacks of pan coating, modern pharmaceutical engineering techniques utilize perforated pans to ensure maximum air flow through the bed of particles. This ensures rapid evaporation of the solvent and uniform coating of active ingredients with control agents like enteric and sustained-release coatings, even on high surface area materials [84,85]. Equilibrium of pan rotation speeds and spray atomization pressure plays a crucial role as a pivotal point of control of the stochastic phenomenon of twinning, a defect of manufacture whereby two or more pellets are united by a permanent bridge of polymer. Deficient rotation speeds cannot provide the required kinetic energy to overcome the adhesive forces of the liquid film. This leads to stagnant areas where particles come into prolonged contact and become bonded as they solidify. On the other hand, higher rotation speeds reduce twinning but can

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lead to attrition of friable core materials. In addition, atomization pressure must be controlled to regulate droplet size and rate of wetting. Although high pressure ensures a fine droplet size, allowing for near-instantaneous solvent and subsequent film formation, it can result in a dry spray, causing a porous and irregular film. The incorporation of anti-tacking agents such as talc or glyceryl monostearate further prevents adhesion of particles, allowing higher spray rates without compromising reservoir integrity. The transition from traditional non-perforated pans to perforated pans such as the Accela Cota has greatly altered the dynamics of the drying kinetics. In traditional non-perforated pans, air flow is only over the surface of the tumbling bed, resulting in a humid dead area within the core of the bed. This area can accelerate the hydrolysis of moisture-sensitive active ingredients. The perforated drum design allows air to be drawn through the tumbling bed, greatly improving the efficiency of heat and mass transfer. This is particularly important for aqueous-based coating formulations, as it ensures minimal core area is exposed to moisture and maximizes throughput to produce a dense, uniform, and stable film, protecting the active ingredient from environmental degradation [86,87].

2.10. In-Situ Polymerization

In-situ polymerization is another chemical encapsulation process that differs from the interfacial method in that the material forming the shells is produced from monomers or prepolymers that are contained entirely within the continuous phase. This is in direct contrast with the interfacial method, which relies on the stoichiometric reaction of monomers that diffuse from two non-miscible phases. The process is usually carried out with an oil-in-water emulsion, with urea-formaldehyde or melamine-formaldehyde prepolymers being dissolved in the continuous phase (Figure 11). By precisely controlling the equilibrium of the system, usually through a reduction in pH (down to 2.0) and an increase in temperature, polycondensation is initiated (Figure 11). As the length of the developing polymers increases and reaches a critical molecular weight, they become insoluble and selectively deposit onto the oil droplets, eventually coalescing into a rigid, highly cross-linked amino resin shell. From an engineering point of view, the shells produced through this process are denser and smoother, thus providing a superior barrier for the diffusion of substances. However, the process is restricted in pharmaceutical and biological applications owing to safety and stability issues. The main problems are the potential for formaldehyde, a known carcinogen, to be present, the potential for degradation of active ingredients owing to the highly acidic conditions, and the thermal instability of sensitive active ingredients owing to the temperature conditions necessary for the process [88,89].

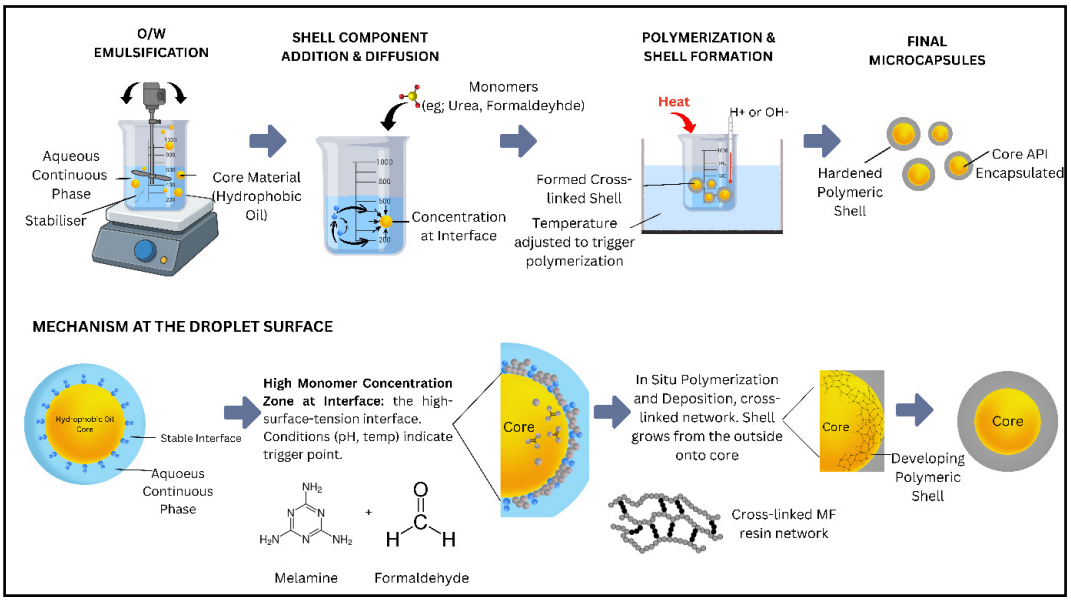

Figure 11. Illustration and practical steps for the preparation of microparticles using the In-situ polymerization method.

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Therefore, in-situ polymerization is best used for applications in fields such as fragrances, pesticides, and encapsulation of Phase Change Materials (PCMs), where the mechanical properties of polymers are given greater importance than their biocompatibility. However, for this methodology to be used for advanced pharmaceutical delivery systems, the active ingredient needs to be chemically inert towards aldehyde groups and stable even in highly acidic conditions. As a result, current research is focused on the design of formaldehyde-free amino resin systems that ensure chemical robustness without sacrificing biological safety. In this methodology, the concentration of the emulsifier is a critical factor that affects the reaction kinetics, having a substantial effect on the induction period as well as the lag time between the start of polycondensation and the subsequent deposition of polymers onto the oil-water interface. The role of the emulsifier, at a molecular level, is critical in providing anchoring sites where the pre-polymer chains come into contact with the stable interface, thereby initiating the formation of a uniform and dense shell [90]. In systems with high emulsifier concentration, a structured and ordered structure develops to act as a steric barrier to prepolymer chains during the initial period of induction. During this period, prepolymer chains need to reach a critical threshold of polymerization and hydrophobicity in the continuous phase before they gain the thermodynamic impetus to cross over the emulsifier layer and start to deposit on the interface of the oil droplet. Emulsifier concentration is the primary factor in determining the total surface area available for shell formation. An exponential decrease in oil droplet size is observed with an increase in emulsifier concentration. Consequently, if the total prepolymer content is kept constant, an increase in surface area results in a proportional decrease in final thickness of the shell. Hence, there is a need to calibrate the ratio of monomer to oil phase so that the final microcapsules possess adequate mechanical strength. The type of emulsifier used also impacts the rate of reaction (Table 3). Anionic emulsifiers like ethylene maleic anhydride (EMA) hasten the rate of shell formation by providing specific sites for hydrogen bonding with urea-formaldehyde prepolymers. This reduces the induction period. However, nonionic emulsifiers like polyvinyl alcohol (PVA) slow down the rate of formation and result in a porous shell. By carefully designing these surface properties, researchers aim to improve the thickness and density of the microcapsules to withstand industrial processing while maintaining the required permeability for therapeutic agents [91,92].

Table 3. Comparison of polymerization techniques for microencapsulation.

Parameter	Interfacial Polymerization	In Situ Polymerization
Monomer Location	Distributed in both phases	Exclusively in continuous phase
Shell Formation	Diffusion limited at interface	Deposition from continuous phase
Shell Characteristics	Thinner, potentially more porous	Denser, smoother, more rigid
Reaction Kinetics	Very rapid (seconds/minutes)	Slower, pH and temperature dependent
Common Polymers	Polyurea, Polyamide (Nylon)	Urea-Formaldehyde, Melamine-Formaldehyde
Typical Use Cases	Pesticides, carbonless paper	Fragrances, Phase Change Materials (PCMs)

2.11. Supercritical Fluid Technology (RESS, SAS, GAS)

Supercritical fluid (SCF) technology is an innovative and environmentally friendly area of pharmaceutical engineering, which utilizes the physicochemical properties of fluids in their supercritical states. Among all fluids, carbon dioxide (CO_2) is widely employed as a processing fluid because of its non-toxic, non-flammable characteristics, and favorable critical properties (T_c = 31.1°C, P_c = 7.38 MPa). The main advantage of using supercritical carbon dioxide (SC-CO_2) is its combination of liquid density and gaseous diffusivity, which can be easily adjusted using small changes in temperature or pressure. The Rapid Expansion of Supercritical Solutions (RESS) method involves dissolving a drug-polymer mixture in SC-CO_2, followed by depressurization of the fluid mixture using a special nozzle (Figure 12). The extremely supersaturated fluid mixture is forced to undergo rapid nucleation, resulting in ultrafine particles. The RESS method is, however, limited by the poor solubility of polar or high-molecular-weight compounds in SC-CO_2. To improve the solubility of these compounds, Supercritical Anti-Solvent (SAS) or Gas Anti-Solvent (GAS) methods are

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employed, in which CO2 is used as an "anti-solvent." In SAS, a drug-polymer mixture is dissolved in an organic solvent, which is subsequently atomized into an SC-CO2 environment. The fast diffusivity of both liquids facilitates fast precipitation of the drug-polymer mixture. The morphology of microparticles is, however, controlled by complex interfacial phenomena and mass transfer rates in the expansion chamber [93–95].

The use of the Particles from Gas Saturated Solutions (PGSS) method has been shown to be quite effective in processing thermostable biologics. The main advantage of PGSS is that, unlike RESS, in which the pharmaceutical substance must be soluble in supercritical carbon dioxide, PGSS takes advantage of the extensive solubility of carbon dioxide in a molten polymer or pharmaceutical substance. This serves as a powerful plasticizer, causing a significant reduction in the glass transition temperature and melt viscosity of the system. This method is thus capable of processing at temperatures well below those of the traditional melting point of excipients, which is a major advantage for preserving the integrity of thermolabile biologics. Although the cost of initial investment in equipment is quite high, it is worth noting that PGSS is quite cost-effective in the long term. The morphology of the microparticles can be precisely controlled by pharmaceutical scientists using PGSS, depending on the pressure and the ratio of carbon dioxide to product. This can be done to optimize the bioavailability of the final dosage form [96].

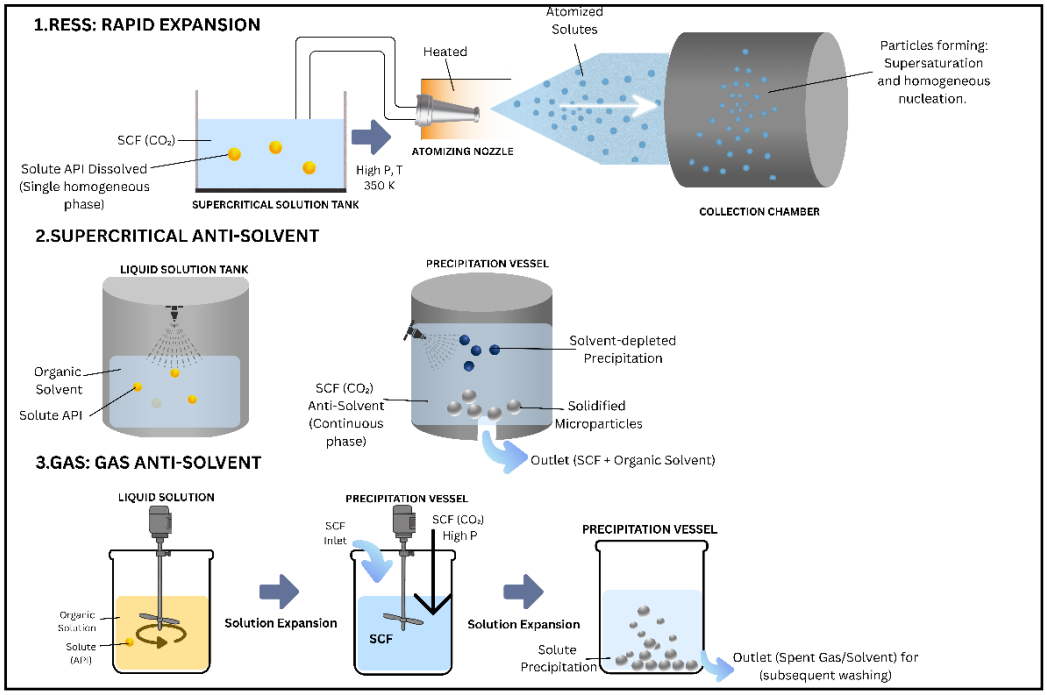

Figure 12. Illustration and practical steps for the supercritical fluid technology (RESS, SAS, GAS) in microparticle fabrication.

The addition of chemical modifiers such as ethanol or methanol to supercritical fluid systems is a sophisticated approach for overcoming the problem of the polarity gap that is inherent in using pure CO2 for SFE. The addition of a small percentage of a polar solvent enables the solvent to exhibit enhanced solvent strength through the ability to engage in specific intermolecular interactions such as hydrogen bonding. During SAS precipitation processes, chemical modifiers play a crucial role as a kinetic bridge that enables rapid mutual solubilization of polar peptides or proteins with very poor solubility in pure CO2 with the organic solvent phase. In addition to their use in overcoming the problem of poor solubility, chemical modifiers play a crucial role as a thermodynamic tool for the design of the internal structure of particles. By altering the critical point and the binodal/spinodal curves for the ternary system, the concentration of the chemical modifier may be adjusted to favor a transition from dense microspheres to highly porous particles with a very low density that are suitable for pulmonary delivery. Moreover, the use of a volatile chemical modifier may also accelerate

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nucleation kinetics to favor the formation of amorphous solid dispersions that may improve the dissolution rate of poor solubility compounds (Table 4). However, the use of chemical modifiers requires careful control to minimize the negative effect that high concentrations may have on the amount of residual solvent that may remain in the particles; therefore, longer purging times may be required to retain the solvent-free advantage that is unique to supercritical fluid precipitation processes. In addition, for biological compounds, the denaturation risk that may arise from the addition of chemical modifiers must also be carefully evaluated to retain the integrity of the protein's three-dimensional structure during the precipitation process [97,98].

Table 4. Summary of modifier effects on SAS processing.

Parameter	Effect of Increasing Modifier Conc.	Application
Solvent Power	Increases (especially for polar drugs)	Encapsulation of proteins/peptides.
Phase Boundary	Shifts the spinodal curve	Creating porous "puffed" particles.
Nucleation Rate	Increases (with volatile modifiers)	Formation of Amorphous Solid Dispersions.
Drying Time	Increases (requires more CO_2 purging)	Regulatory compliance (ICH guidelines).
API Stability	Risk of denaturation (with alcohols)	Biologic/Protein formulation.

2.12. Electrospraying

The technique of electrospraying, also known as electrohydrodynamic atomization (EHDA), is an accurate method of fabrication based on the utilization of electrical potential rather than mechanical stress to disrupt a polymer solution into uniform droplets. This process is mediated by an initial high voltage applied to a capillary nozzle, ranging between 10 and 30 kV. The presence of surface charges leads to a morphological change of the solution meniscium from a drop to a cone-like structure, termed a Taylor cone. A fine jet is then emitted from the apex of this structure and undergoes fragmentation into droplets by Coulomb stress. As these droplets move towards a grounded target plate, rapid evaporation of the solution results in microparticles with very narrow size distributions and high encapsulation efficiency (Figure 13). The efficiency of EHDA is mediated by a complex interplay between solution conductivity, viscosity, and surface tension. Lack of conductivity results in insufficient electrostatic stress to overcome surface tension and induce a Taylor cone. Excessive solution viscosity results in polymer chain entanglement and leads to fiber formation rather than droplets (termed electrospinning). Electrospraying of biocompatible polymers such as PLGA, PCL, and chitosan offers a 'cold' process for fabrication and is therefore suitable for encapsulating potent therapeutics and unstable biological entities such as DNA, enzymes, and cells without risk of thermal and mechanical denaturation [99,100].

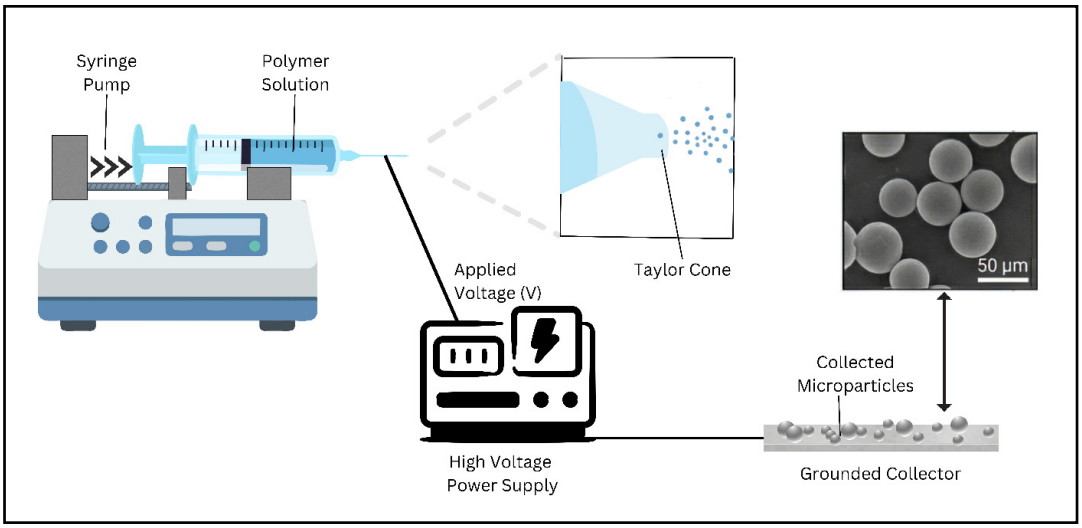

Figure 13. Illustration and practical steps for the electrospray method in microparticle fabrication.

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A major advantage of the transformative capability of the electrohydrodynamic atomization technique is its coaxial operation feature, whereby two immiscible liquids are simultaneously atomized to produce dual compartmentalized core-shell-type micro-particles. This feature enables the efficient encapsulation of hydrophilic drugs within a hydrophobic polymer carrier via a one-step solution-based approach, thus circumventing the difficulties and issues of drug leakage associated with traditional double emulsion-based approaches (Table 5). Despite its accuracy and precision, the major limitation of the electrospraying technique hindering its large-scale implementation is its low throughput capacity, typically measured at single-digit milliliters per hour flow rates per single nozzle. To bridge the gap between lab-scale fabrication and large-scale implementation, current research trends focus on employing multi-nozzle configurations (multiplexing) and needleless electrospray techniques. These high-throughput configurations are thus seen to enhance the large-scale fabrication of precision drug delivery systems with accurately controlled loading and release profiles, thus further establishing the importance of electrospraying as a fundamental component of future personalized medicine (Table 16) [101,102].

Table 5. Summary of electrospray modes.

Feature	Single-Phase	Coaxial (Core-Shell)
Morphology	Homogeneous Matrix	Reservoir (Core-Shell)
Drug Type	Lipophilic (usually)	Hydrophilic & Lipophilic
Burst Effect	Higher risk	Minimized
Complexity	Low	Moderate (Requires 2 pumps)
Scale-up	Multiplexing / Needleless	Primarily Multi-nozzle Arrays

In the precise engineering of the morphology of the resulting electrosprayed microparticles, the tip-to-collector distance and the feed flow rate are the critical parameters that govern the morphology, size, and solvent levels of the resulting microparticles. The tip-to-collector distance plays a critical role in determining the flight time of the droplets, and if this distance is insufficient, the solvent does not have sufficient time to fully evaporate, resulting in the coalescence of the droplets into a single liquid film upon impact with the collection plate. Conversely, if the distances are optimized, the resulting droplets are given sufficient time to reach the Rayleigh limit, where Coulomb fission is induced, resulting in the formation of dry, freely flowing powders upon collection (Table 6). The rate of the feed flow rate, on the other hand, determines the volume of the liquid that is supplied to the Taylor cone, and although low rates are desirable for the formation of ultra-fine, highly monodisperse microparticles, rates that are too high result in instabilities of the Taylor cone, thereby increasing the solvent levels per droplet. From the engineering and regulatory perspective, these parameters are also important in the determination of the environmental temperature and humidity to ensure ultra-low levels of solvent residue, particularly in injectable microparticles. In situations where ambient conditions are not conducive to the evaporation of the solvent, the use of auxiliary dryers and precise tip-to-collector distances is critical to maintaining the structural integrity of the resulting microparticles, thereby ensuring the glass transition temperature of the resulting matrix, which is critical to the reproducibility of the process (Table 7) [103,104].

Table 6. Troubleshooting electrospraying morphologies.

Observed Defect	Probable Underlying Cause	Strategic Remediation
Fiber Formation	Excessive polymer concentration or high solution viscosity preventing jet breakup.	Reduce polymer concentration; introduce a conductive co-solvent (e.g., ethanol); decrease feed flow rate.
Bead-on-String Structures	Viscoelastic forces competing with electrostatic repulsion; insufficient charge density.	Increase applied voltage; decrease polymer molecular weight or concentration; increase solution conductivity.

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Polydispersity/Multi-Jetting	Unstable Taylor cone due to excessive voltage or high flow rate.	Reduce voltage to the stable "single-jet" regime; decrease flow rate to ensure steady cone formation.
Particle Coalescence (Wetness)	Incomplete solvent evaporation before impacting the collector.	Increase tip-to-collector distance; utilize a more volatile solvent system; reduce humidity; increase ambient temperature.
Dripping/Poor Atomization	Insufficient electrostatic force to overcome surface tension; low solution conductivity.	Increase applied voltage; add a small amount of electrolyte (e.g., NaCl) to the solvent; decrease flow rate.

Table 7. Diagnostic tool, correlating defective formation with adjustments in the electrospray method of fabrication.

Defect Observed	Probable Cause	Recommended Engineering Adjustment
Wet Film/Coalescence	Short flight time; High flow rate; High humidity.	Increase tip-to-collector distance; Decrease flow rate; Increase drying temperature.
Fibers instead of Particles	High polymer concentration (entanglement).	Decrease polymer concentration; Increase conductivity (add salt).
Broad Size Distribution	Unstable Taylor cone; High flow rate.	Decrease flow rate; Adjust voltage to find "stable cone" window.
Hollow/Collapsed Particles	Rapid surface crust formation (skinning).	Use a less volatile solvent; Decrease inlet air temperature.
No Atomization (Dripping)	Low voltage; Insufficient conductivity.	Increase voltage; Add a conductive co-solvent (e.g., Ethanol).

The move towards a more "beaded fibers" approach, despite its benefits for tissue engineering, creates a significant risk for microparticle drug delivery systems. In such systems, fibers have a propensity to create an unforeseen burst release based on their increased surface area-to-volume ratio in relation to spherical particles. Solution conductivity is therefore a key consideration; increased conductivity enables a more precise atomization pattern through vigorous Coulomb fission; however, it also increases the risk for corona discharge. This occurs when the atmosphere is ionized, thereby eliminating surface charges that cause the Taylor cone to collapse. Maintaining a stable cone-jet mode is crucial for high encapsulation efficiency and drug loading consistency. Oscillations or pulsing in the cone cause significant changes in stoichiometry that create batch-to-batch variability. Real-time monitoring of the collector current using high-speed imaging is a crucial PAT for a high-performance environment to maintain the steady-state conditions necessary for high-performance microparticle drug delivery systems [105].

2.13. Microfluidics

Significantly, the field of microfluidics represents a paradigm shift in the production of microparticles, offering unprecedented control over the dynamics of fluids within channels with diameters in the range of 10-100 micrometers. In these regimes, the flow of fluids is predominantly laminar, with the absence of turbulence exploited for the production of droplets with high levels of monodispersity and reproducibility. Precise mechanisms for the production of droplets, particularly T-junction and flow focusing, form the architectural basis for the production of these microparticles. In these systems, a dispersed phase is compartmentalized into uniform droplets in response to a balance of forces, with viscous stress from the continuous phase causing deformation of the fluid interface, countered by interfacial tension, which seeks equilibrium in terms of minimum surface area, thereby leading to a regular process of droplet formation (Figure 14). Each of these droplets represents a highly controlled template for the production of the final microparticles, which are

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formed through a variety of downstream mechanisms, including polymerization, curing, and solvent extraction [106].

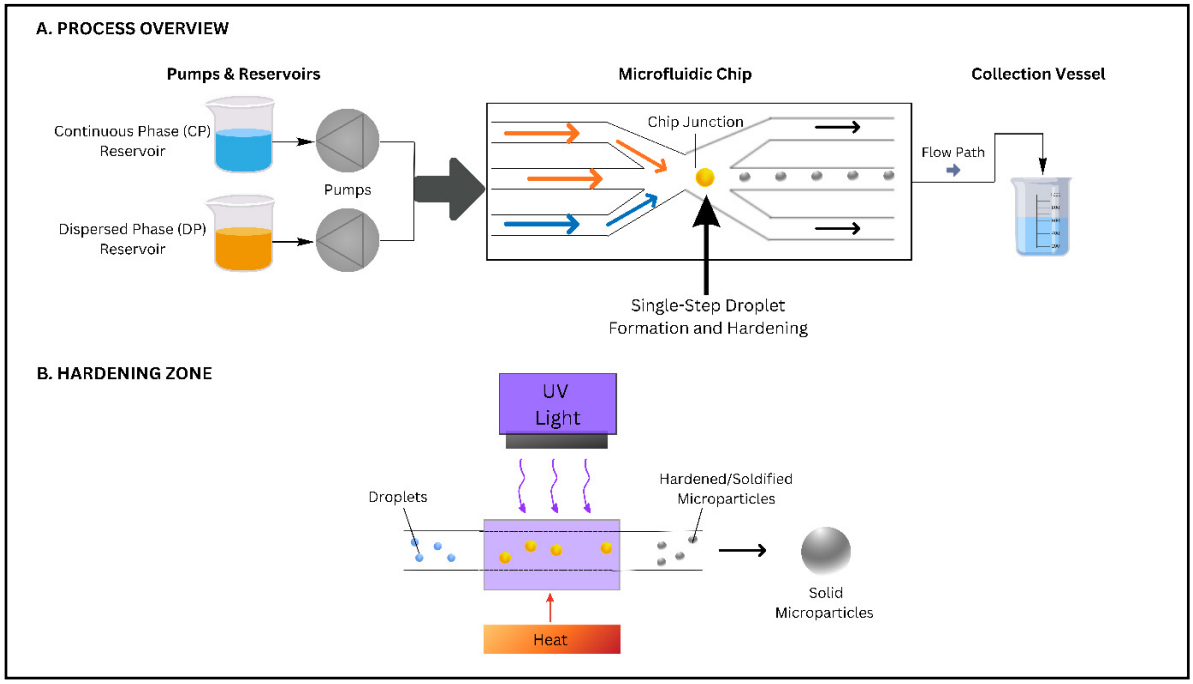

Figure 14. Illustration and practical steps for the microfluidics method in microparticle fabrication.

The main advantage of the microfluidic technique lies in its ability to produce microparticles with near-ideal monodispersity, as indicated by a coefficient of variation (CV) of 2% or less. This level of precision in particle size cannot be achieved with a bulk emulsification technique, which makes the technique highly suitable for high-value applications, particularly in instrument calibration and high-end drug delivery systems where the kinetics of drug release are strictly related to the surface area of the particle. In addition, the technique offers a high level of control in the production of complex particle morphologies, for example, core-shell or Janus particles, through the precise control of the convergence of multiple immiscible fluids. This high level of control, coupled with the mild shear conditions and chemically inert environment in the microchannel, makes the technique highly suitable for the encapsulation of sensitive biological materials, for example, cells and labile molecules. Although the production capacity of a single device is small, as indicated by a production rate in the milliliter/hour range, the technique of numbering up, where thousands of identical channels are used, presents a viable option for scaling up production for industrial purposes. In the production of microparticles, the design of the particle is dictated by fluid dynamics rather than the API; as a result, pharmaceutical scientists can easily switch from a dripping or a jetting regime through the control of fluid viscosity, interfacial tension, and flow rate ratios for the production of particles with a given morphology for a given therapeutic outcome [107,108].

2.14. Sol-Gel Process

The sol–gel process represents a sophisticated bottom-up approach for the synthesis of inorganic or organic inorganic hybrid microparticles, which is based on a series of hydrolysis and polycondensation steps of metal alkoxide-based precursors. When silicon-based alkoxides, such as tetraethyl orthosilicate (TEOS) or tetramethyl orthosilicate (TMOS), are used, the process starts with the hydrolysis of the alkoxide functional groups, leading to reactive silanol groups. These then react in a polycondensation process, allowing for a phase change from a colloidal suspension, or sol, to a rigid three-dimensional porous structure, or gel (Figure 15). This unique phase change enables the encapsulation of active pharmaceutical ingredients at the molecular level, i.e., by doping these

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molecules within a specifically designed 'inorganic cage.' Moreover, as the process occurs at mild reaction conditions, i.e., ambient temperature and near-neutral pH, the sol–gel approach can be particularly useful for encapsulating thermostable or chemically sensitive biomolecules, e.g., enzymes and other therapeutic proteins, in a way that preserves the functional conformation of these molecules (Table 8) [109].

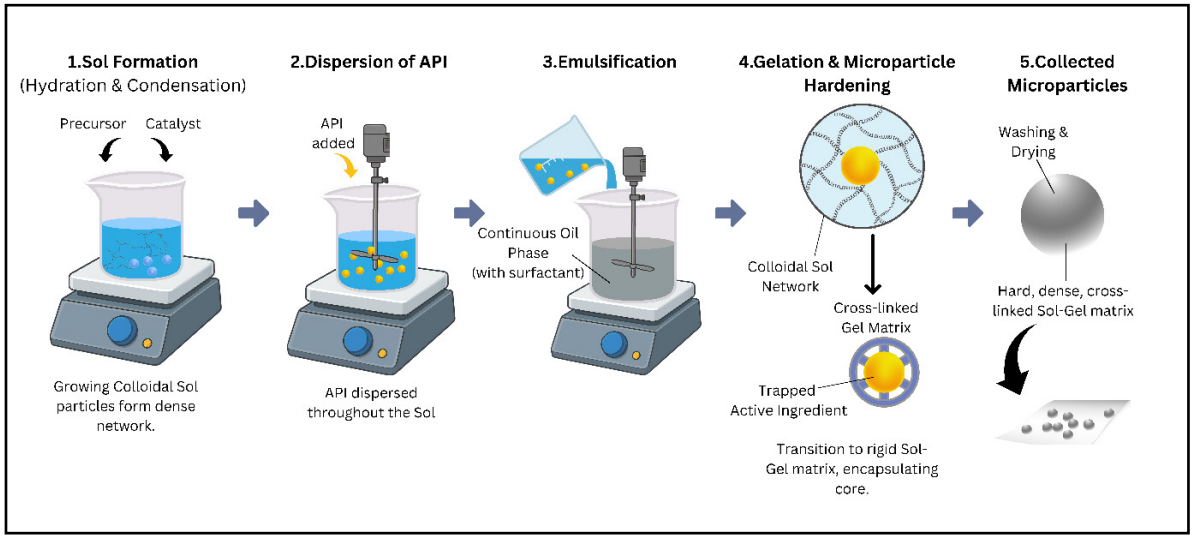

Figure 15. Illustration and practical steps for the sol gel process method in microparticle fabrication.

Table 8. The role of catalysis in sol-gel microparticles.

Catalyst Condition	Mechanism	Resulting Microparticle Structure
Acidic (pH < 2)	Rapid hydrolysis, slow condensation.	Produces linear, weakly branched chains; leads to dense, low-porosity microparticles.
Basic (pH > 7)	Slow hydrolysis, rapid condensation.	Produces highly branched, cluster-like structures; leads to highly porous microparticles.

Silica microparticles prepared by the sol-gel method have been shown to provide advantages related to their chemical inertness, mechanical strength, and architectural flexibility. By controlling the catalyst and water-to-precursor molar ratio, the pore size and specific surface area can be closely controlled to meet specific application needs. This "cage"-like structure protects the protein from the environment by maintaining the tertiary structure and reducing the degradation of volatile fragrances. However, the gel-to-xerogel drying step poses a challenge for engineers. This is primarily related to the high capillary stress-induced cracking and volume shrinkage during the evaporation step. Organic modifiers are added to improve the flexibility of the system by producing Organically Modified Silicates (ORMOSIL), which can be more closely controlled for drug delivery applications. From a biocompatibility point of view, one major disadvantage of this method is the production of alcohol by-products, such as ethanol and methanol, during the initial stages of the reaction. This can be problematic for drug delivery systems if not effectively removed through high dilution factors. Although the sol phase is inherently more compatible with hydrophilic drug delivery systems, lipophilic drug delivery systems require the use of surfactants. Using high-end drying equipment, such as supercritical drying equipment for the production of ultra-porous aerogels, researchers can design high-performance microparticles for a variety of drug delivery applications (Table 9) [110].

Table 9. Comparison: xerogels vs. aerogels.

Property	Xerogel (Ambient Drying)	Aerogel (Supercritical Drying)
Drying Method	Evaporation (High Capillary Stress)	Supercritical Extraction (Zero Capillary Stress)

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Porosity	15% – 50%	**90% – 99%**
Surface Area	300 – 600 m2/g	**600 – 1000+ m2/g**
Structure	Dense, Shrunken	"Frozen Smoke" (Original Gel Volume)
Common Use	Controlled Release / Coatings	**Inhalation / Ultra-lightweight Insulation**

The choice of catalysts in the sol-gel method is a critical kinetic parameter, which controls the morphology of the microparticulate material. In acidic media, i.e., at pH < 2, near the isoelectric point of silica, hydrolysis occurs at a much greater rate than condensation. This kinetically driven mechanism favors weakly branching, elongated polymeric chains, which intertwine to form a gel. The resulting matrix is characterized by a very high degree of structural continuity and extremely fine microporous characteristics, which are favorable for sustained, controlled release of small molecule drugs. However, during desolvation, these flexible chains pack closely, causing considerable volume shrinkage, resulting in a transparent, high-density xerogel. On the other hand, in a basic environment, condensation is the kinetically favored reaction. The silanols are rapidly consumed, forming highly branching, discrete clusters, which intertwine into a colloidal matrix. This mechanism favors a more heterogeneous, macroporous matrix, which is favorable for high drug loadings or for the entrapment of bulky macromolecules, since more efficient ingress and egress of drugs are possible through larger pore diameters. The larger pore radius of the matrix, characteristic of base-catalyzed systems, also helps in minimizing cracking during desolvation, although at the expense of reduced tensile strength of the matrix [110,111].

The significant role played by the catalyst in the microparticle architecture ensures that the release profiles can be controlled by adjusting the pH of the sol initially used in the process. This can be made evident with the use of a two-step acid-base catalysis, which can be used in the development of complex density gradients, as in microparticles with dense cores and porous shells. Aside from the morphological features, the pH of the system also determines the electrostatic nature of the silica surface, where, with a pH near 2.0 for silica, the surface will be negatively charged ($Si\text{-}O^-$). This ensures the ionic binding of positively charged drug molecules, making the inorganic-based system a sophisticated drug delivery vehicle for the drug, considering the pKa and pharmacokinetics of the drug in question. In acidic conditions, where the pH is less than 2.0, hydrolysis occurs, making the structure denser, with microporous networks having high continuity, while in basic conditions, rapid condensation occurs due to the deprotonation of the silanol group, making macroporous colloidal structures possible. Moreover, the use of fluoride anions, which are potent nucleophilic catalysts, ensures faster gelation due to the increase in the coordination number of the silicon atom, making a hybrid system with fast kinetics and mechanical properties a versatile system for the development of the next generation of high-performance drug delivery systems [112,113].

The choice of the catalyst represents a key design criterion in controlling the mechanical properties as well as the diffusion kinetics within the microparticle matrix. The intrinsic mechanical brittleness of acid-catalyzed gels, coupled with the propensity for particle fracture during the process of desolvation, can be ascribed primarily to the extremely high capillary pressure states within these highly refined microporous structures. In direct contrast, the lower density of base-catalyzed particles offers a significantly stronger mechanical framework, particularly for the encapsulation of large molecules such as enzymes and therapeutic proteins. The increased pore volumes within these colloidal networks facilitate unhindered molecular transport, thereby sustaining the requisite hydration states for biological activity. In understanding these structure-function relationships, scientists can then proceed to strategically choose the catalytic route, thereby ensuring that the silica matrix is precisely engineered for the intended clinical application (Table 10) [114,115].

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Table 10. Comparative influence of catalysts on silica microparticle properties.

Catalyst Type	Primary Mechanism	Network Morphology	Surface Area & Pore Volume	Mechanical Properties
Acidic (e.g., HCl)	Protonation of alkoxy groups	Linear, weakly branched chains	High surface area; low pore volume (microporous)	Highly brittle; glassy and transparent; high shrinkage
Basic (e.g., NH3)	Deprotonation of silanol groups	Branched, particulate clusters	Moderate surface area; high pore volume (meso/macroporous)	Less brittle; grainy or opaque; reduced shrinkage
Nucleophilic (e.g., F-)	Coordination expansion of Silicon	Rapidly cross linked hybrid structures	Variable; often yields high surface area with moderate volume	Increased toughness; rapid gelation; specialized for hybrid systems

The inherent brittleness of silica matrices is a critical challenge in designing effective drug delivery systems. This challenge is effectively addressed by synthesizing Organically Modified Silicates (ORMOSILs), where the cross-link density of silica matrices is reduced by incorporating non-hydrolyzable organic spacers. By incorporating organoalkoxysilane reagents, such as methyltrimethoxysilane and phenyltrimethoxysilane, into the sol-gel process, researchers have been able to introduce a degree of flexibility into the otherwise rigid silica framework. This structural modification helps to dissipate mechanical stress and arrest crack propagation due to high capillary pressures developed during desolvation. Moreover, this structural modification of silica matrices allows for molecular-level control of the microenvironment of the silica cage. By incorporating hydrophobic alkyl groups, researchers have been able to control the rate of water uptake to protect hydrophilic agents. From a molecular-level point of view, designing an effective drug delivery system involves choosing an appropriate pendant group. Although methyl groups provide basic flexibility to silica matrices, bulkier pendant groups like phenyl and vinyl groups introduce sterically hindered architectures with a high degree of disorder. By varying the molar ratio of organically modified and purely inorganic silicates like TEOS, a wide range of glassy and rubbery matrices can be synthesized to withstand physiological and mechanical stresses encountered in the human body [116,117].

The architectural design and the release kinetic profiles of Organically Modified Silicate (ORMOSIL) microparticles are primarily controlled by the steric hindrance and the functional groups present in the incorporated organic moieties. Organic groups with low steric hindrance, e.g., the methyl group, occupy a very small volume of space and therefore enable the creation of a very dense lattice structure that is hydrophobic in nature. In contrast, the presence of phenyl rings imposes considerable steric constraints on the polycondensation reaction, which limits the close packing of the silica chains and therefore creates a less dense structure with larger pore volumes and diameters. Although the less dense structure would naturally enable the quicker diffusion of the drug and therefore intensify the phenomenon of "burst release," this is cleverly offset by the supramolecular interactions of the organic domain. The phenyl ring is an aromatic ring and can participate in intermolecular π-π stacking interactions with other aromatic drugs. This would therefore greatly enhance the drug loading capacity and the drug release profiles even for a less dense structure. In addition, the "organic pockets" would act as a partitioning site where lipophilic drugs would preferentially accumulate. In this system, the drug release is controlled by a high thermodynamic energy barrier, where the drug has to diffuse from the hydrophobic environment of the matrix to the aqueous environment of the body [118]. The augmented steric volume, as provided by the phenyl group, has the effect of mitigating the capillary stresses that are involved during the solvent evaporation process, thereby providing the microparticles with improved fracture and shrinkage resistance as compared to the conventional methyl group analogs. By employing these organic modifiers, it is possible to establish the gradient of hydrophobicity and porosity, thereby allowing the transition from passive barriers to active participants in the therapeutic delivery process. This is

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indeed a significant advancement, as it represents a paradigm shift in the field of therapeutic delivery systems, moving from the conventional simple entrapment to the complex covalent tethering that is provided by the silica framework. The intelligent design of the therapeutic delivery systems, as provided by the integration of the organofunctional silanes, allows the drugs to be retained by the microparticles via stable and reversible covalent bonds, thereby mitigating the problem of burst release, as the therapeutic payload is released only in response to the required physiological stimuli [119].

Mechanics of stimuli-responsive release

The inclusion of mercapto (thiol) functional groups is critical for the targeted delivery of substances within the cell. The utilization of disulfide bonds (S-S) between the silicate matrix and the therapeutic agent allows for the formulation of a system that is structurally stable in the presence of oxidative extracellular conditions, yet readily cleavable in the presence of the higher concentrations of intracellular glutathione (GSH), which is 100 to 1000 times higher than that found in systemic circulation. This is an important aspect of targeted delivery for siRNA or potent toxic agents. Similarly, ORMOSILs functionalized with amino groups are commonly used for pH-responsive systems. The inclusion of pH-labile bonds between the therapeutic agent and the ORMOSIL enables the formulation of a system that is stable in physiological conditions (pH 7.4), yet readily cleavable in the presence of a tumor-specific pH (4.5–5.5). This reduces systemic toxicity. The inclusion of epoxy-functionalized silanes provides a potent system for the immobilization of enzymes. The high reactivity of the epoxide group enables the covalent immobilization of enzymes onto the pore walls of the ORMOSIL, thus preventing denaturation via heat or chemical degradation. This provides a potent system for the immobilization of enzymes that process substrates that diffuse into the pores, thus preventing enzyme leakage [120].

The surface density of functional groups in the silica framework is an important design parameter that has a direct bearing on drug loading capacity and release fidelity. This parameter is usually controlled by adjusting the molar ratio of functionalized organosilanes, e.g., APTES, with the primary silica sources, e.g., TEOS. A low functional group density could result in an insufficient number of sites for accommodating a large amount of drug, thereby compromising the loading process. On the contrary, a very high functional group density could result in a substantial amount of steric hindrance, where the functional groups could physically hinder the access of drug molecules. This could, in turn, hinder the release process. From a stability point of view, a very high functional group density is a critical barrier against premature drug leaching, where the drug is held in place through multiple chemical bonds, thereby retaining the drug until a particular physiological event is experienced. On the contrary, a low functional group density could result in a higher amount of drug being held through van der Waals bonds or even hydrogen bonds, thereby increasing the propensity for premature leaching [121,122].

2.15. Hot Melt Encapsulation

Hot melt encapsulation (HME), a solvent-free approach in pharmaceutical technology, relies on the application of the liquid/solid phase change rather than the use of organic solvents for the creation of microparticles. In the HME method, the thermoplastic polymer or the lipid-based carrier for the API is melted, and the API is either molecularly dispersed or finely dispersed as a particulate system. Subsequent to the dispersion of the API within the melted carrier system, the hot melt is atomized or subjected to high-throughput extrusion/spheromization, followed by rapid cooling for the attainment of solidification. The anhydrous nature of the HME method avoids the need for energy-intensive drying steps and the toxicological risks posed by the use of organic solvents. From a design viewpoint, the selection of the carrier system for the API, which includes polyethylene glycols, poloxamers, and low-melting-point waves, plays a crucial part in controlling the API's release kinetics and physical stability [123]. In addition to this, the HME method is a powerful tool for the improvement of the oral bioavailability of poorly soluble APIs by the creation of solid dispersions wherein the API is maintained in a high-energy amorphous form (Figure 16). Although the HME

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method is limited by the thermal stability of the API, the method is found to possess a high degree of compatibility with the requirements for continuous manufacturing and Industry 4.0 standards for the achievement of high batch-to-batch reproducibility. The precise control over the cooling rate is a crucial factor for the fine-tuning of the API's release profiles by controlling the matrix crystallinity and tortuosity. In addition to this, the fine-tuning of the API's release profiles from the HME method is also enabled by the use of plasticizers [124].

Melt viscosity is an important rheological property in hot melt encapsulation, and it has been reported to play a key role in determining both the energy input required for atomization and the resulting microparticle morphology. During atomization, the molten mass is broken into small droplets using aerodynamic or centrifugal forces. The increased viscosity will hinder the melt's cohesive forces from being overcome by the stress of the atomization nozzle. This results in larger and more polydisperse droplets or even non-spherical droplets. On the other hand, low viscosity will allow for the formation of smaller droplets. However, low viscosity may also cause satellite formation, resulting in small particles being incorporated into the final product [125]. In relation to structural design, melt viscosity has been reported to affect microparticle sphericity through an influence on the recoil time, during which time the distorted droplet has an opportunity to recover its spherical shape before being fixed by solidification. For high-viscosity melts, resistance may be so great that sphericity is prevented, resulting in tear-drop or irregularly shaped particles. This problem is particularly critical during extrusion-spheronization, where the friction plate's mechanical energy must be adequate to overcome the melt's yield stress. However, by adjusting the temperature or adding small amounts of rheology modifiers, it is possible to reduce viscosity levels to an optimum value that results in high sphericity and smooth surface finish, both of which are critical for flow and drug release [126]. The topography of the microparticle's surface, as indicated by its roughness and fractal dimension (D_f), represents an essential artifact of the preparation method that influences the flow properties of the powder and the drug's release kinetic profiles (Table 11). In fact, the dimension of a Euclidean surface is 2.0 by definition; however, the self-similar irregularities observed on the surface of a microparticle prepared by various methods, such as the kinetics of the solidification/solvent evaporation process, result in a fractal dimension between 2 and 3. In fact, base-catalyzed sol-gel synthesis often produces a grainy, colloidal-type surface with a high fractal dimension, while the use of more advanced technologies, such as microfluidics and quenched hot melt encapsulation, produces ultra-smooth surfaces approaching a fractal dimension of 2.0. This topography plays a crucial role in determining the effective surface area (SA_eff), which is a key factor according to the Noyes-Whitney equation ($dC/dt = [D \cdot S A_{eff} / h] \cdot [Cs - C]$). This phenomenon fundamentally influences the wetting properties of the dosage form. In fact, according to Wenzel's equation ($\cos \theta^* = r \cos \theta$), the increased roughness (r) of the microparticle's surface enhances the hydrophilicity/hydrophobicity of the carrier material; therefore, an increased fractal dimension can accelerate the drug's release from hydrophilic carriers or cause a "super hydrophobic" lag time for lipid-based carriers. In conclusion, the precise control over the surface topography during the preparation of the microparticles is an essential factor for the predictability and stability of high-performance microparticulate delivery systems [127]. In addition, the viscosity-temperature relationship as per the Arrhenius model and the Williams-Landel-Ferry (WLF) model should be well understood to prevent thermal degradation of the active pharmaceutical ingredient. One of the important strategies employed during the fabrication of microparticles involves carrying out the process at the lowest viscosity possible to form microparticles stably. This involves identifying a "sweet spot" where the carrier is fully molten but not too molten to compromise the integrity of the structure upon contact with the cooling medium. Lastly, the ability to control the rheology of the melt will allow the microparticles to have a uniform diameter with a high density and porosity to protect the active pharmaceutical ingredient from environmental moisture [128,129].

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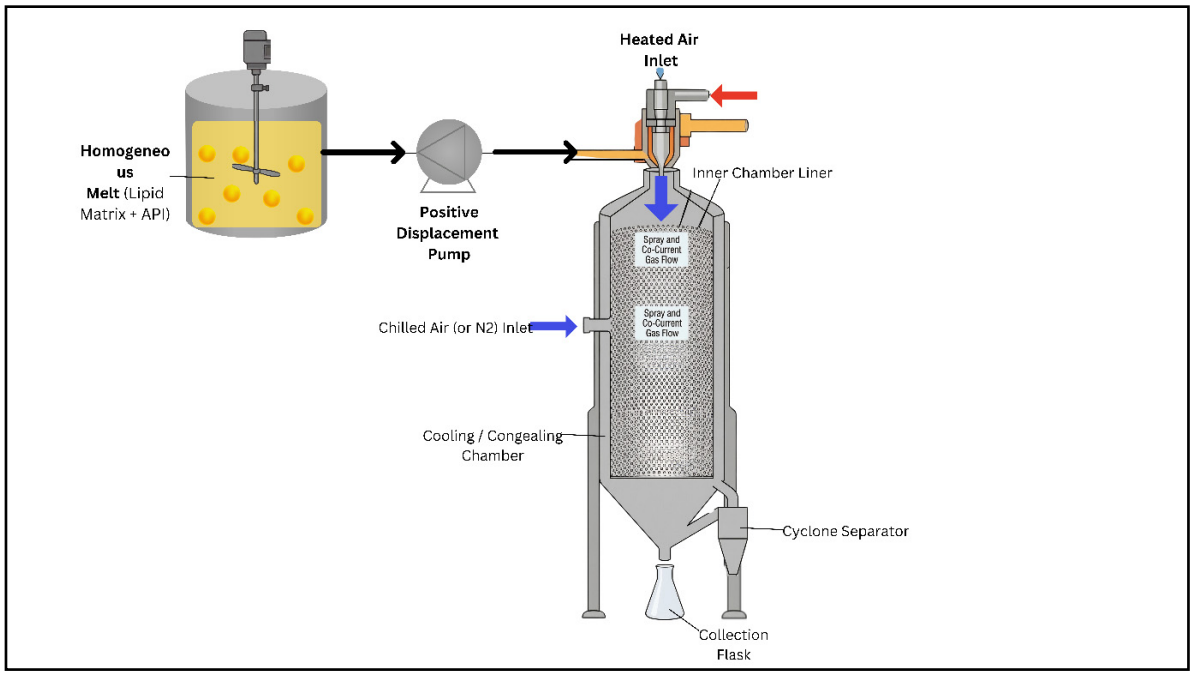

Figure 16. Illustration and practical steps for the Hot Melt Encapsulation (HME) method in microparticle fabrication.

Table 11. Comparison between the thermal and mechanical preparation methods.

Method	Core Driver	Solvent Status	Payload Type	Major Limitation
Hot Melt	Thermal Phase Change	100% Solvent-Free	Thermostable/Lipophilic	Heat-induced degradation
Spray Drying	Thermal Evaporation	Solvent-Dependent	Thermostable/Amorphous	High energy consumption
Spray Congealing	Rapid Cooling	100% Solvent-Free	Low melting waxes/lipids	Lipid polymorphism
Wurster Coating	Air Suspension	Solvent/Aqueous	Robust solid cores	Complexity of air-flow

2.16. Salting Out

The salting-out method is a refined version of traditional solvent extraction that has been developed specifically to counteract the chemical and thermal challenges that often affect biological payloads. This process involves the precise control of solvent miscibility using a combination of electrolytes added to the aqueous phase. By using a water-miscible organic solvent such as acetone or ethanol, combined with a biocompatible polymer such as poly(lactic acid) (PLA) or poly(lactic-co-glycolic acid) (PLGA), the salting-out process begins with the dissolution of the polymer-drug complex in the organic solvent. This organic phase is then emulsified in the aqueous phase containing a salting-out agent such as magnesium chloride ($MgCl_2$) or calcium chloride ($CaCl_2$) (Figure 17). The high concentration of ions in the aqueous phase causes the solvent to become insoluble in the water phase, thus inhibiting its immediate diffusion into the solvent phase. This leads to the formation of a stable oil-in-water (O/W) emulsion. When pure water is then added to the emulsion in a large volume, the concentration of ions in the aqueous phase rapidly decreases, causing the solvent to become miscible with the aqueous phase once again. This leads to a rapid transfer of solvent to the aqueous phase, causing a sudden precipitation of polymer particles with high encapsulation efficiency and integrity [130,131]. The salting-out technique is highly revered owing to its environmentally friendly profile, as the process entirely circumvents the use of hazardous chlorinated organic solvents like dichloromethane, which are predominantly employed in the conventional solvent evaporation technique. Furthermore, the possibility of performing the process at room temperature or refrigerated

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conditions also renders the technique highly advantageous in maintaining the tertiary structure of heat-labile proteins and peptides. However, the technique also faces significant operational challenges owing to the high dilution factors employed to facilitate solvent migration, which generates significant volumes of saline wastewater. Furthermore, the final microparticle product also necessitates exhaustive washing protocols to remove trace electrolytes from the final product, as the retained electrolytes can cause significant disruption to the osmotic balance of the delivery system or induce irritation at the administration site [132]. Finally, with regard to the architectural characteristics of the final microparticle product, the final diameter and surface morphology are highly sensitive to the initial stirring rate employed and the electrolyte concentration used in the formulation. By accurately controlling the ionic strength of the aqueous phase, the researcher can accurately control the 'induction time' of the polymer precipitation phenomenon, which plays a significant role in determining the final EE of the microparticle product. For instance, if the solvent migration rate is excessively high, the initial fraction of the drug can be lost from the polymer matrix before the onset of solidification, which can result in suboptimal EE values. To circumvent this possibility, the aqueous phase can be supplemented with polyvinyl alcohol (PVA) as the stabilizer to maintain the integrity of the interfacial droplets. While the technique is predominantly employed with lipophilic drugs, the protocol can be extended to hydrophilic drugs as long as the compound demonstrates adequate binding affinity with the polymer matrix to prevent initial loss from the matrix during the high-ionic-strength emulsification step. Ultimately, the salting-out technique presents a unique paradigm in the production of high-purity microparticles with the advantage of solvent-free production with the requisite safety requirements of the biopharmaceutical industry [133].

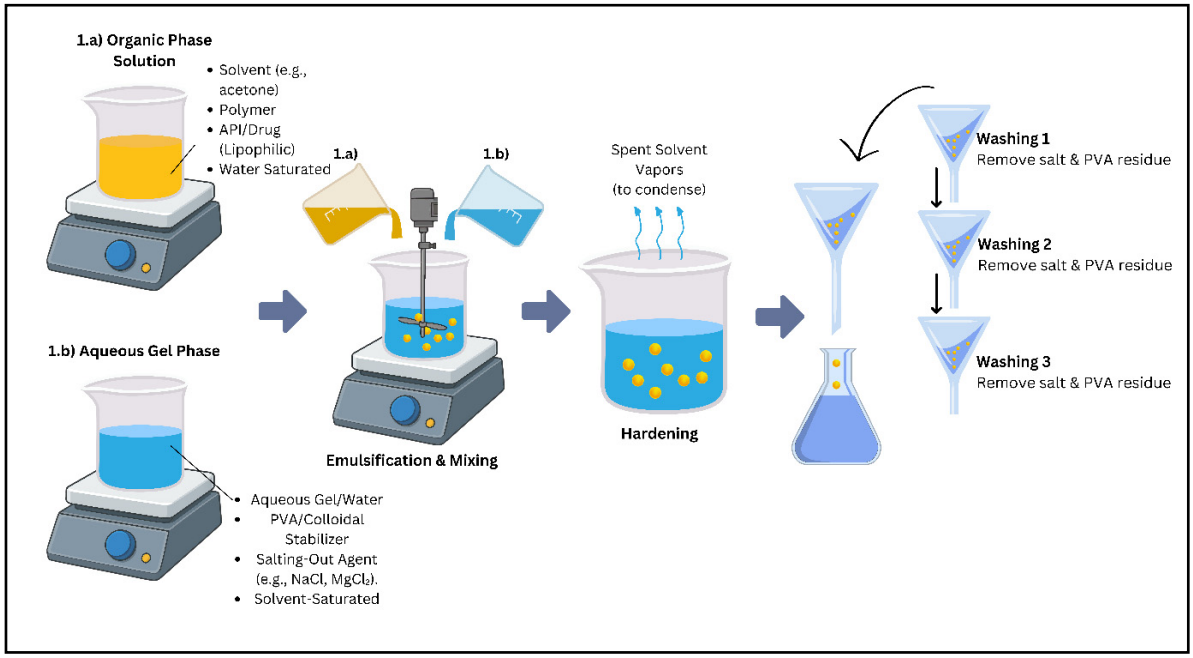

Figure 17. Illustration and practical steps for the salting method in microparticle fabrication.

The efficiency of salting out is deeply influenced by the Hofmeister series, also known as the lyotropic series, in which ions are arranged according to their ability to disrupt the structured nature of water, thereby affecting the solubility of organic solvents as well as polymers. The selection of an electrolyte with high kosmotropic potential is a strategic tool in optimizing the salting-out efficiency in the formulation of microparticulate systems. Strongly kosmotropic ions, such as sulfate ($SO4^{2-}$) or magnesium (Mg^{2+}), are known to possess a high charge density that effectively coordinates with water molecules to create a rigid structure around themselves. As a result, it is thermodynamically unfavorable for a miscible organic solvent, such as acetone, to dissolve in this structured water,

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thereby creating a stable emulsion with minimal electrolyte mass [134]. The kosmotropic nature of the selected salt enables a significant reduction in the amount of required dilution volume. This is because these salts are particularly effective in disrupting the miscibility of the solvent and water, such that the miscibility gap can be eliminated with much less water than what is required when chaotropic or disorder-producing salts, such as Cl- or SCN-, are used. This is particularly important in scaling up the production, as it directly correlates with a decrease in the size of the reactors as well as the amount of saline wastewater discharge. It is also important to note that the kosmotropic nature of the salts used in the microparticle production can lead to an increased efficiency in the microparticle production. This is because the kosmotropic nature of these salts results in a more aggressive salting-out of the organic solvent, thus enabling the polymer to precipitate quickly and effectively, thus entrap the drug in the microparticle prior to partitioning into the aqueous phase [135]. However, the chemical properties of the selected kosmotropic salts must be taken into consideration in terms of the stability of the drug payloads. Although kosmotropic salts are effective in salting-out, it has been noted that sulfates, in particular, can result in the irreversible precipitation of certain proteins due to ionic interactions. In such circumstances, magnesium chloride ($MgCl_2$) is seen as the "Goldilocks" of salts, being sufficiently kosmotropic for efficient microparticle production while being sufficiently mild in nature as not to interfere with the biological activities of the peptides. By selecting the appropriate anion and cation in line with the Hofmeister Series, pharmaceutical chemists can create an environment that is both efficient and protective for the final microparticle product, such that it meets the required purity and potency for clinical application [136].

3. Strategic Engineering of Microparticulate Systems for Long-Acting Injectables

The progression of research on microparticles into the domain of Long-Acting Injectables (LAIs) represents a significant milestone in the management of various chronic conditions, with the primary goal being to extend drug concentration levels for weeks or months following a single injection. The formulation of LAIs differs significantly from conventional drug formulations in that it requires a very high level of control with respect to both internal matrix structure and degradation rate of the polymer. The choice of formulation is the key determining factor in achieving a "zero-order" release profile, as this variable directly affects the patient's experience with a desirable sustained release or undesirable initial burst release phenomenon (Table 12 and 13) [137].

Table 12. Evaluating preparation methods for LAIs.

Method	Suitability for LAIs	Rationale
Hot Melt (Extrusion)	**High**	Produces high-density, monolithic matrices with low porosity, ideal for ultra-slow diffusion of lipophilic drugs over.
Microfluidics	**High**	Exceptional monodispersity ensures that every particle degrades at the exact same rate, preventing the erratic release typical of polydisperse batches.
Salting Out	**Moderate**	Excellent for protein-based LAIs due to its gentle nature, but the resulting porous structures often require secondary coating to achieve multi-week release.
Electrospraying	**Moderate**	Highly effective for high-potency biologics, yet the low density of the particles often leads to faster degradation than required for long-term depots.

Table 13. Comparison of release profiles in LAIs.

Profile Type	Mathematical Description	Clinical Implication	Common Cause
Zero-Order	$dQ/dt = k$	Constant plasma levels; ideal for chronic care.	Synchronized erosion and diffusion.

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First-Order	dQ/dt = -kQ	Declining drug levels over time.	Concentration-dependent diffusion.
Burst Release	High dQ/dt at t → 0	Risk of acute toxicity; shortened duration.	Surface-bound drug; rapid pore formation.
Sigmoidal	Lag phase followed by rapid release.	Delayed onset of action.	Slow initial hydration of the matrix.

4. Key Engineering Strategies for Long-Term Release

4.1. Controlling Matrix "Tortuosity"

A major engineering technique for controlling the release kinetics of long-acting injectables (LAI) is to intentionally increase matrix tortuosity. To achieve a sustained therapeutic window, the pathway of the diffusing drug must be maximally tortuous. Hot melt extrusion (HME) and solvent evaporation (SE) are significant processing techniques for creating dense matrices of low porosity, which are critical for eliminating direct aqueous pathways. Furthermore, using polymers of high molecular weight, which are typically characterized by their high intrinsic viscosity, such as high IV PLGA, can increase the extent of entanglement of the chains. This will create a highly tortuous matrix, causing the diffusing drug molecules to take a much more circuitous route to the surface of the matrix, thus slowing down their diffusion coefficient [138,139].

4.2. Synchronizing Degradation and Diffusion

The intentional control of polymer erosion in synchrony with drug diffusion represents a key criterion for the definition of smart LAI formulations. In order to maintain a constant window for therapy, the rate of matrix degradation must be carefully matched with the diminishing concentration gradient of the entrapped drug molecules. Microfluidic fabrication offers a significant advantage in this respect, as ultra-monodisperse spheres are formed, thereby ensuring a constant surface area-to-volume ratio (SA/V) for the entire dose distribution. As the SA/V ratio is inversely proportional to the radius (3/r), a constant particle size distribution ensures a coordinated rate of polymer thinning and mass loss, which in turn prevents the premature, asynchronous collapse of the smaller spheres, a phenomenon that can result in irregular drug concentration spikes and a diminished window for therapy in a heterogeneous formulation [140].

4.3. Minimizing the "Initial Burst"

The most important problem to be solved during the development of long-acting injectable (LAI) drug delivery systems is the burst effect, where the drug is released in large quantities during the injection of the drug into the body. To overcome the burst effect, the Spray-Dry-Coat method has been proposed as a better alternative to the aforementioned approaches. The Spray-Dry-Coat method involves the formation of the core of the drug, which is achieved by the spray drying method to attain the highest level of encapsulation efficiency, followed by the formation of the secondary coating layer of the drug, which is achieved by the Wurster fluidized bed coating method, to act as the gate of the drug to attain the lag time, thereby avoiding the acute plasma concentration peaks and directly attaining the steady-state therapeutic window [141]. Table 14 shows the suitability of the preparation method based on the drug's nature.

Table 14. Physicochemical suitability of drugs for microencapsulation methods.

Preparation Method	Lipophilic Drugs	Hydrophilic Drugs	Thermolabile (Proteins)	Key Physicochemical Constraint
Solvent Evaporation	High Suitability (O/W)	Moderate (W/O/W - Leakage risk)	Moderate (Interface stress)	Solubility in organic solvent; LogP
Solvent Extraction	High Suitability	Low Suitability	High Suitability (Cold process)	Solubility in the extraction medium

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Coacervation	High Suitability	High Suitability	High Suitability	Charge density; pH sensitivity
Spray Drying	High Suitability	High Suitability	Low/Moderate (Heat risk)	Thermal stability; Tg
Spray Congealing	High Suitability	Moderate (Suspension)	Moderate (Melt temp dependent)	Melting point compatibility
Ionic Gelation	Low Suitability	High Suitability	High Suitability	Ionic charge interactions
Interfacial Polymerization	High Suitability (Oils)	Low Suitability	Low (Chemical reactivity)	Reactivity with monomers
Air Suspension	High Suitability (Solid)	High Suitability (Solid)	Moderate	Core mechanical strength
Pan Coating	High Suitability (Solid)	High Suitability (Solid)	Moderate	Core size (>500 μm)
In-situ Polymerization	High Suitability	Low Suitability	Low (Low pH/Formaldehyde)	Acid/Aldehyde stability
Supercritical Fluid	High Suitability (SAS)	Low Suitability (RESS)	High Suitability (Mild temp)	Solubility in CO2
Electrospraying	High Suitability	High Suitability	High Suitability	Solution conductivity/viscosity
Microfluidics	High Suitability	High Suitability	High Suitability	Fluid viscosity/Interfacial tension
Sol-Gel Process	Moderate	High Suitability	High Suitability	Alcohol tolerance
Hot Melt Encapsulation	High Suitability	Low/Moderate	Low (Heat required)	Thermal stability
Salting Out	High Suitability	Moderate	High Suitability	Salt tolerance

5. Future Prospects and "Smart" Microparticles

The present development of microparticle preparation involves creating environmentally friendly methods that produce exact results. Scientists actively work to replace dangerous chlorinated solvents, including dichloromethane[90] which traditional solvent evaporation uses through the implementation of safe alternatives, which include supercritical CO2 and solvent-free hot melt techniques. The pharmaceutical industry must adopt green chemistry methods for drug production because environmental regulations have established new, strict requirements for the industry. Furthermore, the industry is moving away from batch processing towards continuous manufacturing. The FDA backs Quality by Design (QbD) initiatives through its endorsement of continuous manufacturing techniques, which include spray drying and hot melt extrusion, because these methods provide better operational efficiency and enhanced process control and uniform product quality. The development of advanced therapeutic products will see Microfluidics and Electrospraying precision engineering methods move from university research to specialized industrial manufacturing operations[95,96]. The fabrication techniques allow scientists to develop complex particle structures, which include core-shell and Janus shapes, because they need exact monodispersity to transport important gene therapies and individualized medical treatments [142].

The evolution of microencapsulation technology has moved away from the basic concept of matrix entrapment towards the development of complex and multifunctional constructs that can respond dynamically to the physiological environment. This evolution is based on the understanding that the choice of preparation technology is no longer seen as a technological choice but as a strategic compromise between the unique physicochemical profile of the drug and the unique biological requirements of the target site. While the more traditional and industrialized techniques, such as

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solvent evaporation and pan coating, are still relevant due to the advantage of scale (Table 15), the more recent high-precision techniques, such as ionic gelation and Wurster coating, are also gaining popularity due to the more benign processing conditions that can be achieved with these techniques. The current direction in the development of microencapsulation technology is hybridization, which is the strategic integration of various microencapsulation techniques to overcome the limitations of each technology. The strategic integration of techniques such as emulsion gelation enables the integration of the principles of double-emulsion technology with the principles of ionic gelation to entrap hydrophilic peptides within a hydrogel matrix, thus facilitating the creation of effective diffusion barriers [143]. Furthermore, the strategic integration of high-throughput spray drying technology with secondary fluid bed coating technology enables the creation of complex primary matrices with protective shells. The transition from bulk emulsification to microfluidics-assisted assembly is a significant step forward in the development of microencapsulation technology as it enables the creation of monodisperse microparticles with near-complete EE and highly predictable release profiles. The 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. Future trends in the development of microencapsulation technology by the year 2026 and beyond indicate the development of more personalized medicine with on-demand manufacturing using 3D microparticle printing technology and lab-on-chip fabrication technology [144]. Artificial intelligence is also set to transform the development of microencapsulation technology as it optimizes the choice of polymers and surfactants, thus significantly reducing the trial-and-error approach that defines the current direction in the development of drugs. 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 [145]. The significance of these preparation methods is further evidenced by their patent landscapes. Table 16 summarizes the patentability of each microparticle preparation technique, based on a comprehensive search of the Google Patents database.

Table 15. Scalability and industrial feasibility.

Method	Scalability Potential	Industrial Status	Critical Bottleneck for Scale-Up
Solvent Evaporation	High	Widely Used	Residual solvent removal; Tank geometry
Solvent Extraction	Medium	Used	Large volume of waste water; Solvent recovery
Coacervation	Medium	Niche (Food/Pharma)	Batch-to-batch variation; Precise tank control
Spray Drying	Very High	Standard	Capital cost; Thermal efficiency
Spray Congealing	High	Growing	Cooling capacity; Lipid polymorphism
Ionic Gelation	Medium	Niche	Dripping speed limit (requires jet cutting)
Interfacial Polymerization	High	Agrochemicals	Toxicity control; Exothermic reaction control
Air Suspension	Very High	Standard	Aerodynamics; Humidity control
Pan Coating	Very High	Standard	Drying efficiency; Coating uniformity
In-situ Polymerization	High	Industrial (Non-Pharma)	Reaction time; Toxic byproduct removal
Supercritical Fluid	Low/Medium	Niche	High pressure equipment cost; Yield
Electrospraying	Low	R&D / Pilot	Low throughput; Multi-nozzle engineering

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Microfluidics	Very Low	R&D	"Numbering up" complexity; Channel clogging
Sol-Gel Process	Medium	Specialized	Batch aging time; Brittle product handling
Hot Melt Encapsulation	High	Growing	Screw extrusion design; Cooling rate
Salting Out	Medium	Niche	Water consumption; Salt disposal

Table 16. Patent status and examples.

Method	Patented (Yes/No)	Patent	Google Patent Link
Solvent Evaporation	Yes	US5650173A	Link
Solvent Extraction	Yes	US6379703B1	Link
Coacervation	Yes	US20060105038A1	Link
Spray Drying	Yes	US6451349B1	Link
Spray Congealing	Yes	US6264987B1	Link
Ionic Gelation	Yes	US10085948B2	Link
Interfacial Polymerization	Yes	EP0399911B1	Link
Air Suspension	Yes	US2648609A	Link
Pan Coating	Yes	US5958458A	Link
In-situ Polymerization	Yes	US4626471A	Link
Supercritical Fluid	Yes	US6063910A	Link
Electrospraying	Yes	US12433849B2	Link
Microfluidics	Yes	US20110268803A1	Link
Sol-Gel Process	Yes	WO2022040751A1	Link
Hot Melt Encapsulation	Yes	US20160015703A1	Link
Salting Out	Yes	US8852644B2	Link

6. Limitations

Despite these advances in technology, several formidable hurdles remain, which continue to hinder the smooth transition of these technological advances into practical applications and commercialization [98]. The first and most prevalent hurdle is the fundamental problem associated with scaling precision-based technologies without compromising product quality. For example, although microfluidics offers unparalleled control at the capillary scale, the production of kilogram-scale materials for practical application requires a “numbering up” strategy, which requires the parallelization of thousands of microchannels, a technological feat in itself, which is both complex

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and prohibitively expensive, while technically viable, the capital expenditure (CAPEX) for numbering up currently limits it to high-value therapeutics. Another hurdle in the practical application of these technological advances is the problem associated with regulatory compliance, as solvent-based evaporation techniques often fail to remove trace residues of solvents, whereas in situ chemical encapsulation techniques often leave residues of toxic monomers or catalysts. In addition, the "loading-burst paradox" remains an unresolved formulation-level physicochemical problem, as it has been commonly observed that scientists often face problems in achieving high drug loading in biodegradable matrices without triggering immediate, uncontrolled release of water-soluble active pharmaceutical ingredients, which remains an unresolved problem for all available techniques. Another hurdle in the practical application of these technological advances is the significant capital investment required for specialized equipment, such as high-pressure vessels, for techniques such as supercritical fluid processing, which are often restricted to high-value applications, rendering spray drying the sole financial and practical basis for bulk manufacturing [146,147].

7. Conclusion

The art of creating microparticles is a complex discipline that requires a wide range of physical and chemical techniques. It is becoming increasingly evident that not one specific technique alone can solve all formulation problems, but rather that the choice of a specific technique is a strategic decision based on the fundamental needs of the active ingredient and the specific drug effects. The selection of a specific technique is, in essence, a balance of three key pillars: the thermic and chemical stability of the drug, the release profile over time, and practical aspects concerning volume and safety. While large-scale production is still largely dependent on the excellent performance and large-scale capabilities of spray-drying and pan-coating techniques, we are witnessing a paradigm shift in this industry toward more precise techniques. As we increasingly focus on more valuable drugs with more specific targeting, techniques such as microfluidics and supercritical fluid technology are shifting from being on the periphery to being at the center of pharmaceutical innovation. The future of microencapsulation is found in hybridization, thereby combining the reliability of conventional techniques with the precision and sustainability that are characteristic of modern engineering techniques. The future is found beyond the limits of individual techniques, moving toward a more personal and more effective era of drug delivery.

References

1. Da Silva RYP, De Menezes DLB, Oliveira V da S, Converti A, De Lima ÁAN. Microparticles in the development and improvement of pharmaceutical formulations: an analysis of in vitro and in vivo studies. *Int J Mol Sci*. 2023;**24**(**6**):5441.
2. Siepmann J, Faisant N, Akiki J, Richard J, Benoit JP. Effect of the size of biodegradable microparticles on drug release: experiment and theory. *J Control Release*. 2004;**96**(**1**):123–34.
3. Pöttgen S, Wischke C. Alternative Techniques for Porous Microparticle Production: Electrospraying, Microfluidics, and Supercritical CO2. *Pharm Res*. 2025;**42**(**9**):1461–80.
4. Park H, Kim JS, Kim S, Ha ES, Kim MS, Hwang SJ. Pharmaceutical applications of supercritical fluid extraction of emulsions for micro-/nanoparticle formation. *Pharmaceutics*. 2021;**13**(**11**):1928.
5. Sarabandi K, Gharehbeglou P, Jafari SM. Spray-drying encapsulation of protein hydrolysates and bioactive peptides: Opportunities and challenges. *Dry Technol*. 2020;**38**(**5–6**):577–95.
6. Mawazi SM, Ab Hadi H, Chatterjee B. The impact of carbamazepine crystallinity on carbamazepine-loaded microparticle formulations. *Int J Pharm*. 2021;**602**:120638.
7. Mawazi SM, Hadi HAB, Al-mahmood SMA, Doolaanea AA. Development And Validation of Uv-Vis Spectroscopic Method of Assay of Carbamazepine In Microparticles. *Int J Appl Pharm*. 2019;**11**(**1**):34–7.
8. Mawazi SM, Al-Mahmood SMA, Chatterjee B, Hadi HAB, Doolaanea AA. Carbamazepine gel formulation as a sustained release epilepsy medication for pediatric use. *Pharmaceutics*. 2019;**11**(**10**):1–13.

 doi:10.20944/preprints202604.0403.v1

9. Muhaimin M, Chaerunisaa AY, 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**(**6**):512–21.
10. 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.
11. Mawazi SM. Formulation and Evaluation of Carbamazepine Sustained Released Oral Jelly for Pediatric. *Pharmaceutics* [Internet]. 2019;**11**(**10**):488. Available from: https://doi.org/10.3390/pharmaceutics11100488
12. Quan P, Guo W, 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.
13. Wu J, Ding J, Xiong C, Chen D, Huang D, Xiong Z. An efficient strategy for fabricating and controlling the morphology of hollow poly (p-dioxanone) microspheres using an O/W emulsions solvent evaporation method. *ACS Appl Polym Mater*. 2023;**6**(**1**):1015–22.
14. Liu G, McEnnis K. Glass transition temperature of PLGA particles and the influence on drug delivery applications. *Polymers (Basel)*. 2022;**14**(**5**):993.
15. Otte A, Soh BK, Park K. The impact of post-processing temperature on plga microparticle properties. *Pharm Res*. 2023;**40**(**11**):2677–85.
16. Zhang Z, Zhou D, Tian X, Rafique M, Xiao L, Bányai I, et al. Thermally guided solvent-induced porous bioabsorbable microspheres: Molecular structure and performance. *Biomater Transl*. 2025;113.
17. Ortega-Oller I, Padial-Molina M, Galindo-Moreno P, O'Valle F, Jódar-Reyes AB, Peula-García JM. Bone regeneration from PLGA micro-nanoparticles. *Biomed Res Int*. 2015;**2015**(**1**):415289.
18. 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**(**3**):1567–79.
19. Zhang Y, Fei S, Yu M, Guo Y, He H, Zhang Y, et al. Injectable sustained release PLA microparticles prepared by solvent evaporation-media milling technology. *Drug Dev Ind Pharm*. 2018;**44**(**10**):1591–7.
20. Allison SD. Analysis of initial burst in PLGA microparticles. *Expert Opin Drug Deliv*. 2008;**5**(**6**):615–28.
21. Bayındır ZS, Badıllı U. Preparation of polymeric nanoparticles using different stabilizing agents. *J Fac Pharm Ankara Univ*. 2009;**38**(**4**):257–68.
22. Song B, Cho CW. Applying polyvinyl alcohol to the preparation of various nanoparticles. *J Pharm Investig*. 2024;**54**(**3**):249–66.
23. Maia JL, Santana MHA, Ré MI. The effect of some processing conditions on the characteristics of biodegradable microspheres obtained by an emulsion solvent evaporation process. *Brazilian J Chem Eng*. 2004;**21**(**1**):1–12.
24. Yang Z, Zhang H, Wu Z, Zhang Z, Chen J, Cao Y, et al. Effect of boric acid pretreatment on the formation and structural evolution of polyvinyl alcohol-iodine complex. *J Polym Res*. 2023;**30**(**12**):444.
25. Scholes PD, Coombes AGA, Illum L, Davis SS, Watts JF, Ustariz C, et al. Detection and determination of surface levels of poloxamer and PVA surfactant on biodegradable nanospheres using SSIMS and XPS. *J Control Release*. 1999;**59**(**3**):261–78.
26. Gonsalves KE, Jin S, Baraton MI. Synthesis and surface characterization of functionalized polylactide copolymer microparticles. *Biomaterials*. 1998;**19**(**16**):1501–5.
27. Freitas S, Merkle HP, Gander B. Microencapsulation by solvent extraction/evaporation: reviewing the state of the art of microsphere preparation process technology. *J Control release*. 2005;**102**(**2**):313–32.
28. Katou H, Wandrey AJ, Gander B. Kinetics of solvent extraction/evaporation process for PLGA microparticle fabrication. *Int J Pharm*. 2008;**364**(**1**):45–53.
29. 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*. 2019;**59**(**7**):2892–8.
30. Baena-Aristizábal CM, Fessi H, Elaissari A, Mora-Huertas CE. Biodegradable microparticles preparation by double emulsification—Solvent extraction method: A Systematic study. *Colloids Surfaces A Physicochem Eng Asp*. 2016;**492**:213–29.

 doi:10.20944/preprints202604.0403.v1

31. Kias F, Bodmeier R. Acceleration of final residual solvent extraction from poly (lactide-co-glycolide) microparticles. *Pharm Res*. 2024;**41**(**9**):1869–79.
32. Yukhin YM, Logutenko OA, Titkov AI, Lyakhov NZ. Application of solvent extraction in the preparation of metal nano-and microparticles. *Theor Found Chem Eng*. 2017;**51**(**5**):809–14.
33. Sah H. Microencapsulation techniques using ethyl acetate as a dispersed solvent: effects of its extraction rate on the characteristics of PLGA microspheres. *J Control release*. 1997;**47**(**3**):233–45.
34. Grizić D, Lamprecht A. Microparticle preparation by a propylene carbonate emulsification-extraction method. *Int J Pharm*. 2018;**544**(**1**):213–21.
35. 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**(**3**):383–8.
36. Hyde AM, Zultanski SL, Waldman JH, Zhong YL, Shevlin M, Peng F. General principles and strategies for salting-out informed by the Hofmeister series. *Org Process Res Dev*. 2017;**21**(**9**):1355–70.
37. Li X, Wang B, Liu QJ, Zhao R, Song DP, Li Y. Supersoft elastic bottlebrush microspheres with stimuli-responsive color-changing properties in brine. *Langmuir*. 2021;**37**(**22**):6744–53.
38. A da Trindade R, S de Araujo P, Helena Bueno-da-Costa M. Hoffmeister Ion Series Protected Bee Venom Proteins from Damages Induced by Microencapsulation Process. *Drug Deliv Lett*. 2012;**2**(**1**):54–9.
39. Arshady R. Microspheres and microcapsules, a survey of manufacturing techniques Part II: Coacervation. *Polym Eng Sci*. 1990;**30**(**15**):905–14.
40. Kas HS, Oner L. Microencapsulation using coacervation/phase separation: An overview of the technique and applications. Marcel Dekker, Inc.: New York, NY, USA; 2000.
41. Rane AM, Schwing JA, Jonnalagadda S. Coacervation and phase separation. In: Encyclopedia of Pharmaceutical Science and Technology, Six Volume Set (Print). CRC Press; 2013. p. 497–511.
42. Muzzarelli RAA, 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**(**12**):7314–38.
43. Buldur PM, Kok FN. Encapsulation of food flavors via coacervation method. *Curr Opin Biotechnol*. 2011;**22**:S96.
44. Grabska-Zielińska S. Cross-linking agents in three-component materials dedicated to biomedical applications: a review. *Polymers (Basel)*. 2024;**16**(**18**):2679.
45. D'Agostino I. Design of Biopolymer Nanoparticles for Encapsulation and Delivery of Nutraceuticals. 2016;
46. Moulik SP, Rakshit AK, Pan A, Naskar B. An overview of coacervates: The special disperse state of amphiphilic and polymeric materials in solution. *Colloids and Interfaces*. 2022;**6**(**3**):45.
47. Soussi Hachfi R, Hamon P, Rousseau F, Famelart MH, Bouhallab S. Ionic strength dependence of the complex coacervation between lactoferrin and β-lactoglobulin. *Foods*. 2023;**12**(**5**):1040.
48. Timilsena YP, Wang B, Adhikari R, Adhikari B. Preparation and characterization of chia seed protein isolate–chia seed gum complex coacervates. *Food Hydrocoll*. 2016;**52**:554–63.
49. De Kruif CG, Weinbreck F, de Vries R. Complex coacervation of proteins and anionic polysaccharides. *Curr Opin Colloid Interface Sci*. 2004;**9**(**5**):340–9.
50. Liu W, Chen XD, Selomulya C. On the spray drying of uniform functional microparticles. *Particuology*. 2015;**22**:1–12.
51. Sansone F, Mencherini T, Picerno P, d'Amore M, Aquino RP, Lauro MR. Maltodextrin/pectin microparticles by spray drying as carrier for nutraceutical extracts. *J Food Eng*. 2011;**105**(**3**):468–76.
52. Sansone F, Esposito T, Lauro MR, Picerno P, Mencherini T, Gasparri F, et al. Application of spray drying particle engineering to a high-functionality/low-solubility milk thistle extract: Powders production and characterization. *Molecules*. 2018;**23**(**7**):1716.
53. Sahoo NG, Abbas A, Li CM. Micro/nanoparticle design and fabrication for pharmaceutical drug preparation and delivery applications. *Curr Drug ther*. 2008;**3**(**2**):78–97.
54. Ziaee A. Spray drying of pharmaceuticals and biopharmaceuticals: experimental optimization of process and formulation. 2019.
55. Bhandari BR, Howes T. Implication of glass transition for the drying and stability of dried foods. *J Food Eng*. 1999;**40**(**1–2**):71–9.

 doi:10.20944/preprints202604.0403.v1

56. Edwards DA, Hanes J, Caponetti G, Hrkach J, Ben-Jebria A, Eskew M Lou, et al. Large porous particles for pulmonary drug delivery. *Science (80-)*. 1997;**276**(**5320**):1868–72.
57. Abdul-Fattah AM, Truong-Le V, Yee L, Nguyen L, Kalonia DS, Cicerone MT, et al. 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**(**8**):1983–2008.
58. Maa YF, Nguyen PA, Sweeney T, Shire SJ, Hsu CC. Protein inhalation powders: spray drying vs spray freeze drying. *Pharm Res*. 1999;**16**(**2**):249–54.
59. Candiani A, Milanesi A, Foglio Bonda A, Diana G, Bari E, Segale L, et al. Solid lipid microparticles by spray congealing of water/oil emulsion: an effective/versatile loading strategy for a highly soluble drug. *Pharmaceutics*. 2022;**14**(**12**):2805.
60. Samborska K, Boostani S, Geranpour M, Hosseini H, Dima C, Khoshnoudi-Nia S, et al. Green biopolymers from by-products as wall materials for spray drying microencapsulation of phytochemicals. *Trends Food Sci Technol*. 2021;**108**:297–325.
61. Ilić I, Dreu R, Burjak M, Homar M, Kerč J, Srčič S. Microparticle size control and glimepiride microencapsulation using spray congealing technology. *Int J Pharm*. 2009;**381**(**2**):176–83.
62. Oh CM, Guo Q, Wan Sia Heng P, Chan LW. Spray-congealed microparticles for drug delivery-an overview of factors influencing their production and characteristics. *Expert Opin Drug Deliv*. 2014;**11**(**7**).
63. Sato K. Crystallization behaviour of fats and lipids—a review. *Chem Eng Sci*. 2001;**56**(**7**):2255–65.
64. 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**(**1**):348–57.
65. Passerini N, Perissutti B, Voinovich D, Albertini B, Franceschinis E, Rodriguez L. Screening of the ultrasonic spray congealing process variables by factorial design. In: Proc of the European Conference on Drug Delivery and Pharmaceutical Technology Sevilla, May 10-12, 2004. ESP; 2004. p. 123.
66. Bunjes H. Structural properties of solid lipid based colloidal drug delivery systems. *Curr Opin Colloid Interface Sci*. 2011;**16**(**5**):405–11.
67. Racoviţă S, 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**(**9**):709–18.
68. Rajabimashhadi Z, Masi A, Bagheri S, Mele C, Colangelo G, Paladini F, et al. Development and Characterization of Chitosan Microparticles via Ionic Gelation for Drug Delivery. *Polymers (Basel)*. 2025;**17**(**19**):2603.
69. Manuscript A. Alginate : properties and biomedical applications. 2013;**37**(**1**):106–26.
70. Pawar SN, Edgar KJ. Alginate derivatization: A review of chemistry, properties and applications. *Biomaterials*. 2012;**33**(**11**):3279–305.
71. Anal AK, Stevens WF. Chitosan–alginate multilayer beads for controlled release of ampicillin. *Int J Pharm*. 2005;**290**(**1–2**):45–54.
72. Poncelet D, Lencki R, Beaulieu C, Halle JP, Neufeld RJ, Fournier A. Production of alginate beads by emulsification/internal gelation. I. Methodology. *Appl Microbiol Biotechnol*. 1992;**38**(**1**):39–45.
73. Lin D, Kelly AL, 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.
74. Silva CM, Ribeiro AJ, Figueiredo IV, Gonçalves AR, Veiga F. Alginate microspheres prepared by internal gelation: Development and effect on insulin stability. *Int J Pharm*. 2006;**311**(**1–2**):1–10.
75. Hıncal AA. Microencapsulation technology: interfacial polymerization method. *Handb Pharm Control Release Technol*. 2000;271.
76. 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**:217–22.
77. Song Y, Fan JB, Wang S. Recent progress in interfacial polymerization. *Mater Chem Front*. 2017;**1**(**6**):1028–40.
78. Farzi G, Gheysipour M. Microencapsulation: Air suspension technique. In: Principles of Biomaterials Encapsulation: Volume One. Elsevier; 2023. p. 297–303.

 doi:10.20944/preprints202604.0403.v1

79. 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**(**1**):3.
80. Wurster DE. Preparation of compressed tablet granulations by the air-suspension technique II. *J Am Pharm Assoc*. 1960;**49**(**2**):82–4.
81. Jones D, Godek E. Development, optimization, and scale-up of process parameters: Wurster coating. In: Developing solid oral dosage forms. Elsevier; 2017. p. 997–1014.
82. Christensen FN, Bertelsen P. Qualitative description of the Wurster-based fluid-bed coating process. *Drug Dev Ind Pharm*. 1997;**23**(**5**):451–63.
83. Porter SC. Coating of pharmaceutical dosage forms. In: Remington. Elsevier; 2021. p. 551–64.
84. Salawi A. Pharmaceutical coating and its different approaches, a review. *Polymers (Basel)*. 2022;**14**(**16**):3318.
85. Garg A, Chhipa K, Kumar L. Microencapsulation techniques in pharmaceutical formulation. *Eur J Pharm Med Res*. 2018;**5**(**3**):199–206.
86. Aminahmadi B, Vaes E, Willemse F, Braile D, Gomez LN, Andersen SK, et al. Experimental and Modeling-Based Approaches for Mechanistic Understanding of Pan Coating Process—A Detailed Review. *Pharmaceutics*. 2025;**18**(**1**):19.
87. Porter SC. Tablet coating. *Drug Cosmet Ind*. 1981;**128**(**5**):46–93.
88. Brown EN, Kessler MR, Sottos NR, White SR. In situ poly (urea-formaldehyde) microencapsulation of dicyclopentadiene. *J Microencapsul*. 2003;**20**(**6**):719–30.
89. Nguon O, Lagugné-Labarthet F, Brandys FA, Li J, Gillies ER. Microencapsulation by in situ polymerization of amino resins. *Polym Rev*. 2018;**58**(**2**):326–75.
90. Zhang H, Wang X. Fabrication and performances of microencapsulated phase change materials based on n-octadecane core and resorcinol-modified melamine–formaldehyde shell. *Colloids Surfaces A Physicochem Eng Asp*. 2009;**332**(**2–3**):129–38.
91. Li M, Cao B, Shang R, Mei H, Wang L. Synthesis of poly (urea–formaldehyde) microcapsules for the self-healing system of silicone rubber insulating material. *J Appl Polym Sci*. 2022;**139**(**45**):e53021.
92. Mustapha AN, 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.
93. Yeo SD, Kiran E. Formation of polymer particles with supercritical fluids: A review. *J Supercrit Fluids*. 2005;**34**(**3**):287–308.
94. Jung J, Perrut M. Particle design using supercritical fluids: literature and patent survey. *J Supercrit Fluids*. 2001;**20**(**3**):179–219.
95. Jennings J, Beija M, Richez AP, Cooper SD, Mignot PE, Thurecht KJ, et al. One-pot synthesis of block copolymers in supercritical carbon dioxide: a simple versatile route to nanostructured microparticles. *J Am Chem Soc*. 2012;**134**(**10**):4772–81.
96. Vezzu K, Campolmi C, Bertucco A. Production of Lipid Microparticles Magnetically Active by a Supercritical Fluid-Based Process. *Int J Chem Eng*. 2009;**2009**(**1**):781247.
97. Reverchon E, De Marco I, Torino E. Nanoparticles production by supercritical antisolvent precipitation: a general interpretation. *J Supercrit Fluids*. 2007;**43**(**1**):126–38.
98. Sekhon BS. Supercritical fluid technology: an overview of pharmaceutical applications. *Int J PharmTech Res*. 2010;**2**(**1**):810–26.
99. Jaworek A, Sobczyk AT. Electrospraying route to nanotechnology: An overview. *J Electrostat*. 2008;**66**(**3–4**):197–219.
100. Bock N, Woodruff MA, Hutmacher DW, Dargaville TR. Electrospraying, a reproducible method for production of polymeric microspheres for biomedical applications. *Polymers (Basel)*. 2011;**3**(**1**):131–49.
101. Loscertales IG, Barrero A, Guerrero I, Cortijo R, Marquez M, Ganan-Calvo AM. Micro/nano encapsulation via electrified coaxial liquid jets. *Science (80-)*. 2002;**295**(**5560**):1695–8.
102. Deng W, Klemic JF, Li X, Reed MA, Gomez A. Increase of electrospray throughput using multiplexed microfabricated sources for the scalable generation of monodisperse droplets. *J Aerosol Sci*. 2006;**37**(**6**):696–714.

 doi:10.20944/preprints202604.0403.v1

103. Enayati M, Ahmad Z, Stride E, Edirisinghe M. One-step electrohydrodynamic production of drug-loaded micro-and nanoparticles. *J R Soc Interface*. 2010;**7**(**45**):667–75.
104. Hartman RPA, Brunner DJ, Camelot DMA, Marijnissen JCM, Scarlett B. Electrohydrodynamic atomization in the cone–jet mode physical modeling of the liquid cone and jet. *J Aerosol Sci*. 1999;**30**(**7**):823–49.
105. Rosell-Llompart J, de La Mora JF. 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**(**6**):1093–119.
106. Anna SL, Bontoux N, Stone HA. Formation of dispersions using "flow focusing" in microchannels. *Appl Phys Lett*. 2003;**82**(**3**):364–6.
107. Dendukuri D, Doyle PS. The synthesis and assembly of polymeric microparticles using microfluidics. *Adv Mater*. 2009;**21**(**41**):4071–86.
108. Duncanson WJ, Lin T, Abate AR, Seiffert S, Shah RK, Weitz DA. Microfluidic synthesis of advanced microparticles for encapsulation and controlled release. *Lab Chip*. 2012;**12**(**12**):2135–45.
109. Brinker CJ, Scherer GW. Sol-gel science: the physics and chemistry of sol-gel processing. Academic press; 2013.
110. Ciriminna R, Fidalgo A, Pandarus V, Beland F, Ilharco LM, Pagliaro M. The sol–gel route to advanced silica-based materials and recent applications. *Chem Rev*. 2013;**113**(**8**):6592–620.
111. Klein LC. Sol-gel processing of silicates. *Annu Rev Mater Sci*. 1985;**15**(**1**):227–48.
112. Dilsiz N, Akovalı G. Study of sol–gel processing for fabrication of low density alumina microspheres. *Mater Sci Eng A*. 2002;**332**(**1–2**):91–6.
113. Landau M V. Sol–gel process. *Handb Heterog Catal online*. 2008;119–60.
114. Hench LL, West JK. The sol-gel process. *Chem Rev*. 1990;**90**(**1**):33–72.
115. Avnir D. Organic chemistry within ceramic matrixes: doped sol-gel materials. *Acc Chem Res*. 1995;**28**(**8**):328–34.
116. Sanchez C, Julián B, Belleville P, Popall M. Applications of hybrid organic–inorganic nanocomposites. *J Mater Chem*. 2005;**15**(**35–36**):3559–92.
117. Li CY, Tseng JY, Morita K, Lechner CL, Hu Y, Mackenzie JD. ORMOSILS as matrices in inorganic-organic nanocomposites for various optical applications. In: Sol-Gel Optics II. SPIE; 1992. p. 410–9.
118. Avnir D, Blum J, Nairoukh Z. Better Catalysis with Organically Modified Sol–Gel Materials. *Sol-Gel Handb*. 2015;963–86.
119. Xu B, Li S, Shi R, Liu H. Multifunctional mesoporous silica nanoparticles for biomedical applications. *Signal Transduct Target Ther*. 2023;**8**(**1**):435.
120. Zaidi ZS, Teki SVN, Katti DS. Stimuli-Responsive Mesoporous Silica Nanoparticles for Cancer Therapy. In: Advances in Stimuli-Responsive Nanosystems for Cancer Therapy. Springer; 2026. p. 181–211.
121. Rosenholm JM, Lindén M. Towards establishing structure–activity relationships for mesoporous silica in drug delivery applications. *J Control release*. 2008;**128**(**2**):157–64.
122. Cauda V, Schlossbauer A, Kecht J, Zu¨rner A, Bein T. Multiple core− shell functionalized colloidal mesoporous silica nanoparticles. *J Am Chem Soc*. 2009;**131**(**32**):11361–70.
123. Maniruzzaman M, Boateng JS, Snowden MJ, Douroumis D. A review of hot-melt extrusion: process technology to pharmaceutical products. *Int Sch Res Not*. 2012;**2012**(**1**):436763.
124. Repka MA, Majumdar S, Kumar Battu S, Srirangam R, Upadhye SB. Applications of hot-melt extrusion for drug delivery. *Expert Opin Drug Deliv*. 2008;**5**(**12**):1357–76.
125. Miller DA, McConville JT, Yang W, Williams III RO, McGinity JW. Hot-melt extrusion for enhanced delivery of drug particles. *J Pharm Sci*. 2007;**96**(**2**):361–76.
126. Vervaet C, Baert L, Remon JP. Extrusion-spheronisation A literature review. *Int J Pharm*. 1995;**116**(**2**):131–46.
127. Bao L, Ma J, Long W, He P, Zhang T an, Nguyen A V. Fractal analysis in particle dissolution: a review. *Rev Chem Eng*. 2014;**30**(**3**):261–87.
128. Williams ML, Landel RF, Ferry JD. The temperature dependence of relaxation mechanisms in amorphous polymers and other glass-forming liquids. *J Am Chem Soc*. 1955;**77**(**14**):3701–7.
129. Bochmann ES, Gryczke A, Wagner KG. Validation of model-based melt viscosity in hot-melt extrusion numerical simulation. *Pharmaceutics*. 2018;**10**(**3**):132.

 doi:10.20944/preprints202604.0403.v1

130. Mani N. Microencapsulation of a hydrophilic drug into a hydrophobic matrix using a salting-out procedure and development of tableted microspheres. 2003;
131. Kumar A, Kumar A. Poly (lactic acid) and poly (lactic-co-glycolic) acid nanoparticles: versatility in biomedical applications. In: Materials for Biomedical Engineering. Elsevier; 2019. p. 199–216.
132. Custodio-Mendoza JA, Pokorski P, Aktaş H, Carro AM, Kurek MA. Simultaneous determination of six catechins and caffeine in tea and wine using salting-out assisted liquid–liquid extraction and high-performance liquid chromatography with ultraviolet detection. *J Sep Sci*. 2024;**47**(**9**–**10**):2400142.
133. Hama AA, Aziz D, Qader IN, Ibrahim BM, Meena BI. Nanocarriers for controlled drug delivery A convergence of polymer and nanochemistry. *J Turkish Chem Soc Sect A Chem*. 2024;**11**(**4**):1581–94.
134. Zhang Y, Cremer PS. Interactions between macromolecules and ions: the Hofmeister series. *Curr Opin Chem Biol*. 2006;**10**(**6**):658–63.
135. Boye JI, Barbana C. Protein processing in food and bioproduct manufacturing and techniques for analysis. *Food Ind Bioprod Bioprocess*. 2012;85–113.
136. Arakawa T, Timasheff SN. Mechanism of protein salting in and salting out by divalent cation salts: balance between hydration and salt binding. *Biochemistry*. 1984;**23**(**25**):5912–23.
137. Park K. Controlled drug delivery systems: past forward and future back. *J Control Release*. 2014;**190**:3–8.
138. Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). *Adv Drug Deliv Rev*. 2012;**64**:163–74.
139. Fu Y, Kao WJ. Drug release kinetics and transport mechanisms of non-degradable and degradable polymeric delivery systems. *Expert Opin Drug Deliv*. 2010;**7**(**4**):429–44.
140. Vladisavljević GT, Khalid N, Neves MA, Kuroiwa T, Nakajima M, Uemura K, et al. Industrial lab-on-a-chip: Design, applications and scale-up for drug discovery and delivery. *Adv Drug Deliv Rev*. 2013;**65**(**11**–**12**):1626–63.
141. Kim SM, Patel M, Patel R. PLGA core-shell nano/microparticle delivery system for biomedical application. *Polymers (Basel)*. 2021;**13**(**20**):3471.
142. Mackin-Mohamour ARS, Budzinski J, Bastogne T, Roques-Carmes T, Sadtler V, Marchal P, et al. Agile quality-by-design development of alginate microparticles for encapsulation of hydrophilic drug. *Colloids Surfaces A Physicochem Eng Asp*. 2024;**693**:134053.
143. Ichikawa H, Uemura T, Fukumori Y. Dry particle coating with polymeric nanopowders for fabricating multi-layered, prolonged-release microparticles using Theta-Composer. In: The 10th International Symposium on Agglomeration. 2013.
144. Alam MS, Akhtar A, Ahsan I, Shafiq-un-Nabi S. Pharmaceutical product development exploiting 3D printing technology: conventional to novel drug delivery system. *Curr Pharm Des*. 2018;**24**(**42**):5029–38.
145. Vora LK, Gholap AD, Jetha K, Thakur RRS, Solanki HK, Chavda VP. Artificial intelligence in pharmaceutical technology and drug delivery design. *Pharmaceutics*. 2023;**15**(**7**):1916.
146. Demello AJ. Control and detection of chemical reactions in microfluidic systems. *Nature*. 2006;**442**(**7101**):394–402.
147. Wang J, Wang BM, Schwendeman SP. Characterization of the initial burst release of a model peptide from poly (D, L-lactide-co-glycolide) microspheres. *J Control release*. 2002;**82**(**2**–**3**):289–307.