



Microfluidics for particle production in drug delivery: From physical basics to perspective applications

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ABSTRACT

In recent years, micro- and nanoparticles have gained interest due to their applicability to diverse biomedical fields, especially drug delivery. Typical batch methods, including solvent evaporation or homogenization, achieve high production volumes but are often characterized by low reproducibility and high polydispersity. For this reason, microfluidics has recently emerged as a promising method for producing monodisperse, finely controlled, and highly tunable carriers. Depending on the material and device geometry, a wide range of particles can be obtained, spanning from the microscale to the nanoscale and from metallic to biomimetic systems. Microfluidics can reduce waste and costs because of the limited volumes employed, while enhancing throughput through parallelization. This review provides an overview of microfluidic technologies for particle production, ranging from the underlying physical principles, including dimensionless numbers, to market applications. Particular attention is devoted to the latest device geometries and materials, as well as to the implementation of artificial intelligence and emerging autonomous formulation strategies for reducing industrial costs and development times. The strengths, limitations, and potential improvements associated with each geometry and material are critically evaluated and compared to provide a comprehensive understanding of microfluidics for drug-delivery applications. Although substantial progress is still required for microfluidics to become a leading technology for industrial particle production, owing to limitations such as device clogging, chip-material compatibility, and the cost and standardization hurdles of large-scale GMP manufacturing, an increasing number of FDA-approved drug carriers may be produced through this innovative approach in the coming years.

1. Introduction

Since its conception, nearly 40 years ago, microfluidics has evolved into a leading technology in drug delivery and biomedical engineering [1]. It started with miniaturized analytical systems and quickly expanded to encompass a wide range of disciplines, including chemistry, biology, fluid mechanics and materials science [2,3]. The high precision achievable in microfluidic systems provides unprecedented control over biological microenvironments, heat transfer, and interfacial phenomena [4–6]. Besides, because microfluidic methods operate with extremely small volumes, they drastically reduce reagent consumption and waste generation [7]. The ability to function in a controlled environment with precise and reproducible protocols makes microfluidics particularly interesting for particle production [8,9].

Typical bulk particle-production methods often provide less control over mixing, nucleation, and interfacial phenomena, which may result in broader size distributions and greater batch-to-batch variability than microfluidic processes [9,10]. By contrast, microfluidic platforms precisely manipulate fluids, reagents, and flow conditions. This fine control yields high encapsulation efficiency (EE) and monodisperse particle size distributions, enabling tunable particle sizes from micro to nanoscale and diverse compositions, while also offering straightforward scalability and enhanced reproducibility [8,9]. Although throughput per microfluidic device is typically low, processes can be parallelized to increase production capacity while preserving the operating conditions of individual units [8,11].

Microfluidic device design is highly customizable, not only in terms of particle material or drug encapsulation, but also with respect to chip

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geometry. Emerging fabrication techniques such as micro milling, 3D printing and soft lithography have greatly simplified and accelerated device prototyping, allowing optimization of droplet generation and control of interfacial behavior that influences particle morphology [12, 13]. Considering these advantages, along with the ability to use a wide variety of materials, including biodegradable polymers, the significance of microfluidics in the drug delivery industry has become increasingly evident, spanning applications from drug development to high-throughput drug screening, especially in organ-on-chip systems [14,15]. In particular, the combination of scalability, fine control and design flexibility offered by microfluidics makes it a powerful tool for current and future biomedical engineering efforts and pharmaceutical innovation.

This review aims to provide a comprehensive overview of recent advancements in microfluidics platforms for microparticles (MPs) and nanoparticles (NPs) production in drug delivery. It first introduces the fundamental physical principles underlying microfluidic systems, with particular attention to dimensionless parameters that govern flow behavior and influence particle formation. The discussion then moves to the main device architectures and chip geometries, ranging from simple single-phase channels to multiphase and field-assisted configurations. Subsequently, the importance of numerical modeling and computational optimization is explored, emphasizing their role in refining channel design and flow control. The review then examines the diversity of particles produced through microfluidics, together with the materials and fabrication approaches employed. Finally, the current and emerging applications of microfluidic-based particle systems in drug delivery and beyond are analyzed, offering insights into future research directions in this rapidly evolving field.

2. Microfluidic physics: dimensionless numbers

The dimensionless groups introduced here are used as an application-oriented framework for interpreting mixing, droplet breakup, and viscoelastic effects in carrier production. Their relevance is summarized in Table 1. As a compact hydrodynamic baseline, the relative importance of inertial and viscous effects is obtained from the Navier–Stokes momentum equation. For an incompressible Newtonian fluid in the absence of body forces, the equation can be written as

$$\rho \left(\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} \right) = -\nabla p + \mu \nabla^2 \mathbf{u}, \quad (1)$$

where $\mathbf{u}$ is the fluid velocity vector, t is time, ρ is the fluid density, p is the pressure, μ is the dynamic viscosity, and ∇ denotes the spatial differential operator [16]. Equation (1) is not intended as a universal description of every system considered in this review: field-assisted devices require the relevant electric, magnetic, acoustic, or thermal body-force contribution, whereas non-Newtonian formulations require an additional constitutive relation for the stress.

To identify the characteristic dimensionless numbers governing microfluidic flows, Eq. (1) is recast in dimensionless form. The characteristic length L , characteristic velocity U , characteristic time $t_c = L/U$, and characteristic pressure $p_c = \rho U^2$ are therefore introduced. The corresponding dimensionless variables are defined as

$$\tilde{\mathbf{x}} = \frac{\mathbf{x}}{L}, \tilde{\mathbf{u}} = \frac{\mathbf{u}}{U}, \tilde{t} = \frac{t}{t_c}, \tilde{p} = \frac{p}{p_c}, \quad (2)$$

where $\mathbf{x}$ is the spatial position vector. Accordingly, the dimensionless differential operator is defined as $\tilde{\nabla} = L\nabla$. Substitution of these dimensionless variables into Eq. (1) gives

$$\frac{\partial \tilde{\mathbf{u}}}{\partial \tilde{t}} + \tilde{\mathbf{u}} \cdot \tilde{\nabla} \tilde{\mathbf{u}} = -\tilde{\nabla} \tilde{p} + \frac{1}{\text{Re}} \tilde{\nabla}^2 \tilde{\mathbf{u}}, \quad (3)$$

where

Table 1

Application-oriented map of the dimensionless parameters used in this review. Equations refer to the definitions given once in the preceding text; the table emphasizes their specific connection to microfluidic carrier production rather than repeating general regime definitions.

Parameter(s)	Microfluidic context	Relevance to carrier production	Relevance to the review
ReEq. (4)	Pressure-driven flow in microscale channels.	Indicates when viscous-dominated laminar flow can be expected and whether geometry-induced inertial effects may contribute to mixing.	Continuous-flow micromixers, Section 3.1.
PeEq. (10)	Solvent–antisolvent and reagent mixing.	Distinguishes downstream advective transport from transverse diffusive homogenization; mixing time relative to nucleation influences carrier size and dispersity.	Continuous-flow micromixers, Section 3.1.
Ca and Λ_μ Eq. (13) and viscosity-ratio definition in the text.	Deformation and breakup of immiscible streams.	Used jointly with FRR, wettability, and geometry to interpret dripping or jetting, droplet size, shell thickness, and polydispersity.	Segmented-flow devices, Section 3.2.
We, Oh _d , and χ Eqs. (15) and (14); confinement definition in the text.	Inertial–capillary jet breakup, viscous damping, and wall confinement.	Refine the interpretation of jet stability and breakup length when Ca alone is insufficient, especially at increased throughput.	Jetting and scale-up of segmented-flow systems, Section 3.2.
Bo and Fr Eq. (5) and definition in the text.	Screening of gravitational effects at small length scales.	Explain why gravity is commonly negligible relative to capillarity in droplet-forming microchannels; they are screening parameters rather than primary design variables in the devices reviewed.	Assumption used throughout the microscale analysis.
Wi and De Eqs. (18) and (19).	Non-Newtonian polymeric or biological formulations.	Indicate whether elastic stresses and deformation history can alter focusing, breakup, particle morphology, or encapsulation.	Viscoelastic co-flow formulations, Section 3.2.2.

$$\text{Re} = \frac{\rho UL}{\mu}, \quad (4)$$

is the Reynolds number, which represents the ratio between inertial and viscous effects [17]. For $\text{Re} \ll 1$, viscous effects dominate and the inertial terms become negligible. Conversely, as Re increases, inertial effects become progressively more significant.

Gravity has been neglected in Eq. (1), as is commonly assumed for microscale flows. If the gravitational body-force term $\rho \mathbf{g}$ were retained,

the dimensionless momentum equation would contain a gravitational contribution proportional to Fr^{-2} , where $\text{Fr} = U/\sqrt{gL}$ is the Froude number, which compares inertial and gravitational effects. However, in multiphase microfluidic systems, the relative importance of gravity is more commonly assessed through the Bond number,

$$\text{Bo} = \frac{\Delta\rho gL^2}{\gamma}, \quad (5)$$

where $\Delta\rho$ is the density difference between the phases, g is the gravitational acceleration, and γ is the interfacial tension. For $\text{Bo} \ll 1$, capillary effects dominate over gravitational effects, justifying the omission of gravity. This condition is generally satisfied in microfluidic channels because of their small characteristic dimensions.

For $\text{Re} \ll 1$, the flow is laminar because inertial effects are negligible. In this limit, the Navier–Stokes momentum equation can be simplified as

$$0 = -\nabla p + \mu \nabla^2 \mathbf{u}, \quad (6)$$

which is the governing momentum equation for Stokes flow.

Because the characteristic dimensions of the systems reviewed here are generally no greater than a few hundred micrometres, viscous-dominated laminar flow is common. Conventional pipe-flow transition thresholds are not used as universal criteria, because the onset of inertial or unsteady behaviour depends on channel geometry and inlet conditions. Importantly, laminarity describes the ordered character of the velocity field and does not establish whether solute transport is diffusion- or convection-dominated. In many continuous-flow micromixers, convection carries species downstream while transverse homogenization remains limited by molecular diffusion. Their relative contributions are described by the convection–diffusion equation

$$\frac{\partial C}{\partial t} + \mathbf{u} \cdot \nabla C = D \nabla^2 C, \quad (7)$$

where D is the diffusion coefficient and C is the concentration of the transported species.

To obtain the dimensionless form of Eq. (7), the dimensionless variables are defined as

$$\tilde{\mathbf{x}} = \frac{\mathbf{x}}{L}, \tilde{\mathbf{u}} = \frac{\mathbf{u}}{U}, \tilde{t} = \frac{t}{t_c}, \tilde{C} = \frac{C}{C_c}, \quad (8)$$

where C_c is the characteristic concentration. Using $\tilde{\nabla} = L\nabla$, Eq. (7) can be rewritten as

$$\frac{\partial \tilde{C}}{\partial \tilde{t}} + \tilde{\mathbf{u}} \cdot \tilde{\nabla} \tilde{C} = \frac{1}{\text{Pe}} \tilde{\nabla}^2 \tilde{C}, \quad (9)$$

where

$$\text{Pe} = \frac{UL}{D}, \quad (10)$$

is the Péclet number, which represents the ratio between convective and diffusive transport [18]. For $\text{Pe} \ll 1$, transport is diffusion-dominated, whereas for $\text{Pe} \gg 1$, convection dominates and diffusion becomes comparatively negligible [19].

The Péclet number can also provide information about the length required for mixing to occur. The spatial distance required to achieve complete homogenization is defined as the mixing length, L_m . The characteristic diffusion timescale is given by $t_{\text{diff}} = L^2/D$. Accordingly, the mixing length can be estimated as $L_m = Ut_{\text{diff}}$. Considering Poiseuille flow, it can be expressed as

$$L_m = \frac{1}{2}L \text{Pe}. \quad (11)$$

This linear scaling implies that Pe acts as a geometric multiplier: higher convective rates or lower molecular diffusivities result in a

proportional increase in the microchannel length required to achieve a completely homogeneous solution. Consequently, this expression can be used as a predictive tool for sizing passive micromixers before fabrication.

Microfluidics, as discussed in a later section, is frequently used for droplet production. Droplet formation requires specific flow regimes that depend on the properties of the fluids, particularly on the interfacial tension, γ . In this case, the Navier–Stokes momentum equation can be written as

$$\rho \left(\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} \right) = -\nabla p + \mu \nabla^2 \mathbf{u} + \mathbf{f}_\gamma, \quad (12)$$

where $\mathbf{f}_\gamma \sim \gamma/L^2$ is the volumetric interfacial-force term arising from the interfacial tension. Following nondimensionalization, the ratio between viscous stresses and interfacial-tension stresses defines the capillary number Ca as [20]:

$$\text{Ca} = \frac{\mu U}{\gamma}. \quad (13)$$

Depending on the value of Ca , different droplet-formation regimes can be identified. For $\text{Ca} \ll 1$, interfacial tension dominates, promoting the formation of spherical droplets and stable interfaces. This regime is primarily exploited for the production of monodisperse emulsions, in which the particle size is determined mainly by the channel geometry. For $\text{Ca} \sim 1$, viscous and interfacial-tension stresses are comparable, giving rise to a dripping regime. In this regime, droplet breakup occurs near the nozzle with a well-defined frequency and depends primarily on the flow-rate ratio (FRR) between the two phases. At sufficiently high Ca , viscous stresses can favour the formation of an elongated jet. However, Ca is not a stand-alone criterion for the dripping–jetting transition. The regime depends jointly on the viscosity ratio $\Lambda_\mu = \mu_d/\mu_c$, the phase FRR, interfacial properties, confinement, and device geometry [21]. In this case, flow perturbations can generate sinusoidal disturbances. If λ is the disturbance wavelength and r_0 is the jet radius, interfacial tension amplifies the disturbance when $\lambda > 2\pi r_0$, eventually causing the jet to break up into droplets. This phenomenon is known as the Rayleigh–Plateau instability.

The classical wavelength criterion identifies which disturbances are capillary-unstable but does not specify how rapidly breakup occurs. For a perturbation with wavenumber $k = 2\pi/\lambda$, its amplitude can be expressed as $a(t) = a_0 \exp[\omega(k)t]$, where $\omega(k)$ is the capillary-instability growth rate. Modes for which $\omega(k) > 0$ grow, and the maximum growth rate, ω_{max} , determines the dominant wavelength and sets the characteristic breakup timescale $t_b \sim \omega_{\text{max}}^{-1}$. Consequently, the breakup length scales approximately as $L_b \sim U_j/\omega_{\text{max}}$, where U_j is the jet velocity.

For a liquid jet surrounded by another liquid, the dispersion relation, and therefore ω_{max} , also depends on the viscosity ratio $\Lambda_\mu = \mu_d/\mu_c$, where the subscripts d and c denote the dispersed or jet phase and the continuous phase, respectively. The relative importance of viscous damping and inertial–capillary dynamics can be expressed through the jet-phase Ohnesorge number,

$$\text{Oh}_d = \frac{\mu_d}{\sqrt{\rho_d \gamma r_0}}, \quad (14)$$

where ρ_d and μ_d are the density and viscosity of the jet phase. Increasing Oh_d generally strengthens viscous damping and reduces the growth rate of capillary disturbances [22,23].

Microfluidic confinement also modifies jet breakup by altering the base velocity profile and the instability spectrum. A convenient measure is the confinement ratio $\chi = 2r_0/D_h$, where D_h is the hydraulic diameter of the channel. As confinement increases, the channel walls can shift the dominant wavelength, growth rate, breakup length, and dripping–jetting transition relative to an unconfined cylindrical jet [24,25].

It is commonly observed in flow-focusing microfluidic geometries, which are discussed later in this paper, and may produce polydisperse

droplets because of their sensitivity to flow fluctuations [26]. For $Ca \gg 1$, capillary disturbances may grow more slowly than they are advected downstream. The breakup length can therefore exceed the available channel or observation length, so an apparently stable jet should be interpreted in relation to the viscosity ratio, confinement, and available breakup length rather than as a universal high- Ca regime [27]. Whereas Ca characterizes the relative importance of viscous and interfacial-tension stresses, the Weber number, We , characterizes the relative importance of inertial and interfacial-tension stresses [28]. It is defined as

$$We = \frac{\rho U^2 L}{\gamma}. \quad (15)$$

Similarly to Ca , for $We \ll 1$, interfacial tension dominates over inertial effects, favouring the formation of spherical and stable droplets. For $We > 1$, instabilities may arise in the jet and cause jet breakup. For $We \gg 1$, inertial effects dominate over capillarity, but this does not necessarily produce a universally stable jet. Depending on the geometry and degree of confinement, elongated jets, sinuous instabilities, or atomization-like breakup modes may arise [29–31].

The Newtonian description in Eq. (1) is insufficient for non-Newtonian carrier formulations whose stress depends on deformation history. As a simple illustrative case, a single-mode linear Maxwell viscoelastic fluid is described by the constitutive equation

$$\boldsymbol{\tau} + \lambda \frac{D\boldsymbol{\tau}}{Dt} = 2\eta \mathbf{D}, \quad (16)$$

where $\boldsymbol{\tau}$ is the extra-stress tensor, λ is the relaxation time associated with the elastic response, η is the viscosity, $\mathbf{D}$ is the rate-of-deformation tensor, and D/Dt denotes the material derivative.

For this Maxwell model, use of the characteristic variables gives the dimensionless constitutive equation

$$\tilde{\boldsymbol{\tau}} + \frac{\lambda U}{L} \frac{D\tilde{\boldsymbol{\tau}}}{Dt} = 2\tilde{\mathbf{D}}, \quad (17)$$

where the dimensionless group

$$Wi = \lambda \dot{\gamma}, \quad (18)$$

is the Weissenberg number. It represents the ratio between the material relaxation time and the characteristic deformation timescale.

Only for simple shear, or for pressure-driven flows represented by the characteristic shear-rate scaling $\dot{\gamma} \sim U/L$, Eq. (18) becomes $Wi \sim \lambda U/L$. Under this specific scaling, the Weissenberg number is numerically equivalent to the Deborah number, De , defined as

$$De = \frac{\lambda}{t_c}, \quad (19)$$

where $t_c = L/U$. However, the two dimensionless numbers have different physical meanings. The Deborah number compares the material relaxation time with the characteristic timescale of the overall process, whereas the Weissenberg number compares the relaxation time with the local deformation timescale experienced by the material. Consequently, Wi is generally the preferred parameter for describing elastic effects in non-uniform microfluidic flows, such as contraction–expansion geometries and extensional flows. For $De \ll 1$, or equivalently $Wi \ll 1$ under the simple-flow scaling above, the Maxwell fluid relaxes much faster than the characteristic flow or deformation timescale and approaches Newtonian behaviour. The Maxwell constitutive equation therefore reduces to

$$\boldsymbol{\tau} = 2\eta \mathbf{D}. \quad (20)$$

For $De \gg 1$, or $Wi \gg 1$, elastic stresses cannot fully relax during deformation, and elastic effects dominate the material response. This may lead to nonlinear flow behaviour, normal stress differences,

polymer stretching, and purely elastic instabilities. For $Wi \sim 1$, viscoelastic effects become significant, resulting in the storage of elastic stresses [32,33].

Table 1 maps the parameters defined above to the specific microfluidic operations and drug-carrier attributes for which they are used in the remainder of this review.

Accordingly, the dimensionless analysis is used here as a bridge between operating conditions and carrier formation, not as a stand-alone catalogue of flow regimes. Re and Pe guide the interpretation of continuous-flow mixing, Ca must be combined with property ratios and confinement for segmented-flow breakup, and Wi or De becomes relevant when the formulation is viscoelastic.

3. Microfluidic devices

Microfluidic systems have emerged as cutting-edge technologies in pharmaceutical research, enabling the precise manipulation of small fluid volumes within microscale channels and chambers. This approach has proven to be versatile and efficient for controlled drug delivery, particularly for the synthesis of MPs and NPs, as it addresses many of the limitations associated with conventional production methods [34]. One of the main strengths of microfluidics is its ability to produce particles with high uniformity, tunable sizes, and well-defined morphologies, while ensuring excellent batch-to-batch reproducibility, high encapsulation efficiency (EE), and the potential for scalable, high-throughput manufacturing [9].

Microfluidic systems can generally be classified according to their fluid-dynamic and mixing principles into three main categories: (i) continuous-flow systems, (ii) segmented-flow or multiphase systems, and (iii) field-assisted systems (Fig. 1A–C). In the fabrication of drug carriers, the selection of the microfluidic strategy is closely related to the desired particle size. In particular, droplet-based, segmented-flow configurations are generally more suitable for the production of MPs with sizes ranging from tens to hundreds of micrometres, whereas continuous-flow configurations are typically employed to produce nanoscale particles [10].

3.1. Continuous-flow microfluidic systems

Continuous-flow microfluidic systems generally operate under the low- Re and often high- Pe conditions introduced in Section 2. Their designs therefore enhance transverse transport by shortening diffusion distances, increasing interfacial area, or inducing chaotic advection, namely deterministic aperiodic motion that repeatedly stretches and folds fluid interfaces without generating turbulence [35–37]. By accelerating mixing relative to nucleation or self-assembly, these mechanisms can narrow carrier-size distributions and improve drug-loading reproducibility.

Passive micromixers achieve these effects using pressure-driven flow through engineered channel geometries, without requiring external energy sources. Their relatively simple operation, limited equipment requirements, and ease of integration into lab-on-a-chip platforms make them particularly attractive for chemical and biological applications. Nevertheless, increasingly complex geometries may also increase hydraulic resistance, pressure drop, fabrication difficulty, and the risk of particle deposition in grooves or constrictions.

By contrast, active micromixers rely on external energy sources, such as time-dependent pressure perturbations, acoustic waves, electric fields, thermal gradients, or magnetic forces, to generate disturbances that accelerate transverse mass transport. These systems can achieve faster and more dynamically controllable mixing than passive configurations.

Between these two approaches, hybrid active–passive micromixers combine geometry-induced flow perturbations with external actuation to exploit the advantages of both strategies. Representative configurations include acoustic actuation coupled with sharp edges,

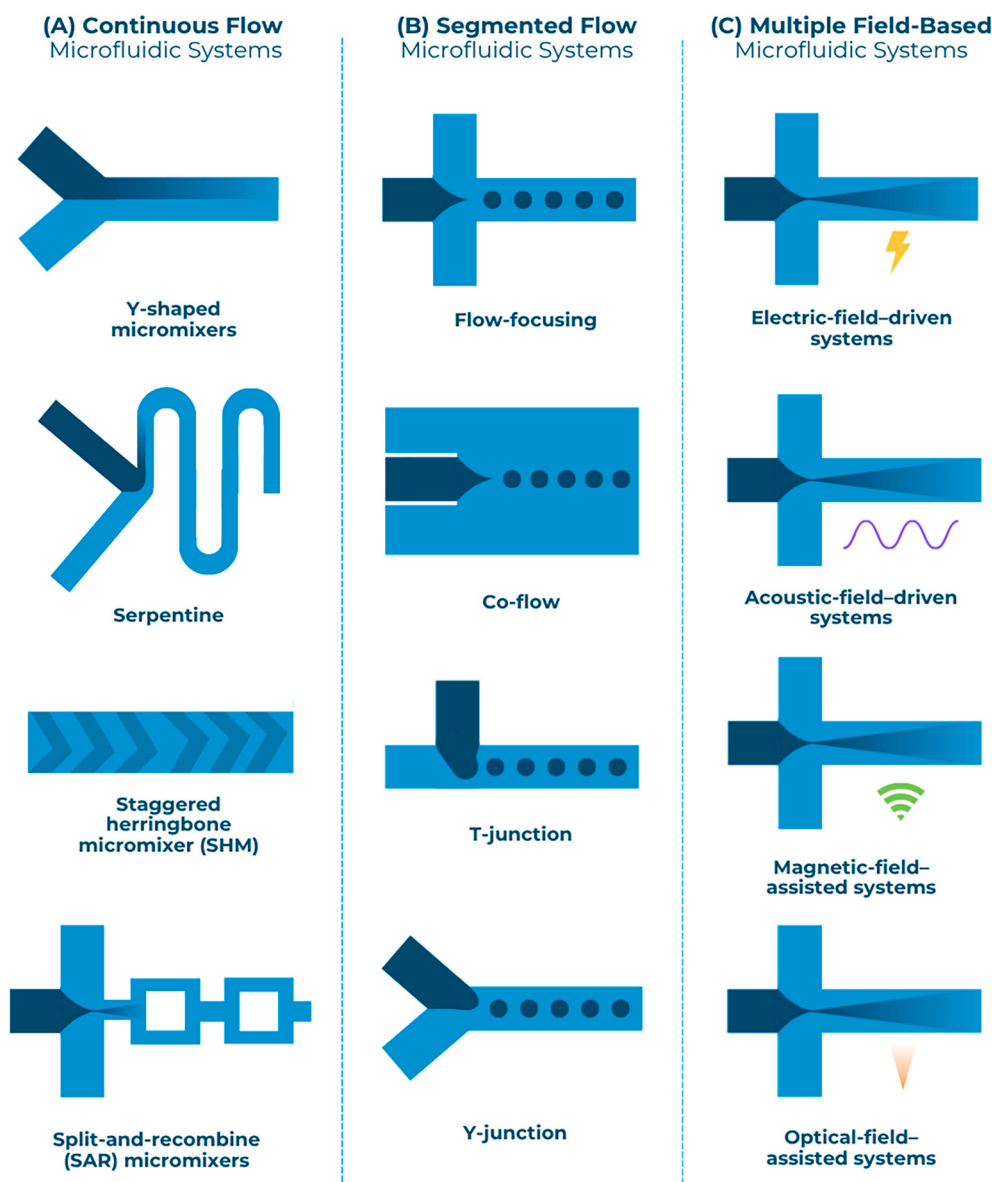


Fig. 1. Classification of microfluidic platforms by flow and mixing mechanisms. (A) Continuous flow: laminar coflow under viscous dominated, turbulence free conditions; enhanced mixing occurs by inducing chaotic advection. (B) Segmented (multiphase) flow: lateral sheath fluids pinch a dispersed stream, which undergoes capillary breakup to form nearly monodisperse droplets, widely used for core/shell MPs. (C) Field assisted systems: external electric, magnetic, acoustic, optical, or thermal fields generate, assemble, or actuate droplets and particles.

contraction–expansion structures, micropillars, or serpentine channels, as well as electro-osmotic actuation combined with rigid baffles [38–41]. In these systems, passive structures intensify acoustically or electrically induced vortices, promoting interfacial stretching and chaotic advection. This synergy can extend efficient mixing to higher flow rates and support the controlled synthesis of NPs. However, the need for additional actuators, power supplies, and control components required by active mixing strategies increases equipment complexity and may constrain compatibility with sensitive biological samples or pharmaceutical formulations [35]. The selection of a mixing strategy should therefore consider not only mixing performance, but also throughput, formulation properties, equipment cost, reproducibility, and compatibility with scalable manufacturing.

3.1.1. Passive mixing

3.1.1.1. Simple geometries for basic mixing. Y-shaped and T-shaped micromixers are among the simplest and most widely used passive

geometries for basic mixing in microfluidic systems. In their conventional configurations, both devices primarily rely on molecular diffusion across the interface between adjacent fluid streams.

A Y-shaped micromixer consists of two inlet channels that converge at a Y-junction and continue into a single outlet channel, as schematically illustrated in Fig. 1A. This configuration is attractive because of its simple fabrication, low geometrical complexity, and predictable flow distribution. However, its mixing performance is strongly dependent on the diffusion coefficient, flow velocity, and contact area between the streams. Therefore, Y-shaped devices can achieve effective mixing over short distances at sufficiently low Pe , whereas higher Pe values generally require longer downstream channels for complete homogenization [42]. Among the geometrical parameters investigated for Y-shaped micromixers, the convergence angle has received particular attention because it can modify the interaction between the inlet streams and the development of their interface. Hsieh et al. reported angle-dependent variations in mixing efficiency and mixing length, identifying an optimal configuration under the conditions examined [43]. Similarly, Rahimi

et al. observed that increasing the confluence angle could improve micromixing in T-, Y-, and oriented Y-shaped devices, although the geometrical modification also influenced the pressure drop [44]. Conversely, the numerical analysis of Farahinia and Zhang indicated that the inlet angle may exert a weaker influence than flow velocity and molecular diffusivity under diffusion-dominated conditions [45]. These findings indicate that the convergence angle can be used to tune mixing performance, but its effect remains strongly dependent on the operating conditions and fluid properties. While the Y-junction operates as a passive mixer under steady-flow conditions, the same geometry can be converted into an active micromixing platform by periodically modulating the inlet flow rates through external actuation, thereby promoting rapid stretching and folding of the fluid interface. This pulsation-assisted strategy is discussed in Section 3.1.2.

In a T-shaped micromixer, two inlet streams enter through opposing or perpendicular channels and meet at the junction before flowing through a common outlet channel. The abrupt change in flow direction can promote interface deformation and, under suitable operating conditions, the formation of vortical or engulfment-flow structures. Nevertheless, at low Reynolds numbers, conventional T-shaped mixers remain largely diffusion-limited. Their performance is influenced by the inlet configuration, FRR, channel dimensions, and cross-sectional geometry.

Modifications of the basic T-shaped geometry have therefore been explored to enhance transverse transport. Variations in channel width, height, and cross-sectional shape, including rectangular, elliptical, and triangular sections, can modify both mixing efficiency and pressure drop [46]. In particular, elliptical channels with selected aspect ratios, as well as channels with wavy or twisted walls [47], may promote secondary flows, interface stretching, and vortex formation. These modifications can improve mixing over shorter distances, but this benefit may be accompanied by higher hydraulic resistance and greater fabrication complexity. Consequently, basic Y- and T-shaped configurations remain advantageous when simplicity, reproducibility, and low manufacturing cost are prioritised, whereas modified geometries are preferable when enhanced mixing justifies the additional pressure and fabrication requirements.

3.1.1.2. Complex geometries for enhanced passive mixing (chaotic advection). More complex passive geometries can enhance mixing by manipulating fluid streamlines and generating transverse flow components. These mechanisms increase the interfacial area between adjacent streams and reduce the diffusion distance without requiring external energy inputs.

A first class of designs includes zigzag channels, in which successive sharp turns repeatedly reorient and deform the liquid–liquid interface, thereby promoting transverse transport and chaotic advection in both two- and three-dimensional layouts [48]. Serpentine (Fig. 1A) and spiral channels similarly exploit curved trajectories to generate secondary flows. Depending on the channel curvature and operating conditions, centrifugal effects can induce counter-rotating Dean vortices, which enhance cross-sectional transport and reduce the mixing length [49]. Spiral configurations are particularly attractive because they provide relatively long mixing paths within a compact footprint while remaining compatible with planar fabrication.

A recent example was reported by Choi et al., who developed a spiral microfluidic chip (SMC) fabricated by CO₂ laser engraving of photopolymerizable perfluoropolyether and poly(ethylene glycol) diacrylate layers (Fig. 2). The repeated spiral units enhanced mixing and were used for the continuous production of lipid nanoparticles (LNPs) with an average size of 73 ± 24 nm and a polydispersity index (PDI) of 0.111 ± 0.011 . A multi-spiral microfluidic chip (MSMC), obtained by parallelizing several spiral units, increased the production capacity up to 960 mL h^{-1} without a reported deterioration in particle size or dispersity [50]. This study highlights the potential of compact spiral

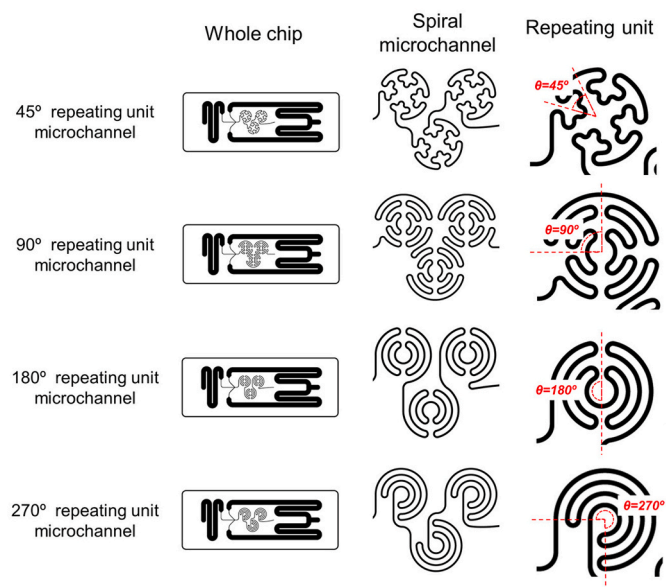


Fig. 2. Comparison of spiral microfluidic chip configurations designed with repeating units at angular orientations of 45°, 90°, 180°, and 270°. For each configuration, the overall chip layout is shown together with the corresponding spiral-channel architecture and an enlarged view of the individual repeating unit. The variation in angular arrangement modifies channel curvature and, consequently, the flow patterns governing mixing during LNPs production. Reproduced from an open-access source [50].

geometries for increasing throughput through parallelization, although their performance remains dependent on the specific channel design, operating conditions, and lipid formulation. While no therapeutic cargo was encapsulated, the resulting LNP platform could be adapted for drug-delivery applications following appropriate formulation optimization.

Another widely adopted geometry is the staggered herringbone micromixer (SHM), illustrated in Fig. 1A, in which asymmetric grooves patterned on the channel surface generate transverse motion and repeatedly stretch and fold the fluid interface. This mechanism enables chaotic advection and efficient mixing even under low-Re conditions [51,52]. Compared with conventional curved channels, SHMs are less dependent on inertially induced secondary flows; however, the fabrication of well-defined three-dimensional grooves introduces additional manufacturing complexity and may affect device-to-device reproducibility.

A representative obstacle-based design is the invasive lipid nanoparticle production (iLiNP) device, which incorporates repeated baffle structures to perturb the incoming streams and accelerate solvent dilution. The geometry enables flow-dependent control of mixing and has been applied to the one-step production of size-controlled NPs for RNA delivery [53]. Compared with the SHM, the iLiNP device uses a planar baffle arrangement that avoids complex three-dimensional groove patterns and may therefore simplify device fabrication, although its mixing performance and the resulting NP characteristics remain dependent on the total flow rate (TFR), FRR, and baffle dimensions. Y-shaped passive micromixers incorporating slanted ridges or staggered herringbone grooves have also been investigated for lipid nanocarrier production [54] (Fig. 3). At an aqueous-to-ethanol FRR of 4, the staggered herringbone design produced more homogeneous DSPC/cholesterol liposomes than the slanted-ridge geometries, with a PDI of 0.18 compared with 0.31–0.32. Using this platform, encapsulation efficiencies of 72–79% for myoglobin, approximately 96% for small interfering RNA (siRNA), and 75–81% for single-stranded DNA (ssDNA) were achieved. Moreover, an LNPs formulation based on the lipid composition of Onpatro (patisiran), a clinically approved siRNA therapeutic, yielded

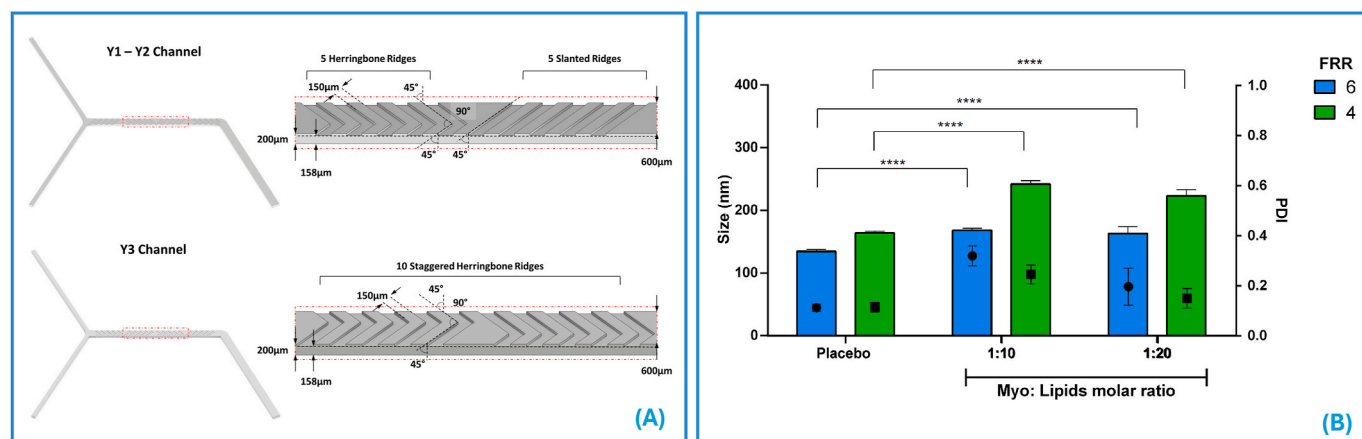


Fig. 3. Passive micromixer architectures and their application to lipid nanocarrier production. (A) Graphical representations of the Y1, Y2, and Y3 microfluidic chips. Y1 and Y2 contain slanted ridges, whereas Y3 incorporates a staggered herringbone structure to enhance mixing. (B) Effect of myoglobin encapsulation on the size and polydispersity index of stealth liposomes composed of DSPC, cholesterol, and DSPE-PEG550 (77:20:3 mol%). Results are reported for flow-rate ratios of 6 and 4 and myoglobin-to-lipid molar ratios of 1:10 and 1:20, together with unloaded control liposomes. The lipid concentration and total flow rate were maintained at 1.10 mM and 8 mL min⁻¹, respectively. Statistical significance is indicated by **** $p < 0.0001$. Adapted from an open-access source [54].

particles of 154 ± 26 nm with a PDI of 0.1 ± 0.1 and an entrapped siRNA concentration of 320 pmol/mL, supporting the applicability of the platform to protein and nucleic-acid delivery.

Beyond obstacle-based layouts, sequential-lamination and split-and-recombine (SAR) micromixers (Fig. 1A) enhance mixing by progressively multiplying fluid lamellae and shortening diffusion paths. A double-layer Y-shaped SAR design achieved mixing indices ranging from 0.966 at $Re = 5$ to 0.9992 at $Re = 100$, while maintaining a pressure loss below 350 Pa across seven mixing units at $Re = 100$. Its performance was experimentally validated through the synthesis of silver NPs with mean sizes of approximately 29–31 nm and size deviations below 5 nm. Although these particles were not investigated as drug-delivery carriers, the results demonstrate the potential of SAR architectures to improve particle-size uniformity and process reproducibility, which are relevant requirements for nanocarrier manufacturing [55–57].

Hydrodynamic flow focusing is more directly established for the production of drug-delivery carriers. In this approach, lateral sheath flows confine the polymer-containing solvent stream, accelerating solvent exchange and nanoprecipitation while limiting precursor contact with the channel walls and, consequently, polymer aggregation and fouling [58]. Using this strategy, Mares et al. produced PLGA-PEG NPs with tunable hydrodynamic diameters of 44–97 nm and PDI values of 0.06–0.15 by adjusting the solvent-to-antisolvent FRR [59]. The particles retained their biocompatibility, enabled the encapsulation of model fluorescent compounds and doxorubicin (DOX), and were internalized by MCF-7 breast-cancer cells, supporting their suitability as drug-delivery carriers (Fig. 4A–F). Coaxial and parallel-lamination mixers extend the same principle by increasing and controlling the contact area between solvent and antisolvent streams, thereby offering additional flexibility in carrier formulation and process scale-up.

Swirl- and chicane-based geometries use channel curvature, abrupt directional changes, and rotational flow components to intensify transverse transport [60]. Although the cited chicane design was primarily characterized as a mixing platform rather than for a specific pharmaceutical formulation, such rapid and reproducible solvent exchange may be advantageous for nanoprecipitation and carrier self-assembly.

Microvortex-based designs provide a more direct link to scalable drug-carrier production. Kim et al. employed a single-layer, three-inlet device in which a central stream of PLGA in acetonitrile was rapidly mixed with lateral aqueous streams containing lecithin and DSPE-PEG, producing lipid-polymer hybrid NPs with a PLGA core and a lipid-PEG corona [61]. Symmetric microvortices promoted rapid nanoprecipitation, while downstream three-dimensional focusing limited

polymer accumulation near the channel walls and reduced the risk of clogging. By varying Re from 30 to 150 and the PLGA-to-lipid ratio, particle diameters could be tuned over approximately 30–170 nm; at a PLGA-to-lipid ratio of 10, increasing Re from 30 to 150 reduced the diameter from 93 to 55 nm. Compared with bulk nanoprecipitation, the microvortex platform produced smaller NPs (55–80 nm versus 80–120 nm) with a lower PDI (~ 0.1 versus ~ 0.2) and achieved productivities up to 0.30 g h^{-1} [62]. These results demonstrate how inertial mixing can simultaneously improve size control, batch reproducibility, and throughput in the manufacture of lipid-polymer drug-delivery carriers.

Despite their operational simplicity and robustness, passive micromixers rely on channel geometry and imposed flow conditions to enhance mass transport. Their performance may therefore be limited when processing highly viscous formulations, multiphase systems, or processes requiring rapid and externally adjustable mixing. More elaborate grooves, obstacles, and recirculation regions may also promote particle retention, fouling, or clogging during prolonged operation [63].

From a manufacturing perspective, passive devices are generally easier to parallelize because multiple channels can be operated using common pressure or flow-control systems without synchronizing external actuators. Nevertheless, numbering-up may introduce flow maldistribution between parallel units, while increasing pressure drop and progressive fouling can compromise batch-to-batch reproducibility and long-term operational stability. Passive designs therefore remain advantageous for low-cost, energy-efficient, and readily integrated continuous-flow operation, provided that hydraulic resistance and fouling are adequately controlled [64–66].

3.1.2. Active mixing

Active mixing strategies use external energy inputs to overcome the diffusion-limited transverse transport characteristic of laminar flow. Compared with passive micromixers, they can provide faster and dynamically adjustable mixing, potentially enabling finer control over particle nucleation and self-assembly. These advantages, however, are generally accompanied by an increased complexity of the device and experimental setup, including the need for additional actuation and control components.

A practical intermediate approach is to retain a simple passive geometry while introducing a time-dependent modulation of the inlet flow rates. In this way, Y- or T-shaped micromixers can be converted into active mixing platforms by imposing coordinated pulsations at one or both inlets. The resulting pressure-field disturbances promote interfacial

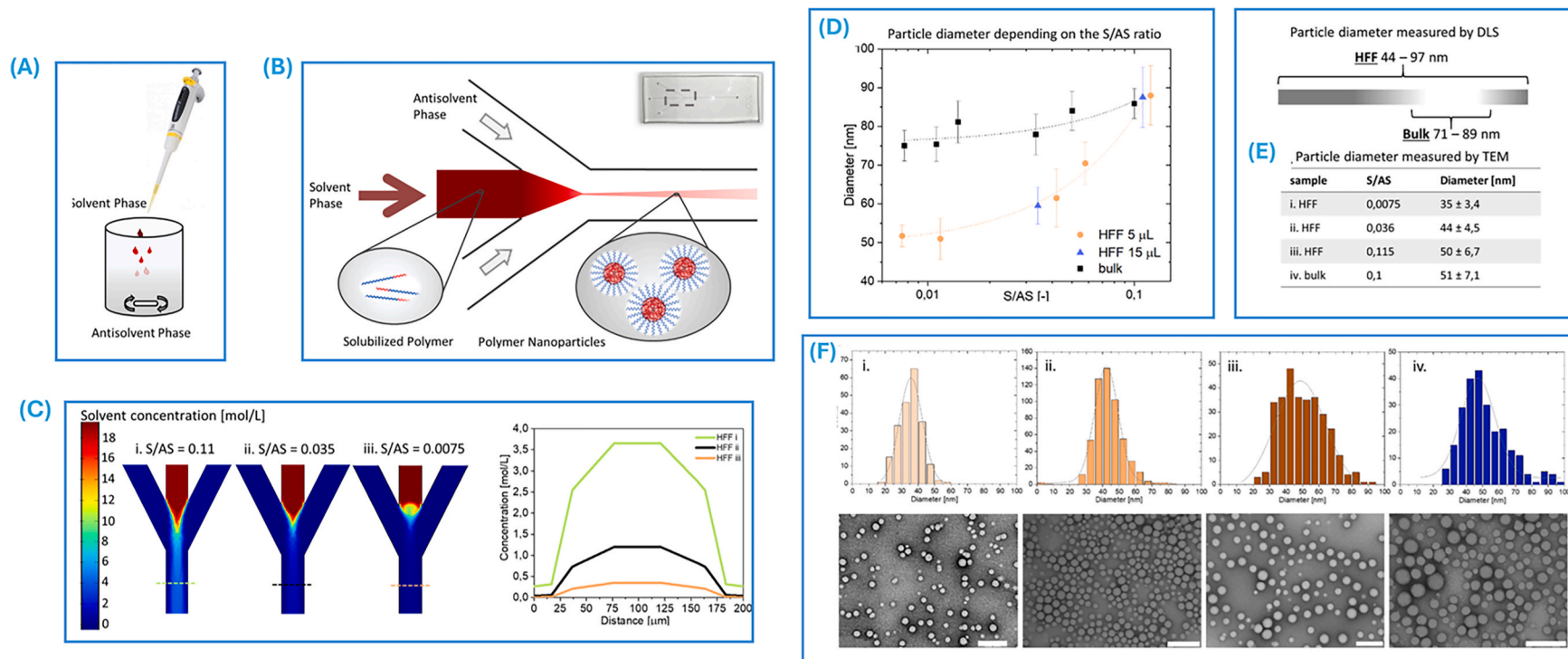


Fig. 4. Hydrodynamic flow focusing for PLGA–PEG NPs formulation and size control. (A) Manual bulk nanoprecipitation by addition of the polymer-containing solvent phase to the antisolvent phase. (B) Hydrodynamic flow focusing (HFF), in which lateral antisolvent streams confine the central solvent stream and induce NPs formation. (C) Numerical simulations of solvent concentration at three solvent-to-antisolvent FRR (S/AS), together with the corresponding concentration profiles evaluated at a cross-section located 0.3 mm downstream of the junction. (D) Particle diameter measured by dynamic light scattering (DLS) as a function of S/AS, with a schematic comparison of the size ranges obtained by HFF and bulk mixing. (E) Mean particle diameters determined from transmission electron microscopy (TEM) images. (F) TEM-derived particle-size distributions for samples i–iv and the corresponding representative TEM images; scale bars: 200 nm. Adapted from an open-access source [59].

deformation and transverse transport, thereby enhancing mixing without requiring substantial redesign of the microchannel and while limiting the additional system complexity. Beyond mixing enhancement, pulsed flows can also improve particle transport and manipulation and mitigate clogging within microchannels [67].

For example, Liu et al. coupled a Y-shaped micromixer with two piezoelectric micropumps operating at controlled frequencies and phase differences. When the inlet signals were shifted by 180°, the resulting pulsating crossover flow promoted rapid stretching and folding of the fluid interface, thereby increasing the contact area between the reagent

streams and shortening the mixing time. The periodic modulation of the inlet flow rates generated unsteady interfacial motion and enhanced chaotic advection, enabling the continuous synthesis of gold NPs with an average diameter of 21.6 nm [68].

Acoustic mixing uses surface or bulk acoustic waves to generate pressure gradients and induce localized recirculation within microchannels. The resulting fluid motion can accelerate homogenization and has been investigated for the production of encapsulating structures ranging from the nanoscale to the microscale [69,70]. In a recent work, an acoustically modulated micromixer based on an oscillating thin

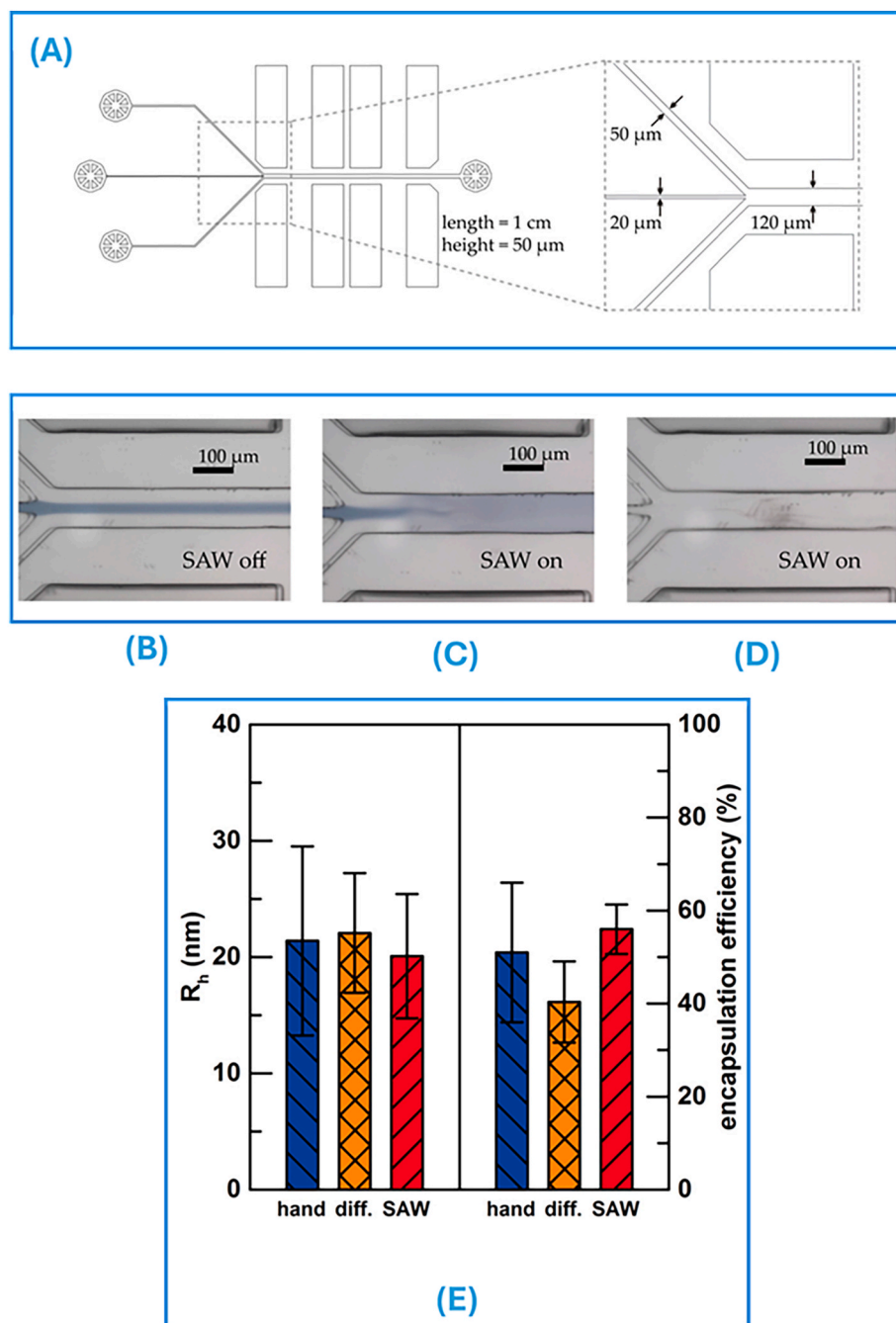


Fig. 5. Surface-acoustic-wave-assisted fabrication of therapeutic NPs. (A) Schematic modification of the conventional Y-shaped microchannel into a three-inlet configuration. (B) Three-inlet channel incorporating an intermediate protective buffer stream that prevents premature contact and interfacial complex formation between bPEI and pDNA. (C) Three-inlet channel under surface-acoustic-wave actuation, which disrupts the separating buffer stream and promotes transverse mixing. (D) Mixing of bPEI and pDNA in the acoustically actuated channel, showing the absence of unwanted interfacial complex formation; only minor precipitation was observed at the channel bottom without interfering with particle formation. (E) Hydrodynamic radius and encapsulation efficiency of mono-nucleic acid/lipid particles prepared by hand mixing, diffusion-based microfluidic mixing, and SAW-assisted microfluidic mixing. Adapted from an open-access source [72].

elastic membrane was used for the high-throughput synthesis of ultrasmall, size-tunable liposomes under both solvent-based and solvent-free conditions [71]. This approach is particularly relevant to the on-chip production of liposomes and other lipid-based nanocarriers. Westerhausen et al. employed a surface-acoustic-wave-driven transverse fluid jet in a three-inlet microchannel, in which an intermediate buffer stream prevented premature contact between branched polyethylenimine (bPEI) and plasmid DNA (pDNA) before acoustic mixing [72] (Fig. 5A–E). At a TFR of $150 \mu\text{L h}^{-1}$, the platform produced bPEI–pDNA polyplexes with a hydrodynamic radius of $55.4 \pm 0.7 \text{ nm}$ and a PDI of 0.283 ± 0.004 . The approach was also applied to lipid-based mono-nucleic acid lipid particles with a hydrodynamic radius of approximately 19 nm , for which acoustic mixing increased encapsulation efficiency and reduced experimental variability compared with hand mixing and diffusion-based microfluidic mixing. This study directly links acoustic actuation to the fabrication of therapeutic nanocarriers; however, the demonstrated NP-production throughput remained modest. Furthermore, mixing performance decreased with increasing fluid viscosity, whereas high acoustic power may induce chip heating. Scale-out would therefore require uniform acoustic coupling and thermal control across parallel channels, together with formulation-specific verification of cargo integrity and encapsulation performance.

Magnetic actuation exploits magnetic-field gradients acting on ferrofluids or suspended magnetic particles to deflect fluid streams and enhance transverse mass transport. Magnetic particles have been widely used in microfluidic platforms to enhance biomarker capture [73]. Beyond direct mixing, magnetic micropellers and magnetotactic bacteria have also been employed to generate local convection and enhance the transport of NPs across vessel–tissue interfaces and collagen matrices in microfluidic models [74]. This example is relevant to the delivery stage rather than to NP synthesis, demonstrating how field-assisted microfluidics may also be used to investigate and improve carrier penetration across biological barriers. Zhou et al. integrated a permanent NdFeB–PDMS micromagnet $150 \mu\text{m}$ from a $150\text{-}\mu\text{m}$ -wide microchannel to promote mixing between a diluted ferrofluid and water

[75] (Fig. 6A–E). At a TFR of 0.3 mL h^{-1} and a ferrofluid concentration of 1.2% (v/v), the initially distinct streams became homogeneously mixed over a channel length of 20 mm . Mixing efficiency decreased as the flow rate increased or the ferrofluid concentration decreased, indicating a trade-off between throughput, residence time, and magnetic-force magnitude. The use of integrated permanent micromagnets reduces dependence on bulky electromagnets and the associated power and heating requirements, and the authors proposed a parallel-channel configuration for scale-out. Nevertheless, neither nanocarrier synthesis nor manufacturing-scale parallelization was experimentally demonstrated. Moreover, because the magnetic NPs remain within the mixed stream, pharmaceutical implementation would require either their intentional incorporation into the carrier formulation or an effective downstream separation step, together with evidence of cargo and formulation compatibility.

Electrically actuated mixing exploits electrokinetic or electrohydrodynamic effects to generate transverse fluid motion and enhance interdiffusion between adjacent streams. Modarres and Tabrizian developed a phase-controlled micromixer containing three sinusoidal electrodes, in which the mixing intensity could be dynamically adjusted by varying the phase difference between the applied AC signals [76]. The device was subsequently adapted for the nanoprecipitation of nanoscale lipid vesicles by mixing an ethanolic lipid solution with aqueous streams. In this biphasic system, differences in the electrical properties of water and ethanol generated electrohydrodynamic instabilities at the liquid–liquid interfaces, improving liposome monodispersity and particle concentration under optimized actuation conditions (Fig. 7A–D). Although no therapeutic cargo was encapsulated, the study demonstrates the direct applicability of electrically assisted micromixing to the production of lipid-based drug-delivery carriers. However, performance remains dependent on fluid conductivity, permittivity, electrode geometry, and applied voltage, while electrode degradation, surface fouling, and unintended Joule heating may complicate prolonged operation with pharmaceutical formulations.

Thermal mixing uses localized temperature gradients to modify fluid properties and induce transverse motion in flows that would otherwise

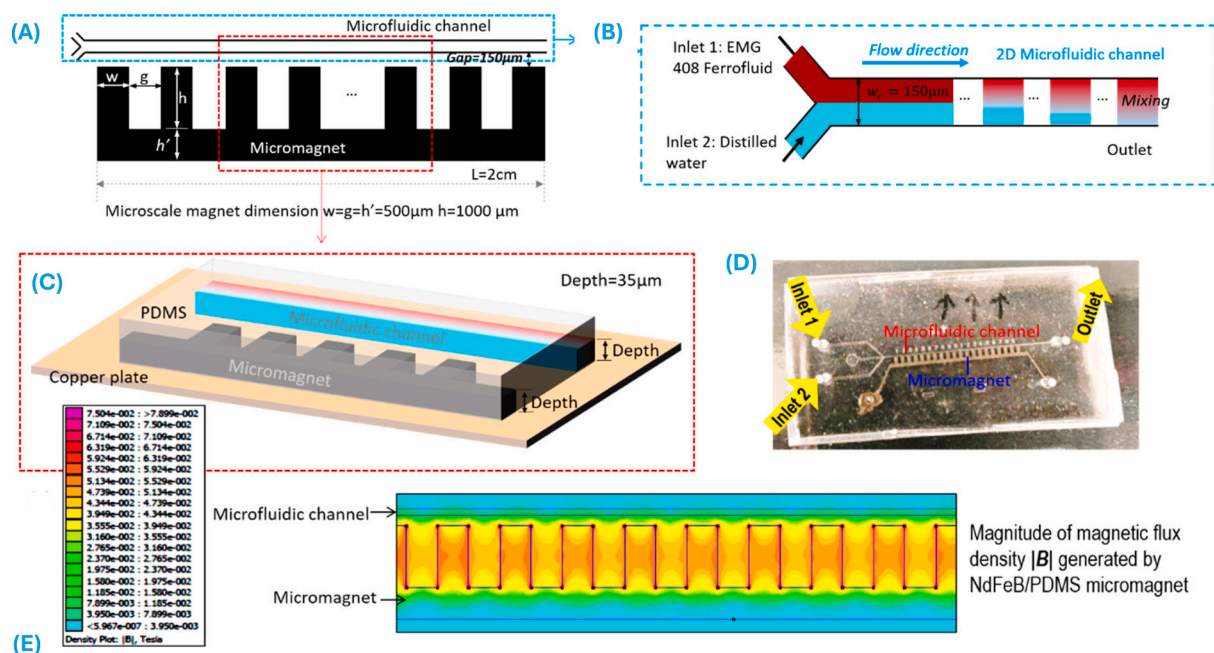


Fig. 6. Magnetofluidic micromixer incorporating an integrated microscale permanent magnet. (A) Two-dimensional layout of the microfluidic channel and adjacent micromagnet, separated by a $150 \mu\text{m}$ gap. (B) Enlarged view of the $150\text{-}\mu\text{m}$ -wide channel, supplied with diluted ferrofluid and water through two separate inlets. (C) Three-dimensional cross-sectional representation of the device, showing the microchannel and micromagnet with a depth of $35 \mu\text{m}$. (D) Photograph of the fabricated magnetofluidic device. (E) Simulated spatial distribution of the magnetic-flux-density magnitude, $|B|$, generated by the integrated micromagnet. Reproduced from an open-access source [75].

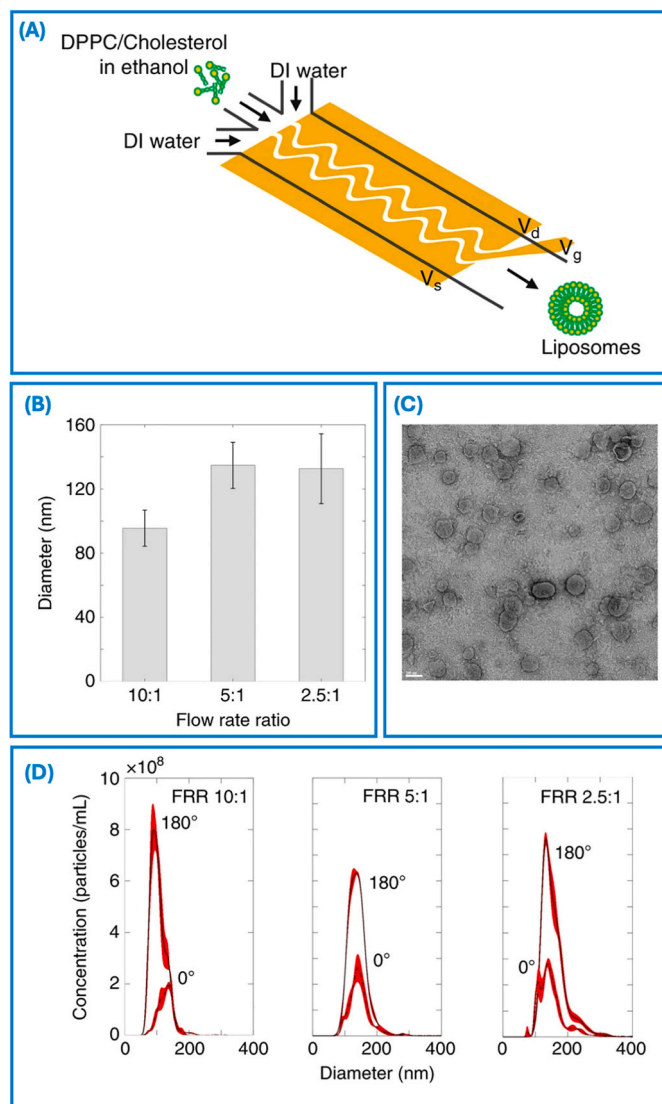


Fig. 7. Phase-controlled electrically actuated micromixer for nanoscale liposome synthesis. (A) Three-inlet device used to combine an ethanolic lipid solution with two aqueous streams. (B) Average liposome diameter obtained at different aqueous-to-solvent FRRs. (C) Transmission electron microscopy image of the resulting lipid vesicles. (D) Particle-size distributions obtained under minimum and maximum electrically induced mixing conditions. Reproduced from an open-access source [76].

remain laminar. Although this approach can enhance mixing and heat transfer, direct heating may compromise thermolabile biomolecules or pharmaceutical compounds. A relevant implementation is alternating-current electrothermal (ACET) mixing, in which localized Joule heating generates temperature-dependent variations in the electrical properties of the fluid, producing electrothermal body forces and microvortices. Sun et al. developed a sequential three-fluid ACET micromixer and applied it to the synthesis of Co-Fe Prussian blue analogue NPs. Compared with conventional two-fluid mixing, the sequential configuration produced particles with improved dispersion and more regular morphologies [77]. Although no therapeutic cargo was investigated, the study demonstrates the applicability of thermally assisted active mixing to controlled NP synthesis. Nevertheless, temperature distribution, electrical conductivity, and residence time must be tightly controlled to avoid formulation degradation or spatially non-uniform particle formation.

Overall, active mixing can reduce mixing times and provide dynamic

control beyond that achievable through diffusion-driven passive approaches, although no single actuation mechanism is universally superior. Acoustic systems are particularly promising for liposome and lipid-based NP production, whereas magnetic actuation is more commonly applied to particle capture, manipulation, and transport. Electrokinetic and electrohydrodynamic approaches can regulate liquid interfaces and support the formation of lipid vesicles, while electrothermal actuation can generate localized microvortices for controlled NP synthesis, although its applicability may be constrained by the thermal sensitivity of pharmaceutical cargos.

3.2. Segmented flow (Multiphase) microfluidic systems

Segmented-flow, or multiphase, microfluidic systems rely on the periodic breakup of immiscible streams to generate droplets that act as discrete microreactors for reactions, self-assembly, or drug encapsulation. The resulting particle size, morphology, shell architecture, and release-relevant structure depend on the breakup regime. As anticipated in Section 2, this regime must be interpreted through Ca together with the viscosity ratio and FRR, confinement, wettability and device geometry. Depending on the configuration, droplets can be generated by flow-focusing, co-flow, or cross-flow geometries.

Compared with continuous-flow mixers, segmented-flow systems provide physical compartmentalisation and greater control over microscale particle architectures. However, their operation requires stable phase immiscibility, appropriate channel wettability, and downstream recovery of the droplets or solidified particles from the continuous carrier phase [78].

3.2.1. Flow-focusing geometries

Flow-focusing geometries typically rely on a dispersed phase introduced through a central channel that is pinched by lateral sheath flows, as schematically represented in Fig. 1B, creating a narrow neck that periodically collapses into uniform droplets due to the Rayleigh–Plateau instability [79]. This configuration is widely applied to the production of core-shell MPs because adjustment of the junction geometry and FRR provides control over particle size and shell thickness, which are

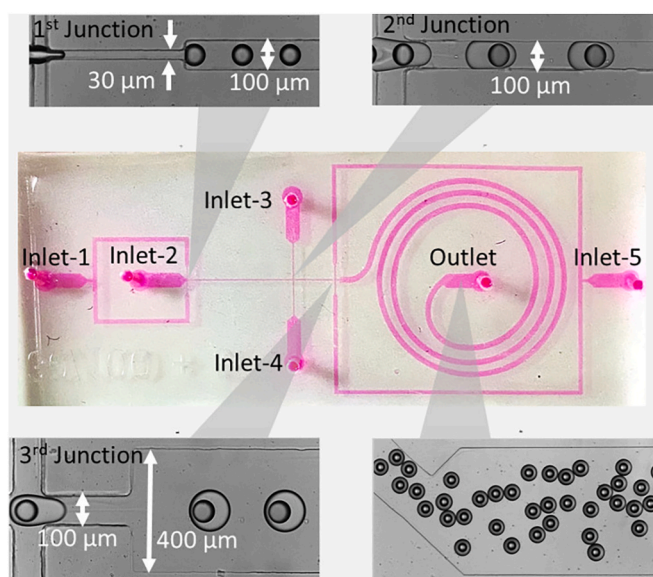


Fig. 8. Schematic representation of a five-inlet microfluidic platform for producing aqueous core-shell droplets. Separate inlets supply the inner aqueous phase, the shell-forming monomer, and the continuous carrier fluids, enabling sequential encapsulation and droplet stabilization. An additional spacing stream limits droplet coalescence, while partial UV-induced crosslinking of the shell occurs along a spiral channel prior to particle collection at the outlet. Reprinted from an open-access source [80].

important parameters for encapsulation and controlled release [80] (Fig. 8).

Pneumatic actuation has further extended this principle by enabling dynamic modulation of the effective width of the flow-focusing junction. Giannitelli et al. used this strategy to produce hyaluronic acid (HA)/polyethyleneimine nanogels with tunable hydrodynamic diameters of 92–190 nm and very low polydispersity (0.015) [81]. When loaded with DOX, the nanogels enhanced the antitlastic effect relative to the non-encapsulated drug in an ovarian-cancer model, directly demonstrating the relevance of the platform to drug delivery.

A conventional flow-focusing configuration was also used to produce curcumin-loaded poly(ethylene glycol) dimethacrylate–gelatin methacrylate (PEG–GelMA) microgels, which were subsequently stabilised by UV photopolymerization [82] (Fig. 9A–C). The resulting monodisperse microgels had a mean diameter of $218 \pm 5 \mu\text{m}$ and were evaluated as injectable carriers for the local treatment of osteoarthritic cartilage defects.

Flow focusing therefore offers particularly strong control over droplet diameter and multilayer architecture. Nevertheless, stable operation depends on a precise pressure balance, channel wettability, and orifice dimensions; small variations in these parameters can shift the breakup regime or alter particle size and shell thickness.

3.2.2. Co-flow geometries

In co-flow geometries, immiscible phases are introduced through coaxial capillaries or aligned channels, so that an inner stream is progressively sheathed by one or more surrounding phases before breaking into droplets downstream (Fig. 1B). The independent control of the concentric streams makes these configurations particularly suitable for generating single and multiple emulsions, which can subsequently be solidified or polymerized into core-shell microcapsules and multi-compartment drug carriers [78].

A related configuration is tri-phasic step-emulsification, in which three co-flowing phases pass through shallow channels before entering a substantially deeper and wider collector. The abrupt loss of confinement drives spontaneous breakup with a lower dependence on local shear than conventional nozzle-based emulsification. Ge et al. implemented this principle in a double-layer PDMS device and generated oil-in-oil-in-

water (O/O/W) and water-in-water-in-oil (W/W/O) double emulsions in a single step [83]. Four emulsification regimes were identified and mapped using two phase-specific capillary numbers, while adjustment of the flow rates yielded shells as thin as 1.4% of the overall droplet diameter. Such control over the diffusion-barrier thickness is relevant to microcapsule release kinetics, although drug encapsulation and release were not experimentally evaluated in that study.

Khan et al. combined two coaxial droplet generators with on-chip UV polymerization to produce core-shell microparticles containing ketoprofen in a poly(methyl acrylate) core and ranitidine hydrochloride in a poly(acrylamide) shell [84]. The particles exhibited coefficients of variation below 5%, overall diameters of 100–151 μm , and independently tunable core diameters of 58–115 μm . Incorporation of a pH-responsive monomer into the shell suppressed the release of both compounds under acidic conditions and increased their release at higher pH, with maximum discharge at pH 7.4, supporting their potential for colon-targeted dual delivery.

Co-flow has also been used to produce silk-based carriers through controlled phase separation between silk fibroin and PVA [85]. Compared with conventional emulsion processing, the microfluidic method reduced the PDI from 0.65 to 0.13. The resulting particles achieved a DOX loading of approximately $41 \mu\text{g mg}^{-1}$ and sustained its release for 23 days, demonstrating that co-flow processing can improve carrier uniformity while retaining prolonged drug-release behaviour in anticancer-drug delivery.

Overall, co-flow geometries provide independent control over the core, shell, and continuous-phase streams, making them well suited to double emulsions and multilayer carriers. Their performance nevertheless depends strongly on phase-specific Ca values, viscosity ratios, interfacial tensions, and surface wettability. Capillary implementations additionally require precise coaxial alignment, which can complicate fabrication, reproducibility, and parallelization for large-scale production.

3.2.3. Cross-flow geometries

In cross-flow geometries, the dispersed phase enters laterally into an immiscible continuous stream and is segmented at the junction (Fig. 1B). Depending on the continuous-phase Ca number, the FRR, and the

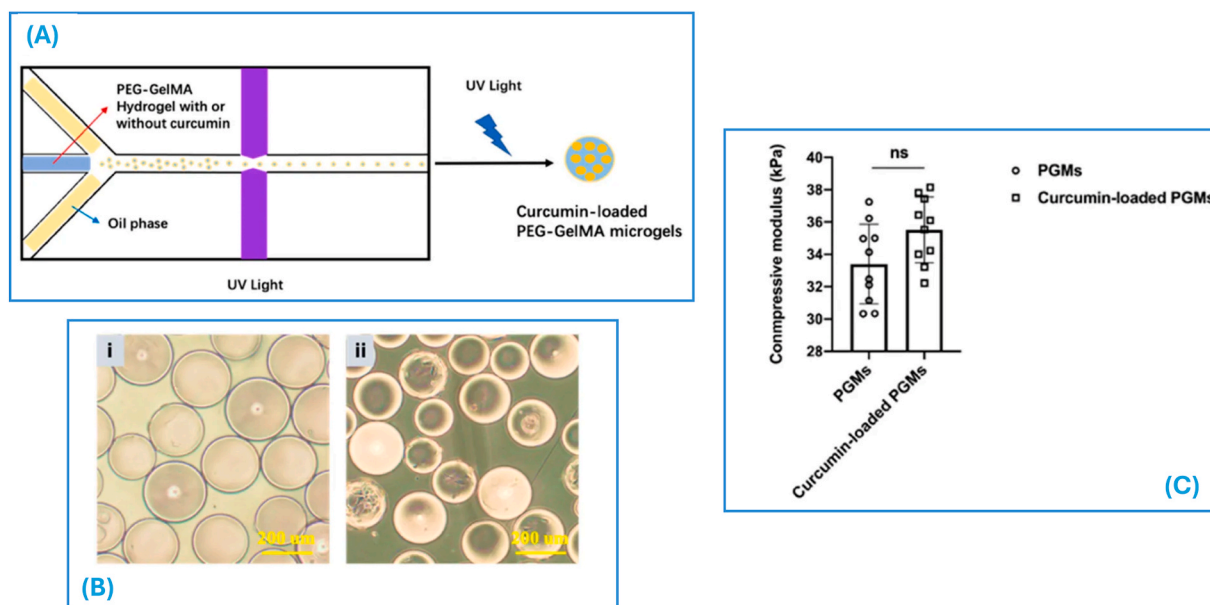


Fig. 9. Flow-focusing fabrication and characterisation of curcumin-loaded PEG–GelMA microgels. (A) Schematic representation of microgel generation using a PDMS flow-focusing device followed by UV photopolymerization. (B) Bright-field microscopy images of unloaded PEG–GelMA microgels and curcumin-loaded microgels. Scale bar: 200 μm . (C) Comparison of the compressive modulus of unloaded and curcumin-loaded microgels. Reproduced from an open-access source distributed under the CC BY licence [82].

relative channel dimensions, breakup may occur in the squeezing, dripping, or jetting regime. These parameters govern droplet size and generation frequency and, consequently, the dimensions and uniformity of the resulting particle templates [78].

Hinojosa-Ventura et al. used a T-junction with a channel width of $600\ \mu\text{m}$ and a depth of $350\ \mu\text{m}$ to generate PEGDA droplets that were subsequently converted into hydrogel MPs by visible-light photopolymerization [86] (Fig. 10A–C). For dispersed-phase flow rates of $5\text{--}10\ \mu\text{L min}^{-1}$, increasing the continuous-phase flow rate from 300 to $400\ \mu\text{L min}^{-1}$ reduced the mean particle diameter from approximately $155\text{--}161$ to $111\text{--}112\ \mu\text{m}$. By contrast, the effect of the dispersed-phase flow rate was not statistically significant within the investigated range. All formulations exhibited PDI values below 0.05 , indicating highly uniform particle populations. Although no active pharmaceutical ingredient was encapsulated, the study established operating conditions for producing monodisperse PEGDA matrices potentially suitable for pharmaceutical or biological cargo incorporation.

A direct drug-delivery application was demonstrated using an L-junction device to prepare magnetic alginate MPs and chitosan-coated magnetic alginate MPs loaded with amoxicillin [87]. The particle diameter could be adjusted from approximately 220 to $1000\ \mu\text{m}$, with the smaller particles exhibiting faster pH-dependent drug release because of their greater surface-area-to-volume ratio. Coating the alginate particles with chitosan approximately doubled the duration of drug release, demonstrating how cross-flow fabrication and subsequent surface modification can be combined to regulate carrier size and achieve sustained release.

Overall, cross-flow junctions offer a comparatively simple route to monodisperse MPs, but their apparent operational simplicity does not necessarily translate into robust scale-up. Droplet size and breakup regime remain highly sensitive to the FRR, Ca, channel-width ratio, interfacial tension, and surface wettability, making performance difficult to transfer across formulations and devices. Step-assisted designs can increase throughput and extend operation toward jetting conditions, although this gain may come at the expense of process stability and monodispersity. Moreover, scale-up by parallelization introduces additional challenges related to flow maldistribution and device-to-device variability. For drug-delivery applications, the use of immiscible carrier phases and surfactants also requires downstream recovery, washing, and removal of residual solvents or stabilizers, which can reduce yield and hinder clinical and industrial implementation.

3.3. Multiple field-based microfluidic systems

Unlike the active mixing strategies discussed in 3.1.2, in which external fields primarily perturb laminar streams to accelerate inter-diffusion, multiple field-based systems use the same fields to directly generate, assemble, or actuate droplets and particles (Fig. 1C). Here, the field is the primary driver of carrier formation or manipulation, often complemented by simple geometries, such as straight channels or co-flow configurations.

3.3.1. Electric-field-driven systems

Unlike electrically actuated micromixers, in which the applied field primarily enhances transverse transport, microfluidic electrospray uses electric stresses to overcome interfacial tension and break a coaxial or focused liquid stream into charged droplets. The applied voltage, phase flow rates, nozzle geometry, and collection distance can therefore be adjusted to control particle size and core-shell morphology, after which ionic gelation or photopolymerization stabilizes the resulting carriers. For example, a coaxial microfluidic electrospray approach was used to fabricate porous alginate core-shell microcapsules encapsulating β cells with tunable size, enabling effective glycaemic regulation in diabetic mice [88] (Fig. 11A–I). Similarly, microfluidic electrospray has been used to fabricate lubricated HA particles for osteoarthritis treatment, providing precise size control and favourable biomedical performance.

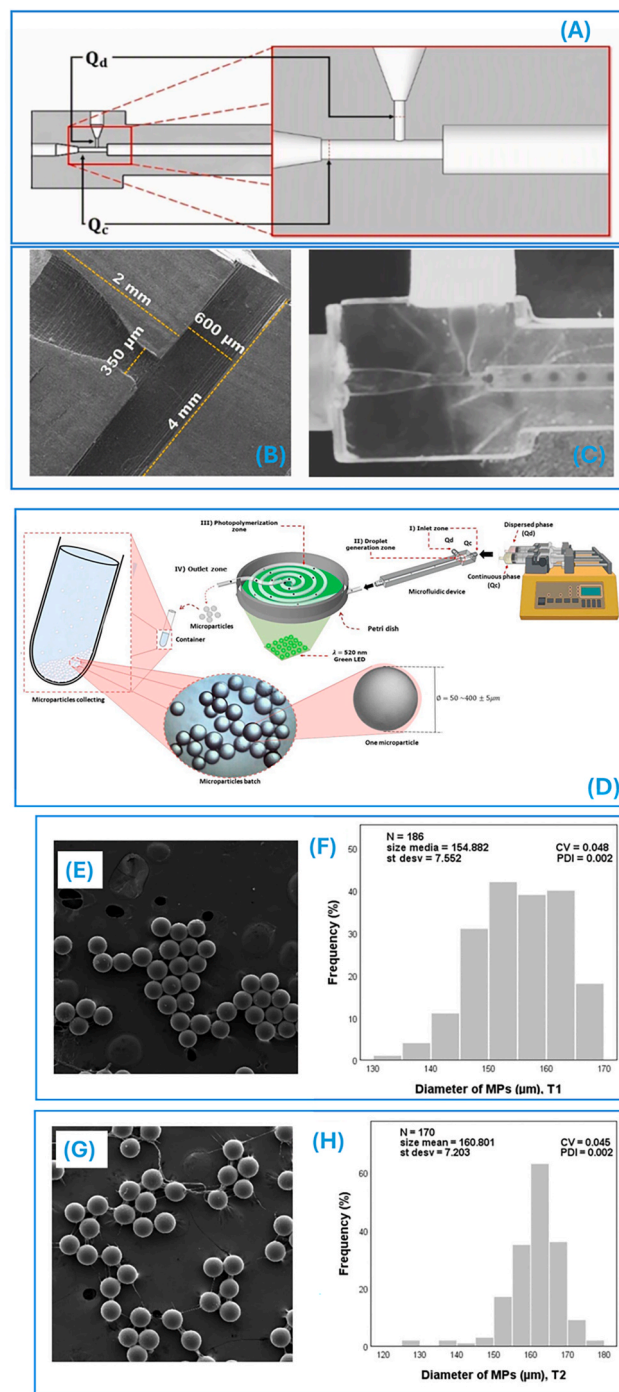


Fig. 10. T-junction microfluidic production and characterization of photo-polymerized PEGDA hydrogel microparticles. (A) CAD representation of the T-junction device, showing the dispersed- and continuous-phase inlet flow rates, Q_d and Q_c , respectively. (B) Scanning electron micrograph of the fabricated microchannels, with a channel length of $4\ \text{mm}$, width of $600\ \mu\text{m}$, and depth of $350\ \mu\text{m}$. (C) Experimental setup showing breakup of the dispersed phase by the continuous phase at the T-junction. (D) Workflow for PEGDA microparticle production, including droplet generation, in-line green-light photopolymerization, collection, and washing. (E) Scanning electron micrographs of particles produced at $Q_d = 5\ \mu\text{L min}^{-1}$ and $Q_c = 400\ \mu\text{L min}^{-1}$. (F) Corresponding particle-size distribution. (G) Scanning electron micrographs of particles produced at $Q_d = 10\ \mu\text{L min}^{-1}$ and $Q_c = 400\ \mu\text{L min}^{-1}$. (H) Corresponding particle-size distribution. Adapted from an open-access source [86]. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

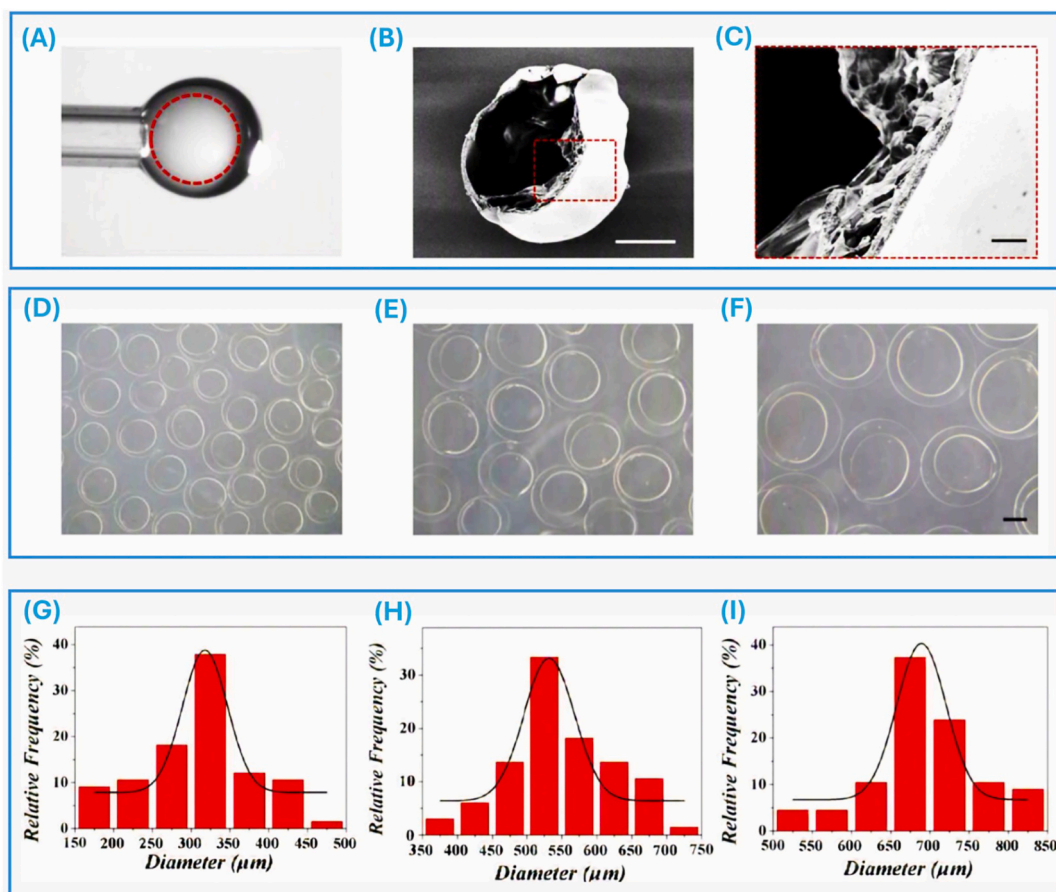


Fig. 11. Microfluidic electrospray fabrication of CMC-ALG microcapsules. (A) Droplet generation during electrospray operation. (B–C) SEM micrographs highlighting internal and external capsule morphology. (D–F) Optical images of core-shell capsules produced with varying nozzle sizes. (G–I) Size distributions of the resulting porous microcapsules based on measurements of 100 particles per condition. Scale bar: 200 μm. Reprinted from an open-access source [88].

The resulting particles were subsequently loaded with diclofenac sodium, thereby combining mechanical lubrication with local anti-inflammatory delivery. These particles mimic the lubricating properties of natural cartilage and are designed to reduce joint friction and local inflammation, leading to improved chondrocyte viability and significant therapeutic relief in osteoarthritic models [89].

These systems excel in producing uniform micro- and submicron capsules with high EE and precise compositional control, making them particularly suitable for cell encapsulation and localized drug delivery. However, their requirement for high voltages and limited compatibility with conductive or heat-sensitive materials may restrict broader biomedical integration. At larger production scales, high-voltage operation also introduces additional safety requirements, while parallel electrospray emitters must maintain uniform electric fields and stable cone-jet conditions to preserve particle reproducibility.

3.3.2. Acoustic-field-driven systems

Acoustic fields generated by surface acoustic wave (SAW) or bulk acoustic wave (BAW) transducers can produce radiation forces and streaming flows that concentrate nanoscale components and promote their loading or assembly. Wang et al. used SAW-induced rotation of a droplet to simultaneously load DOX into porous silica NPs and encapsulate the resulting carriers within exosomal membranes [90] (Fig. 12A–D). The method was effective with 50- and 100-nm spherical NPs and 200-nm silica nanorods, achieving a drug-loading efficiency of approximately 30% within 2 min, compared with 0.08% after 22 h of passive incubation. Exosome coating also enhanced cellular uptake and inhibition of HeLa and MCF-7 tumour-cell proliferation. Notably, the acoustic field did not produce the silica NPs themselves, but enabled

their rapid post-synthesis drug loading and membrane encapsulation.

Compared with electrospray systems, acoustofluidic devices offer good compatibility with biological materials because they avoid direct electrical contact with the processed formulation; however, they may require precise resonance tuning and careful control of acoustic power to avoid cavitation or heating effects. Their scale-up may also require arrays of transducers and radiofrequency generators, increasing equipment cost and making uniform acoustic actuation across parallel channels more difficult.

3.3.3. Magnetic-field-assisted systems

Magnetofluidic platforms integrate magnetic NPs into droplets or capsules, allowing external magnetic fields to control their purification, positioning, and downstream handling. Torres et al. used a serpentine microfluidic device to produce ceftriaxone-containing magnetoliposomes and subsequently evaluated two magnetophoretic microfluidic configurations for their downstream purification [91] (Fig. 13A–E). The magnetic field did not drive liposome formation; instead, permanent magnets generated magnetic-field gradients to assist the separation of magnetoliposomes from non-encapsulated magnetic nanoconjugates. The resulting magnetoliposomes generally exhibited hydrodynamic diameters below 400 nm and PDI values below 0.5, while encapsulation efficiency reached approximately 90% under the best-performing conditions. The second magnetophoretic configuration achieved a maximum separation efficiency of 51.22% at a TFR of 2 mL/min. Their biocompatibility, cellular internalization, and limited endosomal entrapment supported their potential application in the gastrointestinal delivery of difficult-to-transport drugs.

This approach provides excellent controllability and non-invasive

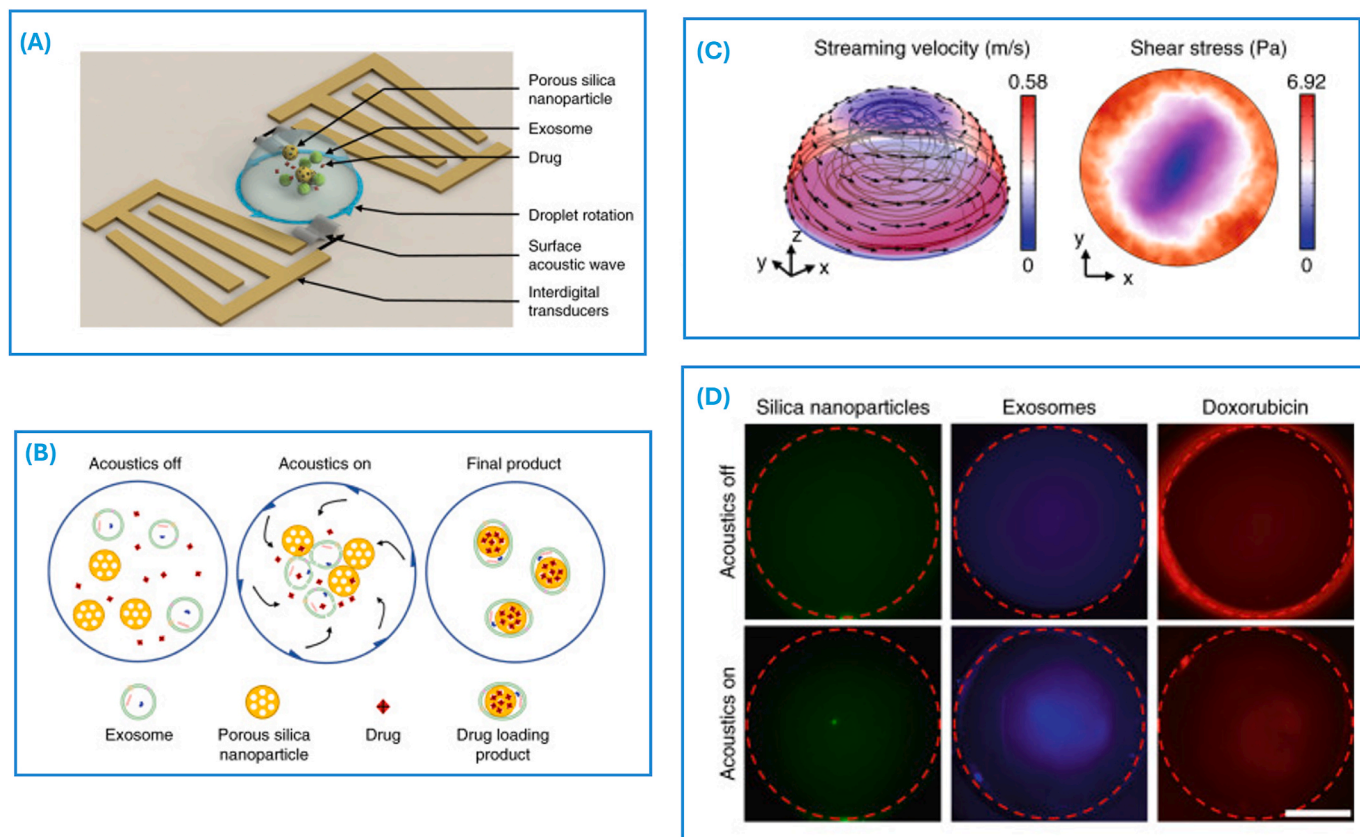


Fig. 12. Principle of acoustofluidic-assisted drug loading. (A) Schematic of the acoustofluidic platform, where angled interdigital transducers generate surface acoustic waves that drive droplet spinning and acoustic streaming. (B) Comparison between inactive and active conditions: without acoustic actuation, NPs, vesicles, and drug molecules remain homogeneously dispersed, whereas activation leads to their accumulation in the droplet core. (C) Computational results illustrating the microstreaming patterns and shear-stress fields induced by acoustic excitation, with flow directed towards the droplet centre. (D) Fluorescence microscopy images confirming enhanced central localization of silica NPs, exosomes, and DOX upon device activation. Scale bar: 1 mm. Reproduced from an open-access source [90].

actuation, well-suited for the purification and downstream handling of magnetically responsive drug carriers, but it requires embedding magnetic materials, which can alter particle density, influence biocompatibility, and limit transparency for optical monitoring. Moreover, non-magnetic carriers require magnetic labels or embedded magnetic NPs, while reproducible operation across parallel channels depends on maintaining sufficiently uniform magnetic fields and gradients.

Overall, electrospray is the most directly applicable of these strategies to particle and microcapsule generation, whereas acoustic systems are particularly useful for carrier loading and assembly, and magnetic fields are better suited to the manipulation, positioning, and recovery of responsive carriers. Their industrial implementation remains dependent on high-voltage safety, acoustic-hardware cost and standardization, and the magnetic responsiveness of the processed formulation.

To summarize, all the methodologies are described in Table 2, while a thorough comparison between all methodologies is described in Table 3 below.

4. Mathematical modeling

4.1. Role of mathematical modeling and simulation

Mathematical modeling and computational fluid dynamics (CFD) play a central role in the design, analysis, and optimization of microfluidic devices for micro- and NP synthesis. By predicting velocity profiles, shear rates, and concentration fields under laminar conditions, CFD allows evaluation of channel geometries and operational parameters before fabrication, thereby reducing experimental iterations and costs, including the field of NP fabrication [36,92]. Computational

analyses have also been extensively applied to passive micromixers (e.g. SHM) to understand chaotic direction mechanisms and guide device design [51,52].

In co-flow systems, CFD modelling can clarify how operating conditions and non-Newtonian phase behaviour affect the size, shell thickness, and formation regime of double-emulsion-templated carriers. Malakshah et al. investigated double-emulsion formation in a double co-flow geometry using a two-dimensional axisymmetric volume-of-fluid model, comparing a Newtonian continuous phase with shear-thinning carboxymethyl cellulose solutions at concentrations of 0.2–0.5 wt% [93]. Increasing the inner-phase velocity enlarged the encapsulated core while leaving the outer droplet diameter comparatively unchanged, whereas increasing the outer-phase velocity reduced both diameters, decreased the shell thickness, and increased the generation frequency. Higher carboxymethyl cellulose concentrations produced smaller compound droplets, demonstrating that carrier dimensions cannot be predicted from flow rates alone when non-Newtonian phases are involved. The transition toward jetting occurred at middle-phase capillary numbers of approximately $Ca_{mid} = 0.11$ – 0.16 , depending on the rheological properties of the continuous phase.

Moreover, CFD-based modeling has been successfully integrated with experimental data to understand the coupling between hydrodynamics and NP formation. For instance, Shokoohinia et al. developed a microfluidic-assisted process for poly(lactic-co-glycolic acid) (PLGA) NP preparation and used CFD to correlate shear stress and flow regime with particle size distribution, confirming that controlled mixing regions enhance nanoprecipitation efficiency [92]. Similarly, Pico et al. employed a combined population balance CFD model to describe silver NP (AgNPs) nucleation and growth in both microfluidic and stirred

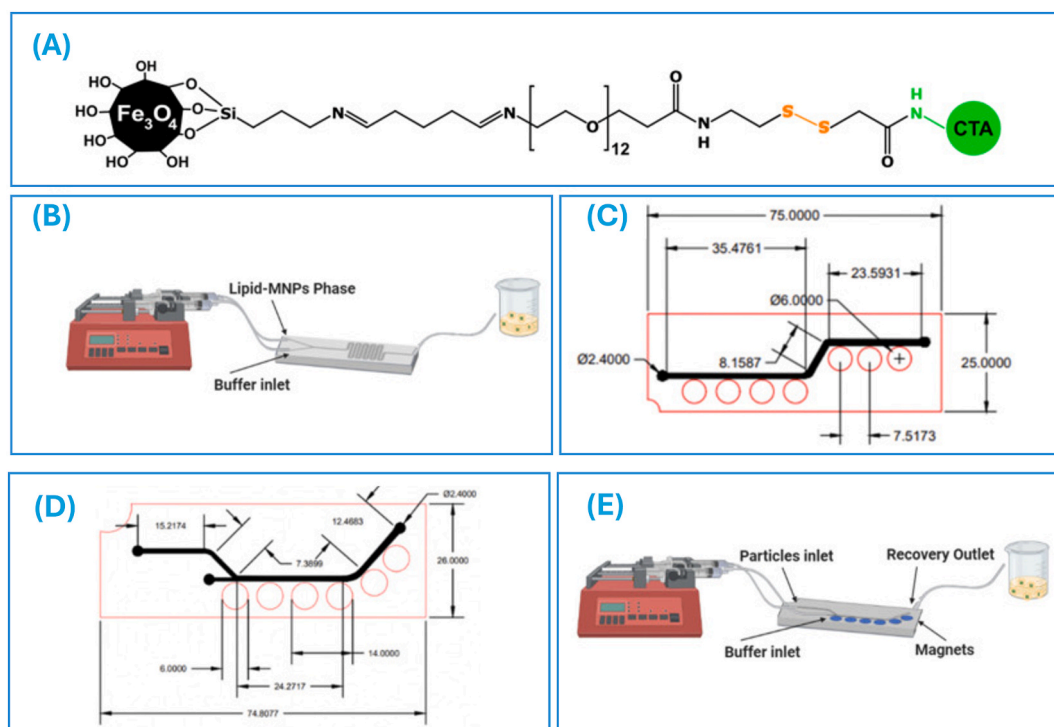


Fig. 13. Microfluidic synthesis and magnetic-field-assisted purification of ceftriaxone-containing magnetoliposomes. (A) Schematic representation of the magnetic nanoconjugate used for magnetoliposome production. (B) Microfluidic experimental setup used for the synthesis step. (C–D) Magnetophoretic microfluidic devices proposed for downstream purification. (E) Experimental separation setup incorporating permanent magnets. Reprinted from an open-access source [91].

reactors, demonstrating CFD's predictive capability for particle size and distribution control [94]. More recently, Abaee et al. applied CFD-assisted optimization to spiral microreactors for zinc oxide (ZnO) NP synthesis, revealing that fine-tuning Dean vortices and channel curvature enhances micromixing and reduces energy consumption [95].

4.2. Role and implementation of design of experiment (DoE) in microfluidics

Integration of DoE methodologies within microfluidics has accelerated the identification of optimal combinations of excipients and process parameters, such as polymer concentration, FRR, and total flow rate [96]. When coupled with CFD predictions, DoE allows researchers to explore parameter spaces systematically and select promising operating conditions before extensive physical experimentation, thereby reducing material use and optimization time [97,98].

4.2.1. Parameter optimization

Parameter optimization represents the most direct and immediate application of DoE in microfluidic synthesis. The objective is to identify the conditions that maximize or minimize one or more responses of interest and to reveal interactions between variables. DoE has been used to optimize the synthesis of various NPs, including silver [99], PLGA [100], and lipid-based NPs, by systematically varying process parameters. As an example, in the synthesis of LNPs for drug delivery, DoE has made it possible to optimize parameters such as the ratio between the aqueous and organic phases, the lipids concentration and the flow rate [101].

A particularly interesting aspect of CFD simulations is multi-objective optimization, where a balance is sought between different and sometimes conflicting properties. Chamseddine et al. employed a computational bi-objective optimization approach, combining vascular tumor growth models with NP treatment simulations to optimize both tumor targeting and size reduction. Unlike traditional DoE methods, this approach uses numerical simulations and Pareto front analysis, allowing

for the identification of optimal NP designs without relying on physical experimentation [102] (Fig. 14).

4.2.2. Predictive modeling

DoE in microfluidics has been able to transform experimental data into reliable forecasting tools by using predictive modeling. It makes it possible to predict the properties of NPs under conditions that have not been experimentally tested yet, accelerating the development process while reducing the need for extensive empirical testing [103]. Predictive modeling is further enhanced when integrated with CFD simulations. In fact, parameters derived from CFD simulations, like mixing time or local concentration gradients, can be provided to DoE models. This hybrid approach is becoming increasingly common in microfluidic process design [97].

4.2.3. Sustainability and scalability

A crucial contribution of DoE in microfluidics concerns the sustainability of the development process and its scalability towards industrial applications. With DoE, the number of experiments required is drastically reduced, reducing the overall environmental footprint typical of the development phase, by minimizing reagent use and reducing both waste products and costs [96]. On the other hand, scalability is one of the most crucial points in translating microfluidic processes from the laboratory to the industrial scale. In such cases, DoE models come in help as they can predict complex interactions between parameters and their role in the scaling-up. DoE can also support scale-up by identifying interactions among formulation variables, flow conditions, and performance responses, although predictions must be revalidated when channel architecture or production scale changes [98,104].

4.3. Machine learning (ML) and artificial intelligence (AI)

AI and ML are emerging as transformative tools for microfluidic-assisted NP synthesis. While traditional methods like DoE can handle just a limited number of variables at a time, ML can manage and

Table 2

Representative microfluidic platforms discussed in the device sections, including particle composition, maximum reported throughput, and pharmaceutical performance. Throughput is expressed using the highest total flow rate, volumetric or mass output, generation rate, or processed volume and time reported in each study.

Category	Geometry/design	Particle composition/cargo	Application	Size/PDI	Maximum reported throughput	EE/loading/release/recovery	Ref.
Continuous flow: passive mixing	Complex passive mixing: spiral SMC/MSMC[a,b]	Phospholipid/cholesterol LNPs; no therapeutic cargo	High-throughput LNP production	72.8 ± 24.1 nm; PDI 0.111 ± 0.011	TFR: 960 mL h ⁻¹	EE and release: n.a.	[50]
	Complex passive mixing: Y-shaped slanted-ridge and SHM devices[b,c]	DSPC/cholesterol/DSPE-PEG liposomes and LNPs; myoglobin, siRNA, or ssDNA	Protein and nucleic-acid delivery	Myoglobin: 163–242 nm; siRNA: 372–392 nm, PDI 0.08–0.10; Onpattro-based LNPs: 154 ± 26 nm, PDI 0.1 ± 0.1	TFR: 8 mL min ⁻¹	EE: 72–79% myoglobin; ~ 96% siRNA; 75–81% ssDNA; release: n.a.	[54]
	Complex passive mixing: planar-baffle iLNP device [b,c,i]	POPC or ionizable-lipid/DSPC/cholesterol/PEG-lipid LNPs; siRNA	RNA delivery and <i>in vivo</i> gene silencing	Approximately 20–100 nm; siRNA formulation: ~ 80 nm	TFR: 500 µL min ⁻¹	EE and release: n.r.	[53]
	Sequential lamination/SAR: double-layer Y-shaped units[c,m]	Silver NPs; no therapeutic cargo	Controlled NP-synthesis benchmark	28.9–31.4 nm; size deviation: 3.8–5.4 nm	Maximum synthesis flow: 810 µL min ⁻¹	EE and release: n.a.	[55, 56]
	Hydrodynamic flow focusing and parallel lamination[b,c,n]	PLGA-PEG NPs; fluorescent probes or DOX	Polymeric anticancer-drug delivery	44–97 nm; PDI 0.06–0.15	TFR: 345 µL min ⁻¹	EE: ~ 80% DiI; ~ 15% DOX; release: n.r.	[58, 59]
	Microvortex-based three-inlet mixer[a,b,c]	PLGA core with lecithin/DSPE-PEG corona; no therapeutic cargo	Scalable hybrid nanocarrier production	Approximately 30–170 nm; PDI ~ 0.1	Mass output: ~ 0.30 g h ⁻¹	EE and release: n.a.	[61, 62]
Continuous flow: active mixing	Pulsation-assisted Y-shaped micromixer[d,m]	Citrate-reduced AuNPs; no therapeutic cargo	Controlled active NP synthesis	21.6 ± 4.8 nm	Flow: 4 mL min ⁻¹	EE and release: n.a.	[68]
	Acoustic mixing: oscillating elastic-membrane micromixer[a, d,e]	Phospholipid liposomes; no therapeutic cargo	Size-tunable liposome production	Approximately 40–900 nm	TFR: 8 mL h ⁻¹	EE and release: n.a.	[71]
	Acoustic mixing: SAW-driven three-inlet transverse jet[d,e]	bPEI-pDNA polyplexes and lipid-based nucleic-acid particles	Therapeutic nucleic-acid carrier formation	Polyplex r_h : 55.4 ± 0.7 nm, PDI 0.283 ± 0.004; lipid-particle r_h : ~ 19 nm	TFR: 150 µL h ⁻¹	EE increased relative to hand and diffusion-based mixing; exact value n.r.	[72]
	Magnetic mixing: integrated NdFeB-PDMS micromagnet[d,l,m]	Magnetic NPs dispersed in ferrofluid; no therapeutic cargo	Magnetofluidic mixing benchmark	Homogeneous distribution over a 20-mm channel	TFR: 0.3 mL h ⁻¹	EE and release: n.a.	[75]
	Electric mixing: phase-controlled electrohydrodynamic micromixer[a,d]	Phospholipid vesicles; no therapeutic cargo	Electrically assisted liposome synthesis	Nanoscale and FRR-dependent; improved monodispersity	TFR: 200 µL min ⁻¹	EE and release: n.a.	[76]
	Thermal mixing: sequential three-fluid ACET micromixer[d,m]	Co-Fe Prussian blue analogue NPs; no therapeutic cargo	Controlled inorganic NP synthesis	Improved particle dispersion and morphological uniformity	Volumetric throughput: n.r.; flow velocity up to 7 mm s ⁻¹	EE and release: n.a.	[77]
Segmented flow	Flow focusing: five-inlet platform[f,g,i]	Polymeric shell with aqueous core; no therapeutic cargo	Core-shell encapsulation template	Outer diameter: ~ 118 µm; tunable core and shell	Maximum combined flow: 600 µL h ⁻¹	EE and release: n.a.	[80]
	Flow focusing: pneumatically actuated junction[d,f]	HA/LPEI nanogels; DOX	Ovarian-cancer drug delivery	92–190 nm; PDI 0.015–0.023	TFR: 12 µL min ⁻¹	EE: 77.5–77.7%; release: up to ~ 10 days	[81]
	Flow focusing: UV-photocrosslinked microgels[f,h,i]	PEG-GelMA microgels; curcumin	Local osteoarthritis treatment	218 ± 5 µm	n.r.	EE and quantitative release: n.r.	[82]
	Co-flow: tri-phasic step-emulsification[f,g,i]	O/O/W and W/W/O double emulsions; no therapeutic cargo	Ultrathin-shell encapsulation template	Shell thickness: down to 1.4% of droplet diameter	Parallel operation demonstrated; maximum output n.r.	EE and release: n.a.	[83]
	Co-flow: dual coaxial generators with in-line UV polymerization[f,g,h]	Poly(methyl acrylate) core/poly(acrylamide) shell; ketoprofen and ranitidine hydrochloride	pH-responsive dual-drug delivery	Outer diameter: 100–151 µm; core: 58–115 µm; CV < 5%	n.r.	Release suppressed at acidic pH; maximum release at pH 7.4	[84]
	Co-flow/flow focusing: silk/PVA phase separation [f,j]	Silk-fibroin MPs; post-loaded DOX	Sustained anticancer-drug delivery	Co-flow: median ~ 6.6 µm, PDI 0.13; flow focusing: 3.0–6.8 µm, PDI 0.05–0.12	Total throughput: n.r.; silk phase up to 0.80 mL h ⁻¹	DOX loading: ~ 41 µg mg ⁻¹ ; release: 23 days	[85]
	Cross-flow: T-junction with visible-light photopolymerization[f,h, m]	PEGDA hydrogel MPs; no therapeutic cargo	Potential encapsulation matrix	111–161 µm; PDI < 0.05	TFR: 410 µL min ⁻¹	EE and release: n.a.	[86]

(continued on next page)

Table 2 (continued)

Category	Geometry/design	Particle composition/cargo	Application	Size/PDI	Maximum reported throughput	EE/loading/release/recovery	Ref.
Multiple field-based	Cross-flow: L-junction[f,i]	Magnetic alginate MPs with or without chitosan coating; amoxicillin	pH-responsive antibiotic delivery	Approximately 220–1000 μm	n.r.	EE: n.r.; smaller MPs released faster; chitosan prolonged release	[87]
	Electric-field driven: coaxial microfluidic electrospray[g,k]	CMC core and porous alginate/PEO shell; β cells	Artificial islets and diabetes treatment	Hundreds of micrometres; nozzle-dependent size	Volumetric output: n.r.; processing time: < 30 min	Cell viability: > 90%; glycaemic regulation demonstrated	[88]
	Electric-field driven: coaxial microfluidic electrospray[i,k]	MPC-modified methacrylated HA MPs; diclofenac sodium	Joint lubrication and local anti-inflammatory delivery	Micrometre-scale; narrow size distribution	n.r.	Quantitative loading and release: n.r.; efficacy assessed <i>in vitro</i> and <i>in vivo</i>	[89]
	Acoustic-field driven: SAW-assisted droplet loading and assembly[d,j]	Porous silica NPs coated with exosomal membranes; DOX	Rapid loading and biomimetic carrier assembly	Silica spheres: 50 and 100 nm; nanorods: ~ 200 nm; exosomes: 30–150 nm	10 μL batch processed in 2 min	Drug loading: ~ 30% in 2 min, versus 0.08% after 22 h	[90]
	Magnetic-field assisted: serpentine synthesis with magnetophoretic purification[j,l]	Phospholipid magnetoliposomes containing ceftriaxone-functionalized magnetic nanoconjugates	Drug delivery and magnetic purification	137–787 nm; PDI < 0.5	Synthesis TFR: 5 mL min^{-1} ; purification TFR: 2 mL min^{-1}	EE: ~ 20–90%; maximum separation: 51.22%	[91]

Table notes. (a) Therapeutic cargo loading and release were not evaluated. (b) High-throughput or scale-out performance was demonstrated only for the reported device and formulation; transferability to other pharmaceutical formulations requires validation. (c) Grooves, baffles, recirculation regions, or narrow focusing sections may increase pressure drop, particle retention, fouling, or clogging during prolonged operation. (d) External actuation hardware increases equipment complexity; performance may also depend on field uniformity, resonance conditions, electrode stability, or thermal control. (e) The reported throughput remained relatively low, and manufacturing-scale parallelization was not demonstrated. (f) Operation depends on stable phase immiscibility, interfacial tension, channel wettability, and surfactant concentration, and requires downstream particle recovery and washing. (g) Precise alignment and balancing of multiple or coaxial streams increase fabrication and operational complexity. (h) Photocrosslinking may limit compatibility with photosensitive cargos and requires control of irradiation conditions and residual photoinitiator. (i) Pharmaceutical throughput, EE, drug loading, or quantitative release data were not reported. (j) The field or microfluidic process was used for post-synthesis loading, coating, or purification rather than for primary carrier formation. (k) High-voltage operation, formulation conductivity, and cone-jet stability may limit material compatibility and parallelization. (l) Magnetic processing requires magnetically responsive materials; incomplete separation may necessitate additional purification. (m) The study used inorganic particles or a model formulation without a therapeutic cargo. (n) Nanoprecipitation may produce diluted suspensions requiring solvent removal, concentration, or additional downstream processing. n.r.: not reported; n.a.: not assessed or not applicable.

Table 3

Comparison of the main microfluidic device families for drug-carrier manufacturing and processing.

Device family	Main applications	Typical size	Advantages	Limitations
Continuous-flow, passive	Nanoprecipitation and self-assembly of lipid, polymeric, and hybrid NPs	Mainly 20–200 nm	Simple operation, no external actuation, and relatively easy parallelization	Fixed mixing conditions, pressure drop, fouling, and possible flow maldistribution
Continuous-flow, active	Field-enhanced mixing for liposomes, polyplexes, and rapidly assembling formulations	Tens to hundreds of nanometers	Fast and dynamically adjustable mixing	Additional hardware, heating, field tuning, and formulation compatibility requirements
Segmented flow	Droplets, hydrogels, MPs, core-shell carriers, and multiple emulsions	Mainly tens to hundreds of micrometres	High monodispersity and precise control of internal structure	Dependence on wettability and surfactants; recovery, washing, and scale-up challenges
Multiple field-based	Electrospray generation, drug loading, carrier assembly, manipulation, and purification	Nano- to microscale	Direct and programmable control of particles and droplets	High-voltage safety, transducer cost, and need for responsive materials or uniform fields

compare a larger number of variables simultaneously, providing a more comprehensive understanding of the factors influencing the results [105]. ML models trained on experimental and simulated data can predict NP properties, such as size, polydispersity, or EE, based on microfluidic design and flow parameters. The integration of supervised ML algorithms within microfluidic control systems enables adaptive, real-time regulation of synthesis parameters and product properties [106]. Nathanael et al. applied ML to optimize the microfluidic synthesis of AgNPs, identifying optimal operational windows and minimizing the number of experiments required to obtain a precise size control (Fig. 15) [107]. ML systems developed to predict the size of PLGA MPs produced using microfluidic devices with 3D flow focusing have demonstrated high accuracy, facilitating the on-demand production of particles with controlled uniformity [106]. Such data-driven approaches represent an evolution from traditional optimization methods based on DoE and of

classical CFD models toward self-optimizing microreactor systems that can autonomously maintain ideal operating conditions. In fact, they enable a significant reduction in development times, perform multidimensional analyses, lower prototyping costs as well as they enable intelligent design with reduced prototype production, superior predictive accuracy and continuous real-time self-optimization [108]. This makes it possible to work with an autonomous adaptive system, transforming the approach from empirical-iterative to predictive-adaptive.

4.3.1. Predictive modeling of nanoparticle properties

Predictive modeling has been examined systematically across the principal classes of pharmaceutical NPs. Moore et al. trained thirteen algorithms on approximately 200 formulations of liposomes, LNPs and PLGA NPs, produced with a SHM, to predict hydrodynamic diameter (d_H), polydispersity index (PDI) and EE from TFR, FRR and reagent

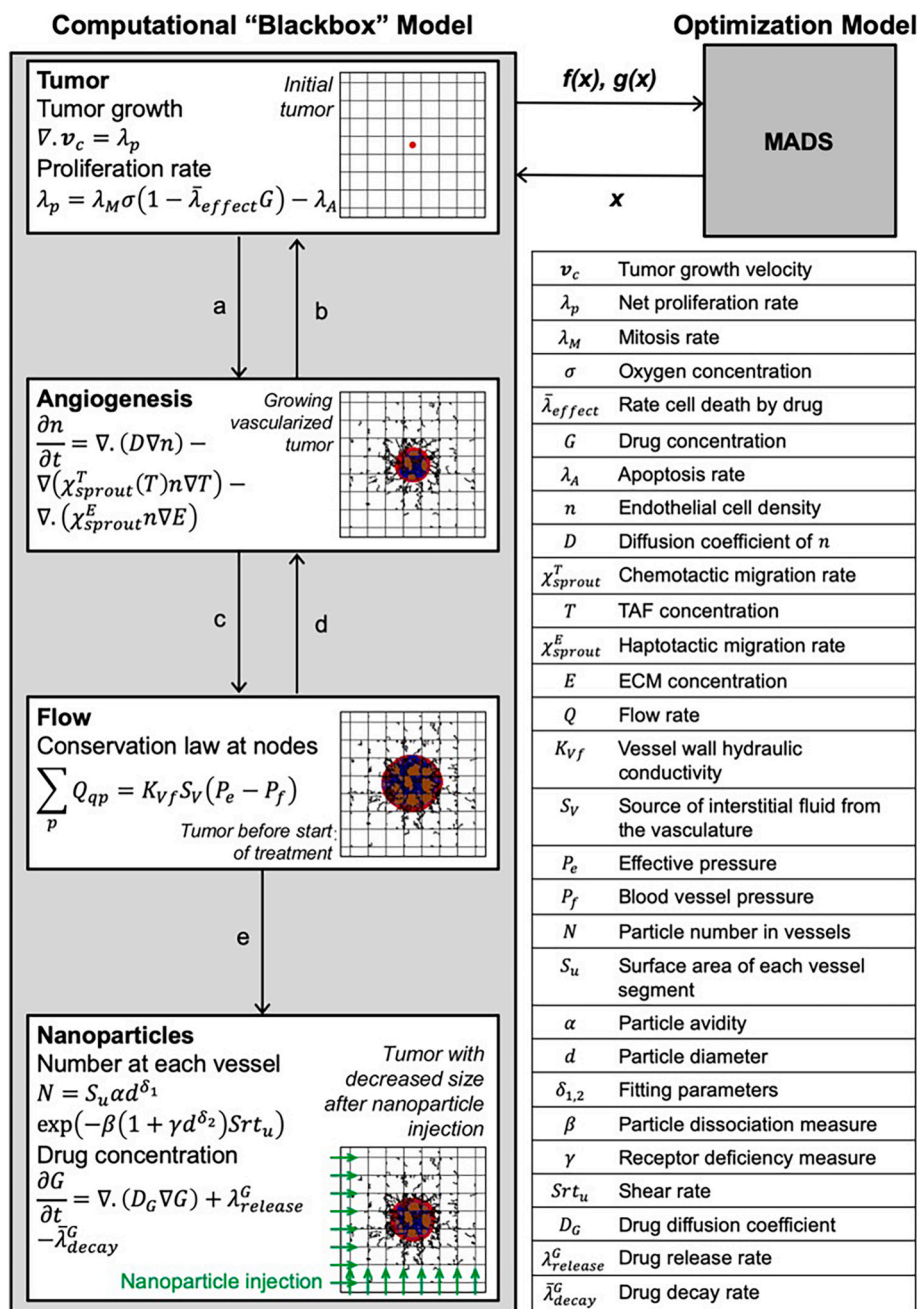


Fig. 14. Hybrid framework for NP-mediated drug delivery optimization. This framework combines a computational “blackbox” model of vascular tumor growth and NP treatment with an optimization strategy based on the mesh adaptive direct search (MADS) algorithm. The model iteratively evaluates NP designs ($\mathbf{x}$), optimizing the objective function $f(\mathbf{x})$ and constraints $g(\mathbf{x})$. The framework accounts for dynamic sub-models, including angiogenesis, nutrient and oxygen transport, capillary junctions, shear stress, and vessel properties. The tumor is simulated at different stages: inception, vascularization, pre-treatment, and post-treatment. Reprinted from an open access source [102].

concentrations: random forest regression proved to be the most accurate, and while d_H and EE were predicted reliably, PDI was not [109]. Similarly enough, Lee et al. studied liposomes, obtaining a coefficient of determination of 0.94 for size against 0.40 for PDI [110]. The two studies converge on the result but attribute it to complementary causes: on the one hand a weak correlation between PDI and the available process descriptors [109], on the other the narrow range over which PDI itself varies, since microfluidic self-assembly yields consistently low polydispersity [110]. Size and EE therefore appear learnable from process parameters alone, whereas PDI requires either more informative descriptors or a wider design space. Trying to solve the PDI issues, Jia et al. predicted size and PDI for liposomes across a 100–600 nm range with a

SHM. They obtained accurate size regression (gradient boosting, $R^2 = 0.91$ on an independent test set) but treated PDI only as a binary classification, above or below 0.2, rather than as a continuous regression target [111].

4.3.2. Bayesian optimization and active learning

Bayesian optimization (BO) is intended for objectives whose evaluation is experimentally expensive. A probabilistic model of the response is updated after each run and used to select the subsequent condition, which is chosen where the anticipated gain is the greatest, accounting both for the predicted response and for the corresponding uncertainty. On the other hand, active learning applies the same uncertainty-driven

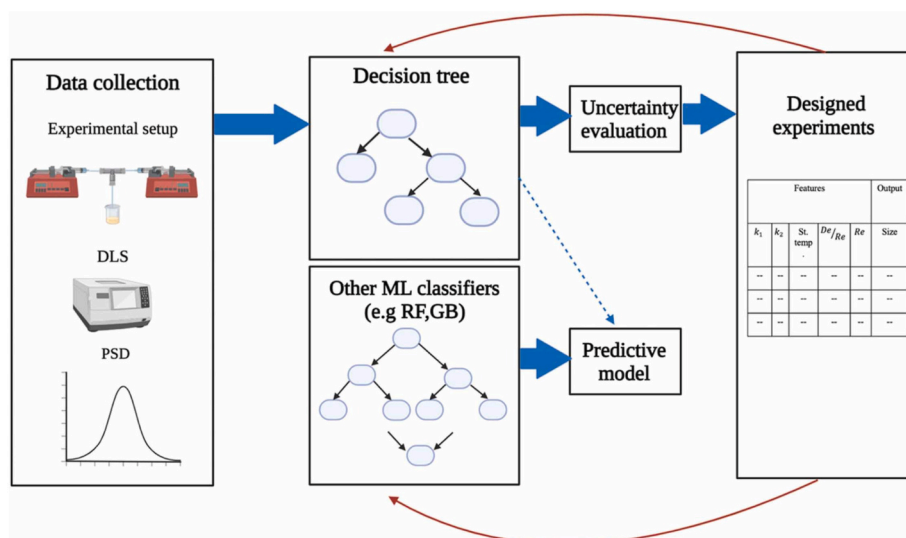


Fig. 15. Schematic overview of the methodological pipeline adopted for machine learning-assisted experimental design, illustrating the decision-tree-based approach used to guide parameter selection and optimization for the microfluidic synthesis of AgNPs. Reprinted from an open access source [107].

sampling to a different end, selecting the experiments that reduce the most the model uncertainty rather than those expected to improve the objective. In both cases, the experimental plan is determined iteratively rather than specified in advance, which is advantageous when each condition consumes drug substance, excipients, and analytical time. Both approaches require the outcome of each run to be measured before the next is chosen, and their adoption has followed the availability of such feedback. In inorganic nanomaterials, where particle size governs the optical spectrum, a single in-line spectroscopic reading identifies the product within seconds, and documented applications are concentrated accordingly. As an example, Tao et al. optimized metal NP synthesis on a self-driving oscillatory microfluidic platform using the Gryffin algorithm [112], while Abdel-Latif et al. combined an ensemble neural network with active learning to navigate a parameter space exceeding 2×10^7 conditions [113]. In drug delivery, an equivalent signal is not yet readily available, since EE, drug loading, and release behavior are generally assessed through separation or dissolution steps that take hours to days. The closest implementation addresses the upstream templating step, the autonomous BO controller of Cho et al., reaching target droplet sizes within approximately fifteen iterations irrespective of channel geometry and fluid properties [114]. Extending these methods to micro- and NPs formulation therefore depends not on the algorithms themselves rather than on the development of in-line techniques capable of tracking these attributes in real time with high precision [110].

4.3.3. Reinforcement learning for adaptive process control

Reinforcement learning (RL) differs from the above mentioned approaches in its objective. Rather than selecting which experiment to perform, an agent learns a control policy by interacting with a running process, adjusting operating variables and receiving a reward proportional to the deviation from the target state. It is therefore suited to conditions that vary over time, such as device-to-device fabrication variability, channel fouling or sensor noise, which would otherwise require manual intervention and limit the autonomy of long experiments. Dressler et al. trained deep Q-network and episodic-memory agents on real-time bright-field images to control interface position in continuous laminar flow and droplet size in segmented flow, both outperforming trained human operators, with the episodic-memory agent converging within minutes [115]. Applications of this kind remain confined to fluid handling rather than particle formulation, and RL is computationally more demanding than BO for comparable optimization tasks [114], while generalization across devices and interpretability of

the learned policy remain open issues [116].

4.3.4. Process Analytical Technology and digital twins

A digital twin is a computational representation of a process maintained in synchronization with it through real-time data. It serves three functions during operation: estimation of quality attributes for which no direct sensor exists, prediction of the effect of a change in operating conditions before implementation, and detection of malfunction from divergence between model and equipment. These functions support real-time release, in which product quality is established from process data rather than from end-product testing [117]. The prerequisite is measurement during operation. Where dedicated sensors are unavailable, the variable may be inferred by a soft sensor, in which a model reconstructs it from in-line signals [117]. Lee et al. demonstrated this studying liposome size, coupling in-line fluorescence spectroscopy to a machine-learning model: the root-mean-square error was 7.18 nm from 48 experiments and 7.53 nm on unseen lipid compositions, against over 10 nm for models trained without the in-line descriptors. The readout reduced the time per sample from over one day to 10–60 min and allowed TFR and FRR to be adjusted during operation, though it remains restricted to a single attribute validated on drug-free formulations [110]. In-line size characterization of concentrated, flowing nanosuspensions has also become instrumentally available [118]. Complete digital twins of microfluidic particle production, in which the model updates itself and returns corrective actions to the equipment, have yet to be established, and depend on extending real-time measurement beyond particle size.

4.3.5. Closed-loop optimization and autonomous laboratories

A closed-loop or self-driving laboratory automates the experimental cycle itself: a model proposes candidate formulations, automated equipment prepares and characterizes them, and the results are returned to the model, which is retrained before the next iteration (Fig. 16) [120]. Microfluidic formulation has been incorporated into such a loop. Ortiz-Perez et al. coupled microfluidic-assisted nanoprecipitation of PLGA-PEG NPs to high-content imaging and active learning, using a Bayesian neural network to select each subsequent set of formulations from a virtual library of 100,000 candidates; formulations were retained only if their predicted PdI, estimated by a separate model, fell below 0.2, providing a quality-control filter for colloidal stability. Two machine-learning-guided iterations raised cellular uptake in a breast cancer line from a mean of roughly five-to fifteen-fold, each iteration

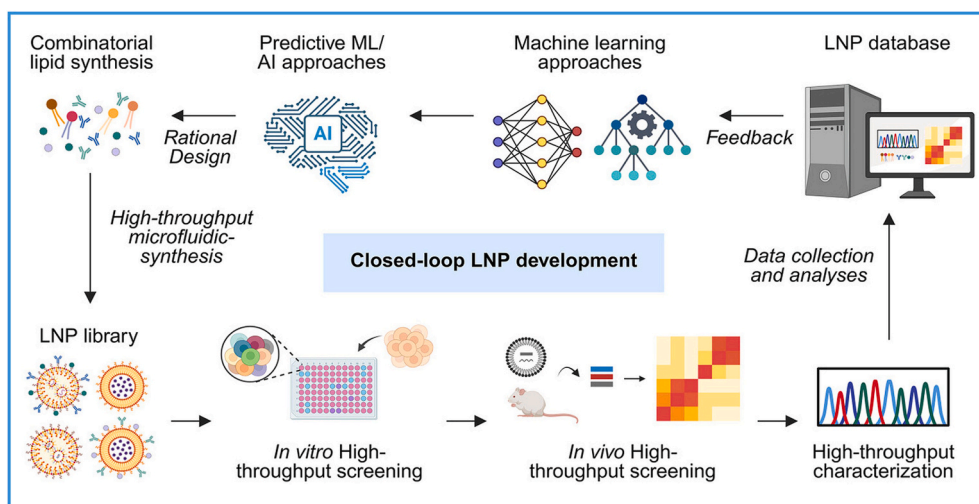


Fig. 16. Closed-loop, or self-driving, laboratory for NP formulation. Combinatorial chemistry generates a library of candidate compositions, which are formulated by high-throughput microfluidic synthesis and evaluated by *in vitro* and *in vivo* high-throughput screening together with high-throughput characterization. The resulting data populate a database on which machine learning models are trained to predict formulation performance and to guide the rational design of the next set of candidates, so that the experimental cycle proceeds iteratively with limited human intervention. Reproduced from Ref. [119].

requiring one week [121]. Comparable architectures have been reported for LNPs, in which combinatorial synthesis, high-throughput microfluidic formulation and deep learning are coupled: the AGILE platform generated a library of 1200 ionizable lipids in a single day to train its model, while LUMilab evaluated 1781 candidates over ten iterations, more than half of the final set exceeding tenfold the transfection efficiency of the initial candidates [119]. These implementations optimize a biological endpoint, uptake or transfection, that is measurable at the throughput of the loop. Manufacturing attributes such as EE, drug loading and release are not, and closed-loop control of the formulation process itself, as distinct from the screening of candidate compositions, remains comparatively undeveloped.

4.3.6. Generative models and foundation models

Whereas the methods discussed so far are predictive, mapping formulation parameters to properties, generative models invert this relation, sampling new candidates conditioned on a target specification. Variational autoencoders, generative adversarial networks and denoising diffusion models have been applied to the inverse design of drug delivery systems, with the recognized limitation that a proportion of generated candidates are physically inadmissible and require expert curation [122].

In the context of microfluidic formulation, these methods have been applied at the level of composition rather than of the fabrication process. The AGILE and LUMilab platforms both rely on deep generative models: a model pre-trained on a large virtual library of ionizable lipids is fine-tuned on experimental data to propose new structures, which are then synthesized and screened microfluidically [119]. This exemplifies the emerging role of foundation models, pre-trained on broad chemical corpora and adapted to a specific formulation task, as a means of mitigating the data scarcity that constrains bespoke models trained from scratch [123].

These capabilities remain confined to the generation of candidate compositions, and their outputs require experimental validation; their realistic near-term contribution is the proposal of formulations upstream of the experimental loop rather than the autonomous control of the manufacturing process itself.

4.3.7. Current limitations and future perspectives

Datasets are typically small and are rarely reported in a standardized form, which is repeatedly identified as a principal barrier to data-driven methods and the reason transfer learning and pre-trained models are

increasingly relied upon [123]. A further constraint is analytical rather than algorithmic: EE, drug loading and release cannot yet be measured in-line at the rate required to close an optimization loop, so that current autonomous platforms optimize biological endpoints or size alone rather than the full set of critical quality attributes [110,121]. Interpretability and regulatory acceptance remain open in parallel, and explainable-AI techniques such as SHAP analysis are becoming a standard requirement where model outputs inform formulation decisions [110].

The most probable near-term development is therefore not the replacement of mechanistic understanding by autonomous systems but the integration of the two, in hybrid workflows where physics-based description and human-defined acceptance criteria constrain data-driven optimization [120]. The transfer of these approaches from inorganic nanomaterials, where they are already established, to micro- and NPs for drug delivery is the direction in which the field is most likely to advance [119].

5. Materials for microfluidic micro and nano particles production

The wide variety of NPs produced using microfluidic devices can be grouped into broad, materials-based categories according to their chemical building blocks: inorganic (e.g., metals, metal oxides, silica (SiO₂), quantum dots (QD)), organic (polymeric and lipid), hybrid, and advanced materials (Fig. 17). The chosen class depends on the target application and required properties, which will be discussed in this paragraph.

5.1. Inorganic materials

The growing adoption of microfluidic platforms to produce inorganic micro/NPs, i.e., metals, metal oxides, SiO₂, and metal-SiO₂ composites, stems from their ability to synthesize particles with fine tunable size, structure, and geometry [124].

5.1.1. Metal particles

Metal particles owe their properties to their microscopic particle size and morphology, which made them suitable for several fields, from which catalysis, sensing, tumor therapy, and drug delivery can be recalled. Thanks to microfluidic technology, it has been possible to synthesize different types of metals NPs, such as gold, nickel and silver NPs [125].

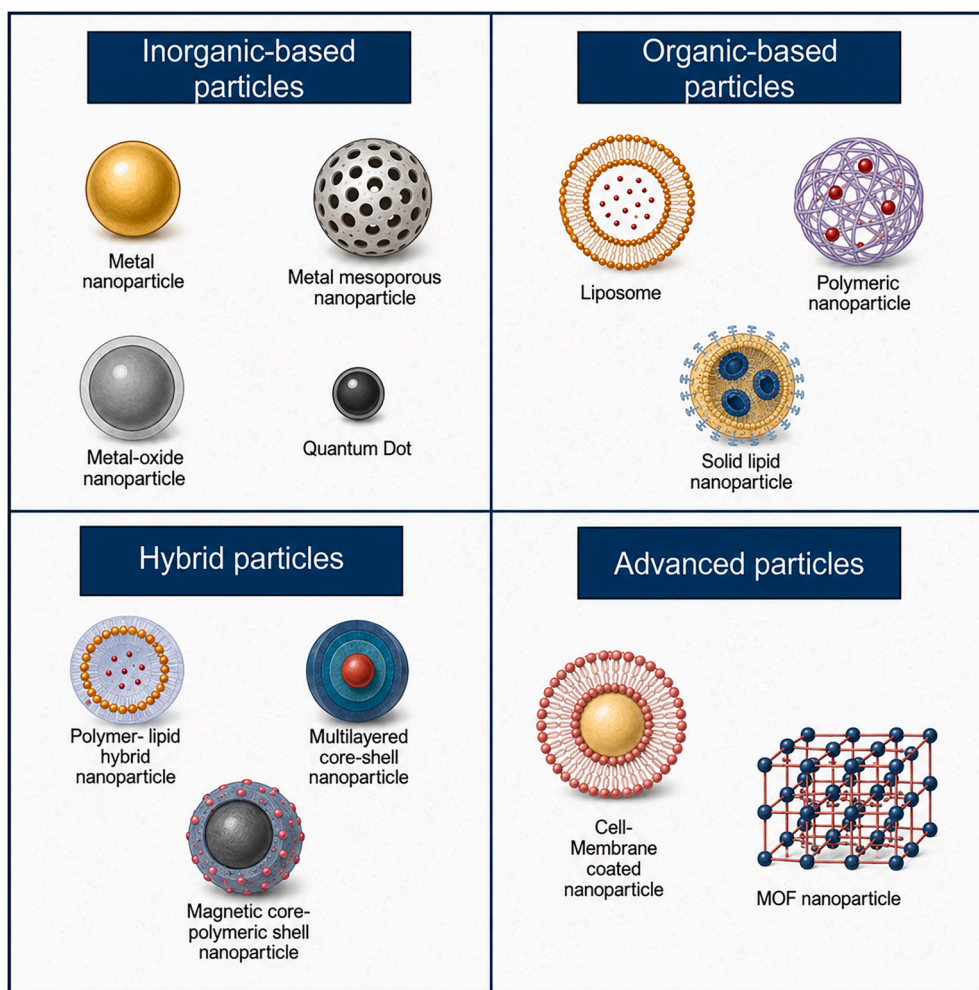


Fig. 17. Schematic representation of some examples of the most produced particles, divided into different categories, based on their chemical nature and functional properties.

Gold NPs (AuNPs), given their unique properties, small size and high surface area-to-volume ratio, have attracted considerable interest in biomedical and drug delivery fields. AuNPs in drug delivery offer various advantages like reduction of side effects, specific targeting, controlled release, high drug loading (DL) and overcoming the blood-brain barrier (BBB) resistance [126]. Regarding the latter, Fan et al. have developed a microfluidic micro physiological model to study the resistance of the BBB experienced by NPs, finding out that smaller AuNPs having a target molecule modification can pass the BBB more easily. This microfluidic chip represented one of the first microfluidic models to study drug delivery across BBB. It combined a 3D architecture with dynamic co-culture, and paracrine communication. Four parallel channels were interconnected by narrow microchannels, where endothelial cells lined a central blood vessel channel adjacent to a 3D brain channel containing astrocytes embedded in collagen gel [127]. In this field, droplet microfluidics could improve the control on the size of the AuNPs. For example, a two-reagent droplet microfluidic device, designed with a serpentine immediately after the cross junction to induce mixing in the droplets, was used for the synthesis of peptide-mediated AuNPs, speeding up the process and leading to the formation of different anisotropic AuNPs, with sizes ranging from hundreds of nanometers to the micron scale [128].

On the other hand, AgNPs are employed for biomedical applications due to their bactericidal and virucidal effects. Using a continuous microfluidic mixer, it is possible to obtain a wide range of particle size by changing chip material, flow rate and drug concentration (Fig. 18)

[129]. For example, Bircă et al. reported the microfluidic synthesis of AgNPs incorporated into alginate and hyaluronic acid (HA) hydrogels for wound-dressing applications, where the NPs are physically embedded within the polymeric network during gelation rather than forming a core-shell structure or undergoing covalent chemical bonding. This homogeneous dispersion enables sustained antimicrobial activity while preserving the biocompatibility and mechanical properties of the hydrogel matrix [129]. Recently, both AgNPs and AuNPs have been employed in the fight against SARS-CoV-2, especially for fast advection of the disease with colorimetric tests. AuNPs and AgNPs exhibit surface plasmon resonance, which changes upon target binding, causing a variation in the color or absorption of the solution which the principle behind many rapid tests [130].

Despite their broad applicability, metallic NPs exhibit potential bioaccumulation and limited biodegradability, which should be considered when selecting materials for drug delivery applications.

5.1.2. Metal oxide particles

Metal oxide NPs have been largely exploited in the biomedical field, especially for tissue engineering, immunotherapy and drug delivery.

5.1.2.1. Magnetic particles. Among metal oxide NPs, magnetic ones can achieve a controlled drug release in a specific area of the body, influenced by tunable magnetic fields [91]. One of the most interesting NPs of this subclass is represented by magnetoliposomes, complex systems consisting of iron oxide (Fe_3O_4) NPs coated with a lipid layer. These

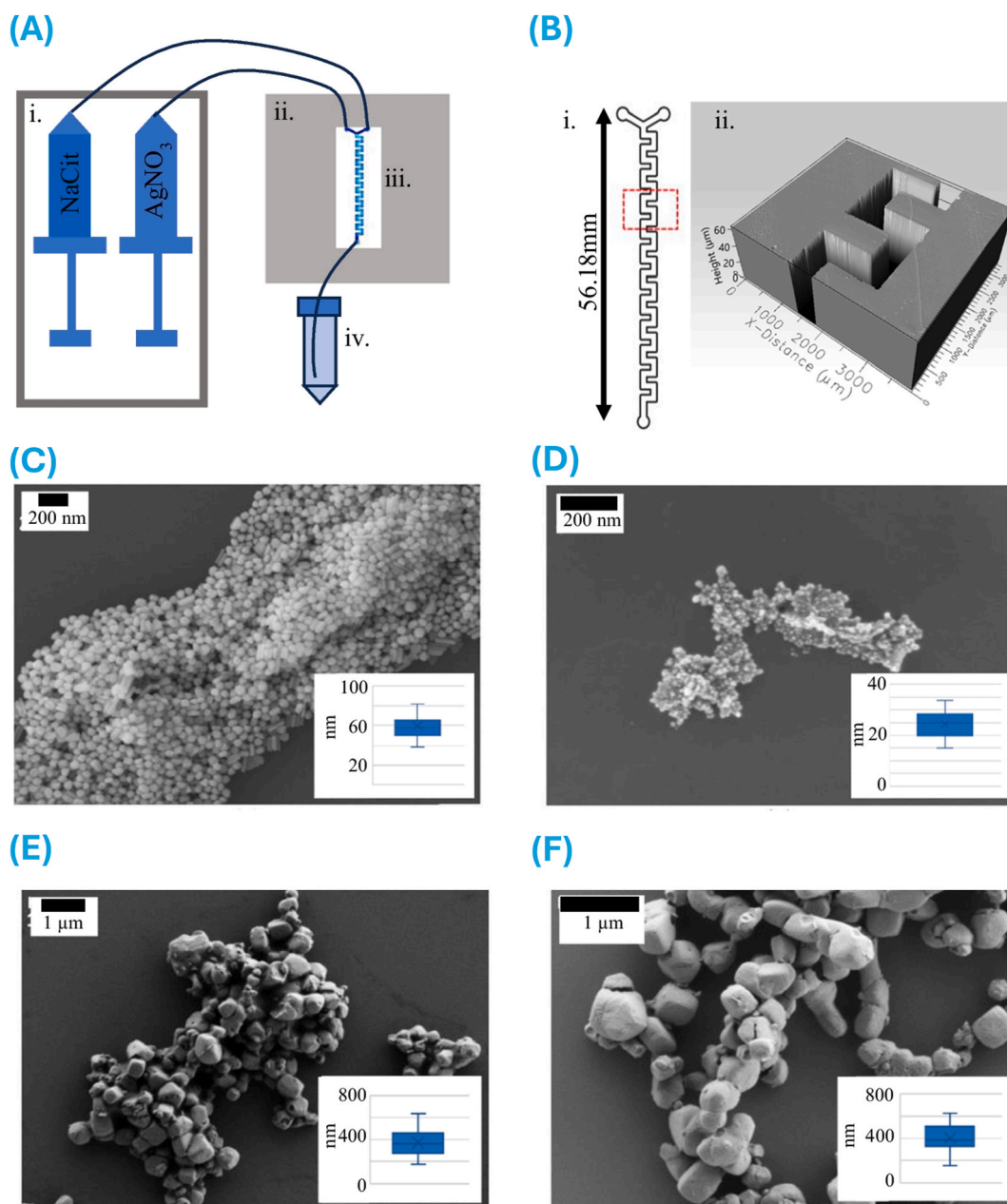


Fig. 18. (A) Microfluidic setup to produce AgNP i. dual syringe pump where one syringe contains NaCit while the other contains AgNO₃, ii. hotplate, iii. microfluidic chip, and iv. centrifuge tube for collection; (B) design of microfluidic chip. (C) SEM images of the AgNP. Box and whisker plots represent AgNP diameter. Positive control optimized batch experiment 37.5 mM NaCit and 1 mM AgNO₃. (D) microfluidic AgNP using 37.5 mM NaCit and 2 mM AgNO₃ at 3 L/min flow rate. (E) microfluidic AgNP 75 mM NaCit and 2 mM AgNO₃ at 1 L/min flow rate, 75 mM NaCit and 2 mM AgNO₃. (F) Zoom of condition E. Reprinted from an open source [128].

kinds of particles are made with a Y-shaped microfluidic device and are mainly used for drug delivery in the digestive system, as they are biocompatible and can efficiently be phagocytosed by cells [91]. Other typical material coatings are alginate and chitosan, which improve the drug release, achieving a sustainable release. This result is achieved by using an L-junction microfluidic platform, with a needle for injecting the disperse phase inserted into the 3/4 of the L-shaped channel [87]. Fe₃O₄-NPs are mainly chosen for their magnetic properties, biocompatibility and intrinsic antimicrobial activity, which allow both a controlled release of drugs and a direct action against pathogens [131]. Unlike the other inorganic NPs discussed here, the defining advantage of magnetic systems is not size control but the field-directed spatial control of release; accordingly, the reported chip geometries track the delivery goal rather than being interchangeable, with the Y-shaped device

favouring lipid-coated magnetoliposomes optimized for phagocytosis and the L-junction favouring alginate/chitosan coatings tuned for sustained release.

5.1.3. Silica (SiO₂) particles

SiO₂ is a widely spread material for NPs production as it is biocompatible, easily chemically customizable, thus making it suitable as a drug carrier for cancer therapy. Li et al., using a Christmas-tree microfluidic platform made of several mixing units, has developed six different sized SiO₂-NPs, achieving a monodisperse distribution. The four-layer serpentine microchannel allowed the simultaneous synthesis of multi-sized SiO₂-NPs. The ability to fine-tune particle size is crucial when optimizing drug delivery efficacy while minimizing side effects on healthy cells. They found out that the size of SiO₂-NPs directly

influenced their ability to reduce cancer cell viability, with larger particles (up to ≈ 400 –500 nm) showing the best anticancer effects. This runs counter to the common assumption that smaller particles are always preferable for cellular uptake, and indicates that the size–efficacy relationship is payload- and target-dependent rather than universal [132]. To achieve a higher surface area and biocompatibility, together with tunable pore size, SiO_2 can be used in its mesoporous form synthesized with a continuous flow-focusing microfluidic platform [133]. For applications requiring high surface area and internal loading capacity, mesoporous silica NPs produced in continuous flow-focusing microfluidic platforms provide tunable pore sizes (typically ~ 2 –10 nm for conventional MSNs, extendable to ~ 10 –50 nm in enlarged-pore or hollow designs), which is advantageous for encapsulating small proteins [134] and peptides [135]. Mesoporous silica NPs can improve specificity in chemotherapy, as shown in the case of breast cancer [136].

5.1.4. Quantum dots (QDs)

QDs are 5–20 nm sized semiconductor nanocrystals that can be classified as zero-dimensional because charge carriers (electrons and holes) are spatially confined in all three directions, preventing their free movement in any direction. This results in discrete, quantized electronic energy levels rather than the continuous energy bands found in bulk materials [137]. Thanks to discrete energy levels, QDs exhibit impressive electronic and optical properties which made them useful in various applications in the biomedical fields such as bioimaging, biosensing, and drug delivery. Microfluidics devices can be used to accurately regulate the nucleation and growth of QDs by varying the reaction parameters, to control their size and composition. Various QDs and QD-doped nanomaterials have been produced using microfluidics [138]. To avoid environmental contamination, research in this field has focused on Graphene QDs (GQDs). GQDs, which are known to cross biological barriers, have been incorporated into ultrasmall chitosan NPs for intranasal delivery of therapeutics in Alzheimer's treatment, showing effectiveness in brain targeting and reduction of the neuroinflammatory environment. These GQDs are produced using a microfluidic chip with a dual-inlet system that converged into an elongated hexagonal mixing chamber to enhance the interaction between the components before exiting through two symmetric outlets [139]. GQDs and ZnO NPs had been employed as photodynamic agents due to their high optical properties. In addition, segmented-flow (droplet-based) microfluidic platforms have been employed to fabricate composite MPs by confining the synthesis and assembly processes within monodisperse droplets. Using this approach, GQDs and ZnO NPs were homogeneously co-encapsulated with chitosan and gelatin to form drug-loaded MPs containing DOX for breast cancer treatment, achieving precise control over particle size, composition, and drug distribution [140].

Despite the significant improvement in the biocompatibility of GQDs, systematic studies are needed on their potential long-term toxicity and how GQDs affect the immune, reproductive and nervous systems in different animal models [141].

5.2. Organic materials

The use of organic materials presents distinct advantages over inorganic counterparts, particularly in terms of biocompatibility, controlled biodegradation and minimal accumulation-related toxicity, making them highly attractive for clinical applications. Microfluidic technologies enable the fabrication of organic NPs made of polymers (either synthetic or natural), liposomes and lipids, offering control over particle size, morphology, and drug release profile [142].

5.2.1. Synthetic polymers particles

Synthetic polymers, such as PLGA, poly- ϵ -caprolactone (PCL), poly (ethylene oxide) (PEO) and PLGA-Polyethylene Glycol (PEG) copolymers are selected for their biocompatibility, biodegradability and

ability to control drug release, with microfluidic techniques providing advantages over conventional batch methods in terms of reproducibility and EE [10,142]. One of the most widely used is PLGA, which, thanks to microfluidic techniques, can be used to produce particles of varying sizes, depending on the width of the channels with excellent dimensional control. PLGA is chosen as it is safe, FDA-approved and it is degradable into non-toxic byproducts [143]. Furthermore, recent studies have shown that PLGA or PEG-PLGA NPs, made with a SHM, co-delivered with scutellarin and paeoniflorin can be used to treat myocardial ischemia, thanks to their ability to effectively deliver drugs and reduce oxidative stress and inflammation, as they prolong the circulation of drugs in the bloodstream, improving bioavailability and therapeutic efficacy [144]. Size-tunable PCL NPs had been synthesized with a specially designed flow-focusing device with a rectangular mixing channel to exploit the PCL high permeability to small drug and its tendency to generate an acidic environment during the degradation process [145]. By doing so, it was possible to produce PCL MPs with controlled particle sizes between 15 and 35 m. They were able to load guggulsterone, a hormone used for Parkinson's disease treatment, obtaining a comparable DL efficiency (49%) to those made in batch. Here the microfluidic advantage lay in the tight control of particle size rather than in drug loading, which matched the batch process; this shows that the benefit of microfluidic synthesis is metric-specific rather than uniform [146].

Despite the impressive results achieved in the synthesis of polymeric particles, not all systems are easily scalable from an industrial point of view: chemical modifications of the raw material may be necessary and chip design is not always reproducible on a large scale. Furthermore, the possible immune response to synthetic polymer particles must also be considered.

5.2.2. Biopolymeric particles

Natural biopolymers like chitosan and alginate have been effectively processed using microfluidics. Microfluidic mixing platforms had enabled the production of chitosan NPs capable of encapsulating various biological molecules, such as β -galactosidase, mRNA, and siRNA, aiming to increase their stability, to protect them and control their release, improving the overall therapeutic efficacy and cell penetration [147]. Additionally, microfluidic technology allows the synthesis of innovative structures, such as pollen-inspired multilobe MPs from alginate and methacrylated gelatin (GelMa), which offer increased adhesion and tunable degradation for localized and prolonged intestinal drug release, as demonstrated by their enhanced anti-inflammatory efficacy in animal models. This peculiar shape was obtained by employing an eight-barrel capillary device. Here four independent channels delivered sodium alginate solutions which form compartmentalized droplets, and then gellified upon contact with calcium chloride solution to create calcium alginate hydrogel MPs [148]. Recently, protein NPs were produced using droplet-based devices. They were made mainly from proteins such as silk fibroin, bovine serum albumin (BSA) and beta-lactoglobulin, intended for the intracellular release of drugs [149]. Proteins are preferred for biological applications due to their natural compatibility with the body and their ability to self-assemble into functional structures [150] (Fig. 19A–F). Zhang et al. used a microfluidic chamber with an electric field applied to improve the mixing of negatively charged proteins like N-oxigenase with the positively charged polymer poly-(4-vinylpyridine) and obtained NPs with low polydispersity [151]. In contrast to the synthetic polymers above, whose translation is limited mainly by immune response and reproducible large-scale chip design, biopolymers offer intrinsic biocompatibility and self-assembly; the trade-off shifts to the batch-to-batch heterogeneity inherent to natural feedstocks, which constrains reproducible control over molecular weight and release.

5.2.3. Lipid based materials

Lipid NPs (LNPs) and liposomes, i.e. spherical vesicles consisting of a

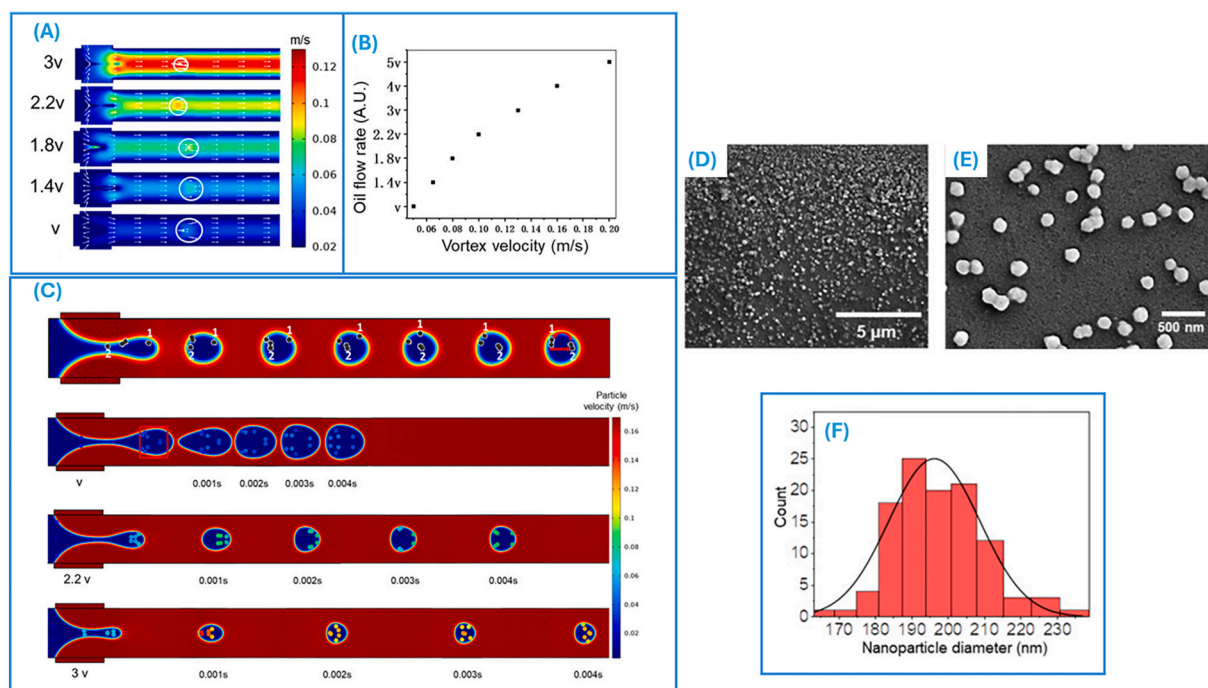


Fig. 19. Finite element simulation results showing the velocity field and molecular tracking in the moving droplets. (A) Simulation results showing the different velocity distributions in the droplet as a function of changing the oil phase flow rate. The white circle corresponds to the edge of the droplet, and the arrows correspond to the flow direction. (B) Graph of droplet velocity field as a function of oil phase flow rate. (C) Simulation results showing NPs' movement within droplets. NPs, which are numbered, can clearly be seen moving as the droplet tumbles. Time-frame tracking of molecular movement within the droplets for different oil phase flow rates is shown. (D, E) SEM micrographs of NPs with a 10 mg/mL protein concentration, a 9:1 ethanol-to-protein ratio, and an oil phase flow rate of 1500 L/h and (F) the corresponding particle size distribution (particles counted: $n > 100$). Reprinted from an open access source [150].

double phospholipid layer containing an aqueous core, are particularly interesting for their biocompatibility and their ability to encapsulate both hydrophobic and hydrophilic molecules.

5.2.3.1. Lipid NPs (LNPs). LNPs have a structure made of a solid core in a glyceride mixture, usually triglycerides, which gives them a rigid structure and kinetic stability. They can be loaded with a broad variety of cargos, as drugs, mRNA, siRNA, DNA. The efficacy of LNPs in the delivery of nucleic acids into cells makes them more appealing than other carriers because the ionizable lipids are near-neutrally charged at physiological pH, permitting easier phagocytosis into cells. LNPs were crucial in the development of mRNA vaccines for COVID-19 as they can protect mRNA, transport it into cells by overcoming the phospholipid bilayer, and release it efficiently into the cytoplasm where it can be translated into immunogenic antigen [152].

The cationic lipid DOTMA and its synthetic analogue DOTAP were the first lipids employed to deliver mRNA; while DODAP and DODMA were the first ionizable lipids used for RNA delivery [153]. In recent years using microfluidic mixer, combinatorial reaction schemes have been used to synthesize large libraries of potential delivery materials, giving several results such as the synthetic ionizable lipids SM-102, which was used in Moderna vaccine against SARS-CoV-2 [154] and ALC-0315, used in the Pfizer-BioNTech [155]. LNP components can themselves trigger an innate immune response, and microfluidic formulation has been used to temper it. Zhang et al. partially replaced cholesterol with dexamethasone, a structurally analogous anti-inflammatory corticosteroid, and formulated the mRNA-LNPs by microfluidic mixing; incorporating the drug into the particle suppressed pro-inflammatory cytokine release while preserving encapsulation and transfection, and improved *in vivo* mRNA expression [156].

The delivery of siRNA was possible thanks to a lipid system composed of a neutral phospholipid and cholesterol, obtained with a passive mixing device based on chaotic advection [157]. They stabilised

LNPs by adding PEG for the local administration of mRNA in the respiratory tract. This system, manufactured using a microfluidics mixing system equipped with a toroidal microchip, produced a double action: while lipids protected mRNA from degradation and promoted cellular absorption, PEG improved the stability of LNPs in aerosolisation [158]. LNPs made with a microfluidic SHM, were also used to deliver genes directly to the brain during traumatic brain injuries, in the field of gene therapy. Once again, the coating influenced the pharmacokinetics and duration of the therapeutic effect without altering the morphology of the particles [159].

5.2.3.2. Liposomes. Liposomes are spherical lipid vesicles composed of one or more lipid bilayers. Given their size and their amphiphilic characteristics, which give them the ability to encapsulate drug molecules either in the aqueous core or in the lipophilic membrane, such carriers are widely used in drug delivery [160]. Research in this field has made rapid progress, enabling the development of highly sophisticated systems. Shan et al. developed an engineered microfluidic mixing device which incorporated flow focusing mixer, a serpentine and a SHM, and a Tesla mixer to produce a programmed death-ligand 1 targeting aptamer modified indocyanine green (ICG)-liposome with high EE and a relatively small average diameter, equal to 118.8 ± 2.8 nm [161]. Despite these advantages, the complexity of such integrated mixer designs increases fabrication and operational demands, and maintaining consistent performance across extended runs or scaled systems remains challenging. Temperature-sensitive liposomes (TSL), i.e., liposomes activated by the photothermal effect of photosensitizers and containing ansamitocin P-3 and ICG were produced with a swirl mixer in a recent work by Jin et al. TSL reacted converting the absorbed near-infrared light energy into thermal energy, increasing the fluidity and permeability of the phospholipid bilayer and thus releasing the drug in a controlled way [162]. Nevertheless, TSL systems are intrinsically sensitive to lipid composition and processing temperature, and unintended

premature leakage or incomplete release may occur if thermal thresholds are not precisely controlled, which complicates formulation robustness and clinical translation.

Liposomes PEG coatings can improve particle stability, masking them from the immune system, avoiding protein corona. For example, liposomes made from a mixture of unilamellar lipids (EYPC, cholesterol and DSPE-PEG 2000) were produced with a serpentine micromixer. Particle size was finely tunable (≈ 64 – 152 nm, $PDI < 0.2$) by adjusting the TFR, FRR, lipid concentration and chip geometry, while a hydrophobic model drug (Nile red) was encapsulated with efficiencies up to 74% [163]. For cancer therapy, paclitaxel (PTX)-loaded PEGylated liposomes were produced and their action was analyzed. They increased the drug stability and obtained an EE greater than 90%, which was slightly affected by the variation in the PEG lipid ratio [164]. Yet, as with many liposomal systems, downstream solvent removal, long-term physical stability, and scale-up to clinically relevant production rates remain non-trivial challenges that must be addressed for successful industrial implementation. Recent high-throughput platforms are beginning to close this gap. Han et al. developed a microfluidic vortex-focusing device that sheathes the lipid stream in a rotating aqueous flow, decoupling size control from throughput: it generated monodisperse liposomes (PDI as low as 0.04) whose diameter was tuned through the flow rates (Fig. 20), reaching 27 nm on inclusion of a

PEG-lipid and mass production rates above 20 g/h that approach manufacturing scale [165].

5.3. Hybrid/composite materials

Composite particles exploit the characteristics of two classes of materials to achieve the maximum yield of the properties, depending on the specific application. It is possible to have core-shell structures and polymer-lipid hybrid systems that combine the advantages of the individual classes of materials including stability, controlled release and localized targeting [166].

5.3.1. Core-shell particles

The core-shell structure of the particles consists of two or more distinct layers with a core, which influences the properties of the particles. The outer shell is typically made of another material that serves to protect the core, stabilize and functionalize the particle [166]. Wu et al. were able to produce hydrogel microcapsules with a core-shell structure using a multi-channel, multi-junction microfluidic device, which had three parallel curved serpentine channels that converged at a Y-junction mixing point. The core was composed of gelatin methacrylate, while the shell was produced either with polyacrylamide, cross-linked by UV, for a thin and robust shell, or with alginate, cross-linked with Ca^{2+} and

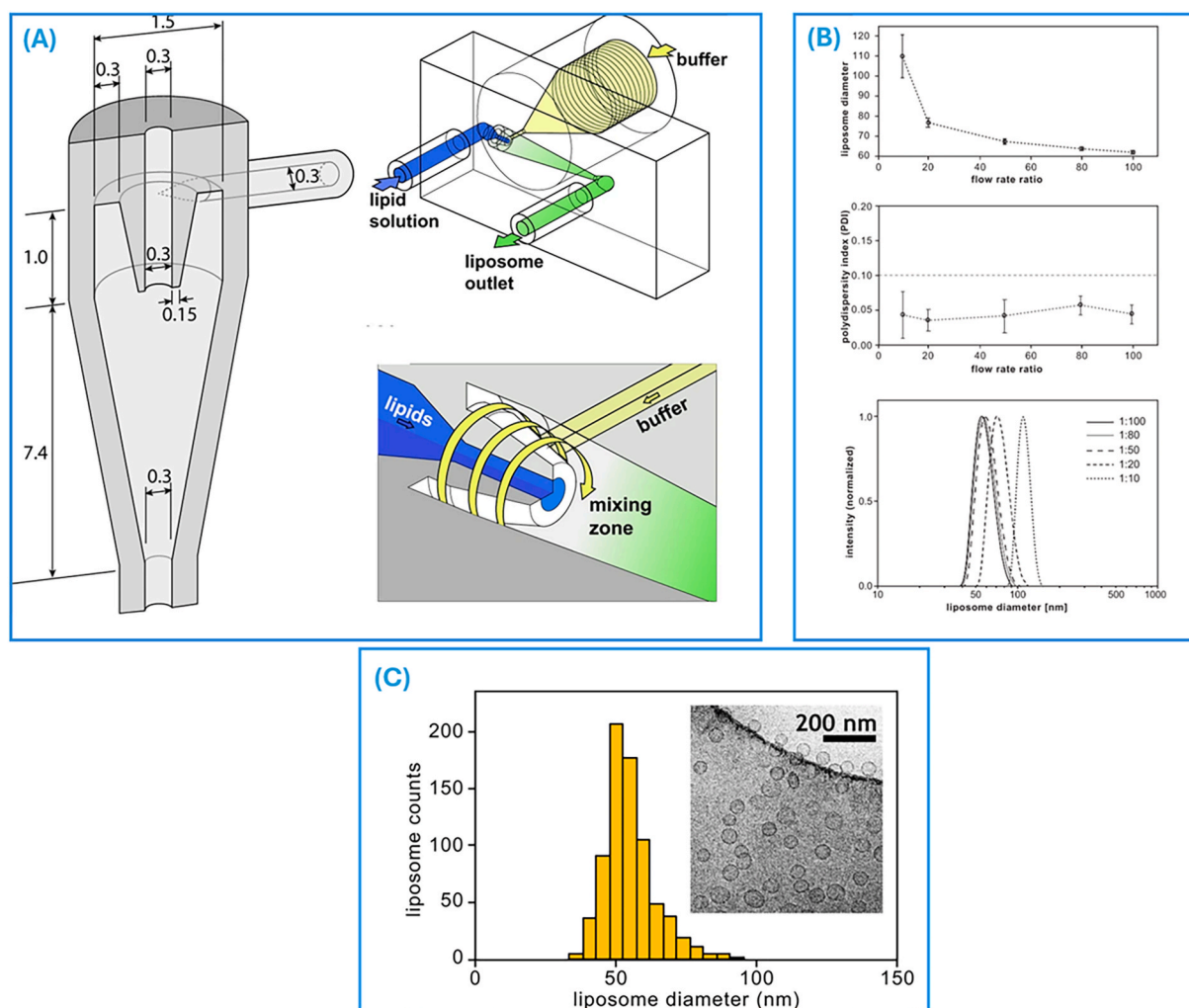


Fig. 20. Size-tunable liposomes by microfluidic vortex focusing. (A) Schematic of the microfluidic vortex-focusing device: two inlets conjoin at an annular junction feeding a conical mixing chamber and a single outlet. (B) Mean liposome diameter (top) and polydispersity index (middle) versus the buffer:lipid FRR, with the corresponding normalized size distributions (bottom), for a DMPC:cholesterol:DCP formulation. (C) Cryo-TEM image of the produced liposomes (scale bar 200 nm). Adapted from [165].

polyethyleneimine, by interfacial polymerization, for controlled release properties and response to thermal-triggered stimuli. The microcapsules allowed the incorporation of different drugs in distinct layers with separate release times [167].

In the field of synthetic polymers, Fabozzi et al. developed a system for the intravenous delivery of irinotecan consisting of PLGA-poloxamers NP formulations (PLGA/PF68+PF127 NPs) decorated with HA. These NPs, produced with a Y-junction device, had a hydrophobic core (PLGA), to encapsulate hydrophobic drug, nonionic polymeric surfactant (poloxamers) which connect the core and a HA hydrophilic shell to increase the colloidal stability, allowing an increase of the *in vivo* circulation time [168].

Regarding magnetic core-shell microspheres, Zhou et al., using a flow-focusing device, developed a double-layer structure, with a magnetic core and a polymeric shell. The core consists of a magnetic fluid based on Fe_3O_4 and polystyrene sulfonic acid, while the shell is made of a photosensitive acrylic resin. The microfluidic device shows three distinct functional zones: a Y-junction preparation zone, where two inlet streams converge, a serpentine UV curing zone with multiple turns, where the mixed solution is exposed to UV light for polymerization, and a collection zone, where the resulting core-shell microspheres are gathered. The microspheres took advantage of magnetism to achieve localized release [169].

In another study, thanks to an innovative 3D vortex-type multilayered microreactor platform, Niculescu et al. employed salicylic acid as the shell layer to obtain a protective organic coating around the Fe_3O_4 core. It was possible to produce spherical NPs of eight different $\text{Fe}^{3+}:\text{Fe}^{2+}$ molar ratios to optimize the $\text{Fe}^{3+}:\text{Fe}^{2+}$ ratio around the required stoichiometry, each with low polydispersity in a short reaction time and under a high flow rate Fig. 21A–E [170]. Across these examples the shell consistently supplies a function the core lacks – stabilization, targeting, or stimulus-responsiveness – so the core-shell architecture is justified precisely when no single material satisfies both loading and interface requirements; the recurring cost is fabrication complexity and a morphology sensitive to small flow perturbations.

5.3.2. Lipid-polymer NPs (multilayered structures)

Hybrid NPs (HNPs) are widely utilized for the possibility of obtaining structural complexity, with multilayered structures often produced by alternating polymers and lipids [171]. Multilayer HNPs have been

designed to deliver low-solubility drugs. They combine the biocompatibility of lipids with the chemical versatility of polymers, offering an advanced solution for the delivery of certain types of drugs that are difficult to be formulated [171]. The hybridization between lipids and polymers overcomes the limitations of purely lipid-based systems (e.g., instability) and polymer-based systems (e.g., poor biocompatibility), improving the stability, loading capacity and dispersion of hydrophobic drugs [172].

Multilamellar structures have been developed with alternating concentric layers of polybutadiene-*b*-polyethylene oxide (PBD-*b*-PEO) block copolymers and DOPC and DPPC and cholesterol lipids, with an average diameter ranging from 80 to 200 nm. The production of these products was made possible by a chaotic mixing microfluidic device using a SHM. The system was used to solubilize a potent low-solubility antimalarial (DSM265) [173].

Lipid-polymer NPs loaded with sorafenib were prepared by Tahir et al. using both bulk nanoprecipitation and microfluidic co-flow nanoprecipitation method with an inner polymeric core of PLGA and a lipid shell made by lecithin and the lipid-polymer conjugate DSPE-PEG 2000 [174]. Although the microfluidic route typically yields improved size uniformity, higher encapsulation efficiency and better colloidal stability than bulk methods, practical drawbacks include limited single-device throughput (necessitating parallelization for scale), sensitivity of core-shell morphology to small formulation or flow perturbations (which complicates robustness), potential long-term instability of the lipid shell (lipid shedding or PEG desorption during storage), the need for downstream solvent removal and purification, and higher process complexity and cost that must be justified for translation and GMP manufacture.

5.4. Advanced materials

Advanced materials include NPs functionalized with ligands for active targeting, stimuli-responsive systems (pH, temperature), Metal-Organic Frameworks (MOFs), and biomimetic and bioinspired NPs. The use of advanced materials in the production of NPs and MPs via microfluidics is transforming drug delivery by enabling the production of multifunctional and customizable platforms. The driving force behind research in this direction is the need to increase specificity, reduce side effects and integrate diagnostic and therapeutic functions into the same

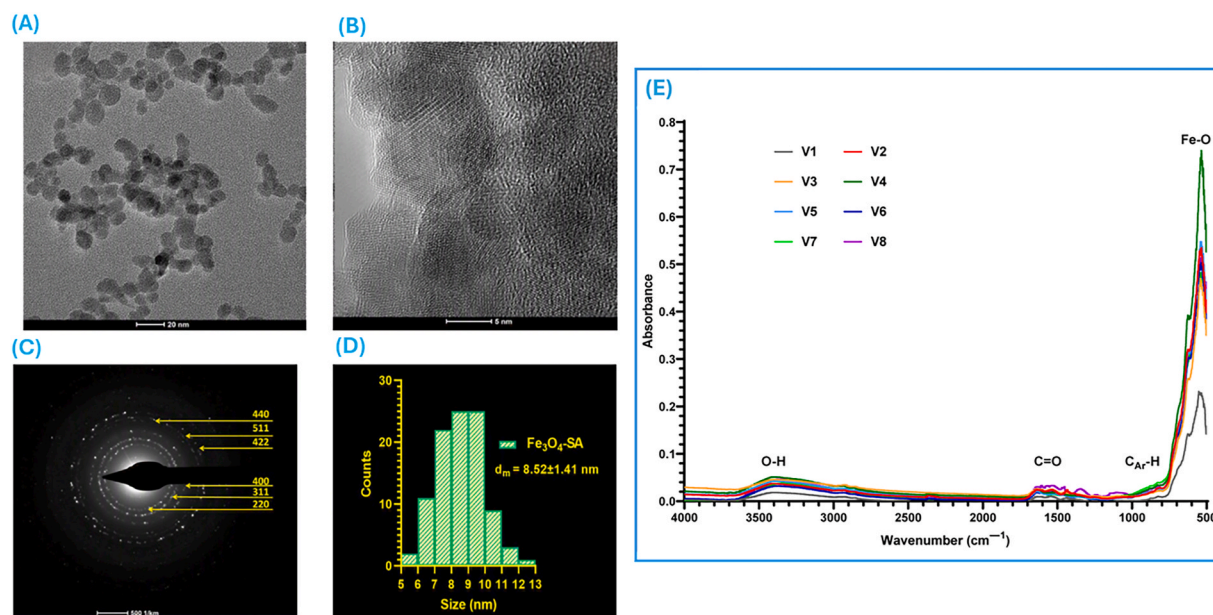


Fig. 21. (A–B) TEM micrographs, (C) SAED pattern, and (D) size distribution of Fe_3O_4 -SA (V3) NPs. (E) FT-IR spectra for the eight variants of Fe_3O_4 -SA NPs. Reprinted from an open access source [170].

vector [124].

5.4.1. Metal-Organic Frameworks (MOFs)

MOFs are porous crystalline materials formed by metal ions or metal clusters coordinated with organic ligands. Their high porosity and loading capacity make them very promising for the controlled release of drugs. Zeolitic imidazolate framework-8 (ZIF-8) MOFs have been developed, incorporating insulin and AuNPs. These structures, produced using SAR channels, are designed to release insulin in response to glucose levels in the treatment of diabetes. The AuNPs within the MOF mimicked the enzyme glucose oxidase, oxidizing glucose into gluconic acid and hydrogen peroxide. This lowered the pH, destabilizing the MOF which in turn released insulin only in the presence of glucose, making the system highly specific and sensitive [175].

Zhang et al. produced with a coaxial capillary microfluidic system bio-inspired MOFs that can be used for multimodal cancer therapy, inhibiting tumor cell proliferation. These highly complex systems are nanometric structures coated with cell membranes, giving them biomimetic characteristics. Here, the MOF consisted of a core of Fe^{3+} ions and meso-tetra(4-carboxyphenyl) porphyrin, into which a platinum prodrug (Pt(IV)-(COOH)_2) is loaded, thus obtaining the FeTPt NP. Each micro-droplet acts as a microreactor, so the MOF size (ca. 130 nm) is governed by nucleation and growth rather than by the droplet diameter (Fig. 22A–C) [176]. What distinguishes MOFs from the other advanced materials is the coupling of crystalline porosity, and thus high loading, with a degradation that can itself be made stimulus-responsive – exploited here as glucose-triggered release and, in the droplet route, as nucleation-controlled sizing decoupled from the droplet. The open

question conditioning translation is the biological stability and potential toxicity of the metal–ligand constituents upon degradation.

5.4.2. Stimuli-responsive particles

Stimuli-responsive NPs can change their properties in response to a trigger like light, temperature, presence of chemicals, pH or magnetic fields. As an example, Guo et al. developed photo-switchable, i.e., light-responsive, microcapsules with an aqueous core containing magnetic NPs and DOX. The structure consisted of a double layer with an outer shell made of PLGA, modified with PEG-b-Poly-N-sulfopropyl aniline, giving the material photosensitive properties. This modification allowed the permeability of the shell to be modified by exposing it to UV or visible light, enabling precise and programmable drug release. The magnetic core allowed the removal of the NPs by external magnetic fields after treatment, reducing potential side effects. This resulted in a spatially and temporally controlled drug release which proved that this system is effective in the localized treatment of cancer cells. To obtain these microcapsules a microfluidic chip consisting of a coaxial geometry is used, in which concentrically aligned inner and outer channels enable the formation of core-shell structure [177]. Hybrid Liposomes (HLPs) were produced, using NanoAssemblr® Benchtop microfluidic system equipped with a SHM cartridge, with pH responsive polydopamine polymer to facilitate pH-responsive drug release in wound healing. The HLPs were loaded with HA or phenytoin for wound healing. Their surface was modified with folic acid to promote the cellular interaction with HLPs [178]. A recently developed microfluidic device with a novel design modular swirl mixer, was used to produce TSL loaded with ICG and ansamitocin P-3. The microfluidic device features three

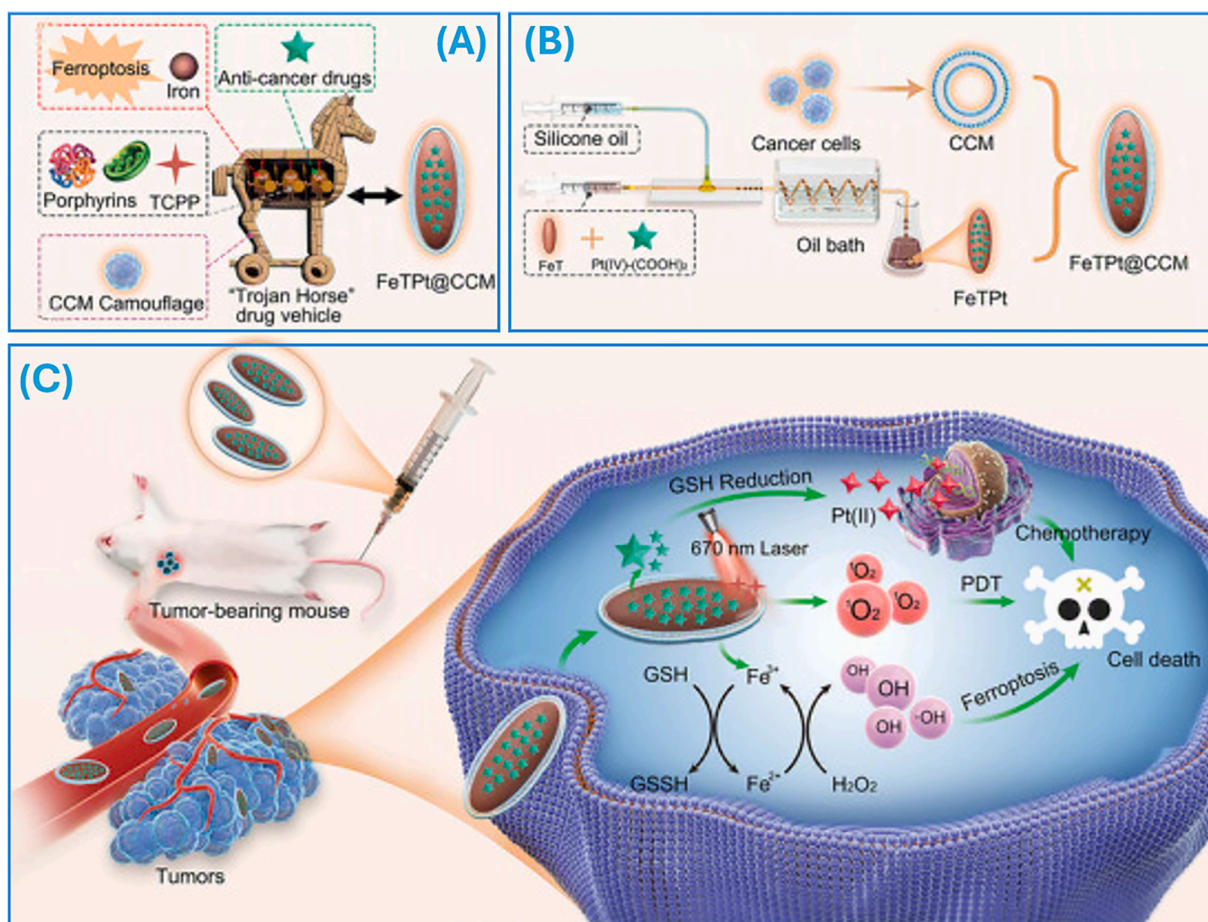


Fig. 22. Schematic illustration of the FeTPt@CCM and its ability to combine chemotherapy, phototherapy and ferroptosis therapy. (A) Design of the "Trojan Horse" drug vehicle. (B) Microfluidic preparation of FeTPt and generation of FeTPt@CCM through CCM coating. (C) FeTPt@CCM accumulates in tumors and triggers combined chemo-, ferroptosis-, and photodynamic therapy. Reprinted from an open access source [176].

configurations available with 1, 2 or 4 mixing elements that can generate three-dimensional vortex flow patterns for efficient passive mixing. These liposomes can be activated by near-infrared stimulation and had been studied to increase the potency, stability and active targeting in photodynamic therapy for breast cancer, without damaging other organs [162]. The unifying principle of these systems is the decoupling of when and where release occurs from what is released, obtained by an external or local trigger; the shared practical bottleneck is reliable triggering *in vivo*, exemplified by the threshold precision required for the thermal systems above, which currently limits robustness more than the chemistry does.

5.4.3. Biomimetic particles

Biomimetic NPs are innovative structures that mimic natural biological systems, combining materials such as lipids, polymers, and metals with cellular components to replicate the functions of biomolecules. The basic idea is to exploit the efficiency and specificity of natural systems for various applications. In fact, these kinds of structures can evade the immune system and target cells more accurately [179].

A biomimetic NP formulation of disulfiram and copper ions that self-assemble into the $\text{Cu}(\text{DDC})_2$ complex under physiological conditions was produced for cancer treatment with a novel Stabilised Metal Ion Ligand complex method, named SMILE. Here, the Metal-organic NPs (MONPs) are composed of a metal-organic core, made of $\text{Cu}(\text{DDC})_2$, and a surface decorated with BSA. The BSA allowed the MONPs to be recognized by the body as a biological component of its own. These NPs are made using a 3D-printed microfluidic device with a serpentine mixer [180].

Biomimetic NPs can also be coated with cell-membrane, encapsulating NPs with an external shell obtained from cell membranes derived from different living cells. Thanks to this feature, they can evade the immune system and immunological reactions, improve the stability and longevity of the NPs themselves, prevent non-specific absorption by healthy cells, and improve the targeting of the desired cells [181].

For example, Cancer-Cell-Membrane-Coated NPs (CCM-NPs) encapsulating DOX can improve its antitumor efficacy as the tumor cell membrane coating allows the extension of circulation time in the body. The combination of prolonged circulation and active targeting results in a higher concentration of DOX at the tumor site compared to healthy tissues. Furthermore, the encapsulation of DOX in the PLGA core and controlled release reduced the exposure of healthy tissues to the drug, decreasing side effects compared to free DOX [182]. Despite the remarkable achievements, coating NPs using conventional methods such as extrusion and ultrasonic energy results in possible damage to the membranes, failure to properly reposition membrane components after extrusion, poor control over the final product, lack of standardization and difficulties in large-scale production.

To overcome these critical issues, the most recent studies have identified that biomimetic CM-NPs can be produced using microfluidic devices. Microfluidic electroporation appears to be a promising technique. With this new approach, cores and cell membrane vesicles are infused into a microfluidic chip, in which there is an electroporation zone equipped with integrated electrodes, that apply electrical pulses to create transient pores in the membranes to promote NPs into membrane vesicles [183]. Rao et al., using this type of device, consisting of a Y-shaped merging channel, a S-shaped mixing channel and the electroporation zone, synthesized Fe_3O_4 magnetic NPs coated with red blood cell membrane-derived vesicles for photothermal therapy. Red blood cell membrane-coated NPs (RBCM-NPs) are notable for their exceptional biocompatibility and long circulation times [183]. The same type of device was also used to obtain white blood cells membrane-coated NPs [184], which can be used to overcome multiple biological barriers and improve therapeutic delivery.

Although further progress and refinement will be necessary, microfluidic synthesis is a very promising strategy for the development of new-generation biomimetic NPs.

The advantages and disadvantages of the main NP classes discussed above are summarized in Table 4. In addition, Table 5 reports selected representative examples of NP systems produced by microfluidics, including their particle size and PDI.

6. Applications

Microfluidic technology has transformed the fabrication and functionalization of micro- and nano-particles by providing precise control over mixing, nucleation and surface chemistry at the microscale [65]. In microchannels, reagents mix with high predictability to produce particles with narrow size distributions, uniform morphology and high EE, improving reproducibility and reducing batch variability compared with traditional bulk methods [187]. These attributes make microfluidic particles highly versatile for biomedical and analytical applications, including drug delivery, biomolecular analysis, and cell-biology models, where tight control over physicochemical properties and scalable production are essential (Fig. 23) [188,189].

6.1. Addressing drug delivery challenges

Microfluidic formulation of NPs has proven highly effective at overcoming common drug-delivery limitations. For example, polymeric and LNP systems can improve poor water solubility and bioavailability and extend drug retention while reducing systemic toxicity. By encapsulating drugs in precisely engineered carriers, microfluidic NPs concentrate the active agents at target sites (e.g., tumors) and spare healthy tissues, enhancing efficacy and patient compliance [190]. Moreover, microfluidics enables continuous, high-throughput production of uniform NPs with very high EE and DL. For instance, one study found that a hydrodynamic flow-focusing microfluidic mixer produced smaller NPs with narrower size distributions and higher EE/DL than conventional bulk mixing. In practice, laminar flow in microchannels provides fine control over mixing and particle self-assembly. This, together with the rapidly scalable manufacturing, allows for a minimal batch-to-batch variability. In short, microfluidic fabrication yields well-defined, reproducible drug carriers that increase payload delivery to the intended site while minimizing off-target exposure [187].

6.1.1. Lipid-based NPs and liposomes

6.1.1.1. Nucleic acid delivery. Microfluidics have been pivotal in formulating RNA therapeutics. For example, the COVID-19 mRNA vaccines (Moderna, Pfizer/BioNTech) use ionizable LNPs, whose discovery and optimization were greatly accelerated by rapid microfluidic screening and mixing [152]. Importantly, by tuning flow rates and channel design, microfluidics can fine-tune LNPs size. As an example, a baffle-mixer device yielded a panel of 20–100 nm LNPs, identifying an optimal 38–78 nm range for efficient hepatic gene silencing.

6.1.1.2. Drug encapsulation. Lipid nanocarriers can encapsulate both hydrophilic and hydrophobic drugs. Clinically approved examples include liposomal DOX (Doxil®) and liposomal amphotericin B, which enhances delivery to tumors or fungal cells while sparing healthy tissues [191,192].

For instance, paclitaxel, a poorly water-soluble anticancer drug, has been encapsulated into PEGylated liposomes by continuous-flow microfluidics, achieving encapsulation efficiencies above 90% and a narrow size distribution [164]. Likewise, sorafenib has been loaded into lipid-polymer hybrid NPs by microfluidic co-flow, reaching encapsulation efficiencies up to 95% with controlled release [174].

6.1.1.3. Targeted delivery. Active targeting moieties can be readily incorporated into LNPs via microfluidics. For example, folic acid or peptide ligands (like TAT peptide) have been attached to microfluidic

Table 4

Advantages and disadvantages of different NPs as drug delivery systems.

Category	Subtype	Advantages	Disadvantages	References
Inorganic	Metal (AuNPs, AgNPs)	High stability, tunable size/shape, easy surface modification, high area-to-volume ratio	Potential toxicity, accumulation in organs, limited biodegradability	[124]
	Metal oxide (Fe ₃ O ₄)	Magnetic targeting, biocompatibility, controlled release	Aggregation, oxidation, need for surface coating	[130,131]
	Silica (SiO ₂)	High surface area, easy functionalization, good DL	Poor biodegradability	[133,134]
Organic	QDs	Optical and electronic properties, tunable properties	Heavy metal content, environmental concerns	[137,141]
	Synthetic polymer (PLGA, PCL, PEG)	Controlled release, tunable properties, versatile drug encapsulation	Complex synthesis, possible immune response	[59,145,185]
	Biopolymers (chitosan, albumin, gelatin)	Biocompatibility, biodegradability, mild preparation conditions	Batch variability, limited mechanical strength, stability issues	[147,149]
Hybrid	Lipid-based (LNPs, liposomes)	Biocompatibility, ability to encapsulate hydrophilic/lipophilic drugs, low toxicity	Stability issues, limited DL	[108]
	Core-shell	Combined properties, improved stability, targeting	Complex synthesis, scalability challenges	[166]
	Polymer-lipid	Enhanced biocompatibility, improved DL	Potential instability, formulation and structural complexity	[171]
Advanced	MOFs (ZIF- 8, ZIF- 67)	High porosity, tunable structure, high DL	Toxicity concerns	[175,185]
	Stimuli-responsive (pH, temperature)	Targeted, controlled release	Complex design, potential unpredictability <i>in vivo</i>	[177,178]
	Biomimetic (cell membrane-coated NPs)	Enhanced biocompatibility, immune evasion, targeted delivery	Complex preparation, reproducibility issues	[179,180]

Table 5

NP systems produced by microfluidics for drug delivery: particle size and polydispersity.

Category	Subtype	Chip	Size (nm)	PDI	Ref.
Lipid-based	Liposomes	Serpentine	~152	≤ 0.063	[163]
Biomimetic	Exosome-coated	Spiral + sonication			[186]
Hybrid	Polymer-lipid	Staggered herringbone (SHM)	~268	~0.6	[173]
Synthetic polymer	PCL	Hydrodynamic flow focusing	(127–193)	0.180 ± 0.009	[145]
Synthetic polymer	PLGA	Staggered herringbone (SHM)	152.3 ± 1.5	0.117 ± 0.023	[143]
Core-shell	Fe 3 O ₄ -SA	Microvortex (3D)	~229.9	~0.233	[169]
Metal	AgNP (citrate)	Simple geometry	~ 24–400 (mean 71)	n.r.	[128]
Metal oxide	Fe 3 O ₄ (magnetoliposomes)	Serpentine	137 ± 17→787 ± 45	< 0.5	[91]
MOFs	FeTPt@CCM	Co-flow		0.122 ± 0.028	[176]
Silica	Mesoporous SiO ₂	Hydrodynamic flow focusing	~ 120	n.r.	[133]
QDs	CS/GQD	Hydrodynamic flow focusing	< 10	n.r.	[139]
Stimuli-responsive	pH-resp. hybrid liposomes	Staggered herringbone (SHM)	~117.3	~0.23	[178]
Biopolymers	Chitosan (CS/TPP)	Serpentine (S-shaped)	~105	~0.22	[147]

n.r.: not reported.

liposomes to recognize tumor receptors, improving cellular uptake. In one case, bacteriophage-loaded liposomes functionalized with TAT were produced on-chip. These TAT-coated liposomes achieved ≥90% uptake by target cells and dramatically increased killing of intracellular Methicillin-Resistant *Staphylococcus aureus*. Their results illustrate how microfluidics can yield multifunctional liposomes bearing targeting ligands and cell-penetrating peptides for enhanced tumor/tissue localization [193].

6.1.1.4. Enhanced stability & bioavailability. Lipid-based carriers can improve the apparent solubility, colloidal stability, and release behaviour of poorly soluble drugs. For example, paclitaxel-loaded PEGylated liposomes produced by continuous-flow microfluidics achieved high encapsulation efficiency and a narrow particle-size distribution [164].

6.1.1.5. Gene editing. Microfluidic LNPs enable advanced genome-editing cargo. In one study, Intellia Therapeutics used a microfluidic NanoAssemblr™ device to co-formulate LNPs carrying Cas9 mRNA and single-guide RNA; the optimized LNP achieved > 97% knockout of a liver gene with a single dose, with effects lasting > 12 months in animals [187]. These precision-formulated LNPs are nowadays key to CRISPR/Cas9 therapies.

6.1.2. Polymeric NPs

6.1.2.1. General encapsulation & release. Biocompatible polymers (e.g. FDA-approved PLGA) offer tunable degradation and release kinetics.

Polymeric NPs can solubilize diverse cargoes and modulate release profiles. For example, PLGA NPs have shown improved drug solubility, retention time and reduced toxicity. Compared to bulk emulsification, microfluidic mixing (e.g. flow-focusing) yields much smaller, more uniform polymeric NPs [194]. One report found PLGA-PEG NPs made by microfluidics having an average diameter of ~ 34 nm (vs. 105 nm bulk) while releasing PTX twice as slowly (half-life ~ 19 h vs ~ 11 h) [59].

6.1.2.2. Anticancer therapy. Microfluidic platforms have been extensively employed to produce polymeric NPs for cancer chemotherapy, offering enhanced control over size, uniformity, and DL. For instance, capsaicin-loaded PLGA nanoparticles were produced in a PDMS-based microfluidic platform after optimization of the total flow rate, flow-rate ratio and surfactant conditions. The resulting formulations were evaluated for their physicochemical properties, drug encapsulation and release, as well as their biological activity. In vitro cytotoxicity assays showed a pronounced reduction in PC3 and MCF-7 cell viability following treatment with capsaicin-loaded nanoparticles, compared with blank nanoparticles, highlighting the potential of microfluidic PLGA carriers for anticancer drug delivery (Fig. 24) [195].

Similarly, microfluidic PLGA NPs encapsulating curcumin demonstrated > 60-fold longer half-life in aqueous media compared to free drug, with enhanced selective cytotoxicity toward leukemia cells [196].

Other agents such as sorafenib and curcumin have been encapsulated in hybrid lipid-polymer NPs or PEG-PLGA carriers using glass-capillary and herringbone mixers, achieving high EE, stable size distributions (~ 55–100 nm), and sustained release profiles, resulting in improved

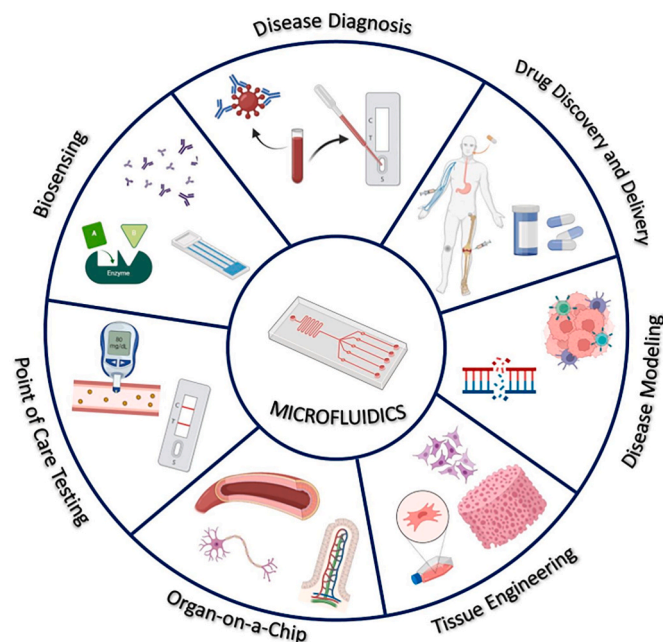


Fig. 23. Schematic overview of the main application areas of microfluidically produced particles discussed in this section, spanning drug and gene delivery, biomolecular analysis and biosensing, cell-biology models (organ- and organism-on-a-chip), and further applications such as tissue engineering and environmental sensing. Reprinted from an open access source [2].

antiproliferative effects in breast and prostate cancer cells [174,197].

6.1.2.3. Targeting & immune evasion. Microfluidic synthesis enables precise surface functionalization of polymeric NPs to improve tumor targeting and immune evasion. For instance, a 3D flow-focusing microfluidic device was used to generate PLGA-PEG NPs conjugated with a ligand targeting prostate-specific membrane antigen, a trans-membrane glycoprotein overexpressed in prostate cancer. These targeted NPs showed ~ 3.5 -fold higher accumulation in tumor tissue compared to non-targeted counterparts. Similarly, PEGylation of PLGA NPs via microfluidics effectively shields them from macrophage uptake, prolonging systemic circulation [197]. To further enhance cellular internalization, cell-penetrating peptides, such as TAT or RRH, have been grafted onto PLGA NPs on-chip, improving membrane penetration while maintaining monodispersity and size control [197]. Additionally, peptide ligands like cyclic RGD, when displayed on PEG-PLGA NPs, significantly increased selective uptake by $\alpha v \beta_3$ integrin-expressing tumor cells, highlighting the potential of microfluidic functionalization to achieve receptor-mediated targeting [198].

6.1.2.4. Combination chemotherapy. Microfluidic co-formulation has enabled precise combination-drug NPs with far higher loadings than bulk methods.

For example, Liu et al. used a 3D microfluidic co-flow (nested-capillary) device to encapsulate methotrexate, PTX and sorafenib together in acetylated-dextran-coated porous-silicon nanocomposites, achieving a uniform, pH-responsive 24-h release of all three drugs [199]. Likewise, a nested-capillary flow-focusing platform combining PLGA and an enteric hypromellose acetate succinate shell with either PTX or sorafenib achieved drug loadings $> 42\%$, far above the $\sim 6\%$ loading of a single-stream microfluidic device and $\sim 4\%$ by conventional bulk precipitation [200]. As a further example, Li et al. recently reported a multi-stage microfluidic chip that sequentially co-encapsulates two agents (e.g., PTX-simvastatin or PTX-lenvatinib) into core-shell hybrid NPs; this system achieved about 100% EE and drug loadings around 15–19% for each dual-drug formulation [201]. By

contrast, conventional batch nanoprecipitation typically yields drug loadings of only a few percent. Together, these studies illustrate that microfluidic platforms can co-deliver multiple chemotherapeutics with dramatically improved loading efficiency and tightly controlled release kinetics, enabling a more effective combination of chemotherapy.

6.1.2.5. Other therapeutic applications. Microfluidic platforms have expanded the therapeutic scope of polymeric NPs well beyond oncology by enabling tightly controlled carriers tailored to specific biological tasks. Flow-focusing and cross-linking routes can produce HANPs in the 140–460 nm range for topical and systemic cosmetic or pharmaceutical delivery [202]. Continuous 3D-focusing nanoprecipitation readily yields poly(β -amino ester) (PBAE)-DNA polyplexes with improved transfection versus conventional reagents [203], while microreactor chemistries enable rapid synthesis of amphiphilic heparin-folate-retinoic acid bioconjugates with high DL and preferential uptake by folate-receptor-positive cells [204].

Microfluidic technologies have also enabled the development of polymeric NPs for a variety of therapeutic applications. For instance, in the field of protein therapeutics, chitosan NPs produced by microfluidic mixing have efficiently encapsulated model proteins and nucleic acids (encapsulation efficiency $> 80\%$), with high reproducibility and sizes around 100 nm [147].

In metabolic disease, microfluidic crosslinked carboxymethyl-chitosan NPs encapsulating metformin ($\sim 77 \pm 19$ nm, $\sim 90\%$ EE) provided controlled release and yielded notable glycemic improvements in diabetic rat models [205].

Tissue engineering strategies have incorporated microfluidically synthesized PLGA NPs encapsulating TGF- $\beta 3$ into alginate/polyacrylamide double-network hydrogels. This composite system significantly improved cartilage regeneration *in vivo*, illustrating how microfluidic NPs synthesis can be integrated with bioengineered scaffolds for regenerative medicine.

6.1.3. Inorganic NPs

Inorganic NPs offer key advantages in drug delivery due to their chemical stability, tunable physical properties, and ease of surface functionalization. Microfluidic platforms enhance their synthesis by offering precise control over size, composition, and morphology, enabling reproducible production of multifunctional, monodisperse NPs with therapeutic and diagnostic capabilities.

6.1.3.1. Metal NPs. Metal oxide NPs, such as ZnO and titanium dioxide, produced through microfluidics have shown strong antibacterial activity, supporting applications in wound healing, photodynamic therapy, and antimicrobial coatings [206].

Similarly, AgNPs synthesized in microfluidic platforms demonstrate potent antimicrobial efficacy and high monodispersity and have been incorporated into wound dressings and composite hydrogels to enhance infection control and tissue regeneration [129]. Superparamagnetic iron oxide nanoparticles (SPIONs) are particularly attractive for MRI and other biomedical applications because of their magnetic properties. Vangijzegem et al. demonstrated the continuous-flow synthesis of very small iron oxide nanoparticles, with TEM diameters of approximately 3.7–4.1 nm across flow rates of 0.5–2 mL min $^{-1}$. While the particle size remained relatively consistent, the flow rate significantly affected the longitudinal relaxivity profiles, demonstrating how continuous-flow conditions can be used to modulate the magnetic properties of iron oxide NPs (Fig. 25) [207]. Collectively, these systems underscore how microfluidics facilitates the scalable production of highly functional inorganic NPs for biomedical use [124].

6.1.4. Hybrid/composite NPs

6.1.4.1. Lipid-polymer hybrids. Combining lipids and polymers can

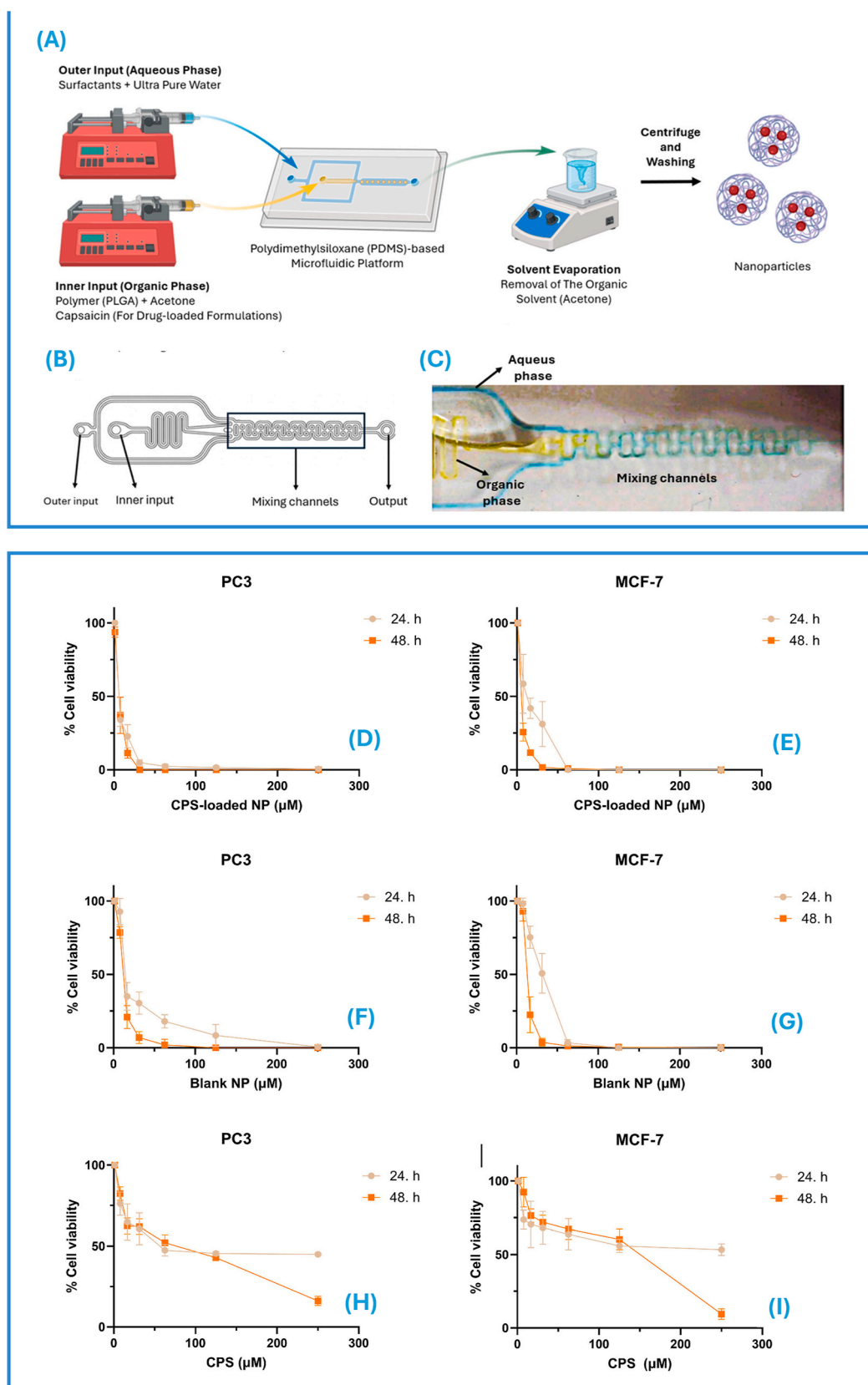


Fig. 24. Microfluidic fabrication and biological evaluation of capsaicin-loaded PLGA nanoparticles: (A) schematic workflow of nanoparticle production using a PDMS-based microfluidic platform, (B) microchannel design, and (C) optical image of the aqueous and organic phases flowing through the mixing channels. Cell viability of PC3 and MCF-7 cells treated with (D–E) capsaicin-loaded nanoparticles, (F–G) blank nanoparticles, and (H–I) free capsaicin for 24 and 48 h. Reprinted from an open access source [195].

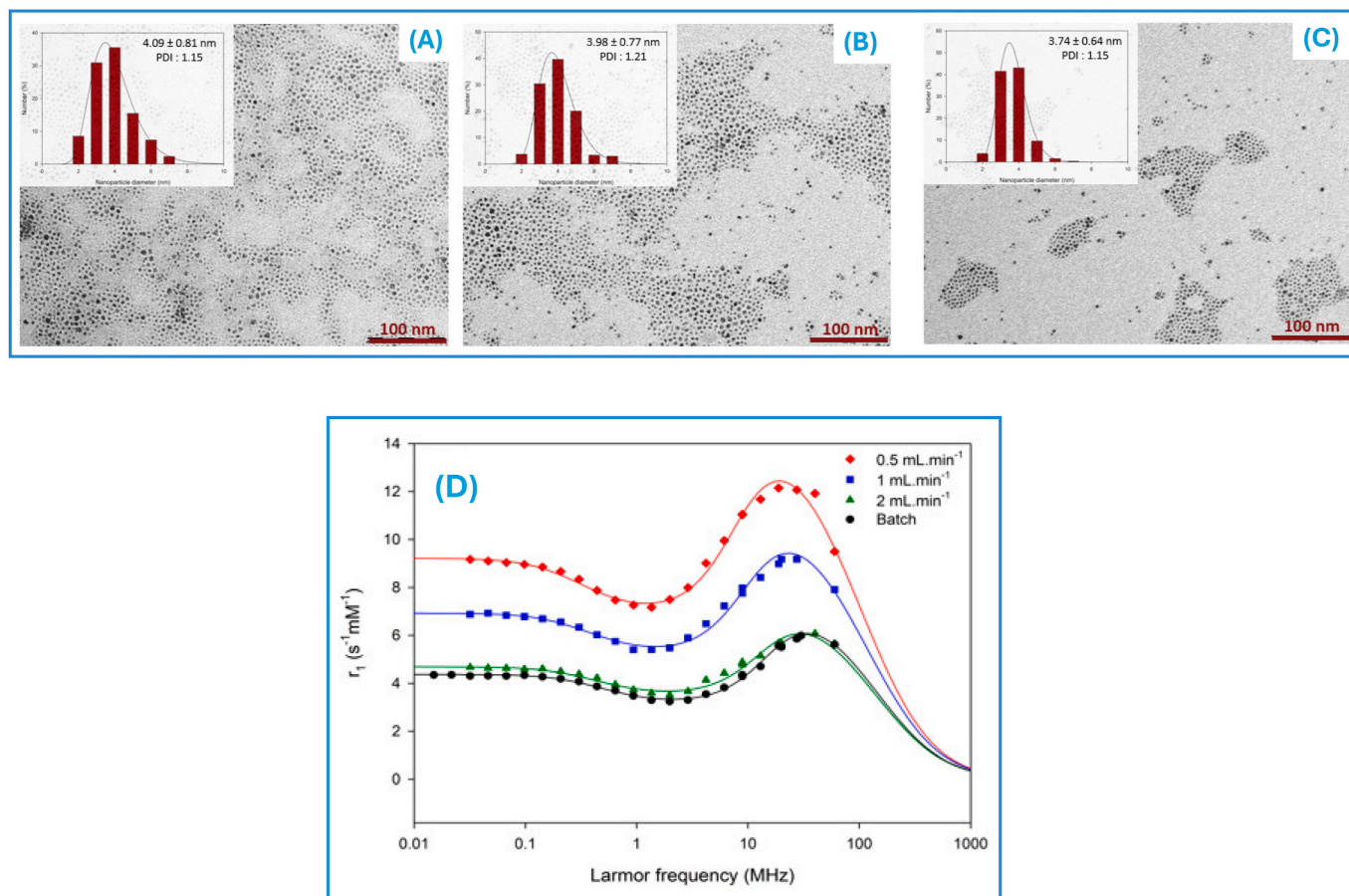


Fig. 25. Characterization of very small superparamagnetic iron oxide nanoparticles produced by continuous-flow synthesis. (A–C) TEM micrographs and corresponding size distributions of nanoparticles obtained at different flow rates, showing sub-5 nm particle sizes. (D) 1 H NMRD profiles of nanoparticles produced at 0.5, 1 and 2 mL min⁻¹ compared with batch-synthesized particles, highlighting the influence of flow rate on longitudinal relaxivity. Reprinted from an open access source [207].

yield carriers with enhanced properties and quality, taking advantage of the best characteristics of both materials. For example, a microfluidic device with upstream micro vortices produced lipid-polymer hybrid NPs (PLGA core, lipid layer) loaded with sorafenib. These hybrid NPs showed higher DL and slower release than polymer-only NPs, while retaining narrow size distribution [174]. Such composites can maintain particle stability and enhance bioavailability of hydrophobic drugs compared to purely polymeric NPs.

6.1.4.2. Biomimetic NPs. Cells and vesicles can be used as templates for the external shell of the NPs. Researchers have made CM-NPs by combining synthetic cores with natural membranes. For instance, polymeric cores (e.g. PLA or PLGA loaded with PTX or DOX) have been cloaked with red blood cell membranes, yielding long-circulating biomimetic NPs that evade immune clearance [179,183]. Similarly, platelet-membrane-coated NPs (PCM-NPs) have been developed for thrombus-targeting or cancer therapy, and leukocyte- or CCM-NPs for inflammation or homotypic tumor targeting [184,208,209].

These hybrid designs inherit natural targeting and stealth properties while carrying therapeutic payloads. In one high-impact example, a PLGA core-SPION-bisphosphonate hybrid (i.e., a bone-seeking HNP) was made on-chip to carry PTX and magnetic contrast; these “theragnostic” NPs accumulated in bone metastases for combined imaging and therapy [210].

Overall, microfluidic synthesis allows precise, one-step assembly of hybrid nanocarriers – whether combining polymers with lipids or integrating biological membranes – to achieve high DL, multifunctionality,

and targeted performance [211].

A selection of representative studies exemplifying the versatility of microfluidic platforms in producing NPs for diverse therapeutic applications is summarized in Table 6.

Taken together, the carrier classes described above are not interchangeable, and the choice among them reflects a series of trade-offs rather than a single “best” platform (Table 7). LNPs are currently the benchmark for nucleic-acid delivery, combining near-quantitative encapsulation with a manufacturing route that is uniquely mature and scalable, which explains their dominance among clinically approved products; their main weaknesses lie in stability and cold-chain requirements and in a cargo scope largely restricted to lipophilic and nucleic-acid molecules. Polymeric NPs, by contrast, offer superior control over sustained and triggered release and a broader cargo range, but at the cost of lower encapsulation of hydrophilic drugs, a greater propensity to foul microchannels during nanoprecipitation, and acidic degradation products that can compromise labile cargo. Inorganic NPs are unmatched for imaging, magnetic manipulation and theranostics, yet concerns over biodegradation, long-term toxicity and limited loading capacity have so far confined most of them to diagnostic rather than therapeutic use. Hybrid and biomimetic carriers are the most sophisticated of the group—the former merging controlled release with stealth, the latter conferring genuine biological targeting and immune evasion—but their multi-step or membrane-coating fabrication makes them the hardest to reproduce and, especially for biomimetic systems, remains the principal obstacle to clinical translation. It is also worth noting that the literature is not always consistent: reported sizes and

Table 6

Representative examples of drug-loaded NPs fabricated by microfluidics, with their reported encapsulation efficiency (EE) or drug loading (DL).

Microfluidic NP system	Cargo	Therapeutic application	EE/DL	Microfluidic Advantage	Reference
Lipid NP (LNP)	mRNA	COVID-19 vaccines, gene therapy	EE $\approx$ 90%	High encapsulation, scalable, clinical translation	[65,187]
Liposome	Paclitaxel	Cancer (poorly soluble drug)	EE > 90%	Narrow size, high homogeneity, stability	[164]
Liposome	DOX	Tumor therapy	High loading (D/L > 0.2)	Single-step loading, pH-triggered release	[189]
Polymeric micelle (PLGA-PEG)	Docetaxel	NSCLC/anticancer	DL $\approx$ 11% (3 $\times$ bulk)	Smaller size, higher loading than bulk	[212]
Polymeric NP (PLGA)	Capsaicin	Cancer therapy	EE 55.4–76.1%	Controlled formulation and drug delivery; tunable particle properties through flow and surfactant conditions	[195]
Polymeric NP (PLGA, HA-decorated)	Irinotecan	Cancer (CD44 targeting)	EE 87.8%	High EE, tumor targeting, reproducibility	[168]
Chitosan NP	Protein/mRNA/siRNA	Delivery of biologics	EE > 80%	Versatile cargo, reproducible, $\sim$ 100 nm	[147]
Hybrid (lipid-polymer)	Sorafenib	Hepatocellular carcinoma	EE 88.7–95.0%	Core-shell control, high EE, slow release	[174]

encapsulation efficiencies for nominally identical systems vary widely with device geometry, FRR and solvent, which complicates direct comparison and underlines the need for standardized reporting. From an industrial standpoint, this landscape currently favours the simplest and most robust chemistries—above all LNPs—for near-term scale-up, while polymeric, hybrid, inorganic and biomimetic carriers face progressively steeper manufacturing and regulatory barriers.

6.2. Biomolecular analysis

Microfluidic-produced particles underpin modern biomolecular analysis by enabling on-chip synthesis and functionalization of narrowly dispersed plasmonic, fluorescent and magnetic probes integrated directly into sensing and imaging workflows. This combination of enhanced precision and throughput has made possible highly reproducible contrast agents, multiplexed particle libraries, and low-volume assays that improve sensitivity and reduce sample requirements.

6.2.1. Biosensing and detection

Microfluidic platforms couple reproducible NPs synthesis with immuno- and nucleic-acid assays to deliver sensitive point-of-care and laboratory diagnostics. Examples include chemiluminescent microfluidic immunoassays for cardiac biomarkers and plasmonic or SERS-active probes for cancer markers; such approaches reduce reagent consumption and accelerate time-to-result [125].

6.2.2. High-throughput screening

On-chip barcoding and parallelized formulation enable pooled, sequencing-readout screens (e.g., barcoded LNP libraries) and rapid optimization of NPs composition, size and targeting *in vivo* or *in vitro*. These high-throughput microfluidic workflows markedly shorten formulation cycles and allow data-rich selection of lead candidates [188]. Beyond formulation screening, droplet microfluidics has become a cornerstone of advanced single-cell analysis: by compartmentalizing individual cells within picolitre droplets, it enables massively parallel encapsulation, barcoding and multi-omic profiling that resolve cell-to-cell heterogeneity inaccessible to bulk assays. Coupled with the same NP-formulation platforms, this allows the response of individual cells to distinct carrier formulations to be screened in a single run, linking particle design directly to single-cell phenotype [213].

6.3. Cell biology

Microfluidic systems recreate physiologically relevant microenvironments (flow, gradients, 3D matrices) and therefore serve as powerful platforms to study NPs–cell interactions, delivery, efficacy and toxicity under conditions closer to the *in vivo* state than static cultures.

6.3.1. Organ-on-a-chip models

Organ-on-chip devices reproduce flow, mechanical cues, biological barriers, and multicellular architecture, enabling the evaluation of NP transport, uptake, efficacy, and toxicity under conditions that are more physiologically representative than static culture. Reported applications include vascular and tumour models, barrier-transport studies, and organ-specific nanotoxicology [214].

6.3.2. Organism-on-a-chip and engineered 3D constructs

At the organism and tissue scale, microfluidic chips for zebrafish, *C. elegans* and *Drosophila* enable live imaging, controlled dosing and phenotypic screens, bridging *in vitro* and *in vivo* testing. Complementary microfluidic fabrication of cell-laden hydrogels and aligned microfibers supports tissue engineering and high-content assays. Examples of which are engineered hydrogel constructs and magnetic microfibers [65,142]. In the same direction, microfluidically produced microcarriers have emerged as vehicles for live-cell delivery: by encapsulating cells within tailored hydrogel or core-shell microparticles, they shield payloads from shear and immune recognition while preserving viability during handling, injection and transplantation. Such carriers extend microfluidic particle engineering from acellular drug delivery toward cell-based therapies and regenerative medicine [215].

6.4. Additional applications

Microfluidic-produced NPs support tissue engineering by enabling biomimetic scaffolds, cell-laden microgels and growth-factor delivery with precise control over geometry and composition [88,140,216]. They also power portable, multiplexed environmental sensors—through on-chip synthesis of plasmonic, magnetic and catalytic NPs—for rapid advection of contaminants and pathogens [12]. Microfluidic routes can also produce reproducible nanomaterials with tailored optical and catalytic properties for sensing and materials-processing applications [12, 65]. Microfluidic devices have additionally been used as test platforms for the propulsion and transport of polymeric soft microrobots intended for gut-targeted delivery [217].

7. Current challenges and future perspectives

Microfluidic manufacture of drug-delivery particles offers precise control but faces practical barriers to translation: limited single-channel throughput (g h^{−1} vs. industry-scale kg h^{−1}), persistent channel clogging and fouling for precipitative processes, and frequently dilute outlet streams that require off-chip concentration and buffer exchange. Device materials and surface adsorption (e.g., PDMS sorption of hydrophobic drugs) also limit pharmaceutical relevance, while incomplete mechanistic understanding for some inorganic/hybrid syntheses and the

Table 7
Comparison of the main particle classes produced by microfluidics: advantages, limitations, typical size and encapsulation efficiency (EE), scalability, and clinically approved examples.

Particle class	Key advantages	Main limitations	Size/EE	Scalability	Approved examples
Lipid NPs/ liposomes	High encapsulation of nucleic acids and hydrophobic drugs; biocompatible and biodegradable; simple microfluidic self-assembly; clinically validated Tunable sustained and triggered release; biodegradable; broad cargo range; easy surface functionalization for targeting Unique optical, magnetic and catalytic properties for imaging, hyperthermia and theranostics; precise size control Combine polymer-core controlled release with lipid-shell stealth; high loading; multi-drug co-delivery; tunable core-shell architecture Immune evasion and long circulation; homotypic and biological targeting (red-blood-cell, platelet, cancer-cell, leukocyte membranes)	Stability and cold-chain requirements; possible PEG-related immunogenicity; cargo largely limited to lipophilic or nucleic-acid molecules Lower EE for hydrophilic drugs and burst release; fouling/clogging during nanoprecipitation; acidic degradation products (PLGA) Biodegradation, clearance and long-term-toxicity concerns; hard-aggregate clogging; low (surface) loading; regulatory hurdles Complex multi-step synthesis; harder to reproduce and scale; intermediate deposition/clogging Source-material variability; low-throughput coating; scale-up and standardization very difficult; complex characterisation and regulation	~ 30–150 nm; EE high (> 90%, near-quantitative for RNA) ~ 30–200 nm; EE moderate-high (cargo-dependent) ~ 2–100 nm; loading surface-limited ~ 50–200 nm; EE high (e.g. sorafenib up to ~ 95%) ~ 100–200 nm; EE core-dependent	Excellent; mature commercial GMP platforms Good, but fouling-prone; needs sheath focusing/parallelization Segmented/droplet flow effective; harsh chemistries challenging Moderate; complexity limits throughput Poor/early-stage—the main translational barrier	Cominraty/Spokevax, Onpatro; Doxil, Ambisome PLGA an approved biomaterial; no microfluidic product yet Ferumoxytol; several imaging agents None yet (emerging class) None (research stage)

current paucity of robust inline Process Analytical Technology (PAT) slow process robustness and regulatory readiness [64,187,218]. Finally, fabrication/operation complexity and the need for cross-disciplinary expertise raise economic and adoption hurdles [64,187,188,218].

7.1. Clogging and fouling: mechanisms and mitigation

Because channel dimensions are comparable to, or only slightly larger than, the particles being formed, clogging and surface fouling are among the most important factors limiting the operational lifetime and, ultimately, the industrial adoption of continuous microfluidic particle manufacture. Three canonical clogging mechanisms have been identified for suspensions flowing through microchannels: *sieving*, when a particle or aggregate larger than the local constriction is captured; *bridging*, when several particles arrive simultaneously at a constriction and form a stable arch; and *aggregation/deposition*, when particles adhere successively to the walls, progressively narrowing the channel until flow is blocked [66]. In particle-synthesis devices these generic mechanisms are compounded by process-specific phenomena. During nanoprecipitation, the steep supersaturation generated at the solvent–antisolvent interface nucleates material directly at the walls of the mixing zone, where it deposits and grows into films that are especially problematic in high-surface-area geometries such as staggered herringbone mixers; the chemical complexity of multicomponent formulations (ionizable lipid, cholesterol, helper lipid, RNA and solvent in LNPs) makes a single passivation strategy difficult to achieve [219]. Preferential adsorption of hydrophobic drugs, polymers or lipids onto hydrophobic surfaces—PDMS being the worst offender, as it both adsorbs and absorbs such species—seeds further deposition, while in segmented-flow devices insufficient surfactant or an unfavourable wall wettability causes the dispersed phase to wet the walls, leading to droplet smearing, coalescence and loss of monodispersity.

Mitigation strategies act on the surface, the fluid, or the geometry. At the surface, the aim is to prevent the first layer of material from adhering: hydrophilic and antifouling coatings (PEG, zwitterionic polymers, poly(vinyl alcohol)), fluorophilic treatments for droplet systems, and—most effectively for the multicomponent LNP case—immobilized-liquid or lubricant-infused surfaces. A perfluorodecalin lubricant layer applied to a staggered herringbone mixer, for instance, extended stable operation more than fifteen-fold (to over 3 h) and remained compatible with a 256-mixer parallelized platform producing at litre-per-hour rates, without altering the physicochemical properties or *in vivo* performance of the RNA-LNPs [219]. Intrinsically low-sorption materials (glass, silicon and fluoropolymers) are generally preferred over PDMS for pharmaceutically relevant syntheses. At the fluid level, adequate stabiliser or surfactant concentrations (PEG-lipids, Pluronic and PVA for nanoprecipitated particles; fluorosurfactants for droplets) suppress aggregation and coalescence, while matching the wall wettability to the continuous phase keeps the dispersed phase from wetting the surface. At the geometric level, hydrodynamic (sheath) focusing confines the precipitating stream to the channel centre so that nascent particles never contact the walls, high wall shear sweeps incipient deposits, and the elimination of stagnation zones and sharp corners removes preferential nucleation sites. Operating below a critical supersaturation by tuning the FRR and TFR, controlling temperature to avoid crystallisation, and degassing to suppress bubble-templated deposition provide further process-level control. Compartmentalizing the reaction inside surfactant-stabilised droplets is a particularly robust route: by isolating nucleation from the channel walls it largely eliminates wall fouling, which is why segmented-flow formats are favoured for aggressive inorganic chemistries. Finally, periodic solvent flushing, back-flushing or acoustic actuation can dislodge deposits, and upstream in-line filters or pillar traps remove pre-formed aggregates, although such filters are themselves prone to clogging and thus represent a design trade-off.

The dominant failure mode and the most effective countermeasure

are strongly material-dependent, as summarized in Table 8.

7.2. Cost and standardization barriers of field-assisted manufacturing

The field-assisted strategies described in Section 3.3—electrospray, acoustofluidics and magnetofluidics—offer capabilities that passive continuous-flow devices cannot easily match, but their translation to large-scale, GMP-compatible manufacturing is constrained by distinctive equipment-cost and standardization barriers that compound the per-method scaling limits noted where the methods are introduced.

On the cost side, each modality relies on specialised active hardware that is considerably more expensive and complex than the pumps and passive micromixers used in continuous-flow production. Electrospray requires precision high-voltage supplies together with the associated insulation and safety enclosures, and raising throughput demands multiplexed emitter arrays whose electric fields and cone-jet conditions must each be individually stabilised [88,89]. Acoustofluidic systems depend on microfabricated piezoelectric or interdigital transducers, radiofrequency generators, amplifiers and impedance-matching electronics, as well as thermal management to avoid cavitation and heating; parallelization multiplies this transducer-and-electronics cost and makes uniform acoustic actuation across channels progressively harder to maintain [90]. Magnetofluidic platforms add the cost of electromagnets or high-field permanent magnets and gradient sources—together with their power and cooling—and require magnetic material to be embedded within the carriers themselves, which alters particle composition and biological behaviour and restricts the approach to magnetically responsive formulations [91]. Relative to a passive micromixer, these capital and operating costs are a central reason why field-assisted routes have so far been reserved for specialised functions rather than primary high-throughput synthesis.

Standardization poses an equally serious obstacle. Field-assisted devices are typically bespoke: electrode geometries, transducer-to-chip coupling and magnet configurations are device-specific, so designs transfer poorly between laboratories and are difficult to qualify as interchangeable manufacturing modules. Reproducibility across the many parallel emitters, transducers or magnets needed for scale-up is hard to guarantee, because small unit-to-unit differences in field strength or resonance translate directly into particle-size heterogeneity. Unlike passive micromixer cartridges—for which commercial, increasingly GMP-ready instruments already exist—there are currently no widely adopted, standardised, off-the-shelf field-assisted platforms, and the calibration and validation of field parameters (voltage, frequency, field strength) impose a further regulatory burden that slows qualification for pharmaceutical production [64,187,188,220].

Consequently, and in line with the throughput and fouling considerations discussed above, field-assisted methods are at present best positioned as complementary tools—electrospray for capsule generation, acoustofluidics for post-synthesis loading and assembly, and magnetic fields for the positioning and recovery of responsive carriers—whereas passive continuous-flow platforms, once equipped

with parallelization and anti-fouling coatings, remain the more readily scalable and standardisable route to industrial NP manufacture.

7.3. From bench to GMP: industrial platforms, quality control and regulation

Beyond the physical scaling considerations discussed above, the routine industrial production of microfluidic nanomedicines depends on the availability of standardized, GMP-compatible equipment, and here the field has matured considerably. Two families of commercial platforms now dominate LNPs manufacturing: the NanoAssemblr series (Precision NanoSystems/Cytiva), which uses single-use, closed toroidal (NxGen) micromixers that retain the same mixing geometry from benchtop screening (of the order of 10 mL/min) to GMP and commercial batches (tens of litres per hour), thereby minimizing the process re-development normally incurred on scale-up; and the NanoScaler and NanoProducer systems (Knauer), stainless-steel platforms based on impingement-jet mixing that span laboratory to production scale [187, 220]. The industrial relevance of these approaches is no longer speculative: parallelized impingement-jet and micromixer systems underpinned the manufacture of billions of doses of mRNA-LNPs COVID-19 vaccines, and parallelized, antifouling-coated micromixer arrays and spiral chips are extending the same principle to still higher, GMP-compatible throughput [50,219].

A distinctive constraint of NP manufacturing is sterilisation. Because lipids, polymers and nucleic-acid cargoes degrade under heat, irradiation or chemical treatment, nanomedicines generally cannot be terminally sterilised and are instead produced by aseptic processing with sterile (0.22 µm) filtration, which in turn requires the particles to be small and monodisperse enough to pass the filter without loss of dose or change in size—an additional constraint that couples product quality directly to the manufacturing route [218]. Quality control poses a complementary challenge: whereas critical quality attributes such as size and polydispersity can increasingly be monitored in-line (for instance by process-analytical technology based on light scattering), assays for encapsulation efficiency, drug loading and potency remain largely off-line, so that a fully closed-loop, real-time-release workflow is still an aspiration rather than standard practice.

Finally, translation is shaped by a demanding regulatory and economic landscape. Regulatory agencies require the identification and tight control of critical quality attributes within a quality-by-design framework, and the associated nano-specific chemistry, manufacturing and controls (CMC) burden—extensive physicochemical characterisation, stability testing and batch-to-batch consistency—adds substantially to development time and cost, a difficulty compounded by regional differences in approval requirements between agencies [218]. The specialised analytical techniques required to characterise nanomedicines are themselves expensive and expertise-intensive and, together with reagent costs (notably those of ionizable lipids), dominate the manufacturing economics. Standardised, GMP-ready microfluidic platforms that integrate in-line monitoring therefore represent not

Table 8

Clogging/fouling mechanisms and mitigation strategies across material classes.

Material class	Dominant clogging/fouling mechanism	Most effective mitigation	Effectiveness/notes
Lipid NPs/liposomes	Lipid adsorption and interfacial nanoprecipitation films (multicomponent)	Lubricant-infused/antifouling coatings; hydrophilic glass or fluoropolymer walls; PEG-lipids; controlled FRR/TFR	Coated herringbone mixers give > 15× longer stable runs and parallelize to L h – 1
Polymeric NPs (PLGA, PLGA-PEG)	Polymer deposition at the solvent-antisolvent interface; wall adsorption	Sheath/hydrodynamic focusing; PVA or Pluronic stabilisers; glass/fluoropolymer devices; sub-critical supersaturation	Moderate-to-high propensity; sensitive to solvent choice and FRR/TFR
Inorganic NPs (metal, oxide, silica)	Crystallisation and hard-aggregate bridging at constrictions; aggressive reagents	Droplet/segmented-flow compartmentalisation; centre-focusing; robust materials (glass, ceramic, PTFE); high shear	Compartmentalisation avoids wall contact and is highly effective
Hybrid/core-shell NPs	Intermediate deposition during multi-step assembly	Sequential or segmented designs; compartmentalisation; low-sorption surfaces	Complexity raises risk; staged designs mitigate
Droplet-templated microparticles	Dispersed-phase wetting; surfactant-depletion coalescence	Fluorophilic coatings plus fluorosurfactants; wettability matched to the continuous phase	Very effective once wettability and surfactant are matched

merely a technical convenience but a key enabler for making nanomedicine manufacture reproducible, compliant and economically viable.

7.4. Future perspectives

Several concrete research directions are likely to shape the coming decade of microfluidic particle manufacturing. The first is the consolidation of modular parallelization: replacing single channels with standardized, stackable micromixer modules that raise throughput to litre-per-hour rates and beyond while preserving the mixing control of an individual unit, as already demonstrated with antifouling-coated herringbone arrays and parallelized spiral chips [50,219]. Closely coupled to this is the development of robust, low-fouling device materials and coatings—glass, fluoropolymers, zwitterionic and lubricant-infused surfaces—that extend stable continuous operation from minutes to many hours, as detailed in the preceding subsection on clogging and fouling. A third direction is end-to-end process integration, in which the formation step is coupled on a single line with in-line concentration and buffer exchange (for example, tangential-flow filtration), purification and even fill-finish, together with embedded process-analytical technology (Raman spectroscopy, dynamic light scattering, small-angle X-ray scattering) that provides real-time read-outs of size, encapsulation and stability. Perhaps the most transformative direction is data-driven and autonomous formulation: coupling microfluidic synthesis with high-content characterization and active machine learning to navigate the high-dimensional composition space with a minimum of experiments and, ultimately, to operate as closed-loop, self-driving platforms in which the algorithm proposes a formulation, the chip produces it, and the instrument measures it without human intervention. Early demonstrations have already integrated microfluidic formulation, high-content imaging and active learning to improve NP uptake several-fold within a few iterations, and machine-learning-guided, automated LNP design pipelines are maturing rapidly [121,221]; digital twins of micromixers and generative models for lipid and polymer design (Section 4.3) are natural extensions. Such tools should also broaden the accessible chemical space beyond current mRNA LNPs toward self-amplifying and circular RNA, CRISPR gene-editing payloads, organ- and cell-targeted carriers, and protein-, peptide- and cell-based therapeutics.

These advances will be shaped in parallel by emerging materials—next-generation ionizable lipids, biodegradable and stimuli-responsive polymers and cell-derived carriers—and by a growing emphasis on sustainable manufacturing, including greener solvents, lower reagent and energy consumption and the reduced footprint of continuous relative to batch processing.

Realising these directions poses well-defined technological challenges. Foremost is preserving deterministic, single-channel control at manufacturing scale, since unit-to-unit variability across large parallel arrays translates directly into product heterogeneity; field uniformity across parallel devices (Section 3.3), flow balancing and in-line feedback therefore become critical. Long-term robustness against clogging and fouling, the compatibility of device materials with organic solvents and sterilisation, and the integration of downstream purification, concentration and lyophilisation without degrading particle quality remain only partially solved. On the computational side, the scarcity of large, standardised and openly shared datasets, together with the limited transferability of models between formulations and instruments, currently constrains the reliability of machine-learning-guided design.

Translating these platforms into the clinic will finally require dedicated manufacturing and regulatory pathways. The most immediate is GMP-compatible continuous manufacturing built on quality-by-design principles and the ICH continuous-manufacturing framework, in which embedded process-analytical technology enables real-time quality monitoring and, ultimately, real-time release. A second and more disruptive pathway is distributed, point-of-care manufacturing: because

microfluidic platforms are compact, parallelizable and digitally controlled, they are uniquely suited to on-demand, small-batch production of personalised nanomedicines and to rapid, regionally distributed responses to emerging pathogens—a feasibility underscored by the central role of microfluidically manufactured mRNA–LNP vaccines during the COVID-19 pandemic. Building on the precedent of approved products such as these vaccines and liposomal chemotherapeutics, and on the growing availability of GMP-ready microfluidic instruments, these routes offer a credible trajectory from bench-scale formulation to precision, patient-specific nanomedicines [187,218,220].

8. Conclusions

This review has traced microfluidic particle manufacturing from its physical foundations to its translational frontier. Beginning with the dimensionless groups that govern mixing, droplet break-up and viscoelastic response, it showed how these principles are embodied in three complementary device families—continuous-flow micromixers, segmented-flow (droplet) chips and field-assisted microreactors—and how mathematical modelling, design-of-experiments and machine learning turn their operation from empirical tuning into predictive, rational design. On this basis, a broad palette of organic, inorganic, hybrid, stimuli-responsive and biomimetic carriers can be produced with tight control over size, dispersity, internal architecture and composition, and deployed across drug and gene delivery, biosensing, high-throughput screening and organ-on-chip systems. The unifying theme is that, in contrast to batch methods that rely on poorly controlled mixing and yield heterogeneous products, microfluidic reactors exploit laminar flow, short diffusion lengths and confined volumes to engineer particle formation deterministically, directly linking chip geometry and flow conditions to final material performance.

The broader implication is a shift in how nanomedicines are conceived and produced. By making particle attributes reproducible and tunable, microfluidics allows formulation to become a design discipline rather than a craft, shortening the path from molecular idea to validated carrier and supporting the move toward precision and personalised nanomedicine. The clinical importance of this capability is no longer hypothetical: microfluidically manufactured LNPs vaccines were central to the global COVID-19 response, and a growing number of NP therapeutics are reaching the market. At the same time, this review has made explicit the barriers that still separate laboratory demonstrations from routine manufacture—limited throughput, clogging and fouling, device-material and downstream-processing constraints, the cost and standardization of field-assisted hardware, and the need for inline quality control and regulatory integration—and has indicated concrete engineering, analytical and data-driven strategies to overcome them.

Viewed as a whole, microfluidic nanomanufacturing stands at an inflection point at which transport physics, programmable device architectures, data-driven optimization and regulatory strategy are converging. As parallelized, antifouling and GMP-compatible platforms mature and are increasingly coupled with autonomous, machine-learning-guided workflows, microfluidics is poised to evolve from a specialised laboratory technique into a standardised and scalable manufacturing paradigm, and it is reasonable to expect that a growing share of approved particle-based therapeutics will be produced in this way in the years ahead.

CCRediT authorship contribution statement

Lilia Losco De Cusatis: Investigation, Validation, Writing – original draft, Writing – review & editing. **Maria Sofia de Gregorio:** Data curation, Validation, Writing – original draft, Writing – review & editing. **Stefania Carbone:** Data curation, Writing – original draft, Writing – review & editing. **Raffaele Crispino:** Conceptualization, Data curation, Formal analysis, Investigation, Supervision, Validation, Writing –

original draft, Writing – review & editing. **Daniele Tammaro:** Supervision, Writing – review & editing. **Concetta Di Natale:** Conceptualization, Project administration, Resources, Supervision.

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Declaration of competing interests

I have nothing to declare

Abbreviations

Abbreviation	Definition
5-FU	-Fluorouracil
AgNPs	Silver nanoparticles
AI	Artificial intelligence
ALC-0315	((4-Hydroxybutyl)azanediyl)bis(hexane-6,1-diyl) bis(2-hexyldecanoate)
AuNPs	Gold nanoparticles
BAW	Bulk acoustic wave
BBB	Blood–brain barrier
BO	Bayesian optimization
BSA	Bovine serum albumin
CCM-NPs	Cancer-cell-membrane-coated nanoparticles
CFD	Computational fluid dynamics
CMC	Chemistry, manufacturing, and controls
CM-NPs	Cell-membrane-coated nanoparticles
DL	Drug loading
DLS	Dynamic light scattering
D/L	Drug-to-lipid ratio
DODAP	,2-Dioleoyl-3-dimethylammonium-propane
DODMA	,2-Dioleoyloxy-3-dimethylaminopropane
DoE	Design of experiments
DOPC	,2-Dioleoyl- <i>sn</i> -glycero-3-phosphocholine
DOPE	,2-Dioleoyl- <i>sn</i> -glycero-3-phosphoethanolamine
DOTAP	,2-Dioleoyl-3-trimethylammonium-propane
DOTMA	<i>N</i> -[1-(2,3-Dioleoyloxy)propyl]- <i>N,N,N</i> -trimethylammonium
DOX	Doxorubicin
DPPE	,2-Dipalmitoyl- <i>sn</i> -glycero-3-phosphocholine
DSPC	,2-Distearoyl- <i>sn</i> -glycero-3-phosphocholine
DSM265	-(1,1-Difluoroethyl)-5-methyl- <i>N</i> -[4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[1,2,4]triazolo[1,5- <i>a</i>]pyrimidin-7-amine
DSPE	,2-Distearoyl- <i>sn</i> -glycero-3-phosphoethanolamine
EE	Encapsulation efficiency
EYPC	Egg-yolk phosphatidylcholine
FDA	Food and Drug Administration
Fe ₃ O ₄	Iron(II,III) oxide (magnetite)
FRR	Flow-rate ratio
GelMA	Gelatin methacryloyl
GMP	Good manufacturing practice
GQDs	Graphene quantum dots
HA	Hyaluronic acid
HDL	High-density lipoprotein
HLPs	Hybrid liposomes
HNPs	Hybrid nanoparticles
ICG	Indocyanine green
ICH	International Council for Harmonisation
IONPs	Iron oxide nanoparticles
LNPs	Lipid nanoparticles
ML	Machine learning
MOFs	Metal–organic frameworks
MONPs	Metal–organic nanoparticles
MPs	Microparticles
MRI	Magnetic resonance imaging
NPs	Nanoparticles
NSCLC	Non-small-cell lung cancer
PAT	Process analytical technology
PBAE	Poly(β -amino ester)
PBD	Polybutadiene
PCL	Poly(ϵ -caprolactone)
PCMPN	Platelet-membrane-coated nanoparticle
PDI	Polydispersity index
PDMS	Polydimethylsiloxane
PEG	Polyethylene glycol
PEGDA	Poly(ethylene glycol) diacrylate
PEO	Poly(ethylene oxide)
PF127	Pluronic F-127
PF68	Pluronic F-68

(continued on next page)

(continued)

Abbreviation	Definition
PLGA	Poly(lactic-co-glycolic acid)
PTFE	Polytetrafluoroethylene
PTX	Paclitaxel
PVA	Poly(vinyl alcohol)
QDs	Quantum dots
quasi-BIC	Quasi-bound state in the continuum
RBCMNP	Red-blood-cell-membrane-coated nanoparticles
RGD	Arginylglycylaspartic acid
RL	Reinforcement learning
RRH	Retinal-pigment-epithelium-derived rhodopsin homolog
SAR	Split-and-recombine
SAW	Surface acoustic wave
SERS	Surface-enhanced Raman spectroscopy
SHM	Staggered herringbone micromixer
SiO ₂	Silicon dioxide (silica)
siRNA	Small interfering RNA
SLNPs	Solid lipid nanoparticles
SM-102	Heptadecan-9-yl 8-[2-hydroxyethyl-6-oxo-6-(undecyloxy)hexyl]amino]octanoate
SPC	Soy phosphatidylcholine
SPION	Superparamagnetic iron oxide nanoparticle
ssDNA	Single-stranded DNA
TAT	Trans-activator of transcription peptide
TEM	Transmission electron microscopy
TFR	Total flow rate
TGF	Transforming growth factor
TPGS	D- α -tocopheryl polyethylene glycol 1000 succinate
TSL	Temperature-sensitive liposome
ZIF	Zeolitic imidazolate framework
ZnO	Zinc oxide

Data availability

No data was used for the research described in the article.

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