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Advances in the Fabrication, Mechanisms, and Applications of Monodisperse Droplets in Microfluidics

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ABSTRACT

Monodisperse microfluidic droplets, with precisely controlled size, high stability, and compartmentalization, have emerged as powerful tools in biomedicine, chemistry, and materials science. This review systematically summarizes key droplet generation methods, including T-junction, flow-focusing, and co-flow configurations, emphasizing how droplet size, frequency, and morphology are governed by channel geometry and operating parameters. Numerical modeling approaches—particularly Volume-of-Fluid (VOF), Level-Set (LS), and Phase-Field (PF) methods—are evaluated for their capabilities in capturing droplet formation dynamics and guiding device design, with VOF highlighted as the most reliable due to its mass-conservation properties. Applications of monodisperse droplets are further discussed in three major domains: biomedicine, chemical reactions, and materials fabrication. Overall, this review consolidates current advances in droplet fabrication, mechanisms, applications and outlines future directions to promote cross-disciplinary innovations.

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1. Introduction

Microfluidic monodisperse droplets, with their precisely tunable size, high stability, and isolation, have emerged as a versatile platform across disciplines [1, 2]. Each droplet functions as an independent “microreactor,” enabling high-throughput and well-controlled experimentation while minimizing reagent consumption [3]. Owing to these advantages, droplet microfluidics holds great promise in precision medicine, single-cell analysis, chemical synthesis, and the fabrication of advanced materials [2].

Despite these advantages, several fundamental challenges persist [4]. The formation process is governed by the complex coupling of multiphase fluid dynamics, which experimental methods struggle to fully capture, particularly in transient regimes [5]. Traditional approaches suffer from poor controllability, risk of cross-contamination, and excessive reagent consumption. Moreover, experimental observations provide only fragmented snapshots of droplet formation, hindering the establishment of a generalizable theoretical framework [6-8]. These limitations severely constrain the precise control of droplet size, frequency, and morphology [9].

To address these bottlenecks, computational fluid dynamics (CFD)-based numerical simulation has emerged as a powerful tool for studying droplet formation [10]. Simulations can resolve details inaccessible to experiments, including flow field distribution, interface evolution, and stress transfer, while also guiding channel design and optimization of operating conditions, thereby reducing costs [10, 11]. Although still developing, CFD studies of microfluidic droplet formation have already proven invaluable in elucidating formation dynamics, optimizing device structures, and tuning operating parameters [12]. A comprehensive and up-to-date review of these advances is therefore timely and essential.

In recent years, advances in microfabrication and novel materials have expanded the applications of microfluidic droplet systems into biomedicine, chemical engineering, and advanced manufacturing [13-18]. These developments place increasing demands on droplet size, structure, composition, uniformity, and generation frequency. However, most existing studies remain focused on specific device geometries or application scenarios, and a comprehensive review that integrates preparation methods, dynamic mechanisms, and application prospects into a unified framework is still lacking. This review therefore aims to provide a systematic summary of droplet generation mechanisms, highlight recent progress in numerical simulations of droplet formation dynamics, and explore representative applications in biomedicine, chemical reactions, and materials fabrication. The article is organized as follows: Section 2 introduces typical droplet generation methods and their underlying physical mechanisms; Section 3 reviews numerical simulation approaches for elucidating droplet dynamics; Section 4 summarizes case studies across key application domains; and Section 5 discusses current challenges and outlines future directions.

Fig. (1) outlines the methodology adopted in this review. Literature was retrieved from the Web of Science, PubMed, and Google Scholar databases, with a focus on journal articles and related publications from 2015 to 2025 to capture current research hotspots and emerging trends. The search employed keywords such as microfluidic monodisperse droplets, droplet generation mechanism, biomedical applications, numerical simulation, VOF method, and phase-field model. In total, 216 studies related to microfluidic droplet generation were identified. Among them, 100 addressed experimental and theoretical investigations of droplet formation, biomedical applications, and strategies for numerical simulation and validation. By synthesizing and comparing these works, this review aims to provide a comprehensive reference for future advances in droplet design, application, and multi-physics simulation.

2. Microfluidic Techniques for Monodisperse Droplet Generation

Methods for generating monodisperse droplets in microfluidics can be broadly categorized into flow-driven and array-based strategies. Flow-based approaches rely on the shear between two immiscible fluids to induce droplet breakup [19]. Array-based approaches, by contrast, generate droplets through specially designed micropores, microcavities, or hydrophilic micropattern arrays, often combined with an oil-water separation step [20, 21]. Among flow-based techniques, the most common configurations are the T-junction, flow-focusing, and

co-flow methods. These devices operate without external forces; instead, droplet size and frequency are governed by parameters such as flow-rate ratio, fluid properties, and channel geometry. Collectively, they are referred to as passive droplet generation methods. The following sections introduce the basic principles and recent advances of these three representative structures.

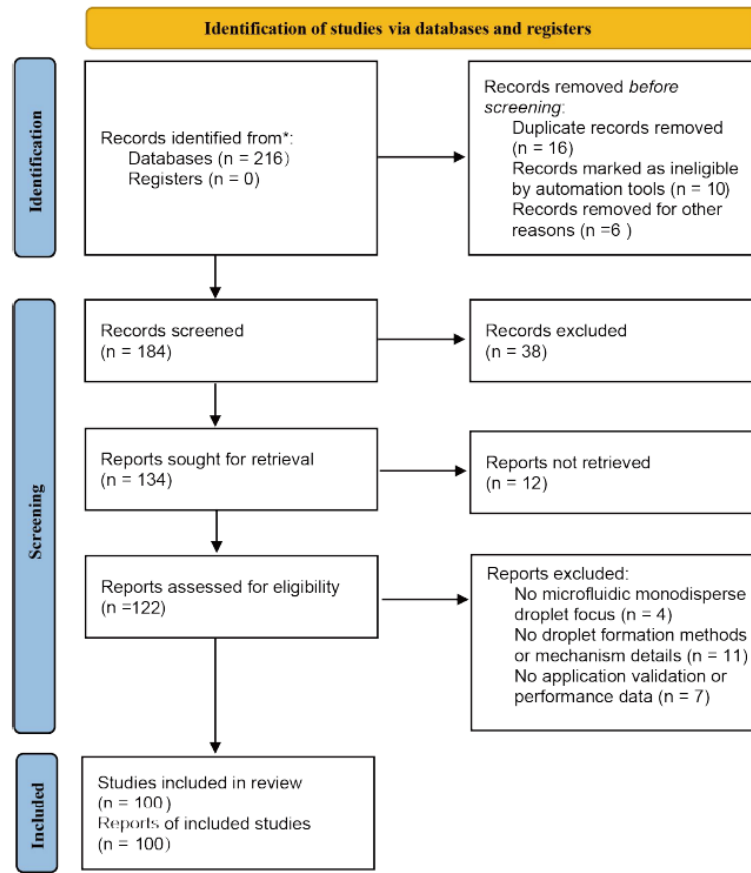


Figure 1: PRISMA flow diagram illustrating the study selection process.

2.1. T-channel Method

The T-channel was the earliest microfluidic unit employed for droplet generation, first proposed by Thorsen *et al.* [22]. Its principle is straightforward (Fig. 2a,b): shear and compression from the continuous phase induce momentum instabilities in the dispersed phase, leading to the formation of monodisperse droplets. In this configuration, hydrodynamic parameters are the key determinants. For example, when the flow rate ratio of the dispersed phase to the continuous phase decreases, the droplet generation rate rises markedly [23].

Geometric factors also exert strong influence. Using a T-channel system (Fig. 2d), Yin *et al.* [11] demonstrated that increasing the channel width ratio of dispersed to continuous phases from 0.33 to 1.0 reduces droplet diameter from $\sim 112\ \mu\text{m}$ to $\sim 52\ \mu\text{m}$, while the generation frequency rises from 5 Hz to 18 Hz. Numerical simulations by De Menech *et al.* further revealed three formation modes—squeezing, dripping, and jetting—strongly governed by the width ratio of the two inlets and the size of the orifice [24–26]. Operating conditions are equally critical. Cramer *et al.* [27] showed that higher continuous-phase velocity yields smaller droplets, and greater interfacial tension likewise reduces droplet size. Shen *et al.* [28] reported that raising the continuous-to-dispersed phase flow ratio from 2:1 to 10:1 decreases droplet size from $\sim 90\ \mu\text{m}$ to $\sim 35\ \mu\text{m}$, while increasing generation frequency from 8 Hz to 26 Hz. Efforts have also been made to optimize T-channel designs. Kumar *et al.* [29] inserted a $30\ \mu\text{m} \times 25\ \mu\text{m}$ rib $30\ \mu\text{m}$ downstream of the junction (Fig. 2e), lowering the critical flow-rate ratio from $\phi_c \approx 0.08$ to 0.0667 and enabling monodisperse droplets even at low capillary numbers ($\text{Ca} \approx 0.012$). Additional rib arrangements further transformed unconfined droplets into confined ones, allowing symmetric splitting in branch channels. Building on the classical T-junction, numerous variants have been developed,

including asymmetric T-type (Fig. 2c), Y-type (Fig. 2f), double-T (Fig. 2g), modified T-type (Fig. 2h), K-type (Fig. 2j), V-type (Fig. 2k), and designs with variable downstream channels [30-33]. Rhee *et al.* [32] further integrated a micro-dispensing pump into a variable downstream channel chip (Fig. 2i), enabling on-demand droplet generation. This strategy allows droplets to form only when target particles are detected, thereby avoiding the large number of empty droplets characteristic of conventional passive methods.

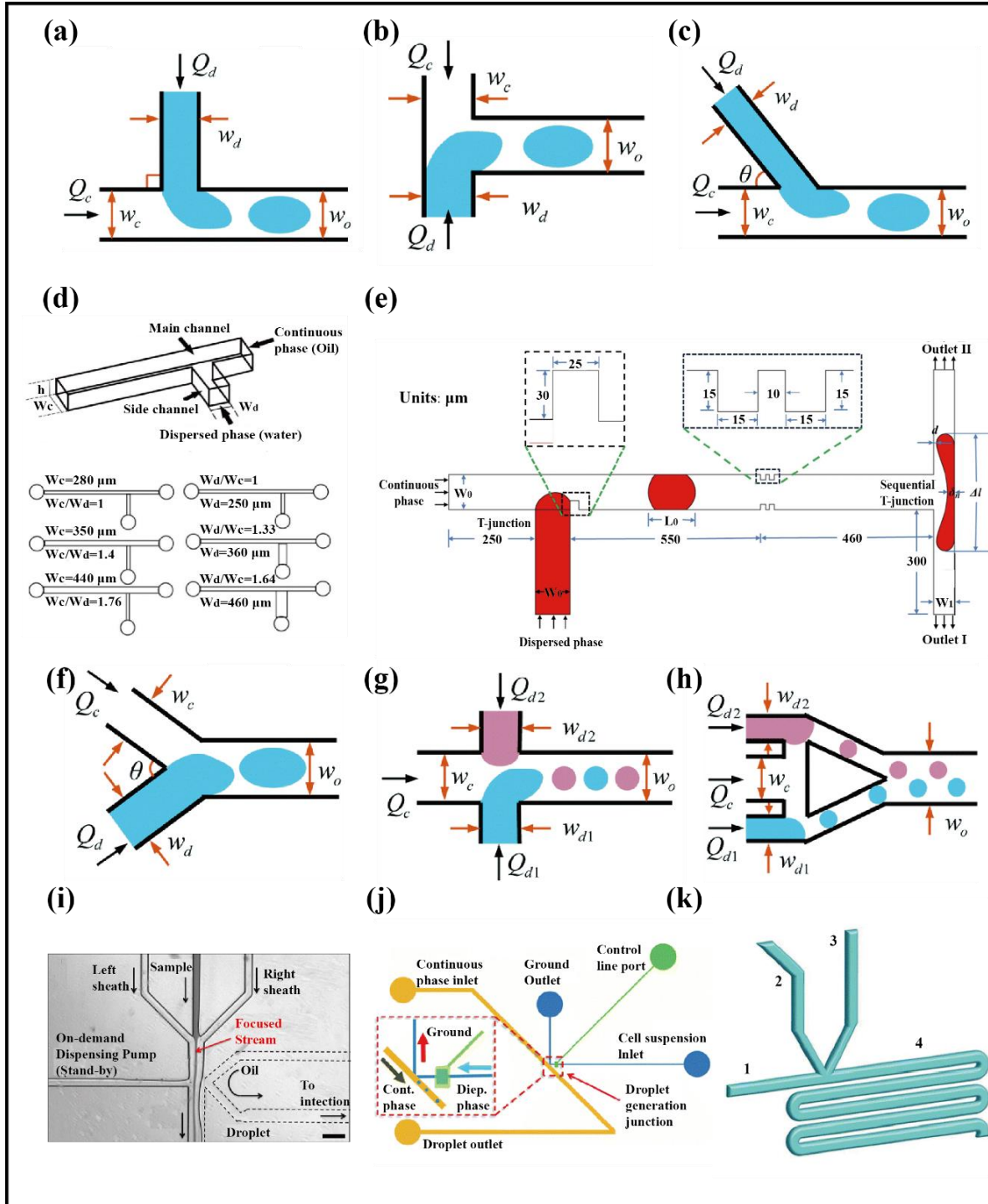


Figure 2: Schematics of T-junction microchannel structures and their variants. (a,b) Conventional T-junction microchannels for droplet generation [34]. (c) T-junction with an inlet angle between dispersed and continuous phases less than 90° ($0^\circ < \theta < 90^\circ$) [34]. (d) Influence of T-junction geometry and operating parameters on droplet formation [11]. (e) Modified T-junction structure [29]. (f-h) Y-junction ($0^\circ < \theta < 180^\circ$) and double T-junction configurations [34]. (i). Improved K-junction design in a microfluidic chip [33]. (j) K-junction structure [35]. (k) V-junction structure [31].

2.2. Co-flow method

The co-flow method, also referred to as coaxial focusing, employs a capillary aligned along the axis of the continuous-phase channel [36]. The dispersed phase flows through the inner capillary and merges with the continuous phase at the outlet, where droplets are generated. Cramer first introduced this technique and identified two primary regimes of droplet formation: tip dripping and downstream jetting [27]. In the dripping regime, increasing the continuous-phase flow rate reduces droplet size. At low dispersed-phase flow rates, surface tension governs droplet breakup. At higher flow rates, inertial forces dominate, and droplets are produced via jetting [37].

Building on this, Shao *et al.* [38] used a co-flow device to generate W/O/W double emulsions. They systematically analyzed the relationship between flow rates and droplet size, and showed that modifying channel geometry significantly affects droplet characteristics. Wang *et al.* [39] developed a self-assembled co-flow device using a 200 μm inner-diameter steel needle and an 800 μm outer-diameter capillary (Fig. 3a). Experiments in a styrene/SDS-PVP system, combined with 3D surface fitting, revealed droplet diameters ranging from 70 to 377 μm , which were negatively correlated with continuous-phase flow rate (0.5–3 mL/min) and surfactant concentration (0.5–7%). Furthermore, Zhang *et al.* [40] employed a co-flow microplatform with a 0.16 mm oil-phase needle and a 4.8 mm aqueous channel (Fig. 3b), successfully preparing B/Bi₂O₃ high-energy microspheres. In terms of mechanism, Deng *et al.* [41] generated W/O droplets using a co-flow device (Fig. 3c) and applied the VOF method to show that higher continuous-phase flow rates and viscosities both significantly reduced droplet size. Jiang *et al.* [42] investigated three types of collection capillaries—conical, concave, and parallel straight—across flow rates from 0.5 to 20 mL/h (Fig. 3d). They demonstrated that the conical capillary produced the strongest necking effect, yielding smaller droplets ($\approx 150 \mu\text{m}$) at relatively low outer-phase flow rates and lowering the threshold for the transition from single-core to multi-core double emulsions to 6.5 mL/h.

2.3. Flow Focusing Method

Flow focusing was first introduced by Anna and Dreyfus [45, 46]. In this design, the continuous phase enters from two lateral channels and exerts shear and compression on the dispersed phase injected from a vertical channel. Droplets are then formed at the junction. Compared with the T-channel structure, flow focusing enables more stable droplet formation, better size uniformity, and a broader size range [34].

When the chip was transversely stretched by 25%, the neck width increased, causing the droplet diameter to grow from 88 μm to 102 μm ($\approx 20\%$), while the generation frequency dropped from 14 Hz to 8 Hz ($\approx 45\%$). Jung *et al.* [43] used a similar device (channel height 80 μm , neck width controlled by flow rate; Fig. 3e) to generate PVCL-TA aqueous droplets under pH 8.4. Gelation was triggered downstream by introducing an acid phase, producing spherical microgels of 130–150 μm . By adjusting the aqueous-phase flow rate (10–40 $\mu\text{L/h}$), rod-shaped microgels with aspect ratios of 2.5–3.9 were continuously produced. Roshan *et al.* [44] fabricated a flow focusing chip (continuous-phase channel width 40 μm , dispersed-phase inlet 63 μm , neck 29 μm ; Fig. 3f) that yielded highly monodisperse droplets.

Structurally, axisymmetric flow focusing provides additional advantages. Takeuchi [47] showed that droplet diameters remain consistently between 50–300 μm , with droplets stably aligned in the channel center and minimally affected by external disturbances, thus enhancing integrity and uniformity. Castro-Hernández *et al.* [48] further proposed four optimized designs based on numerical simulations and validated them through photolithography. In 50 μm -wide channels, they successfully generated monodisperse droplets as small as $\sim 1 \mu\text{m}$, demonstrating the critical role of simulation-guided design in enhancing device performance and reliability.

2.4. Summary

In summary, the T-channel, flow focusing, and co-flow methods represent the most widely used passive droplet generation strategies. As summarized in Table 1, all three rely on the shear and compression of the continuous phase to break up the dispersed phase into monodisperse droplets. Nevertheless, they differ markedly in controllability, uniformity, and application scope. The T-channel is conceptually the simplest, with droplet size

primarily determined by flow-rate ratio and channel-width ratio. Flow focusing provides superior stability and uniformity, with a broader tunable size range. Co-flow, owing to its axial symmetry, is well suited for generating both single and double emulsions, and is highly sensitive to continuous-phase flow rate, viscosity, and interfacial tension. Future progress will rely on integrating high-fidelity simulations with experimental validation to optimize device architectures and broaden the scope of droplet-based applications. Future optimization of these passive structures will increasingly rely on high-fidelity simulations to refine geometries and physical mechanisms of droplet formation.

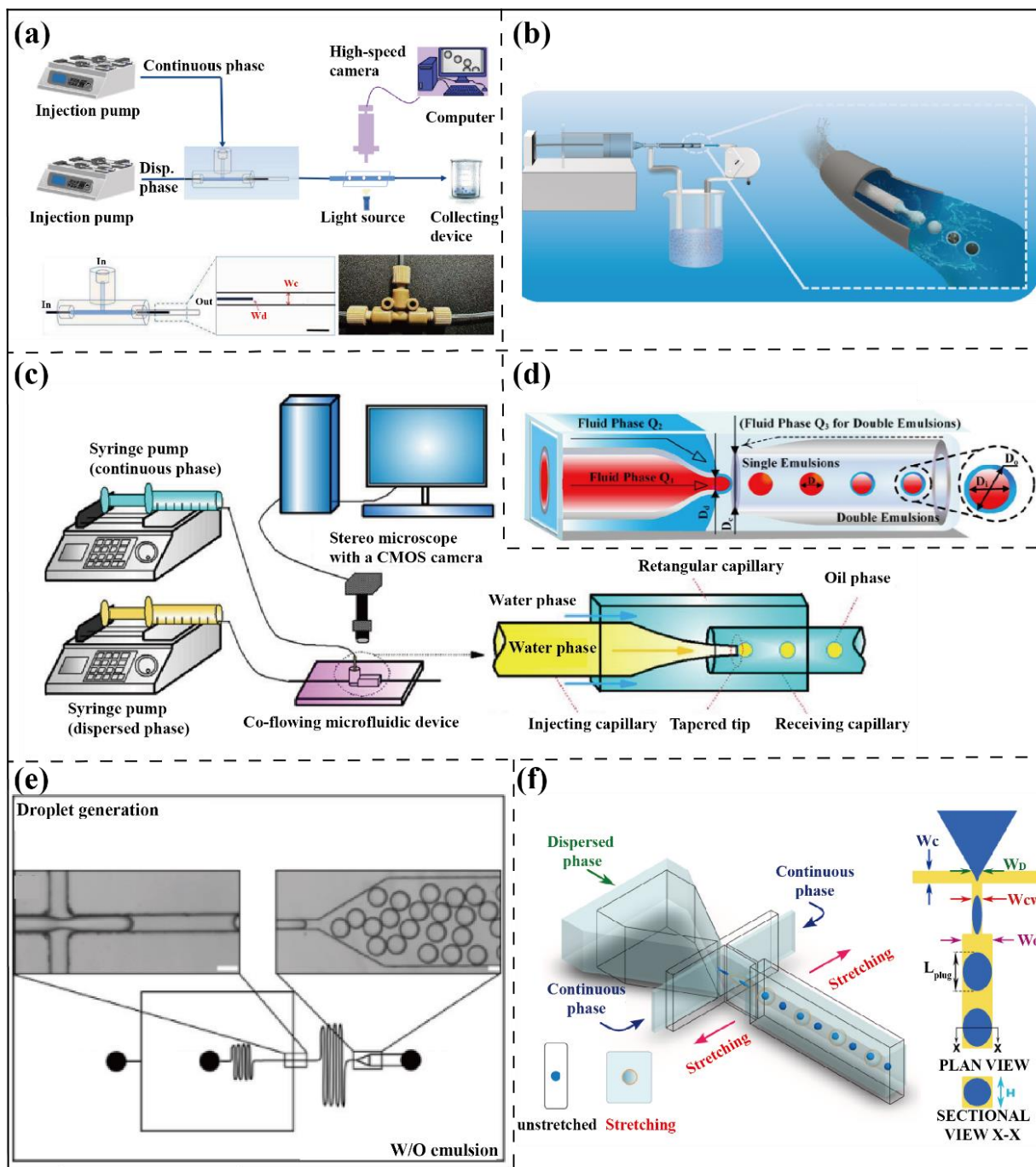


Figure 3: Schematics of co-flow and flow-focusing microfluidic devices. (a) Co-flow device for generating styrene droplets [39]. (b) Co-flow device for synthesizing B/Bi₂O₃ high-energy microspheres [40]. (c) Oil-in-water (O/W) droplet formation in a co-flow capillary system [41]. (d) Glass capillary co-flow device for producing colloidal single or double emulsions [42]. (e) Flow-focusing chip for preparing cylindrical supramolecular microgels with tunable aspect ratios [43]. (f) Droplet generation process in a flow-focusing microfluidic chip [44].

Table 1: Comparison of three representative passive droplet generation structures.

Structural Feature	Key Parameters	Advantages	Ref.
T-junction method	Width ratio, flow rate ratio, surface tension	Simplest principle and intuitive design; Easy to fabricate and compare in experiments; Clear and well-defined relationship between droplet size, flow rate ratio, and channel ratio; Highly suitable for studying droplet generation mechanisms and validating simulations	[27, 28]
Co-flow	Continuous-phase flow rate, viscosity, surface tension, collection tube structure	Suitable for preparing multiple emulsions (single, double, and composite emulsions); Droplet diameter can be flexibly tuned by adjusting outer/inner phase flow rates; Coaxial configuration enhances interfacial stability and reduces droplet coalescence; Compatible with diverse material systems (polymers, particle suspensions, etc.)	[40, 41]
Flow focusing	Channel geometry, flow rate, external stress	Provides better droplet uniformity and stability than T-junction; Droplets remain centered in the channel with minimal external disturbance; Covers a wider droplet size range; Suitable for functional droplet and multiphase system preparation	[43, 34]

3. Numerical Simulation of Monodisperse Droplet Generation

3.1. Numerical Methods and Implementation Platforms

Computational fluid dynamics (CFD) offers distinct advantages for studying microfluidic droplet generation, including low experimental cost, flexible parameter control, and powerful visualization capability. It provides direct access to key parameters such as pressure distribution, flow evolution, and phase volume fraction inside microchannels.

Numerical methods for droplet simulation are generally divided into discrete methods and continuous interface-tracking methods [49]. The lattice Boltzmann method (LBM) is the most representative discrete approach. Continuous methods, in contrast, describe the dynamics of multiphase fluid interfaces and include the volume of fluid (VOF), level set (LS), and phase field (PF) methods [50]. When parameters are properly configured, simulations based on these methods typically show deviations from experimental data that are minimal or even negligible [51].

In practice, these methods are implemented on both commercial and open-source platforms. ANSYS Fluent is widely employed for VOF-based simulations of droplet formation, coalescence, and breakup [52]. COMSOL Multiphysics, by contrast, commonly integrates LS and PF methods to track interface evolution [53]. The modular structure and multiphysics coupling capabilities of these platforms allow researchers to flexibly construct microfluidic models and systematically probe the complex interfacial dynamics underlying droplet generation.

3.2. Numerical Simulation of Two-phase Flow

Van der Graaf *et al.* [54] applied the lattice Boltzmann method (LBM) to simulate droplet formation at junctions and reported that the method cannot independently prescribe interfacial tension, thereby limiting its accuracy. Although LBM shows advantages for certain microscale flows, its weak mass conservation significantly constrains its ability to capture interfacial tension effects [55]. The level set (LS) method suffers from another drawback—its high computational cost [54]. To overcome these issues, Li *et al.* [56] developed a full-cycle multiphysics model using the phase-field (PF) method, covering droplet generation through mixing evolution. Their study revealed that co-flow focusing structures can regulate both the initial component distribution and vortex patterns within droplets. A contraction-type focusing nozzle enhanced mixing efficiency by ~15%, underscoring the role of structural optimization in strengthening internal mixing.

In contrast, the volume-of-fluid (VOF) method inherently conserves mass by solving the transport of volume fractions across computational cells [57]. This property has made VOF one of the most widely adopted approaches in microfluidic droplet simulations. For instance, Nguyen *et al.* [58] employed a three-dimensional VOF model to analyze droplet formation in a double T-junction. They introduced a droplet-generation phase diagram incorporating the channel aspect ratio (ϵ), identifying four distinct regimes and their stability boundaries. Similarly, Mardain *et al.* [59] applied a 3D VOF framework to flow-focusing geometries, systematically evaluating the effects

of flow-rate ratio, capillary number, and channel dimensions on droplet frequency and mass flux. Their work proposed an optimal parameter set ($Q = 5$, $AR = 1$) and established a predictive scaling law between droplet size and channel geometry. The applicability of VOF extends to more complex conditions. Bi *et al.* [60] demonstrated controllable generation of monodisperse droplets using the VOF model by microfluidic chips and the relative error between experiment and simulation results was less than 5.43%. Nek *et al.* [61] examined droplet generation under high viscosity ratios ($\lambda = 1$ -100). They found that extrusion time increased markedly with λ , while filling time remained nearly constant, causing their ratio to approach unity. Furthermore, Rajes [62] validated the method against experiments on gas-liquid-liquid segmented flows in microchannels. At oil, water, and air flow rates of 5.00, 2.76, and 5.24 mL/min, the simulated droplet length (2.5 mm) closely matched the experimental measurement (2.45 mm), with only a 2% error. Jammula *et al.* [63] used VOF to simulate 3-D oil breakup into droplets driven by carboxymethylcellulose(CMC) aqueous flow in a microchannel, and confirming VOF's accuracy for high-throughput droplet control in non-Newtonian fluids.

Together, these studies demonstrate that while LBM, LS, and PF each provide valuable insights under specific conditions, the VOF method has emerged as the most robust and reliable approach for capturing the complex dynamics of droplet formation in microfluidics.

3.3. Machine Learning-assisted Microfluidic Droplet Generation

In recent years, machine learning (ML) has become a key driver advancing microfluidic droplet generation toward automation and intelligent control. The research focus has shifted from pure prediction accuracy to a balanced pursuit of efficiency, interpretability, and automated design [64-66]. Solanki *et al.* [67] employed convolutional neural networks to rapidly predict droplet behavior directly from complex geometries, while Wang *et al.* [68] developed a bidirectional deep learning model with active learning, achieving precise droplet size control under limited data. The model predicts both droplet size and flow regime while inversely determining the discrete phase flow rate from a target droplet size. It achieved an average relative error of only 9.90%, a 45.6% improvement over the unidirectional model, demonstrating high accuracy in droplet control under small-sample conditions. Chagot *et al.* [69] used Bayesian-regularized neural networks and XGBoost models to predict surfactant-laden droplet size in flow-focusing microchannels. By introducing variational autoencoders for synthetic data generation, they showed that data-driven methods outperform semi-empirical models and effectively address data scarcity, and Talebjedi *et al.* [70] integrated neural networks with multi-objective genetic algorithms for inverse design of droplet size, frequency, and quality. At the mechanistic insight level, Liu *et al.* [71] applied tree-based models with Shapley Additive exPlanations (SHAP) analysis to over 1,800 experimental data, systematically quantifying feature contributions and revealing that geometric parameters alone account for 22.9% of the droplet size prediction. Eslami *et al.* [72] constructed a metaheuristic-optimized hybrid model for rapid droplet size prediction, which achieved an R^2 of 0.937, and its reliability was further verified through symbolic regression and SHAP analysis.

3.4. Summary

This section has reviewed the critical role of numerical simulation in elucidating the dynamics of monodisperse droplet generation. Established computational methods, particularly the VOF technique, have proven indispensable for reliably predicting droplet formation across various microgeometries, owing to their robust mass conservation and accuracy. Emerging ML paradigms are now instigating a shift towards intelligent design and autonomous control, utilizing generative AI for inverse design and reinforcement learning for real-time optimization. The convergence of high-fidelity physical simulations with data-driven ML algorithms is poised to underpin the next generation of predictive and scalable droplet-based microfluidic systems.

4. Applications of Microfluidic Monodisperse Droplet Technology

Conventional bulk droplet generation methods, such as high-speed stirring, often suffer from poor selectivity, high reagent consumption, safety concerns, and limited reproducibility [73]. In contrast, microfluidic monodisperse droplet technology has rapidly emerged as a powerful alternative, offering high precision, efficiency, and minimal material consumption [74]. By enabling exquisite control over droplet size, morphology, and

generation frequency, microfluidic systems not only improve experimental reliability but also expand opportunities across biomedicine, chemical synthesis, and advanced materials engineering.

4.1. Biomedical Applications

Microfluidic droplets have become a versatile platform for three-dimensional (3D) cell culture and disease modeling. Unlike conventional two-dimensional culture, 3D droplet-based culture more faithfully reproduces the *in vivo* microenvironment, thereby capturing physiologically relevant cell states [75]. The intrinsic laminar flow protects fragile cells from shear-induced damage, while the picoliter-scale volume makes droplets ideal carriers for bacteria, viruses, and even single cells.

A number of studies illustrate these advantages. Kwak *et al.* [76] used a flow-focusing device to encapsulate cancer cell suspensions, precisely controlling cell number while tuning droplet diameters between 50 and 150 μm . The resulting spheroids closely mimicked *in vivo* tumors, providing a robust model for cancer pathogenesis. Similarly, Jing *et al.* [77] adopted a jetting mode with mineral oil as the carrier phase, achieving efficient single-cell encapsulation. At a cell concentration of 10^6 cells/mL, the encapsulation efficiency reached 80%, enabling single-cell assays of metalloproteinase activity. Lin *et al.* [78] reviewed microfluidic systems for COVID-19 diagnosis and antiviral research. These lab-on-a-chip devices detect viral targets with high sensitivity and low cost. They also enable drug screening and mRNA vaccine production. Wang *et al.* [79] combined optoelectrowetting and deep learning for droplet control. The system precisely manipulates droplets in real time without sensors. It enables automated, parallel cell culture. This work advances intelligent digital microfluidics.

Microfluidics also facilitates multicellular tumor spheroid formation. Wang *et al.* [80] employed alginate-matrix hydrogels to generate highly monodisperse spheroids, achieving > 90% viability in cervical cancer cells. Sun *et al.* [81] reported a high-throughput system that produced 200 alginate-based spheroids per minute, with tunable composition and uniform morphology. A hybrid 3D glass-PDMS chip has further been developed, where electric-field modulation controlled droplet size, and CaCl_2 -induced crosslinking preserved ~90% viability of encapsulated *E. coli*. Beyond modeling, microfluidic droplets are being engineered as therapeutic carriers. Wang *et al.* [82] created nitric oxide-responsive γ -polyglutamic acid microgels that shielded probiotics in gastric acid and selectively released them at inflamed intestinal sites, markedly improving oral bioavailability and mitigating colitis (Fig. 4a). Sandra *et al.* [83] reported lipid-polymer hybrid nanoparticles co-loaded with siRNA and budesonide, achieving macrophage-targeted dual anti-inflammatory and gene-silencing effects. Melika *et al.* [84] used enzymatic crosslinking within microfluidic reactors to fabricate phenol-functionalized PVA microspheres for sustained dexamethasone release over seven days (Fig. 4b,c). These microspheres exhibited excellent cytocompatibility and mechanical stability, supporting applications in localized anti-inflammatory therapy and tissue regeneration. Collectively, these advances underscore how microfluidic droplets provide precise, high-throughput, and physiologically relevant platforms for biomedical research. Their ability to combine cell encapsulation with therapeutic delivery positions them as a cornerstone technology for next-generation cell models and drug screening.

4.2. Chemical Reactions

Microfluidic monodisperse droplets offer distinct advantages for chemical reactions owing to their microscale volume, rapid kinetics, operational simplicity, and intrinsic safety [86]. With typical sizes ranging from 50 to 300 μm , droplets provide a dramatically enlarged interfacial area, which accelerates reaction rates, reduces reagent consumption, and minimizes hazardous exposure. Each droplet functions as an isolated microreactor, independent from its neighbors and from channel walls, thereby eliminating cross-contamination. Several studies illustrate how this technology reshapes chemical processing. Bringer *et al.* [87] demonstrated that droplet volume can be tuned by adjusting the cross-sectional geometry of microchannels, while reactant concentrations can be controlled by regulating the two-phase flow rates. Moreover, twisted or folded channel designs induce efficient internal recirculation within droplets, ensuring rapid mixing and uniform reaction conditions—an essential feature for analytical chemistry. Loh *et al.* [88] developed a droplet-on-demand microfluidic system coupled with ESI/MS for real-time monitoring of single-cell biocatalysis. Using hydrodynamic gating, the method enabled precise nanoliter droplet generation and successfully detected yeast-catalyzed ketoester conversion by mass spectrometry with high sensitivity.

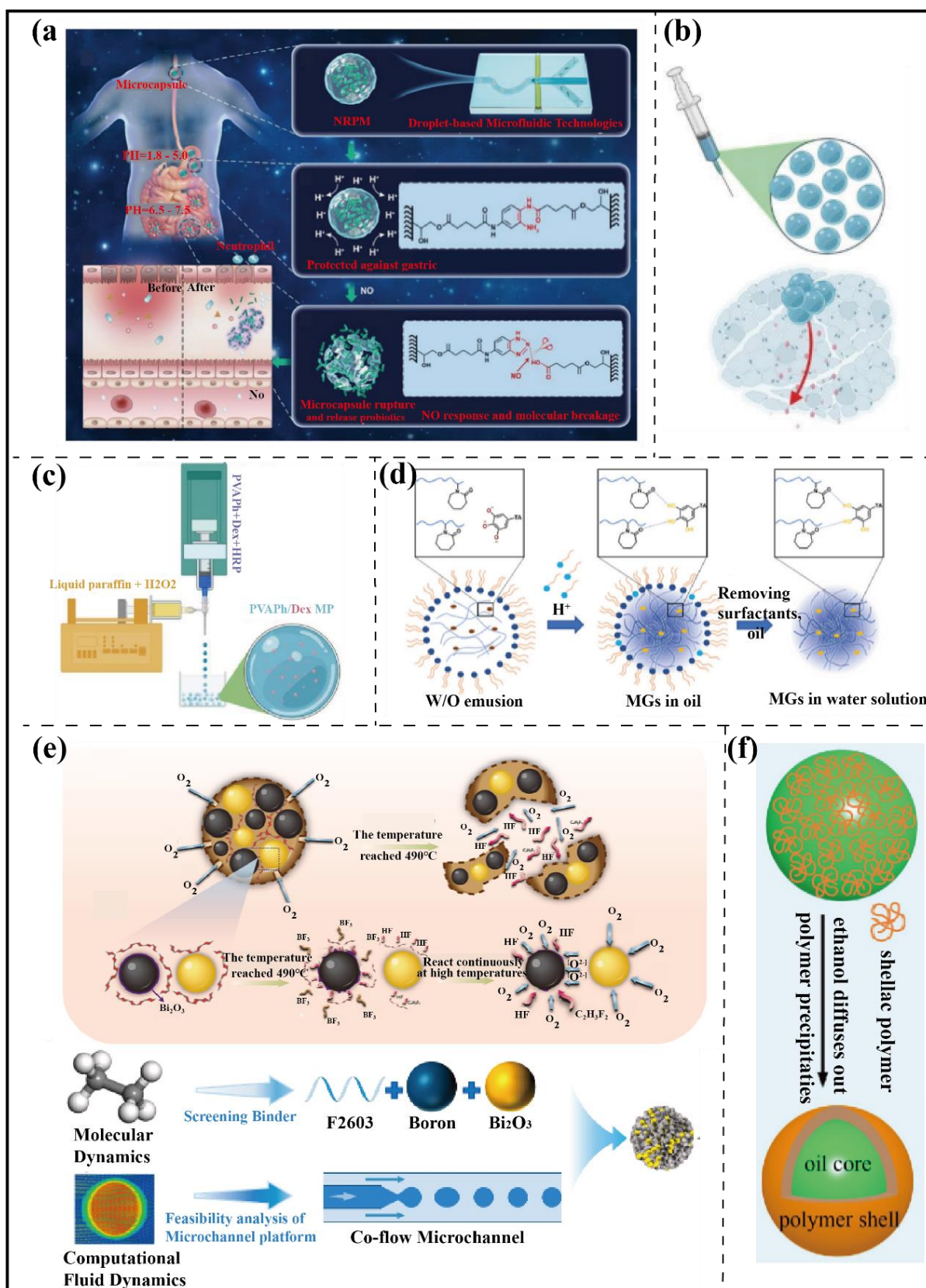


Figure 4: Representative applications of microfluidic monodisperse droplet technology. **(a)** γ -Polyglutamic acid microgels for colitis relief [82]. **(b,c)** Dexamethasone-loaded droplets prepared by microfluidics [84]. **(d)** pH-responsive supramolecular microgels constructed from tannic acid and PVCL [43]. **(e)** Boron/Bi₂O₃/F2603 composite microspheres synthesized via microfluidics [40]. **(f)** Microcapsules for encapsulating drugs, flavors, or nutrients [85].

To expand throughput, Kikutani *et al.* [89] developed an integrated parallel reactor by etching microchannels onto a glass substrate. This system enabled 2×2 combinatorial amide syntheses, achieving yields above 90% without detectable cross-contamination. Nonetheless, the device complexity poses challenges for large-scale implementation. In another example, Chen *et al.* [90] employed a flow-focusing device to generate monodisperse droplets, followed by argon-segmented flow in downstream heated serpentine channels. The enhanced heat transfer facilitated the controlled synthesis of nanoparticles, underscoring the promise of droplet reactors for fine chemical production. Microfluidics also enables the creation of stimuli-responsive soft materials. Jung *et al.* [43] engineered pH-responsive supramolecular microgels from tannic acid and PVCL (Fig. 4d). These microgels could encapsulate microcapsules or cells and rapidly release their payload in alkaline environments. Furthermore, droplet templates allowed precise control over particle morphology, yielding spherical or rod-shaped carriers that are degradable and suitable for probiotic or drug delivery applications. Together, these advances highlight how microfluidic droplet technology transforms chemical synthesis into a process that is faster, safer, and more controllable, while enabling novel functional materials that would be difficult to achieve with bulk methods.

4.3. Material Preparation

Microfluidic monodisperse droplets enable precise control over droplet size, morphology, composition, and spatial arrangement during generation. Such tunability imparts the resulting materials with exceptional uniformity and predictable performance [91]. This capability not only improves the structural homogeneity of materials but also facilitates reproducible tuning of their physical and chemical properties. At the same time, microfluidic platforms support high-throughput droplet generation and manipulation, markedly enhancing the efficiency and cost-effectiveness of material production [92]. With modular chip architectures, multifunctional units can be integrated, allowing one-step synthesis and complex structure construction, thereby expanding the design space of functional materials. At the theoretical level, the formation and stability of droplets are governed by the Young-Laplace equation, which defines the relationship between interfacial pressure differences and surface tension [93]. In microscale environments, surface effects dominate droplet dynamics, making this equation fundamental for both modeling and simulation. Thus, numerical simulation of droplet dynamics not only clarifies formation mechanisms but also provides a powerful framework for the rational design and fine-tuned control of functional materials.

Practical applications illustrate the versatility of this approach. Deng *et al.* [94] fabricated embolic microspheres using chitosan (CS) as the base and genipin as the crosslinker. The microspheres (20-90 μm) exhibited tunable size, a coefficient of variation below 5%, and favorable swelling and elasticity, making them suitable for interventional radiology. Wang *et al.* [95] prepared intestinal-targeted probiotic microcapsules by combining bacterial nanoencapsulation with microfluidics. *Lactobacillus* was encapsulated with chitosan/polydopamine coatings (CS@PDA-LAB) and further embedded in calcium alginate droplets, significantly improving probiotic survival and oral delivery. Yu *et al.* [96] reported fiber materials composed of a superelastic polyurethane shell and a liquid metal core via programmed microfluidic spinning. These fibers showed tunable morphologies and conductive properties, functioning as pressure sensors and motion monitors when integrated into elastic films, and offering promise for energy conversion and wearable electronics.

Microfluidics also enables high-energy and responsive materials. Zhang *et al.* [40] employed coaxial channels to generate boron/ Bi_2O_3 /F2603 droplets, which solidified into spherical composite microspheres with improved flowability, ignition, and combustion. Sun *et al.* [85] developed a one-step microfluidic strategy for microcapsules capable of controlled release triggered by pH, mechanical stress, or time (Fig. 4f), suitable for drugs, fragrances, and nutrients. Han [74] fabricated PMMA-PETRA-coated n-hexadecane microcapsules that combined high monodispersity, low supercooling, and optical switching across UV-visible-mid-infrared ranges. These capsules are promising for intelligent radiative cooling and energy storage applications.

4.4. Summary

As summarized in Table 2, microfluidic monodisperse droplet technology offers distinct advantages across three domains. In biomedicine, it accelerates the development of three-dimensional cell culture, disease modeling, and drug screening. In chemical reactions, it enhances efficiency and safety by confining processes within isolated

microreactors. In materials science, it enables high-precision construction and functional customization of advanced materials. Overall, microfluidic monodisperse droplets are not merely an experimental technique, but a strategic platform driving interdisciplinary innovation and translational applications. The next critical step for the field lies in translating these compelling laboratory demonstrations into scalable, robust, and standardized platforms that can meet the stringent demands of industrial manufacturing and clinical practice.

Table 2: Representative applications of microfluidic monodisperse droplet technology across different fields.

Application Field	Main Functions and Advantages	Potential Application Directions	Ref.
Biomedicine	3D cell culture closely mimics the in vivo environment; Protects cell morphology and prevents mechanical damage; Enables high-throughput and controlled encapsulation of single cells or bacteria	Construction of in vitro disease models; Drug screening; Probiotic delivery; Gene therapy	[77, 79, 82, 83]
Chemical Reactions	Droplets act as independent microreactors, avoiding cross-contamination; High reaction uniformity with efficient mass/heat transfer; Reduced reagent consumption and improved safety	Fine chemical synthesis; combinatorial chemistry; High-throughput reaction screening	[43, 88-90]
Materials Preparation	Droplets allow precise control over size, arrangement, and solidification; Enable scalable fabrication of functional materials; Facilitate construction of complex structures and performance tuning	Photonic crystals; Sensors; Smart materials; Energy storage systems	[74, 85, 76-96]

5. Lab-to-industry Translation

Recently, numerous efforts have been devoted to translating microfluidic droplet technologies from laboratory research to industrial applications [97]. Li *et al.* [98] introduced a centrifuge-assisted droplet generation method using injection-molded microchannel arrays. The approach produces uniform droplets within minutes and supports applications such as hydrogel synthesis and droplet digital polymerase chain reaction. It is low-cost, efficient, and easy to operate, offering a practical route from laboratory research to scalable production. Chen *et al.* [99] simplified droplet digital polymerase chain reaction by introducing a device-free droplet generation method using crescent-shaped microbeads, achieving high droplet uniformity and detection accuracy comparable to commercial systems while eliminating the need for complex instruments. In contrast, Cong *et al.* [100] emphasized a manufacturing-oriented perspective, outlining a roadmap from laboratory prototypes to scalable production through design-for-manufacturing, early team integration, material selection, and process standardization. Overall, these studies highlighted the deployment of advanced microfluidic technologies from laboratory innovation to industrial-level commercialization.

6. Conclusion

Microfluidic monodisperse droplets have demonstrated unique advantages as controllable multiphase systems, enabling precision in droplet size, frequency, and morphology regulation. Through this review, three major contributions can be distilled. First, passive droplet generation strategies—T-junction, flow-focusing, and co-flow—each provide distinct benefits, yet their performance remains highly sensitive to geometry and operating parameters. Second, computational fluid dynamics (CFD), particularly the volume-of-fluid (VOF) method, has proven indispensable for revealing interfacial dynamics and guiding device optimization, though limitations in mass conservation (LBM), computational cost (LS, PF), and resolution persist. Third, applications across biomedicine, chemical engineering, and materials science illustrate the interdisciplinary potential of droplet microfluidics, from single-cell assays to functional material fabrication.

Despite this progress, current research faces three major shortcomings: (i) insufficient balance between accuracy and efficiency in numerical modeling; (ii) weak integration between simulations and experiments, limiting predictive reliability; and (iii) inadequate frameworks for scaling droplet technologies toward industrial and clinical use.

Looking forward, future development will rely on three directions. The first is the creation of high-fidelity yet computationally efficient algorithms capable of capturing complex interfacial phenomena. A deeper theoretical understanding is also needed, moving from empirical correlations to predictive, universal scaling laws that govern droplet formation for complex fluids and multi-physical fields. The second is the establishment of systematic experiment-simulation integration, including unified parameter calibration and iterative validation. Concurrently, a dedicated focus on addressing industrialization challenges is crucial. This includes developing high-throughput, parallelized systems for mass production, ensuring long-term operational stability, and promoting standardization to bridge the gap between laboratory prototypes and robust commercial and clinical applications. The third is the incorporation of AI and ML into microfluidic design and droplet control. AI/ML frameworks are expected to autonomously discover design rules from high-dimensional simulation and experimental data, thereby accelerating geometry optimization, parameter tuning, and process control. Furthermore, the coupling of AI-driven models with digital twins could enable real-time feedback and self-optimization in droplet microfluidic systems, bridging the gap between virtual prototyping and physical realization.

In summary, microfluidic monodisperse droplets are not only a versatile research tool but also a strategic innovation platform. By overcoming current methodological bottlenecks and embracing data-centric, AI-driven design paradigms, the field is poised to evolve toward fully autonomous, predictive, and scalable droplet technologies with broad impact in both fundamental science and translational technologies.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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