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REVIEW

Microfluidic-enabled nanomedicine: a comprehensive review of recent advances and translational potential

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Abstract

Microfluidic technology is designed for the liquid handling and manipulation of fluids and materials at a small scale. This technology offers distinct advantages that address the limitations of conventional methods such as precision control, reproducibility, efficiency, and rapid processing. These advantages signify a paradigm shift in the field of biomedical and pharmaceutical research, particularly in the preparation of nanomedicines. This review briefly introduces microfluidics along with its principles and fundamentals, including the key components, different types of microfluidic mixing mechanisms, and materials used in microfluidic devices. It also comprises a detailed discussion of the benefits and challenges of using microfluidics in preparing nanoformulations (such as lipid-based, polymer-based, inorganic-based, and hybrid-based) and biomedical applications. This review also discusses the advancement of microfluidic and nanomedicine preparation, such as modular microfluidics, digital microfluidics, three-dimensional (3D) printed chips, automated microfluidics, artificial intelligence (AI), and healthcare wearable devices (HWDs). The review concludes by encouraging cooperation between multiple parties for the success of nanomedicine and offering better patient care to the public.

Keywords Microfluidics · Nanomedicine · Nanoparticles · Drug delivery system

1 Introduction

Nanomedicine integrates biomaterials, nanotechnology, biomedicine, and pharmaceutical sciences to formulate medicine. It encompasses different types of drug delivery systems in the 1–100 nm range (Aftab et al. 2018; Gonzalez-Valdivieso et al. 2021; Heshmati Aghda et al. 2022; Yang et al. 2022). Conventionally, it is prepared using two main approaches: top-down and bottom-up approaches. The top-down approach is a size-reduction approach that

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uses mechanical forces. In contrast, the bottom-up approach includes chemical reactions and self-assembly of structures from atomic or molecular precursors (Mark et al. 2010; Kumar et al. 2013; Niculescu et al. 2021a).

The lack of tight control of the conventional method can lead to wide size distributions and large variability between manufactured batches, which can be overcome by microfluidic technology (Niculescu et al. 2021a). Microfluidics, as illustrated in Fig. 1, can be referred to as a set of tools for liquid handling and manipulation of fluids and materials that use the small volume capacity (atto- to nanolitre) of the fluid and pass through the channel of the device with a diameter between 1 and 500 µm (Nge et al. 2013; Niculescu et al. 2021a; Nunes and Stone 2022; Trinh 2023). This technology allows accurate, rapid, and uniform mass transfer and control over nanomedicine characteristics owing to its continuous and segmented flow in the microfluidic channel (Mark et al. 2010; Liu et al. 2018; Niculescu et al. 2021a; Mohammadi et al. 2024). Over several decades, this technology has experienced exponential growth, significant developmental potential, and evolution, with the most common advancement being the introduction of lab-on-a-chip and "micro total analysis systems", illustrated in Fig. 2.

Over the years, increasing interest has been observed in the development of microfluidics and its application in nanoparticles and nanomedicine, as shown in the publication statistics from 2004 to 2024 in Fig. 3. The number of publications on microfluidics (blue bars) has consistently increased. This expansion is indicative of the ongoing research and interest in microfluidic technology in a variety of disciplines. The prominence of publications addressing microfluidics and nanoparticles (orange bars) began to increase consistently around 2007. This research scope concentrates on the utilization of microfluidic systems in the synthesis, characterization, and optimization of nanoparticles, irrespective of drug incorporation. The green bars, which represent articles in microfluidics and nanomedicine, demonstrate a consistent yet modest upward trend over time. The increasing interest in the application of microfluidics in nanomedicine (drug-loaded formulations) is predominantly due to its potential in drug delivery, diagnostics, and personalized medicine, as evidenced by this growing trend. Microfluidics technology has achieved great advancement based on the combination of principles, ranging from physics, chemistry, biology, material science, and microelectronics, which are later employed in the biotechnology, biomedical, and biopharmaceutical industries (Niculescu et al. 2021b).

AI denotes the emulation of human intelligence by a system or machine that aims to enhance ideas, methodologies, strategies, and practical systems (Zhang et al. 2024). The ongoing advancement of AI algorithms driven by machine learning (ML) presents a significant potential for integrating these methodologies into healthcare systems, thereby transforming conventional techniques (Doganay et al. 2024). AI-integrated microfluidics has emerged as an integrated technological solution representing revolutionary methodology in nanomedicine, utilized for nanoparticle synthesis, cell flow analysis, disease diagnosis, drug development and screening, and simulating in vivo conditions using organ-on-a-chip technology (Asadian et al. 2024).

In this article, we provide an overview and principles of the microfluidic system and technology and its uses in nanomedicine preparation, with its benefits and challenges. We also highlight the applications of microfluidics in development of various nanomedicines and discuss the advancement of microfluidic and nanomedicine preparation, such

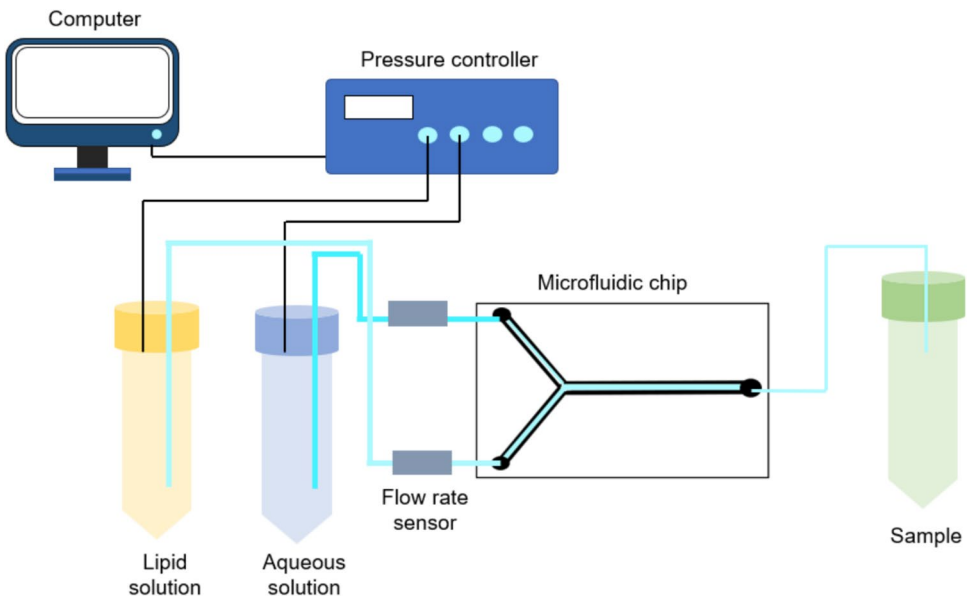
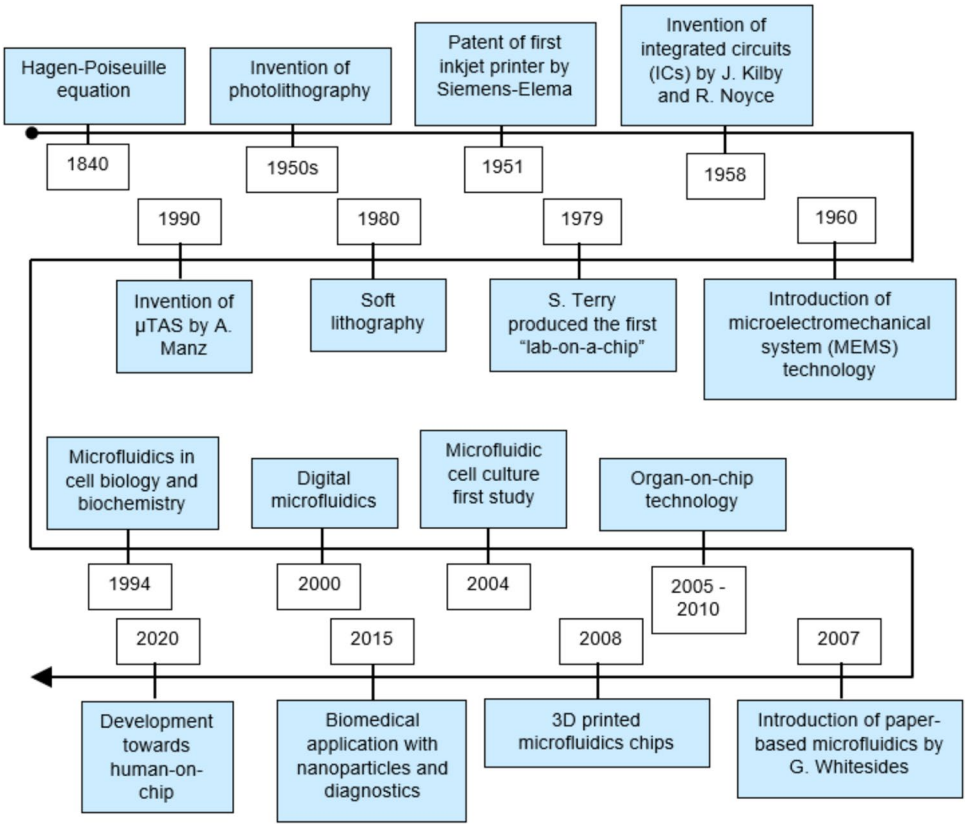


Fig. 1 Schematic diagram of the main component in a microfluidic system (Luka et al. 2015; Zhang and Zhang 2019; Ballacchino et al. 2021a)



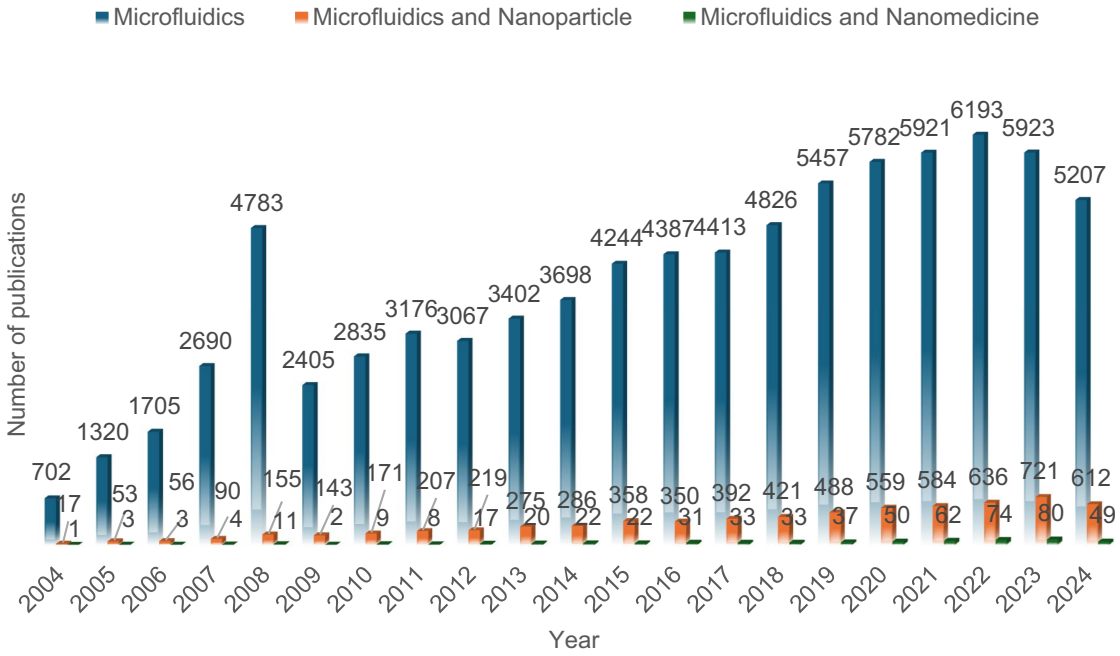


Fig. 2 Timeline of the evolution of microfluidics (Hung et al. 2005; Martinez et al. 2007; Bhattacharjee et al. 2016; Syama and Mohanan 2021; Farhang Doost and Srivastava 2024; Su et al. 2024; Terry et al. 1979; Manz et al. 1990; Xia and Whitesides 1998; Duffy et al. 1998; Whitesides et al. 2001; Kilby 2002; Hejun and Bogue 2007;Sutera and Skalak 1993; Mark et al. 2010; Khorsandi et al. 2021; Sharma and Sharma 2022; Preetam et al. 2022)

Fig. 3 Publication statistics on journals related to microfluidics (blue bars) and its application on nanoparticles (orange bars) and nanomedicine (green bars) generated from Scopus

as modular microfluidics, digital microfluidics, and AI. This review provides insights into the future refinement of microfluidic technologies that can further aid the advancement of nanomedicine production.

2 Principles and fundamentals of microfluidic systems

2.1 Fundamentals of microfluidic systems

Inertial forces (arising from fluid momentum), capillarity (capillary pressure that drives liquids into small capillaries), and viscous pressure (inherent forces that resist the flow of the liquid imparted by the channel walls) act on the fluid in the microfluidic system, impacting the flow regimes through the microchannels of the microfluidic device (Pihl et al. 2005; Forigua et al. 2021; Rapp 2022; Alavi et al. 2024). The fluid regimes or motion can be categorized into laminar flow (fluid flow in parallel layers at constant velocity) and turbulent flow (lacking streamlines and displaying differences in fluid pressure and velocity), as shown in Fig. 4 (Mohammadi et al. 2024).

Laminar flow predominantly occurs in the microfluidic system owing to the microscale size of the device, which exerts viscous and inertial forces that are calculated by the Reynolds number (Re) and Péclet number (Pe) (Capretto et al. 2013; Forigua et al. 2021). Re is a dimensionless parameter that characterizes the flow properties of a fluid and represents the ratio between the inertial and viscous forces. Another dimensionless number is Pe, which refers to the proportion between the convection and diffusion rates and provides information about the mass transport of the fluid.

2.2 Microfluidic device design and its functionality

Microfluidic systems are classified into continuous and segmented flow types, each of which has distinct advantages and limitations. Continuous-flow microfluidics functions under laminar flow conditions, with nanoparticle formation regulated by precisely controlled parameters, including flow rate and temperature. This flow regime demonstrates high reproducibility and scalability, rendering it advantageous for applications that require consistent output (Capretto et al. 2013; Niculescu et al. 2021b; Lei et al. 2024; Mohammadi et al. 2024). Continuous-flow systems may be susceptible to flow instability, as their performance is dependent on the system parameters for accurate control. Geometric enhancements in microchannels, including bending, folding, and stretching, can mitigate these limitations by promoting turbulent mixing and improving the efficiency (Niculescu et al. 2021a; Lei et al. 2024).

Segmented flow microfluidics employs immiscible phases (gas–liquid or liquid–liquid) to generate droplet or slug interfaces, enhancing mixing and mass transfer through internal recirculation within segments (Mark et al. 2010; Niculescu et al. 2021a; Mohammadi et al. 2024). This system mitigates the risk of channel clogging and enhances control over particle size distribution. Segmented flow systems require a greater sample volume during the run-in phase, which may be inefficient for applications with restricted sample availability. Their intricate designs and increased fabrication complexity may lead to greater variability in the presence of minor inconsistencies (Mark et al. 2010; Lei et al. 2024).

Microfluidic mixing strategies are typically categorized as passive and active methods. Passive mixing utilizes device geometry and internal channel configurations to improve the mixing efficiency without requiring external energy inputs. In contrast, active mixing employs external forces, including acoustic, electric, magnetic, or thermal inputs, to influence fluid dynamics and improve mixing efficiency (Lee et al. 2011; Cai et al. 2017; Gharib et al. 2022;

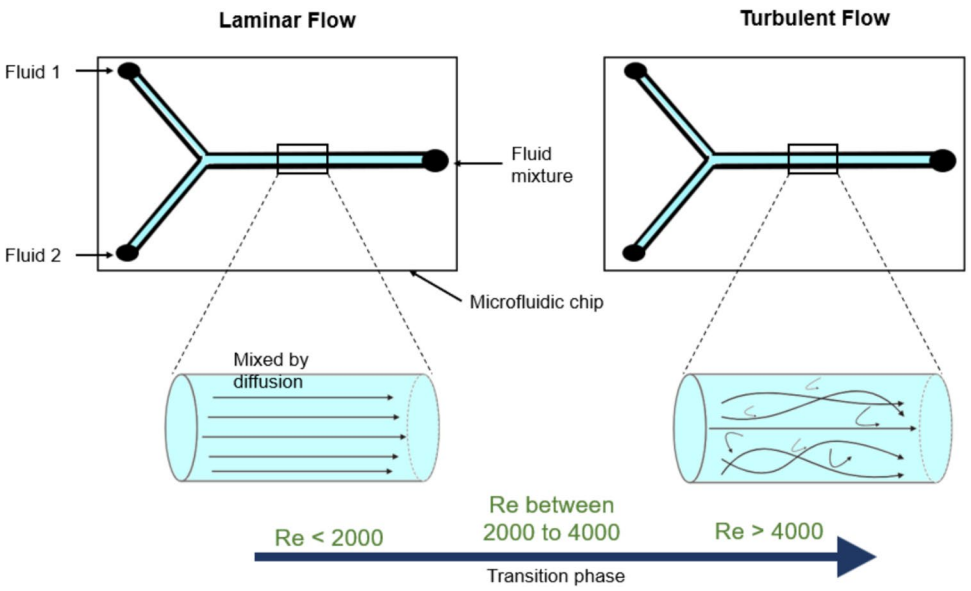


Fig. 4 Schematic diagram of fluid flow, laminar flow, and turbulent flow and its Reynolds number (Re) (Azizipour et al. 2020)

Agha et al. 2023). For instance, acoustic pressure-driven systems utilize frequencies between 1 kHz and 1 GHz to produce micro streams via bulk acoustic waves (BAW) or surface acoustic waves (SAW), facilitating rapid and efficient microscale mixing (Lee et al. 2011; Gharib et al. 2022; Agha et al. 2023). Vardin et al. recently demonstrated that acoustic oscillations can induce mixing for liposome production, resulting in uniform particles with a reduced size of approximately 40 nm (Vardin et al. 2024). Similarly, Rasouli et al. used a SAW device to improve copper diethyldithiocarbamate (CuET)-loaded liposomes in tumor spheroids, resulting in enhanced cytotoxicity and high viability retention (>92%) (Rasouli et al. 2023).

Micromixers driven by electrical means utilize embedded electrodes to apply direct current (DC) or alternating current (AC) voltages, thereby inducing electrohydrodynamic (EHD) flow instabilities at fluid interfaces. Instability occurs as a result of variations in fluid conductivity or permittivity, resulting in transverse mixing (Lee et al. 2011; Cai et al. 2017; Gharib et al. 2022; Agha et al. 2023). Chung et al. utilized an electrochemical implantable micro-electro-mechanical-system (MEMS) microreservoir device for the regulated release of vasopressin; however, oxidative degradation of the drug was observed following extended activation (Chung et al. 2009). Magnetic field-driven systems, grounded in magnetohydrodynamic (MHD) principles, utilize Lorentz forces to agitate electrolyte solutions in microchannels. Wang et al. developed a diagnostic platform that integrates magnetic bead-based DNA isolation within a microfluidic chip for the detection of methicillin-resistant Staphylococcus aureus (MRSA), achieving high specificity and a detection limit of 10^2 colony forming unit (CFU)/mL, with analysis completed in 60 min (Wang et al. 2011a).

Thermally driven microfluidics employs temperature gradients to induce fluid motion through mechanisms such as thermophoresis or thermal convection. Thermophoresis induces particle migration through temperature-driven forces, whereas convection results from variations in the fluid density due to heating (Vincent et al. 2012). Zhang et al. applied these principles to a DC-induced thermal buoyancy convection microfluidic platform to synthesize cuprous oxide (Cu_2O) nanoparticles through the convection-driven mixing of glucose and Benedict's solution. Through the modulation of the voltage and reactant concentrations, tuneable particle size was achieved, demonstrating scalable production potential (Zhang et al. 2020).

Passive microfluidic mixing devices do not utilize energy inputs; instead, they leverage geometric alterations to facilitate mixing and use pumps to drive the fluid at a constant rate (Lee et al. 2016). Among the various configurations, intersecting channels, grooved staggered herringbone patterns, hydrodynamic focusing, and serpentine designs have demonstrated notable efficacy in nanomedicine synthesis. The intersecting channel mixer (Fig. 5a) enhances diffusion through the repeated splitting and recombination of fluid streams at designated angles (Bertsch et al. 2001; Hessel et al. 2005; Lee et al. 2011). Mutlu et al. developed monodisperse porous alginate films utilizing a T-shaped microfluidic chip. The homogeneous microbubbles produced during fluid mixing ruptured on a glass substrate, resulting in the formation of porous films. A decrease in overall flow rate (from 100 to 25 µL/min) resulted in smaller bubble sizes and a lower polydispersity index, suggesting potential utility as a drug delivery vehicle (Mutlu et al. 2019). The grooved staggered herringbone micromixer (Fig. 5b) operates through chaotic advection induced by the alternating orientations of the grooves in the channel, which facilitates improved fluid folding and stretching (Stroock et al. 2002; Hessel et al. 2005; Du et al. 2010). Chiesa et al. employed a commercial herringbone chip for the synthesis of chitosan/tripolyphosphate (TPP) nanoparticles, optimizing formulation parameters to attain narrow particle sizes (~ 100–200 nm) and high

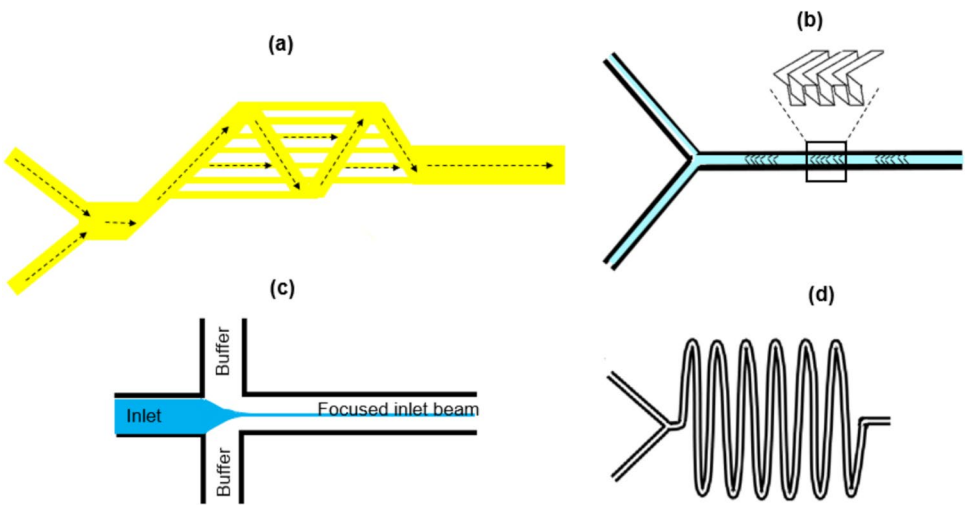


Fig. 5 Passive microfluidic mixing devices. **a** A type of intersecting microfluidic channel by He et al. **b** Grooved staggered herringbone microfluidic channel. **c** Hydrodynamic focusing microfluidic channel. **d** Serpentine microfluidic channel (He et al. 2001; Lee et al. 2011; Tóth et al. 2015; Lu et al. 2016a)

encapsulation efficiency. The nanoparticles also demonstrated low cytotoxicity, supporting their potential for drug delivery applications (Chiesa et al. 2019).

Hydrodynamic focusing (Fig. 5c) utilizes sheath flows to confine a central stream, enabling diffusion-based mixing. This method allows for control over mixing time and particle formation through the optimization of flow rate and geometry (Mijajlovic et al. 2013; Hood et al. 2014; Lu et al. 2016b; Zizzari et al. 2021). Arzi et al. synthesized nanoparticles of kinase inhibitors (imatinib, dasatinib, and tofacitinib) without excipients, utilizing T- and Y-shaped silicon microfluidic devices. The amorphous nanoparticles exhibited hydrodynamic diameters ranging from 90 to 350 nm, as verified by dynamic light scattering, scanning electron microscopy, powder X-ray diffraction, and differential scanning calorimetry analyses. Their findings highlighted the impact of flow rate and chip geometry on particle size (Arzi et al. 2021). Serpentine microfluidic channels (Fig. 5d), characterized by zigzag geometries, produce Dean vortices that improve mixing through the winding or'zigzag' pattern which enhances the mixing through the successive cycle of stretching, folding, and reorientation of the particles in the fluid as it moves along the microchannel (Liu et al. 2000; Wang et al. 2015; Shingte et al. 2022; Ebrahimi et al. 2023). Alizadeh et al. utilized this design to develop gefitinib-loaded chitosan/alginate nanoparticles. Microfluidics facilitated uniform particle size and drug loading, while the pH-responsive carriers effectively released gefitinib in acidic tumor environments, indicating enhanced therapeutic potential and diminished off-target toxicity (Alizadeh et al. 2024).

Microfluidic chip design is essential for determining fluid behavior, mixing effectiveness, and, eventually, the physicochemical properties of formulations used in nanomedicine (Alavi et al. 2024). Because of their simplicity of control, scalability, and reproducibility, continuous-flow systems such as hydrodynamic flow-focusing chips are preferred for creating highly homogeneous drug-loaded vesicles, polymeric carriers, and lipid-based nanoparticles (Valencia et al. 2010a; Tresset et al. 2013; Kawamura et al. 2020; Nguyen et al. 2020; Xu et al. 2023). When exact control over reaction time, compartmentalization, and cross-contamination minimization are required, segmented flow systems that introduce immiscible phases to form droplets or plugs are beneficial. Design decisions are further distinguished by passive and active mixing techniques (Song et al. 2006; Xiao et al. 2012; Keyon et al. 2014). Passive mixers, which rely on geometrical modifications (e.g., serpentine channels, staggered herringbone structures), are widely adopted for their simplicity and energy efficiency, making them ideal for producing nanoparticles (Chung et al. 2004; Kang and Anderson 2014; Xu et al. 2016).

In contrast, active mixers employ external forces to improve mixing, which is advantageous in high-viscosity fluids or when rapid mixing is necessary for reaction kinetics (Ober et al. 2015; Guan and Sun 2019). Ultimately, the choice of chip design is dictated by the intended biomedical application, throughput requirements, and the need for control over physicochemical properties such as particle size, polydispersity, and encapsulation efficiency. Understanding and utilizing microfluidic mixing principles is crucial for ensuring formulation quality and reproducibility, while also enabling advancements in precision nanomedicine design, personalized therapy, and scalable clinical manufacturing (Zhang et al. 2023a).

2.3 Key components and materials used in microfluidics

The selection of suitable materials is essential in the development of microfluidic devices, as microscale effects significantly influence performance, scalability, and application (Alavi et al. 2024; Lei et al. 2024; Mohammadi et al. 2024). Glass and silicon have historically been utilized for their chemical stability and thermal resistance. Various types of glass, such as borosilicate, quartz, and soda-lime, provide superior optical clarity, compatibility with solvents, and cost-effectiveness (Capretto et al. 2013; Niculescu et al. 2021b). However, fabricating glass chips is a costly and complex process that necessitates cleanroom conditions, elevated temperatures, and pressures, as well as specialized bonding techniques (Ren et al. 2013; Niculescu et al. 2021b). Hood et al. utilized a 3D glass-based hydrodynamic focusing system to synthesize liposomes by introducing alcohol-solvated lipids into an aqueous stream (Hood et al. 2014). On the other hand, silicon provides thermal stability, chemical compatibility, simplicity of microfabrication, and integration with electronics (Niculescu et al. 2021a; Mohammadi et al. 2024). Its disadvantages encompass opacity, hence restricting optical detection, fragility, and elevated cost relative to polymers. Monserrat Lopez et al. presented a silicon-on-insulator platform for droplet formation via electrostatic control, which alleviates some optical constraints (Monserrat Lopez et al. 2023).

Polymeric materials have become increasingly favored owing to their reduced cost, simplicity of manufacture, and diverse characteristics. Poly(dimethyl siloxane) (PDMS) is extensively utilized due to its superior optical transparency, elasticity, biocompatibility, and ease of integration with microvalves and pumps. Notwithstanding these benefits, PDMS absorbs organic solvents, resulting in swelling and distortion (Capretto et al. 2013; Forigua et al. 2021; Alavi et al. 2024). Chen et al. employed PDMS-based soft lithography to construct a micro-solid phase extraction (μSPE) device that interfaces with microdialysis and mass spectrometry for real-time pharmacological investigation (Chen et al. 2022b). Thermoplastics such as polylactic acid (PLA), cyclic

olefin copolymer (COC), and polymethyl methacrylate (PMMA) exhibit superior solvent resistance and mechanical rigidity compared to PDMS, along with moderate alcohol resistance, low water absorption, and cost-effectiveness. Nonetheless, their gas impermeability restricts application in prolonged cellular investigations, and adhesion to other substrates may pose difficulties (Ren et al. 2013; Giri and Tsao 2022). Ongaro et al. demonstrated the efficacy of PLA in microfluidic cell culture and organ-on-chip platforms, emphasizing its optical clarity and minimal autofluorescence (Ongaro et al. 2020).

Hybrid strategies are increasingly utilized to address the limitations of individual materials. This involves the integration of soft and hard substrates, exemplified by glass-PDMS "sandwich" structures for diaphragm valves, as well as the incorporation of electrodes (e.g. glass into polymer-based) and photocurable materials for advanced channel functionalities (Ren et al. 2013; Niculescu et al. 2021b). Material layering can modulate gas permeability and facilitate localized structural features. Horstman et al. created a 72-well PDMS–COC platform for the crystallization of drug-loaded solid forms, showcasing its effectiveness in generating high-quality drug crystals via meticulous control of seed solutions. Hybrid approaches provide customized material properties to satisfy the requirements of particular microfluidic applications in nanomedicine and other fields (Horstman et al. 2015).

In addition to material selection, fabrication techniques significantly influence the functionality and scalability of microfluidic devices. Injection molding (Fig. 6a) is a prevalent and highly automated technique suitable for mass production of thermoplastics. Although it demonstrates efficiency and a low per-unit cost, it is constrained by material compatibility issues and the high costs associated with low-resolution mold fabrication (Gharib et al. 2022; Akbari et al. 2023; Mohammadi et al. 2024). Wiedemeier et al. addressed the limitations of injection molding by integrating it with plasma coating to enhance droplet generation stability on a superhydrophobic microtopography chip composed of COC and polycarbonate (PC) (Wiedemeier et al. 2017). Utko et al. demonstrated a cost-effective nanofluidic chip utilizing thermoplastics through injection molding, validated by single-molecule DNA stretching (Utko et al. 2011).

Hot embossing (Fig. 6b) is a thermoplastic-compatible technique that provides enhanced resolution and minimizes material stress, rendering it appropriate for rapid prototyping and medium-scale production. Nonetheless, it is labor-intensive and necessitates costly apparatus (Alavi et al. 2024; Mohammadi et al. 2024). Debono et al. presented a one-step hot embossing technique for the fabrication of 3D microchannels (Debono et al. 2016). In a subsequent study, Bishnoi et al. applied this method to create Zeonor-based chips for microgel synthesis, resulting in a 40% drug release in simulated intestinal media (Bishnoi et al. 2023). Soft lithography (Fig. 6c), or replica molding, is crucial for PDMS-based microfluidics owing to its ability for high-resolution replication, optical clarity, and rapid prototyping. The limitations include reliance on a semi-cleanroom environment and restricted compatibility with PDMS solvents (Becker and Locascio 2002; Forigua et al. 2021). Xie et al. employed this method to create a PDMS chip for the production of nanoparticles albumin-bound paclitaxel (nab-PTX) intended for glioblastoma treatment. The macrophage-mediated particles demonstrated enhanced cytotoxicity relative to free drugs, underscoring the technique's potential in sophisticated drug delivery systems (Xie et al. 2024).

The selection of microfluidic fabrication methods is crucial in determining the performance, adaptability, and translational capacity of microfluidic chips in nanomedicine applications. Injection molding provides advantages for the large-scale, effective manufacture of thermoplastic chips, rendering it appropriate for the commercialization of standardized nanomedicine delivery systems and diagnostic tools; nevertheless, it is restricted by limited material compatibility and resolution (Akbari et al. 2023; Alavi et al. 2024; Mohammadi et al. 2024). Hot embossing provides superior structural integrity, facilitating the development of intricate microenvironments like organ-on-chip platforms and 3D tissue models, which are essential for drug screening and nanoparticle-cell interaction research, although it is time-consuming (Alavi et al. 2024; Mohammadi et al. 2024). Conversely, soft lithography, characterized by its exceptional flexibility and compatibility with PDMS, is particularly advantageous for pioneering nanomedicine research, encompassing the swift prototyping of drug-loaded nanoparticle production systems and microfluidic tumor models (Miranda et al. 2021; Forigua et al. 2021; Alavi et al. 2024).

The capacity for swift design iteration of devices enables precise control over nanoparticle characteristics and biological interface parameters (Bezelya et al. 2023). Moreover, hybrid fabrication techniques that combine PDMS with rigid substrates or incorporate functional components such as electrodes improve device efficacy, facilitating multifunctional platforms for nanoparticle formulation, real-time monitoring, and targeted delivery, thus broadening the scope of microfluidics in precision nanomedicine (Johnson et al. 2012; da Silva et al. 2019; Ayoib et al. 2024).

3D printing (Fig. 6d) facilitates the rapid and tailored production of microfluidic chips through the direct assembly of complex geometries layer by layer (Tiboni et al. 2021a). Techniques such as Stereolithography (SLA) and Digital Light Processing (DLP) provides high-resolution capabilities that are ideal for complex microchannel designs, rendering them advantageous for the controlled synthesis and delivery of nanomedicines (Bahati et al. 2023; Alparslan

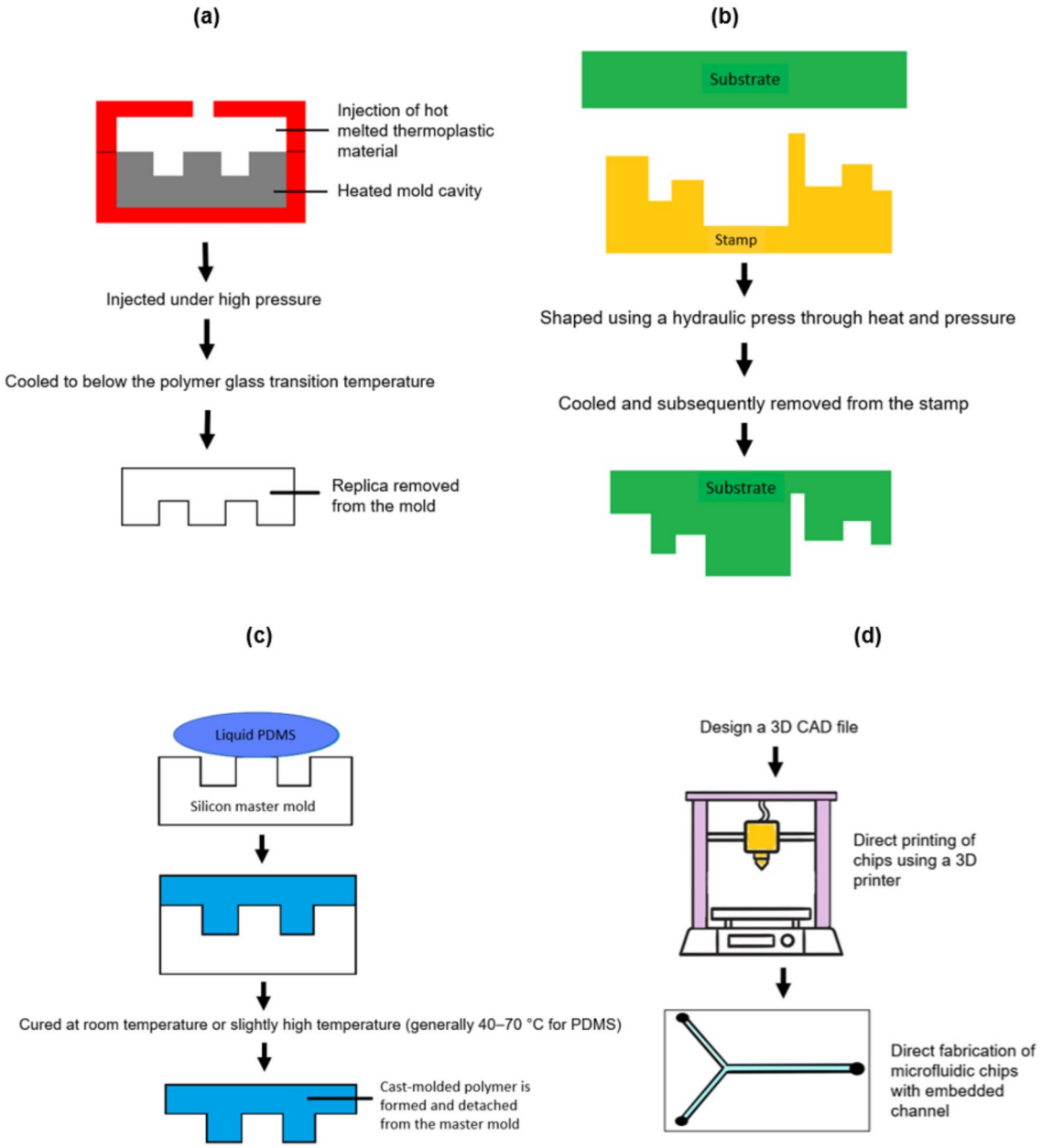


Fig. 6 Common microfluidic fabrication techniques. **a** Injection molding. **b** Hot embossing. **c** Soft lithography. **d** 3D printing (Pihl et al. 2005; Forigua et al. 2021; Ahmed et al. 2022; Akbari et al. 2023; Alavi et al. 2024; Mohammadi et al. 2024)

and Bayraktar 2025). For a more comprehensive discussion, please refer to Sect. 5.2.

3 Applications for various nanomedicines

3.1 Lipid-based nanomedicine

Lipid-based nanomedicines such as liposomes, lipid nanoparticles (LNP), and extracellular vesicles (EVs) are recognized as one of the most clinically accepted nanomedicines approved by the regulatory agencies for disease treatment, accounting for more than 30% of the marketed nanomedicines (Farjadian et al. 2019; Chen et al. 2023; Agha et al. 2023; Mohammadi et al. 2024; Souto et al. 2024; Biscaia-Caleiras et al. 2024). Lipid-based nanomedicines have gained attention worldwide after the approval of Pfizer's (Comirnaty®) and Moderna's (Spikevax®) Covid-19 mRNA vaccines by the US FDA (Chen et al. 2023; Souto et al. 2024). With the first clinically approved nanomedicine, Doxil® (PEGylated liposomal doxorubicin) in 1995 by the US FDA (Farjadian et al. 2019; Yan et al. 2020b).

Table 1 Summary of various-based nanomedicine prepared using different types of microfluidic platforms

Type of nanomedicine	Main material	Drug	Microfluidic chips		Microfluidic parameters		Target/application	Reference
			Design	Material	Flow rate ratio (aqueous: organic)	Total flow rate		
Lipid-based nanomedicine	Exosome	Doxorubicin Hydrochloride	Multi-parallel	PDMS	–	8 µL/min	Non-small cell lung cancer	(Hao et al. 2021)
	DSPC, DOPC, DOPE, DOPS, SM, cholesterol	Small interfering RNA	Chaotic mixer	PDMS-glass	2:1, 3:1, and 9:1	100 and 500 µL/min	Gene therapy	(Kimura et al. 2021)
	PC, cholesterol	Propofol	Herringbone	–	1:1 and 5:1	0.5–6 mL/min	-	(Kastner et al. 2015)
	HSPC, cholesterol, PEG-DSPE, and DODAP	Small interfering RNA	Staggered herringbone	–	1:5	1 – 3 mL/min	Gene therapy	(Terada et al. 2021)
	MC3, DSPC, cholesterol, PEG-DMG	mRNA	Y-shaped chaotic	PDMS	3:1	0.5 mL/min	Cancer immunotherapy	(Kimura et al. 2018; Sasaki et al. 2022)
	DOTAP, DC-Chol, DOPE, DOPC	pDNA	Y-shape staggered herringbone	–	3:1	2 mL/min	Tumor treatment	(Cui et al. 2022)
	DSPE, PEG, maleimide	Paclitaxel	3-Dimensional hydrodynamic flow-focusing	Glass	5:1	60 ml/min	Tumor treatment	(Arduino et al. 2021)
	PC, DMPC, DPPC, DSPC, cholesterol	Ovalbumin	Y-shape staggered herringbone	–	1:1, 3:1 and 5:1	5–20 mL/min	–	(Forbes et al. 2019)

Table 1 (continued)

Type of nanomedicine	Main material	Drug	Microfluidic chips		Microfluidic parameters		Target/application	Reference
			Design	Material	Flow rate ratio (aqueous: organic)	Total flow rate		
Polymer-based nanomedicine	Chitosan	β-Galactosidase, small interfering RNA, mRNA	Serpentine	Polycarbonate	2.3:1 and 3:1	0.5 and 0.6 mL/min	Gene knockdown	(Greco et al. 2023)
	PLGA-PEG	Diclofenac	H-interface and 4-way linear connector	Glass	1: 0.1	550 µL/min	Anti-inflammatory	(Gimondi et al. 2022)
	Alginate	TGF-β3	T-junction with hydrodynamic flow focusing	PDMS	1: 0.01 – 1: 0.2	–	Chondrogenic differentiation of mesenchymal stem cells	(Mahmoudi et al. 2020)
	Shellac	Curcumin	3-Dimensional hydrodynamic flow-focusing	Polyethylene	–	10 mL/min	Cancer therapy	(Baby et al. 2021)
	PLGA-PEG	–	3-Dimensional hydrodynamic flow-focusing	PDMS	33:1, 14:1,	51.5–428 µL/min	–	(Lim et al. 2013)
	HDPE	–	Y-shape staggered herringbone	–	1:1, 3:1	12 mL/min	Esterase/oxidation study	(Hong et al. 2018)
	PLGA, PMMA	R18/F5-TPB	Cross-shaped multi lamination, split and recombine, herringbone, impact-jet	Zeonor, glass	9:1	–	–	(Chen et al. 2022a)
Inorganic nanomedicine	Silver	*Ipomea quamoclit* L	Y-shaped serpentine	PDMS	1:1	–	Antimicrobial	(Magdalene et al. 2021)
	Mesoporous silica	Doxorubicin and Paclitaxel	3D coaxial flows	Glass	1:1	2–40 mL/h	Breast cancer	(Yan et al. 2020a)
	Iron oxide	Dextran	Capillary-based droplet	Glass-silicon-PTFE	–	–	MRI	(Kumar et al. 2012)
	Zinc nitrate hexahydrate	Doxorubicin	T-junction	PDMS	–	100 mL/min	Cancer therapy	(Hu et al. 2018)
	Gold	–	T-junction droplet	PDMS	10:1, 13:1	550–2150 µL/hr	–	(Abalde-Cela et al. 2018)

Table 1 (continued)

Type of nanomedicine	Main material	Drug	Microfluidic chips		Microfluidic parameters		Target/application	Reference
			Design	Material	Flow rate ratio (aqueous: organic)	Total flow rate		
Hybrid nanomedicine	Eudragit E100 polymer, DC-cholesterol	pDNA	bifurcating (toroidal)	COP	3:1 and 5:1	6 mL/min	in vitro DNA transfection	(Santhanes et al. 2024)
	Tannic acid, copolymers	Doxorubicin	Hydrodynamic flow-focusing	Glass	–	–	Anti-proliferative and anti-cancer	(Brzeziński et al. 2021)
	Silver, poliglusam	*Calotropis gigantea* extract	Droplet segmented flow	PMMA	1:1.5 and 1:3	–	Ductal carcinoma	(Aftab et al. 2023)
	PLGA, cholesterol	–	–	–	1:1–5:1	10 mL/min	Brain study	(Ottonelli et al. 2021a)
	PLGA, lecithin, PEG, quantum dots	–	Hydrodynamic flow-focusing	PDMS-glass	5:1–10:1	55–60 µL/min	–	(Valencia et al. 2010b)
		Rifampicin	Herringbone-patterned Multi-inlet vortex	PDMS	–	12 mL/min	Antibacterial	(Bokare et al. 2019)

PDMS Polydimethylsiloxane, *DSPC* 1,2-distearoyl-sn-glycero-3-phosphocholine, *DOPC* 1,2-dioleoyl-sn-glycero-3-phosphocholine, *DOPE* 1,2-dioleoyl-snglycero-3-phosphoethanolamine, *DOPS* 1,2-dioleoyl-sn-glycero-3-phospho-L-serine (sodium salt), *SM* sphingomyelin (chicken egg); *RNA* ribonucleic acid, *PC* egg phosphatidylcholine, *HSPC* hydrogenated soy phosphatidylcholine, *PEG-DSPE* 1,2-distearoyl-sn-glycero3-phosphoethanol amine-N-[methoxy-(polyethylene glycol)-2000] (ammonium salt), *DODAP* 1,2-dioleoyl-3-dimethylammonium propane, *MC3* DLin-MC3-DMA, *PEG-DMG* 1,2-dimirystoyl-rac-glycero, methoxyethyleneglycol 2000 ether; *mRNA* messenger ribonucleic acid, *DOTAP* 1,2-Dioleoyl-3-trimethyl-ammonium-propane, *DC-Chol* (3β-[N-(N′,N′-dimethyl-aminoethane)-carbamoyl])-cholesterol; *pDNA* plasmid deoxyribonucleic acid, *PEG* poly(ethylene glycol), *DMPC* 1,2-dimyristoyl-sn-glycero-3-phosphocholine, *DPPC* 1,2-dipalmitoyl-sn-glycero-3-phosphocholine, *PLGA-PEG* poly(lactide-co-glycolide)-block-poly(ethylene glycol), *TGF-β3* transforming growth factor beta 3; High-density polyethylene (HDPE), *PLGA* poly(D-L-lactide-co-glycolide), *PMMA* poly(methyl methacrylate-comethacrylic acid), *DHA* dihydroartemisinin, *R18/F5-TPB* rhodamine B octadecyl ester perchlorate and lithium tetrakis(pentafluorophenyl)borate ethyl etherate, *PTFE* polytetrafluoroethylene, *MRI* magnetic resonance imaging, *COP* cyclic olefin copolymer, *PMMA* polymethyl methacrylate

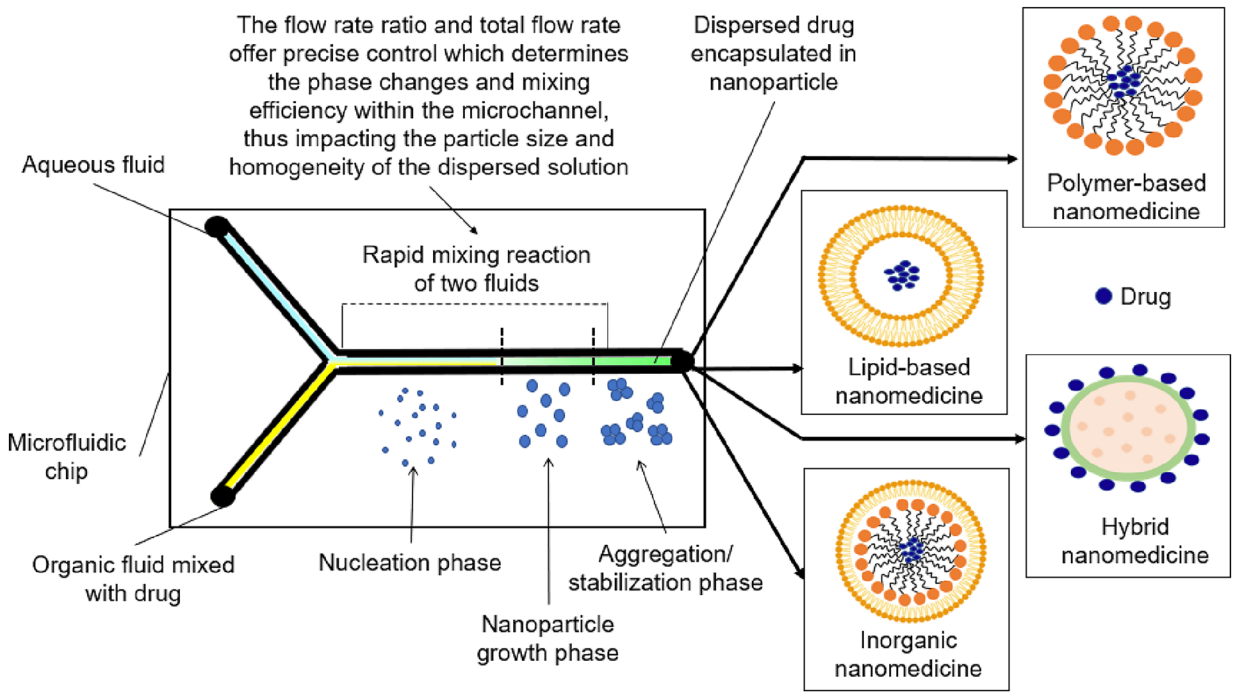


Fig. 7 Schematic illustration of microfluidic-assisted controlled synthesis of nanomedicine. (Aghajani et al. 2013; Liu et al. 2022)

Table 1 tabulated some studies on the synthesis of lipid-based nanomedicine prepared by microfluidics. The use of different lipid compositions and microfluidic chip designs with precise control over formulation conditions underscores the ability to produce nanoparticles with varied characteristics to create tailored nanoparticles for specific medical applications.

Liposomes are made up of one (unilamellar) or multilayer (multilamellar) membrane-enclosed spherical vesicles composed of phospholipid, cholesterol, and other lipids, which separates the inner aqueous core from the external environment (Gimondi et al. 2022; Mahmoudi et al. 2020; Lim et al. 2013). Liposomal nanomedicine is extensively investigated due to its favorable product stability, biocompatibility, biodegradability, controlled release features, and its ability to deliver both hydrophilic (encapsulation within the aqueous core) and hydrophobic drugs (encapsulated in the lipid bilayer) (Chen et al. 2023; Agha et al. 2023; Mohammadi et al. 2024; Souto et al. 2024; Biscaia-Caleiras et al. 2024). Active targeting due to the modifiable surface of liposomes allows ligand binding at the surface, which promotes advantages relevant to the nanomedicine application (Yan et al. 2020b; Chen et al. 2023).

LNP, micelle-like nanoparticles formed by ionizable lipids and nucleic acids, are another subclass of lipid-based nanomedicine (Chen et al. 2023; Mehraji and DeVoe 2024). The solid lipid nanoparticles (SLNPs) consist of a lipid or surfactant layer encircling the solid lipid core, while the nanostructured lipid carriers (NLCs) comprise a combination of both solid and liquid lipids (El Moukhtari et al. 2021; Souto et al. 2024). This subclass offers several advantages, such as enabling higher drug-loading for hydrophobic drugs, improving colloidal stability, enhancing oral drug absorption by carrying the drug across the gastrointestinal barrier, and being a promising non-viral nanocarrier for delivering genetic material (El Moukhtari et al. 2021; Chen et al. 2023; Mohammadi et al. 2024; Souto et al. 2024). LNPs most notable application is their robust capability to deliver various nucleic acid molecules of different sizes of nucleotides (e.g. RNA, DNA, chromosomes) to cells for the treatment of various acute and chronic diseases (Zhao and Huang 2014; Pozzi and Caracciolo 2023).

EVs are recognized as the next generation promising nanomedicine due to their inherent bioactive components, which offer several advantages such as immune escape, biobarrier crossing, incorporation of hydrophobic drugs, and cell-targeting (Herrmann et al. 2021; Chen et al. 2023). It is a heterogeneous group of small, lipid bilayer nanoparticles with a diameter ranging in size from 20 to 10,000 nm, acting as key mediators of intracellular communications, maintaining cellular homeostasis, and the transfer of functional biomolecules (Herrmann et al. 2021; Phillips et al. 2021; Chen et al. 2023; Jeppesen et al. 2023). Microfluidics plays an important role in ensuring the drug-loading capabilities of lipid-based nanomedicine and enhancing its mixing efficiency, which produces a homogeneous mixture

(Mohammadi et al. 2024). Table 1 tabulates studies and Fig. 7 illustrates the synthesis of lipid-based nanomedicine prepared by microfluidics.

3.2 Polymer-based nanomedicine

Natural and synthetic polymeric nanomedicine has made significant progress in the application of drug delivery (Farjadian et al. 2019; Agha et al. 2023; Mohammadi et al. 2024). It has attracted considerable interest due to its advantages of becoming a vehicle for the controlled release of drugs, its ability of drugs and other molecules with biological activity against the environment, bioavailability, and therapeutic index improvement, and a large specific surface area to ease the active targeting and loading of model drugs (Han et al. 2018; Zielinska et al. 2020; Mohammadi et al. 2024). Polymer-based nanomedicines can be divided into two types, which are nanocapsules and nanospheres, which differ based on their morphology (Zielinska et al. 2020; Mohammadi et al. 2024).

A spherical polymeric matrix known as nanocapsules (reservoir system) is made of an oily core surrounded by a polymeric shell that regulates the drug release from the core, which can be employed as a vehicle for different bioactive compounds. Nanospheres (matrix system), on the other hand, is a continuous polymeric network where the drug or bioactive materials are retained inside a central aqueous core or absorbed onto the surface (Zielinska et al. 2020; Mohammadi et al. 2024). Table 1 tabulates studies and Fig. 7 illustrates the synthesis of polymer-based nanomedicine prepared by microfluidics.

As mentioned above, polymeric nanomedicine can be synthesized by using both natural and synthetic polymers. Some of the natural polymers that are used are chitosan, gelatin, hyaluronic acid, starch, and cellulose while the synthetic polymers are such as poly(lactide-co-glycolide) (PLGA), poly(lactic acid) (PLA), polyanhydrides, polycaprolactone (PCL), polyurethane (PU), and polyvinyl alcohol (Han et al. 2018; Agha et al. 2023). However, PLGA and chitosan are the most commonly used polymers to prepare polymer-based nanomedicine.

PLGA is an FDA-approved biodegradable and biocompatible polymer that is widely used in nanocapsules and nanospheres preparation of lipophilic and hydrophilic controlled drug release approaches. Examples include chemotherapeutics, antibiotics, fertility-regulating hormones, vaccines, and other drugs (Han et al. 2018; Maged et al. 2022). Its adjustable degradation rate is also crucial to ensure the controlled drug release over a predetermined period, and it is also widely used as a scaffolding material for regenerative medicine (Zhou et al. 2021; Alsaab et al. 2022). The droplet microfluidic preparation method can be controlled independently through shear stress of fluids in immiscible phases with predetermined flow ratios, which leads to precise control of the formation of the nanomedicine (Zhou et al. 2021).

In polymer-based nanoparticles, chitosan has been applied as an adjuvant due to its biocompatibility and biodegradability characteristics. Additionally, chitosan can interact electrostatically with a negatively charged protein or plasmid DNA, forming a composite that prevents it from enzymatic degradation (Han et al. 2018; Frigaard et al. 2022). Chitosan nanomedicine has received wide attention due to its mucoadhesive properties, ease of modification, positive surface charge, stability in biological fluids, and affinity for cancer-specific biomarkers. Hence, it serves as a promising agent for the target delivery of drugs, adjuvants, and carriers of vaccines (Frigaard et al. 2022; Grewal and Salar 2024). However, there are also some limitations to this polymer, such as having a degree of swelling, low thermal stability, and low solubility. Hence, chitosan derivatives were synthesized and modified with certain functional groups obtained through acylation, quaternization, and carboxymethylation processes to improve solubility and reduce toxicity effects (Han et al. 2018; Grewal and Salar 2024).

3.3 Development of inorganic nanomedicine

Inorganic nanomedicine refers to the use of materials such as metal nanoparticles, silica nanoparticles, and quantum dots as a drug carrier and imaging contrast agent, as it possesses unique magnetic, optical, electrical, and photothermal/radioactive characteristics and also exhibits non-toxicity, biocompatibility, hydrophilicity, and exceptional stability (Nasirzadeh et al. 2016; Agha et al. 2023). Gold nanoparticles are one of the most studied metal nanoparticles as it can be used in all areas of medical applications such as diagnostics, therapy, prevention, and hygiene due to their attributes such as water solubility, surface charge, and specific and unspecific recognition (Arvizo et al. 2010; Dykman and Khlebtsov 2011; Agha et al. 2023). Other than gold, silver nanoparticles have also been greatly studied due to their similar characteristics to gold, such as optical, electrical, and thermal, high electrical conductivity, and biological properties, which are used for several applications such as antibacterial drugs and anticancer drugs (Zhang et al. 2016). Table 1 tabulates studies and Fig. 7 illustrates the synthesis of inorganic nanomedicine prepared by microfluidics.

The types of silica nanoparticles are non-porous silica nanoparticles (NSNs), which are the most important type of nanoparticle, and mesoporous silica nanoparticles (MSNs), which are the most meticulously researched (Nasirzadeh et al. 2016; Li et al. 2021; Huang et al. 2022; Lee et al. 2023; Mohammadi et al. 2024). NSNs are a type of amorphous silica nanoparticle with highly controllable size and shape, have no special structural shape, and a lipophilic surface with ease of surface modification (Nasirzadeh et al. 2016;

Huang et al. 2022). MSNs have attracted attention due to their high porosity and morphology (size and shape), high biocompatibility, easy surface modification, and self-adjuvanticity, which is significant for the application of nanomedicine, particularly in the drug delivery system (Nasirzadeh et al. 2016; Li et al. 2021; Lee et al. 2023; Mohammadi et al. 2024).

Semiconductor quantum dots are fluorescent semiconductor crystals made of different types of elements (typically synthesized from groups III-V and II-VI elements of the periodic table), which are used in various applications such as bioimaging, detection, and drug delivery. Due to their unique intrinsic features such as high brightness, wide and continuous absorption spectra enabling simultaneous excitation of multiple fluorescence colors, narrow emission spectra, high resistance to photobleaching, high fluorescence quantum yield, and small particle size which makes it a distinctive type of fluorophore that can be utilized in comparison with the conventional organic fluorophore (Volkov 2015; Nasirzadeh et al. 2016; Hunt et al. 2021; Abdellatif et al. 2022; Mohammadi et al. 2024).

3.4 Hybrid nanomedicine formulations

Hybrid nanomedicine consists of a combination of two or more types of nanocomponents, which can be further classified into three groups which are organic/organic nanoparticles, organic/inorganic nanoparticles, and inorganic/inorganic nanoparticles (He et al. 2015; Thorat and Bauer 2020; Rajana et al. 2022; Agha et al. 2023). The capability to integrate both organic and inorganic nanoparticles can bring out the beneficial characteristics of both molecules for the selected applications (He et al. 2015; Thorat and Bauer 2020). Nanoscale metal–organic frameworks (NMOFs) are a class of nanoparticles built from metal ions or clusters and bridging ligands, explored for various applications, which include acting as a potential carrier for the delivery of anticancer drugs (He et al. 2015). Magnetoliposomes, on the other hand, consist of a magnetic nanoparticle encapsulated in the lipid bilayers of liposomes, which are developed for the application of drug delivery, MRI imaging, and controlled-release property hyperthermia (Tomitaka et al. 2019; Agha et al. 2023). Table 1 tabulates studies and Fig. 7 illustrates the synthesis of hybrid nanomedicine prepared by microfluidics.

Nano-theranostics involves the merging of therapeutics and modern diagnostic tools into a single agent by nanoparticles, which include metallic nanoparticles, gold nanoparticles, lipid-based nanomaterials, magnetic nanoparticles, mesoporous silica nanoparticles, and quantum dots (Ladju et al. 2022). It maximizes the inherent potential of nanomedicine with options of adjunct treatment, which brings several advantages such as guided imaging, an early diagnostic tool, targeted therapy, a drug delivery agent, efficient vascular perfusion, and permeability to nanocarriers and drugs, and real-time monitoring of patient response towards the drug (Thorat and Bauer 2020; Ladju et al. 2022).

In one study by Ottonelli et al., the optimization of hybrid nanomedicine of PLGA-cholesterol stabilized with Pluronic® F68 was performed using the microfluidic device from a formulation prepared using a conventional nanoprecipitation method. The outcomes demonstrated that the direct translation of the conventional to a microfluidic method requires extensive work and time to determine the optimal device setting and formulation combination to achieve reproducible and desirable outcomes of the nanomedicine (Ottonelli et al. 2021b). In another study, Zeolitic Imidazolate Framework (ZIF) nanocarrier for the delivery of doxorubicin (DOX) and hydrophobic photosensitizer IR780 loaded into the spermine-modified acetalated dextran (SAD) shell was prepared using microfluidics. Both results from the in vitro and in vivo study demonstrate that it is effective for synergistic dual-mode chemo-photodynamic therapy against cancers with controllable production of the nanocarrier (Shen et al. 2020).

In another study by Hong et al., a curcumin-loaded enzyme-targeted hybrid nanomedicine was prepared using a microfluidic device and tested for its antitumor activity (Hong et al. 2021). The prepared nanomedicine demonstrated dose-dependent tumor cell growth inhibitory activity against the human malignant glioblastoma multiforme, U251 cells. Similar findings (inhibitory tumor growth activity of up to 78.63%) were also observed in the in vivo study performed on the U251 tumor-bearing mice (Hong et al. 2021). Yang et al. also studied the artesunate-loaded polydopamine/iron nanocomplexes coated with fibronectin synthesized using microfluidics (Yang et al. 2023). This developed nanocomplex serves as a promising theranostics nanoplatform for precision T_1 magnetic resonance imaging-guided tumor combination therapy comprising chemotherapy, chemodynamic therapy, and immune therapy due to its fibronectin-mediated tumor targeting and pH-responsive enhancement of r_1 relaxivity in the tumor microenvironment (Yang et al. 2023).

4 Utilization of microfluidics in nanomedicine: benefits and challenges

4.1 Benefits of microfluidics in nanomedicine preparation

As discussed earlier, the conventional method of nanomedicine preparation has many limitations, which may require controllable, reproducible, and scale-up preparation technologies (Shan et al. 2022). Microfluidic systems offer several

advantages, such as the precision control of the molecule's particle size and distribution. This is due to the microchannels' high surface area to volume ratio and the control of flow and mixing conditions in microfluidics (Yu et al. 2009; Shrimal et al. 2020; Maged et al. 2022). In the conventional method, the produced nanomedicine may suffer from particle aggregations and separation due to its wide particle size distribution (Maged et al. 2022).

In one study, a conventional co-processing batch-flow method versus microfluidic was used to prepare magnetic chitosan nanoparticles loaded with cisplatin. Results demonstrated that the conventionally prepared nanoparticles produce a larger size of 423 ± 53 nm with a polydispersity index (PDI) of 0.384, while microfluidic-prepared nanoparticles produce particles of 104 ± 15 nm with a PDI of 0.029. The particle size and distribution are larger in the conventional method compared to the microfluidic method due to the turbulent mixing, lack of proper, rapid, and homogeneous mixing which is highly dependent on the user's skill, and the size and distribution are also influenced by the flow-focusing state and flow rate ratio which is controlled in the microfluidic system (Siavashy et al. 2021).

Other than the precise control of particle size and their distribution, microfluidics also offers higher drug loading and encapsulation efficiency (Xu et al. 2017). The excellence of drug loading (DL) and entrapment efficiency (EE) of the microfluidic system due to precise control to prepare a homogeneous mixture and slow transport of molecules (Fabozzi et al. 2023) can be observed in one study conducted by Vu et al. in the design of the antioxidant, rutin-loaded poly(lactic-coglycolic acid) nanoparticles prepared using both, conventional single emulsion evaporation method and microfluidics. The produced nanomedicines were analyzed for multiple characteristics, including DL and EE in comparison. The microfluidic-prepared nanoparticle showed a higher EE of $34 \pm 2\%$ and higher DL of $0.015 \pm 0.001\%$ compared to those in the bulk method (EE of $27 \pm 1\%$ and DL of $0.009 \pm 0.001\%$) (Vu et al. 2019).

Generally, apart from the advantages discussed above, microfluidics also offers a promising, reproducible production of nanoparticles. The conventional method of producing nanomedicine remains technically challenging due to its inability to control the physicochemical properties of each synthesis batch (Fabozzi et al. 2023). This can be overcome using microfluidics for the preparation due to its shorter mixing time in the millisecond and microsecond range, which can result in a more homogeneous nanomedicine preparation by reducing the aggregation of its precursors (Kim and Langer 2015).

The physicochemical properties of the nanomedicine play a critical role in determining the interaction of the nanomedicine and the targeted cells in the body, and in the determination of the nanomedicine's biodistribution and the pharmacokinetics of the drugs, which can impact the optimal therapeutic efficacy of the drug in the body (Wang et al. 2011b). Microfluidics facilitates the production of nanomedicines with highly controlled sizes and narrow size distributions, which is crucial for their biological behavior, including cellular uptake and biodistribution. Monodisperse nanomedicine ensures its consistency and reproducibility and, subsequently, its efficacy (Trinh 2023; Gimondi et al. 2023). Other than that, microfluidics also enables the integration of surface modifications in nanomedicine synthesis. Integrating functional groups and coatings enhances the nanomedicine biocompatibility and target specificity, which are essential for targeted drug delivery systems (Fabozzi et al. 2023; Gimondi et al. 2023). In a nutshell, the physicochemical properties of nanomedicines are important to ensure safe, good-quality, and effective medicines are provided to the patient.

4.2 Challenges in microfluidic nanomedicine development

Microfluidic devices, although providing a lot of advantages, also face some challenges. One of the leading obstacles in the microfluidic device is the clogging of the microchannels due to the deposition and assembly of particles (Yoon et al. 2016; Dressaire and Sauret 2016). Due to the narrow construction of the microchannels, the solid particles that pass through them may cause clogging, which is due to the sieving, bridging, and aggregation of particles (Dressaire and Sauret 2016; Bakhtiari and Kähler 2024). Sieving is the blockage of hard and soft particles based on their size, which contributes to the separation of particles in the filtration process (Sauret et al. 2014; Dressaire and Sauret 2016). Clogging occurs when the diameter of the microchannel is equal to or smaller than the particle diameter, and this usually occurs at the inlet of the microchannel or constriction through direct hydrodynamic transport (Sauret et al. 2014; Dressaire and Sauret 2016).

Clogging can also occur when the diameter of the particle is smaller than the diameter of the microchannel, which may be due to the high viscosity of the fluid passing through the microchannels or the steric effects (Dressaire and Sauret 2016). Converging flow and viscous fluid form bridge-like structures made up of typically 2–10 particles that block the cross-section of the channel. However, this is intermittent as the arch can break under flow fluctuations (Dressaire and Sauret 2016). Other than the two types of clogging described above, the self-assembly of particles into clusters, aggregation, can occur in the bulk of a suspension or on a fluid interface due to the van der Waals forces when the particles are near to each other (Dressaire and Sauret 2016).

Although the preparation of nanomedicine using microfluidics faces the clogging obstacle, anti-clogging methods

may be employed to overcome this limitation. In one study conducted by Bakhtiari and Kähler (Bakhtiari and Kähler 2024), they introduced a fast-3D-flow perturbation of microbubble streaming, which induces shear stress via modulation of excitation frequency and amplitude. A varied velocity flow field is introduced at the constricted site, which influences the particles to flow through at a different speed and direction, reducing the likelihood of arch formation. On the pre-existing arch, the varied velocity gradient will relocate the blocked particle in different directions, which will unclog the microchannel (Bakhtiari and Kähler 2024).

Other than the clogging challenge, the manufacturing of nanomedicine in the pharmaceutical industry under a Good Manufacturing Practice (GMP) facility also presents challenges (Agrahari and Agrahari 2018; Liu and Meng 2021; Gimondi et al. 2023). This is because of the limitation of data related to the scaling up of nanomedicine, and also the low production throughput due to the low flow rate and small reaction volume, which may be difficult when working at a larger batch volume (Agrahari and Agrahari 2018; Gimondi et al. 2023). As process optimization on various parameters may vary with the batch volume, this meticulous process may be complex and time-consuming to ensure reproducible results and quality of the nanomedicine from the lab and subsequently, technology transfer to the production floor (Gimondi et al. 2023).

To address this challenge, a few approaches were explored. One of the most common approaches suggested is the parallelization of microchannels where multiple devices are in simultaneous processing, enabling high throughput without compromising their precision (Gimondi et al. 2023). On this topic, a parallelized microfluidic device that features 128 mixing microchannels operating simultaneously was able to achieve > 100-fold production rate while maintaining a desirable physicochemical property of the nanoparticle, which includes the reproducible synthesis of small < 100 nm nanoparticles (Shepherd et al. 2021). A continuous flow microfluidic system is also another approach for the scaling production of nanomedicine. It is commonly used for liposome-based nanoparticle production via the hydrodynamic flow focusing method controlled by the molecular diffusion of interface substances between miscible liquids (Zhang et al. 2023a).

Apart from the challenges faced during the manufacture of nanomedicine, the regulatory standards in the examination of nanomedicine as a unique category of therapeutic agent are inadequate (Desai 2012). Over the decade, several regulatory agencies have approved nanomedicines for commercialization and transformation has been made in nanomedicine regulation, whereby these agencies, such as the United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA), have provided some general and scientific regulations to the nanomedicine developers and clarified some regulatory expectations for their marketing authorization application (EMA; FDA; Colombo et al. 2018; Farjadian et al. 2019).

Some of the regulatory expectations revolve around the basic principles that guide the regulatory agencies toward public safety due to the complexity of the product (Desai 2012; Agrahari and Hiremath 2017). The characterization of the products that are essential for the nanomedicine's activity and safety, such as the particle size distribution, surface charge and functionality, drug loading, solubility, and porosity, should be adequately addressed. In vitro and in vivo evaluations of nanomedicine obtained from the preclinical models are not always extrapolatable to humans due to differences in the biological systems of different species. Hence, the selection of preclinical screening techniques and animal or cell models is critical for successful clinical translation (Desai 2012; Agrahari and Hiremath 2017). Thus, it is important to ensure the expectations are thoroughly addressed for a successful commercialization of nanomedicine.

5 Emerging trends and future opportunities in microfluidic nanomedicine

5.1 Innovations in microfluidics and integration with advanced manufacturing techniques

Innovations and advancements in nanomedicine preparation have been made possible with microfluidic devices. However, due to the lack of industry standards on the microfluidic design, highly trained specialists are required (Wu et al. 2023). In recent years, modular microfluidics has gained much attention compared to the common monolithic system due to its advantages, such as the standardized and customizable independent modules that can be integrated into a whole, complex platform, its flexibility, and ease of use (Lai et al. 2022; Wu et al. 2023). Modular microfluidics are made of different module libraries (e.g. microvalve, pump, mixer, separator, droplet generator, gradient generator), different connection methods (e.g. LEGO®, tubing, luer, o-ring/gasket, adhesive, plasma) and biological application (e.g. cancer cell isolation, polymerase chain reaction, organs-on-a-chip, biomarker research, particle synthesis) to assemble the customized system for the preparation of nanomedicine (Wu et al. 2023).

Electrowetting on Dielectric (EWOD), a type of digital microfluidics, is one of the numerous prospects in the advancement of pharmaceutical research and has contributed to the development of lab-on-chip multifunctional technology (Barman et al. 2020; Rui et al. 2020). A typical system consists of electrodes etched by lithography on a substrate

covered in a thin hydrophobic and dielectric layer with a droplet of liquid placed in the intermediate position, which leads to the generation of an electric field and thus, switching a droplet between beading and wetting (Barman et al. 2020; Li and Kim 2020; Torabinia et al. 2021). The key advantages of this device are faster reaction time, precise control over droplet size, higher selectivity, and being free from high pressure and clogging of the microchannel (Barman et al. 2020; Torabinia et al. 2021).

5.2 Integration with advanced manufacturing techniques

Conventional fabrication techniques are associated with disadvantages such as time-consuming, multistep processing, and expensive facilities required (Ballacchino et al. 2021b; Sommonte et al. 2023). 3D printing (Fig. 6d) is gaining vast attention and acts as an alternative method for the fabrication of microfluidic devices (Tiboni et al. 2021a; Sommonte et al. 2023; Su et al. 2023). Several printing methods, such as extrusion-based printing, fused deposition modeling, selective laser sintering, digital light processing, material jetting, and stereolithography, have been used for the fabrication of the device each offering specific advantages and limitations depending on resolution, material compatibility, and intended application (Prabhakar et al. 2021; Su et al. 2023).

Multiple printing modalities are employed, each with unique capabilities and constraints. For example, Fused Deposition Modeling (FDM) extrudes thermoplastic filaments layer-by-layer and is limited by low resolution (~ 100 µm) and poor transparency, making it suboptimal for intricate nanomedicine microchannels (Kotz et al. 2020; Quero et al. 2021; Rodríguez et al. 2023). In contrast, SLA and DLP use photopolymerization of resin via light projection (laser or digital mask, respectively), allowing for higher resolution features ($\leq$ 100 µm) and smooth surface finishes ideal for precise nanomedicine mixing and nanoparticle fabrication. SLA and DLP also support materials with good biocompatibility and optical transparency, making them particularly relevant for organ-on-chip platforms, and nanomedicine delivery systems such as hydrogels (Bahati et al. 2023; Alparslan and Bayraktar 2025).

In comparison to conventional PDMS-based soft lithography, 3D printing presents several significant advantages for the fabrication of microfluidic devices. The capabilities encompass the construction of complex 3D microchannels, enhanced resistance to organic solvents, expedited and more consistent prototyping, exhibit greater scalability and robustness, and the seamless integration of functional components such as valves or optical sensors (Li et al. 2024; Xu et al. 2025). Recent studies have utilized these advantages to develop lab-on-a-chip systems (Wang et al. 2021), solvent-resistant drug delivery platforms (Tiboni et al. 2021b), and portable nucleic acid extraction units (Kalathil Balakrishnan et al. 2023; Kibar et al. 2024).

In the study conducted by Ongoren et al., a 3D printed microfluidics printed using the stereolithography method was used to prepare Melatonin-loaded self-nanoemulsifying drug delivery systems (SNEDDS) for ocular administration. The nanomedicine has been successfully prepared and optimized using the fabricated T-shaped toroidal microfluidic chip, which demonstrates the potential of microfluidic chips in yielding a high-quality product (Ongoren et al. 2024). In another study, a digital light-processing printed microfluidic device is compared to the conventional thin film hydration-sonication approach for the preparation of exosome-like Genistein-loaded nanoparticles. It was demonstrated that the complex biomimetic liposomes that contain a higher content of cholesterol are superior when prepared using the 3D-printed microfluidic device due to their lower polydispersity index (Tsakiri et al. 2024). These cases demonstrate that 3D printing facilitates the creation of intricate internal geometries and enhances the regulation of nanomedicine characteristics (Jain et al. 2021). Furthermore, the study by hybrid methodologies that integrate 3D-printed molds with PDMS casting has demonstrated the ability to surmount the constraints of both conventional soft lithography and direct 3D printing, providing a quick, economical, and biocompatible option for the fabrication of intricate microfluidic devices (Abbed et al. 2025).

Automated microfluidics represents the next evolution in this domain, supporting high-throughput and scalable nanomedicine production. In the study conducted by Langer et al., fully automated liquid-handling robots are paired with a 3D-printed droplet microfluidic for rapid production and cell spheroids recovery. The automated device was then tested on scaffold-free HEK, RT4, and A-431 cell spheroids, allowing for the generation of more than 17,000 spheroids in a single 12-min run, whereby the system has a maximum throughput of 85,000 spheroids per hour, an output scale that is unfeasible with PDMS. The advancements indicate that SLA/DLP-based microfluidics offer both resolution and material benefits, while also facilitating automated, scalable fabrication suitable for high-throughput nanomedicine applications (Langer and Joensson 2020). Ongoing developments in fabrication techniques, printable materials, and automated integration highlight a promising future for microfluidics in nanomedicine.

5.3 Clinical translation and ongoing trials of microfluidic nanomedicine

Despite the absence of FDA approval or registered clinical studies for microfluidically manufactured nanomedicine, microfluidic systems are progressively exhibiting translational potential in relevant fields of nanomedicine. A notable

example of microfluidic application in clinical research is the study registered as NCT05101655, titled "Construction of Microfluidic Exosome Chip for Diagnosis of Lung Metastasis of Osteosarcoma." This study explored the utilization of a microfluidic exosome chip for the isolation and analysis of exosomes from blood samples, aimed at the early diagnosis of lung metastasis in osteosarcoma patients. Nanoscale extracellular vesicles possess molecular signatures indicative of disease states, and the microfluidic platform facilitated their efficient capture and biomarker analysis. The researchers integrated microfluidics to improve the early detection of lung metastasis, illustrating the clinical potential of microfluidic devices in non-invasive cancer diagnostics. Currently, there is only one completed clinical trial that involves microfluidics in nanomedicine synthesis, with no regulatory submissions to date. However, the distinct advantages of microfluidic technologies, including precise control, reproducibility, and scalability, continue to underscore their potential for future clinical applications.

5.4 Opportunities for personalized medicine using microfluidics

Personalized medicine has been well recognized for the treatment of diabetes which allows patients to measure their blood sugar level in real time to assess their individual needs (Mathur et al. 2020). It offers a magnitude of advantages such as enhanced diagnostic precision, customized treatment recommendations based on patient characteristics, targeted therapy that boosts treatment efficacy, minimizes adverse effects, cost-effectiveness, and promotes innovation and research (Mathur and Sutton 2017; Stefanicka-Wojtas and Kurpas 2023).

Personalized medicine can be greatly advanced by microfluidic system as it allows for precise, rapid, and scalable methods for diagnosis, and therapeutic interventions with its capability to integrate various materials, such as cells, gene sequences, proteins, and lipids, and its ease to adjust the process parameters such as flowability, speed and pressure (Alavi et al. 2024). It can control the drug release in a time-regulated manner which is shown in the study conducted by Barbato et al. on the permeable on-chip microvasculature for accessing the permeation of molecules and nanomedicines across the double-channel microfluidic device with vascular and extravascular compartments connected with a tunable micropillar membrane. Through fluorescence microscopy, it was observed that a change in permeability and flow conditions will lead to different vascular behavior of molecules such as permeable enhancers (mannitol and lexiscan), which selectively enhance the perivascular accumulation of approximately 200 nm particles in a dose- and time-dependent manner, with no effect on the larger particle size particles (Barbato et al. 2021).

HWDs have been highlighted for continuous patient monitoring and providing real-time data using non-invasive or minimally invasive methods (Zhang et al. 2021; Apoorva et al. 2024; Alavi et al. 2024). The integration of microfluidic wearable sensors with other wearable technologies enables real-time bodily fluid analysis which offers high throughput, high sensitivity, and low power consumption which can be further enhanced with the cooperation of AI and the Internet of Things (IoT) which ultimately leads to a personalized approach of healthcare, thus, improve the overall health of the patient (Apoorva et al. 2024).

5.5 Integration of artificial intelligence

AI has attained significant advancements that have introduced new influences in various fields, including microfluidic technology (Liu et al. 2021). Machine learning, a subset of artificial intelligence, utilizes mathematical models to allow machines to independently learn from data and identify relationships between the data and relevant aspects (Tsai et al. 2023; Shah et al. 2024). The continuous-flow characteristic of microfluidics facilitates real-time modifications, rendering it an optimal platform for machine learning applications in nanomedicine (Liu et al. 2021). In a study by Di Francesco et al. (Di Francesco et al. 2023), machine learning was applied to synthesize curcumin-loaded liposomes using microfluidics. A combination of feed-forward artificial neural networks and the Python programming language was used to establish a roadmap for synthesizing liposomes. The prediction of these two support-vector machine models was able to achieve an accuracy of 93% on liposome dispersity and 92% on the liposome's stability (Di Francesco et al. 2023).

Another subset of AI, artificial neural networks (ANN), which are collections of interrelated computational units referred to as artificial neurons, analogous to the hypothesized models of biological neurons in living beings (Revignas and Amendola 2022). In a study performed by Damiati et al., ANN models were used to predict and optimize the droplet and particle size of PLGA microparticles produced by several microfluidic systems, either separately or collaboratively integrated. The generated ANN models yielded precise predictions and valuable insights into the critical factors necessary for PLGA microparticle manufacturing via microfluidics, which effectively produce PLGA particles with adjustable size (Damiati et al. 2020).

The study by Ali et al. introduced an ANN model for the identification of correlations among variables influencing drug nanoprecipitation in microfluidic reactors. This model accurately predicted particle size from reaction parameters, including the microreactor angle and inner diameter during prednisolone nanoprecipitation, aligning with the experimental data (Ali et al. 2009).Other than that, artificial intelligence

improves the functionality of micro/ nanorobots in microfluidics by enhancing their motion control and environmental perception, which is essential for biomedical applications. These robots possess the capability to autonomously synthesize materials and adapt to intricate microenvironments, presenting novel opportunities for nanomedicine (Dong et al. 2024).

In another study by Yu et al., swarming magnetic photonic-crystal microrobots (PC-bots) comprising pH-responsive hydrogel microspheres containing encapsulated one-dimensional periodic assemblies of iron oxide nanoparticles capable of on-the-fly visually detecting pH changes and facilitating self-regulated drug delivery were demonstrated (Yu et al. 2023). In the presence of an abnormal pH condition (e.g., ulcerated superficial tumor lesion), PC-bots can detect it in real-time through the pH-responsive structural colors, thus enabling self-regulated drug release (Yu et al. 2023).

AI techniques, particularly machine learning, and ANN, present significant advantages over traditional optimization methods like the design of experiments (DoE) in managing complex, high-dimensional datasets typical in microfluidic nanomedicine development (Dipankar et al. 2025). Conventional approaches often depend on established models and restricted experimental variations, potentially neglecting nonlinear interactions or necessitating extensive experimental trials (Fontana et al. 2023). AI models can learn from existing datasets, enhance predictive performance over time, and reveal complex interdependencies among variables with a reduced number of experimental trials (Arboretti et al. 2022). For instance, while the DoE can effectively optimize three to four parameters, machine learning algorithms are capable of handling and accurately predicting outcomes from a significantly larger set of input variables, as evidenced in studies involving curcumin-loaded liposomes. The ANN model proficiently identified nonlinear correlations among these variables, resulting in enhanced encapsulation efficiency, hence showcasing the model's ability to handle many input parameters beyond the conventional limits of traditional DoE methodologies (Cardoso-Daodu et al. 2022). AI methodologies necessitate comprehensive datasets for effective model training and often exhibit a lack of transparency in their decision-making processes, commonly referred to as the "black-box" issue (Arboretti et al. 2022). This indicates that an integrated approach, merging AI with traditional strategies, may be optimal for the accurate and data-informed design of nanomedicine (Zhao et al. 2018; Zhang et al. 2023b).

6 Conclusion and future prospects

In nanomedicine, microfluidics has emerged as a groundbreaking technique and innovation that revolutionizes formulation and provides precision, customizable drug delivery, and patient-centric therapies. Numerous functionalities of the latest designs for microfluidic systems solve the shortcomings of the earlier models. This technology is now an efficient tool for the fabrication of a variety of nanomedicine formulations due to significant advancements. Microfluidics enhances drug loading efficiency, encapsulation performance, and the potential for controlled drug release, which are crucial for enhancing patient outcomes. Although the many benefits that come with the advancement of microfluidics, the technology transfer of this process from the laboratory to production is still deemed challenging. Effective cooperation between multiple parties, such as academics, industries, and regulatory bodies, is required to narrow the knowledge gaps in nanomedicine development to develop strategies for the successful scale-up and commercialization of nanomedicine to the public. Advancements in multifunctional nanoparticles, point-of-care applications, regulatory standardization, and enhanced drug customization will be crucial for the progression of microfluidics. The future of medicine is intricately linked to the continuous progress in microfluidics and nanomedicine, offering the potential for better patient care and a brighter, healthier future.

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Declarations

Conflict of interest The authors declare no competing interests.

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