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Continuous manufacturing of nanomedicines using 3D-printed microfluidic devices

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ABSTRACT

Microfluidic technologies have emerged as a promising strategy, utilizing nano and microscale manufacturing devices to create highly controllable and reproducible fluid microenvironments. These technologies have enormous potential in various applications, including drug delivery systems, diagnostics, and tissue engineering. Developing nanomedicines, which can provide targeted and controlled drug release with minimal side effects, is an appealing application. Until now, microfluidic devices have been manufactured using glass or polydimethylsiloxane (PDMS) materials based on soft lithography or microinjection molding technology. However, 3D printing has arisen as an advanced novel technique capable of manufacturing microfluidic devices. 3D printing, also known as additive manufacturing, deposits materials layer by layer to create complex structures with high precision and accuracy. Rapid prototyping, customization, and low-cost production are all advantages of this manufacturing technique in producing microfluidic devices. Recent advances in 3D printing have enabled the fabrication of intricately designed microfluidic devices, resulting in improved functionality and performance for tuning nanoparticle size, and drug loading allowing more precise fluid flow and mixing control, less material waste, and improved reproducibility. Combining 3D-printed microfluidic devices with other industrial, scalable drying technologies, such as spray coating and spray drying, can bridge the gap in the continuous manufacturing of nanomedicines. This review will focus on the role of 3D printing in creating microfluidic devices, its capability to fabricate nanomedicines in a single batch, and the implementation of continuous manufacturing methodologies for reproducibility at an industrial scale. The combination of microfluidics and 3D printing provides a promising avenue for developing and producing novel nanomedicines that can revolutionize manufacturing strategies and improve patient outcomes.

1. Nanomedicines

Nanomedicine is a scientific and technological approach that uses molecular tools to diagnose, treat, and prevent diseases and injuries, relieve pain, and maintain or improve human health [1]. As a specialized medical field, nanomedicine combines nanotechnology with pharmaceutical and biomedical sciences, and it has seen a significant surge in growth over recent years [2–5]. The term refers to complex nanoscale systems with at least two components, one of which is an active pharmaceutical ingredient. These nanoparticulate systems range in size from a few to thousands of nanometers and include nanocrystals, liposomes, solid lipid nanoparticles, micelles, nanospheres, nanocapsules, polymers, metals, proteins, and other inorganic materials [2]. The precise targeting of specific cells, tissues, and organs is a key focus of nanomedicine. Also, these sophisticated nanosystems are intended to improve drug solubility, stability, and bioavailability while minimizing side effects and toxicity.

One of the most significant advantages of nanomedicine over traditional drugs is its ability to improve drug delivery and enable targeted therapy. These advanced drug delivery systems can be functionalized with various targeting ligands such as antibodies, peptides, or small molecules that bind to receptors or antigens expressed on the surface of target cells. This allows the drug to be selectively accumulated at the desired site, reducing off-target and systemic side effects common with

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traditional chemotherapeutic agents [6]. Furthermore, nanomedicines can be designed to release their therapeutic cargo in a controlled manner, ensuring a sustained and therapeutic drug concentration at the target site [7].

Nanomedicine production involves complex and sophisticated processes that are often time-consuming and require high expertise. Traditional methods for producing nanomedicines, such as solvent evaporation, nanoprecipitation, and homogenization, have been widely used [8]. However, these techniques frequently have limitations, such as batch-to-batch variability, low reproducibility, and scalability issues, which can have a negative impact on the final product's quality attributes and efficacy. As a result, these constraints have hampered and slowed down the widespread use of nanomedicines in the clinic [9].

Microfluidic technology has emerged as a potential solution to the challenges associated with nanomedicine manufacturing [10]. Microfluidics is a multidisciplinary field concerned with manipulating and controlling fluids at the microscale, typically measured in micrometers to millimeters [11]. The use of microfluidics in manufacturing nanomedicines benefits from precise control over fluid flow, reduced reagent consumption, and efficient continuous and controlled mixing of reactants. These characteristics help improve nanomedicines' reproducibility, scalability, and uniformity, which are important parameters for successful clinical translation [12].

Combining microfluidics and additive manufacturing techniques such as 3D printing has increased its applicability in nanomedicine, allowing for higher versatility and design customization. 3D printing allows the creation of personalized and complex microfluidic devices tailored to specific needs for manufacturing and formulating nanomedicines [13]. 3D printing's flexibility enables rapid prototyping and optimization of microfluidic devices, lowering overall costs and time associated with the device development process. Furthermore, 3D printing with biocompatible materials ensures that the fabricated devices are compatible with biological systems and can be used for various applications such as tissue engineering, drug screening, and point-of-care diagnostics [14].

Several studies in recent years have demonstrated the successful use of 3D-printed microfluidic devices for the continuous production of nanomedicines [13,15]. These devices utilize the distinct advantages of microfluidics and 3D printing to precisely control synthesized nanoparticles' size, shape, and composition, which are crucial to ensure targeting, efficacy, and safety. Furthermore, these devices enable the integration of additional functionalities, such as *in-situ* particle formation monitoring and real-time quality control, which improves the manufacturing process's reliability and reproducibility [16].

The introduction of 3D-printed microfluidic devices has transformed the field of nanomedicine by providing a versatile and efficient platform for the continuous production of high-quality nanotherapeutics. The distinct advantages of these devices, e.g. precise control over fluid flow, rapid prototyping, and the ability to incorporate multiple functionalities, can potentially address the challenges associated with traditional nanomedicine manufacturing. As this technology advances, the development of innovative and customized 3D-printed microfluidic devices is expected to pave the way for the widespread use of nanomedicines in the clinic [17,18].

Advancements in nanotechnology, biotechnology, and pharmaceutical sciences have contributed to the creation of innovative drugs, gradually outperforming traditional medications. This area employs nanoscale structures such as nanoparticles, nanocapsules, micelles, liposomes, transferosomes, nanocrystals, polymersomes, and dendrimers to accurately deliver therapeutic agents to specific disease sites (Fig. 1). The development of these nanocarriers stems from research focused on enhancing drug delivery efficacy while minimizing adverse effects [19–22].

Lastly, these therapies have opened new opportunities for personalized medicine. One of the main advantages of this approach is the targeted drug delivery to specific cells, tissues, or organs [23]. This precision is achieved by modifying nanoparticulate systems with ligands like antibodies, peptides, or small molecules that selectively bind to receptors or antigens on target cells [24]. This selectivity reduces off-target and systemic side effects often associated with conventional methods. Increasing the surface area and dissolution rate of drug molecules enhance solubility and bioavailability, leading to better therapeutic outcomes and decreased dosing frequencies [25,26].

These advanced therapies also provide improved stability and shelf life compared to conventional drug delivery systems [27]. Encapsulating drugs within nanoparticulate systems prevents degradation and reduces the need for additional stabilizers and preservatives [5,28–30]. Furthermore, using biodegradable materials ensures safe metabolism and excretion from the body, lowering the risk of accumulation and toxicity [31].

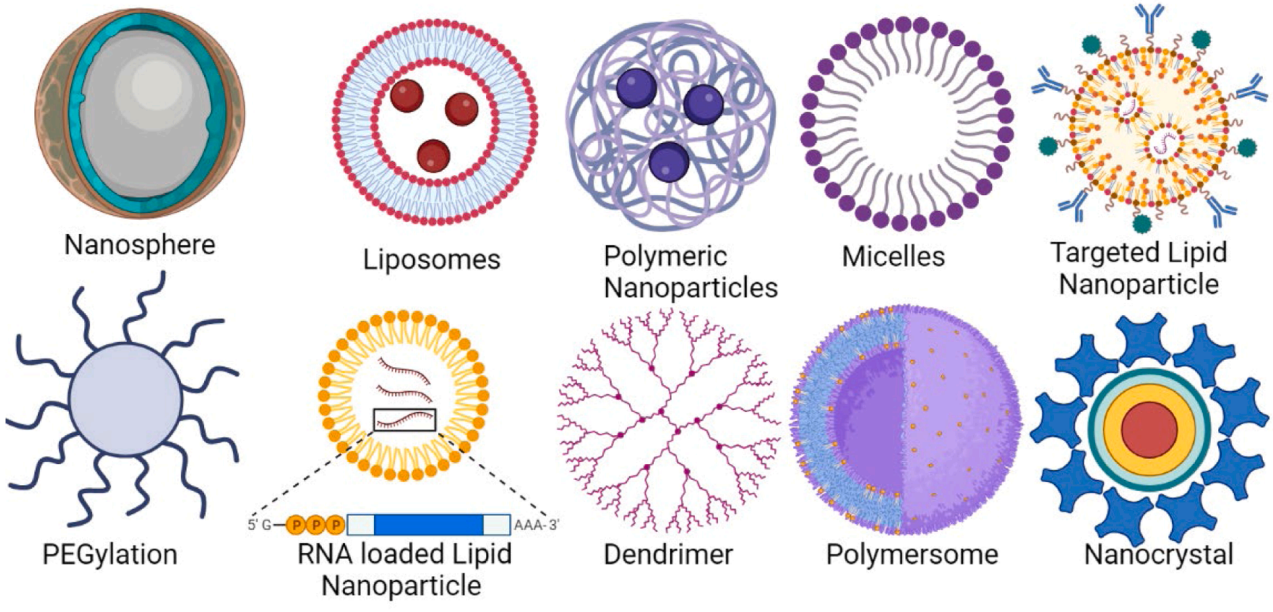


Fig. 1. Examples of different nanomedicines.

As an example of nanomedicines with excelled performance compared to an unencapsulated drug, Ambisome® and Caelyx® are among the first nanomedicines authorized in Europe and introduced to the market in the 90s. Ambisome® is a liposomal formulation containing an antifungal drug, amphotericin B, widely used to treat severe fungal systemic infections. The main advantages of this nanomedicine over conventional amphotericin B are the enhanced drug targeting towards infected tissues and the reduced nephrotoxicity that allows the administration of higher doses without causing severe toxicity [30]. The price to complete a full treatment in a patient of 70 kg varies from ~1000€ with Ambisome® to 15€ with Fungizone®, the conventional formulation [32]. Similar economic facts occur with Caelyx®, a long-circulating pegylated liposomal formulation containing an anticancer drug, doxorubicin hydrochloride. These are just two examples of nanomedicines' potential use in clinical practice. However, up to date, only a handful of nanomedicines are authorized in Europe [33]. As far as we know, all of these nanomedicines are mass-produced by pharmaceutical companies, and none are personalized or patient-centered.

2. Conventional approach to nanomedicine manufacturing

A complex interplay of scientific advances, technical challenges, and regulatory frameworks distinguishes nanomedicine manufacturing [34]. Translating laboratory-scale research into industrial-scale production remains a significant barrier, limiting the widespread adoption and commercialization of these novel therapies [35]. There are numerous conventional techniques for producing nanomedicines at the laboratory scale which can be divided into two main manufacturing methods, bottom-up and top-down [36]. The bottom-up method involves constructing nanoparticles from the molecular level. In contrast, the top-down approach starts with larger particles (millimeter or micrometer-sized) and reduces their size to the nanoscale through an energetic comminution process. Both methods have advantages and challenges, and ongoing research aims to refine these techniques to make them more suitable for large-scale, cost-effective nanomedicine production [37].

2.1. Bottom-up manufacturing, from the molecular level to nanoparticles

The solvent evaporation-precipitation method (a bottom-up approach) is one of the most common [36,38]. However, this technique is difficult to scale-up for industrial production. This is due to the need to remove large quantities of residual solvents. Additionally, tank volume, impeller speed, and liquid media can all significantly impact the final properties of the particles. Investment in nanomedicine manufacturing at the industrial level is limited for several reasons: (1) a lack of infrastructure and in-house expertise, (2) slower production rates compared to capsules and tablets (1 million/h), (3) insufficient batch-to-batch reproducibility requiring rigorous control of particle size, and (4) concerns about chemical and physical stability [39]. As a result, the development and market authorization costs for nanomedicines are much higher than for conventional medicines, making them financially unfeasible for public healthcare systems and patients. In Europe, the commercialization of nanomedicines is primarily driven by startups and small- to medium-sized enterprises [40]. Therefore, there is a pressing need to bridge the gap between developing high-quality nanomedicines and efficient production processes.

Bottom-up manufacturing is frequently used to create nanocrystalline, nano-amorphous, or nano-polymeric suspensions [41,42]. Molecules are firstly dissolved and then precipitated by adding a solvent to a non-soluble medium (Fig. 2). Condensation techniques produce nanoparticles during this process by nucleating particles and growing crystals.

In this approach, the active pharmaceutical ingredient (API) and lipophilic stabilizer are suspended in a water-miscible organic solvent, forming a nanocrystalline or nano-amorphous state. Meanwhile, hydrophilic stabilizers and polymers dissolve entirely in water, such as biocompatible and biodegradable polylactides, polyglycolide, and poly

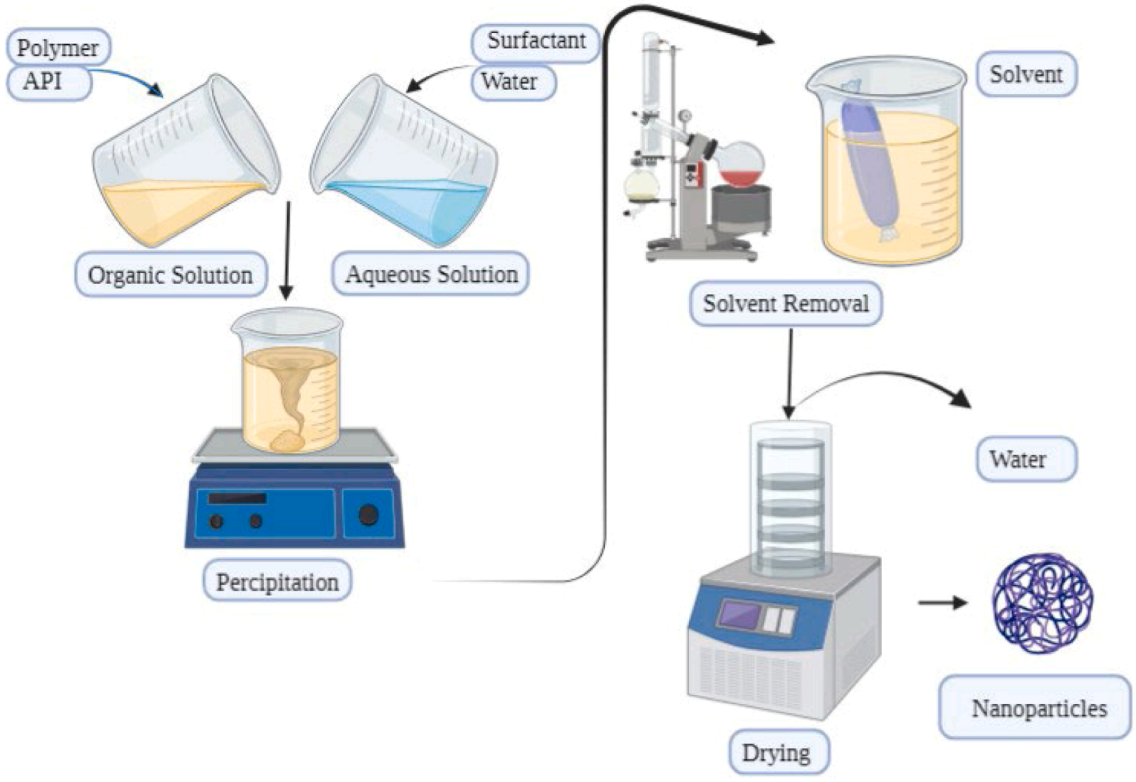


Fig. 2. Schematic representation of bottom-up approach for nanomedicine manufacturing.

(lactide-co-glycolides), creating a nano-polymeric suspension. By mixing these two solutions, the organic solvent diffuses into the water, forming a precipitate with a particle size below one micrometer. Finally, the organic solvent is removed through extraction or evaporation [37].

2.2. The top-down approach, bulk to the nanoscale

The top-down approach typically involves the reduction of large crystalline drug particles (pre-synthesized polymers) into nanoparticles through the use of mechanical or chemical energy, such as milling, extrusion, sonication, or laser ablation, with a surfactant added to prevent aggregation [43–45]. The main methods of top-down production for nanocapsules and nanospheres include high-pressure homogenization, ultrasonication, and ball milling (Fig. 3).

To summarise, manufacturing nanomedicines is a complex process with several challenges to overcome at the industrial level, such as the lack of batch-to-batch reproducibility in particle size and drug loading and the slow production speed. Novel approaches are required to ensure more reliable and efficient manufacturing methods for nanomedicines.

3. Understanding the fundamentals of microfluidics

Microfluidic systems offer unique advantages over bulk mixing due to their specific dimensions, which enable (1) small volumes, (2) controlled flow patterns, and (3) laminar Hagen-Poiseuille fluid dynamics. These characteristics help determine the crucial parameters involved in microfluidic processes which determine the final nanoparticle's attributes (Table 1) [46].

Several parameters within microfluidic systems influence the behavior of fluids. Temperature (T) is the measure of a fluid's thermal energy, which affects properties such as viscosity, density, and diffusion coefficient. Viscosity (η) represents a fluid's resistance to deformation or flow, impacting the Reynolds number, flow resistance, flow rate, Dean number, and diffusion coefficient. Density (ρ) is the mass per unit fluid volume, affecting both the Reynolds and Dean numbers. Pressure force (P) is applied to a fluid by a pump or other external system, influencing the flow rate under laminar flow conditions [47–50].

The length parameter (L) refers to the length of the microfluidic channels or the diameter of the tubes used in the system, affecting the Reynolds number, flow rate, flow resistance, and Dean number. Different geometries of microfluidic channels, such as curvature, can

Table 1
Factors affecting mixing in microfluidic systems.Key: Kelvin (K°), Pascal*Second (Pa*s), Viscosity (η), Temperature (T), Density (ρ), Pressure force (P), Length (L), Density (ρ).

Component	Parameter	Id	Unit
Perimeter	Temperature	T	K°
Fluids/media	Viscosity	η	Pa*s
Fluids/media	Density	ρ	kg/m³
Pump/system	Pressure force	P	Pa
Channels	Length (section/diameter)	L	m
Geometry	Curvature	-	-

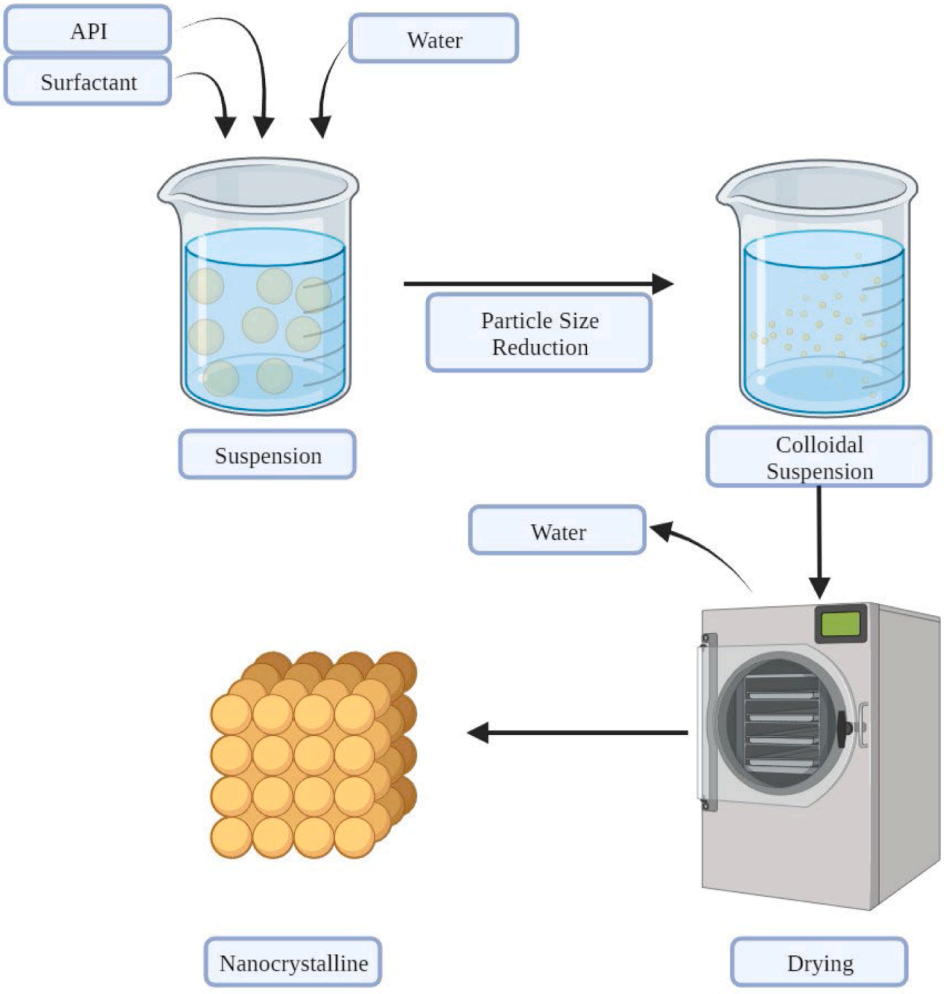


Fig. 3. Schematic representation of the top-down approach for nanomedicine manufacturing.

impact fluid flow behavior within the system [51].

Thus the smaller size of the microchannel makes a lengthy and time-consuming mixing. Most of these microfluidics benefit from the laminar flow and help disperse liquids mix where dissolved or suspended compounds react or precipitate nanoparticles into their form [46,52].

Several parameters and dimensionless descriptors help understand microfluidic systems' overall performance and utility (Table 2). Flow resistance (RF) is the opposition to fluid flow within a channel or tube. Flow rate (Q) is the volume of fluid passing through a channel or tube per unit of time. Velocity (v) represents the speed at which a fluid flows through a channel or tube. The diffusion coefficient (D) measures a substance's ability to spread through a fluid due to concentration gradients.

Dimensionless descriptors, such as the Reynolds number (*Re*), indicate the flow regime; the Peclet number (Pe) represents the ratio between convective and diffusive transport mechanisms; the Fourier number (Fo) indicates diffusion within a volume; the Dean number (De) predicts the appearance of vortices in a curved channel; the Capillary number (Ca) demonstrates phase interaction in droplet formation; and the Stokes number (Stk) describes particle interactions and separation processes in changing fluid flow (Table 3) [51].

Reynolds number (*Re*) is one of the essential factors for microfluidic devices. It indicates whether the microchannel's flow regime is laminar (orderly and smooth) or turbulent (disordered and chaotic). Laminar flows are characterized by a low Reynolds number (typically *Re* 2000), ensuring fluid layers flow parallel without significant mixing. Optimizing this parameter for nanomedicine manufacturing with a microfluidic device requires considering factors such as fluid density (ρ), fluid velocity (v), channel length (L), and fluid viscosity (η). By carefully selecting fluid properties and microchannel geometries, achieving an optimal Reynolds number that results in the desired flow regime is possible. For instance, using low-viscosity fluids and reducing the channel length can help maintain a low Reynolds number and ensure laminar flow. Controlling fluid flow rates within the microchannel and using appropriate device materials can also aid in optimizing the Reynolds number [53].

Maintaining a laminar flow regime to manufacture nanomedicine using microfluidic devices can be advantageous. Laminar flow is characterized by fluid layers' orderly, parallel movement with minimal mixing [54]. This flow type is necessary for precisely controlling fluid interactions in microchannels, which is required to produce uniform droplets, particles, or emulsions. Consistency in nanomedicines' size, shape, and composition is essential for their therapeutic efficacy and safety.

Using chaotic mixing, as seen in turbulent flow regimes to manufacture nanomedicine can result in nanoparticles with inconsistent size, shape, and composition. These inconsistencies may compromise the therapeutic efficacy and safety profiles of nanomedicines and make it challenging to scale up the manufacturing process for mass production. In addition, turbulent flow may result in an uneven distribution of reactants and products within the microfluidic device, resulting in a lower yield and reproducibility of nanomedicine [55].

While it is true that laminar flow in a microfluidic device results in less mixing than turbulent flow, the device can be designed to promote controlled and efficient mixing via several techniques, for instance, passive mixing strategies that exploit the inherent properties of laminar flow, such as diffusion or chaotic advection [56]. These techniques can induce mixing in a highly regulated manner without disturbing the laminar flow regime. In addition, using micro-scale channels in microfluidic devices reduces diffusion distances, allowing for adequate mixing even under laminar flow conditions. Therefore, despite the decreased mixing in laminar flow, it is still possible to achieve the efficient and controlled mixing required for nanomedicine production by carefully designing the microfluidic device and optimizing its parameters.

As a result of the laminar flow occurring in microfluidic devices used to manufacture nanomedicine, diffusion is an important parameter. It determines the behavior of mass transport in microfluidic systems (Table 4) [66]. Due to their small dimensions, these systems exhibit faster and more efficient diffusion processes than larger-scale systems. This enhanced diffusion is advantageous for applications requiring rapid mixing, reactions, or separations, such as chemical synthesis, drug delivery, and biological research. The following formula can be used to estimate diffusion lengths:

$$L = \sqrt{Dt}$$

In which L is the distinctive length of diffusion, D is diffusivity and t is time.

The Peclet number (Pe) is the ratio between advection and diffusion in fluid dynamics and heat and mass transfer processes. It is defined as (v * L) / D, where L is the characteristic length scale of the system, v is the fluid velocity, and D is the diffusion coefficient [57,58]. Analyzing the Peclet number gives insights into the relative balance between convective and diffusive forces that govern fluid flow. In microfluidic systems, the efficient and controlled mixing of different fluids is essential for accurately forming nanoparticles or other therapeutic agents. A high Peclet number indicates that advection (bulk fluid motion) plays a dominant role, while a low Peclet number implies that diffusion (molecular dispersion) is the primary transport mechanism.

Optimizing the Peclet number to ensure maximum mixing in laminar flow within microfluidic devices for nanomedicine manufacturing involves balancing the advection and diffusion forces in the system. One way to optimize the Peclet number is by controlling the flow rates of the fluids in the microfluidic channels. Adjusting the flow velocity to an appropriate level can help balance advection and diffusion forces, enhancing the mixing efficiency [59]. This can be achieved using pressure-driven or syringe-pump-assisted flow control methods commonly employed in microfluidic systems. Another approach is to modify the microchannel geometries to facilitate improved mixing.

Table 2
Parameters and influences on mixing in microfluidic systems.

Influenced by	Parameter	Id	Unit	Description
Geometry, μ, L	Flow resistance	RF.	(nd)	Defined by cross-section, that is, for tube = L^4 / (η * diameter)
P	Flow rate	Q	m^3/s	Proportional to P in laminar flow, defined as ΔP*RF
Geometry, P, Q	Velocity	v	m/s	Vectorial force
RH, T, v, η	Diffusion coefficient	D	m^2/s	(kb * T) / (η * 6π * radius * v); kb = Boltzmann coeff.

Table 3
Non-dimensional parameters in microfluidic systems.

Descriptor	Id	Formula
Reynolds number	*Re*	(ρ * v * L) / η
Peclet number	Pe	(v * L) / D
Fourier number	Fo	Dt / L^2, where t is time
Dean number	De	((ρ * v * L) / η) * (L / (2 * radius of curvature))$^{1/2}$
Capillary number	Ca	(η * v) / γ, where γ is the phase surface tension depending on the angle and physical characteristics of the phases
Stokes number	stk	(τ * v) / L, where τ is the relaxation time

Table 4
Characteristic diffusion lengths for various diffusion coefficients [51].

D – Time (s)	1 s	10 s	100 s	1000 s
10^{-5} cm^2 /s	32 μm	100 μm	320 μm	1000 μm
10^{-6} cm^2 /s	10 μm	32 μm	100 μm	320 μm
10^{-7} cm^2 /s	3.2 μm	10 μm	32 μm	100 μm

Incorporating complex channel designs, such as serpentine or herringbone patterns, can induce transverse flows and chaotic advection that support diffusion-driven mixing without significantly affecting the overall flow rates [60].

Additionally, increasing the surface area to volume ratio within the microchannels can promote diffusion by creating more opportunities for molecular interactions and reducing diffusion distances [46]. Introducing active mixing strategies, such as applying external force fields like magnetic or electric fields, can also aid in optimizing the Peclet number. By controlling the movement of fluids with specific magnetic or electric properties within the laminar flow, diffusion, and mixing can be enhanced without directly impacting the advection rates [61]. Also, selecting fluids with appropriate physicochemical properties, such as higher diffusivities or lower viscosities, can improve their ability to diffuse and mix within the laminar flow regime, thus affecting the Peclet number and overall mixing efficiency [46].

The Fourier number (Fo) represents a system's diffusive transport ratio to inertial transport or storage. It is defined in Eq. 2:

$$\mathrm{Fo} = \alpha t / L^2 \tag{2}$$

where α is the thermal or mass diffusivity, t is the time, and L is the characteristic length scale of the system.

Several strategies can be employed to enhance diffusive transport and balance it with the storage effects to ensure maximum mixing in laminar flow while optimizing the Fourier number. These approaches aim to maximize the mixing process's efficiency, leading to improved control over nanomedicines. One method is to adjust the residence time of the fluids in the microfluidic channels. Increasing the duration of fluid-fluid interactions allows more time for the diffusion process to occur, and hence, better mixing. This can be achieved by controlling the flow rates of the fluids or by altering the microchannel geometries to increase the flow path length [62]. Another strategy is introducing temperature gradients in the microfluidic device, which can aid in creating convective-like flows within the laminar regime, enhancing mixing. Careful control of the temperature profile within the microchannels can drive diffusion processes and promote the homogenization of the fluids [63]. The choice of materials and the physicochemical properties of the fluids can also impact the Fourier number and mixing efficiency. Selecting fluids with higher diffusivities, lower viscosities, or appropriate thermal properties can improve their ability to diffuse and integrate within the laminar flow regime [46].

In understanding and controlling the flow behavior of microfluidic systems, the Dean number, Capillary number, and Stokes number are also crucial parameters [64]. Optimizing fluid flow, particle manipulation, and overall process efficiency are especially important for enhancing nanomedicine production using microfluidic devices, as they improve fluid flow and particle manipulation.

The Dean number characterizes secondary flow patterns generated by centrifugal forces in curved channels. It is the ratio between centrifugal forces and viscous forces. The Dean number influences nanoparticle transport, mixing quality, and particle residence time on the microfluidic device in nanoparticle production. By precisely regulating the Dean number, it is possible to optimize process conditions for enhanced mixing, particle dispersion, and, ultimately, more uniform and efficient nanomedicine production. To optimize the Dean number in nanomedicine production, consider a microfluidic device with curved channels to improve mixing and particle dispersion. Adjusting the channel's curvature and flow velocity can achieve the desired Dean number. For instance, increasing the radius of curvature or decreasing the flow velocity can decrease the Dean number, thereby minimizing secondary flows and particle dispersion and resulting in more concentrated and uniform particle transport [65].

The capillary number is a crucial non-dimensional parameter that signifies the proportion of viscous forces to surface tension forces in a fluid. It significantly determines the stability and dynamics of droplets, bubbles, and other interactions within microfluidic systems. Managing the capillary number in nanomedicine production is essential for creating stable, uniform droplets or particles, which are critical for the final product's quality and effectiveness. By altering fluid properties and flow rates, one can control the capillary number to achieve the desired droplet or particle size distribution, improve encapsulation efficiency, and avoid unwanted particle aggregation [66]. A droplet-based microfluidic system produces liposomes or polymeric nanoparticles, which optimizes the capillary number in nanomedicine manufacturing. To attain the desired capillary number, one can adjust the properties of the continuous phase fluid, the dispersed phase fluid, and the flow rates [67]. For example, enhancing the continuous phase's viscosity or reducing the dispersed phase's flow rate can lower the capillary number. This results in stable, monodisperse droplets that can be transformed into uniform nanoparticles [68].

The Stokes number is a parameter characterizing the relative motion of suspended particles in a fluid. It represents the ratio between particle inertia and fluid drag forces [69]. This factor is crucial for manipulating and transporting nanoparticles in microfluidic systems during nanomedicine production. Adjustments can be made to flow rates, channel geometries, and particle properties to optimize this parameter. These modifications enable precise control over particle motion, improved reaction kinetics, and enhanced efficiency in the nanomedicine production process [70].

4. Unlocking the potential of microfluidic devices in the fabrication of nanomedicines

Microfluidic devices are microscale fluidic circuits that manipulate liquid at the nanoliter scale. Microfluidic technology in nanomedicine manufacturing offers numerous advantages, making it a promising method for creating precise and highly controlled nanoparticles. One key benefit is the accurate control over particle size and shape, as manipulating fluid flow rates and mixing conditions within these devices allows for optimised drug delivery and assured safety and effectiveness. Moreover, the well-defined and highly controlled conditions result in consistent and reproducible nanoparticle manufacturing, essential for maintaining nanomedicines' quality and ensuring batch-to-batch uniformity [71].

Another advantage is the rapid production and reduced reaction times due to the small volumes and quick mixing of reagents within the devices, leading to faster nanoparticle formation and shorter synthesis times (Fig. 4). These devices also provide improved control over the encapsulation process, ensuring high drug loading efficiency and uniform distribution of therapeutic agents within the nanoparticles, which can enhance drug delivery and therapeutic outcomes [72]. The technology requires low reagent consumption, making the process more cost-effective and environmentally friendly. Scalability and potential for continuous manufacturing are additional advantages since multiple devices and parallel channels can be easily integrated for industrial production. This enables a transition from batch-to-batch to continuous manufacturing processes, improving productivity and reducing costs. These devices can incorporate multiple processes within a single unit, such as nanoparticle manufacturing, purification, and characterization. This integration reduces the need for additional equipment, simplifies the manufacturing process, and can lead to continuous production workflow [73].

However, the engineering of microfluidic devices is complex, and there have been some barriers to commercializing these devices that traditional fabrication methods, such as **injection molding** using polydimethylsiloxane (PDMS) and glass manufacturing **have failed** to address. The main challenges of microfluidic device manufacturing with injection molding are creating complex and intricate channel designs while maintaining the precision and reproducibility required for biological and chemical applications. This is primarily due to the high aspect ratios, small dimensions, and tight tolerances in microfluidic

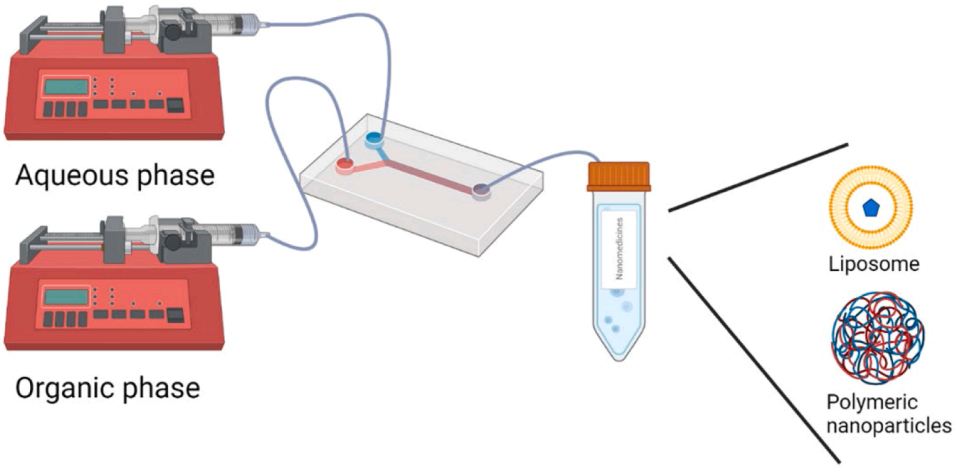
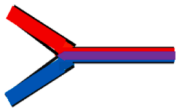
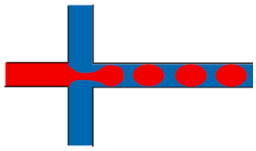
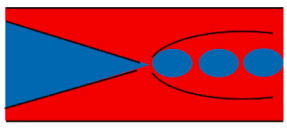
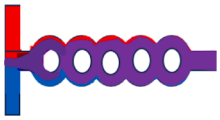


Fig. 4. Schematic representation of the nanomedicine production using microfluidic devices.

devices [85]. Polymer shrinkage, flow-induced stresses, and warpage can all cause dimensional inaccuracies and defects, further complicating the manufacturing process [86]. Furthermore, selecting biocompatible, chemically resistant, and optically transparent materials is critical for the functionality of microfluidic devices, posing an additional challenge for injection molding. Finally, optimizing the mold design, injection

Table 5
Comparison of microfluidic device channel geometries. In this table, blue indicates the aqueous phase, and red shows the organic phase.

Geometry	Advantages	Disadvantages	Examples of nanomedicines	Ref.
T-Junction 	• Controlled droplet formation • Good for producing uniform emulsions or polymeric nanoparticles • Enhanced mixing of fluids	• It may require precise pressure control for optimal performance • Limited ability to handle a wide range of fluids	• Emulsion-based nanoparticles • Polymeric nanoparticles • Liposomes	[74–76]
Y-Junction 	• Enhanced mixing of fluids • Controlled droplet formation • Suitable for producing uniform emulsions or polymeric nanoparticles	• It may require precise pressure control for optimal performance • Complex flow patterns may lead to low production efficiency	• Polymeric nanoparticles • Liposomes • Dendrimers	[77,78]
Serpentine 	• Improved mixing due to chaotic advection • It may lead to higher production efficiency	• Complex geometry • It may be challenging to manufacture and clean	• Emulsion-based nanoparticles • Polymeric nanoparticles • Liposomes	[13,71]
Flow Focusing 	• Precise control over droplet size and production rate • Suitable for producing highly uniform nanoparticles.	• It may require complex fluid control systems • High-pressure conditions may lead to instability	• Emulsion-based nanoparticles • Polymeric nanoparticles • Liposomes	[79,80]
Coaxial 	• Allows for the fabrication of core-shell or multilayered nanoparticles • Precise control over nanoparticle size and morphology	• Complex geometry • It may require advanced fluid control systems and accurate pressure control	• Core-shell nanoparticles • Multilayered nanoparticles • Drug-loaded liposomes	[81–83]
Bifurcating 	• Enhanced fluid mixing due to repeated splitting and combining of streams • Suitable for rapid nanoparticle synthesis.	• Complex geometry • It may require precise pressure control and advanced fluid handling systems	• Emulsion-based nanoparticles • Polymeric nanoparticles • Dendrimers • Liposomes	[67,84]

molding parameters, and quality control measures requires significant expertise and resources, making it a complex and potentially costly process [87].

The disadvantages associated with microfluidic device fabrication using glass are multiple. First, glass is a fragile material, making it susceptible to shattering during handling or operation. This fragility may decrease device dependability and higher costs due to the need for replacements. Also, the manufacturing process for glass microfluidic devices can be time-consuming and costly, as it frequently involves wet etching, photolithography, and bonding. These procedures can be labor-intensive and require specialized equipment. In addition, glass microfluidic devices are difficult to modify once manufactured, limiting their adaptability to design changes or new applications. Due to the material's inherent properties, it can be challenging to incorporate additional components, such as electrodes or sensors, into glass microfluidic devices. These disadvantages render glass manufacturing unsuitable for some microfluidic applications, mainly when cost, ease of fabrication, and adaptability are crucial [88].

The personalization of microfluidic devices adds another layer of complexity to the injection molding process on top of the challenges listed above (Table 5). Customizing specific user needs, such as tailored channel geometries or specialized surface properties, involves ongoing mold design and fabrication adjustments. This demand for personalized solutions may result in longer production times and higher manufacturing costs, especially when rapid prototyping and iterative design revisions are required. Furthermore, ensuring consistent quality and performance across customized microfluidic devices requires strict process control and extensive testing, emphasizing the difficulty of integrating personalization into microfluidic device manufacturing via injection molding [89].

However, these barriers may be overcome by 3D printing, which is a more cost-effective technology that has shown great improvement in terms of channel resolution. There are commercialized a variety of materials ready to use with ideal properties such as being transparent, non-fluorescent, and biocompatible [90].

5. 3D-printed microfluidic devices for the fabrication of nanomedicines

Using 3D printing to fabricate microfluidic devices capable of high throughput synthesis of nanomedicines with tunable dimensions is feasible [91–95]. Utilizing a **high-resolution 3D printing process** based on fuse deposition modeling, stereolithography, or digital light projection, reliable patterning of channel features with dimensions of ~200 μm has been demonstrated, resulting in the production of nanomedicines (<100 nm at a production rate of 4 mg/min) [96]. This can be achieved with a single device due to the engineering of flow-focusing microchannels with high aspect ratios, together with the seamless fabrication of high-pressure fluidic ports for world-to-device interfacing that supports sizeable volumetric flow rates and high-throughput nanoparticle synthesis (Fig. 5) [97].

Microfluidic device technology has shown great potential in revolutionizing nanomedicine manufacturing, providing precise control over particle size, morphology, and composition [98,99]. Despite the challenges faced in manufacturing microfluidic devices through injection molding, such as maintaining intricate channel design, ensuring biocompatibility, and addressing personalization demands, the technology has proven to be a valuable tool for developing advanced and targeted therapeutics. 3D printing has emerged as a promising alternative for manufacturing microfluidic devices, with benefits such as design flexibility, rapid prototyping, and lower production costs. This additive manufacturing technology allows researchers and developers to create complex and personalized microfluidic structures without using expensive molds or specialized equipment. Furthermore, 3D printing enables the fabrication of devices with integrated components such as valves and mixers, simplifying assembly and improving microfluidic device functionality. However, it is critical to fully realize its potential in microfluidic device manufacturing to address 3D printing challenges such as surface roughness, limited material options, and resolution constraints. Microfluidics can continue to play a pivotal role in advancing nanomedicine and other cutting-edge applications by embracing these innovative fabrication techniques and working to overcome their limitations. By overcoming these challenges and continually refining the fabrication process, microfluidic devices can pave the way for more efficient and cost-effective nanomedicine production, ultimately improving patient care and advancing personalized medicine (Fig. 6) [100–102].

Some nanomedicine applications of 3D-printed microfluidics devices are shown in Table 6. Using microfluidic devices for manufacturing nanomedicine can be significantly enhanced [103] by replacing traditional two-dimensional (2D) micromixers with three-dimensional (3D) micromixers. 3D printing allows for the manufacture of microfluidic devices as monolithic structures, eliminating the challenges associated with bonding separate parts and ensuring high-quality fabrication. This capability facilitates the use of 3D micromixers, which greatly increase mixing efficiency within microfluidic systems.

Typically, microfluidic devices operate under laminar flow conditions. Previous studies have attempted [104] to achieve chaotic flow (Reynolds number >2300) by employing higher flow rates and flow rate ratios, resulting in better particle size control and enhanced drug encapsulation. However, these approaches are challenging due to the high pressures required and the associated setup complexities. In contrast, 3D micromixers can address these issues by utilizing secondary flows, such as those characterized by the Dean number, to achieve

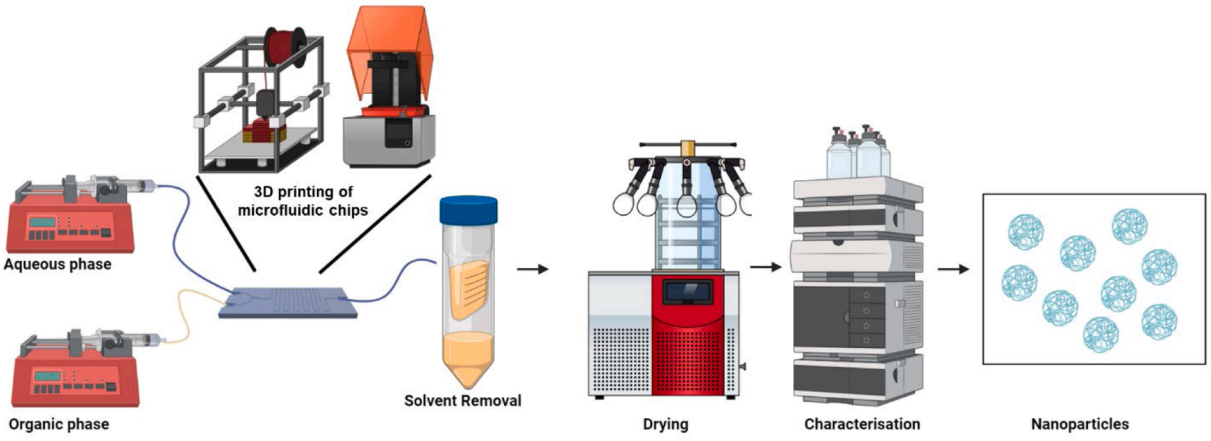


Fig. 5. Schematic representation of the single-batch manufacturing of nanoparticles using a 3D-printed microfluidic device.

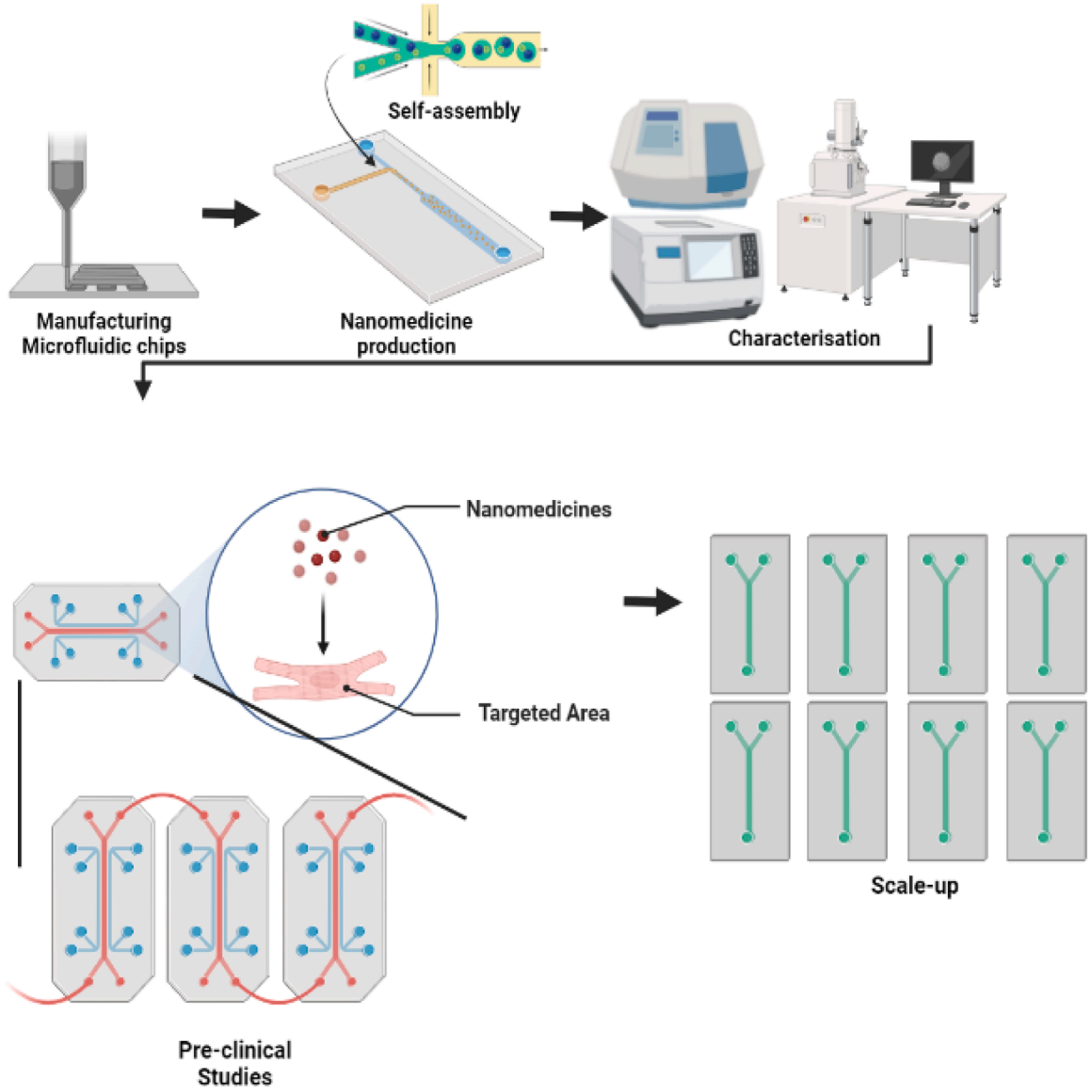


Fig. 6. Schematic presentation of integrating the microfluidic device for nanomedicine manufacturing and scale-up development.

mixing effectiveness similar to chaotic mixing without necessitating high flow rates.

Advanced 3D printing techniques, such as micro-stereolithography (μSL), enable the fabrication of these complex designs [105,106]. Traditional methods face significant challenges in producing such structures, including the need for multiple layers, precise alignment, and bonding processes. Incorporating 3D micromixers into microfluidic devices not only improves mixing performance but also adds design flexibility, making them highly advantageous. The ability to fabricate intricate 3D geometries expands the possibilities for microfluidic applications in nanomedicine, facilitating more efficient and scalable production processes. Also, 3D microfluidics can be created using fugitive ink deposition, a process in which filaments of a sacrificial "fugitive" ink are extruded through a nozzle into a fluid reservoir such as isomalt, a sugar alcohol that cools rapidly to below its glass transition temperature forming a stiff optically clear glass resistant to recrystallization. Once printing is finished, the reservoir is cured, and the ink is extracted through suction [107].

6. Fabrication of microfluidic devices using 3D printing technology

3D printers work on the layering principle, stacking layers of material on the x-y-z axes to create three-dimensional objects. The variety of 3D printing raw materials available is critical in determining its applications and versatility. As filaments in 3D printers, various materials, including plastics, metals, and ceramics, can be used, allowing for tailored solutions in multiple industries. However, to achieve the best results, printers designed for specific raw materials must be used [114]. As the number of filaments available grows, so will the applications and potential of 3D printing technology, revolutionizing how we create and manufacture products in the future [115–117].

Regarding the production of nanomedicines, 3D printing technology offers several significant advantages over traditional methods in fabricating microfluidic devices, particularly in the creation of complex three-dimensional (3D) micromixers and customized designs (Fig. 7). Traditional soft lithography techniques using polydimethylsiloxane (PDMS) can achieve extremely high resolutions down to the nanometer scale and produce high-quality surfaces. However, they are often time-consuming, costly, and involve multiple fabrication steps. Fabricating

Table 6
Some of 3D printed microfluidic devices used in nanomedicine applications.

3D Printing Technique	Type of nanomedicine	Channel Design	Channel Width	Organic Phase Composition	Aqueous Phase Composition	Total Flow Rate/ Flow Ratio	Average Particle Size	Ref
Projection micro-stereolithography (PμSL)	Nanoliposomes	Cross-Shaped	400 μm	1,2-Dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), cholesterol and Isopropyl alcohol (IPA)	Phosphate buffered saline (PBS) (0.1 M, pH 7.4)	474 (ml. min^{-1}) / 48.7	80.62 (nm)	[108]
Fused Deposition Modeling (FDM)	Nanocarriers (polymeric nanoparticles and liposomes) loaded with cannabidiol as a model drug	"Z" (zigzag design) and "C" (split and recombine design)	600 μm	PLGA and CBD dissolved in acetonitrile (ACN)	Water	12 (ml. min^{-1}) / 1:1 and 1:3	Between 80 and 160 nm	[109]
Fused Deposition Modeling (FDM)	Nano-sized emulsions	Cross-Shaped	500 μm	Standard sunflower oil and pro-pylene glycol monostearate	Demineralized water	Multiple	Around 450 μm	[110, 111]
Fused deposition modelling (FDM) and liquid crystal display (LCD)	Liposomes	Y shaped with multiple different central channel design	1 mm	Phospholipids (DMPC) combined with cholesterol (2:1)	PBS, pH 7.4	1 and 3 mL min^{-1} / 1:1	Multiple results between 190 to 365 (nm)	[112]
Stereolithography (SLA) and fuse deposition modeling (FDM).	Nifedipine polymeric nanoparticles	Y shaped followed with radiator design	1 mm	Nifedipine, Eudragit L100- 55 dissolved in Ethanol	Water with Tween-80	2.5 mL/ 1:4	67 ± 1 nm	[113]

complex 3D structures with PDMS typically necessitates additional manufacturing processes, such as multi-layer lithography and precise alignment, followed by bonding to assemble the layers into a single device. These steps not only increase fabrication time and complexity but also introduce potential sources of error, such as misalignment and delamination at bonded interfaces, which can compromise device integrity and performance.

Recent advancements in micro-stereolithography (μSL) 3D printing have enabled the fabrication of microfluidic devices with resolutions and surface qualities comparable to or even surpassing those achieved by soft lithography methods. μSL 3D printing allows for rapid prototyping and offers unparalleled design flexibility for complex 3D geometries, effectively eliminating the need for separate bonding steps. Techniques like stereolithography (SLA) and digital light processing (DLP) cure photopolymer resins layer by layer, seamlessly integrating intricate internal features without additional assembly. This monolithic construction enhances the structural integrity of the device, reducing the likelihood of leaks or mechanical failures that can occur at bonded interfaces in PDMS devices.

Further research is necessary on microfluidics engineering to overcome the fabrication of intricated geometries (Fig. 7). Complex designs like serpentine channels are more difficult to fabricate using photolithography and soft lithography compared to simpler T- and Y-shaped channels due to the complexities involved in mold creation. The production of intricate molds is time-consuming and labor-intensive for both methods. Moreover, introducing three-dimensional serpentine structures increases the fabrication difficulty, often necessitating multilayer lithography and precise alignment, which further complicates the manufacturing process. Regarding 3D printing technologies such as SLA and DLP, the primary challenge lies in issues like light bleeding, where unintended areas of the liquid resin are cured due to scattered light. This phenomenon requires extensive parameter fine-tuning to achieve the desired precision and feature resolution. However, further advancements in printer technology and optimization of printing parameters can mitigate these issues towards the automation of 3D printing into a more straightforward, "plug and play" method compared to traditional manufacturing techniques.

Another advantage of 3D printing in microfluidic device manufacturing is the lower cost and faster prototyping. Traditional methods frequently involve sophisticated equipment, cleanroom facilities, and skilled technicians, which are costly and time-consuming.

With 3D printing, intricate channels, chambers, and structures within microfluidic devices can be created and tailored to specific applications in nanomedicine [14]. The ability to fabricate complex geometries—including twisting channels, internal baffles, and other three-dimensional features—allows for the design of micromixers with superior mixing efficiencies. These designs promote chaotic advection and enhance fluid mixing at the microscale, which is crucial for applications in nanomedicine where precise control over mixing influences the production of nanoparticles.

Additionally, 3D printing technology accelerates the development cycle by enabling researchers to test and optimize their designs more quickly. Designers can easily modify and refine micromixer geometries using computer-aided design (CAD) software and rapidly produce new prototypes without the need for new molds or masks required in PDMS fabrication. This flexibility reduces costs associated with tooling and fabrication and fosters innovation through iterative design processes. Moreover, eliminating the bonding process simplifies manufacturing workflows and reduces potential contamination risks associated with adhesives or bonding agents used in PDMS devices.

3D printing not only overcomes the limitations of traditional PDMS methods but also expands the possibilities for innovative micromixer designs, making it a superior choice for microfluidic device manufacturing in nanomedicine. The combination of high-resolution fabrication, design flexibility, streamlined processes, and enhanced device performance positions 3D printing as an attractive alternative for advancing microfluidic applications [118].

6.1. *Fused deposition modelling (FDM)*

FDM 3D printing utilizes a solid material known as a filament, which is fed from a spool attached to the 3D printer to a heated nozzle that melts the material (Fig. 8) [119]. As the filament is heated above the glass transition temperature, it can be extruded along a predetermined path created by computer software. The material cools and solidifies upon extrusion, forming the basis for subsequent layers until the entire object is produced [120].

Several factors significantly impact the quality and properties of FDM-fabricated components (Fig. 9). The surface finish and complexity of the final product are primarily influenced by the print resolution, which is determined by the nozzle diameter and layer height. In addition, printing speed affects both production time and part quality, as printing at a faster rate may compromise print accuracy. In addition, the choice of material determines the completed part's mechanical, thermal,

Geometry	Parameters	Photolithography and Etching (for Glass)	Soft Lithography (using PDMS)	3D Printing (FDM, SLA)
T-Junctions	Difficulty of manufacturing			
	Cost			
	Time			
	Adaptability			
	Customization			
	Overall			
Y-Junctions	Difficulty of manufacturing			
	Cost			
	Time			
	Adaptability			
	Customization			
	Overall			
Serpentine Channels	Difficulty of manufacturing			
	Cost			
	Time			
	Adaptability			
	Customization			
	Overall			
Flow Focusing Channels	Difficulty of manufacturing			
	Cost			
	Time			
	Adaptability			
	Customization			
	Overall			
Coaxial Channels	Difficulty of manufacturing			
	Cost			
	Time			
	Adaptability			
	Customization			
	Overall			
Bifurcating Mixer	Difficulty of manufacturing			
	Cost			
	Time			
	Adaptability			
	Customization			
	Overall			

Fig. 7. Comparison of several manufacturing techniques for microfluidic devices. This color scheme indicates different difficulty levels, with green representing the easiest and red meaning the most difficult.

and chemical properties and its compatibility with the FDM printing system. Also, print orientation plays a crucial role in determining the overall strength, surface finish, and support structure requirements, as different directions correspond to varying levels of stress and support requirements.

Furthermore, the temperature settings for the nozzle and build plate must be optimized to ensure proper material extrusion, interlayer adhesion, and overall part quality. The temperature should be high enough to extrude the material but not too high to cause degradation or deformation. However, it is essential to consider the material's specific properties and follow the manufacturer's guidelines for temperature settings [121]. The build plate's temperature directly affects the adhesion of the printed material to the build surface. An adequately heated build plate prevents warping and ensures proper adhesion of the first layer of the print. Different materials have varying adhesion properties, so the optimal build plate temperature depends on the material used. For example, PLA typically requires a lower build plate temperature than materials such as ABS or PETG. In the case of custom filaments, such as API-loaded, it is crucial to conduct temperature experiments to determine the optimal nozzle and heated bed temperature.

Regarding nozzle diameter, the choice depends on the desired level of precision and print speed. Smaller nozzle diameters, such as 0.2 mm or 0.3 mm, can provide greater precision and finer details, but they can also result in slower print times and a higher risk of clogging. Larger nozzles, such as 0.4 mm or 0.6 mm, may provide faster print times at the expense of precision and resolution. It is necessary to balance these factors for optimal print quality and productivity. Finally, a precise calibration must be performed to ensure the print model is appropriately attached to the platform for a successful printing process. To address the challenges of using nozzles smaller than 0.4 mm for microfluidic device fabrication, several strategies have been implemented including reducing speed and layer height, selecting materials with suitable flow properties, and designing specialized nozzles to prevent clogging with smoother internal surfaces nd made from hardened steel to withstand the wear and tear caused by high-precision extrusion. Additionally, post-processing techniques like surface smoothing and channel sealing, as

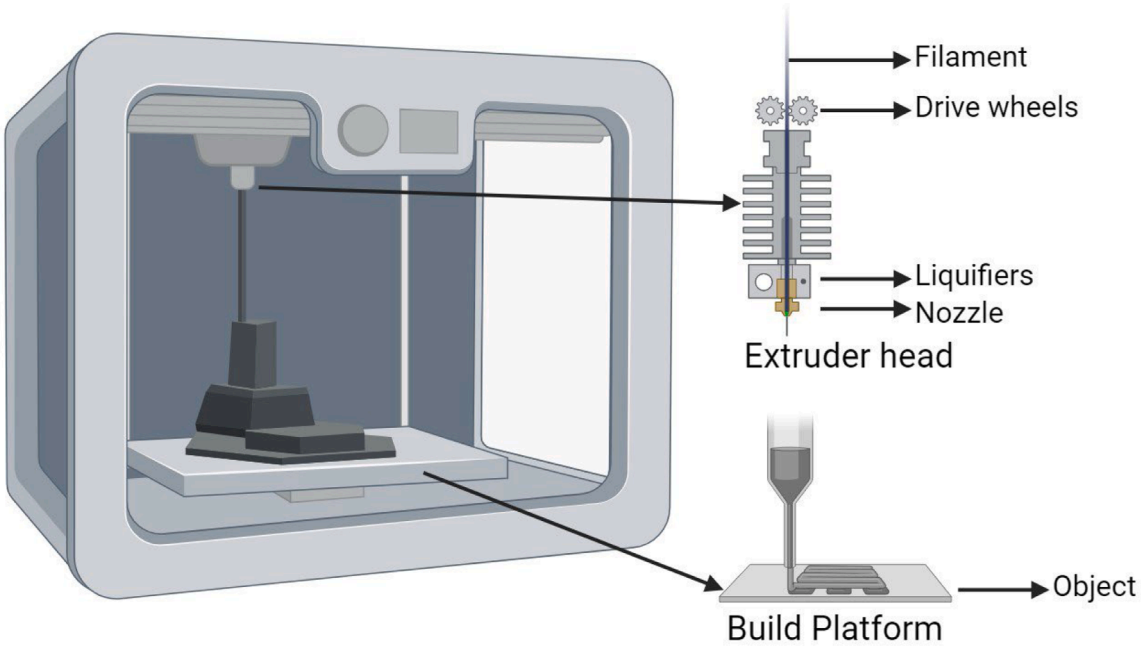


Fig. 8. Schematic illustration of FDM 3D printer.

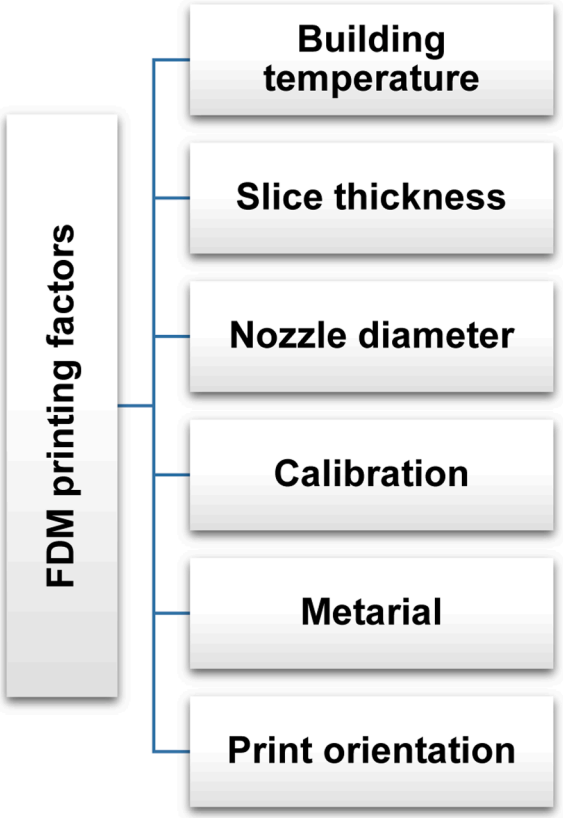


Fig. 9. Parameters affecting the FDM print process.

well as hybrid manufacturing approaches combining FMD, SLA and SLS, have been employed to enhance precision and functionality in microfluidic applications [113,122].

FDM 3D printers for manufacturing microfluidic devices have become an emerging area of interest due to the technology's versatility and affordability [123]. Utilizing FDM printers for microfluidic device fabrication in nanomedicine production presents benefits and difficulties. A significant advantage is their capability for rapid prototyping, which enables the rapid design and fabrication of microfluidic devices customized for specific nanomedicine applications. In addition, FDM printers offer a wide range of material options, allowing the selection of materials based on the requirements of the nanomedicine production process, such as chemical resistance or biocompatibility (Table 7).

However, the use of FDM printers for microfluidic device fabrication in nanomedicine presents several challenges. First, the resolution of FDM printing may not be adequate for creating the fine features and complex geometries frequently required in nanomedicine applications [137]. The resulting surface roughness within the microfluidic channels may result in inconsistent flow behavior and affect nanomedicine's qaulity attributes [13]. Second, certain materials commonly used in microfluidics, such as PEG or PMMA, are difficult to process with FDM, thereby limiting the range of materials suitable for specific nanomedicine applications [138]. Lastly, the potential presence of voids or defects in FDM-printed parts may result in leakage or cross-contamination within the microfluidic device, posing obstacles to producing reliable and reproducible batch-to-batch nanomedicine. Examples of successfully 3D printed microfluidics using FDM are illustrated in Fig. 10.

Despite the challenges associated with FDM printing for microfluidic applications, recent technological advancements have led to significant improvements in print resolution and the development of new materials tailored for microfluidics. These advancements include: (i) high-resolution FDM printers that can fabricate fine features and intricate geometries essential in microfluidic devices (Resolution of 40 μm [139]), (ii) advanced slicing software incorporating adaptive layer height features, which optimise the balance between print resolution and print time by allowing variable layer thickness within a single print [140], (iii) composite materials developed by filament manufacturers to enhance mechanical, thermal, or electrical properties, making them more suitable for microfluidic applications, (iv) custom filament formulations created by researchers that incorporate additives like nanoparticles or hydrophilic polymers, resulting in modified surface properties and improved device performance [141], and (v) dual

Table 7
Examples of FDM printing materials with their advantages and disadvantages for the fabrication of microfluidic devices.

FDM Printing Material for the fabrication of microfluidic devices	Characteristics		Ref.
	Advantage	Disadvantage	
Polylactic acid (PLA)	• Biocompatible • Biodegradable • Easy to use • Can be transparent • Recyclable • Inexpensive	• Can show a cytotoxic effect • Hygroscopic material • Not suitable for high-stress applications	[124,125]
Polymethyl methacrylate (PMMA)	• Biocompatible • Heat resistant • UV-resistant • Resistant to chemicals • Impermeable to air • Transparent	• No resistant to many organic solvents	[125–130]
Polycarbonate (PC)	• Transparent • Biocompatible • Heat resistant • Acid resistant • Hydrophilic surface • Easy to print	• Expensive • Difficult post-process • Sensitive during printing • Poor adhesion during printing	[125, 131–133]
Polypropylene (PP)	• Inert and does not leach chemicals • Strong and durable • Easy to print • Inexpensive	• Not biocompatible • Not transparent • Diffucult post-process	[15,134]
Cyclic olefin copolymer (COC)	• Biocompatible • Transparent • Easy to print • Resistant to chemicals • Compatible with sterilization processes	• Expensive • Require heated bed • Difficult post-process	[13]
Thermoplastic polyurethane (TPU)	• Flexible and elastic • Biocompatible • Resistant to chemicals • Easy to print	• Expensive • Require heated bed • Difficult post-process	[135]
Polyethylene glycol (PEG)	• Biocompatible • Water-soluble • Transparent	• Difficult to print • Not durable • Not strong	[136]

extrusion capabilities in FDM printers that enable the simultaneous use of two different materials or the combination of a primary material with a dissolvable support material, allowing the creation of complex microfluidic structures that would be challenging to achieve with a single extrusion system. These advancements have made FDM printing a more viable option for microfluidic applications by improving resolution and expanding the range of available materials designed explicitly for microfluidics [142]. As FDM printers continue to evolve, it is expected that their capabilities in manufacturing microfluidic devices will also improve, offering a viable alternative to traditional microfluidic device fabrication methods and fostering further advancements in this field.

6.2. Stereolithography (SLA)

SLA technology is a 3D printing technique that utilizes light to solidify liquid resin through photo-polymerization, creating a three-dimensional object in layers (Fig. 11).

During the process, a laser beam emitting ultraviolet light hardens selected areas, causing the resin layer to adhere to the previously solidified layer. This procedure is repeated layer by layer until the entire part is created. The printed object is extracted from the resin tank upon completion, and any support structures are separated mechanically. Photopolymer resins formulated specifically for SLA technology serve as raw materials, offering a wide range of material properties and expanding their potential applications, such as microfluidic devices. As one of the most stable and precise forms of 3D printing, it has gained significant attention for various applications. SLA allows for the utilisation of a variety of light source techniques, each with its own distinctive characteristics. (Table 8) [143].

The resin components include a mixture of monomers, oligomers, photoinitiators, and various additives. Monomers are reactive molecules that polymerize when exposed to ultraviolet (UV) light, forming the fundamental structural components of the final product. Oligomers, which are short chains of monomers, contribute to the mechanical properties of the printed part, including tensile strength and flexibility. Photoinitiators are crucial chemical compounds that absorb UV light and initiate polymerization [144].. When the resin is exposed to UV light, the photoinitiator molecules absorb the light's energy and split into highly reactive free radicals or cations. These radicals initiate a polymerization reaction, bonding monomers and oligomers to form polymers, which are long chains. This procedure converts the liquid resin into a solid substance (Fig. 12) [143].

To print a microfluidic device for nanomedicine applications, choosing resin components with biocompatibility, chemical resistance, and appropriate mechanical properties is crucial. Poly(ethylene glycol) diacrylate (PEGDA) is a prevalent monomer for biocompatible SLA resins owing to its hydrophilic nature and low protein adsorption (Fig. 13) [145]. Resins can be formulated using oligomers derived from aliphatic urethane acrylate [146] or polyester acrylate oligomers derived from polycaprolactone [147]. The biocompatible photoinitiators such as lithium phenyl-2,4,6-trimethylbenzoylphosphinate (LAP) [148], 2-nitrophenyl phenyl sulfide (NPS), and avobenzone [145] are ideal for microfluidic device printing due to their low toxicity and reduced potential for leaching into the microfluidic channels.

If additives are required, selecting those that improve the biocompatibility and chemical resistance of the resin without compromising its mechanical properties or printability is essential. Hydrophilic additives or surfactants, for instance, can improve the resin's wetting properties and reduce biofouling. To meet requirements for color or opacity, biocompatible pigments or dyes that do not interfere with the intended application should be employed.

The resolution of SLA 3D printers varies depending on the model and settings of the printer. Nevertheless, many modern SLA 3D printers can achieve resolutions below 100 μm in the XY plane, with some high-resolution printers reaching resolutions as low as 20–50 μm [121]. In the Z-axis, the layer thickness can be modified to provide an even finer resolution, typically between 5 and 25 μm [142]. These resolutions should be sufficient for most applications when fabricating microfluidic devices with less than 100 μm channel dimensions. However, light bleeding, also known as light scattering, can affect the resolution and precision of SLA 3D printers, especially when fabricating microfluidic channels smaller than 100 μm [149]. Light bleeding occurs when the UV light used to cure the resin spreads beyond the intended area, resulting in unintended curing and larger or more irregular features than desired.

Several strategies are available for mitigating the effects of light bleeding on printed structures. Optimizing the printing parameters, such as exposure time and laser power, minimizes unintended curing. Incorporating advanced light-curing systems that offer improved control over light intensity and distribution can also aid in reducing light bleeding [150]. Utilizing resins with enhanced photosensitivity enables a more precise and regulated curing process. Some researchers have investigated photoinitiators with reduced absorption in regions adjacent to the intended curing area, which can aid in minimizing light scattering and improving resolution [151]. By carefully considering the printing

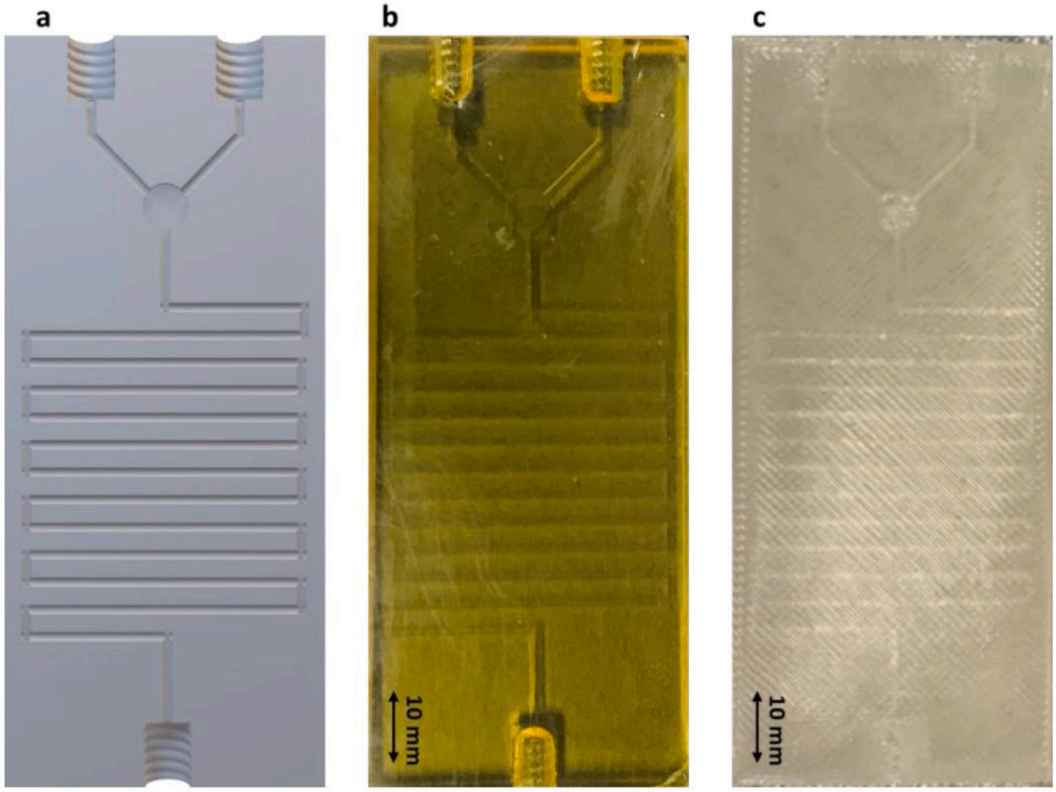


Fig. 10. Schematic representation and 3D printed chips. Key: (a) Sliced version (.stl file) of the microfluidic chip design; (b) Photograph of 3D printed microfluidic chip by SLA using Anycubic commercial resin; (c) Photograph of 3D printed microfluidic chip by FDM using COC material. Scale: 10 mm. Reproduced from: [113].

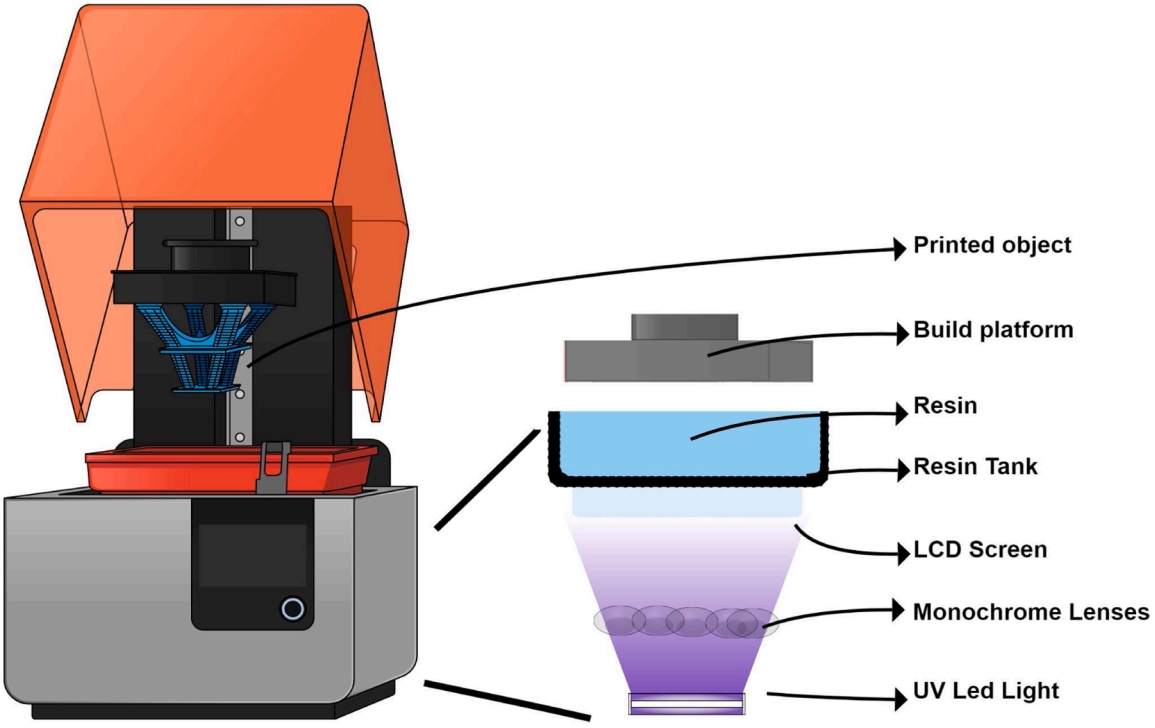


Fig. 11. Schematic illustration of SLA 3D printer.

parameters, light-curing systems, and resin properties, it is possible to minimize the effects of light bleeding and achieve the required resolution for using SLA 3D printers to fabricate microfluidic channels with a wall thickness of less than 100 μm.

The use of SLA printers in fabricating microfluidic devices for nanomedicine production offers several benefits, including rapid

Table 8
Overview of stereolithography (SLA) technologies in microfluidic fabrication.

Technology	Definition	Light Source & Curing Method	Advantages	Applications
Laser-Based SLA	Uses a laser beam to cure photopolymer resin point by point, tracing each layer's geometry with high precision	Laser beam; point-by-point curing	High precision; smooth surface finish	Complex parts requiring exceptional detail; intricate microfluidic devices
Digital Light Processing (DLP)	Utilizes a digital projector or digital micromirror device (DMD) to project and cure entire resin layers simultaneously by displaying the cross-sectional pattern of each layer	Digital projector or DMD; layer-by-layer curing	Faster printing speeds; high resolution suitable for microfluidics	Rapid production of detailed devices; high-throughput prototyping
Masked SLA (MSLA) / LCD-Based SLA	Employs an LCD screen as a dynamic mask to selectively block or allow light from an LED array, curing entire resin layers simultaneously	LCD screen with LED array; layer-by-layer curing	Combines high resolution with faster print times; cost-effective	Desktop printers; accessible fabrication of microfluidic devices; high-detail applications
Micro-Stereolithography (μSL)	An advanced form of SLA that achieves ultra-high resolutions by using specialized optics and shorter wavelengths of light, allowing for the fabrication of microscale and nanoscale features with exceptional detail	Specialized laser optics; sub-micron layer curing	Ultra-high resolution; capable of microscale and nanoscale features	Devices requiring sub-micron precision; advanced microfluidic components; nanochannels

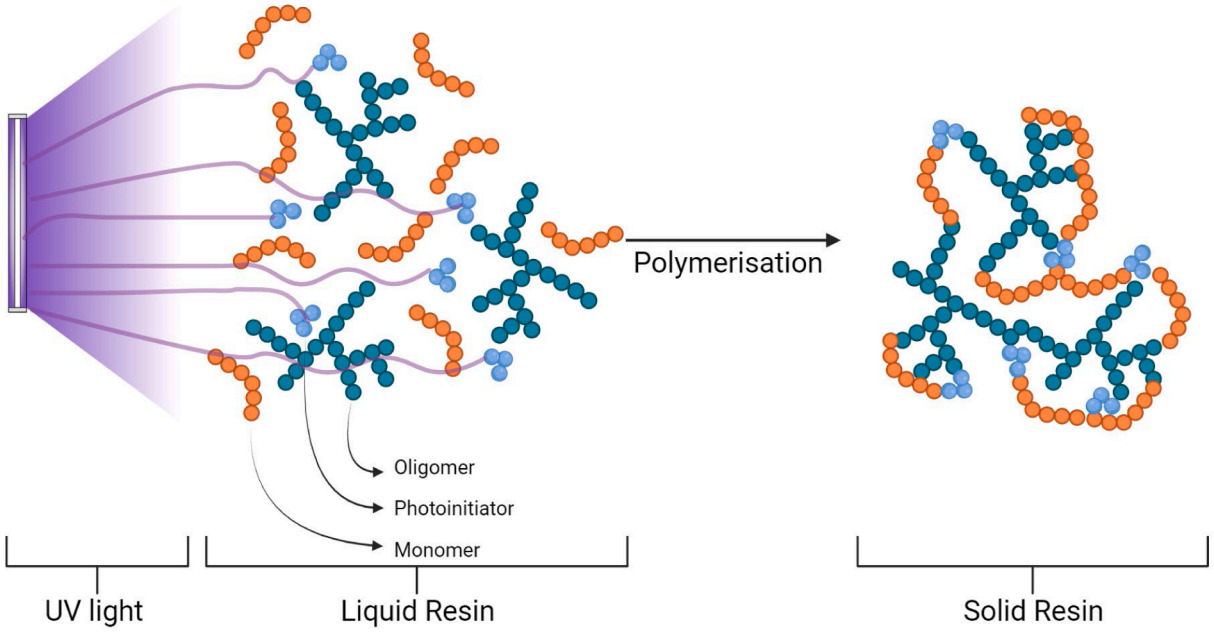


Fig. 12. Photopolymerization process of resin while using SLA printers.

prototyping and high resolution, surpassing the capabilities of other 3D printing techniques, such as FDM [13]. Rapid prototyping enables rapid design iterations, saving time and resources. This expedites device design and performance optimization [152]. By rapidly testing various channel geometries or flow patterns, for instance, researchers can accelerate the creation of effective drug delivery systems or nanoparticle manufacturing. In addition, SLA printers offer exceptional resolution and accuracy in designing intricate structures and complex geometries, which is essential for precisely controlling fluid dynamics and chemical reactions in nanomedicine applications [142]. This permits the controlled production of liposomes and polymeric nanoparticles with improved drug encapsulation efficiency and uniform particle sizes.

However, SLA 3D printing to produce microfluidic devices still faces challenges. Material selection is crucial, as many commercially available resins may lack the biocompatibility or chemical resistance required for nanomedicine applications, leading to cytotoxicity or adverse reactions with reagents (Table 9) [153]. This includes unintended interactions between the resin material and therapeutic agents, which can reduce drug efficacy or produce unwanted side effects. Another significant challenge is the possibility of resin leakage during the printing or post-processing stages, which could contaminate microfluidic channels and negatively impact the device's performance or the nanomedicine's safety [13]. For instance, resin leakage may result in blockage or cross-contamination in the microfluidic channels, affecting the quality and purity of the synthesized nanoparticles.

In addition, issues such as light bleeding, over-curing or under-curing, shrinkage, and deformation can compromise the resolution and accuracy of printed microfluidic devices, potentially affecting their functionality in nanomedicine production [149]. The potential toxicity of residual photoinitiators or monomers in cured resin may pose safety concerns [154]. For the successful implementation of SLA 3D printing in microfluidic device manufacturing for nanomedicine, rigorous cleaning and post-curing procedures and the development of novel biocompatible resin materials are essential for overcoming these problems. As SLA printers advance and new materials emerge, their capacity to produce high-quality microfluidic devices is anticipated to increase, thereby driving further innovation in the future.

7. Continuous manufacturing of nanomedicines coupling 3D-printed microfluidic devices with drying industrial techniques

Still, there are two main challenges associated with the fabrication of nanomedicines using microfluidic devices: (1) the removal of solvents without altering the final characteristics of the formed particles in an

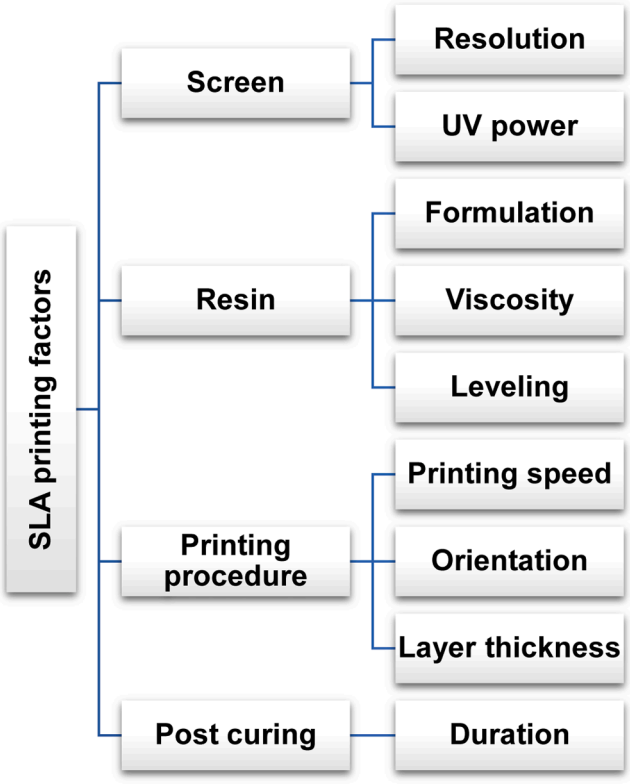


Fig. 13. Parameters affecting the SLA printing process.

Table 9
LD50 oral (mg/kg) values of commercial resins with their applications.

Resin	Manufacturer	LD50 oral (mg/kg)	Biocompatible	Applications
Formlabs Clear Resin®	Formlabs®	2000	No	Dental models, figurines, jewelry
Formlabs BioMed Clear Resin®	Formlabs®	5000	Yes	Medical devices, implants
Formlabs Tough 2000 Resin®	Formlabs®	1000	No	High-stress parts
Elegoo Standard Resin®	Elegoo®	500	No	Toys, figurines, prototypes
Elegoo ABS-Like Resin®	Elegoo®	500	No	Functional parts, cosplay props
Anycubic Eco Resin®	Anycubic®	500	No	Toys, figurines, models
Anycubic Tough Resin®	Anycubic®	500	No	Functional parts, cosplay props
Formlabs Dental SG Resin	Formlabs®	5000	Yes	Dental models, implants
EnvisionTEC E-Model Resin®	EnvisionTEC®	5000	Yes	Medical devices, implants

efficient and low-cost manner and (2) the continuous manufacturing of nanomedicines.

The removal of solvents from the final product is a critical step in the fabrication of nanomedicines, as residual solvents can affect the efficacy, stability, and safety profile of the drug delivery system [155]. Traditional solvent removal techniques, such as tangential flow filtration, evaporation, filtration, and centrifugation, are time-consuming, labor-intensive, and may alter the final properties of the formed particles. In addition, these techniques may not be compatible with the typically small volumes associated with microfluidic systems. Due to limitations in equipment capacity and the increased complexity of handling larger volumes of materials, such as the need for larger filtration systems in tangential flow filtration, scaling up these techniques can be difficult. In addition, the ability to regulate particle size throughout the manufacturing process is essential for optimizing the therapeutic efficacy of nanomedicines. Traditional methods like dialysis may not provide precise control over particle size distribution, resulting in a larger size range and suboptimal drug delivery characteristics.

Integrating 3D-printed microfluidic devices with industrial drying techniques can significantly improve the production of nanomedicine formulation (Fig. 14). Combining these technologies creates a continuous manufacturing system capable of producing stable, easily-managed final products such as liposomes, polymeric nanoparticles, and solid lipid nanoparticles.

Spraying, freezing, and fluidized bed drying are well-established industrial techniques for removing solvents or water from nanomedicine formulations, ensuring product stability and preservation. For instance, a continuous manufacturing process may involve synthesizing nanomedicines using a 3D-printed microfluidic device, in-line coupling with a spray drying system, and packaging and storing the resulting dry powder [71]. This integration reduces the downtime and waste associated with traditional batch-to-batch operations while enhancing control over particle size, distribution, and drug encapsulation efficiency, thereby enhancing the quality and performance of the nanomedicine product.

However, the efficiency and quality of nanomedicine production must be optimized. Implementing process control and monitoring in real-time can solve this issue. This can be accomplished by employing process analytical technology (PAT), which provides continuous feedback on critical process parameters and enables necessary adjustments. Manufacturers can ensure consistent product quality, decrease waste, and enhance overall efficiency by incorporating PAT into production. This strategy can also address the primary challenges of nanomedicine production, including batch-to-batch variability, cost, time consumption, labor intensity, and overall variability.

Incorporating PAT into the production process can also facilitate the implementation of successful continuous manufacturing methods. This is a desirable objective, as it may allow for enhanced process control, increased throughput, and decreased costs compared to batch processes. Incorporating in-line monitoring techniques, such as Raman or Near-infrared spectroscopy or dynamic light scattering, can provide real-time feedback on particle characteristics such as drug loading and particle size, allowing for more precise process control (Fig. 15) [156].

Furthermore, 3D printing allows for exploring new materials and integrating multiple functions into a single microfluidic device. This could lead to the creation of multifunctional microfluidic platforms capable of performing numerous tasks, such as nanomedicine synthesis, purification, and analysis, all within a single, compact device. This integration can potentially improve efficiency and reduce the overall cost of producing nanomedicines.

There are several startups and established companies advancing continuous manufacturing technologies for nanomedicines, particularly through microfluidic systems. This momentum increased substantially following the success of COVID-19 vaccines, as biotechnology companies intensified their focus on mRNA-LNP (lipid nanoparticle) development. A prominent example is the Canadian startup Precision NanoSystems [157], acquired by Cytiva, which developed the NanoAssemblr™ platform. This system utilizes microfluidic device technology to produce nanomedicines across scales, from laboratory research to GMP-compliant manufacturing, enabling seamless scaling for clinical and commercial applications. Another notable company is DIANT

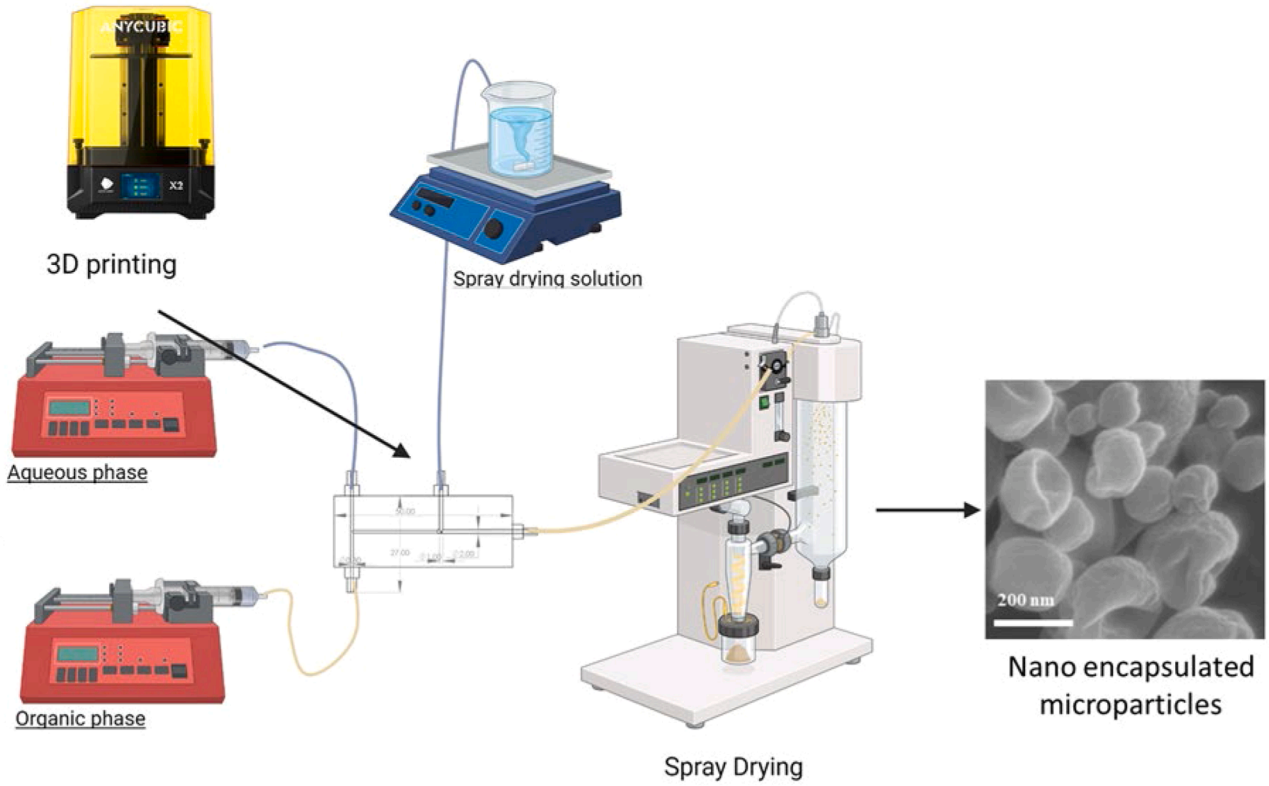


Fig. 14. Schematic representation of the continuous manufacturing of nano-in microparticles using 3D-printed microfluidic device coupled with a spray drier.

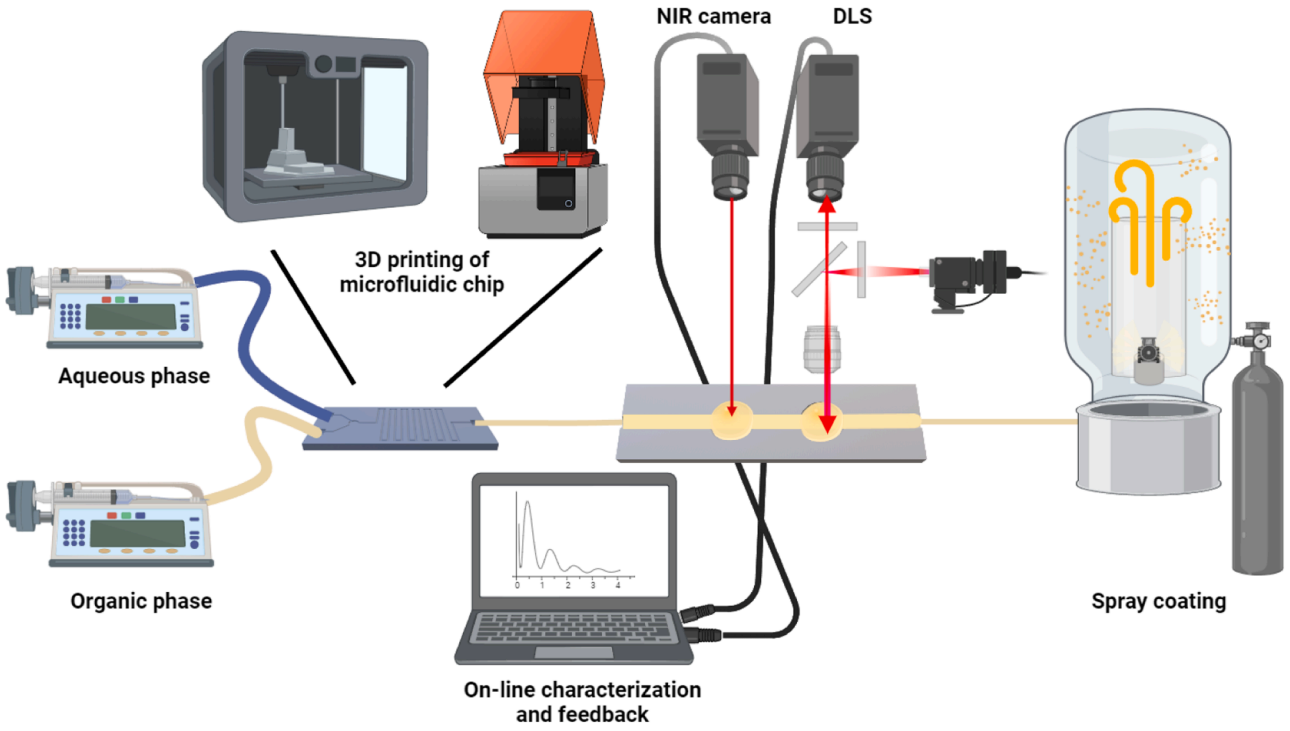


Fig. 15. Schematic representation of the continuous manufacturing nanomedicines with the integration of PAT module and spray coating.

Pharma Inc. [158], which offers continuous nanomedicine manufacturing systems integrated with Process Analytical Technology (PAT). DIANT's system minimizes human intervention by providing real-time quality control through automated, in-line monitoring, ensuring consistently high-quality nanomedicine production. Inside Therapeutics [159] is also advancing this field, employing microfluidic technology specifically for lab-scale nanomedicine manufacturing, facilitating rapid prototyping and experimental drug development.

An essential next step for these continuous manufacturing systems is incorporating Artificial Intelligence (AI) and PAT for real-time feedback

and adaptive control [160]. By using AI, these systems can autonomously adjust manufacturing parameters in response to real-time data, optimizing production processes and maintaining rigorous quality standards. This convergence of microfluidics, PAT, and AI marks a significant leap forward in achieving efficient, scalable, and high-quality nanomedicine production.

8. Future perspectives and conclusions

3D-printed microfluidic devices have the potential to fabricate nanomedicine with comparable quality to traditional PDMS and glass devices in terms of particle size and drug loading. Although PDMS and glass techniques have a longer history, providing more information on toxicity and overall performance, they still face particular challenges that cannot be easily overcome. Conversely, 3D printing is a more recent technology and has the potential to resolve existing issues as it continues to advance. At present, glass microfluidic devices are expensive and time-consuming to produce. Additionally, they struggle to adapt to new developments in microfluidic technology. While PDMS techniques are more established, they also lack customization and adaptability.

3D printing offers significant advances due to its customizable and automated manufacturing process. A well-developed manufacturing method could produce microfluidic devices with minimal material waste, low cost, and full customization. However, 3D printing technology still needs to grow and address various challenges. Each printing method, such as FDM and SLA, faces its own set of obstacles. Although more affordable and offering a wider range of biocompatible materials, FDM printers lack the resolution and smoothness of SLA printers. These issues can be addressed through advancements in high-resolution printers and improved slicing techniques.

On the other hand, SLA printers have high resolution and accuracy but currently lack biocompatible materials. Light bleeding during printing also prevents the production of channels smaller than 100 μm. Potential solutions to light bleeding include using light sources with resolutions below 10 μm or even nanometers. Furthermore, research should focus on developing biocompatible non-cytotoxic, and pharmaceutically safe materials. Resin leaching during nanomedicine manufacturing with microfluidic devices is another concern that must be addressed, as it can lead to contamination and regulatory issues. Potential solutions include improved post-printing techniques, developing solvent-resistant formulations, or coating the microchannels with solvent-resistant materials.

Implementing microfluidic technology in continuous nanomedicine manufacturing has immense potential. Combining an online process analytical technique with a drying process can produce nanomedicine with desired characteristics, minimal waste, and a fully automated system. This approach can also address the main challenges of nanomedicine manufacturing, such as batch-to-batch variability, cost, time consumption, labor intensity, and overall variability. As research and development in this area continue, accessibility and interest in nanomedicine will likely increase.

Scaling up 3D printing for mass production and integrating automation for high-throughput nanomaterial fabrication are indeed crucial challenges in the transition from laboratory-scale research to commercially viable solutions, especially in the field of nanomedicine. These challenges span a range of technical, logistical, and regulatory issues that need to be addressed to make 3D printing a viable tool for large-scale production and clinical applications.

One of the biggest hurdles is the lack of suitable materials and their standarisation to ensure reproducibility, the right balance of mechanical properties, biocompatibility and functionality. Additionally, for mass production, implementing robust QC (quality control) protocols that can monitor and verify the consistency of each print is essential. Traditional QC methods are not sufficient for ensuring the quality of 3D-printed microfluidic devices for the continuous manufacturing of nanomedicines, necessitating the development of new specialized techniques.

For scaling up production capacity, there is a trade-off between the speed of production and the resolution or precision of the printed object. Scaling up from small, slow, high-resolution prints to mass production without sacrificing quality is a difficult challenge. Current 3D printers are typically optimized for research-scale applications. Scaling up involves not only increasing the size of the print bed but also improving the ability of the printer to handle larger volumes of materials, faster printing speeds, and the maintenance of fine resolution over time. From an economic feasibility point of view, high-throughput production and continuous operation of 3D printers for mass manufacturing can lead to significant energy consumption. Developing energy-efficient printing processes is an important consideration for large-scale production. The cost of high-quality, and specialized equipment for 3D printing can be prohibitively expensive. For large-scale production to be economically viable, the cost of raw materials, printers, and maintenance must be reduced.

Regulatory approval from agencies like the FDA and EMA is also a significant challenge. The materials, processes, and final products need to meet rigorous safety standards. With 3D printing, ensuring that every printed batch is identical and meets regulatory standards adds complexity to the scaling process. Addressing these challenges will be vital for transitioning from small-scale prototypes to fully functional, mass-produced nanomaterials and devices, making it possible to harness the full potential of 3D printing in nanomedicine. Collaboration between materials scientists, engineers, medical professionals, and regulatory experts will be essential for advancing 3D printing from the lab to the clinic.

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CRediT authorship contribution statement

Aytug Kara: Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Baris Ongoren:** Writing – review & editing, Software, Data curation. **Brayan J. Anaya:** Writing – review & editing, Formal analysis, Data curation. **Aikaterini Lalatsa:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Data curation, Conceptualization. **Dolores R. Serrano:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization.

Declaration of competing 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.

Data availability

Data will be made available on request.

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