Review

Microfabricated particulate drug-delivery systems

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Micro- and nanoparticulate drug-delivery systems (DDSs) play a significant role in formulation sciences. Most particulate DDSs are scaffold-free, although some particles are encapsulated inside other biomaterials for controlled release. Despite rapid progress in recent years, challenges still remain in controlling the homogenicity of micro-/nanoparticles, especially for two crucial factors in particulate DDSs: the size and shape of the particles. Recent approaches make use of microfabrication techniques to generate micro-/nanoparticles with highly controllable architectures free of scaffolds. This review presents an overview of a burgeoning field of DDSs, which can potentially overcome some drawbacks of conventional techniques for particle fabrication and offer better control of particulate DDSs.

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1 Introduction

Micro- and nanoparticulate drug-delivery systems (DDSs), such as liposomes, hydrogels, micelles, and dendrimers, are a major topic of current drug-delivery research [1–7]. These DDSs overcome the problems of free drugs (poor solubility, poor distribution, rapid degradation, and rapid clearance) and greatly increase the pharmacological and therapeutic properties of drugs [8]. To obtain ideal DDSs that can deliver the drug to the target site effectively, their preparation methods have been continuously optimized [9]. In recent years, these DDSs have been incorporated into polymeric scaffolds for controlled drug release [10, 11]. Such scaffolds were fabricated using natural and synthetic polymers, metals, ceramics, and glasses [12]. Due to their biodegradabilities and mechanical strengths, scaffold-based micro-/nanoparticles could be used to deliver drugs to disease sites [13]. However, the fabrication processes of these scaffolds were complex [12, 13]. Furthermore, they were mostly special DDSs with limited clinical applications [7, 14–16]. The challenges of conventional particulate DDSs are still the focus of current research. One of the challenges is to control particle size, shape, and surface properties. For example, liposomes and micelles are amphiphilic particles formed spontaneously by self-assembly. Such self-assembled processes allow isolated molecular units to move into ordered structures randomly without intervention from external forces. Molecular units are mostly realigned into spherical aggregates with nonuniform size distribution, which influences their in vivo performances. Apart from particle size

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Abbreviations: CFL, continuous-flow lithography; **DDS**, drug-delivery system; **Dex-HEMA**, dextran-hydroxyethyl methacrylate; **DOX**, doxorubicin; **EDA**, ethylenediamine; **FDA**, Food and Drug Administration; **HFL**, hydrodynamic focusing lithography; **PAMAM**, poly(amidoamine); **PDMS**, poly(dimethylsiloxane); **PEGDA**, poly(ethylene glycol) diacrylate; **PEO-PCL**, poly(ethylene oxide)-*b*-poly(ε-caprolactone); **PFPE**, photocurable perfluoropolyether; **PLGA**, poly(lactic-co-glycolic) acid; **PRINT**, particle replication in non-wetting templates; **PS**, polystyrene; **RES**, reticuloendothelial system; **S-FIL**, step and flash imprint lithography; **SFL**, stop-flow lithography

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and shape, the surface properties of a particle are also important. Although polymers (e.g., PEG) and targeting ligands are commonly used to modify the surface of particles to improve the efficacy of particles, current methods of incorporating ligands mainly depend on chemical conjugation, which is difficult to control [17]. To address these challenges, various micro- and nanofabrication technologies, such as soft lithography and photolithography, have emerged as powerful tools. These technologies provide novel approaches for producing scaffold-free micro-/nanoparticles with complex geometries and functions.

Herein, we review these particulate DDSs, including important features of these particles and new strategies for their fabrication (Table 1).

2 Micro- and nanoparticles

The family of micro- and nanoparticles includes hydrogels, liposomes, micelles, and dendrimers. They differ in drug-loading capacity, particle stability, drug-release rates, and targeting ability. Hydrogels have been reported as excellent candidates for injectable DDSs. The hydrophilic nature of hydrogels can be utilized in the encapsulation of bioactive macromolecules, such as peptides and proteins, for controlled release [18]. Liposomes with both lipid bilayers and inner aqueous spaces are for the preparation of several cancer drugs. The anthracycline doxorubicin (Doxil, Myocet) is one of the liposomal formulations that received approval from the Food and Drug Administration (FDA) for sale [19]. For micelles, their core/shell structures serve as a suitable vehicle for hydrophobic drugs. For example, a polymeric micelle formulation containing paclitaxel was tested for pancreatic, colonic, and gastric tumor treatments [19]. Lastly, dendrimers, with branched monomer units, possess great potential in conjugating drugs and ligands to lead to possible improvement in controlled and targeted DDSs [20]. These important particulate DDSs are briefly reviewed to illustrate conventional approaches.

2.1 Hydrogels

Hydrogels can be synthesized by physically or chemically cross-linking water-soluble polymers [21]. According to size, hydrogels can be classified into bulk gels (>1 mm), microgels (0.1–100 μm), and nanogels (1–100 nm) [22]. The sizes of hydrogels can be controlled by several factors, including polymer concentrations, pH, temperature, and ionic strength [23]. Currently, nanogels are considered as promising drug-delivery particles because the nanoscale dimension facilitates higher cellular internalization and longer circulation times [24]. Kabanov and Vinogradov [25] recently reviewed the manufacturing, chemical modification, swelling, and drug loading of nanogels. They summarized current techniques used to generate nanogels, including (1) physical self-assembly of interactive polymers; (2) polymerization of monomers in homogeneous or micro- or nano-heterogeneous environments; (3) chemical cross-linking of preformed polymers; and (4) template-assisted nanofabrication of nanogel particles [25]. Hydrogels are also useful to mimic extracellular matrix structures for tissue-engineering application [26, 27].

2.2 Liposomes

Liposomes are spherical lipid vesicles used for the delivery of biological molecules, drugs, and cells [28]. Although differences may exist in their preparation methods, the preparation principle includes basic processes for lipid dispersion, solvent removal (evaporation/extraction techniques), and extrusion [29].

Liposomal particles can be used to improve the therapeutic efficacies of drugs by increasing their stability and circulation time, but also present challenges. Klibanov et al. prepared liposomes with an amphipathic PEG coating, which effectively prolonged the circulation time of the liposomes [30]. However, long circulation times may cause the drug to be retained in unexpected sites. In addition, other challenges such as high cost and lack of targeting ability also exist in liposome preparation [19].

Table 1. Important characteristics and new fabrication methods for classic particulate DDSs

Micro-/nanocarriers	Important characteristics of particles for drug delivery	Micro-/nanofabrication technologies[a)]
hydrogel liposomes micelles dendrimers	particle size particle shape surface properties	PRINT S-FIL film stretching flow lithography flow-focusing microfluidics bioprinting

a) PRINT, particle replication in non-wetting templates; S-FIL, step and flash imprint lithography.

Recently, Cao et al. reported the controlled formulation of aptamer-conjugated, cisplatin-encapsulating multifunctional liposomes to provide an aptamer-mediated cancer-targeting strategy [31].

2.3 Micelles

Micelles, which are self-assembling lipid monolayers, can spontaneously form when amphiphilic or surfactant molecules are dispersed in a liquid. Micelles have been extensively studied for water-insoluble drug delivery due to the hydrophobic core and hydrophilic shell [32]. Polymeric micelles used as carriers of anticancer drugs were reported by Kazunori et al. 20 years ago [33–35]. Polymeric micelles are more stable than those composed of small surfactant molecules. Polymers can form the shell of micelles and prevent loaded drug from undesirable release [36]. To achieve active targeting, polymeric micelles can also be fabricated by conjugation of ligands or addition of pH-sensitive moieties. For example, transferrin, folate residues, and peptides can be used as ligands for polymeric micelles that actively target cancer cells [37]. It was reported that micelles of different morpologies had different advantages in DDSs. Cai et al. [38] prepared worm-like and spherical micelles from the same amphiphilic diblock copolymer, poly(ethylene oxide)-*b*-poly(ε-caprolactone) (PEO-PCL), and encapsulated paclitaxel into the micelles. Compared with spherical micelles, worm-like micelles showed a higher hydrophobic drug-loading capacity for drug-delivery applications.

2.4 Dendrimers

Dendrimers are another class of polymers that are highly branched structures composed of a core, branched units, and surface groups [39, 40]. Different types of dendrimers are characterized by the core structures that initiate the polymerization process [41]. Poly(amidoamine) (PAMAM) spherical dendrimers with ethylenediamine (EDA) as a tetravalent initiator core is the most widely studied dendrimer [42, 43]. PEG has been frequently employed to modify PAMAM dendrimers to improve the solubility of drug particles, reduce possible cytotoxicity, and clearance by reticuloendothelial system (RES) [44]. Recently, Zhu et al. [45] used partly PEGylated PAMAM dendrimers as the carrier of the anticancer drug doxorubicin (DOX) to test the effects of PEGylation degree and drug conjugation style.

Despite the progress, challenges still remain because most of these conventional particulate DDSs are lack of precise control over several different design criteria, such as size, shape, and particle surface properties [46]. These criteria reviewed herein are important factors to be considered for the development of reliable particulate DDSs.

3 Characteristics important for micro- and nanoparticle drug delivery

There are a number of parameters governing the performances of particulate DDSs, namely, particle size, particle shape, and the surface properties of the particles. The relationship between these parameters and some drug-delivery functions are summarized in Table 2.

3.1 Particle size

The impact of particle size on particle function has been extensively investigated. Size influences particle biodistribution, clearance, and cellular uptake [47–53]. When particles are less than 5 nm, they are excreted by the kidney. Particles from 30 to 150 nm can be found in the bone marrow, kidney, stomach, and heart [54]. Particles 1–5 μm in size are mainly retained in the liver and removed by Kupffer cells [53, 55]. For particles more than 15 μm, they are cleared by mechanical filtration in capillaries [56]. In general, particles above 500 nm can be phagocytosed by macrophages and smaller ones can be endocytosed by phagocytic or non-phagocytic cells [57, 58].

Table 2. A brief summary of the relationship between particle parameters and drug-delivery functions

	Blood circulation time	Cellular uptake
particle size	decreasing size, increasing circulation time 100–200 nm in size have the highest potential for prolonged circulation	nanoscale particles show higher cellular uptake than microscale particles
particle shape	increasing length to width aspect ratio, increasing blood circulation time	nonsymmetrical particles show higher cellular uptake than symmetrical ones
surface properties	increasing hydrophobicity, charged properties decreasing circulation time	positively charged particles lead to non-specific internalization

Table 3. Micro- and nanoscale technologies for drug delivery

Micro-/nanofabrication methods	Size range	Shape variability
PRINT	20 nm–100 μm	spheres, cylinders, discs, toroids with defined aspect ratios
S-FIL	50–400 nm	squares, pentagons, triangles
film stretching	60 nm–30 μm	20 different shapes, e.g., worms, ellipses, circular disks, barrels
flow lithography	as small as 1 μm	triangles, squares, hexagons, high-aspect-ratio objects
flow-focusing microfluidics	10–50 μm	spheres

3.2 Particle shape

Recent studies suggest that particle shape is also important in the in vivo performance of delivery vehicles [59, 60]. Specifically, shape and shape-related factors such as the aspect ratio affect particle transport and cellular internalization [59, 61, 62]. Geng et al. [60] demonstrated that nanoparticles with higher length-to-width aspect ratios had longer blood circulation times in vivo. Gratton et al. [63] reported that cylindrical particles exhibited higher cell-uptake ratios than other shapes of particles. In addition, shape also affects the targeting ability of particles. It has been shown that the higher degree to which the surface structure fits the contours of cell membranes the greater the targeting ability of the particles [59].

3.3 Surface properties of particles

The influence of surface properties is mainly reflected by the interactions of particles with cells and tissues in the body. Hydrophobic and charged particles are rapidly cleared from the body by the RES [54]. Thus, particle surfaces modified with a hydrophilic polymer (e.g., PEG) can minimize particle recognition by the immune system and prolong the circulation time of the particles [60]. Attachment of ligands to the particle surface enabled micro- and nanoparticles to target specific cells and tissues [56].

4 Micro- and nanofabrication technologies

In light of the characteristics that govern particulate DDSs, micro- and nanofabrication technologies have been introduced to this field. Ranging from soft lithography and photolithography to etching, various fabrication techniques offer precise control over size, shape, and surface properties of particles. For example, microparticles generated by a flow-focusing microfluidic device exhibited a narrow and nearly uniform particle size distribution [64]. The surface features of these particles are particularly important for scaffold-free systems because the release of drugs from these particles is directly linked to these features. In contrast, the release profiles of particles embedded inside scaffolds are mostly dictated by the properties of the scaffolds. In addition, the architecture of micro-/nanoparticles can also be adjusted by physical methods. The film-stretching technique provided a simple method to produce particles with various 2D and 3D structures [65]. For surface properties, in contrast with liposomes and micelles for which the concentration of functional groups relies on kinetic trapping of functional molecules, particles in non-wetting templates (PRINT) particles are compatible with a wide range of functional agents and concentration of such agents can be chosen to meet specific needs [46]. Several recent technologies are given in Table 3.

4.1 Particle replication in non-wetting templates (PRINT)

Rolland et al. [66] reported a PRINT method for the fabrication of monodisperse particles with controlled particle structures. Briefly, fluoropolymeric molds in the method made of a low-surface-energy perfluoropolyether (PFPE) network were nonwetted with organic materials (Fig. 1) [46, 66, 67]. It was easier to harvest particles by using PFPE than poly(dimethylsiloxane) (PDMS) because with PDMS it was hard to remove the residual material between objects [66, 68, 69].

PRINT allowed for the precise control of particle sizes (20 nm to 100 μm) with the master template. In addition, particle shapes and geometries, such as spheres, cylinders, and discs with defined aspect ratios, were also controllable through the choice of templates. The replication of identical master features can be conveyed to all particles [46]. An increase of cellular internalization and decrease of uptake by RES were reported by using these particles [63]. PRINT particles were more stable when compared with particles, such as mi-

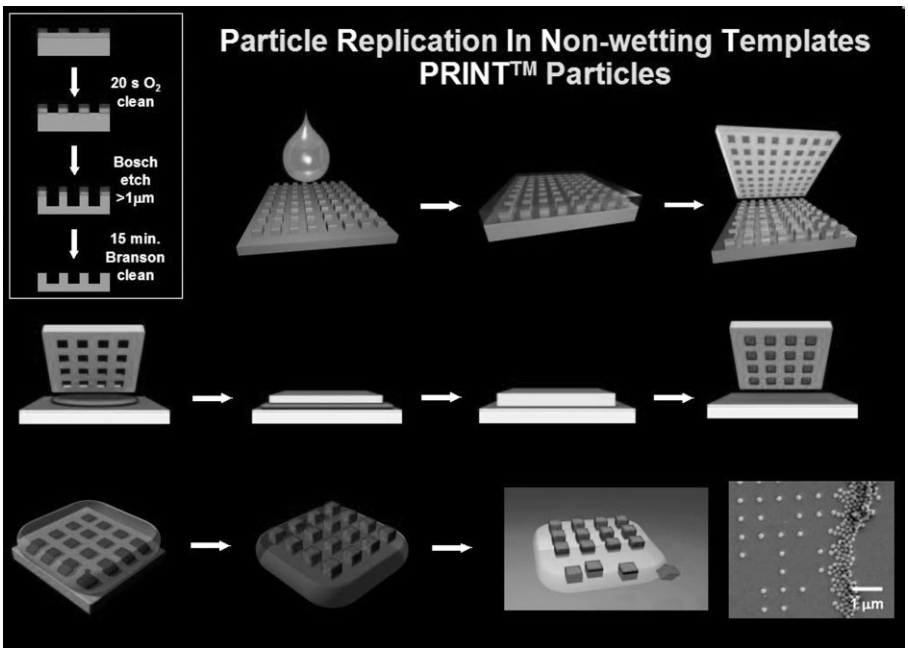

Figure 1. Schematic illustration for the whole process of the PRINT method. Fabrication of the silicon master template (inset), followed by wetting of the silicon master with liquid fluoropolymer, and curing (top row). A PFPE elastomeric mold is produced with nanoscale features from the master (upper right). Organic liquid is confined to the cavities by applying pressure between the mold and a PFPE surface (middle row). The organic particles are removed from the mold with an adhesive layer (bottom left), and finally, dissolution of the adhesive layer produces free particles (bottom right). (Reprinted from reference [46] with permission.)

celles, liposomes, and protein aggregates [46]. Recently, Petros et al. [70] reported a Trojan horse PRINT particle composition that incorporated a disulfide cross-linker to realize active release of DOX. A cell viability study revealed that PRINT particles were more efficient at killing HeLa cells than free DOX.

4.2 Step and flash imprint lithography (S-FIL)

Glangchai et al. [71] reported the application of step and flash imprint lithography (S-FIL) to fabricate stimuli-responsive nanoparticles of precise sizes, shapes, and compositions. A quartz template was used to mold nanoscale particles of varying sizes (50–400 nm) and shapes (square, pentagonal, and triangular) on a silicon wafer by using e-beam lithography. The main process was imprinting and isolation of the imprinted particles (Fig. 2). Prior to imprinting, silicon wafers were spin-coated with an anti-reflective coating, followed by spin-coating of a release layer of water-soluble poly(vinyl alcohol) (PVA). Poly(ethylene glycol) diacrylate (PEGDA) was also applied to the silicon surface. Then, the quartz template was pressed onto PEGDA and exposed to UV light to produce the particles.

It has been reported that particles with sizes below 100 nm were particularly important for transportation [72]. With S-FIL, particles as small as 50 nm can be fabricated. Second, S-FIL allows one-step release of the nanoparticles from the silicon wafer without mechanical scraping, such as that required for PRINT [46, 66]. To separate the imprinted particles, the residual layer between the nanoparticles was removed by oxygen plasma etching. Then, water was applied to dissolve the PVA release layer. Furthermore, a particle matrix (PEGDA-GFLGK-DA) cross-linked by the degradable peptide was created. In this way, the encapsulated cargo can be released after exposure to the enzymes.

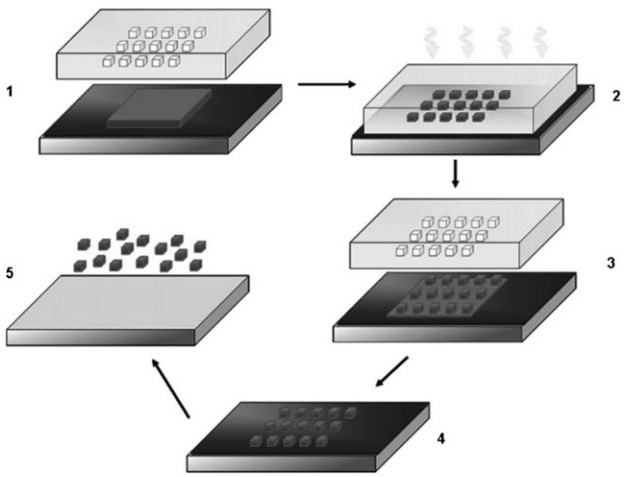

Figure 2. Schematic illustration of the S-FIL method. (**1**) The PVA release layer and PEGDA are applied to the coated silicon surface. (**2**) The quartz template is pressed onto PEGDA and exposed to UV light. (**3**) The template is removed to reveal particles in a thin residual layer. (**4**) A rapid oxygen plasma etch is performed to remove the residual layer. (**5**) The particles are harvested directly in water or buffer by one-step dissolution of the PVA layer. (Reprinted from reference [71] with permission.)

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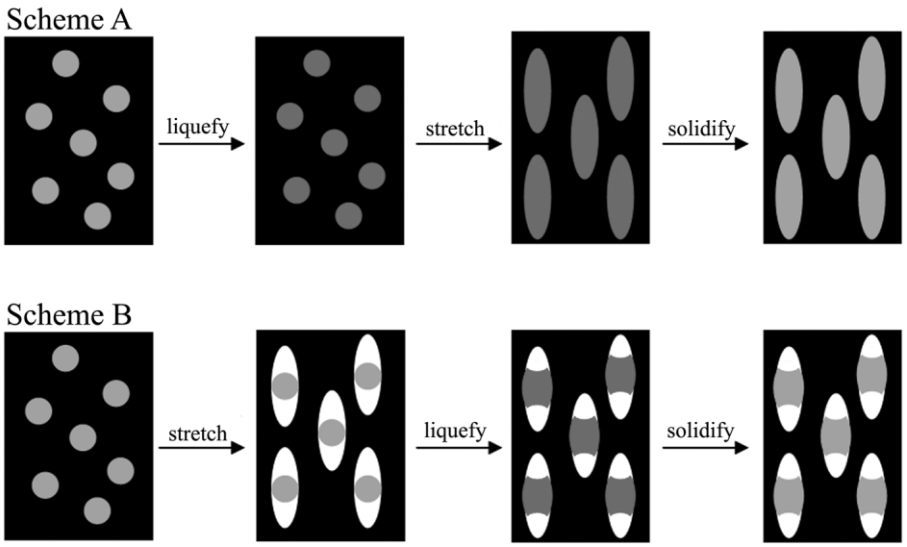

Figure 3. Schematic illustration of the film-stretching method. Scheme A involves the liquefaction of particles by using heat or toluene, stretching of the film in one or two dimensions, and solidifying the particles by extracting toluene or cooling. The example given here produces elliptical disks. Scheme B involves stretching the film in air to create voids around the particle, followed by liquefaction using heat or toluene, and solidification. The example shown here produces barrels. (Reprinted from reference [65] with permission.)

4.3 Film stretching

Champion et al. [65] presented a simple method to create particles with more than 20 distinct shapes and sizes ranging from 60 nm to 30 μm. They used spherical polystyrene (PS) particles to prepare particles of complex shapes that were suspended in an aqueous solution of PVA and cast into films. These films can be further stretched to generate particles with desirable sizes and shapes, such as worms, elliptical, circular disks, and barrels (Fig. 3). The resulting shape depended on the strong association between the liquefied particles and the film. Particle viscosity, film thickness, and the interplay between the particle–film wetting properties were the factors that controlled the shape of the particles. The particle volume remained constant during stretching.

Doshi et al. [73] used a new kind of idealized synthetic microvascular network to determine the adhesion properties of these particles with different shapes and sizes in a hydrodynamic environment. They found that particles of different geometries exhibited different adhesion tendencies, which proved the importance of particle shape for the target site. For example, the adhesion propensity of both elongated and flattened particles was greater than that of spherical particles. Doshi and Mitragotri [74] investigated the role of particle geometry and surface properties in their interactions with cell membranes. They evaluated the response of endothelial cells to particles of different shapes (spheres, elongated, and flat particles), sizes, and surface charges (positively and negatively charged). In their study, the impact of needle-shaped particles on cell morphology and motility was significant, whereas spherical and elliptical disc-shaped particles did not have such effect. It was also shown that needle-shaped particles led to cell membrane disruption, which was demonstrated by the release of lactate dehydrogenase and uptake of extracellular calcein. Furthermore, they demonstrated that the attachment of different particles to macrophages was correlated with the size and shape of the particles [75]. For all sizes and shapes studied, particles with the longest dimension showed the highest attachment ratio. These findings decoded some of the puzzles of micro-/nanoparticle passage mechanisms in vivo, including particle recognition by immune cells, the adhesion of particles in vascular tissue, and the response of endothelial cells to particles.

4.4 Flow lithography

Dendukuri et al. [76] reported a series of studies concerning flow lithography technology from continuous-flow lithography (CFL) to stop-flow lithography (SFL), and hydrodynamic focusing lithography (HFL). Starting from CFL, they developed a photolithography-based microfluidic technique that permitted the high-throughput generation of polymeric particles with varied shapes and multiple chemistries. They used a PDMS-coated microfluidic device containing rectangular channels through which the flow of an acrylate oligomer stream of PEGDA containing a photosensitive initiator passed continuously. Particles of defined sizes and shapes were formed by exposing the flowing oligomer to controlled pulses of UV light.

With this approach, particle size, shape, and aspect ratios could be controlled by designing masks

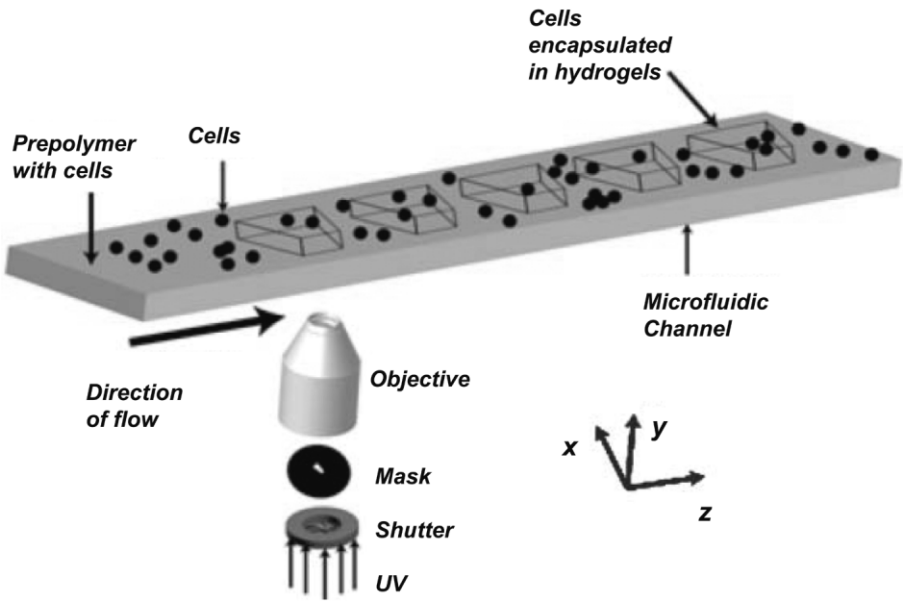

Figure 4. Schematic illustration of the SFL method. A prepolymer solution containing cells flows through a microchannel and is polymerized by UV light through a photomask and a microscope objective. (Reprinted from reference [78] with permission.)

with various features and selecting channels of different heights. The shapes they could synthesize included triangles, squares, hexagons, high-aspect-ratio objects, and curved objects with particle sizes greater than 3 μm. In addition to the size and shape, the chemistry of particles can also be controlled. However, due to the continuous nature of this method, CFL had limited resolution, which restricted the size of the smallest particle that could be generated.

To increase the resolution, Dendukuri et al. [77] developed SFL. In SFL, they used a three-way solenoid valve to shift rapidly between atmospheric pressure (stop) and the input pressure (flow) to control the flow inside the channels and designed three distinct steps—stop, polymerize, and flow—repeated in a cyclical manner. Therefore, particles were created in a stationary layer of monomer inside a PDMS microchannel to achieve good resolution. Moreover, the stop-polymerize flow mode of SFL allowed high velocity of the oligomer stream, which increased the throughput of particle formation. On the other hand, there was an upper limit to the flow velocity for CFL because increasing the velocity above the limit would lead to smearing and deformation of the particles formed. It was found that the particles in SFL showed a much sharper interface than those in CFL due to the difference of velocity. SFL was applied to cell-laden microgel particle generation, which may be used for diagnostic tools in drug delivery, DNA sequencing, and tissue-engineered constructs (Fig. 4) [78–82].

Recently, a new method called HFL was reported and it enabled the creation of stacked flows in two-layered channels for complex particle synthesis [83]. In HFL, multiple monomer streams could be stacked in both the *z* and *y* directions to generate more complex particles.

4.5 Flow-focusing microfluidic device

The "flow-focusing" technique was designed to produce highly monodisperse gas bubbles [84]. Afterwards, it was used for drop formation in liquid–liquid systems. Anna et al. [85] reported that mono- and polydisperse emulsions could be generated by this technique. The drop size could be controlled by adjusting the flow rate, flow rate radio, and inlet pressures of the two phases [86]. Because of the advantage of producing microparticles with monodispersity in size, the flow-focusing microfluidic device attracted great interest for synthesizing microgels for drug delivery. De Geest et al. [87] fabricated 10 μm sized, monodisperse dextran-hydroxyethyl methacrylate (Dex-HEMA) microgels by using flow-focusing microfluidic channels. It was also applied to 3D cell cultures useful for tissue engineering and drug testing [79, 88]. Tsuda et al. [89] reported a microfluidic flow-focusing device to produce cell-encapsulating microgels for 3D cell culture.

Recently, Xu et al. [64] presented a method to generate monodisperse microparticles in microfluidic devices and discussed the influence of particle size and fabrication procedure on drug-release kinetics (Fig. 5). They fabricated microchannels by soft lithography and oxygen plasma treatment [69, 90]. An aqueous solution of Tris buffer containing

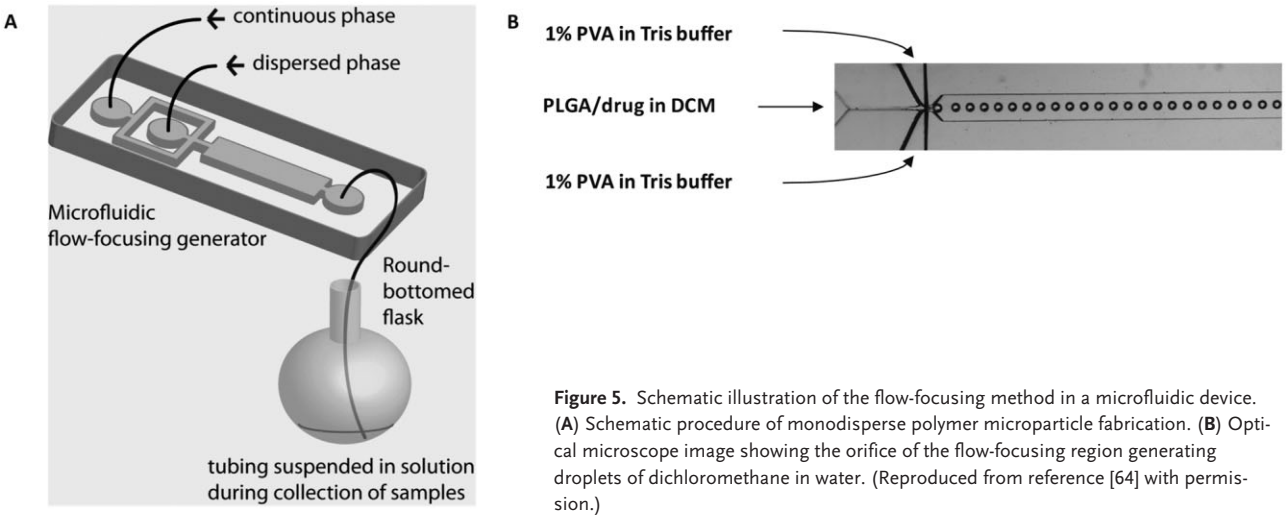

Figure 5. Schematic illustration of the flow-focusing method in a microfluidic device. (**A**) Schematic procedure of monodisperse polymer microparticle fabrication. (**B**) Optical microscope image showing the orifice of the flow-focusing region generating droplets of dichloromethane in water. (Reproduced from reference [64] with permission.)

PVA as a surfactant flew into the two side channels of a flow-focusing device. Dichloromethane containing poly(lactic-*co*-glycolic) acid (PLGA) and bupivacaine in its free base form as the encapsulating drug flew in the central channel. The stream of CH_2Cl_2 broke up at the junction of three inlets to generate droplets of CH_2Cl_2/PLGA/drug of uniform size. They designed three different sets of flow rates to obtain particles of different diameters. After particle generation in the microfluidic device, dichloromethane within the droplets was evaporated under reduced pressure. Then, the particle suspension was lyophilized under reduced pressure to remove the aqueous phase. Compared with the PLGA particles fabricated by a single emulsion method in their study, microfluidics-based microparticles showed a narrow distribution of sizes and reduced burst release and higher yields.

4.6 Bioprinting

In recent years, bioprinting technologies have been developed to fabricate 3D constructs for tissue engineering [91–93]. Bioprinting is a method to mold materials in designed structures with computer-aided processes [91]. It is a potential approach for controlling the size and shape of drug-delivery particles. One common method is inkjet printing. Tan et al. [94] created a parylene-coated silicon wafer with designed openings and filled the openings with proteins by using an inkjet printer. The parylene films were peeled off subsequently to generate finely patterned arrays of protein features. Parylene is a biocompatible polymer that can be used to form microstructures due to its chemical inertness [95]. Another emerging method is laser printing. Barron et al. [96] developed a laser-based printing technique to deposit a small volume of biomaterials with high spatial accuracy. In their study, a supporting quartz layer was coated with a laser-absorbing layer (metal or metal oxide), followed by coating with a layer of biomaterials. Depending on the energy from the photoabsorption process, each laser pulse propelled the removal of biomaterial from the supporting layer to a receiving substrate. Although current bioprinting methods were mostly used for tissue-engineering applications, the size and shape control ability made bioprinting a potential useful method to fabricate particulate DDSs.

Some other methods, including core/shell systems, co-jetting, and microcutting, also contributed to the fabrication of multicompartmental particles with controlled sizes and aspect ratios [97–99]. These methods may be explored more for the preparation of multifunctional drug-delivery particles as more and more research focuses on this area.

5 Conclusion

With increased complexity of particulate DDSs, particle geometry and composition control become more and more challenging. These challenges can be addressed, to some extent, by using microfabrication techniques. The PRINT and the S-FIL methods can be used to create monodisperse particles with precise sizes and shapes. The shape of the particles can also be controlled by stretching spherical particles in a polymer film. The SFL method can be applied for the fabrication of a huge number of cell-laden microgel particles by combining the advantages of microfluidics and photo-

lithography. Microfluidic-based devices (e.g., flow-focusing devices) have been developed to generate monodisperse, drug-loaded microparticles for controlled drug delivery. Evidently, micro- and nanofabrication techniques have made a big impact on the fabrication of particulate DDSs and their applications. To date, however, practical applications of these microfabrication techniques in particulate DDSs still remain largely unexplored. The advantages of engineered drug-delivery particles have not been fully verified, especially their stability, drug release, and targeting ability in vivo. Through future development, these microfabricated particulate DDSs might overtake some of the conventional delivery systems by providing precisely controlled particle properties. The novel particles can also provide new approaches for targeted drug delivery. In addition, cell-laden particles made by using these fabrication methods are potentially beneficial for studying specific cell-delivery and tissue-engineering applications.

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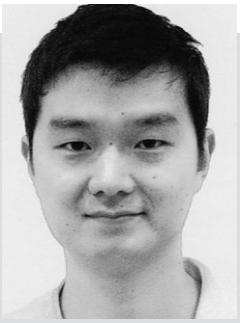

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