Microfabrication Methods for Biodegradable Polymeric Carriers for Drug Delivery System Applications: A Review

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***Abstract*— A drug delivery system is used for targeting drugs to specific cells. Various drug carriers, that also reduce the side effects of unbound drugs, have been introduced and commercialized in the pharmaceutical field. Among them, synthetic biodegradable polymers have received much attention attributed to their low toxicity, controllable biodegradation rates, manufacturability, and low costs. This paper reviews the salient characteristics of biodegradable polymers as drug carriers and their microfabrication methods. The reviewed microfabrication methods include laser micromachining, rapid prototyping, replication, emulsification, microfluidic fabrication, and X-ray-lithography-based methods. For these microfabrication methods, critical dimensions, feature variety, solvent compatibility, production throughput, and tooling requirements are also summarized. [2014-0070]**

***Index Terms*— Drug delivery systems (DDS), drug carriers, biodegradable polymers, poly-capro-lactone (PCL), poly(lactic-co-glycolic acid) (PLGA), microfabrication, laser micromachining, rapid prototyping, replication, emulsification, microfluidics, x-ray-lithography.**

I. Introduction

WHILE NUMEROUS drugs have been developed in pharmaceutical research areas, unbound drugs involve several critical problems, including poor solubilities in the human body, potential tissue damages from extravasation, a rapid breakdown of plasma concentration of drugs, and the lack of selectivity for target cells [1]–[3]. To ameliorate these problems drug delivery systems (DDS) have drawn significant attention in recent years. Various particulate drug carriers have been developed and utilized in DDS which can offer targeted drug delivery and controlled drug release at desired therapeutic levels [4]. However, the use of high quantities of carriers can lead to problems of carrier toxicity, effects on metabolism, and difficulties in carrier eliminations [3]. Therefore, the selection of appropriate carriers plays an important role in DDS.

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Attributed to advantages in biocompatibility, controllable biodegradation rates, manufacturability, and low costs, various synthetic biodegradable polymers have already been successfully used in commercial DDS. This paper reviews the salient characteristics of biodegradable polymers as drug carriers in section II. The biodegradable polymeric carriers can be fabricated by various microfabrication methods, such as laser micromachining, rapid prototyping techniques, replication techniques, emulsification, microfluidic fabrication, and x-ray-lithography-based methods, which are reviewed in detail in section III.

II. Biodegradable Polymeric Carriers for DDS

A. Synthetic Biodegradable Polymers

Synthetic polymers are known to have the characteristics of structural stability, ease of processing, and controllability in drug release [5]. Synthetic polymers, such as polyanhydrides, polyamides, phosphorous-based polymers, and biodegradable polymers have been utilized to develop polymeric particles for drug delivery [6]. Among the different classes of biodegradable polymers, poly-capro-lactone (PCL), polyglycolic acid (PGA), polylactic acid (PLA), and poly(lactic-co-glycolic acid) (PLGA) are generally used as building blocks. These biodegradable polymers are biocompatible, as approved by the United States Food and Drug Administration (US FDA) for biomedical devices, such as scaffolds for tissue engineering (in the case of PCL, PGA, PLA, PLGA), temporary prostheses (PCL, PLA, PLGA), and drug delivery vehicles (PCL, PLA, PLGA).

These biodegradable polymers are suitable for sustained drug release applications, attributed to their slow biodegradability for prolonged periods [7], [8]. The PCL compound is dissolved by hydrolysis of its ester linkages in the human body, and the rate of degradation is very slow typically taking 2-3 years to dissolve [7]. Since it has a very low toxicity, low cost, and slow degradation rate, it is suitable for long-term implantable devices, such as drug carriers and sutures [9]. The PCL polymer also has an excellent biocompatibility, making it suitable material for scaffolds to assist tissue and cell growth during formation of artificial organs for tissue engineering [9].

Various PLGA compounds undergo hydrolysis in the body, producing biodegradable metabolite monomers (namely, lactic acid and glycolic acid). The human body effectively deals with these two monomers, and therefore, there is only a minimal

carrier toxicity for implantable devices [10]. As a result, PLGAs have received significant attention in drug delivery and biomedical applications [6], and several pharmaceutical companies have already commercialized PLGA-based DDS [4]. The biodegradability of PLGAs can be adjusted by changing the proportion of PLA and PGA in the co-polymer. The PLGA (85:15) polymer containing 85% L-lactic acid (LA) and 15% glycolic acid (GA) degrades in approximately 5–6 months. On the other hand, PLGA (75:25) and PLGA (50:50) polymers take 4-5 months and 1–2 months, respectively for degradation [7].

B. Drug Loading and Release

The task of loading drugs in biodegradable polymers is generally performed by the following three methods: (1) surrounding the drug with biodegradable polymer shells to form drug-encapsulated carriers or laminating a solid or gelled drug layer with top and bottom biodegradable polymer films to fabricate drug-entrapped carriers, (2) mixing drugs in a biodegradable polymer solution to create a homogenous mixture and then emulsifying to fabricate drug-incorporated carriers, and (3) soaking pre-fabricated biodegradable polymer particles in a drug solution to fabricate drug-adsorbed carriers [11]–[17].

The mechanisms of the drug release process are slightly different for each of the three methods of drug loading. In the case of the drug-encapsulated or entrapped carriers, the drug release occurs mainly by a diffusion process from the core across the polymeric wall or by a direct effluence to the outside of the carrier [12]. A burst release can occur when the degradation rate of the biodegradable polymer shell is much higher than the diffusion rate [13]. In the case of the drug-incorporated carriers, the drug release occurs by the diffusion process as well as by the erosion of the biodegradable polymer [14]. If the diffusion rate of the drug is faster than the erosion rate of the biodegradable polymer, the drug release occurs by diffusion; otherwise it occurs by erosion [15]. In the case of the drug-adsorbed carriers, the drug release occurs mainly by diffusion [16]. The drug release processes are also affected by the molecular weight and the functional group of the polymer, the shape of the carriers, and the loaded volume of the drugs [5], [17].

C. Examples of DDS

Biodegradable polymers have already been successfully used in several commercial DDS [4]. The FDA-approved DDS using biodegradable polymeric carriers are summarized in Table I.

TABLE I
EXAMPLES OF DDS IN THE MARKET

Product name	Distributors	Dosage forms	Used polymers
Arestin	OraPharma	Subgingival administration	PLGA
Atridox	Tolmar	Subgingival administration	PLA
Eligard	Tolmar Therap	Subcutaneous injection	PLGA
Lupron Depot	Abbvie Endocrine Inc.	Intramuscular injection	PLGA, PLA
Nutropin Depot	Genentech	Subcutaneous injection	PLGA
Sandostatin LAR Depot	Novartis	Intramuscular injection	PLGA
Trelstar	Watson Labs	Intramuscular injection	PLGA
Zoladex	AstraZeneca	Implant	PLGA

Source: United States Food and Drug Administration website (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/).

III. COMMON MICROFABRICATION METHODS FOR BIODEGRADABLE POLYMERS

A. Laser Micromachining

Laser micromachining is a single-step process and a non-contact method used to pattern biodegradable polymeric materials [18]. Since the biodegradable polymers are sensitive to a heat [7], minimizing the thermal damage to materials is important in patterning microstructures. The most popular lasers used for micromachining are the ultra-violet (UV) lasers which have various sources, such as excimer, argon-ion, tripled and quadrupled neodymium-doped yttrium aluminum garnet (Nd: YAG), fluorine, helium–cadmium, metal vapor, and nitrogen [19]. The emitted photon energy from a UV laser is high which can break the chemical bonds of irradiated polymers directly. This photochemical process can minimize the heating effects compared to the photothermal process in other lasers, and thus the thermal damage to non-irradiated parts can be minimized [20]. This characteristic makes UV laser micromachining very appealing for microfabrication of biodegradable polymers. Another approach is the pulsed CO_2 laser [21]. The CO_2 laser rapidly heats up the polymer, which leads to melting and vaporization of the material. Therefore, it is important to consider the thermal properties of the biodegradable polymers being laser machined. An alternative tool is the solid-state femtosecond lasers with a near infrared (NIR) wavelength. These femtosecond lasers can reduce the interaction time of the lasers and materials, and the influence of the heat conduction around the micromachined area can almost be ignored [18], [22], [23].

Figure 1(a) shows a microhole in a PCL polymeric film etched by a UV laser, and Fig. 1(b) shows a microhole etched by a femtosecond laser [18]. The results show minimal melting and debris along the edges, but the features are somewhat rough. The irregularities in the shape of the hole are attributed to the non-circularity of the original laser beam. The micromholes have sizes of tens of micrometers. Figure 1(c) shows the cutting line in a PCL polymeric surface fabricated by a CO_2 laser [21].

The melted line solidifies on the surface along the cutting line. The width of the melted line is 128 μm. Nevertheless, the edges are better defined when compared to those of UV lasers and femtosecond lasers.

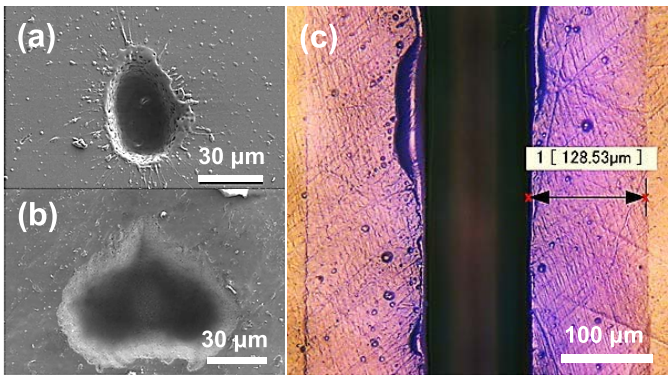

Fig. 1. SEM images of PCL polymeric surfaces ablated with laser micromachining. (a) Microhole etched by UV laser with exposure energy of 14 mJ [18], (b) microhole etched by femtosecond laser with exposure energy of 0.4 mJ [21], and (c) cutting line fabricated by CO_2 laser with melted line of 128 μm [21].

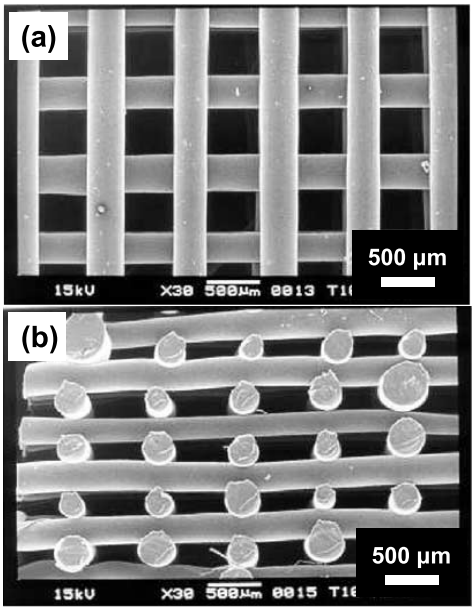

Fig. 2. SEM images of cut surface of PCL scaffold fabricated by direct deposition method. (a) Top view of PCL scaffold and (b) side view of PCL scaffold [26].

Laser micromachining is a one-step process and solvent free method used to pattern polymeric materials. However, thermal damages to surrounding areas hinder accurate control of critical dimensions, limiting its applications.

B. Rapid Prototyping

Rapid prototyping techniques have been used to fabricate structures with complex geometries which include laminated parts [20]. The fabrication process is usually assisted by computer-aided design (CAD) for arbitrary shapes. The common methods include direct deposition [24]–[26], three-dimensional printing [27]–[30], and stereolithography [31]–[33].

Direct deposition is essentially micro-scale extrusion [24]. A pressure assisted micro-syringe is used to create a biodegradable polymer scaffold with micro-scale porosity [25]. Figure 2 shows PCL scaffolds fabricated using micro-extrusion

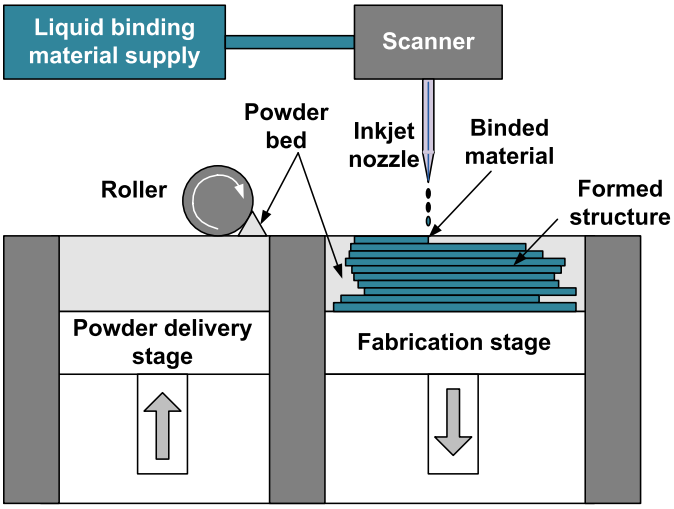

Fig. 3. Schematic setup of 3DP system [28].

of PCL filaments, resulting in a resolution of several hundred microns [26]. Three-dimensional scaffolds can also be easily made by stacking 2D layers. However, the geometry is limited since a structure has to be fabricated by stacking filaments [20].

Three-dimensional printing (3DP) fabricates parts by a layered printing process. From a CAD of a desired part, a slicing algorithm draws detailed information for every layer [27]. Figure 3 shows the schematic setup of a 3DP process [28]. Each layer begins with a thin distribution of powder spread over the surface of a powder bed. Using a technique of ink-jet printing or spray coating, a binder material selectively joins particles where the structure is to be formed. A piston which supports the powder bed and the stage lowers so that the next powder layer can be spread and selectively joined. This layer-by-layer process is repeated until the part is completed. Unbound powder serves as a support material during the process and is removed after fabrication. The scaffold systems can encapsulate drugs and can be used for drug carrying purposes [28]. The 3DP method has a distinct advantage in feature variety, which increases its potential for industrial applications from the micro scale to the macro scale. However, most of 3DP systems are not suitable for micro-scale parts, which limits the applicability of this method for the fabrication of small particulate drug carriers [29], [30].

Laser stereolithography is similar to 3DP, and the difference is working in a liquid environment [31], [32]. Figure 4 shows a schematic setup of a laser stereolithography process [33]. A 3D model designed with CAD is numerically converted into a series of sliced 2D layers with an equal thickness. Each sliced file is to control a motorized x–y–z platform immersed in a liquid photopolymer. The liquid polymer is selectively exposed to a focused laser light, and forms a solid. The elevator platform moves downward according to the design after each layer is solidified.

The most desirable characteristic of rapid prototyping techniques is shaping complex geometries, which can be assisted by CAD. The layer-by-layer stacking process is good for fabricating 3D scaffolds for tissue engineering. However,

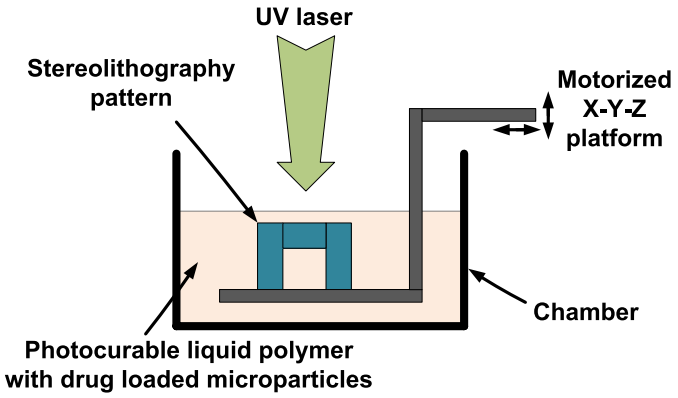

Fig. 4. Schematic setup of laser stereolithography system [33].

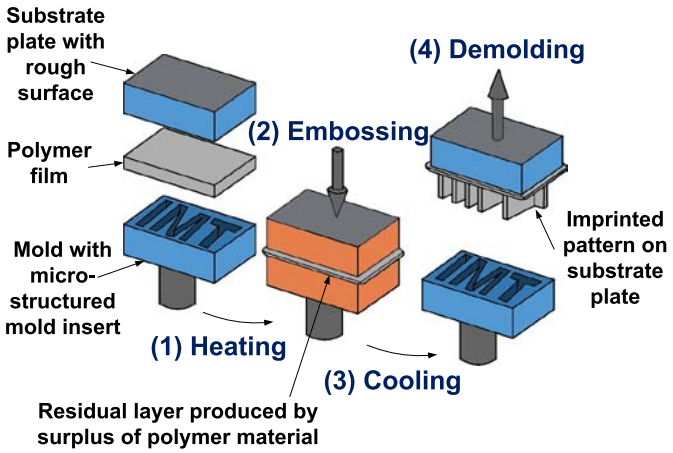

Fig. 5. Schematic of nanoimprinting lithography process [40].

the size of the stacked filaments which is determined by the nozzle diameter is hard to decrease [28]. The sizes of these nozzles with inner diameter can be as small as 20 μm [30]. Therefore, the applicability for fabrication of micron scale devices is restricted. The throughput of rapid prototyping techniques is relatively low compared to other microfabrication methods, due to the time required for the completion of product with the layer-by-layer process.

C. Replication

Replication techniques including nanoimprinting lithography and soft lithography are widely used microfabrication methods for biodegradable polymers [34]. The underlying principle is the replication of a microfabricated mold, which has the inverse geometry of desired polymeric structure. The mold can be expensive, but the replication step can be applied many times. A variety of geometric shapes can be fabricated in these techniques [35]. The multi layered polymer structures with polygonal shapes can also be fabricated [36]. Therefore, the replication techniques have attracted much interest in fabricating DDS carriers [37].

Nanoimprinting lithography is widely used to transfer micro patterns from a master mold onto a polymeric substrate at a proper pressure and temperature [38]. A typical nanoimprinting lithography process is composed of four major steps, as shown in Fig. 5 [39], [40]: (1) heating the mold and substrate, (2) embossing microstructure patterns, (3) cooling the mold and substrate, and finally (4) demolding the microstructure by opening the mold. After the major steps, the resulting polymer film with a surface pattern is peeled off easily.

In soft lithography, an elastomeric stamp with patterned structures on its surface is used to generate patterns and structures. The polydimethylsiloxane (PDMS) elastomer including a liquid silicone rubber base and a curing agent can be mixed and poured to a master mold. The PDMS is heated and solidified with a few hours, and a PDMS stamp is peeled off from the master mold. The polymeric solution which is mixed with solvent is poured on the silicon wafer. The PDMS stamp is then applied to the silicon wafer with little force. The solvent is evaporated at room temperature for 24 hours and the formed polymeric film is peeled off from

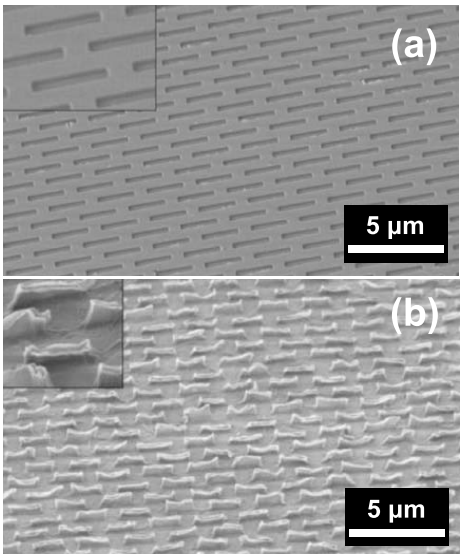

Fig. 6. SEM images of imprinted PCL patterns. (a) PDMS stamp and (b) PCL film with surface relief structures fabricated by solvent assisted molding. Scale bars in 5 μm [20].

the stamp. The polymeric film has the surface relief structures which are the same structures on the master mold. Figure 6(a) shows the PDMS stamp and Figure 6(b) shows the generated PCL micro patterns, while the walls are slightly distorted [20]. This distortion is attributed to the remaining internal stress caused by adhesion between PCL and the PDMS stamp at the corners and to the lack of robustness of the material itself. The minimum feature size is 50 nm, corresponding to the resolution of conventional e-beam lithography which is used for fabricating the master mold [20].

In addition to these replication techniques, biodegradable polymeric nano and microparticles can be fabricated by the PRINT (Particle Replication In Nonwetting Templates) process, which utilizes the low surface energy of novel fluoropolymeric molds [41]. The molds are solidified from liquid perfluoropolyether (PFPE) which are photochemically cross-linked polymers at room temperature. These elastomeric molds are then used to fabricate a variety of organic particles with a high resolution, as shown in Figs. 7(a) and 7(b) [42], [43].

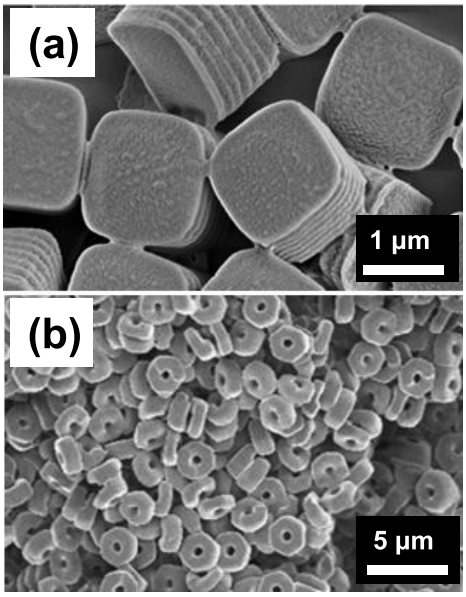

Fig. 7. SEM images of PLGA microparticles fabricated by the PRINT process. (a) Cubes with size of 2 μm and (b) center fenestrations particles with size of 3 μm [43].

Note that the critical step to be considered in all replication processes is the release process which is separating the final structures from the mold. Because the surface conditions and geometry of the microstructures have an influence on the demolding process, the release of final polymeric structures is very critical for the quality of fabricated patterns [34]. Nevertheless, inexpensive tool cost and high throughput make these replication techniques one of the most popular microfabrication methods for biodegradable polymers.

D. Emulsification

The emulsification (or emulsion-evaporation) technique is the simplest method of forming nanoparticles [44], [45]. This method involves dissolving the polymer in a volatile organic solvent such as acetone or dichloromethane, and pouring this solution into a rapidly stirred second aqueous solution, resulting in emulsification. The volatile solvent rapidly evaporates, leaving behind hardened polymeric particles suspended in the stirred second solution. The stirring condition can control the sizes of particles with ranges from 50 nm to 50 μm [44]–[47]. These particles are filtered or freeze-dried to collect free-flowing powder of particles [46]. This type of emulsion, where an organic solvent-based internal phase is poured into an aqueous external phase, is a water-in-oil emulsion, and spherical shapes are fabricated.

To load drugs in the biodegradable polymeric carriers, drugs need to be added at the internal phase. This process is straightforward when drugs are soluble in an organic solvent, as the therapeutic substances can simply be added to the internal phase along with the polymers [47]. When drugs and polymers are not soluble in the same solvent, additional steps are needed [46]. One method is using multiple solvents in the internal phase, creating a three-phase emulsion. Drugs are solubilized in an aqueous solution and emulsified in the polymer solution to create an external phase. The polymeric particles containing drugs are then emulsified in a second aqueous solution, fabricating the double emulsions [47].

The throughput of emulsification can be somewhat higher than that of replication techniques, because of the simplicity of forming particles. The only required tools are a beaker and mixer to stir the solution. However, conventional emulsification techniques used to fabricate drug carriers have disadvantage in non-uniform sizes. One potentially approach to overcome the limitation is the use of microfluidic devices, producing highly controlled and uniform emulsion-based templates, which in turn, can be used for the fabrication of microparticles.

E. Microfluidic Fabrication

Advances in microfluidics have presented exciting opportunities to improve the fabrication of particulate drug carriers [48]. Since microfluidic approaches to droplet formation use flows at low Reynolds number, fluid streams are laminar and easily controlled [49]. These stable flows can fabricate highly-controlled emulsions, resulting in microparticles with uniformsizes [50]. Microfluidic chips are easily fabricated using standard soft lithography techniques [51].

As an example, two continuous and immiscible streams (i.e., oil and water) are infused into two separate inlets, as shown in Figs. 8(a) and 8(b) [52]. The monodisperse droplets could be generated at the junction where the two streams meet due to high shear stress, as shown in Figs. 8(c) and 8(d). The droplet sizes observed in this study ranges from 20 to 100μm, and other studies show the sizes of droplet diameters ranging from 50 nm to 800 μm [53]–[58]. Compared to the double emulsions from the emulsification method, multiple components are easily generated by a single-step emulsification in the microfluidic device. By introducing the second stream, the droplet could be re-encapsulated to form oil-in-water (W/O/W) double emulsions which are useful for preparing core-shell structures [54]. The DDS of monodisperse double emulsions that have various inner components could then be fabricated with precise control over their volume. These particles are attractive since they can be used to co-deliver two drugs with distinct effects. In addition to double emulsions, Janus particles, which have interesting anisotropic structure and are difficult to prepare using conventional methods, could be readily fabricated in a microfluidic platform [54].

Several advantages make the microfluidic fabrication one of the most successful methods in the field of DDS. Microfluidics can be used to synthesize a wide variety of materials [11]. Microfluidics can be easily scale-up for high throughputs [4], [51]. Other advantages includes: rapid mixing of reagents, homogeneous reaction environment, flexibility for multi-step reaction design, processing accuracy and efficiency, good heat transfer properties due to high surface-to-volume ratio, ease of miniaturization, and cost savings from reduced consumption of reagents [55]–[58]. The throughput is extremely high when materials for the fabricating DDS carriers are supplied continuously ($\sim$50,000 particles with the size of 20 μm fabricated per second in one fabrication lot) [51].

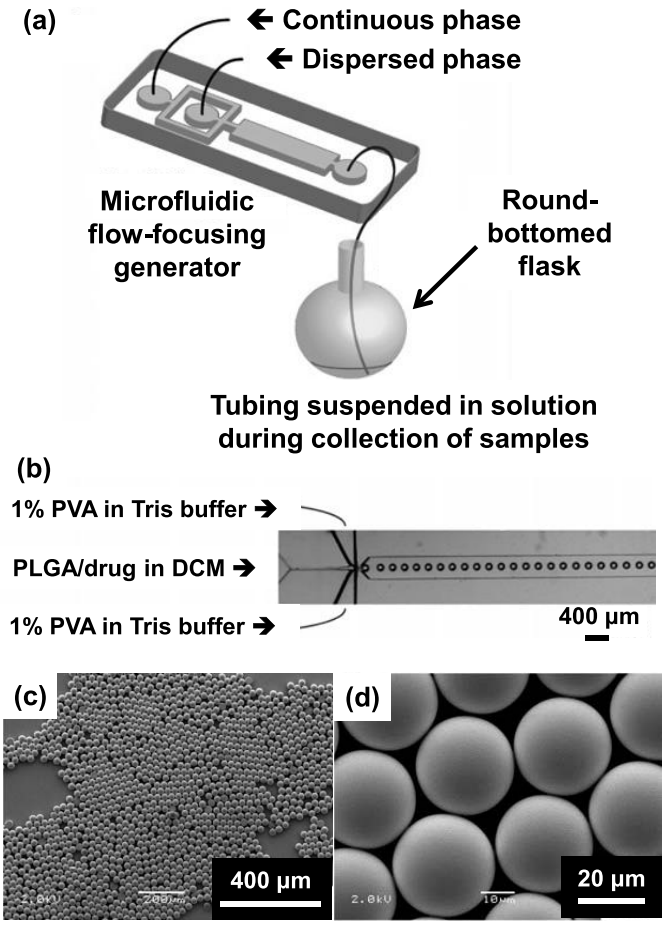

Fig. 8. (a) Schematic illustration of the procedure to fabricate monodisperse polymer microparticles. (b) Optical microscopy image showing the orifice of the flow-focusing region generating droplets of dichloromethane (DCM) in water. (c, d) SEM images of monodisperse PLGA microparticles [52].

With the emulsification techniques, the microfluidic fabrication techniques are the most popular methods to fabricate drug encapsulated droplets, which can easily achieve the mass production of DDS. A drawback is that only the spherical shapes can be fabricated.

F. X-Ray-Lithography-Based Methods

Since x-ray synchrotron irradiation was first demonstrated for use in exposing a thick resist layer in 1976 [59], deep x-ray lithography has been utilized for the fabrication of microstructures with a high aspect ratio (HAR) and significant structural height. This is based on combining synchrotron radiation lithography, electroplating, and plastic molding (in German, Lithographie, Galvanoformung, Abformung (LiGA)) [60]. For the microfabrication of biodegradable polymeric carriers, x-ray-lithography-based methods have also been investigated [61], [62]. It was shown that the poly-L-lactide acid (PLLA) and PCL polymers which have poly(lactides) can be patterned by x-ray synchrotron irradiation. Using an alkaline solution as the developer, the irradiated biodegradable polymers can be dissolved and non-irradiated parts can be the structures.

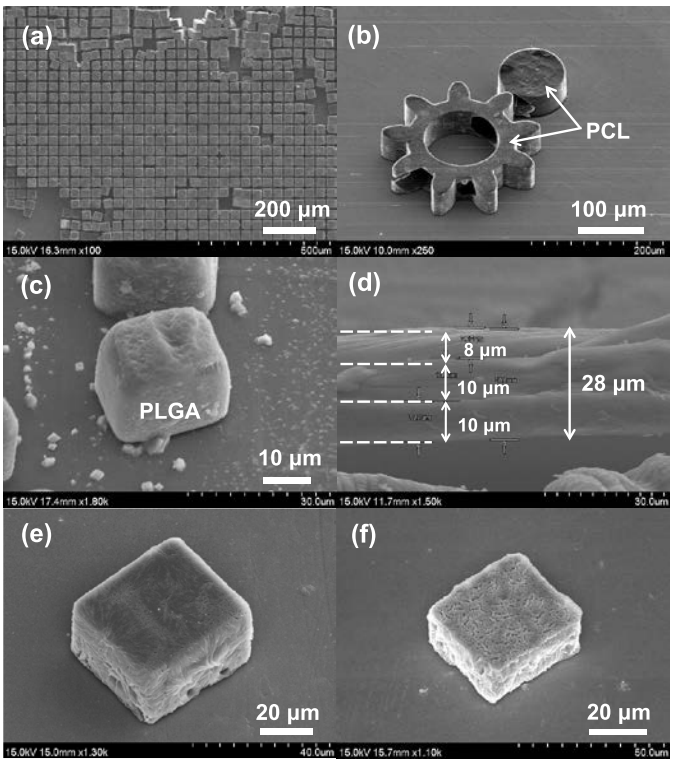

Fig. 9. SEM images of microstructures made of biodegradable polymers. (a, b) Top and side view of fabricated PCL microstructures. (c) Side view of fabricated PLGA (85:15) microstructures. (d) PCL structures are made of 3 layers of laminated films. (e) Microstructure with smooth surface and (f) microstructure with porous surface [63].

Shapes and sizes of structures can be varied corresponding to the gold mask used for the x-ray-lithography. The minimum feature size is approximately 50 nm, and large and small shapes can be fabricated in the same batch. The fabrication results of the x-ray synchrotron irradiation process for microstructures made of the PCL polymer are shown in Figs. 9(a) and 9(b), and microstructures made of PLGA (85:15) polymer are shown in Fig. 9(c) [63]. The PCL structures are made of 3 layers of laminated PCL polymeric film as shown in Fig. 9(d). Figures 9(e) and 9(f) show various surface morphologies of biodegradable polymers. The morphology is controlled by the exposure. The exposure dose to the structure is 0.05 KJ/cm^3 in the case of the smooth surface in Fig. 9(e), and 1 KJ/cm^3 in the case of the porous surface in Fig. 9(f).

While this method can be used to fabricate multiple-layered polymeric structures with arbitrary shapes, the limited accessibility to x-ray synchrotron irradiation facilities hinders this method for being a common microfabrication method. In addition, some exposure of x-ray to drugs can affect their characteristics, which requires further studies.

G. Summary of Microfabrication Methods for Biodegradable Polymers

In this section, various microfabrication techniques for biodegradable polymeric drug carriers were reviewed. The important characteristics of each fabrication method are summarized in Table II. By employing appropriate fabrication

TABLE II
CHARACTERISTICS OF MICROFABRICATION METHODS FOR BIODEGRADABLE POLYMERS

Fabrication methods	Critical dimensions	Feature variety	Solvent compatibility	Throughput	Tool costs & requirements	References
Laser micromachining	~10 μm	Polygons, Vertical tilt possible	None	Low	High-resolution positioning system required	[18-23]
Direct deposition	~20 μm	3D structures	Organic	Low to moderate	Moderate cost	[24-26]
Three-dimensional printing	~20 μm	3D structures	Organic	Low	High-resolution ink-jet system required	[27-30]
Stereolithography	~100 μm	3D structures	Water	Low	High-resolution positioning system required	[31-33]
Replication	~50 nm	Polygons	None or organic	High	Inexpensive	[34-43]
Emulsification	~50 nm	Spherical shapes, but sizes can vary	Organic	Very high	Inexpensive	[44-47]
Microfluidic fabrication	~50 nm	Spherical shapes	Organic	Very high	Inexpensive	[48-58]
X-ray-lithography	~50 nm	Polygons, Vertical tilt possible	Alkaline solution	High	X-ray synchrotron facility required	[59-63]

techniques, considering the critical dimensions, feature variety, solvent compatibility, throughput, and tool costs, inexpensive and reliable microfabrication of micro and meso-scale DDS can be achieved.

IV. DISCUSSIONS

The purpose of drug delivery system is delivering the functional carriers of drug at the target area of the human body with suitable bioavailability. To enhance the bioavailability of drugs, two of the features are required: (1) sustained drug delivery for specific therapeutic levels and (2) targeted drug delivery to avoid the side effects of drug in unwanted parts of the human body.

The first requirement can be met by the choice of appropriate carrier materials of DDS. This paper reviewed the salient characteristics of biodegradable polymers as a carrier material.

Various biocompatible polymers can be designed with different biodegradation rates, and the release time of loaded drugs can be controlled to achieve a sustained release of drugs and to maintain a desired therapeutic level. This paper reviewed various microfabrication techniques for biodegradable polymeric devices as drug carriers. The reviewed microfabrication methods allow fabricating a plethora of shapes and sizes of biodegradable polymeric devices for carrying drugs. The microfabrication methods reviewed are the laser micromachining, rapid prototyping, replication, emulsification, microfluidic fabrication, and x-ray-lithography-based methods. Among them, the emulsification and microfluidic fabrication methods are the most promising methods for DDS fabrication. A drawback is that only spherical shapes can be fabricated. On the other hand, the x-ray-lithography-based methods under development can fabricate other shapes.

To achieve a true targeted drug delivery, an actuation method is necessary, since the polymers have no self-propelling property. Several approaches are investigated by various researchers, and a noteworthy new approach is using bio-actuators to achieve the locomotion or actuation of drug delivery system [64]–[66]. This bio-actuation method requires no external power. One particular example is using tumor tracing bacteria as actuators for a solid-tumor targeted delivery [67]. The topic on actuation is beyond the scope of this paper and not treated here.

V. CONCLUSIONS

This paper reviewed characteristics of biodegradable polymers as drug carriers. Attributed to advantages in biocompatibility, controllable biodegradation rates, manufacturability, and low costs, the biodegradable polymers show a great possibility for DDS. The microfabrication methods reviewed in detail were the laser micromachining, rapid prototyping, replication, emulsification, microfluidic fabrication, and x-ray-lithography-based methods. By employing appropriate microfabrication techniques, inexpensive and reliable microfabrication of micro and meso-scale DDS can be achieved.

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