Colloids: Applications and Remaining Challenges

Majid Molaie[1*]
[1]Department of Mechanical Engineering, Azad University of Tabriz, Tabriz Northern Bypass Expy, East Azerbaijan, Iran
[*]Email of Corresponding Author: molaietimf@gmail.com
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Abstract
Using of colloids and polymeric microparticles are gradually increasing. It is observed that the positive effects of particles stems in both traditional applications such as column pickings, coatings and paints to more recent technologies in diagnostics, drug delivery and optical devices are well documented. This review focuses on importance of colloids and covers their applications on three level: (1) The cell/tissue level; (2) The single device level; (3) Self-assembly. Then I state the working principles and developments in fabrication methods. Key advantages and challenges of colloids and polymeric microparticles are discussed as well. Papers reviewed in this study show that while there are practical methods to the synthesis of such particles but accurate control of anisotropy and morphology that is essential for specialized particles is a critical problem. Therefore, a new approach is desired, which generates geometrically and chemically anisotropic particles with high throughput. In addition, this approach should be able to generate particles with complex composition, and preferably have adaptability.

Keywords
Colloid, Polymeric microparticles, Single device, Cell/Tissue, Self-assembly

1. Introduction

Colloids are usually referred to as micro or nanometer sized particles dispersed throughout another phase [1]. This range of size is of particular interest because Brownian motion, which is the random motion caused by collisions from surrounding molecules of the dispersed phase [2], is important at this scale. Colloidal dynamics is generally observable under optical microscopes, making colloids a perfect candidate for fundamental research. Besides, colloids can be considered as giant molecules in a loose manner, and find increasing applications in foods, drinks, inks, paints, coatings, cosmetics, photographic films, rheological fluids and magnetic recording media etc. [3]. Although Graham [4] and Ostwald [5] pioneered the field more than 150 years ago, preparation of colloid particles with well-defined size, shape and composition at high throughput remains a challenge. A relatively new but powerful approach to generating colloids is made possible with the emergence of micro fluidics. By co-flowing immiscible phases and introducing instability, emulsion drops are generated inside micro fluidic channels. These drops are then photo-polymerized to form stable hydrogel or polymeric particles. This approach is widely used, as it manufactures colloid particles in large quantities not only in spherical shape, but also in rods and discoids with appropriate micro fluidic channel design [6]. These colloids can be modified with cell-adhesive legends for manipulating cultured cells [7]. Moreover, taking advantage of laminar flow, researchers are able to generate Janus particles, named after the two-face Roman god Janus, which has two or more distinct surface properties [8]. A literature review on these topics is covered below.

2. Applications

2.1 On the cell/tissue level

Colloids have a characteristic size in the micrometer region, comparable to cells. They can be modified with biological functionalities, like ligands to interact and even control cell behavior. One representative demonstration of such kind is the addition of amino acids like arginine-glycine-aspartic acid (RGD) peptide sequence to a copolymer system, which enhances both adhesion and spreading of mammalian cells [9]. This kind of materials potentially acts as a scaffold for tissue regeneration or repair. Dissociated cells are encapsulated by the polymer scaffold and delivered to the appropriate site. The polymer scaffold defines the space for tissue growth and confines the total size and shape for the engineered tissue. This approach has shown success in engineering skin, bone and cartilage tissues and recently in growing bone tissues [10]. It enables in vivo tissue engineering from a small number of implanted cells, in contrast to in vitro tissue growth and transplantation. An improvement is grafting poly (ethylene glycol) (PEG) to an artificial protein with functionalities such as cell adhesion, heparin binding and degradation since PEG reduces undesired protein adsorption and colloid aggregation. Halstenberg et al. show that protein-graft-poly (ethylene glycol) diacrylate (PEGDA) featuring cell survival, spreading, migration and proliferation serves as an excellent candidate for tissue repair [11]. PEGDA is also utilized to generate cell encapsulations [12], cell carriers [13] and protein detectors [14]. Other materials like 1, 6-hexanedioldiacrylate (HDDA) are also investigated for biomedical purposes (Figure 1) [15].

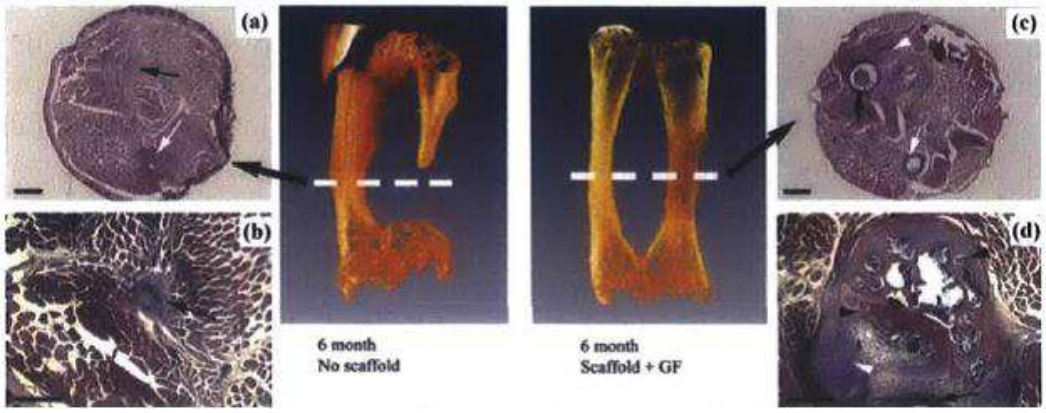

Figure1. Histology of frog tarsus segments 6 months after surgery. Dashed white lines indicate position of the displayed histological sections. (a) And (b) show sections 6 months after tarsus extirpation without scaffold. The missing tarsus gap is filled with intact tarsus (white arrow) and muscle and scar tissue (black arrow). (b) Image of the tarsus gap is a magnified (c) And (d) show section 6 months after tarsus extirpation with scaffold implantation. The tarsus gap is completely bridge with ossifying tissue (white arrowhead). (d) Shows magnified view of the ossifying cartilage sement in (c). Scale bars: a, c, 1.0mm; b, d, 500µm. Figure reprinted with permission [15]

2.2. On the single device level

Polymers capable of switching configurations in response to environmental stimuli such as temperature, hydration, pH, specific molecules, magnetic or electric field are referred to as "smart" materials [16]. One example is hydrogel that swells or shrinks when hydrated or dehydrated. Another example involves shape-memory polymer (SMP) that recovers from a temporary shape to its permanent shape upon heating. A demonstration of shape memory effect is shown in Figure 2(a)

[17]. It promises application in implanting large devices through a small incision, for example, laparoscopes in a minimally invasive surgery. A potential candidate is a stent that expands and supports a blocked artery. Conceptual demonstrations are done both theoretically (see Fig .2(b)) [18] and experimentally [19, 20, 21]. Polymer-coated stents have also been approved for controlled drug delivery in both Europe and the US [16]. Another promising application of SMP is to accomplish programmed complex mechanical deformation in vivo, such as suturing. A biocompatible multi-block copolymer is developed by Lendlein et al. and demonstrates the ability to close an incision with programmed force. Their SMP has mechanical stresses resembling those of soft tissues (~1 MPa). After tying a loose knot in a conventional way, the SMP suture tightens and presses the wound lips together under proper pressure to avoid formation of necrosis or hernias (Fig .2(c)). Moreover, the suture is biodegradable through hydrolyzation [22]. We expect more biomedical devices that accomplish subtle and complex tasks to be developed.

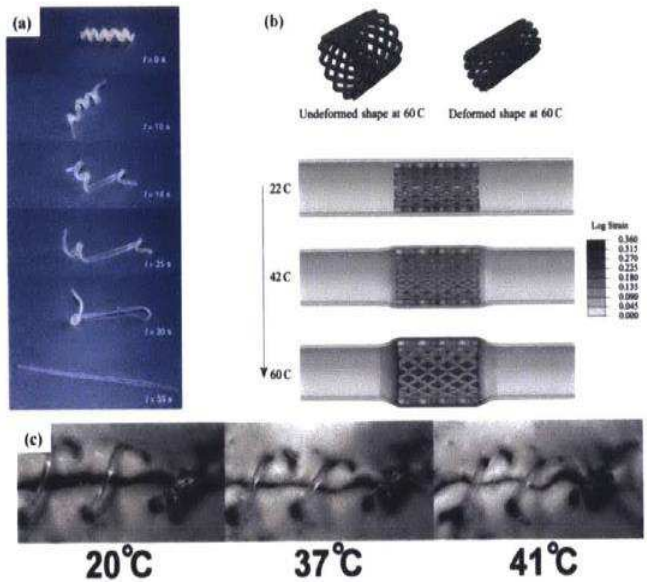

Figure2. Application of shape-memory polymer. (a) Shows SMP made of poly (coprolactone) dimethacrylate and butylacrylate at 50 wt% transits from the temporary spiral shape to the permanent rod shape. The whole recovery process takes 35 seconds at 70ºC. (b) Shows simulation result for the recovery cycle of a PEGDMA/tBA vascular stent. The stent is injected at deformed shape, and recovers to its permanent shape at 60ºC inside the artery for added support. (c) Shows biodegrable SMP suture for would closure. This photo series from an animal experiment shows the shrinkage of the suture with temperature. Figure reproduced with permission [17, 18, 22]

2.3. Self-assembly

In tissue engineering, scaffolds are introduced for in vivo tissue regeneration/repair to avoid immune responses. Besides, it minimizes the incision size needed compared to transplantation. Smart materials like SMP further reduce the size of devices like a scaffold to be implanted. However, more significant reduction is desired for minimally invasive surgery. In other cases, it is difficult or even impossible to implant a device directly. It is desired that small colloidal building blocks self-assemble into large functional devices in vivo, in a similar way as DNA strands bond together to finally form lives. In fact, traditional materials are selected by their properties; the next generation of materials is supposed to be designed from building blocks according to applications and programmed for self-assembly [7]. The most straightforward assembly is closely packed

spheres. A flow cell [23, 24, 25] or wedge-shaped cell [26,27,28] is used to crystalize 3D or 2D granular crystals consisting of colloidal spheres as shown in Fig .3(a). The colloidal beads are initially monodispersed in an aqueous solution. As the solvent evaporates, these beads pack and crystalize. Embedding polystyrene spheres in PVA matrix and stretching at elevated temperature results in ellipsoidal beads due to viscoelasticity. Closely packed ellipsoids are achieved in this way [29]. Peanut and rod shaped colloids of iron oxides are synthesized, offering options as building blocks for self-assembly [29, 30].

During the crystallization, physical confinement such as cylindrical hole array patterned on the substrate renders polygonal or polyhedral clusters consisting of colloidal beads as shown in Fig.3(b)-(e). The structure of resulting cluster is mainly determined by the ratio between the dimensions of the holes and the radius of the colloidal sphere [31]. This provides even complex building blocks for medical and biological applications as well as photonics.

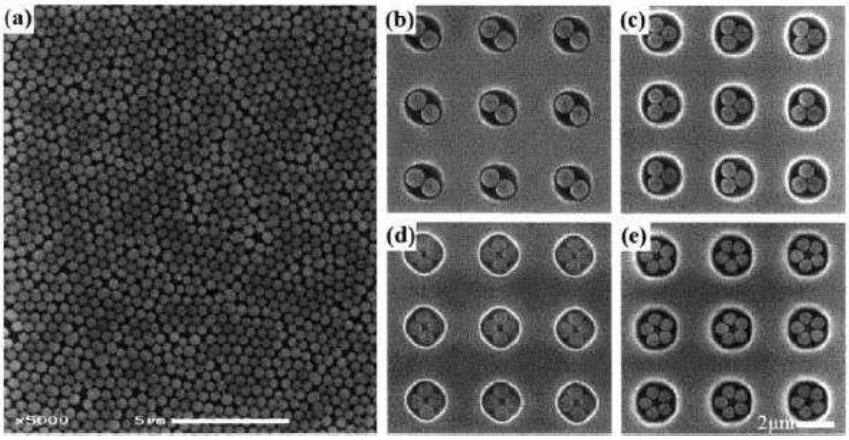

Figure 3. (a) 2D colloidal crystal of polystyrene (PS) beads formed by a wedge-shaped cell. (b)-(e) Examples of well-defined aggregates formed by templating spherical PS beads on patterned substrate. All cylindrical holes are 2µm in diameter. (b) Dimer clusters formed from 1.0µm PS beads; (c) trimer clusters formed from 0.9µm PS beads; (d) square tetramers formed from 0.8µm PS beads; (e) pentagon aggregates formed from 0.7µn PS beads. Scale bar: a, 5µm; b-e, 2µm. Figure b-e reproduced with permission [31]

Another powerful approach for assembly granular crystals is through flow-lithography. In microfluidic channels, aqueous latex particle suspension turns into water-in-oil emulsion caused by droplet break-off. As the droplet moves along the channel, water keeps diffusing into the oil phase and the droplet shrinks to a spherical colloidal aggregate. This aggregate serves as an efficient scatterer, and could be used for diffusers. Thus, it is named as "photonic balls" [32]. Further improvement is achieved by combining lithographic approach with flow-lithography. After careful study of the jamming phase diagram, a very dense suspension of silica microspheres in a photocurable solution can flow inside a microfluidic channel without jamming [33]. Granular crystals are shaped by shining patterned UV light with a physical photomask. To increase the structural integrity, a sintering process follows to create dense glassy silica structures (See Figure 4) and a partial sintering renders porous structures [34].

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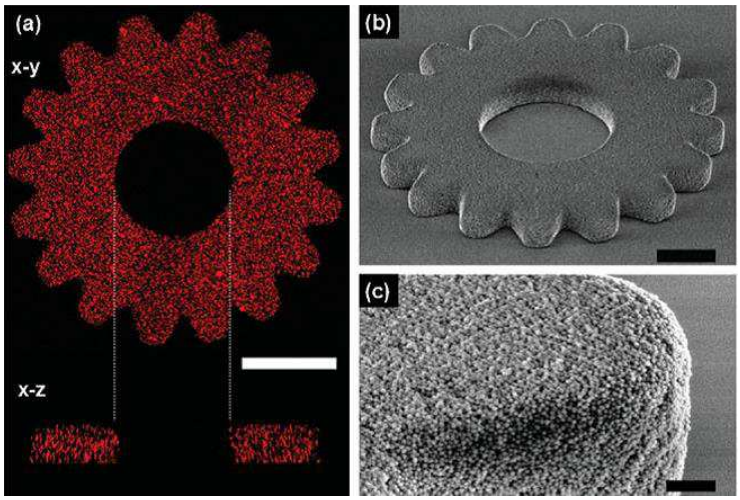

Figure4. (a) Confocal image of the x-y plane (top) and x-z plane (bottom) of the colloidal microgear. The x-y scan is carried out at z=20µm. (b) and (c) SEM image of the synthesized colloidal microgear made of densely packed silica microbeads. Scale bar: a, 100µm; b, 50µm; c, 5µm. Figure reprinted with permission [34]

More recently, trajectory engineering by manipulating particle shape is demonstrated both theoretically [35] and experimentally [36]. A method for synthesizing anisotropic colloids suitable for trajectory engineering also shows up [37]. Though this does not achieve assembly yet, it could potentially serve as a means to orient nonspherical particles. As Younan Xia once proposed for self-assemble complex shaped building blocks, positional ordering and orientational ordering would do the job [29].

It's not only shape, but also composition that plays a role in organizing particles into assembly [38]. Flow-Lithography allows researchers to fabricate amphiphilic Janus building blocks in large quantities. In emulsions, these Janus particles move to the water oil interface and assemble to minimize their total surface energy [39]. In another case, fluorescent latex particles are coated with gold and hydrophobically treated on their poles, resulting in "triblock Janus". The particles are thus electrostatically repulsive in the middle and hydrophobically attractive on the poles to each other. After further self-assembly conditions are applied, these particles form a quasi-two-dimensional colloidal kagome lattice (See Fig .5) [40]. Assembly can also be initiated by magnetophoresis when there exists a magnetic susceptibility contrast between suspended building blocks and fluid. By embedding nickel grid pattern just below PDMS channel, strong spatially varying magnetic field immerses the channel. The difference between suspensions and fluid of their magnetic susceptibilities molds a template for assembly, just as optical traps do. This approach works not only for single but multiple component assembly [41].

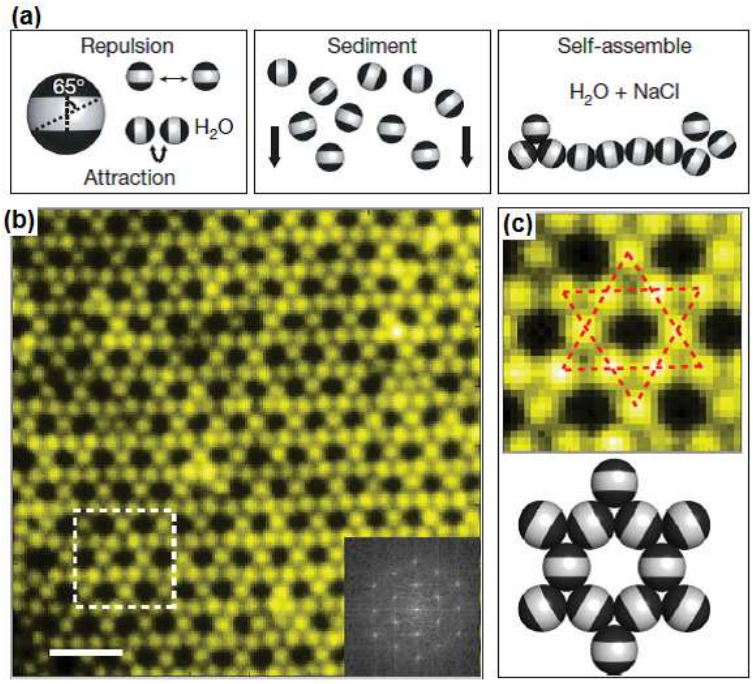

Figure5. (a) Triblock Janus spheres which are hydrophobic on two sides (black) and charged in the middle (white) sediment in DI water. NaCl is then added to screen the electrostatic repulsion to allow for self-assembly through short-range hydrophobic attraction. (b) and (c) show the fluorescence image of colloidal kagome lattice and its FFT image (inset). Bottom of (c) illustrates the orientation of Janus particles. Scale bar: 4ptm. Figure reprinted with permission [40]

3. Fabrication methods

In the recent years several fabrication methods such as micro-stereolithography [42, 43], microinjection molding [44, 45], electroplating and molding (LIGA), lithography [46, 47], stop-flow lithography and microfluidic devices [48-50], micro-extrusion [51], micro- electro-discharge machining [52], PRINT (Particle Replication In Nonwetting Templates) [55] and the emulsification (or emulsion-evaporation) technique [56] have been developed. In following section some useful and innovative methods will be explained.

3.1. Projection Micro-StereoLithography (PμSL)

Stereolithography refers to a technique patented in 1986 by Charles W. Hull. It is described as an additive manufacturing method where patterned ultraviolet (UV) light polymerizes or crosslinks a thin layer of photocurable material into solid and construct a 3D structure in a layer-by-layer fashion. Inspired by it, our group has previously developed the technique into Projection Micro-Stereolithography (PμSL) where a spatial light modulator (SLM) is used instead of a series of physical photomasks [53, 54]. A SLM is a device that modulates incoming light spatially. With the SLM as a dynamic mask that reconfigures pattern digitally, there are no more needs for replacing physical photomasks and doing alignments for each layer.

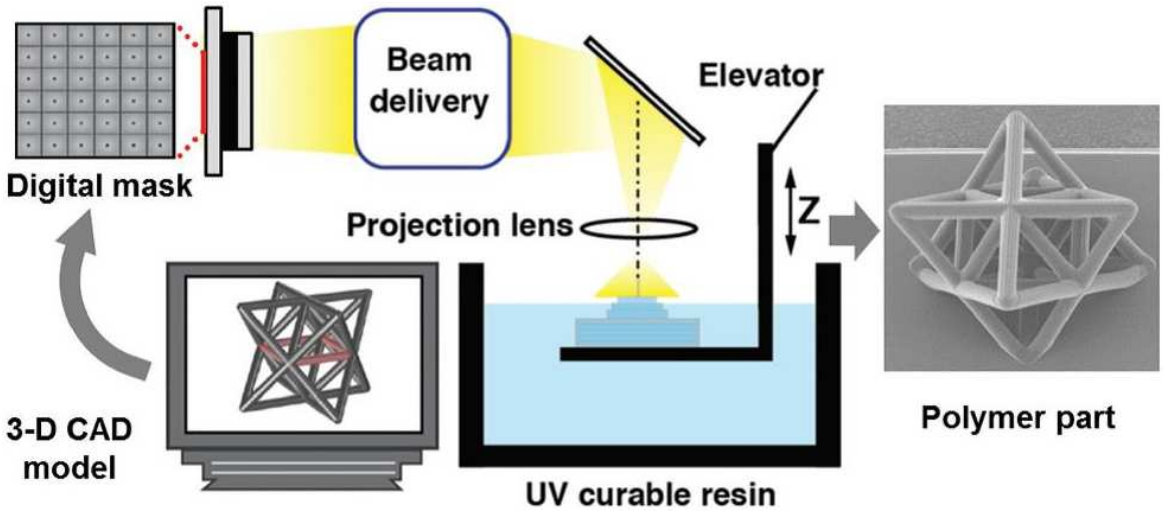

Figure6. Schematic of projection micro-stereolithography. A 3D model is sliced and sent to the dynamic mask. The mask patterns UV light and cures one layer of photocurable resin. The substrate then is lowered to allow for fresh resin. 3D structure is fabricated in this layer-by-layer fashion. Figure reproduced with permission [54]

Figure 6 schematically shows PμSL and its process flow. Surface geometry of complex 3D structure is stored in a st l (stereolithography) file and is then digitally sliced into a series of cross-sectional images by open-source software (Creation Workshop). Each cross section image functions as a digital photo mask to fabricate the corresponding layer. After an image is sent to SLM, the UV LED is turned on for a proper period of time. The UV light is reflected off the SLM to be patterned and then projected onto the surface of the photocurable resin, cross linking the illuminated area and generating a thin patterned layer corresponding to the image sent to SLM. After the layer is formed, the substrate which holds the sample lowers itself from the surface of photocurable resin by the thickness of the next layer. Fresh photocurable resin comes in and covers the area above the polymerized structure and the next image is sent to the SLM so as to polymerize the next layer on top of the previous one. A 3D structure is fabricated in this layer-by-layer fashion until all layers are complete. A state-of-the-art SLM is capable of displaying high-definition images, which means there are more than 1,000,000 pixels on the SLM. However, the pixel size is usually ~10μm by 10μm, much larger than the resolution required in micro fabrication. Fortunately, during the projection process, a reduction of lateral resolution can be achieved. With a 10:1 projection, the theoretical resolution is reduced from 10μm to 1μm. Taking into account the practical limit imposed by point spread function (PSF) of the optical system, the image experiences certain degree of blurriness and the real resolution is usually worse than the naive calculation given above.

3.2. PRINT (Particle Replication In Nonwetting Templates)

PRINT technique developed to fabricate biodegradable polymeric nano and micro particles which are very useful in drug delivery systems (DDS). This method utilizes the low surface energy of molds of fluoropolymers [55]. The molds are formed by using photo chemically cross-linked polymers such as perfluoropolyether (PFPE). Therefore these molds are able to fabricate a variety of organic particles (Figure 7) [57, 58].

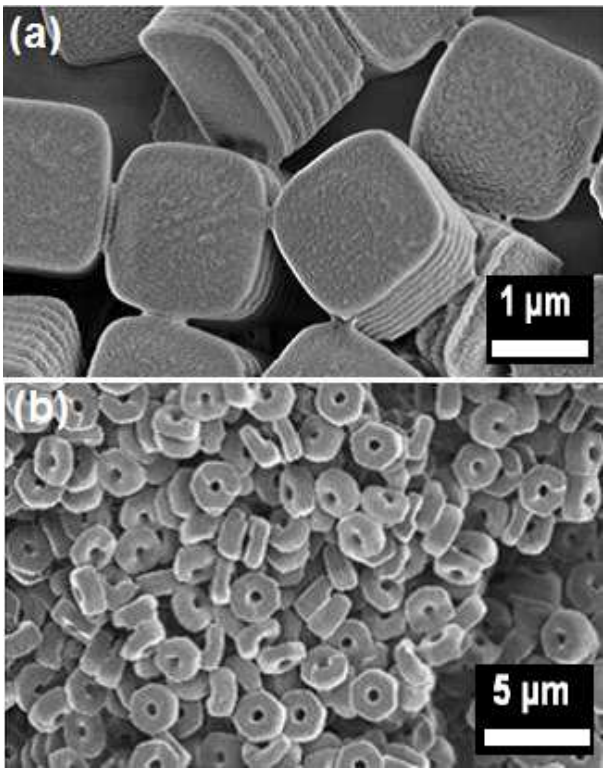

Figure7. SEM images of poly(lactic-co-glycolic acid) PLGA. (a) 2 µm Cubes, (b) 3 µm center fenestrations particles. Figure reprinted with permission [58]

3.3. Stop-Flow Lithography (SFL)

Stop-flow lithography is first developed in Patrick Doyle's group for high throughput generation of colloid particles [59]. A stream of photo curable material flows inside a micro fluidic channel which is held on the sample stage of a microscope. A transparency photo mask is inserted between the UV illumination light and objective, and is focused into the micro fluidic channel. The flow is first stopped before it is exposed to pattern UV light. The illuminated part of photo curable material is cross-linked instantaneously and forms the desired geometry. The synthesized polymers are then flushed away before the next 'stop-polymerize-flow' cycle is performed (see Figure 8). Considering the high flow rate (driven by compressed air) and short exposure time (usually ~ 100ms), the overall throughput is very high, generally ~ 104-106 particles/h. With laminar nature of micro fluidics, complex composition/chemical anisotropy is introduced through co-flow. Last but not least, it is convenient to switch materials inside the micro fluidic channel [59-61].

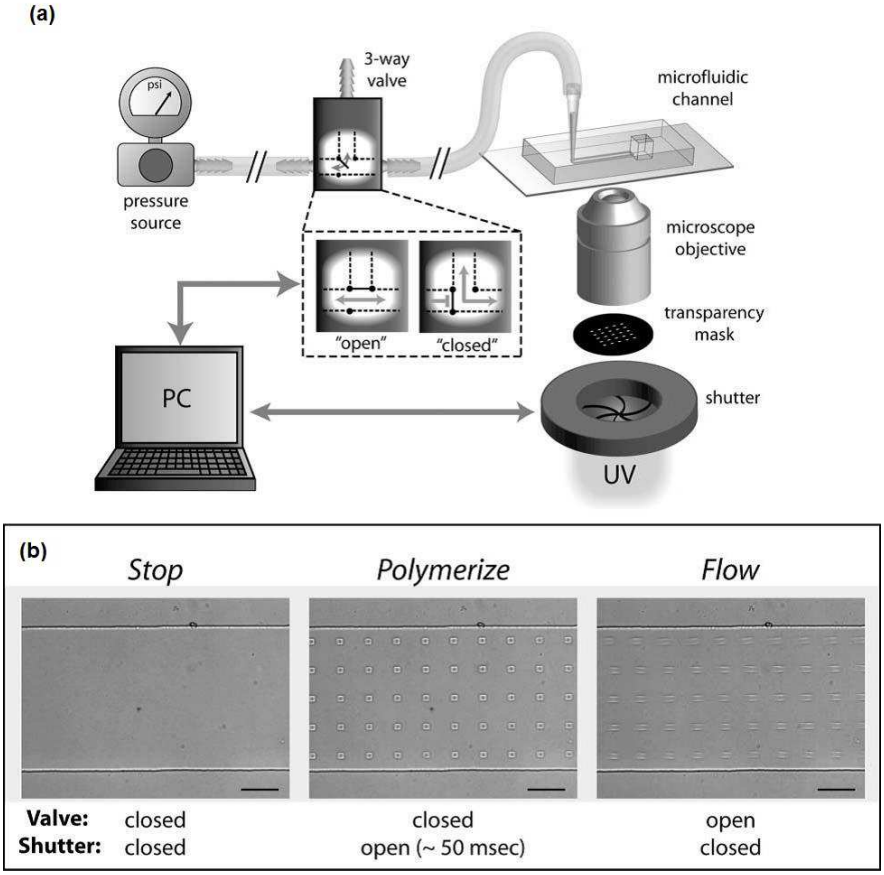

Figure8. (a) Setup of stop-flow lithography. Photocurable resin flows in a microfluidic device driven by a pressure source controlled by PC through a valve. The PC also controls UV exposure. (b) Microscope images showing the stop, lithography/polymerize, flow process. Figure reprinted with permission [59]

4. Conclusion: Challenges and Opportuites

Although all these methods differ significantly, the basis is generating building blocks with well-defined shape, size and composition in large quantities. As we can see from previous examples, the ability to self-assemble largely depends on how many "patches" one building block has. In addition to particles with spherical shape, particles with chemical anisotropy and exotic non-spherical shapes are expectedly practical. They are widely used in a range of technologies from multiplexed diagnostics to photonic crystals. While there are practical methods to the synthesis of such particles but accurate control of anisotropy and morphology that is essential for specialized particles is a critical problem. Therefore, a new approach is desired, which generates geometrically and chemically anisotropic particles with high throughput. In addition, this approach should be able to generate particles with complex composition, and preferably have adaptability. As well as, the process should provide the use of biocompatible and functionalizable material. Furthermore, a selection of these materials belong to "smart" materials, which means they have properties that responds to external stimuli in a controlled fashion, such as stress, temperature, hydration, pH. To name a few [54], shape memory polymer made of poly (ethylene glycol) dimethacrylate (PEGDMA) and benzyl methacrylatc (BMA), which responds to temperature and stress; poly(N-isopropylacrylamide) (PNIPAAm) which responds to temperature and hydration and poly(ethylene glycol) diacrylate (PEGDA) which responds to hydration only. Therefore most appropriate method

provides the opportunity of designing and fabricating building blocks made from a combination of these smart materials. This allows extra freedom in self-assembly, reconfigurable and tunable devices.

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