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Technical Note

Fabrication of polymeric microparticles for drug delivery by soft lithography

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Abstract

Soft lithographic techniques were used to fabricate polymeric microparticles for drug delivery applications. The microparticles were made of thermoplastics and thermosets from different types of precursors including reactive resin and polymer solutions in organic solvents or water. The microparticles produced using these methods were made of widely used polymers for drug delivery with highly uniform sizes, plate-like morphology, and well-defined lateral sizes and shapes, making them potentially useful for drug delivery applications and as platform for the construction of multi-functional drug delivery devices.

Keywords: Drug delivery; Soft lithography; Microfabrication; Microparticle

1. Introduction

Polymeric microparticles are widely used in numerous drug delivery applications [1–5]. A number of methods such as spray drying, emulsion/solvent evaporation, phase separation, and grinding have been developed for manufacturing polymeric microparticles [6,7]. These methods are limited to the production of microparticles with relatively wide size distribution, spherical or irregular shapes, and either symmetrically monolithic or core-shell structures. To further exploit the potential of the particulate systems towards the highly engineered, multi-functional, and even ''intelligent'' next-generation drug delivery devices, novel particle production technology is needed.

Microfabrication technology has been used to fabricate particulate drug delivery microdevices with highly uniform sizes, well-defined, and asymmetrical structures that are impossible by conventional microparticle manufacturing methods, offering the devices many attractive features for oral delivery of macromolecules [8–10]. However, the current processing methods involve highly corrosive etching solutions, toxic solvents, ionizing radiation, plasma etching, and/or elevated temperatures. Most importantly, the high cost associated with the materials, facilities, and processing would likely be a limiting factor hindering the practical implementation of this technology.

On the other hand, many lower cost techniques have been developed or are under development for polymer microfabrication. They typically possess greater versatility in materials and processing approaches than silicon-based microfabrication techniques. Soft lithography is such a group of techniques using an elastomeric stamp with topological microfeatures to generate micro- or even nanostructures [11–17]. Among various soft lithographic techniques, microContact Printing (μCP) [12,13], microTransfer Molding (μTM) [14], and microFluid Contact Printing (μFCP) [15] are able to create discrete polymer microstructures. By combining μCP and μTM with lift-off strategy, we have developed simple approaches to fabricate polymer microparticles [16]. In this paper, we further extend these techniques to produce microparticles aimed for drug delivery applications.

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2. Experimental section

2.1. Materials

Poly(dimethyl siloxane) (PDMS, Silastic T2) was purchased from Dow-Corning. Chitosan, poly(ethylene glycol methacrylate) (PEGMA) with an average number molecular weight (M_n) of 526, poly(ethylene glycol dimethacrylate) (PEGDMA) with M_n of 330, cold water soluble poly(vinyl alcohol) (PVA), and 50 wt% glutaraldehyde aqueous solution were purchased from Sigma-Aldrich. 2, 2-dimethoxy-2-phenylacetophenone (Irgacure 651) was donated by Ciba Specialty Chemicals (Tarrytown, NY, USA). Poly(lactic-*co*-glycolic acid) (PLGA, lactic acid to glycolic acid ratio = 50:50, $T_g = 48.5\,^{\circ}C$ according to the manufacturer) was purchased from Alkermes (Cincinnati, OH, USA).

2.2. PDMS stamp and release slide preparation

PDMS stamps were prepared using soft lithography techniques. Silicon masters with designed microfeatures were produced by standard photolithography using either chrome or transparency masks. Positive photoresist (Shipley S1813) or negative photoresist (SU8-2005) were used for pattern production. PDMS stamps were prepared by casting PDMS resin and curing agent at a 10:1 weight ratio against the masters for 48 h at room temperature. Stamps with five different types of microfeatures were used in the work. Fig. 1(A) displays a stamp with round-cornered square protruding microfeatures. The width and height of the micropillars was 24.7 and 6.5 μm, respectively. The center-to-center distance between the adjacent microfeatures was 40 μm. A stamp with cross-shaped protruding microfeatures is shown in Fig. 1(B). The microfeatures had an end-to-end length of 197 μm, arm width of 40 μm, and height of 6.8 μm. Fig. 1(C) shows a stamp consisting of 30 μm wide, and 1.22 μm deep square recessed microfeatures, or microwells, separated by 20 μm-wide ridges. Fig. 1(D) shows a stamp bearing rectangular microwells 95 μm long, 20 μm wide, and 6.9 μm deep. The last stamp was an array of circular microwells with 5.0 μm-diameter opening, 3.5 μm-diameter bottom, 8.0 μm center-to-center distance, and 1.94 μm depth as shown in Fig. 1(E).

Release slides were fabricated to provide a substrate, which released the fabricated particles into water following fabrication. The slides were prepared by casting a 2 wt% PVA/water solution on a standard glass slide.

2.3. Fabrication of PLGA microparticles using stamps with protruding microfeatures

Fig. 2(A) illustrates the process for the fabrication of PLGA microparticles using stamps with protruding microfeatures shown in Fig. 1(A and B). First, the stamp was immersed in a PLGA/acetone solution for 30 s and pulled out at a speed of ~1 cm/s. Low concentration solutions of PLGA formed isolated structures on the microfeatures, while higher concentrations formed a continuous PLGA film. PDMS stamps with either round-cornered square or cross-shaped microfeatures were used.

For a stamp with the round-cornered square protruding microfeatures that was dipped in PLGA/acetone solutions with concentrations of 1 and 3 wt%, the stamp was dried in air for about 20 s and placed on a release slide. After maintaining the contact for about 20 s, the stamp was peeled away, leaving the PLGA microparticles on the release slide. Water was then added to release the microparticles. The same protocol was applied when a stamp with cross-shaped protruding microfeatures and a 2 wt% PLGA solution was used.

For a stamp with the square microfeatures that was dipped in PLGA/acetone solutions with concentrations of 5 and 7 wt%, the stamp was dried in air for about 1 min and then placed on a release slide on a hotplate and removed immediately from the slide (contact time: ~5 s), leaving the PLGA microparticles on the release slide. The printing temperatures were 80 °C for a 5 wt% and 120 °C for a 7 wt% solution, respectively. The same protocol was applied when a stamp with cross-shaped protruding microfeatures and 3, 4, 5, and 6 wt% PLGA solutions were used.

2.4. Fabrication of PLGA microparticles using a stamp with recessed microfeatures

Fig. 2(B) shows the process for the fabrication of thermoplastic microparticles using the stamp with square microwells shown in Fig. 1(C). The stamp was first immersed in a PLGA/acetone solution for 30 s and pulled out at a speed of ~1 cm/s. After the stamp was dried in air for about 1 min, it was placed on a glass slide heated on a hotplate and removed immediately (contact time: ~5 s), leaving a PLGA grid film on the slide. For a stamp dipped in a 2 wt% PLGA/acetone solution, 80 °C was set as the temperature for printing. For 3, 4, and 5 wt% PLGA/acetone solutions, the printing temperature was 120 °C. The stamp was then placed on a release slide immediately after (<5 s) the slide was briefly (~5 s) exposed to water vapor from a 90 °C water bath. A pressure of ~90 kPa (measured by a balance on which the slide was placed) was manually applied to the stamp for 10 s. The stamp was removed with square PLGA microparticles left on the slide. Water was finally added to release the microparticles.

2.5. Fabrication of chitosan microparticles from aqueous polymer solution

The fabrication process for producing chitosan microparticles is shown in Fig. 2(D). An aqueous solution of 3 wt% acetic acid was used as solvent

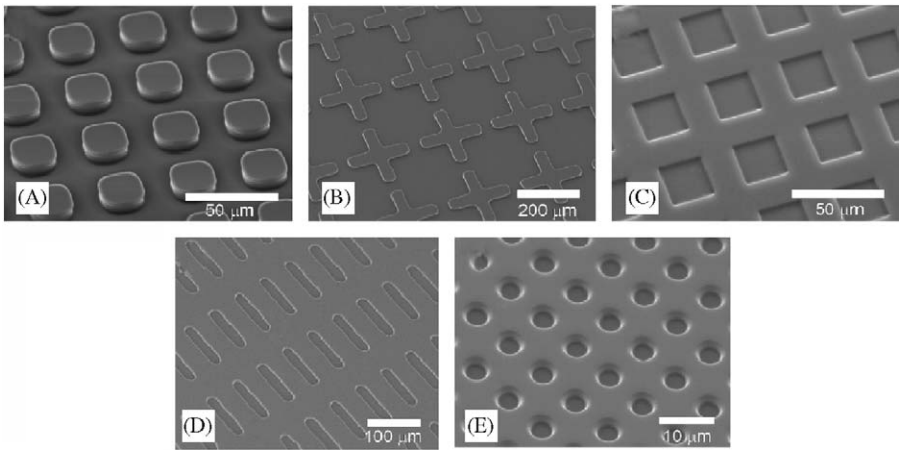

Fig. 1. SEM images of PDMS stamps with (A) round-cornered square and (B) cross-shaped protruding microfeatures, and (C) square, (D) rectangular, and (E) circular microwells.

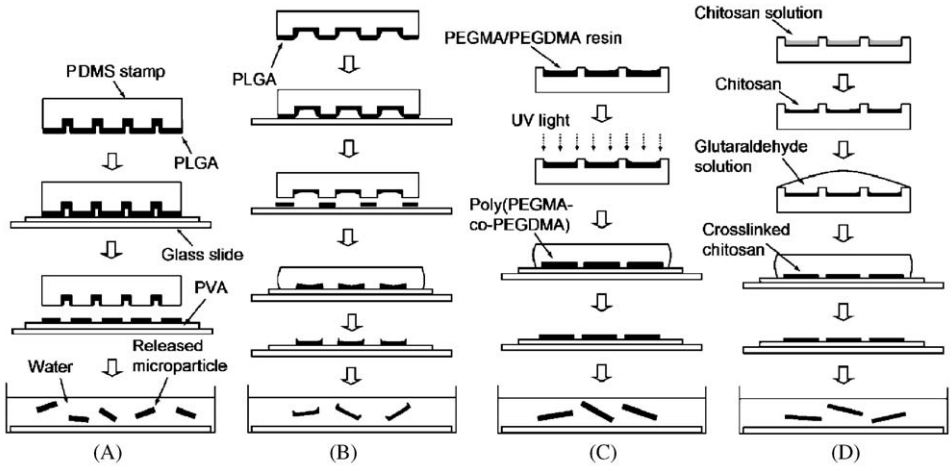

Fig. 2. Schematic illustrations of processes for the fabrication of PLGA microparticles using stamps with (A) protruding and (B) recessed microfeatures, respectively, (C) poly(PEGMA-*co*-PEGDMA) microparticles from liquid reactive resin, and (D) chitosan microparticles from aqueous polymer solution.

to make a 3 wt% chitosan solution. The chitosan solution was brushed across the stamp surface (Fig. 1(D)) with an applicator. The solution was trapped in the discrete microwells due to discontinuous dewetting [17]. Water in the solution evaporated immediately, leaving a chitosan film on the bottom of the microwells. Glutaraldehyde aqueous solution (50 wt%) was added on the PDMS stamp to cross-link the chitosan in the microwells for 10 min. The sample was then rinsed with deionized water and dried in air. To transfer the chitosan microstrips from the microwells, the stamp was placed on a release slide immediately after (<5 s) the slide was briefly (~5 s) exposed to water vapor from a 90 °C water bath. A solid weight was set on the PDMS stamp to generate a pressure of ~30 kPa for 5 min. The stamp was then peeled away with the microstrips stuck to the release slide. Water was added to release the microstrips from the PVA film.

2.6. Fabrication of poly(PEGMA-co-PEGDMA) microparticles from liquid reactive resin

Microparticles were also made from a reactive resin consisting of PEGMA and PEGDMA with a weight ratio of 1:1 and 3 wt% Irgacure 651 as photoinitiator. Fig. 2(C) shows the fabrication process. The PEGMA/PEGDMA resin was brushed across the stamp surface (Fig. 1(E)) with an applicator. It was trapped in the microwells without wetting the surrounding areas due to the higher surface tension than the PDMS. The resin was then exposed to UV light with an intensity of 31.4 mW/cm^2 (EXFO Novacure 2000 Ultraviolet/Visible Spot Curing System) for 2 min under nitrogen environment. The stamp was placed on a release slide immediately (<5 s) after the slide was briefly (~5 s) exposed to water vapor from a 90 °C water bath. The stamp and the slide were then maintained on the hotplate at 100 °C for 1 min. After they cooled down to room temperature, the stamp was peeled off, leaving the microparticles on the slide. Finally, the microparticles were released by adding water.

2.7. Characterization

An optical profilometer (WYKO NT3300, Veeco Instruments, Woodbury, NY, USA) and a scanning electron microscope (SEM, Hitachi S-3000 H) were used to characterize the stamps. Micrographs of the microparticles were captured using an Olympus BH-2 optical microscope and a Nikon TMS inverted phase contrast optical microscope. The lateral size and thickness of the microparticles were characterized using an optical profilometer.

3. Results

3.1. PLGA microparticles fabricated using the stamps with protruding microfeatures

Fig. 3 shows the results of the important steps in the fabrication of PLGA microparticles using the stamp with the round-cornered square protruding microfeatures and PLGA/acetone solutions for a series of concentrations. Concentration had a significant effect on the size of the microparticles. PLGA/acetone solutions with low concentrations, 1 and 3 wt%, produced dot-like PLGA microparticles on the surface of the protruding microfeatures as shown in Fig. 3(A-1) and (B-1), with a positive correlation between the lateral size and the concentration. A 5 wt% PLGA solution created a PLGA film covering almost the entire surface of individual protruding microfeatures with only very small areas left uncovered at the corners as shown in Fig. 3(C-1). When the concentration reached 7 wt%, the entire surface of a protruding microfeature was covered by PLGA (Fig. 3(D-1)).

The PLGA on the surface of protruding microfeatures could be transferred onto the release slide while keeping their shapes and sizes. The thicknesses were measured at the centers of the microparticles using the optical profilometer. The results are listed in Table 1. Due to the significant lateral contraction of the PLGA solutions on the protruding microfeatures, the thicknesses of the microparticles produced from 1 and 3 wt% solutions were even higher than that of the microparticles produced from 5 wt% PLGA solution, which spread across the protruding microfeatures. Within each group (contracted or spread), a higher concentration correlates to a greater thickness. The lateral sizes of the microparticles were acquired from the optical micrographs. They are also shown in Table 1, indicating a positive correlation between the concentration of the PLGA solution and the lateral size of the

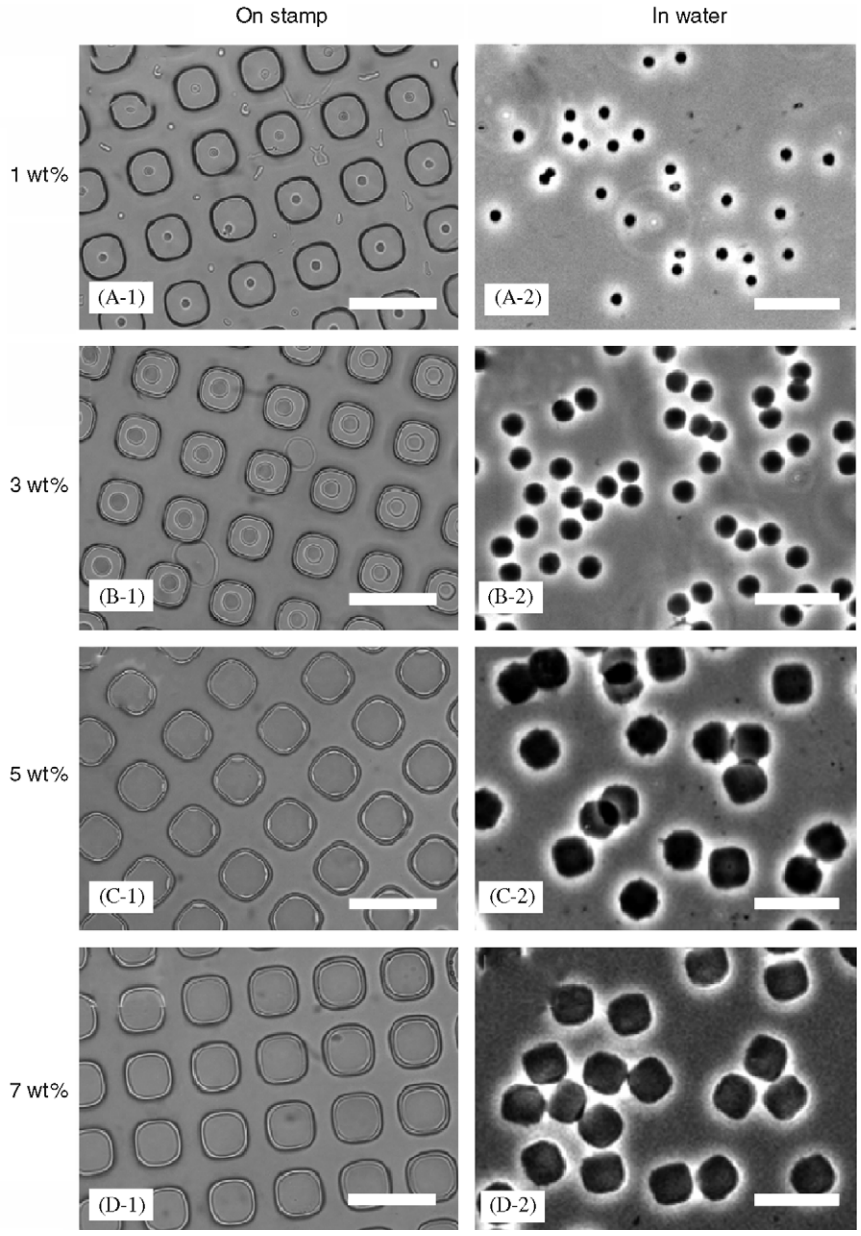

Fig. 3. Optical micrographs of PLGA on stamp with (A-1, B-1, C-1, and D-1) round-cornered square protruding microfeatures and (A-3, B-3, C-3, and D-3) released PLGA microparticles in water produced form different PLGA concentrations: (A) 1 wt%, (B) 3 wt%, (C) 5 wt%, and (D) 7 wt%. The scale bars = 50 μm.

Table 1
The thickness and width of the PLGA microparticles on PVA produced using a stamp with round-cornered protruding microfeatures and PLGA/acetone solutions with concentrations of 1, 3, 5, and 7 wt%

Conc. of PLGA solution (μm, $n = 10$)	1 wt%	3 wt%	5 wt%	7 wt%
Thickness	0.99 ± 0.09	1.75 ± 0.08	0.76 ± 0.05	1.16 ± 0.08
Width	6.1 ± 0.2	11.1 ± 0.5	24.3 ± 0.5	26.1 ± 0.3

microparticles. However, when the PLGA started to cover the entire top surface of the microfeatures, increasing concentration had a minimal effect of the lateral size of the microparticles. The microparticles produced from 5 wt% PLGA/acetone solution had almost the same size as the microfeatures of the stamp while 7 wt% solution produced microparticles slightly larger than the microfeatures on the stamp.

PLGA/acetone solutions of a series of concentrations were also applied on the stamp with cross-shaped protruding microfeatures to fabricate microparticles. However, 1 wt% PLGA/acetone solution created discrete and irregular PLGA microstructures on the protruding microfeatures that were not suitable for making microparticles. PLGA solutions with higher concentrations produced uniform microparticles on the protruding microfeatures as shown in Fig. 4. The PLGA coverage on the protruding

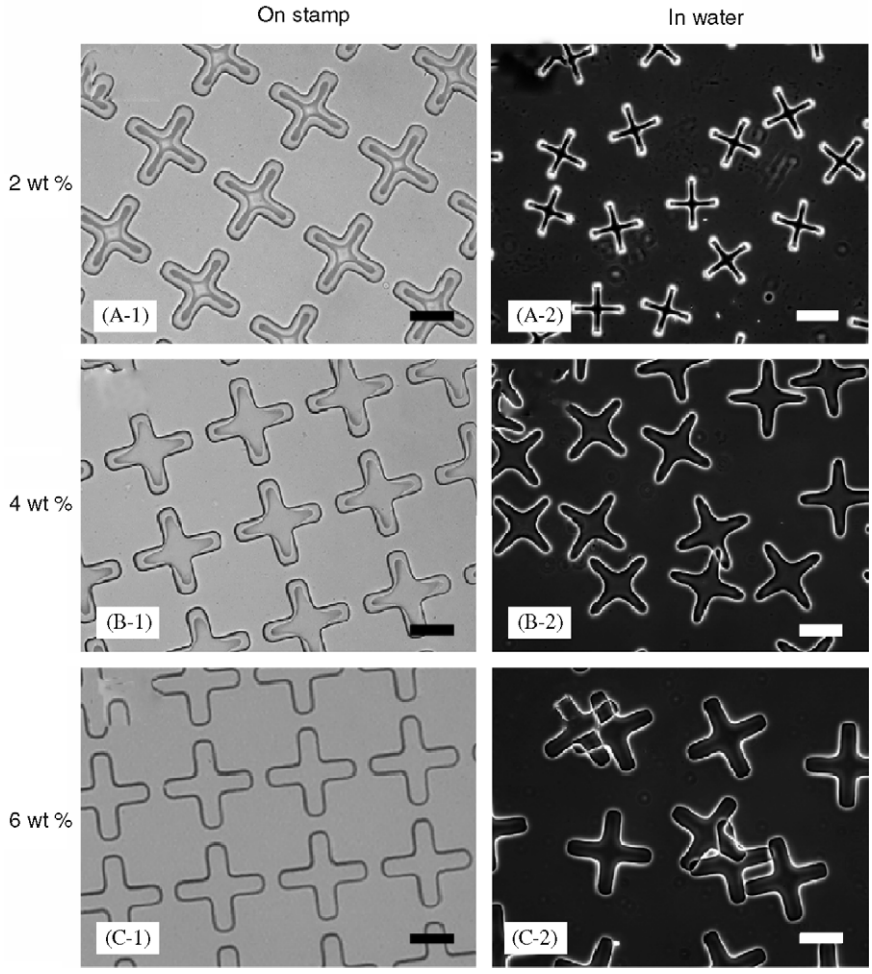

Fig. 4. Optical micrographs of PLGA on stamp with (A-1, B-1, and C-1) cross-shaped protruding microfeatures and (A-2, B-2, and C-2) released PLGA microparticles in water produced from different PLGA concentrations: (A) 2 wt%, (B) 4 wt%, (C) 6 wt%. The scale bars = 100 μm.

Table 2
The thickness and width of the PLGA microparticles on PVA produced using a stamp with cross-shaped protruding microfeatures and PLGA/acetone solutions with concentrations of 2, 3, 4, 5, and 6 wt%

Conc. of PLGA solution (μm, $n = 10$)	2 wt%	3 wt%	4 wt%	5 wt%	6 wt%
Thickness	0.90±1.16	0.77±0.08	0.97±0.03	1.15±0.10	1.26±0.09
Length	156±4	176±2	177±3	192±1	198±2

microfeatures was proportional to the concentration of the PLGA/acetone solution and a full coverage was reached at 6 wt%. Microparticles were produced by printing the PLGA on the protruding microfeatures on PVA and releasing them in water. The PLGA microparticles on PVA were characterized using the optical profilometer. The thicknesses at the centers of the microparticles on PVA are listed in Table 2. With the exception of 2 wt% solution, the thickness of the microparticles increased with the increase of the PLGA solution. The lateral sizes of the microparticles are also listed in Table 2. In general, the size increased with the increase of the concentration of the PLGA solution. At 6 wt%, the size of the microparticles was the same as the protruding microfeatures on the stamp.

3.2. PLGA microparticles fabricated using a stamp with recessed microfeatures

After being dipped in 1 wt% PLGA/acetone solution for 30 s and pulled out at a speed of ~1 cm/s, a PLGA film with numerous holes formed in the microwells, indicating 1 wt% was too low to fabricate microparticles with a well-defined structure. Dipping in 2 wt% PLGA/acetone solution produced improved coverage of the PLGA on the stamp as shown in Fig. 5(A). Although the PLGA film was not continuous at the edge of the microwells, the bottom of the microwells was completely covered by PLGA. 3, 4, and 5 wt% solutions produced PLGA films covering the entire stamp. The results of the other critical steps in the fabrication using 2 wt% PLGA/acetone solutions are also

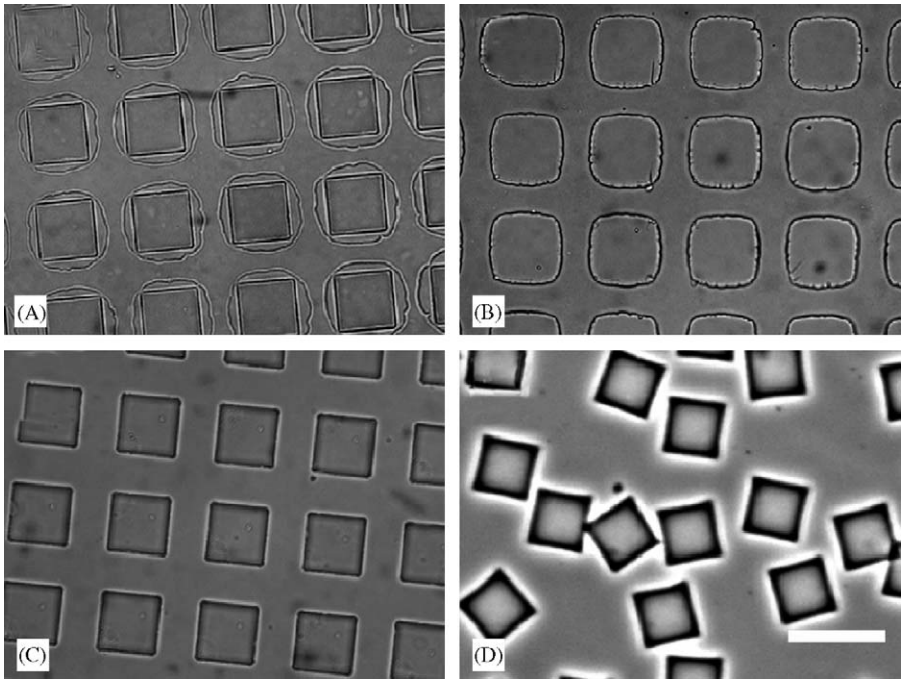

Fig. 5. Optical micrographs of PLGA on stamp with (A) square microwells, (B) mesh-like PLGA film on PVA, (C) PLGA microparticles on PVA, and (D) released microparticles in water. The scale bar = 50 μm.

Table 3
The thickness the PLGA microparticles in the microwells of a stamp produced using PLGA/acetone solutions with concentrations of 2, 3, 4, and 5 wt%

Conc. of PLGA solution (μm, $n = 10$)	2 wt%	3 wt%	4 wt%	5 wt%
Thickness	0.05 ± 0.03	0.27 ± 0.08	0.43 ± 0.05	1.08 ± 0.03

shown in Fig. 5. PLGA film on the ridges was transferred on the glass slide while retaining its shape (Fig. 5(B)) and the microparticles printed on PVA (Fig. 5(C)) and released in water (Fig. 5(D)) had the same shape and size as the microwells. The microparticles in the microwells were characterized using the optical profilometer after the PLGA film on the ridges was transferred on glass. The thicknesses were measured at the centers of the microparticles. The measured thicknesses are listed in Table 3, indicating a positive correlation between the thickness and the concentration of the PLGA solution.

3.3. Chitosan microparticles fabricated from aqueous polymer solution

The produced chitosan microparticles or microstrips had the same size and shape as the microwells as shown in Fig. 6(A). The thickness at the center of the chitosan microstrips is 0.15 ± 0.02 μm ($n = 10$).

3.4. Poly(PEGMA-co-PEGDMA) microparticles fabricated from liquid reactive resin

The produced poly(PEGMA-*co*-PEGDMA) microparticles are shown in Fig. 6(B). The thickness at the center of the microparticles is 0.18 ± 0.03 μm ($n = 10$).

4. Discussion

In this work, we used, modified, and extended previously reported soft lithography methods for the production of microparticles. These techniques were modified and optimized to provide completely independent particles of a wide variety of polymer characteristics, thus providing an array of similar techniques for producing drug delivery vehicles for a wide variety of drugs. The use of a water-soluble release layer allowed for the transfer and release of particles under benign conditions necessary for maintaining the viability of sensitive drugs.

The conditions that provided geometrically stable particles were explored through variation of polymer solution concentrations and mold geometry. The use of cross-shaped raised features on the molds demonstrated the ability of these techniques to produce microparticles with lateral shapes more complex than circles or squares.

Three polymers, PLGA, chitosan, and poly (PEGMA-*co*-PEGDMA), were used to demonstrate the feasibility of the above approaches. PLGA/acetone represents systems consisting of a common thermoplastic polymer dissolved in an organic solvent that has comparable surface tension as PDMS and relatively high evaporation rate. This type of

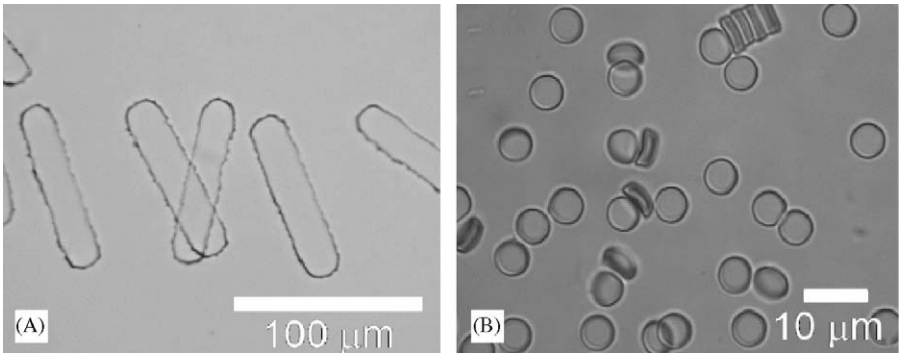

Fig. 6. Optical micrographs of released (A) chitosan and (B) poly(PEGMA-*co*-PEGDMA) microparticles in water.

solution can form isolated microstructures on PDMS stamp when used at low concentrations and a pinhole-free film when the concentration increases to a certain point. Polystyrene/chloroform is another system that has been used with μCFP [15]. Chitosan solution represents polymer solutions with a much higher surface tension than PDMS. This type of solutions could be filled only in microwells of a PDMS stamp due to discontinuous dewetting. Formation of the solid microparticles is a result of the evaporation of the solvent. Further treatment might be needed to render them stable in water as chitosan was crosslinked by glutaraldehyde. The poly(PEGMA-*co*-EGDMA) was produced from a liquid-reactive resin in this work. Although numerous polymers can be prepared in this way, some criteria must be met to use this modified μTM for producing microparticles. First, the liquid resin must have high enough surface tension required for discontinuous dewetting. Second, the resin must have low enough evaporation rate to ensure no significant mass loss before it is fully polymerized. Third, the reactive agents in the resin should not diffuse into PDMS significantly. Otherwise, they may react within the PDMS matrix, damaging the stamp and preventing the produced microparticles from being removed from the microwells.

Besides being used as model materials for the fabrication techniques, PLGA, chitosan, and poly(PEGMA-*co*-EGDMA) are also important polymers for drug delivery. PLGA is perhaps the most widely used class of synthetic polymers in drug delivery due to its excellent biocompatibility, controllable biodegradability, ease of processing, and commercial availability. Numerous formulations have been developed based on the PLGA microparticles as drug delivery vehicles. They are administered through a variety of routes to treat a large number of medical conditions. Chitosan has also been widely studied for drug delivery [18,19], and is soluble in aqueous acidic solutions. This property makes it possible to avoid the use of the hazardous organic solvents in chitosan processing. The primary amine groups are also readily available for crosslinking. Glutaraldehyde is a commonly used crosslinking agent for chitosan [20]. The poly(PEGMA-*co*-PEGDMA) synthesized in this work is a highly crosslinked, PEG-based polymer. PEG has also been used extensively in drug delivery. Its water-soluble characteristic makes it a widely used material for hydrogels, whose volume-changing ability has been employed in various advanced drug delivery systems.

Polymeric microparticles with a wide range of size (5–198 μm) were fabricated in this work. This size range covers the majority of the microparticles currently studied and used for drug delivery. Moreover, since the size is determined by the microfeatures of the stamp used and the fabrication conditions, in principle, microparticles smaller than 5 μm and larger than 198 μm can be produced using the above methods.

A common feature of the microparticles produced in this work is their plate-like geometry. This type of microparticles has more surface-to-volume ratio than microspheres, making them more likely to aggregate. On the other hand, the area available for bioadhesion of these plate-like microparticles is much larger than that of microspheres. Moreover, if attached to a biosurface, a plate-like microstructure would have smaller side area subject to the detaching force exerted by liquid flow and mechanical abrasion than a microsphere with the same volume. As a result, drug delivery microdevices constructed based on the plate-like microparticles may have stronger and longer bioadhesion on biosurfaces including the walls of the buccal cavity, esophagus, GI tract, genital tract, blood vessels, and the surface of the eyes.

5. Conclusion

Soft lithography-based techniques were employed successfully to fabricate polymeric microparticles. These techniques are much more versatile than conventional microparticle manufacturing methods in controlling the size and shape of the microparticles while are less expensive, require milder processing conditions, and possess greater versatility in materials and processing approaches than silicon-based microfabrication techniques with respect to the fabrication of microparticles for drug delivery. The microparticles with highly uniform and controllable sizes, plate-like structure, and well-defined lateral shapes have been

produced using widely used polymers, rendering them potentially applicable in drug delivery and as the components for the construction of multi-functional drug delivery microdevices.

Acknowledgments

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References

[1] Okada H. One- and three-month release injectable microspheres of the LH–RH superagonist leuprorelin acetate. Adv Drug Deliv Rev 1997;28:43–70.
[2] Edwards DA, Caponetti JG, Mintzes J, Hrkach J, Lotan N, Langer R. Large porous particles for pulmonary drug delivery. Science 1997;276:1868–71.
[3] Bastian P, Bartkowski R, Köhler H, Kissela T. Chemo-embolization of experimental liver metastases. Part I: distribution of biodegradable microspheres of different sizes in an animal model for the locoregional therapy. Eur J Pharm Biopharm 1998;46:243–54.
[4] Andrianov AK, Payne LG. Polymeric carriers for oral uptake of microparticulates. Adv Drug Deliv Rev 1998;34:155–70.
[5] Zimmer A, Kreuter J. Microspheres and nanoparticles used in ocular delivery systems. Adv Drug Deliv Rev 1995;16:61–73.
[6] Jain RA. The manufacturing techniques of various drug loaded biodegradable poly(lactide-*co*-glycolide) (PLGA) devices. Biomaterials 2000;21:2475–90.
[7] Nykamp G, Carstensen U, Müller BW. Jet milling—a new technique for microparticle preparation. Int J Pharm 2002;242:79–86.
[8] Tao SL, Lubeley MW, Desai TA. Bioadhesive poly(methyl methacrylate) microdevices for controlled drug delivery. J Control Release 2003;88:215–28.
[9] Ahmed A, Bonner C, Desai TA. Bioadhesive microdevices with multiple reservoirs: a new platform for oral drug delivery. J Control Release 2002;81:291–306.
[10] Ahmed A, Bonner C, Desai TA. Bioadhesive microdevices for drug delivery: a feasibility study. Biomed Microdevices 2001;3:89–96.
[11] Xia Y, Whitesides GM. Soft lithography. Angew Chem Int Ed 1998; 37:550–75.
[12] Granlund T, Nyberg T, Roman LS, Svensson M, Inganäs O. Patterning of polymer light-emitting diodes with soft lithography. Adv Mater 2000;12:269–73.
[13] Yan L, Huck WTS, Zhao XM, Whitesides GM. Patterning thin films of poly(ethylene imine) on a reactive SAM using microcontact printing. Langmuir 1999;15:1208–14.
[14] Yang H, Deschatelets P, Brittain ST, Whitesides GM. Fabrication of high performance ceramic microstructures from a polymeric precursor using soft lithography. Adv Mater 2001;13:54–8.
[15] Wang M, Braun HG, Kratzmüller T, Meyer E. Patterning polymers by micro-fluid-contact printing. Adv Mater 2001;13:1312–7.
[16] Guan J, Chakrapani A, Hansford DJ. Polymer microparticles fabricated by soft lithography. Chem Mater 2005;17:6227–9.
[17] Jackman RJ, Duffy DC, Ostuni E, Willmore ND, Whitesides GM. Fabricating large arrays of microwells with arbitrary dimensions and filling them using discontinuous dewetting. Anal Chem 1998; 70:2280–7.
[18] Hejazi R, Amiji M. Chitosan-based gastrointestinal delivery systems. J Control Release 2003;89:151–65.
[19] Illum L, Jabbal-Gill I, Hinchcliffe M, Fisher AN, Davis SS. Chitosan as a novel nasal delivery system for vaccines. Adv Drug Deliv Rev 2001;51:81–96.
[20] Genta I, Costantini M, Asti A, Conti B, Montanari L. Influence of glutaraldehyde on drug release and mucoadhesive properties of chitosan microspheres. Carbohydr Polym 1998;36:81–8.