Polymer Microparticles Fabricated by Soft Lithography

Jingjiao Guan, Aravind Chakrapani, and Derek J. Hansford*

Biomedical Engineering Center, The Ohio State University, Columbus, Ohio 43210

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Polymer microparticles in the forms of microbeads, microspheres, microbubbles, and microcapsules have been widely used in biological and medical analysis,[1,2] drug delivery,[3−5] bio-separation,[6] and clinical diagnosis.[7,8] A variety of manufacturing methods, such as spray drying, phase separation, and emulsification, have been well-developed. However, the microparticles produced are typically limited to spherical shapes and have a wide size distribution.[9] For certain envisioned applications, such as targeted drug delivery, it would be advantageous to produce nonspherical (flat) particles due to their relatively large surface area for cell or tissue binding as compared with spherical microparticles. Tight control of particle geometry would also be beneficial for precise bio-analysis and controlled drug delivery. Microfabrication techniques (e.g., photolithography and RIE), conventionally used for making integrated circuits, have recently been employed to prepare microparticles out of silicon dioxide and a photocurable polymer.[10,11] Microparticles with precise shape, uniform size, and surface chemistries were made as drug-carrying vehicles. However, the method suffers from the use of photolithography for every particle and limited choices of materials for microparticles. Moreover, rigorous fabrication requirements such as using highly corrosive etching solution to release the microparticles may damage fragile compounds if incorporated.

Soft lithography is a collective name for a group of non-photolithographic microfabrication techniques using an elastomeric stamp with relief features to generate micro- and even nano-structures.[12] Among the soft lithographic techniques, microContact Printing (μCP), microTransfer Molding (μTM), and microFluid Contact Printing (μFCP)[13] have produced isolated polymer structures and thus can be used to make microparticles in combination with a lift-off approach. In this communication, we introduce a soft lithographic technique to prepare thin-film microparticles with well-defined lateral shapes out of common thermoplastic polymers. The technique is based on selectively transferring polymer features from a continuous film on a stamp to a substrate. Since an elevated temperature is used to increase the adhesion between the polymer and the substrate and facilitate the separation of the polymer features from the rest of the film, we call the technique microContact Hot Printing (μCHP). Stamps with both isolated protruding and recessed features can be used to make microparticles with this method.

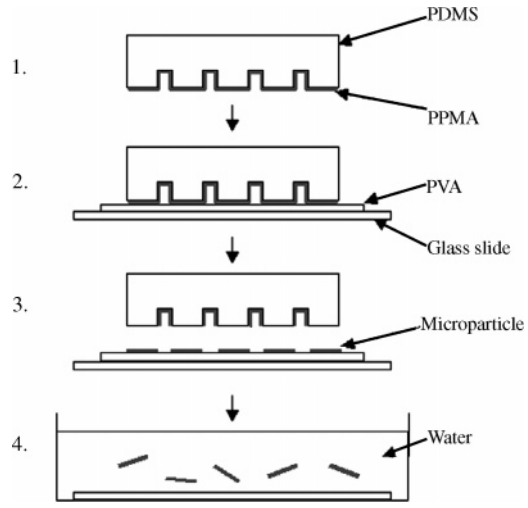

Figure 1. Illustration of μCHP fabrication of microparticles with micro-pillar stamp. (1) Apply a thin polymer film on PDMS stamp. (2) Place polymer-coated stamp on a hot glass slide with a sacrificial layer. (3) The stamp is removed with polymer on the micro-pillars left on substrate as microparticles. (4) Microparticles are released by dissolving the sacrificial layer with water.

PPMA (polypropyl methacrylate) is used in this study to demonstrate particle fabrication and characterization. Besides PPMA, microparticles have also been prepared with other common thermoplastic polymers such as polylactic-*co*-glycolic acid, polycaprolactone, polymethyl methacrylate, and polystyrene. PDMS (polydimethyl siloxane) stamps with two types of features, protruding squares with round corners (micro-pillars) and recessed squares (micro-wells), are used.

Figure 1 shows the μCHP process using a stamp with micro-pillar features. The stamp was dipped into a 5.8 wt % PPMA/acetone solution. A thin, continuous, conformal layer of PPMA formed immediately on the stamp as observed under optical microscope. The stamp was placed on a glass slide with a film of PVA (poly(vinyl alcohol)), which was prepared by brushing 1.5 wt % PVA aqueous solution on the slide with a cotton swab. The film on the slide served as a sacrificial layer and PVA was chosen for its water solubility and high melting temperature. A pressure of 320 Pa was

* Corresponding author e-mail: hansford.4@osu.edu.

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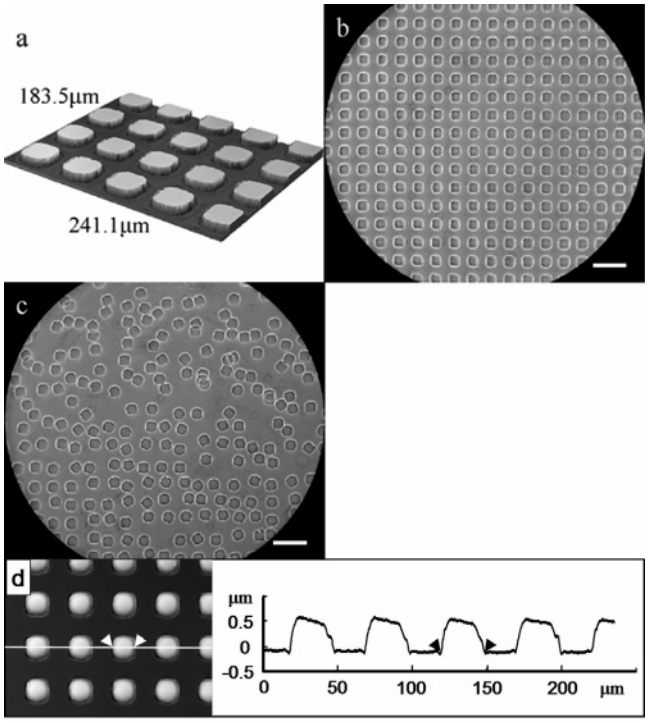

Figure 2. (a) 3-D image of the PDMS stamp with micro-pillar features generated by optical profiler. (b) Optical micrograph of microparticles on PVA/ slide. (c) Optical micrograph of released microparticles in water. (d) Contour plot of microparticles on bare glass slide. The scale bars are 100 μm.

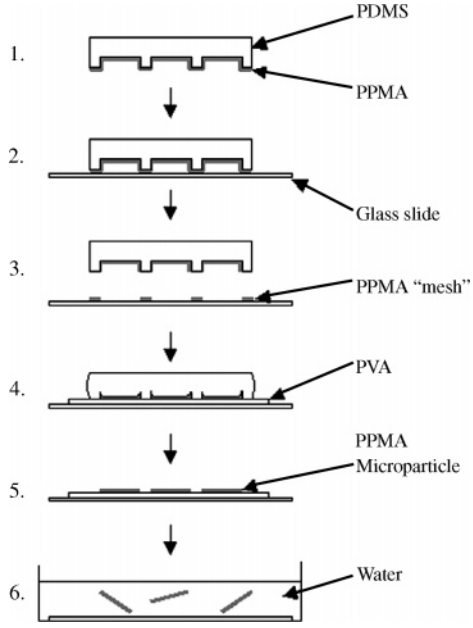

Figure 3. Illustration of μCHP fabrication of microparticles using micro-well stamp. (1) Apply a thin polymer film on PDMS stamp. (2) Place polymer-coated stamp on a hot glass slide. (3) Remove stamp, leaving polymer on the raised regions on substrate as mesh pattern. (4) Place stamp on a hot substrate with a sacrificial layer and press to make polymer in the wells contact with the sacrificial layer. (5) Remove stamp, leaving polymer in the micro-wells on substrate as microparticles. (6) Microparticles are released by dissolving the sacrificial layer with water.

applied on the stamp by a solid weight to ensure a complete conformal contact between the stamp and substrate. If too large of a pressure was applied, the stamp deformed enough to let the polymer in the wells contact the slide, leading to the undesirable transferal of a continuous polymer film with microfeatures onto the slide. The weight, stamp, and slide were then moved onto a hot plate at 110 °C, well below the maximum operating temperature of PDMS (>200 °C). After being left on the hot plate for 10 s, they were taken off the hot plate, and the stamp was peeled off the substrate, leaving isolated microparticles on the PVA/slide. Because of the low surface energy of PDMS, the adhesion of the PPMA to the PVA is much higher, resulting in a complete transfer of the polymer. The microparticles were released by adding water to dissolve the PVA layer.

The stamp and microparticles were characterized by optical microscope and optical profiler. The results are displayed in Figure 2. Figure 2a shows an optical profiler-generated 3-D image of the PDMS stamp used in this demonstration, which is composed of an array of round-cornered square micro-pillars with width and height of 30 μm and 3.7 μm, respectively. Figure 2, panels b and c, shows optical micrographs of PPMA microparticles on PVA and released microparticles in water, respectively. Released microparticles remained dimensionally stable in water solution indefinitely (over a period of several weeks). Since the PVA sacrificial layer is likely deformed during the printing, there was difficulty in measuring microparticle dimensions on the PVA accurately. Therefore, microparticles were also printed on a bare glass slide using the same experimental conditions for the purpose of dimensional characterization using an optical profiler. Figure 2d is a contour plot of microparticles on bare glass slide, showing that the microparticles had steep sides and a relatively flat top area. Analysis based on a series of contour plots reveals that the microparticles printed on a bare glass slide had a width of 29.9 $\pm$ 0.4 μm and thickness of 618.5 $\pm$ 9.9 nm.[14]

A two-step μCHP process, shown in Figure 3, has been developed for producing particles from a PDMS stamp with micro-well features. A thin PPMA layer on the stamp was obtained by dipping the stamp in 2.5 wt % PPMA/acetone solution. Pressure of 550 Pa was applied on the stamp by a solid weight, to induce a full conformal contact between the polymer on the raised regions and the glass slide across the entire stamp. If too large of a pressure was applied, the stamp deformed enough to let the polymer in the wells contact the slide, leading to the undesirable transferal of a continuous polymer film with microfeatures onto the slide. The slide/ stamp/weight were moved together onto a hot plate at 110 °C and left for 10 s. The stamp was then removed, leaving the polymer originally on the raised areas attached to the

(14) Twenty-four microparticles in two different areas were measured using software installed with the optical profiler. A straight line was drawn across the center of a set of particles each time to generate a contour plot as shown in Figure 2d. The width of the particles was measured from edge to edge of the microparticles on the plot. To measure the thickness, a cursor was placed at the center of the measured microparticle, and another was placed besides the measured microparticle and at the center of the area between two adjacent microparticles. To obtain the average of thickness of measured microparticle, the cursor on microparticle was set to be 20 μm wide because the microparticles had steep sides and a relatively flat top area, which is approximate 20 μm wide. The cursor placed on substrate area was set to be 10 μm wide to minimize errors caused by noise. The height is averaged across the width of the region denoted by the cursors and the difference between two heights was the thickness of the microparticle. For each set of data, mean and standard deviation were calculated.

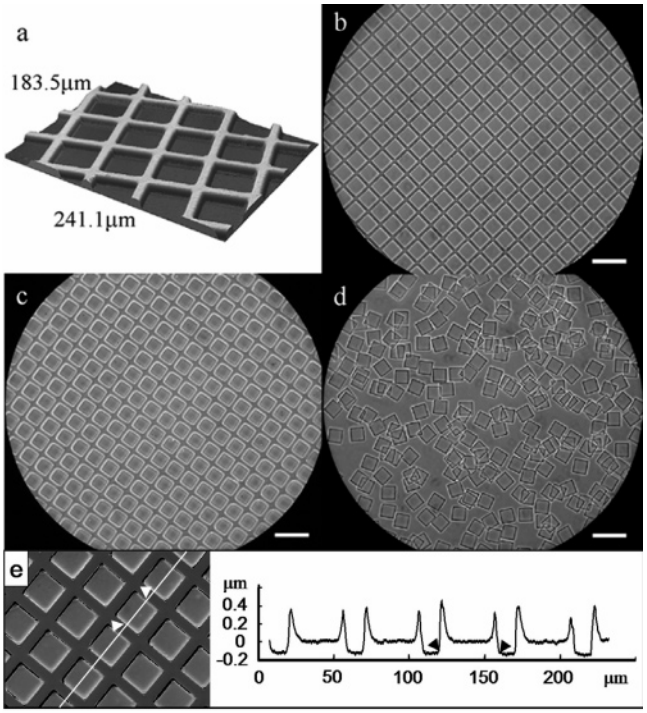

Figure 4. (a) 3-D image of the PDMS stamp with micro-well features generated by optical profiler. (b) Optical micrograph of polymer film with a mesh pattern on glass slide transferred from the raised regions on the stamp. (c) Optical micrograph of square microparticles on PVA/slide. (d) Optical micrograph of released microparticles in water. (e) Contour plot of microparticles on bare glass slide. The scale bars are 100μm.

slide as a mesh-like pattern. The second printing was performed on a glass slide with a PVA sacrificial layer at 110 °C. Pressure was manually applied to push the polymer in the micro-wells to contact the substrate for 5 s. Polymer in the micro-wells was left on the PVA/slide as isolated microparticles after the stamp was removed. The microparticles were released in water.

Characterization of the stamp and microparticles is shown in Figure 4. Figure 4a is a 3-D image of the PDMS stamp used in this demonstration, which is composed of 40-μm-wide square micro-wells separated by 10-μm-wide and 1.4-μm-high ridges. Figure 4b−d is optical micrographs of PPMA film with a mesh pattern on PVA, PPMA isolated microparticles on PVA, and released microparticles in water, respectively. Figure 4e is a contour plot of microparticles on bare glass slide, showing that the microparticles have thick edges and that the thickness gradually decreases and levels off as approaching the center. Line analysis of the microparticles on bare glass slide reveals that the microparticles have a width of 40.3 ± 0.4 μm and that the flat area in the middle is approximately 20 μm wide, with a thickness of 131.7 ± 6.4 nm.[15] The thickness of the thick edges varies considerably, ranging from 150 to 650 nm.

From both micro-pillar and micro-well stamps, μCHP produced uniform microparticles as shown in the optical micrographs over large areas. The optical profiler data further illustrates that the microparticles have the same lateral sizes as the stamp features for both micro-pillar and micro-well stamps and shows that the microparticles made with the micro-pillar stamp are generally thicker in the middle area, while the microparticles made with micro-well stamp have a thin central part but a thick edge. In principle, polymer microparticles with arbitrary lateral shapes can be produced with this method as long as a continuous film is formed on stamp with the contour of the micro-features. The concentration of polymer solution for dip coating is critical for film formation. Solutions with low polymer concentrations lead to discontinuous features, and solutions with too high of polymer concentrations lead to films that are too thick to maintain the contour of the stamp, preventing the removal of polymer from the raised regions. In general, for a specific polymer solution, within a certain concentration range, a continuous thin film forms on a stamp, and its thickness is proportional to the concentration, as is the thickness of the microparticles produced.

Although similar to each other, μCHP processes using stamps with two different types of features have their own advantages, which can be extended in different ways. Printing with micro-pillar stamp is simple and easy to perform. Multiple printing steps could prepare polymer structures with more than one layer. Each layer can be made of different materials and have different patterns. Microparticles with bilayer structures have also been prepared by double printing.[16] Use of micro-well stamp requires an additional stamping step to remove polymer film on the ridges before printing out the microparticles. This technique, as well, can be used to make microparticles with more than one layer by filling the micro-wells with polymer layers multiple times.[16] An advantage of this method is that printing particles out of micro-wells can be done without using elevated temperature, which is only needed to remove polymer between the micro-wells in the first printing. The second printing, which transfers the polymer from the micro-wells onto the sacrificial film, can be done at room temperature by making the sacrificial layer tacky, which is easily achieved transiently through a brief exposure of the dry PVA layer to the vapor from hot water.

To conclude, isolated polymer microfeatures were printed on a substrate coated with a sacrificial layer by soft lithography using stamps with protruding and recessed features. The polymer features had thin-film structure and well-defined lateral geometries and were released as free microparticles by dissolving the sacrificial layer in water.

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(15) Twenty-three microparticles in two different areas were measured using the same method as above. The microparticles had a central flat area of approximately 20 μm wide surrounded by thick edges. The thickness of the flat area was measured and analyzed by placing a cursor of 20 μm wide at the center of the particle and another of 5 μm wide besides the measured microparticle in the center of the area between two adjacent microparticles.

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