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Polymer particle-based micromolding to fabricate novel microstructures

Jung-Hwan Park · Seong-O Choi · Rachna Kamath · Yong-Kyu Yoon · Mark G. Allen · Mark R. Prausnitz

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Abstract Conventional micromolding provides rapid and low-cost methods to fabricate polymer microstructures, but has limitations when producing sophisticated designs. To provide more versatile micromolding techniques, we developed methods based on filling micromolds with polymer microparticles, as opposed to polymer melts, to produce microstructures composed of multiple materials, having complex geometries, and made using mild processing conditions. Polymer microparticles of 1 to 30 μm in size were made from PLA, PGA and PLGA using established spray drying and emulsion techniques either with or without encapsulating model drug compounds. These polymer microparticles were filled into PDMS micromolds at room temperature and melted or bonded together to form microstructures according to different protocols. Porous microstructures were fabricated by ultrasonically welding microparticles together in the mold while maintaining the voids inherent in their packing structure. Multi-layered microstructures were fabricated to have different compositions of polymers and encapsulated compounds located in different regions of the microstructures. More complex arrowhead microstructures were fabricated in a two-step process using a single mold. To assess possible applications, microstructures were designed as microneedles for minimally invasive drug delivery. Multilayer microneedles were shown to insert into cadaver tissue and, according to design, detach from their base substrate and remain embedded in the tissue for controlled release drug delivery over time. We conclude that polymer particle-based micromolding can encapsulate compounds within microstructures composed of multiple materials, having complex geometries, and made using mild processing conditions.

Keywords Micromolding · Microparticles · Micro-electro-mechanical-system

J.-H. Park · R. Kamath · M. G. Allen · M. R. Prausnitz (✉)
School of Chemical and Biomolecular Engineering, Georgia Institute of Technology,
Atlanta, GA 30332, USA
e-mail: prausnitz@gatech.edu

J.-H. Park
e-mail: junghwan.park@gmail.com

R. Kamath
e-mail: gtg656m@mail.gatech.edu

M. G. Allen
e-mail: mark.allen@ece.gatech.edu

J.-H. Park · S.-O. Choi · Y.-K. Yoon · M. G. Allen
School of Electrical and Computer Engineering, Georgia Institute of Technology,
Atlanta, GA 30332, USA

S.-O. Choi
e-mail: sochoi@ece.gatech.edu

Y.-K. Yoon
e-mail: yongkyu.yoon@ece.gatech.edu

1 Introduction

Microelectromechanical system (MEMS) techniques have been adapted to fabricate biomedical devices, including biosensors (Aytur et al., 2002), drug delivery systems (Li et al., 2004), microfluidic channels for biochemical assays (Carlier et al., 2004) and scaffolds for tissue engineering (Vozzia et al., 2003). Often, silicon-based fabrication processes are used to make such biomedical microdevices because of their ability to precisely engineer surfaces (Li et al., 2004; McAllister et al., 2000) and the expected biocompatibility of silicon (Voskerician et al., 2003). However, silicon-based processes are often expensive, especially for disposable medical microdevices (Noh et al., 2004). As

an alternative, MEMS fabrication using polymer materials has been gaining popularity, motivated by the large variety of polymers that have a range of physical properties and can meet compatibility requirements of biological and chemical applications (Bhushan and Burton, 2005). However, the large expense and optical diffraction associated with polymer fabrication by photolithographic methods have limited the development of polymer microdevices (Xia and Whitesides, 1998).

Instead of photolithography, micromolding techniques have been developed to fabricate microstructures with low cost, simple processing methods, and the potential for mass production by injection molding, embossing and other methods (Xia and Whitesides, 1998; Yu et al., 2000). Micromolds have often been made of poly-di-methyl-siloxane (PDMS) because PDMS is durable, optically transparent, inexpensive, and moldable (Kim et al., 2000). PDMS micromolds have been used to make analytical biological microdevices, such as microchips and microfluidic devices (Shin et al., 2003; Jakeway et al., 2000; Silva et al., 2004). Injectable and implantable microdevices for therapeutic applications have also been micromolded out of biodegradable polymers, such as poly-lactic-co-glycolic acid (PLGA), because they safely degrade within the body and can be easily molded (Armani and Liu, 2000).

Despite the many advantages of polymer molding, conventional micromolding methods have difficulty making microdevices with complex geometries or composed of multiple materials in a single mold. Using techniques based on injection molding or embossing, microstructures with high aspect ratios or complex geometries have been difficult to copy from molds because the high viscosity of the thermoplastic polymer melt often leads to premature cooling of the polymer before it completely fills the mold cavity (Ahn et al., 2004). The metal molds used for conventional processing are also not friendly to the high aspect ratios of intricate structures. Furthermore, the high temperatures and pressures of traditional processing are not conducive to the copying processes necessary to create structures with multiple compositions or complex geometries. Polymer microstructures are being developed for a diversity of pharmaceutical, biological, chemical, and mechanical applications involving assays, sensors, scaffolds, and microfluidic channels. Meeting the needs these many microsystems will require methods to mold microstructures having a wide range of device architectures and compositions.

To address these unmet needs, this study introduces a novel micromolding method based on filling molds with solid polymer microparticles instead of a polymer melt to copy microstructures with complex geometries and composed of multiple materials using mild processing conditions. Microparticles can flow easily into the cavities of micromolds at room temperature and low pressure, which facilitates making microstructures with high aspect ratios. Moreover, polymer microparticles can encapsulate chemical compounds, such as drugs, and can be filled into molds in sequential layers to accommodate multiple material compositions. After filling the mold, the final microstructures can be created by welding the microparticles within the mold by plastic welding methods, including thermal and ultrasonic welding. In this study, we demonstrate the ability of this polymer particle-based micromolding approach to fabricate microstructures of varying chemical composition as well as complex and high aspect ratio geometries, such as porous and arrowhead-shaped structures.

We have used polymer microneedles as a case study to examine the capabilities of particle-based micromolding. Microneedles are arrays of solid or hollow needles measuring microns in dimensions that can painlessly pierce into the skin to deliver drugs in a minimally invasive manner (Prausnitz, 2004). Solid polymer microneedles have been made for this application by melting polymers into PDMS micromolds under vacuum (Park et al., 2005). Using a similar method, polymer microneedles have also been fabricated to encapsulate drugs within the polymer matrix to slowly release drug within the skin (Park et al., 2006). This system should be suitable for self-administration without the pain or complexity of current controlled release devices based on hypodermic injection. It would be advantageous to expand on these capabilities to include microneedles with multiple layers that each contain different polymers and/or drugs to facilitate more complex drug release profiles and delivery of multiple drugs. Moreover, porous microneedles could be useful for applications requiring large surface areas, such as using microneedle structures as biosensors or tissue engineering scaffolds. Microneedles with arrowheads could be useful for better needle retention in the skin.

The microparticles used to fill micromolds in this study were made of biodegradable polymers—poly-lactic acid (PLA), poly-glycolic acid (PGA) and their co-polymers (PLGA)—which are already approved by the Food and Drug Administration (FDA) because they can safely degrade into biocompatible monomers in the body (Kohn and Langer, 1996; Lee et al., 1997). This class of polymer microparticles has been studied extensively to encapsulate compounds for sustained release for many applications, including vaccine delivery (Lee et al., 1997a, b), cancer treatment (Birnbaum and Brannon-Peppas, 2003), hormone therapy (Lee et al., 1997a, b), protein delivery (Jain et al., 2005), gene delivery (Little et al., 2004), and diagnostic applications (Lee et al., 2005). These microparticles are typically prepared using an oil-water, double-emulsion system; spray drying methods; supercritical conditioning methods; and milling methods (Benoit et al., 1996).

2 Materials and methods

2.1 Microparticle preparation

Microparticles were prepared from biodegradable polymers using emulsion and spray drying methods. The emulsion method was used to fabricate microparticles of various sizes, but encapsulation efficiency was low compared to the spraying drying method due to drug loss in the external phase. Spray drying was used as a simple method to obtain microparticles with efficient drug encapsulation and a monodisperse size distribution, albeit limited to microparticles smaller than 10 μm due to the small size of the atomizing nozzle. Particle size and distribution were measured by scanning electron microscopy (3500 H, Hitachi, Tokyo, Japan) and a multisizer (Multisizer II, Beckman Coulter, Fullerton, CA).

2.1.1 Emulsion technique

Using the well-known double-emulsion technique to make PLA microparticles (Benoit et al., 1996), 50 mg of calcein was dissolved in 15 ml deionized water. In addition, 0.2 g of PLA (L-PLA, inherent viscosity 1.0 dL/g; Absorbable Polymers International, Pelham, AL) was separately dissolved in 2 ml methylene chloride (Sigma-Aldrich, St. Louis, MO). Then, 200 μl of the calcein solution was homogenized in 2 ml of PLA solution for 2 min at 15,000 rpm (PowerGen 700, Fisher Scientific, Pittsburgh, PA). The resulting water-in-oil emulsion was homogenized in 50 ml of an aqueous solution of 0.1% polyvinyl alcohol (Sigma-Aldrich) for 2 min at 10,000 rpm, which produced a water-in-oil-in-water, double emulsion. After mixing the double emulsion for 3 h at 300 rpm, the methylene chloride was extracted into the continuous phase (i.e., polyvinyl alcohol solution), which solidified the discontinuous phase (water-in-methylene chloride emulsion) into PLA microparticles encapsulating calcein. Microparticles of 1–30 μm in size were isolated by filtration (Park et al., 2006).

2.1.2 Spray drying technique

Polymer microparticles with 0.1% (w/w) hydrophobic dye (Oil Soluble Dye Flake, Candle Resource, NY) were prepared. Poly-lactic-co-glycolic acid (PLGA 50/50, 1.12 dL/g; Absorbable Polymers International) and the hydrophobic dye were dissolved in ethyl acetate to form a 3% (w/w) polymer solution, which was spray dried (Buchi 290 Mini Spray Dryer, Flawil, Switzerland) using the following process parameters: inlet temperature was 55°C, outlet temperature was 45–47°C, aspirator ratio was 100%, and the polymer solution feed rate was 3.5 ml/min.

To make PLGA microparticles encapsulating Vitamin B by spray drying, 5 ml of an aqueous solution continaing 3% Vitamin B (riboflavin-5′-phosphate sodium salt dehydrate, Avocado Organics, Lancashire, England) was emulsified in 100 ml of an ethyl acetate solution containing 3% (w/w) PLGA 50/50 by homogenization (PowerGen 700), using the conditions described above, except the inlet and outlet temperatures for this process were 60°C and 40–45°C, respectively.

2.2 Fabrication of microstructures from microparticles

2.2.1 Preparation of micromolds

Micromolds were prepare by (i) photolithographically creating a female master mold made of SU-8 photoresist, (ii) molding a male master structure out of PDMS from the female master mold and (iii) molding a female replicate mold out of PDMS from the male master structure. To make the female master mold, an SU-8 layer was spin coated (1 mm thickness) onto a clean silicon water, baked at 95°C for 18 h, and then exposed to UV light (365 nm wavelength, 9000 mW/cm^2) through a mask patterned with square holes. The UV exposure was carried out at an angle while the sample was rotated, which resulted in a tapered, conical shape of non-crosslinked SU-8 (Yoon et al., 2003; Sato et al., 2004). The geometry of the microneedle structure was defined by both the geometry of the mask and the exposure angle. The SU-8 mold was finally formed by developing the non-crosslinked SU-8 in PGMEA for 12 h.

The PDMS male master structure was prepared by casting PDMS epoxy (Sylgard 184, Dow Corning, Midland, MI) into the SU-8 mold. After curing, the flexible PDMS structure was easily released from the rigid SU-8 mold. This PDMS master structure was then covered with PDMS epoxy, which, after curing, produced the PDMS replicate mold. To prevent bonding between these two PDMS structures during the curing process, a gold layer of 500 Å thickness was sputter deposited on the PDMS master structure (601 Sputtering System, CVC Products, Rochester, NY) before PDMS epoxy casting.

2.2.2 Fabrication of porous microstructures by ultrasonic welding

The process to make porous microstructures by ultrasonic welding is summarized in Fig. 1. First, a PDMS mold was covered with 100 mg of PLA microparticles encapsulating calcein prepared by the double-emulsion technique. A PDMS male master structure was used to push the microparticles into the cavities of the mold. The process was repeated until the mold was fully filled. Then, a metal plate was placed

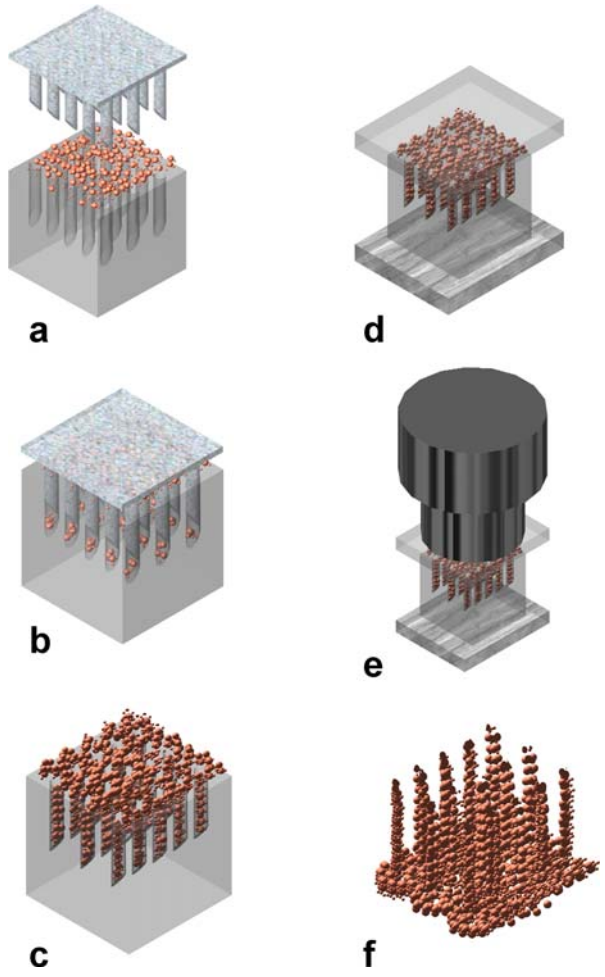

Fig. 1 Fabrication of porous microstructures out of polymer microparticles by ultrasonic welding. Biodegradable polymer microparticles are (a) placed on the surface of a PDMS micromold and (b) pushed into the cavities of the mold using the male master structure. (c) The process is repeated until the mold is fully filled. (d) A metal plate is placed on the bottom of the mold and a PDMS sheet is placed on the top of the mold. (e) An ultrasonic horn is pressed against the PDMS sheet on top of the mold to weld the microparticles together. (f) The resulting porous microstructure is removed from the mold

below the mold and a 1 mm-thick PDMS sheet was placed on top of the PLA particle cake on the top of the mold. The tip of an ultrasonic horn was pressed against the PDMS film with a force of 1 kg (ASM International, 1997). The polymer particles were ultrasonically welded by applying 20 pulses of ultrasonic energy at a pulse length of 1 s, duty cycle of 50%, and pulse power of 125 W using a 20-kHz ultrasonic device (Vibracell VC 505, Sonics & Materials, Danbury, CT). The sample was cooled to room temperature and then removed from the mold. A similar process was used to make porous microstructures out of PLGA microparticles, except the ultrasound power was reduced to 105 W.

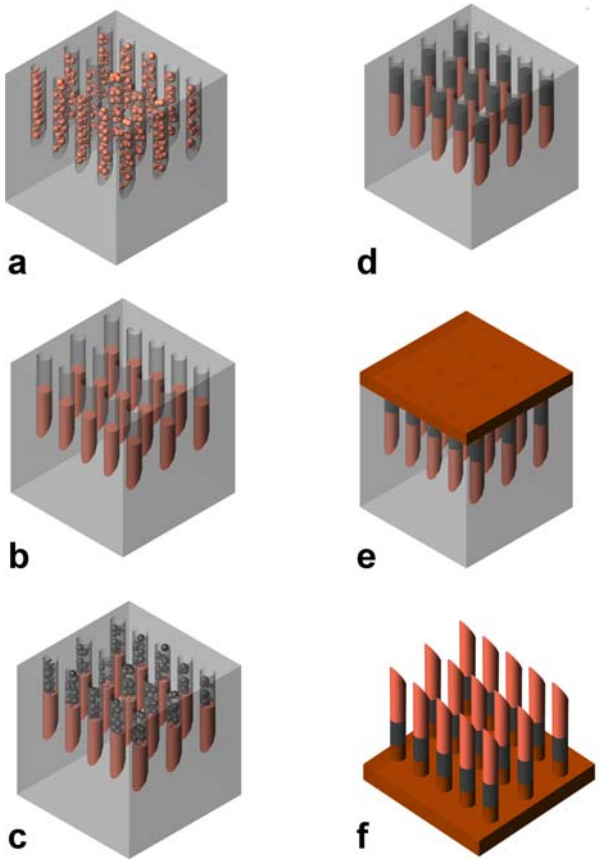

Fig. 2 Fabrication of microstructures layered with multiple materials. (a) Polymer microparticles are filled into a mold and residual particles are removed from the surface. (b) The microparticles are melted, which reduces their volume due to filling in the void spaces between particles. Polymer microparticles with a lower melting point are (c) filled into the remaining space of the mold and, after removing residual particles from the surface, (d) are melted. (e) To form the base substrate, either polymer pellets with an even lower melting point are melted or a polymer sheet is ultrasonically welded on the top of the mold. (f) The resulting microstructure layered with multiple materials is removed from the mold

2.2.3 Fabrication of microstructures layered with multiple materials

The process to make microstructures composed of multiple materials is summarized in Fig. 2. First, spray-dried, PLGA microparticles encapsulating 0.1% (w/w) hydrophobic dye were spread on a PDMS mold and pushed into the cavities of the mold by a PDMS male master structure. Excess particles on the surface of the mold were removed by adhesive tape (Self adhesive tape, Fisher Scientific) so that microparticles remained only within the mold cavities. The mold was placed in a 140°C oven (Vacuum Oven 1415M; VWR, West Chester, PA) for 5 min to melt the microparticles and simultaneously held at -70 kPa of vacuum to remove entrapped bubbles (Park et al., 2005). After cooling, this melting process eliminated the voids between microparticles, thereby reducing

the volume of this layer. The final volume of the layer was controlled by the size of the microparticles, and thereby the size of the inter-particle voids, and the number of times this process was repeated. In this way, a first layer composed of PLGA encapsulating hydrophobic dye was created, which formed the tips of the microneedles.

We next formed a second layer, which served as the rest of the microneedle shaft and its base substrate. A mixture of polyethylene glycol (PEG, 30,000 Da; Sigma-Aldrich) and spray-dried PLGA microparticles encapsulating Vitamin B was spread on the PDMS mold and placed in a 70°C oven at −70 kPa vacuum for 5 min. At this temperature, the PEG melted, but the PLGA tips and the PLGA microparticles dispersed within the PEG did not melt. This process formed the second layer of the microstructure. In some cases, we wanted to create a third layer to give the base substrate different properties. To accomplish this, excess PEG and PLGA microparticles were removed from the mold surface before the melting step so that they only filled the microneedle shaft. After melting and cooling, a 250-μm sheet of polystyrene (Sheet Styrene, Raboesch, Zeewolde, Netherlands) was ultrasonically welded to the bottoms of the array of microneedles using 5 to 10 pulses of ultrasonic energy at a pulse length of 1 s, duty cycle of 50%, and pulse power of 105 W at 20 kHz, as described above.

2.2.4 Fabrication of microstructures with complex arrowhead geometry

The process to fabricate complex microstructures with an arrowhead geometry is summarized in Fig. 3. First, PLA microneedles were prepared from a PDMS mold using polymer melt micromolding at 185°C, as described above. After removing the PLA microstructures, the same mold was filled with PLGA microparticles encapsulating Vitamin B. The PLA microstructures were then aligned and inserted part way into the cavities filled with PLGA microparticles. The assembly was placed in a 140°C oven for 5 min under –70 kPa vacuum, which was hot enough to melt the PLGA microparticles, but cool enough to prevent melting or deforming the PLA microstructures. After cooling, this process yielded arrow-shaped microneedles consisting of a PLA shaft and an arrowhead made of PLGA encapsulating Vitamin B.

2.3 Imaging microneedle insertion into tissue

2.3.1 Histological analysis

Microneedles were manually inserted into pig cadaver skin with approval from the Georgia Tech IACUC. With the microneedles still in place, a 1 cm^2 piece of skin was placed in a cryomold, immersed in O.C.T. compound (Tissue-Tek, Sakura Finetechnical, Tokyo, Japan) and frozen using liquid nitrogen. Thin tissue sections (12 μm) were prepared using a cryostat (Cryo-Star HM 560MV, Microm, Walldorf, Germany) maintained at –23°C. Alternating samples were collected on microscope slides (Micro-frost, VWR) and later analyzed by microscopy (E600 Microscope/Image System, Nikon, Kawasaki, Japan).

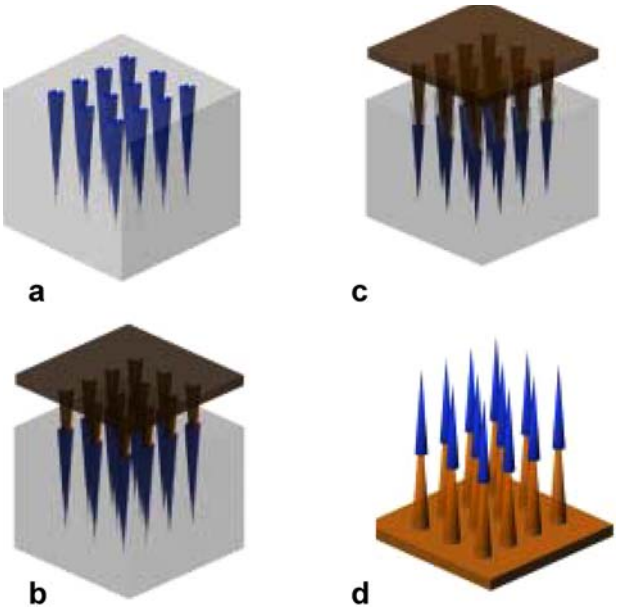

Fig. 3 Fabrication of microstructures with complex arrowhead geometry. (a) Polymer microparticles are filled into a mold and residual particles are removed from the surface. A microstructure previously prepared out of a polymer with a higher melting point using the same mold is aligned and inserted part way into the mold. (c) The microparticles are melted. (d) The resulting microstructure with a complex arrowhead geometry is removed from the mold

2.3.2 Real-time imaging

To visualize insertion of microneedles into human tissue in real time, microneedles were inserted into human cadaver cornea (Georgia Eye Bank, Atlanta, GA), which is transparent and thereby facilitates viewing. This use of human tissue was approved by the Georgia Tech IRB. Microneedles made of a PLGA tip encapsulating Vitamin B and a PEG shaft containing PLGA microspheres encapsulating a hydrophobic dye were inserted into cornea and incubated in a humid chamber at 37°C. After 1 h, water was applied to the surface of the cornea to complete the dissolution of the PEG needle base; residual PEG was gently removed with wet tissue paper. The PLGA microneedle tips embedded within the cornea were imaged by light microscopy (IX-70, Olympus, Mellville, NY).

3 Results

3.1 Motivation for process design

Conventional micromolding methods use polymer melts processed at high temperatures and pressures, which are needed to overcome the large shear viscosity of polymer melts (e.g., 1,000–10,000 cP). Given the complexity of the processing conditions, conventional micromolding can typically only produce microstructures with uniform composition and relatively simple geometry. In this study, our goal was to develop methods to make microstructures with multiple materials and complex geometries using mild processing conditions. This requires filling the molds with materials that have good flowability at low temperature and pressure through micron-sized openings and high aspect ratio channels.

To achieve this goal, we chose to use polymer microparticles, because in the pharmaceutical and other industries the flow of powders has been extensively studied and is known to be easily manipulated and to flow through small channels at mild processing conditions (Prescott and Barnum, 2000). The flowability of microparticles is generally much better than polymer melts. Moveover, the flowability of microparticles is generally independent of temperature, in contrast to that of polymer melts, which require hot processing conditions. Also, unlike polymer melts, which often do not fully fill micromold cavities because of the inability of air to escape during rapid polymer injection, the space between microparticles allows air to escape and thereby facilitates reliable filling of micromold cavities. Finally, selection of the size of polymer microparticles provides another degree of freedom that can be optimized based on flowability, micromold dimensions, and other factors.

3.2 Fabrication of microparticles

To study polymer particle-based micromolding, we first fabricated microparticles suitable for molding of biomedical microdevices. As discussed below, we were first interested to fabricate porous microstructures. For this scenario, larger microparticles were desirable, since larger particles pack at lesser density and thereby leave larger voids between particles. As shown in Fig. 4(a), spherical microparticles were prepared by a double-emulsion technique and filtered to yield a size range of 1 to 30 μm. These microparticles were made of PLA encapsulating calcein as a model drug.

We were also interested to make solid microstructures, which required smaller microparticles that pack at greater density and thereby leave smaller voids. As shown in Fig. 4(b), irregularly shaped microparticles were prepared by spray drying with a smaller diameter range of 1 to 7 μm and an average diameter of 3.8 $\pm$ 5 μm. These microparticles were made of PLGA encapsulating either Vitamin B or a hydrophobic dye as model drugs.

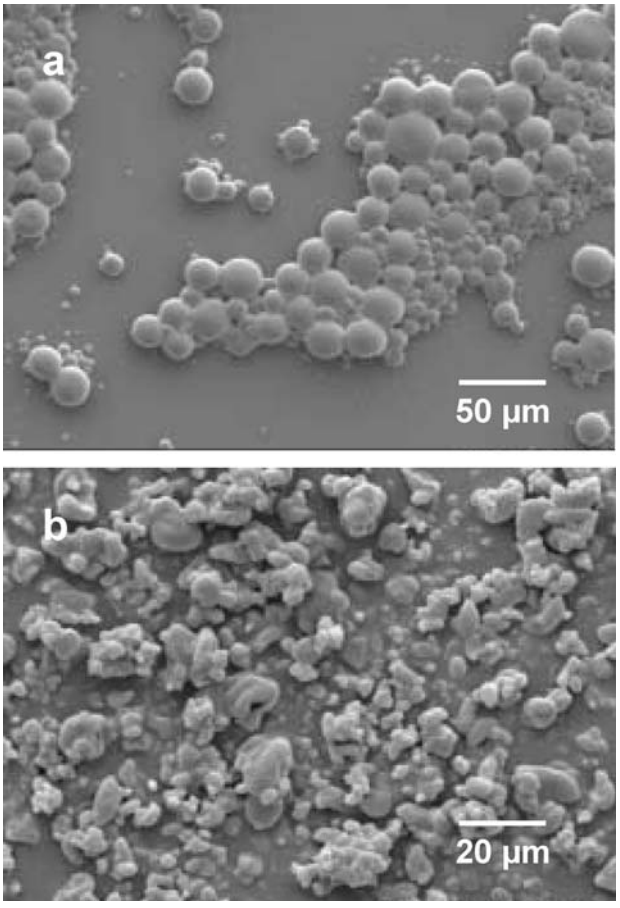

Fig 4 Microparticles used for particle-based micromolding imaged by scanning electron microscopy. (a) PLA microparticles prepared by a double-emulsion technique. (b) PLGA 50/50 microparticles prepared by spray drying

3.3 Three-dimensional microstructures fabricated from microparticles

We used microneedles as a model microstructure to investigate the capabilities of polymer particle-based micromolding. Polymer microneedles have been used to facilitate minimally invasive delivery of drugs into the skin (Park et al., 2005), but have not previously been molded with multiple layered materials or with complex geometries, such as porous structures or arrowhead shapes. Given the micron dimensions of microneedles, this model microstructure provided suitable challenges to assess polymer particle-based micromolding.

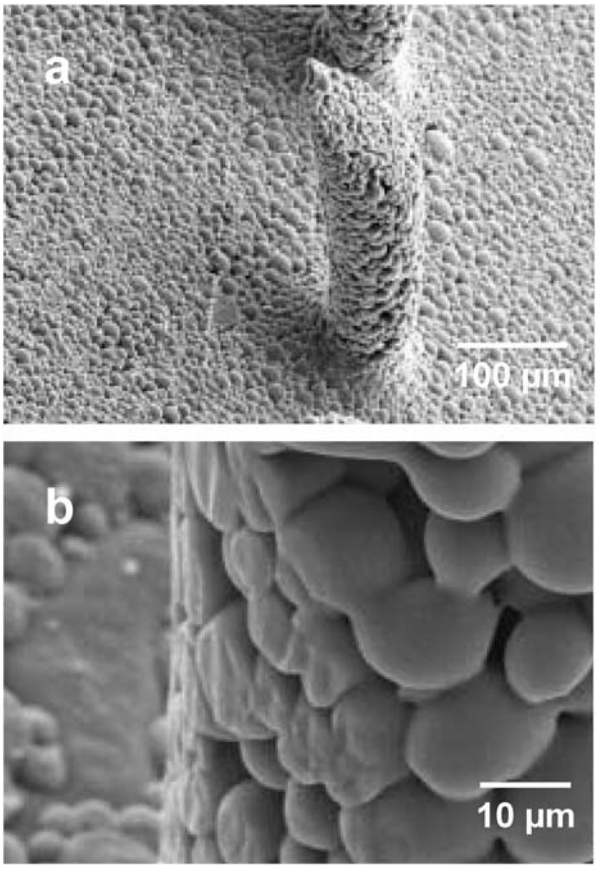

Fig 5 Porous microstructure fabricated by ultrasonic welding imaged by scanning electron microscopy. (a) A portion of an array of porous, beveled microneedles measuring 600 μm in height and 100 μm in base diameter. (b) A magnified view showing the individual PLA microparticles welded together to form the microstructure

3.3.1 Porous microstructures fabricated by ultrasonic welding

Porous microstructures were fabricated by filling micromolds with PLA microparticles at room temperature and then bonding them to each other within the molds by ultrasonic welding. As shown in Fig. 5(a), this process produced an array of beveled microneedle structures having the same shape as the micromold used to produce it. The microneedles each measure 600 μm in height and 100 μm in base diameter; the base substrate of the array measures 5 mm in diameter and 1 mm in thickness. Based on comparing the density of porous and solid microdevices each containing 100 needles prepared using the same mold, the overall porosity of the porous microneedle structures was determined to be 75%.

These results highlight an important difference between polymer particle-based micromolding and conventional micromolding methods. The high temperatures and pressures of conventional methods make it difficult to fabricate porous structures with large surface areas, unless sophisticated processes are used. The ultrasonic welding method uses mechanical vibrations of polymer microparticles at room temperature to cause local, frictional heating at the particle-particle interfaces, which bonds the microparticles together, as shown in Fig. 5(b).

The fabrication of porous microneedles was motivated in part by applications involving insertion of microneedles into the skin to serve as biosensors, tissue engineering scaffolds, or other structures requiring large surface areas. Previous results have shown that solid PLA microneedles with the same geometry as the microneedles shown in Fig. 5 can insert into the skin without failure (Park et al., 2005). However, the porous microneedles fabricated in this study were unable to insert into human cadaver skin (data not shown), which is consistent with the expectation that porous structures should be weaker than solid structures (Park, 1980). To enable microneedles to insert into skin, porous microneedle strength could be increased by changing microneedle material composition, geometry, porosity and other parameters.

3.3.2 Microstructures layered with multiple materials

Microstructures were fabricated with layers of multiple materials by sequentially adding polymer particles and melting them into a mold. Unlike conventional micromolding using a polymer melt, the volume occupied by polymer particles after they are melted within the mold decreases as the melted polymer fills the voids between particles. In this way, a mold can be completely filled with polymer particles at room temperature, but only partially filled after the particles are melted. This process can be repeated to fill the mold with layers of different materials. The volume reduction of each layer is controlled by particle packing, which is in turn controlled by particle size. Optimally, the melting point of the polymer particles should decrease with each iteration to prevent re-melting of polymer already in the mold. An iterative process like this by partially filling molds is much more difficult to control using conventional molding methods.

Figure 6 shows microneedles made in this way, exhibiting a first layer of transparent PLGA encapsulating a hydrophobic green dye that forms the microneedle tip and a second layer of opaque PEG containing PLGA microparticles encapsulating Vitamin B that forms the microneedle shaft and base substrate. The microneedles shown in Fig. 6 have a square base measuring 250 μm by 250 μm and a shaft height of 600 μm. Similar microneedle arrays were also made with three layers, in which the needle composition was the same, but the base substrate was made of polystyrene that was applied in a third step involving ultrasonic welding of a polystyrene film to the bases of the microneedles (not shown).

These results demonstrate that polymer particle-based micromolding can be used to fabricate microstructures with multiple layers of materials with different properties and that

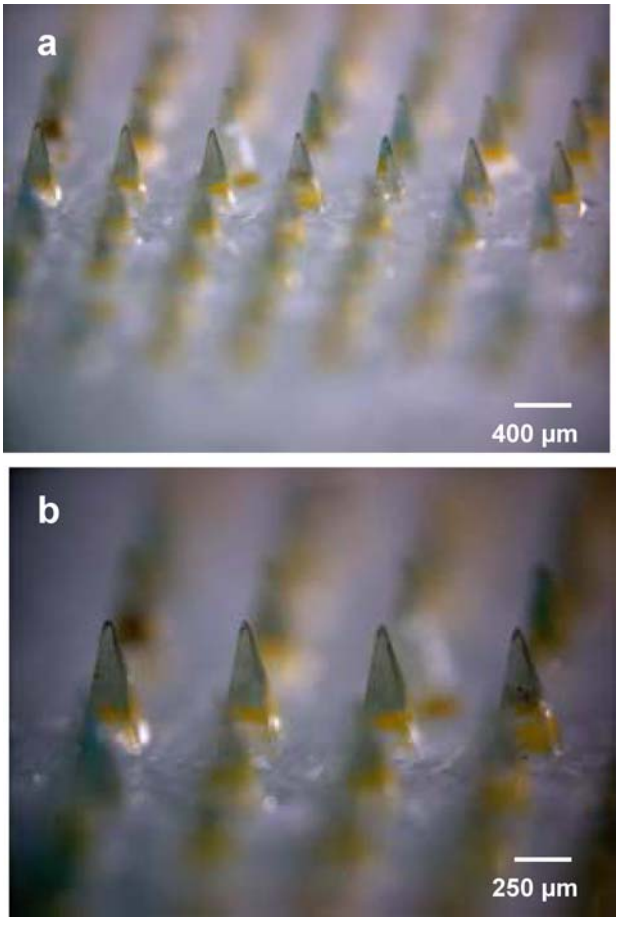

Fig. 6 Microstructures layered with multiple materials viewed by brightfield microscopy. (a, b) A portion of an array of 200 microneedles is shown at two different magnifications. The transparent green tips are made of PLGA encapsulating green dye and the opaque yellow shafts are made of PEG containing PLGA particles encapsulating Vitamin B. Each multi-layered microneedle has a base length of 250 μm, a tip length of 5 μm, and a height of 600 μm

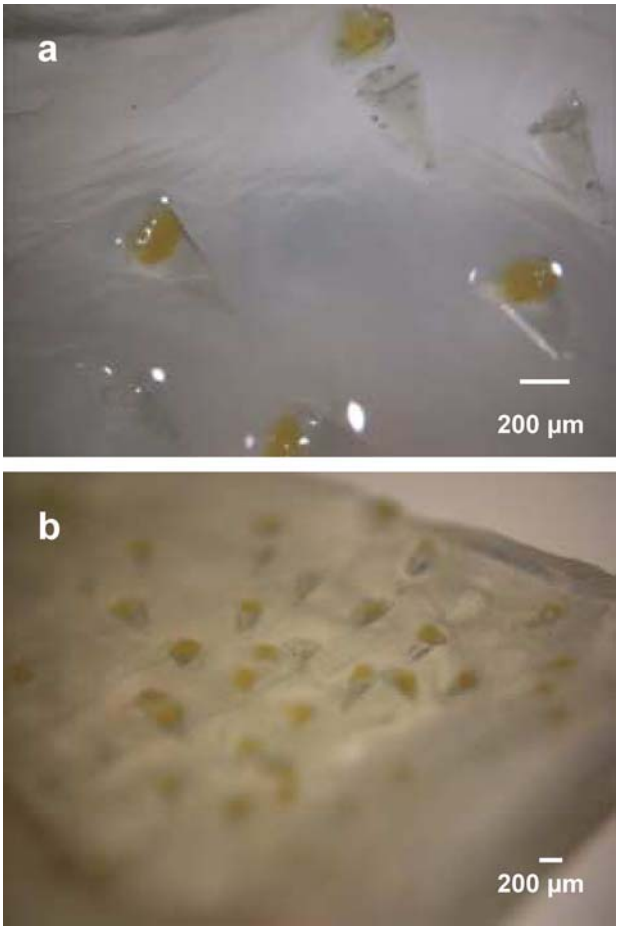

Fig. 7 Multilayered microneedles inserted and left embedded in human cadaver cornea after intentional detachment from their base substrate viewed by brightfield microscopy. Multilayered microneedles (see Fig. 6) were designed to have mechanical strength sufficient to insert into tissue, afforded by the strength of the transparent green PLGA tip, and water solubility sufficient to detach from their base substrate, afforded by the opaque yellow PEG shaft. In this way, microneedles could remain embedded within tissue for controlled release of drugs over time. Cornea was selected as a model tissue, because of its optical transparency that facilitated *in situ* imaging. (a, b) These multilayered microneedles inserted into tissue and detached from their base substrate according to their designed functions

different molecules and intact microparticles can be encapsulated within each layer. More specifically, the microneedle design shown in Fig. 6 may be useful for drug delivery, because it can insert into skin due to the strength of the PLGA tip and can rapidly separate from its base substrate due to the water solubility of the PEG shaft. In addition, it can deliver two different model drugs at different rates: a hydrophobic dye is encapsulated within the PLGA tips and Vitamin B is encapsulated within PLGA microparticles released from the PEG shafts.

To better assess their suitability for drug delivery, multilayered microneedles were inserted into tissue. Figure 7 shows an *en face* image of the surface of a human cadaver cornea after insertion of multilayered microneedles and their intentional separation from the base substrate due to weakening of the PEG shaft caused by swelling and dissolution of the PEG. The cornea was used for this study, because of its transparency that allowed visualization of microneedles embedded inside the tissue. This demonstrates the feasibility of inserting multi-layer microneedles into tissue, separating the needles from their base substrate, and leaving the needles embedded in the tissue for slow drug release over time.

In a parallel study, multi-layer microneedles were inserted into pig cadaver skin and then examined histologically after vertical cryosectioning. As shown in Fig. 8, the microneedles pierced the skin. The tip, made of PLGA with encapsulated green dye, was embedded in the superficial dermis and the shaft, made of PEG with PLGA microparticles encapsulating Vitamin B, was embedded near the epidermis.

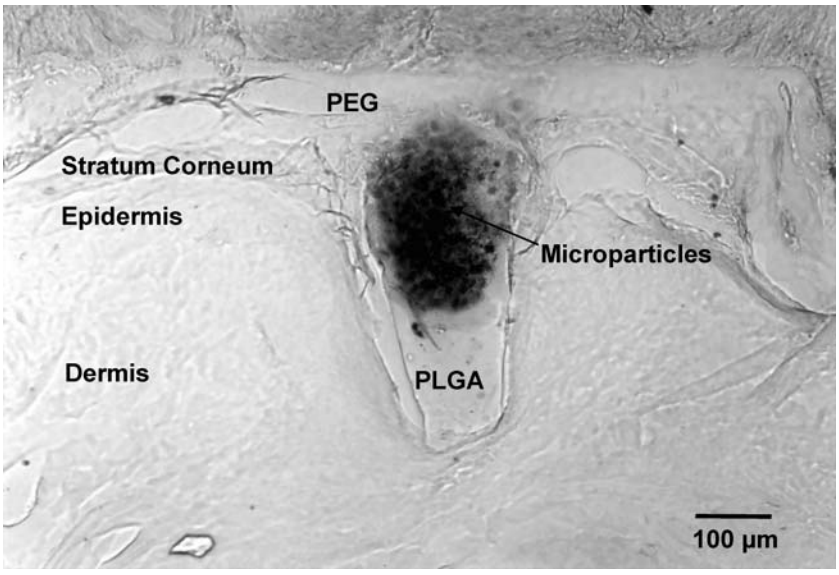

Fig. 8 Multi-layered microneedle inserted into pig cadaver skin, cryo-sectioned vertically and viewed by brightfield microscopy. Multi-layered microneedles (Fig. 6) were inserted into the skin. The green PLGA needle tip penetrated into the superficial dermis and the PEG shaft filled with microparticles (black dots) was partially inserted across the epidermis

3.3.3 Microstructures with complex arrowhead geometry

Microstructures with an arrowhead geometry were fabricated to demonstrate polymer particle-based micromolding of complex geometries. Using a two-step process, PLA microneedles with a base substrate were first fabricated by polymer melt micromolding. These PLA microneedles were then aligned by viewing through a microscope and inserted part way into the cavities of a micromold filled at room temperature with PLGA microparticles. After melting and cooling the PLGA microparticles (without melting the PLA microneedles, due to the higher melting point of PLA), this process yielded an embedded double-microneedle structure having a PLGA arrowhead bonded to a PLA shaft.

Figure 9 shows a representative image of arrowhead microneedle structures. For drug delivery applications, the yellow arrowheads of the microneedles are composed of PLGA encapsulating Vitamin B as a model drug and the clear shafts, composed of PLA, serve as the mechanical supports during insertion into skin. If designed appropriately, the arrowheads of this microneedle structure could intentionally separate from the shafts after insertion into the skin. In this way, the shafts could be removed from the skin and discarded, while the biodegradable, drug-loaded arrowheads could remain embedded in the skin for slow drug release.

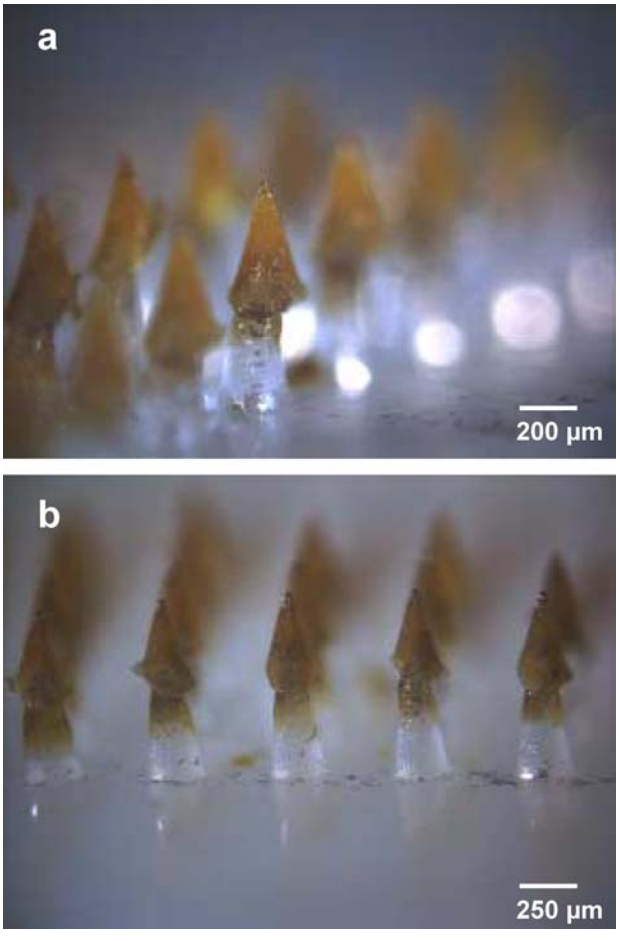

Fig. 9 Microstructures with complex arrowhead geometry. A portion of an array of 200 microneedles is shown at two different magnifications. The yellow/brown arrowheads are made of PLGA encapsulating Vitamin B and the transparent shafts are made of PLA. Each microneedle has a 250 μm base diameter and a 750 μm height (a) side view (b) front view

4 Discussion

4.1 Conventional vs. polymer particle-based micromolding

Microdevices are receiving increasing attention for use in medical, pharmaceutical and research applications in part because they can often be molded with a low cost of manufac-

turing, high resolution of feature size, and ability to be rapidly prototyped. However, conventional micromolding methods based on injection molding, embossing, solvent casting and other approaches can limit the functionality of these microdevices; in this study we focused on the limitations imposed on microneedles for drug delivery as a case study example. It would be advantageous to develop simple methods to mold microstructures with complex geometries, high aspect ratios and composed of multiple materials in a single mold. The requirements of conventional molding—i.e., high temperature, high pressure, and a continuous, liquid/deformable polymer phase—are not conducive to the need for multi-functional microdevices to fill molds and solidify evenly throughout the mold.

Polymer particle-based molding described in this study addresses many of these limitations of conventional molding, because it is performed under mild conditions as a two-step process. First, microparticles are filled into the mold at room temperature. Then, thermal or ultrasonic welding is used to connect the particles within the mold. With this particle-based process, microdevices that have high aspect ratios, are composed of multiple materials, and contain complex architectures can be more readily replicated.

4.2 Characteristic features of polymer particle-based micromolding

An inherent aspect of the polymer particle molding process is that there are voids between the particles filled into the mold. For porous structures, these voids present the opportunity to weld the microparticles together to form a continuous polymer particle network that maintains the voided structure. By selecting the appropriate particle size(s), the porosity and pore size can be controlled. For solid structures, these voids can be eliminated upon melting the microparticles, and thereby offer the inherent capability to reduce the volume of the polymer particles. This facilitates partially filling molds to fabricate microstructures composed of multiple layered materials.

Another aspect of polymer particle molding is that the different melting points of different polymers present opportunities and constraints on the process. In general, multi-step fabrication processes used to make microstructures with multiple materials or complex geometries require that the first polymer particles used have the highest melting point and subsequent polymer particles have progressively lower melting points. While this constrains the choice of polymers and their architecture within the microdevice, it nonetheless provides the capability to sequentially fabricate different parts of a microdevice without disturbing previously-fabricated components. Moreoever, the use of ultrasonic welding, which selectively heats and bonds at interfaces, can relax the constraint on melting points and permit attachment of a higher melting point polymer subsequent to fabrication of a lower melting point component.

These particle-based processes are influenced by the choice of the size of microparticles to use, which depends on the intended functionality of the microdevice and the geometric resolution of the micromold. For example, the size of the microparticles should be smaller than the smallest feature size of the micromold in order to completely fill it. In addition, smaller particles are preferred to fabricate solid microstructures due to their higher packing density that more efficiently fills the mold. In contrast, larger particles are preferred to fabricate porous microstructures, which give them a greater void fraction, and to fabricate solid microstructures with multiple thin layers of different materials, which leads to a greater volume reduction upon melting.

A final distinction of polymer particle-based molding is that encapsulation of drugs or other compounds within microstructures can be dissociated from the micromolding process. For conventional molding processes, drugs usually need to be added to the polymer melt and encapsulated during polymer solidification in the mold, which can damage the drug and makes it difficult to control the encapsulation process, for example, to assure uniform drug distribution throughout the device. Using the methods developed in this study, drugs or other compounds can be encapsulated within polymer microparticles during a separate initial step using a variety of well-established techniques, such as spray drying and emulsion protocols. The encapsulation method can be selected to suit the delivery and stability needs of the encapsulated compounds. As a separate, subsequent step, the microparticles are thermally or ultrasonically welded to form the final microdevice.

4.3 Porous microstructures

Porous microstructures fabricated by ultrasonic welding can be used for a variety of applications that take advantage of their open voids, large surface area, mild processing conditions that do not require melting the polymer particles, and other features. The open voids and large surface area lend themselves to biosensor applications, in which sensing molecules are coated onto the porous microstructures with high surface-to-volume ratio, and to tissue engineering applications, in which the porous structure can serve as a scaffold on which cells can grow and the open voids permit transport of nutrients to the cells. The mild processing conditions lend themselves to drug delivery scenarios in which the encapsulated drug is not exposed to the high temperature of a polymer melt, because the heating during ultrasonic welding is localized to the microparticle interfaces. In contrast to these and other advantages, porous microstructures are inherently weaker than solid structures, which is usually a disadvantage. For example, the porous microneedles

fabricated in this study did not have sufficient mechanical strength to penetrate the skin.

Porous microstructures have previously been fabricated by other methods, which typically involve encapsulating inorganic microparticles (i.e., "porogens) within the polymer matrix that are subsequently removed to leave behind porous voids (Draghi et al., 2005). This approach is limited to microdevice geometries that permit complete porogen removal. Also, this technique includes the use of solvents to remove porogens, which can leave a residual toxic solvent in the microstructure or can cause drugs encapsulated in the matrix to be released together with the porogen. In contrast, ultrasonic welding of microparticles avoids the use of porogens and leaching solvents.

4.4 Microstructures with multiple materials and complex geometries

Many microdevices benefit from fabrication using multiple materials. Conventional molding methods can more easily accommodate mixtures or homogeneous composites of different materials introduced into the mold at the same time. However, other designs require different parts of a microdevice to have different materials to achieve different local properties. This is much harder to do using conventional micromolding techniques unless separate molds are used for each part with a different material. The microparticle-based molding methods described here provide a simple method to fabricate microstructures with multiple materials as layers. While this capability is not sufficient to fabricate any device design involving multiple materials, it can be adapted to accommodate many designs using appropriate mold geometry, microparticle size, filling strategy and other parameters.

Another limitation of conventional micromolding methods is that it is difficult to remove molded structures that have a cross-sectional diameter larger than the opening of the mold cavity without breaking the mold. In the present study, we were able to prepare a serrated arrowhead structure without breaking the mold by using a two-step process based on the use of two polymers with different melting points. While this technique could be done using a series of conventional molding processes, the procedure was simplified by integrating the shaft into the arrowhead mold at ambient condition, which was enabled by the use of microparticle-based molding. Although the arrowhead structure developed in this study was motivated by applications to drug delivery to the skin, similar structures might be utilized as radio-frequency antennae and inductors after metallization of the surface.

4.5 Limitations of polymer particle-based micromolding

Despite the many advantages of polymer particle-based micromolding, the method has limitations, some of which are discussed in the preceding paragraphs. In addition, it is worth noting that polymer microparticles need to be fabricated by methods that often involve exposure to organic solvents. If proteins or other sensitive compounds need to be encapsulated within these particles, they may be damaged during the encapsulation process. The polymers used to make microparticles must also have good solubility in an appropriate solvent to facilitate particle formation by spray drying or emulsion methods. When thermal melting is used, the elevated temperature during the melting process can also degrade encapsulated compounds. However, bulk melting can be replaced by ultrasonic welding, or possibly laser welding or radio-frequency welding, to localize heating and thereby minimize damage to encapsulated compounds. When making multi-layer microstructures, care must be taken when filling the micromold to be sure that the cavities are uniformly filled so that the layers are consistently thick throughout the device. Finally, fabrication of multi-layered microstructures also requires that the chemical and physical properties of the polymer and encapsulated compounds be tailored to the needs of each layer.

5 Conclusions

Due to the limitations of conventional micromolding methods, this study tested the hypothesis that polymer particle-based micromolding can encapsulate compounds within microstructures composed of multiple materials, having complex geometries and made using mild processing conditions. Because microparticles flow into narrow channels more readily than viscous polymer melts, we found that filling molds with polymer microparticles at room temperature was a facile process that enabled the fabrication of novel microstructures.

First, biodegradable polymer microparticles, either with encapsulated drugs or without drugs, were prepared by emulsion and spray drying methods. Porous microstructures with void fractions determined by the packing structure of the microparticles were made by ultrasonically welding the particles together within the mold. Solid microstructures layered with multiple materials were fabricated using an iterative process of filling and melting microparticles in the mold. More complex, arrowhead microstructures were fabricated by a two-step molding process. The use of microparticle-based molding facilitated encapsulating model drugs within each of these microstructures for controlled release or other applications.

The microstructure designs investigated in this study were demonstrated in the context of microneedles for drug delivery to the skin, where porous microneedles lend themselves to development into biosensors or tissue engineering scaffolds; solid multi-layered microneedles could be

used to encapsulate different drugs in different parts of the needles for different release properties or to facilitate controlled dissociation of the microneedle shaft within the skin; and arrowhead microneedles were designed to enable retention of the arrowhead within the skin for slow drug release after breaking off the microneedle shaft. Overall, this study showed that polymer particle-based micromolding is a versatile fabrication technique suitable to make microstructures with multiple materials and complex geometries using mild processing conditions.

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