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UV-assisted embossing of microgel shapes with varying geometries for oral macromolecule delivery

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In the current work, successful fabrication of biocompatible microgel shapes of various geometries is demonstrated. The novel fabrication process yields individual microgel shapes with lateral dimensions of 25-100 µm and a height of 25 µm on a water-soluble substrate in a simple two-step process. These microgel shapes are embossed from aqueous solutions and crosslinked using UV exposure at ambient temperature, thereby providing a method that is highly desirable for the fabrication of drug delivery systems (DDS) loaded with fragile cargo such as macromolecules.

The use of drug-loaded micro and nano-devices to improve the drug bioavailability has become increasingly popular. However, DDS for oral administration fabricated by traditional bottom-up fabrication techniques face the challenge of low intestinal mucosal adhesion and residence times due to their spherical shape.[1] Thus the use of top-down fabrication methods has been explored more recently to provide control over the physical characteristics including the shape, size and surface properties of the DDS. Most of these techniques are multi-step processes employing elastomeric molds which are difficult to handle and prone to breakage after a few runs, resultantly making batch-to-batch replicability tedious.[2][3]Alternatively, micromechanical punching has been recently described as a fabrication technique using a polymeric film with a drug polymer matrix. [3] However, the use of high embossing temperatures makes this technique unsuitable for macromolecule loaded particle fabrication. As a result, we explore a microgel shape fabrication technique that is compatible with ambient temperature and has a low batch-to-batch variability.

For microgel shape fabrication, initially a Silicon (Si) master template with the desired particle geometry is patterned using photolithography and reactive ion etching (RIE) (Fig.1A-B). Microscale topologies are attained in the given geometries (Fig.2A). The inverse of these microscale topologies are transferred into a cyclo olefin polymer (COP) sheet by hot embossing with the fabricated Si master template (Fig.1C-D). A flexible yet structurally rigid COP stamp is thus obtained with wells corresponding to the desired final particle geometry (Fig.2B-C). Microgel shapes are thereafter fabricated in a two-step process (well-filling and particle fabrication) using this COP stamp. For well-filling, the COP stamp is wetted with a photoactive Polyethylene glycol (PEG) formulation and roll-to-plate embossing fills its wells with this formulation (Fig.3A-C). The resultant filled COP stamp is then used for the particle fabrication, by bringing it in contact with a transparent and flexible poly-vinyl alcohol (PVA) substrate. A UV Nanoimprint lithography (UV-NIL) tool is used to emboss and irradiate this stack with UV @ 365nm. The irradiation initiates the hydrogel formation, while the embossing at ambient temperature leads to mechanical punching through the hydrogel flash layer and partially into the PVA substrate, thus transferring the microgel shapes onto the PVA. On demolding, the PVA substrate contains individual particles devoid of a flash layer (Fig.3D-F). These microgel shapes on a PVA substrate are then easily harvested in solution by dissolving the water-soluble substrate. (Fig.3G-H). PEG microgel shapes are fabricated with circular, elliptical, square and rod-like shapes (Fig.4).

The novel process employs easy to handle, non-toxic materials and has a vast potential for scalability. The loading of these microgel shapes with bovine serum albumin (BSA) as a model protein is currently being investigated.

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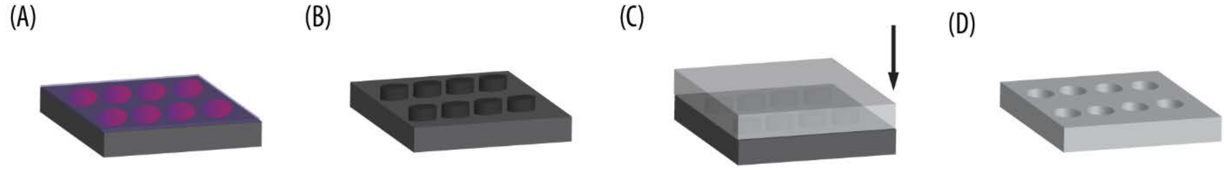

Figure 1. (a)-(b) Illustration of the patterning of particle geometry into a Si master and (c)-(d) transfer of the pattern onto a COP stamp The steps involved are (a) Photolithography defining the particle shapes in a photoresist mask (b) RIE of Si master with microscale topologies (c) hot embossing of the COP sheet with FDTS coated Si master (d) Demolded COP stamp with wells

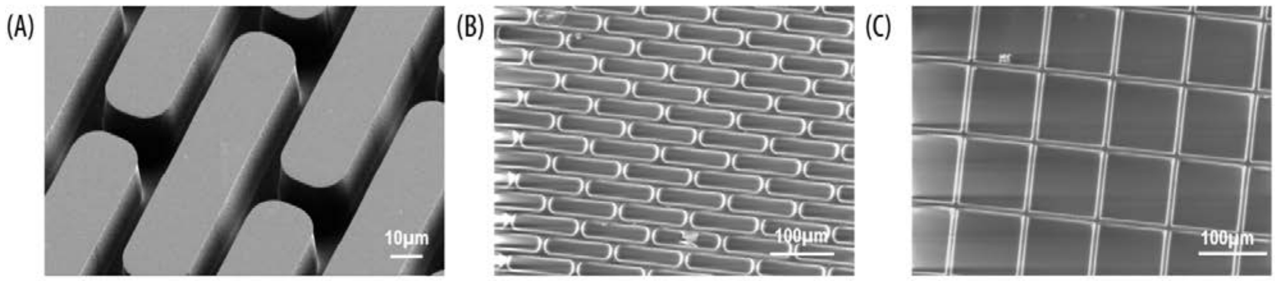

Figure 2. SEM images of - (a) rod shaped structures fabricated on a Si master by photolithography and RIE, (b) rod shaped wells imprinted on a COP stamp via hot embossing and, (c) square shaped wells imprinted on a COP stamp

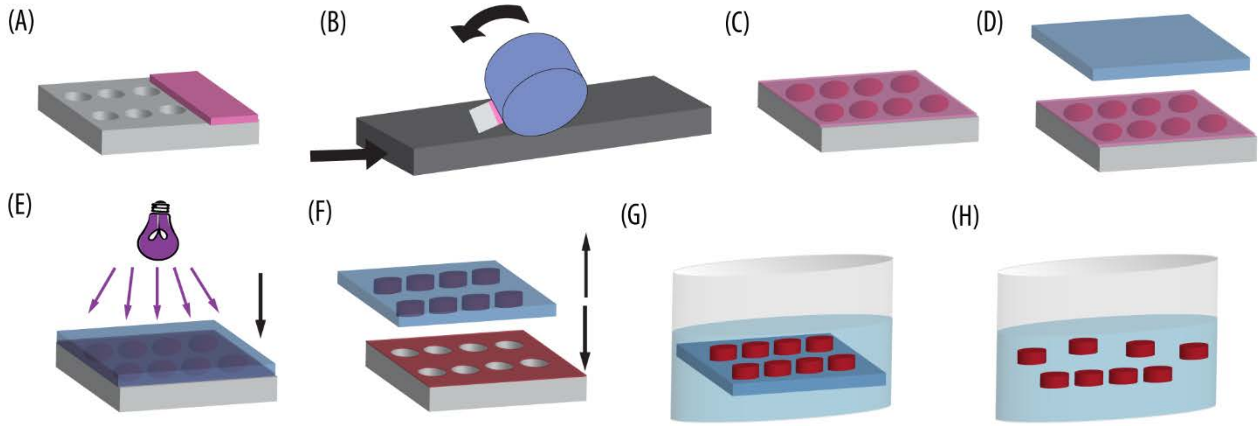

Figure 3. Illustration of (a)-(c) the steps involved for well filling with PEG, (d)-(f) the fabrication of PEG microgel shapes and (g)-(h) the harvesting of microgel shapes. Well Filling: (a) COP stamp wetted with uncrosslinked PEG, (b) well filling by roll-to-plate embossing and (c) filled COP stamp. Microgel shape fabrication: (d) assembly of the filled COP stamp and a PVA sheet, (e) UV-assisted embossing leading to mechanical punching of the particles, UV crosslinking of the hydrogel and transfer to the flexible PVA substrate and (f) manual demolding. Harvesting of microgel shapes: (g) PVA substrate with microgel shapes immersed in water to harvest the shapes and (h) individual microgel shapes suspended in solution after the PVA dissolves

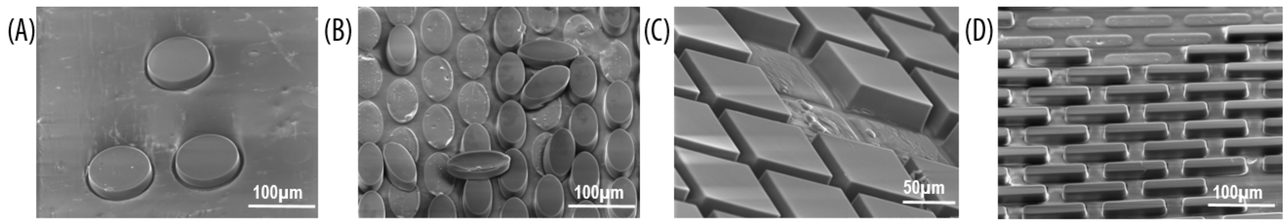

Figure 4. SEM images of PEG microgel shapes in - (a) circular, (b) elliptical, (c) square and (d) rod-like geometries