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The assembly of cell-encapsulating microscale hydrogels using acoustic waves

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ABSTRACT

Microscale hydrogels find widespread applications in medicine and biology, *e.g.*, as building blocks for tissue engineering and regenerative medicine. In these applications, these microgels are assembled to fabricate large complex 3D constructs. The success of this approach requires non-destructive and high throughput assembly of the microgels. Although various assembly methods have been developed based on modifying interfaces, and using microfluidics, so far, none of the available assembly technologies have shown the ability to assemble microgels using non-invasive fields rapidly within seconds in an efficient way. Acoustics has been widely used in biomedical arena to manipulate droplets, cells and biomolecules. In this study, we developed a simple, non-invasive acoustic assembler for cell-encapsulating microgels with maintained cell viability (>93%). We assessed the assembler for both microbeads (with diameter of 50 μm and 100 μm) and microgels of different sizes and shapes (*e.g.*, cubes, lock-and-key shapes, tetris, saw) in microdroplets (with volume of 10 μL, 20 μL, 40 μL, 80 μL). The microgels were assembled in seconds in a non-invasive manner. These results indicate that the developed acoustic approach could become an enabling biotechnology tool for tissue engineering, regenerative medicine, pharmacology studies and high throughput screening applications.

1. Introduction

Hydrogels have attracted increasing interest as intelligent biomaterials with their controllable properties [1–3]. Recently, the convergence of nano and microscale technologies and hydrogels has resulted in the emergence of microscale hydrogels (microgels) with widespread applications [4–6]. For instance, microgels can be used as building blocks for tissue engineering and regenerative medicine [7–10], and as carriers for cell/drug delivery [11,12]. In these applications, directed manipulation of microgels is required to fabricate larger constructs via assembly. Various nano and microscale technologies have been employed to assemble microgels. While manual manipulation provides control over individual microgels [13], it has limited scalability and throughput. Directed assembly approaches, such as programmable molecular recognition and binding scheme [14], hydrophilic–hydrophobic interactions [7], surface template [15], microfluidics [16,17], and magnetic assembly [10], are promising technologies to assemble microgels. Although large gel patterns with controlled features (*e.g.*, shape, size, spatial resolution) have been achieved through directed assembly, there are several challenges associated with these methods including involvement of additional invasive molecules around the gels to facilitate assembly such as cytotoxic organic solvents. These methods also suffer from complexity of the assembly process, long assembly times, and limited throughput. Therefore, there is an unmet need for efficient methods to direct microgel assembly.

It has been possible to manipulate bioparticles (*e.g.*, cells, cell-laden microgels) in microscale volumes to address challenges in medicine [1,18–21]. Acoustics have been traditionally used for medical imaging applications [22–24]. Recently, acoustic techniques, such as ultrasonic standing waves and acoustic droplet based bioprinting [25] have been used as actuation technologies integrated with microfluidics [26–30] to manipulate particles and cells. Examples include particle trapping and aggregation [31–34], continuous-flow-based separation and manipulation of particles and cells [35–39], cell synchronization [40], cell patterning [41], droplet movement, merging, mixing and concentration [42–44], and microcentrifugation [45,46]. Acoustic technologies offer

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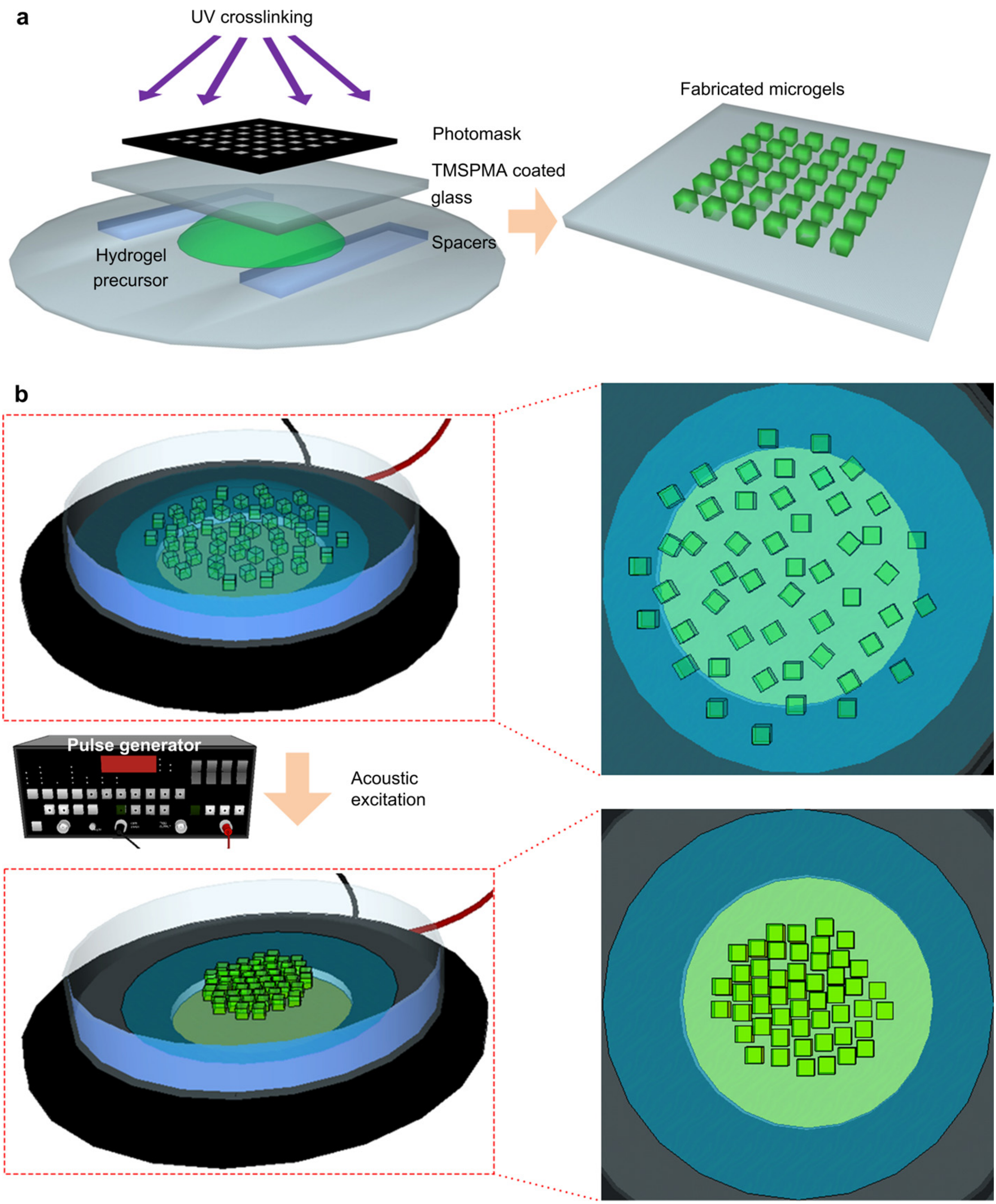

Fig. 1. Acoustic microgel assembly process. (a) Fabrication of microgels using photolithography. (b) Assembly of the microgels within a liquid droplet using an acoustic assembler. Distributed microgels were assembled by a transducer during the acoustic excitation.