A ROBUST MICROFLUIDIC PLATFORM FOR FABRICATION OF METER-LONG HYDROGEL MICROFIBERS

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ABSTRACT

Hydrogel fibers have drawn a great deal of attention during the past few years for a wide range of applications, spanning from tissue engineering to biosensing. Here, we present a double-coaxial flow microfluidic device to assemble fiber-shaped, meter-long fibers consisting of a hydrogel core and an alginate shell. Various hydrogel fibers from collagen type I, GelMA, NiPAM, and agarose have been fabricated with this approach. These fibers were mechanically characterized exhibiting Yong's moduli between ~10 to ~200 kPa, making them mechanically suitable for tissue engineering applications. Moreover, we encapsulated human mesenchymal stem cells (MSCs) in collagen fibers and observed proliferation and spreading after 7 days of culture indicating the biocompatibility of the process. The fiber-shaped structures we fabricated can be potentially used for creating three dimensional tissue constructs, wound patches, and flexible biosensors.

KEYWORDS: Hydrogel fibers, Microfluidics, Cell-laden Fibers, Tissue Engineering

INTRODUCTION

Fibers are building blocks for many applications ranging from clothing and decorative purposes to more recently surgical meshes, vascular grafts, and scaffolds for engineering tissues for research and organ replacement. Hydrogel fibers hold a great promise for engineering tissue constructs or cell delivery as they resemble the extra cellular matrix of native tissues [1]. Moreover, bioactive molecules or sensing elements can be encapsulated in the hydrogel fiber for drug delivery applications or long-term monitoring of several physiological parameters [2]. Creating microfibers using hydrodynamic flows in a microfluidic device is an attractive method that enables producing fibers with different functionalities [3]. However, the use of microfluidic systems for fabricating fibers has been limited to fast crosslinking materials such as alginate. **Here, we introduce a novel and universal approach that enables creating microfibers from any type of hydrogels.** The proposed approach relies on creating coaxial streams of a prepolymer (flow 1), an alginate solution (flow 2), and $CaCl_2$ (flow 3) in a microfluidic setting (Figure 1). The diffusion of Ca^{+2} ions into the alginate matrix forms a hydrogel layer around the core prepolymer and protects the core from dispersion. The core polymer is crosslinked consequently, either chemically, thermally, or by exposing to UV. The alginate layer can then be selectively removed by immersing the fibers in EDTA or PBS.

METHOD

Schematic of the microfluidic device is shown in Figure 1. The double coaxial flow microfluidic device is fabricated by capillary pulling method in PDMS. A core glass capillary is centered in the main channel using a spacer forming a core flow of the hydrogel in pre-gel state. Alginate enters the main channel from a side channel and surrounds the core gel. A third stream of $CaCl_2$ is injected in the main channel to crosslink the alginate layer. Photocrosslinkable hydrogels (NiPAMM and GelMA) were exposed to UV light (intensity of 6.9 mW/cm^2 for 30 seconds). Collagen I and agarose fibers were crosslinked physically at 37 degree Celsius or room temperature.

RESULTS AND DISCUSSION

Figure 1a depicts the schematic of the microfluidic device. Figure 1c-e illustrates the core-shell fibers with various hydrogels in their pre-gel state and the crosslinked alginate (2% w/v) layer around them. After crosslinking the core hydrogel, we selectively removed the alginate layer by using EDTA, a calcium chelator. This approach enabled the fabrication of meters-long hydrogel fibers (Figure 2a) that were not possible to fabricate by other methods (Figure 1c-h). For instance, the present study is the first demonstration of pure GelMA fibers (Figure 1c,i). Depending on the hydrogel material, these fibers can possess different mechanical properties (Figure 2b). We have encapsulated hMSCs in

GelMA fibers and showed that the process was harmless to the cells, evidenced by the cell proliferation and spreading inside the fiber (Figure 3).

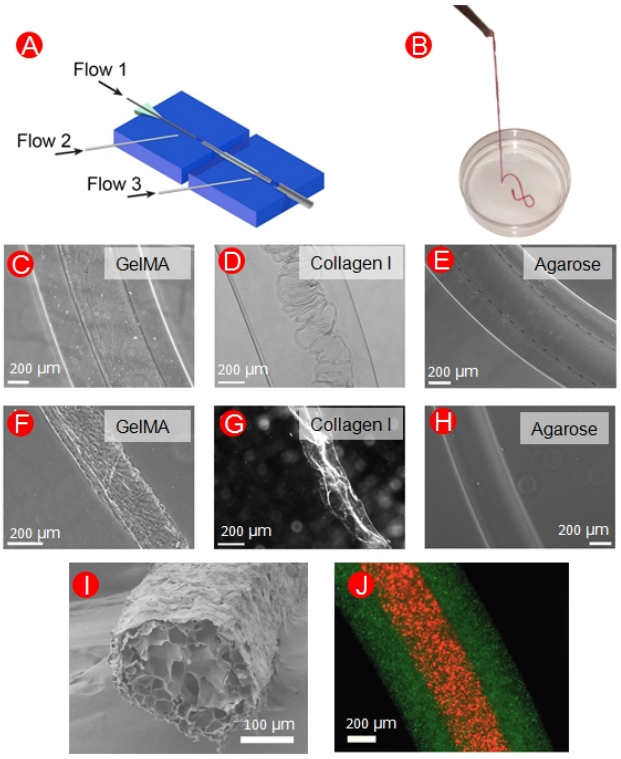

Figure 1: Fabrication of hydrogel fibers using double-coaxial flow microfluidic device. (a) Schematic of the microfluidic device. (b) Alginate improves the mechanical integrity of the fiber (c-e) Core-shell fibers with hydrogel) in pre-gel state protected by an alginate layer. (f-h) Hydrogel fibers after crosslinking and removal of the alginate shell. (i) SEM image of GelMA fibers showing the porous e structure of the hydrogel. (j) Core and shell fiber loaded with fluorescent beads for clarification. The core is made from GelMA while the shell is made up of alginate. Cross-sectional view of the fiber shows a slight offset of the core from the center caused by misalignment of the core flow.

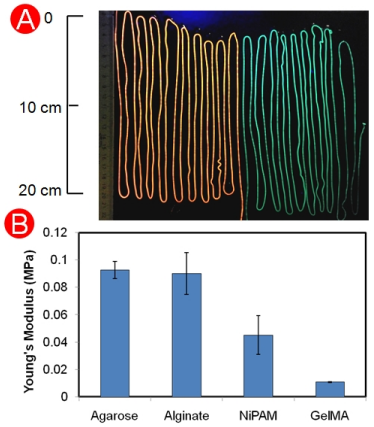

Figure 2: Fabrication of meter-long fibers.(a) ~7 meters of hydrogel fibers. (b) Mechanical properties of the fabricated hydrogel fibers.

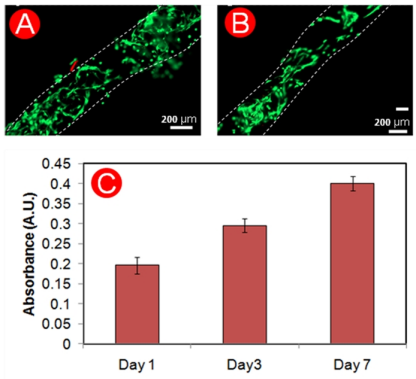

Figure 3: Encapsulation of hMSCs in GelMA fibers.(a, b)Cells after 3 and 7 days of culture. Inset in (b) shows (c) Proliferation rate of cells over 7 days of culture.

SUMMARY

In this study, we introduce a universal approach for manufacturing of hydrogel fibers. This approach allows creating fibers from any materials spanning from thermally crosslinkable ones to photocrosslinkable gels. We tested the ability of our method to create microfibers from several materials such as agarose, GelMA, colagen type I, and NiPAM. We proved that the method is robust and meters of fibers can be fabricated in a short period if time. We also showed that the method is biocompatible as encapsulated hMSCs in GelMA fibers remained viable and active over 7 days of culture.

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