MICROFLUIDIC MANIFOLD SYSTEM TO REDUCE THE NUMBER OF SYRINGE PUMPS IN MULTI-PHASE SYSTEMS FOR GENERATING ALGINATE BEADS

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ABSTRACT

This paper proposes a microfluidic manifold system for the generation of uni-form-sized alginate beads to reduce the number of syringe pumps. Flow rates of flu-ids (calcified oleic acid, alginate solution including cells, and mineral oil) are con-trolled by a microfluidic manifold to control the flow rates, and more mono-disperse beads were generated by one syringe pumps than by 4 syringe pumps.

KEYWORDS: Cell encapsulation, Mono-disperse beads

INTRODUCTION

Microencapsulation is one of the promising strategies for tissue engineering and cell therapy for 3-D culture of cells to mimic a tissue in vivo. Many efforts have been widely performed to develop platforms for the generation of mono-disperse alginate beads [1. 2]. But, when beads were generated in the previous two-phase mi-crofluidic devices, careful controlling of the fluids by several microsyringe pumps was required for the polymerization of alginate beads, the control of bead size, or the maintenance of cell viability.

The operation of the device is therefore possible by only a trained microfluidic engineer. Therefore, we proposed microfluidic manifold system to reduce the number of syringe pumps in multi-phase systems for generating alginate beads.

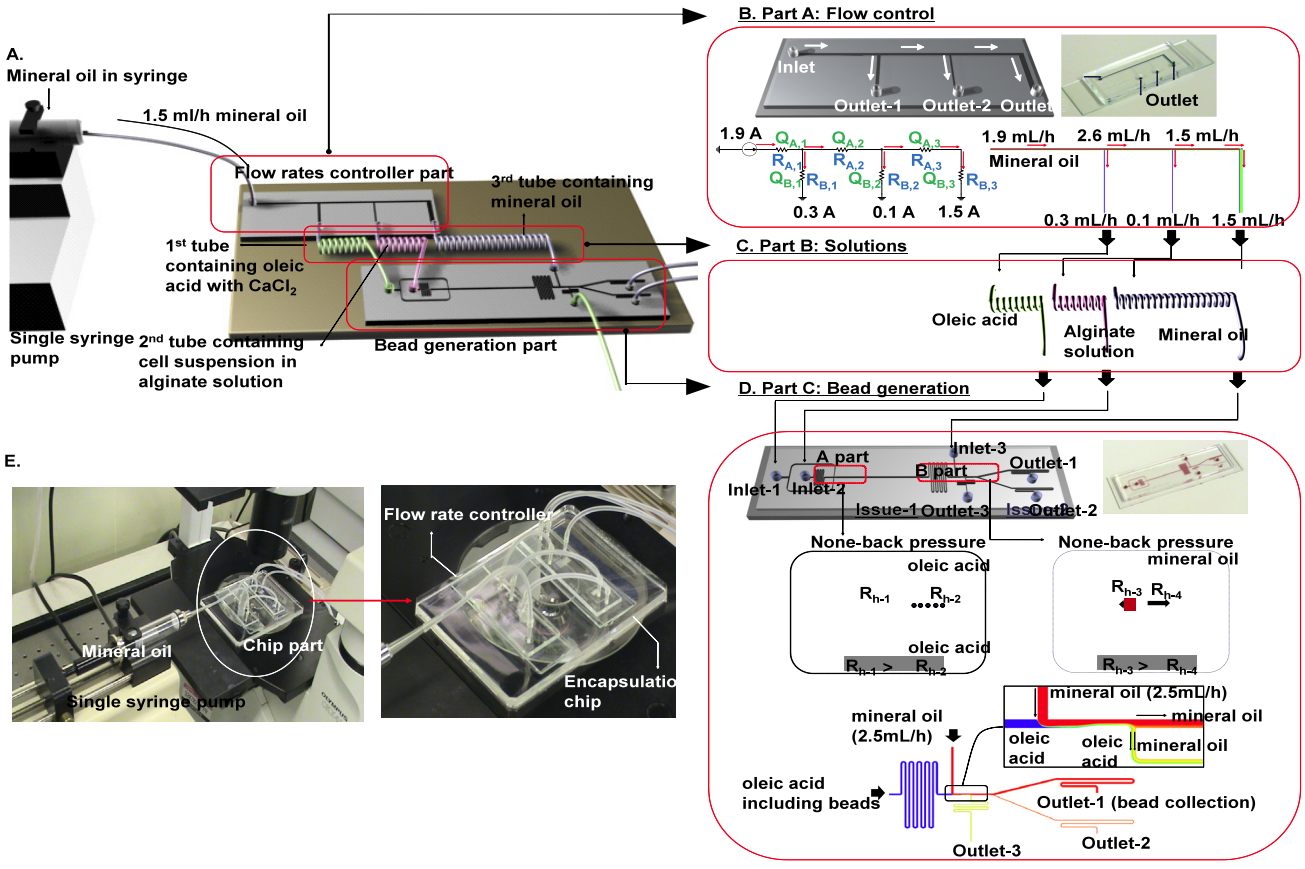

Figure.1 The schematic view of microfluidic device; A. Total system, B. Flow rate controller, C. Silicone tube including each solution, D, Bead generation chip, E. Real images on the microfluidic device

RESULTS AND DISCUSSION

The microfluidic manifold systems was made up of three parts; microfluidic manifold chip for flow rate control, silicone tubes containing each fluid (calcified oleic acid as continuous fluid, alginate solution including cells, and mineral oil to remove oleic acid), and bead generation chip (Fig. 1A, E). The flow rates of three fluids had to be controlled by each pump and it is advantageous in studying the ex-perimental conditions of each flow rate. After the flow rates are set up, however, the initial setting of flow rate is only a tedious work. Hence, the desired flow rates of the fluids were automatically regulated via manifold chip without any handling for con-trol of flow rates.

The volumetric flow rates (outlet-1 for oleic acid: 0.3 mL/h, outlet-2 for alginate: 0.1 mL/h, and outlet-3 for mineral oil: 1.5 mL/h) in the microchannel network were controlled by the adjustment of the hydrodynamic resistance of microchannels in manifold (Fig. 1B).

Three solutions were first filled into silicone tubes by syringe respectively and these tubes were connected to outlet ports in flow rate controller chip and also to the inlet ports in bead generation chip (Fig. 1C).

As a fluid power source, 10 mL microsyringe containing mineral oil was mounted on one microsyringe pump. The mineral oil was injected into flow rate controller chip and distributed in the chip with the desired flow rates. Three fluids in silicone tubes were entered into bead generation chip by the mineral oils (Fig. 1D). It should be noted that the injected calcified oleic acid shouldn't be flowed into alginate solution channel; it was guaranteed by the hydrodynamic resistance control (Rh-1 > Rh-2) (Fig. 1D & Fig. 2a-1).

After arrival of alginate solution, they were met at the bottleneck of the junction, and then the alginate droplets were made by the shear flow of oleic acid (Fig. 2a-2 &2b-1, 2). If alginate solution arrived before calcified oleic acid, the surface of junc-tion part will be wetted by alginate solution first, and alginate droplets were not broke up because of change of surface property from hydrophobic to hydrophilic.

But, oleic acid always arrives before alginate solution because the flow rate of oleic acid is bigger than the one alginate solution. The hydrodynamic resistances of B-part channels were also designed to obtain the desired fluid flowing (Rh-3 > Rh-4) (Fig. 1D, Fig. 2a-3, 4 & 2b3, 4).

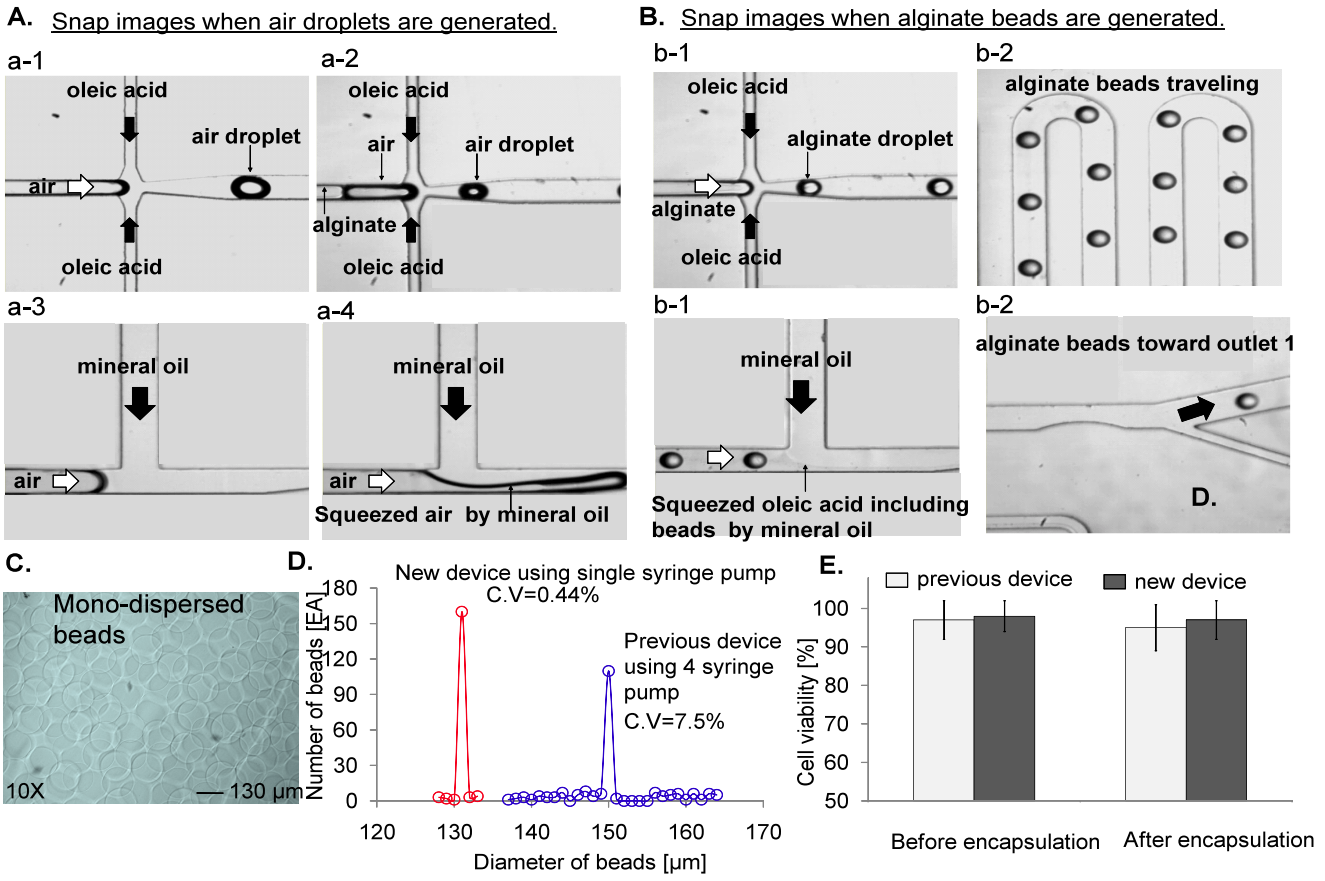

Figure.2. A. B: Mono-disperse beads generation in bead generation chip, C:The collected beads, D: Bead size distribution, E: Cell viability in alginate beads.

We assessed the mono-dispersity of the collected beads from new device, which used only single syringe pump and manifold device compared with using 4 syringe pumps (Fig. 2C, D). The size-distribution of bead was extremely sharp in new device (C.V=0.44%) compared with previous device without manifold (C.V=7.5%). The reason is that fluid flows were stabilized in new device because all pressure was synchronized by one pressure source. We also conducted cell viability in alginate beads with P 19 EC cells (Fig. 2E). In both devices, cell viability in alginate beads were lived more than 95 % after encapsulation.

CONCLUSION

We believe that this manifold system will contribute to enhance the mono-dispersity in generating hydrogel beads by multi-phase microfluidic system. The proposed method is potentially applicable to anti-cancer drug testing on the spherical cell cluster or stem cell differentiation study.

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