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Regular Article

Controlled fabrication of multi-core alginate microcapsules

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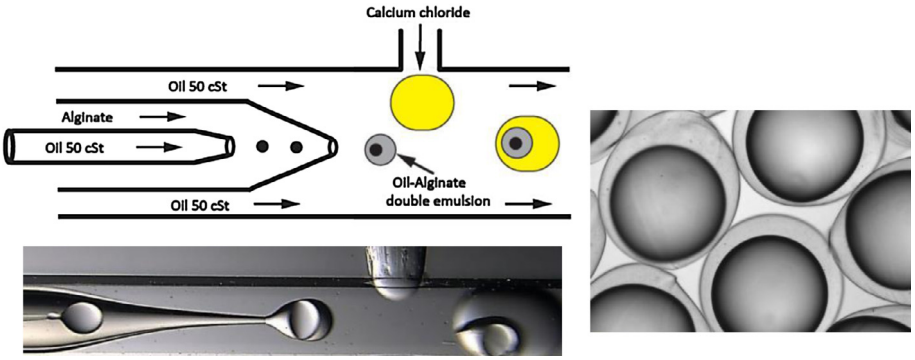
GRAPHICAL ABSTRACT



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ABSTRACT

In this work, we present a robust microfluidic platform for controlled and complete on-chip generation of alginate microcapsules with single and double liquid cores. A combined Coflow and T-junction configuration implemented in a hybrid glass-PDMS (Polydimethylsiloxane) device is used for the generation of microcapsules with oil as liquid core. Frequency matching of oil-alginate double emulsion generation with that of aqueous Calcium chloride droplet generation allows for controlled merging of the two, resulting in reliable production of microcapsules. Confocal imaging of microcapsule cross-section reveals presence of intact liquid core. In the case of double core microcapsules, the two cores are well separated by alginate layer ensuring their long term stability. The current approach is expected to have advantages over existing techniques for liquid core microcapsule generation in terms of continuity of the process, control over core stability, and non-damage to cells when used for cell encapsulation applications.

1. Introduction

Microparticles and microcapsules have multitude of applications in photonics, self-assembly, disease diagnosis, drug delivery, therapeutic applications [1] and tissue engineering [2–4]. Microgels, which are microparticles of cross-linking polymers, are particularly suitable for drug delivery [5] and tissue engineering applications due to their unique properties like mechanical strength, controlled release, semi-permeability, and non-toxicity [6]. Among the various natural and artificial polymers [5] like chitosan, collagen, alginate, gelatin and agarose, alginate is the most attractive microgel material due its properties like less toxicity, easy gelation, good biocompatibility and long term stability [7,8].

A number of techniques such as coacervation [9], emulsification [10,11], spray-drying [12], micro-nozzle [13], etc. are currently in use for the production of microgels. However these techniques suffer from problems like coagulation, low control on particle size, and non-homogeneity. Microfluidics offers promising route for the production of microgels due to its numerous advantages of

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miniaturization [14], precise control over shape, size and composition of particles, and low cost, to name a few [15,16]. Microfluidics based techniques have used photopolymerization [17], external gelation [18,19], internal gelation [20], partial gelation [21], fusion of droplets [22], centrifugal microfluidics technique [23] etc. for the production of both bulk microgels as well as microgels with core-shell morphologies (microcapsules).

Compared to bulk microgels, core-shell microgels allow far better control over drug release and cell encapsulation. When the core is a liquid, different types of cells can be encapsulated into the core and the shell, enhancing their loading efficiency and applicability as cell encapsulation and drug delivery systems [24]. Existing microfluidic approaches to generation of this important class of liquid-core polymer-shell microgels include photopolymerization [17,25], external polymerization [11,18,26], and on-chip polymerization using coflowing streams [27,28]. While photopolymerization can cause damage to the encapsulated cells, external polymerization is a multi-step process defeating the purpose of a controllable microfluidics approach. In the case of on-chip polymerization using coflow, there is high possibility of blocking of the device due to the continuous contact between the precursor liquid stream and polymerization inducing liquid stream at the capillary tip.

To address the above challenges, in this paper we show for the first time the use of droplet coalescence for complete on-chip generation of liquid-core polymer-shell alginate microcapsules with single and double cores. Polymerization is achieved through controlled coalescence of oil-alginate double emulsion and aqueous Calcium chloride droplets within a glass-PDMS hybrid device. We also demonstrate the generation of alginate microparticles and triple-core alginate microcapsules using this approach.

2. Materials and methods

2.1. Materials

Sodium alginate was purchased from Sigma Aldrich, UK, Calcium chloride from Merck specialities Private Limited, India, Silicone oils (10 cSt and 50 cSt) from MR Silicone Industries, India, Tween-20 from Sigma Aldrich, UK, Sudan I fluorescent dye from Sigma Aldrich, Germany, and Silicon elastomer PDMS from Dow Corning, Germany. Glass capillaries were procured from Vitrocom, USA and New Era syringe pumps (New Era pumps, USA) were used for pumping liquids.

2.2. Device fabrication

The working principle of the microfluidic device involves generation of oil (core)-alginate (shell) double emulsion droplet using co-axial flow, aqueous Calcium chloride droplet using a T-junction and controlled merging of the two in order to generate oil-alginate microcapsules, as shown in the schematic of Fig. 1a. In case of alginate microparticles, alginate single emulsion droplets are used. The device is a hybrid of glass capillaries and PDMS (Fig. 1b). The glass capillary part of the microfluidic device is for the generation of coaxial flow, while the PDMS part stations the T-junction and the droplet-merging section.

A PDMS slab of width 250 mm and length 450 mm containing a main (square) channel of size 1.4 mm is made using a standard technique [28]. Briefly, a mixture of PDMS and curing agent in ratio 10:1 is poured (after thorough mixing and degassing for one hour) onto a long 1.4 mm side square glass capillary supported by a Teflon frame and is then cured in an oven for about 8–10 h. The square capillary is then carefully removed to leave a square channel of size 1.4 mm inside the PDMS slab. Holes are drilled into the slab using a sharp 16 G needle, to provide inlets for the outer silicone oil (continuous phase, of viscosity 10 cSt or 50 cSt) and Calcium chloride. The intersection of the Calcium chloride inlet with the main channel acts as a T-junction for the generation of Calcium chloride droplets. The PDMS slab is then glued onto a glass substrate. Into one end of the main channel, coaxially aligned cylindrical capillaries pulled to tip diameters of 110 μm and 80 μm, which act as inlets for alginate (shell) and inner silicone oil (of viscosity 50 cSt) respectively, are inserted. Into the other end, a cylindrical capillary connected to a silicon tubing, is inserted and is the outlet for the generated microcapsules, as shown in Fig. 1b. For the generation of alginate microparticles, a single cylindrical capillary of tip diameter 110 μm is used instead of coaxial capillaries.

2.3. Experimental methods

For alginate microparticles, 4% (w/w) alginate solution, 30% (w/w) aqueous Calcium chloride solution containing Tween-20 surfactant (0.1% w/w) and 10 cSt silicone oil were injected through their respective inlets. Experiments using 50 cSt silicone oil were also conducted to obtain smaller particles. For oil-alginate microcapsules, 50 cSt silicone oil was used as both inner core liquid as well as external coflowing liquid.

In these experiments, matching of frequency of alginate droplets with that of aqueous Calcium chloride droplets is critical for the efficient generation of microparticles and microcapsules. So, initial experiments involved obtaining the frequencies of alginate droplets at the capillary tip and aqueous Calcium chloride droplets at the T-junction at various flow rates. The flow rate of the outer 10 cSt oil was kept at 40 ml/h and the flow rate of alginate was varied from 0.5 ml/h to 5 ml/h, while switching off the Calcium chloride flow. Imaging was done on a stereo microscope (Leica S8AP0, Germany) and videos were recorded using a camera (Leica MC 120 HD, Germany) to obtain the frequency of alginate droplet generation through coflow. For obtaining frequency of Calcium chloride droplet generation from T-junction, outer 10 cSt oil flow rate was set to 40 ml/h and the flow rate of Calcium chloride was varied from 0.5 ml/h to 12 ml/h, while switching off the alginate flow. The measured frequencies were plotted as functions of the two flow rates. Similar frequency measurement experiments were done for oil-alginate double emulsions, required for the generation of microcapsules.

In the next set of experiments, simultaneous generation of alginate and $CaCl_2$ droplets was carried out. Flow rate combinations of alginate and $CaCl_2$ that would give matching frequencies as per the plots from the earlier experiments were used and frequency measurements were done to verify precise matching. A number of flow rate combinations yielded matching frequencies and could all be used for particle generation. However, one flow rate combination was chosen for particle generation based on ease of device operation and particle collection. The flow rates used for the generation of microparticles using 10 cSt or 50 cSt oil, and single and double oil core microcapsules using 50 cSt oil are summarized in Table 1. For single core microcapsules, the external coflowing oil flow rate was varied to investigate its effect on the overall capsule size. The generated microparticles and microcapsules exited the device through silicone tubing and were collected in a vial containing distilled water. The collected particles were dried at room temperature for 30 min and imaged before and after drying using optical microscope. The captured images were analysed using ImageJ software to obtain particle size distributions. Single and double oil core microcapsules were imaged using confocal microscope (attached with EMCCD laser camera) to capture the cross-sectional view that would depict the liquid core and the polymer shell. A fluorescent dye (Sudan I) was added to the inner core oil in the case of single core microcapsules.