SYNTHESIS OF TWIN ALGINATE MICROPARTICLES VIA MICROFLUIDIC EMULSIFICATION AND SORTING

Yung-Sheng Lin[1], Jiann-Shiun Kao[1], Chih-Hui Yang[2], Keng-Shiang Huang*[3], Yu-Shun Dong[2], Wan-Yi Hsu[2]*
[1]Instrument Technology Research Center, National Applied Research Laboratories, Taiwan
[2]Dept. of Biological Science & Technology, I-Shou University, Taiwan
[3]Dept. of Biomedical Engineering, I-Shou University, Taiwan

ABSTRACT

Based on the microfluidic emulsification process, the regular and stable formation of parent and satellite droplets can be achieved. The purpose of this study is to accurately separate the satellite (smaller) droplets from their parent (larger) droplets to obtain twin monodispersed microparticles by a bi-T-junction hybrid microchannels design controlling both emulsification and separation. Results show that both of the collected larger and smaller droplets are highly monodispersed (RSD < 2% and 6%, respectively), and featured with high reproducibility as well. This microfluidic device was also employed to present a facile one-step synthetic approach for the preparation of twin monodispersed alginate microparticles The proposed microfluidic chip is capable of generating relatively uniform twin microparticles with well controllable sizes, and it has the characteristics of a simple, low cost, and high throughput process. In the future this apparatus can be further applied to manufacture various twin monodispersed composite micro-vehicles to act as a smart drug delivery system.

KEYWORDS

twins, monodisperse, emulsification, separation, alginate

INTRODUCTION

In recent years, microfluidic methods have received a great deal of attention because of their potential use in microreactors for chemical kinetics, chemical and biological analysis, material synthesis, protein crystallization, and analytical and chemical processes, which are being developed by a number of groups [1-6]. In addition, several groups have used microfluidic approach for the fabrication of monodispersed *water-in-oil* (*w/o*), *oil-in-water* (*o/w*) emulsions, and bubbles [7-8] as well as on monodispersed polymeric microparticles after curing emulsion droplets containing a monomer solution [9-10]. For the purpose to obtain a uniform size of microparticles, microfluidic devices with the advantages of continuous, reproducible, and scalable production are ideal for considering the regular formation of droplets or bubbles.

Formation of droplets in a liquid/liquid emulsification system is a classic topic because of the wide variety of engineering and scientific applications such as inkjet printing, DNA microarray systems, depositions of chemicals on biomedical strips, and spray cooling. The mechanism of droplet formation in emulsification has already been studied extensively from both theoretical and experimental perspectives. At certain flow conditions of dispersed/continuous phases, satellite droplets follows parent droplets in a regular one by one and stable rhythm [11]. It is therefore the sizes of satellite/parent droplets can be fairly uniform, respectively.

There are a number of methods to prepare monodispersed microparticles such as microfluidics [1], electrospraying [12], membrane emulsification [13], and dripping [14-15]. To the best of our knowledge, the double T-junction geometry has not yet been proposed as the channel geometry for the generation of twin monodispersed droplets. The goal of this study is to develop a method for producing twin alginate microparticles of precisely controlled monodispersed size distribution by the microfluidic channels.

EXPERIMENTAL

Based on the microfluidic sorting, the larger droplets were easily and accurately separated from the smaller droplets which created as a byproduct of microfluidic emulsification process. The purpose of this study is to separate the satellite (smaller) droplets from their parent (larger) droplets to enhance the size uniformity of the twins microspheres. A bi-T-junction hybrid microchannels design was employed to control the both emulsification and the separation. **Fig. 1** illustrates the process to obtain the twin uniform microparticles. Alginate water solution is sheathed by oil flow to form regular parent and satellite droplets at the 1st T-junction in the microchannels. The 2nd T-junction design (down stream) can provide a separation (sorting) function in the microfluidic device. When satellite droplets travel to the 2nd T-junction channel, they are drawn to the side channel, while parent droplets keep traveling the main stream. The main channel is free of satellite droplets after the 2nd T-junction. Both large and small droplets are desired because both of them are with uniform size. A microscope was used to observe the experimental results. The image and detection system consist of an optical microscope (TE2000U, Nikon, USA) and a digital camera (Evolution color VF, Nikon, USA). The diameter of 100 microspheres was measured to provide an average size. Results were expressed as the means ± standard deviation.

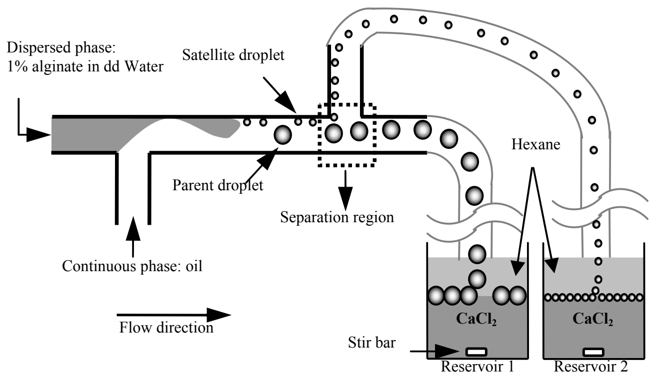


Fig. 1 Schematic illustration of the working principle (not to scale, the side view). Based on the ability of microfluidics to exert control over the cross-flowing streams a large set of self-assembling spheres can be obtained. The 1st T-junction channel was used to elicit control over the spontaneous self-assembly of w/o emulsions from a solution of dissolved alginate. The 2nd T-junction channel design is employed to control the sorting of the droplets.

RESULTS

In order to investigate the separation mechanism in more detail we employed the finite volume simulation software CFD-ACE+ (ESI CFD, Huntsville, USA) to study the motion of the droplets in fluid. In the analysis of microfluidic simulation, **Fig. 2**. shows the streamlines of the flow field in the 2nd T-junction microchannel. Before the entrance of the 2nd T-junction, the bottom streamlines alongside the main channel evolve directly into the side channel, but the other streamlines go through the junction straightforward with a little shift to the side wall especially for those streamlines close to the bottom wall. Initially the parent/satellite droplets have located near the middle and alongside the main channel, respectively. Fully immersed in the bottom streamlines, the satellite droplet travels toward the side channel and filters out at this junction. However the parent droplet goes directly through the 2nd T-junction but deviates from the original line towards the side wall due to the change in flow field. Therefore the satellite droplet is completely drawn to the side channel and the main channel is free of satellite droplets after the 2nd T-junction. Utilizing this successful separation strategy, we can obtain uniform smaller droplets and larger droplets at the outlets of side channel and main channel, respectively.

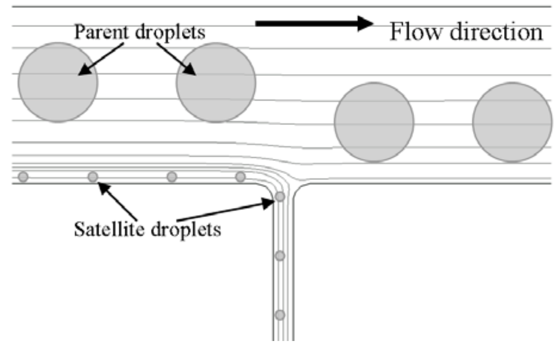
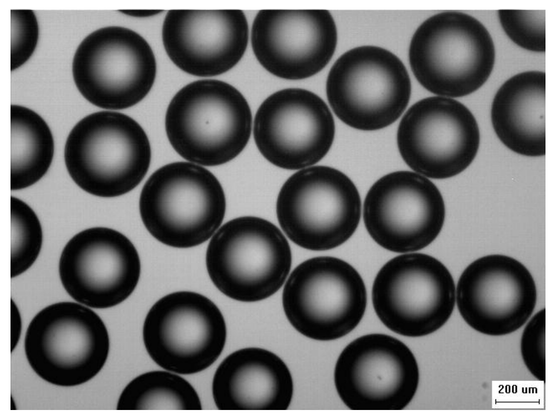
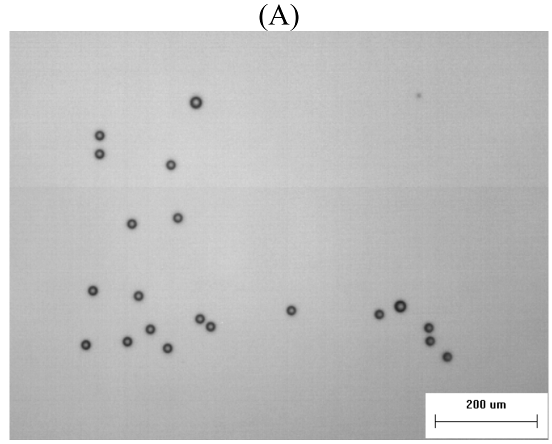


Fig. 2 Streamlines of the 2nd T-junction channel.

Fig. 3 shows the microscope images of the alginate microparticles collected in the reservoirs. In reservoir 1 (**Fig. 3A**), larger microparticles are very uniform in both morphology and size, and the average diameter is close to 385 µm (**Fig. 3C**). In reservoir 2 (**Figs. 3B**), the smaller microparticles are also uniform and the size distribution is < 6%, ranging from 17 to 23 µm in diameter (**Fig. 3D**).



(A)



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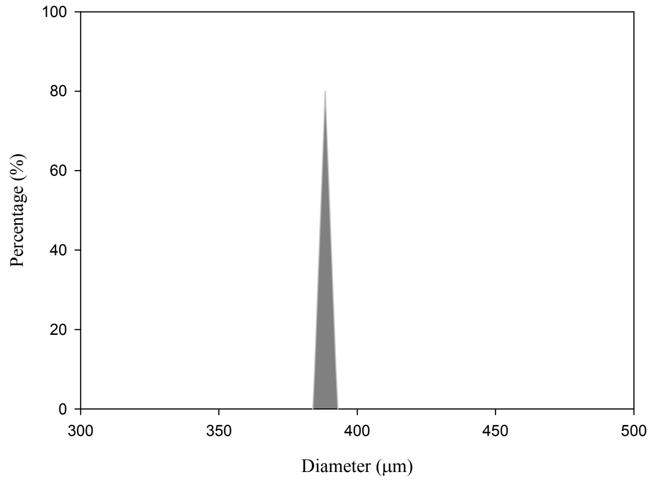
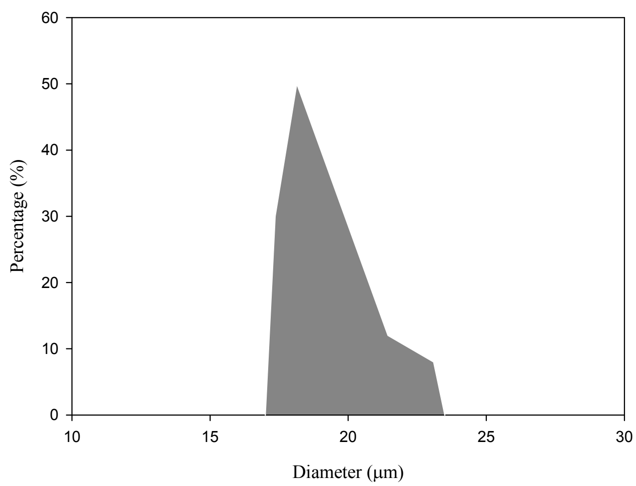


(C)



(D)

Fig. 3 *Microscope images of alginate microparticles (A) in the Reservoir 1, and (B) in the Reservoir 2. The size distribution regarding (C) is corresponding to (A), and (D) is corresponding to (B). (The scale bars are 200 μm)*

Table 1 shows the relationships among the average droplet diameter, sorting efficiency, and various flow velocities. The results show that the droplet size and gap are comparable to the channel diameter and can be tuned by varying the shear rates of the oil phase relative to the aqueous phase. Each droplet represents an independent spherical microliter volume. Both of the large/small alginate microparticles are with high reproducibility and high monodispersity (RSD, relative standard deviation defined as the ratio of standard deviation to average, are < 2% and 6%, respectively). The experimental results show no significant difference between sorting efficiency and flow velocities (statistical p value > 0.05). The effect of the oil/water flow rates on the trend of the droplet size corresponds well with the prediction of previous literatures [16-17]. It is worth noting that the small RSD in droplet size in **Table 1** reflects the good uniformity of the droplets obtained in each flow condition. This RSD agrees with the result of the monodispersed images in **Fig. 3**. In addition, a separation ratio of above 99% is observed. Although The relative standard deviation (RSD) data in the satellite droplets is larger than in the parent droplets, it still satisfies the general criterion in monodispersed size distribution below 10%. Therefore, the bi-T-junction hybrid microchannels herein make facile one-step synthetic approach for preparing twin monodispersed alginate microparticles.

Table 1 *The relationships among the average droplet diameter, sorting efficiency, and various flow velocities*

Dispersed phase (mL/min)	Continuous phase (mL/min)	Larger droplet[a]		Smaller droplet[b]		Sorting efficiency (%)
		Average size (μm)	RSD[c] (%)	Average size (μm)	RSD[c] (%)	
0.002	0.15	392.31	1.214	10.38	2.647	100.0
	0.20	276.92	0.723	10.29	2.229	99.4
	0.25	223.07	1.147	11.15	3.068	99.4
	0.30	192.31	1.425	13.08	5.096	99.6
0.003	0.15	407.69	0.642	10.42	4.105	99.2
	0.20	315.38	0.648	10.88	2.903	99.6
	0.25	253.85	1.246	11.70	2.756	99.4
	0.30	215.38	1.624	12.05	3.694	99.4
0.004	0.15	446.15	0.987	13.23	3.278	99.6
	0.20	338.46	1.425	12.76	4.178	99.6
	0.25	284.61	0.847	12.35	4.012	100.0
	0.30	223.07	0.877	13.47	4.057	99.4
0.005	0.15	469.23	1.124	14.42	4.958	99.6
	0.20	356.92	0.841	15.26	5.207	99.6
	0.25	300.09	0.915	13.58	3.154	99.4
	0.30	238.46	0.993	11.83	5.252	99.2
0.006	0.15	482.45	0.963	14.89	3.247	99.4
	0.20	369.23	1.321	17.01	3.756	99.2
	0.25	315.38	1.124	12.84	3.654	99.6
	0.30	246.15	1.225	14.23	4.205	99.4
0.007	0.15	507.79	1.425	13.47	5.278	99.6
	0.20	388.46	1.813	18.10	3.371	99.4
	0.25	330.85	0.822	13.10	2.718	99.2
	0.30	269.23	1.105	13.71	4.808	99.2

a: droplets in the reservoir 1; b: droplets in the reservoir 2; c: RSD (relative standard deviation)

CONCLUSION

We successfully developed a facile method for producing twin alginate microparticles. The proposed microfluidic chip is capable of generating relatively uniform micro-droplets with well controllable diameter, and it has the added advantages of being a simple microstructure, low cost of fabrication, and high throughput. In the future, our approach can be further used to fabricate various size-controlled monodispersed composite microvehicles to act as a smart drug delivery system.

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CONTACT

* Dr. Chih-Hui Yang, chyang@isu.edu.tw

* Dr. Keng-Shiang Huang, huangks@isu.edu.tw