Chemical Engineering Journal 320 (2017) 144–150

Contents lists available at ScienceDirect

Chemical Engineering Journal

journal homepage: www.elsevier.com/locate/cej

# Preparation of microparticles through co-flowing of partially miscible liquids

Yinghe He [a,b,*], Sarah Battat [b,c], Jing Fan [b,d], Alireza Abbaspourrad [b,e], David A. Weitz [b]

[a] College of Science and Engineering, James Cook University, Douglas, Queensland 4811, Australia
[b] School of Engineering and Applied Sciences, and Department of Physics, Harvard University, Cambridge, MA 02138, USA
[c] Department of Physics, Princeton University, Jadwin Hall, Princeton, NJ 08544, USA
[d] Department of Mechanical Engineering, The City College of New York, NY 10031, USA
[e] Department of Food Science, Cornell University, Ithaca, NY 14853, USA

## HIGHLIGHTS

- Microparticles generated by co-flowing of two partially miscible liquid phases.
- Liquid miscibility varied by changing the amount of co-solvent in inner phase.
- The miscibility influenced the flow, the particle size, distribution & morphology.
- The approach facilitated the formation of small particles with large apertures.

## ARTICLE INFO

*Article history:*
Received 27 December 2016
Received in revised form 13 March 2017
Accepted 14 March 2017
Available online 16 March 2017

*Keywords:*
Microparticles
Partially miscible liquids
Controlled mixing

## ABSTRACT

Monodisperse microparticles find applications in a wide range of areas. Generation of such particles of several microns in size at a large scale is a difficult task. This paper reports a proof of concept using a microfluidic device that coaxially flows partially miscible liquids for the production of microparticles. The approach makes use of both the physical forces of the process and the chemical properties of the liquid systems that allows for careful control of the mixing and droplet formation processes. Initial results show that, with this approach, particles with a reasonably narrow size distribution can be produced and liquid miscibility can be used as an additional avenue to manipulate the mean particle size and morphology.



## 1. Introduction

Monodisperse microparticles are much desired as they afford better performance control in their end use applications [1–3]. A common approach for the production of such particles is to use a monodisperse liquid-liquid dispersion as a template, which can be generated by either a chemical or a physical method, and convert the dispersed droplets into solid spheres through solvent evaporation or extraction [4,5]. Currently, chemical methods such as microemulsions make use of interfacial properties of two immiscible liquids to produce uniformly-sized particles in the nanometer range, typically less than ~800 nm, due to limitations of the chemical nature of the extremely low interfacial tension of the systems [6,7]. In contrast, physical methods such as microfluidic shearing [8,9] and co-flowing [10–12], as well as flow-focusing processes [13–15], manipulate physical forces of the system to produce monodisperse droplets, which are usually larger than tens of micrometers in diameter. Therefore, there exists a size gap between ~800 nm and low tens of microns in which monodisperse particles can neither be readily produced by chemical nor physical methods; however, the desired size range for some applications such as controlled drug release via intramuscular injection lies within this very gap [22,23].

By means of a physical method, droplets can be formed in two broad flow conditions or regimes termed dripping and jetting. In dripping, droplets are formed individually at the nozzle whereas in jetting they are formed at the end of a jet emitted from the nozzle as a result of Rayleigh instability [1,11,18–19]. The size of the droplets formed in the dripping regime is linearly correlated to the diameter of the injection nozzle [16,17]. The size of the droplets formed in the jetting regime, on the other hand, is determined by the diameter of the jet at the point of breakage into

* Corresponding author at: College of Science and Engineering, James Cook University, Douglas, Queensland 4811, Australia.
*E-mail address:* yinghe.he@jcu.edu.au (Y. He).

http://dx.doi.org/10.1016/j.cej.2017.03.059
1385-8947/

droplets. Two types of jets have been observed in a co-flowing arrangement. Type I jets (Jetting I) are those where the jet diameter expands, while Type II jets (Jetting II) contract, downstream. The initial diameter of the jet emitted from the nozzle is determined by the size of the injection nozzle. Making injection nozzle openings of several micrometers precisely and consistently is difficult. In addition, the use of micron-sized nozzles also causes high back pressure and blockage problems. The diameter of the jet at the point of breakage can be reduced in a co-flowing process by increasing the ratio of the outer-to-inner phase flow rates. However, there is a limit to which the jet diameter can be reduced in each flow device via this approach. When the ratio is too high, the jet flow becomes unstable and discontinuous and the droplet size becomes large again [20,21].

Largely because of its simple physical construction and well defined flow field, co-flowing microfluidics remains one of the most popular physical methods for the generation of monodisperse liquid droplets. In this arrangement, it is shown that the transition from dripping to jetting can be mapped on an inner-phase-based Webber number ($We_{in}$) versus an outer-phase-based Capillary number ($Ca_{out}$) state diagram [11]. $We_{in}$ and $Ca_{out}$ are defined as

$$We_{in} = \frac{\rho_{in} d_{tip} u_{in}^2}{\gamma} \quad \text{and} \quad Ca_{out} = \frac{\mu_{out} u_{out}}{\gamma} \tag{1}$$

where $\rho_{in}$ – density of the inner phase; $d_{tip}$ – inner diameter at the tip of the injection nozzle; $u_{in}$ – velocity of the inner phase; $\gamma$ – interfacial tension between the inner and outer phases; $\mu_{out}$ – viscosity of the outer phase; and $u_{out}$ – velocity of the outer phase.

In theory, processes that utilize both the chemical and physical properties of the liquids should be able to produce particles of sizes in the gap region. In fact, researchers have previously attempted to utilize chemical properties of liquids in their production of particles by mixing partially miscible liquids using conventional stirring methods [24,25]. Although the approach did produce solid particles in the required size range, the size distribution was very broad. This is not unexpected considering that the flow field and hence the shear stresses and shear forces are very complex and can hardly be controlled in conventional stirring systems. The uncontrollability is further exacerbated by the diffusion of the co-solvent between the two liquid phases in the system.

This paper reports a new method for the generation of microparticles through the co-flow of partially miscible phases in a microfluidic device. This arrangement is expected to provide a more defined flow field that allows for better control of the co-solvent diffusion and droplet formation processes. The miscibility of the inner and outer phases is manipulated by altering the amount of co-solvent added to the inner phase. Initial results show that the method can yield microparticles with a much narrower size distribution than those produced by the previously reported bulk mixing approach and a mean particle diameter in the range of submicrons to hundreds of microns. More importantly, it confirms that liquid miscibility can be employed as an additional avenue to manipulate particle size and morphology.

## 2. Experimental

All experiments were conducted using a device made from two cylindrical glass capillary tubes (outer diameter of 1 mm) coaxially aligned in a square glass capillary (outer diameter of 1.5 mm and inner diameter of 1.05 mm). One cylindrical glass capillary was pulled using a micropipette puller (Sutter P-97 Flaming/Brown Micropipette Puller) so as to form a tapered end, from here on referred to as the injection nozzle. Two nozzle sizes were tested; their inner diameters were 20 μm and 40 μm, respectively. Fig. 1 shows the schematic of the co-flowing device.

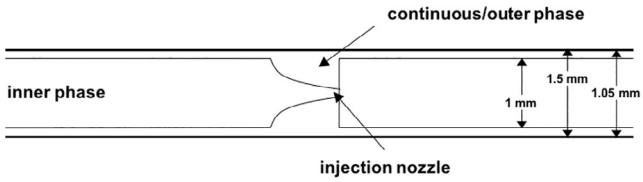


**Fig. 1.** Schematic of the co-flowing microfluidic device used in this investigation.

The inner phase was composed of varying amounts of polycaprolactone (PCL, average MW = 45,000) dissolved in a mixture of dichloromethane (DCM) and acetone of different proportions. The outer phase was either a 1 wt% or 5 wt% aqueous polyvinyl alcohol (PVA; MW = 13,000–23,000; degree of hydrolysis = 87%–89%) solution. In this system, DCM is immiscible with water. Acetone is completely miscible with both DCM and water and serves as the co-solvent. PCL is a solid polymer soluble only in DCM. All chemicals were Analytical Reagent grade and were purchased from Sigma-Aldrich. Milli-Q deionized water was used throughout the experiment.

Two syringe pumps (Harvard Apparatus PHD 2000) were used to pump the inner and outer phases coaxially through the capillary tubes. The inner phase was injected into the tapered capillary, while the outer phase flowed through the empty space between the injection capillary and the square glass capillary. The drop formation process under each flow condition was recorded with a high-speed camera (Phantom High-Speed Camera V7 and V9). The droplets were collected in glass vials, which were left uncovered to allow the solvent to evaporate, leading to the formation of PCL particles. The particles were washed with Milli-Q deionized water to remove PVA residue and vacuum-dried. The size and morphology of the PCL particles were determined using a scanning electron microscope (Zeiss Ultra Plus FESEM and Zeiss Supra55VP FESEM).

## 3. Results

### 3.1. State diagram

The addition of a co-solvent to the inner phase changes the physical and chemical properties of the liquid system, namely, density, viscosity, and interfacial tension. Accordingly, it is expected to alter the flow behaviour of the liquids. The instantaneous diffusion of the co-solvent (acetone) from the inner phase to the outer phase upon contact makes it impossible to measure the interfacial tension between the two phases. Nevertheless, droplet formation in this partially miscible system is observed to be similar to that in immiscible liquid systems insofar as it occurs by either dripping or jetting under all investigated flow conditions.

To compare our results with those from immiscible liquid systems, a $We_{in}$ versus $Ca_{out}$ state diagram was produced by assigning the same nominal value of unity (1 N/m) to the interfacial tension of all pairs of investigated liquid systems. The results are shown in Fig. 2. The outer phase of the liquid system is either a 1 wt% or a 5 wt% PVA aqueous solution and the inner phase is a DCM-acetone mixture with 0%, 40%, 60% and 90% volume fractions of acetone. Similar to the previous findings on immiscible liquid systems (Utada et al. 2007), for all pairs of the partially miscible liquids that we tested, the dripping region is always confined to the bottom-left corner of the diagram where both the viscous and inertial forces are relatively small. The significant difference (as compared to the immiscible liquid systems) is that there are multiple demarcation lines for the transition from dripping to jetting instead of a single line reported by Utada et al. (2007). As the acetone concentration in the inner phase increases, the demarcation