FULL PAPER

Scale-out production in core-annular liquid–liquid microextractor

Cheng-Yan Lin[1] · Yung-Ying Chen[1] · Po-Ying Chen[1] · Mei-Chun Chen[1] · Tyng-Fwu Su[1] · Ya-Yu Chiang[1,2]

Abstract

In the miniaturization process, enhanced mass and heat transport enable the production of fine chemicals and pharmaceuticals; therefore, this process has become an attractive research field. The scale-out core-annular liquid–liquid microextractor can further enhance the mass and heat transfer because of its increased total liquids contact area. In the current study, one such microextractor was employed, and four stretchable helix wires were placed in parallel and square arrangements for the aqueous stream to maintain the aqueous and solvent solution volume ratio at 1:10; these wires were surrounded by an organic solvent to ensure a stable aqueous–organic contact interface. A scale-out core-annular liquid–liquid microextractor was applied in 10 vol% acetone–toluene extract as a robust screening tool for process development; it demonstrated > 90 % extraction efficiency within 10 min and > 3 ml/hr production rate. These scale-out strategies revealed that the effective surface area–volume ratio applied in this study was more than 6 m^{-1} and substantially mitigated insufficient production.

Keywords Liquid–liquid extraction · Scale-out · Parallel flow · Core-annular flow · CALLME

Introduction

Liquid–liquid extraction is an essential process in the chemical and pharmaceutical industries. Microextractors have a short diffusion distance, high specific interfacial area, and small heat capacity, making them suitable for the development of extraction and separation technology [1–3]. Common types of extraction include droplet-based extraction and co-current flow extraction. Droplet-based extraction is useful for enhancing mass transport because of the high surface-to-volume ratio. However, droplet-based extraction requires an extra phase

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Highlights
• Two scale-out microextractors were developed for continuous process.
• An input flow rate range of 0.5–1700 µL/min with a stable interface was achieved through CALLMEs.
• The extraction efficiency in CALLMEs could reach over 95% and the scalability for continuous mass production using CALLMEs configuration is demonstrated.

Cheng-Yan Lin and Yung-Ying Chen contributed equally to this work.

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separator to split the aqueous and organic phase [4, 5]. The high-frequency droplet formation and fast movement cause problems in the monitoring of mass transfer kinetics in the droplets [6]. Co-current flow microextractors have the advantage of continuously processing the extraction at the interface of two parallel flows, and they typically require no extra phase separator [7]. Co-current flow microextractors are usually fabricated using microelectromechanical systems to achieve an H-shape microchannel [8]. The contact interface is determined by the depth and length of the channel. However, maintaining the interface between two flowing immiscible liquids is challenging. Using a surfactant and increasing the viscosity and flow speed can help maintain a stable contact interface [9, 10]. However, the operational range is narrow and limited models can be extracted. A countercurrent flow and capillary extractor uses porous membranes to stabilize the liquid–liquid interface. However, the membrane thickness and porosity should be considered for effective retention [11, 12]. In contrast to droplet-based and co-current extractors, the extraction efficiency of the aforementioned extractor is also limited by membrane porosity.

To obtain a stable liquid–liquid contact interface and overcome the aforementioned challenges, a strategy was developed that enables the core-annular flow of two immiscible liquids [13]. Microextractors are also advantageous in robust structures, offering straightforward scalability for mass production[14, 15]. This is particularly

attractive for the synthesis of petrochemicals, active pharmaceutical ingredients, or value-added materials in industry [16–19]. In this study, a single helix wire was expanded to four wires, which were placed at the core position and arranged in parallel to the aqueous stream (upstream reactant) and surrounded by organic solvent to ensure a stable aqueous–organic contact interface. We investigated two scale-out configurations and utilized the large contact area and short diffusion distance to facilitate overall system mass transport. Extraction efficiency was estimated and compared with a single CALLME to demonstrate the system's scalability and rapid process decision-making. A reduction in the use or generation of solvent in the design and manufacture of products was also demonstrated.

Design theory

The single CALLME comprised a straight glass tube (internal diameter [ID], 5.75 mm; thickness, 1 mm) and a 304 stainless steel helix wire (length, 4.0 cm; ID, 1.4 mm; wire diameter, 0.15 mm) to confirm its extraction efficiency. Another experiment was conducted with the goal of increasing the productivity of CALLME: we scaled out the numbers of the microchannels and helix wires instead of expanding their size (scaling up) to avoid unstable interference occurring during the extraction. Thus, we designed two types of devices consisting of various arrays of four helix wires to realize the aim of scaling CALLME. The two forms of arrays used for scaling were CALLME with four helix wires in a parallel arrangement (pCALLME) and CALLME with four helix wires in 2×2 square matrix arrangement (2sCALLME). These arrays maintained the aqueous and solvent solution volume ratio at 1:10; the helix wire arrangement is illustrated in Fig. 1. The aqueous stream and organic steam in both devices were injected in a co-current flow configuration that was driven by a syringe pump and a flow control system (Flow EZ, Fluigent, France), respectively. The aqueous stream was surrounded by organic solvent. The interference between the aqueous stream and the organic stream remained clear and stable throughout the process. Moreover, the extraction efficiency when passing through the channels was maintained in each configuration. The countercurrent model (cCALLME) was also tested to demonstrate the possible extraction efficiency differences that may exist.

To obtain a stable cylindrical aqueous–organic interface, the Laplace pressure ($\Delta P_{Laplace}$) and pressure drop effect along the stream must be considered. Laplace pressure is used to determine the liquid–liquid menisci, which can be regarded as the piece of the divided stable interface of two liquids. We adjusted the menisci by altering the pitch of our helix wires according to the method employed in related studies [13, 20–22]:

$$\Delta P_{Laplace} = P_{aq} - P_o = \frac{\gamma \cdot \sin(\theta-)}{\left(\frac{x}{2}\right) - r_w sin} + \frac{\gamma}{R_{aq}}$$

where P_{aq} and P_o are the pressure of aqueous and organic streams; γ is the surface tension; r_w is the wire diameter; and θ and   are the contact angle and angle between the y axis and interface contact line, respectively. R_{aq} and x are the radius and pitch of the helix wires, respectively. Flow rates are critical in constructing a stable liquid–liquid interface. Flow moves proportionally to the pressure gradient according to the different viscosity and density of aqueous and organic liquids: this generates a pressure drop difference between two streams. We estimated pressure drop per unit length of the aqueous and organic streams using the Darcy–Weisbach equation and Poiseuille's law [13]. The pressure balance between $\Delta P_{Laplace}$ and ΔP_{drop} can be used to predict whether the interface between the organic and aqueous streams can remain stable or not. However, in practice, pressure balance depends on many parameters, physical properties, and complicated structures. In short, if the Laplace pressure is greater than the pressure drop difference, then the interface can be expected to remain stable (Fig. 2):

$$\Delta P_{Laplace}(\gamma, \theta, x^{-1}, r_w^{-1}) > \Delta P_{drop}(f, L, Q, \mu, R^{-4})$$

To quantify the extraction, we applied extraction efficiency—which is determined by the ratio of the amount of solute to the maximum transferable amount—which is determined by the thermodynamic characteristics [23].

$$E(\%) = \frac{C_{aq,in} - C_{aq,out}}{C_{aq,in} - C_{aq}^*} \times 100$$

where $C_{aq,in}$ and $C_{aq,out}$ are the inlet solute concentration (10 vol% acetone) and the outlet solute concentration in the aqueous phase. C^*aq is the equilibrium concentration of acetone in the aqueous phase that can be attained by applying the mathematical exponential decay function, which was reported in a previous study [13]. The outlet solute concentration in the aqueous phase was determined using high-performance liquid chromatography (HPLC; Shimadzu Prominence LC-20AT HPLC, Japan) with an ACE 5 C18 RP column. The mobile phase in the HPLC comprised a mixture that included a 20 vol% methanol and 80 vol% aqueous solution, which was mixed with 0.2 % formic acid in deionized water. In the analytical method, the mobile phase comprised 1.0 mL/min with a gradient of methanol from 20 to 75 % over 3 min. The samples were subjected to a 9-min equilibration and detection at 274 nm. All samples analyzed using HPLC were diluted 25× in 0.2 % trifluoroacetic acid in deionized water.
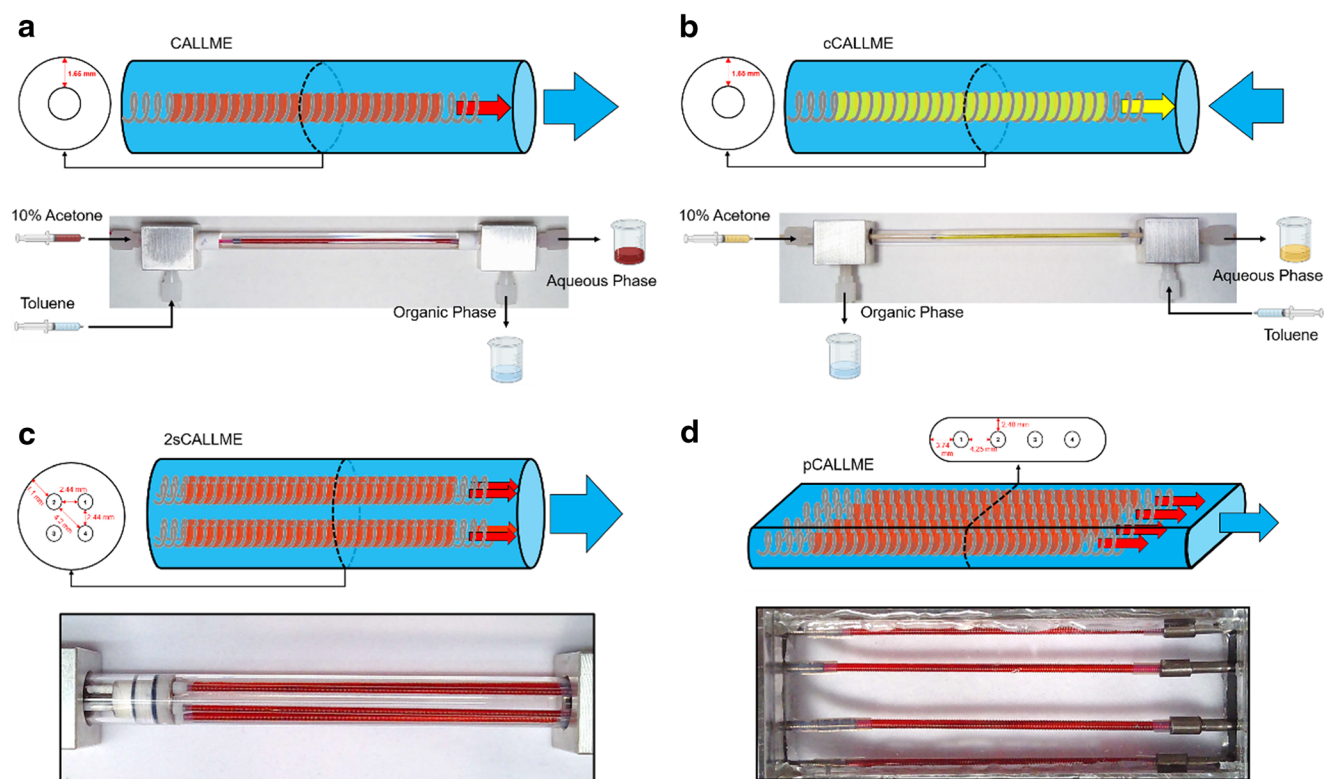
Fig. 1 Schematic and photograph of the CALLMEs setup: CALLME (**a**), cCALLME (**b**), 2sCALLME (**c**) and pCALLME (**d**)

Results and discussion

Investigation of flow patterns stability

The operating range was defined as an intact contact interface that formed between the aqueous and organic stream without any droplet formation. To clarify the operating range of the system, interface stability experiments were performed to identify the critical input flow rate of the two streams for maintaining a stable interface. The 0.335-mm pitch configuration was used in cCALLME, pCALLME, and 2sCALLME.

We screened and documented interface stability at the aqueous stream flow rate from 0.5 to 2000 µL/min, and the flow rates of the organic streams were 0.5–500 µL/min. This result indicates that a stable interface was observed with an aqueous flow rate of 0.5–800, 0.5–800, and 0.5–1700 µL/min in the cCALLME, pCALLME, and 2sCALLME, respectively (Fig. 3). In comparing the co-current CALLME (from our previous study) with the countercurrent cCALLME system, we noted that the cCALLME had a smaller operational range (aqueous stream flow rate: 0.5–800 µL/min) than the CALLME (0–1500 µL/min). This may be because of the

Fig. 2 Wire structure and pressure balancing across the interfacial area and along the channel showing the menisci position of the wire–liquid interface (**a**) and the extraction scheme of the acetone into organic phase by toluene (**b**)
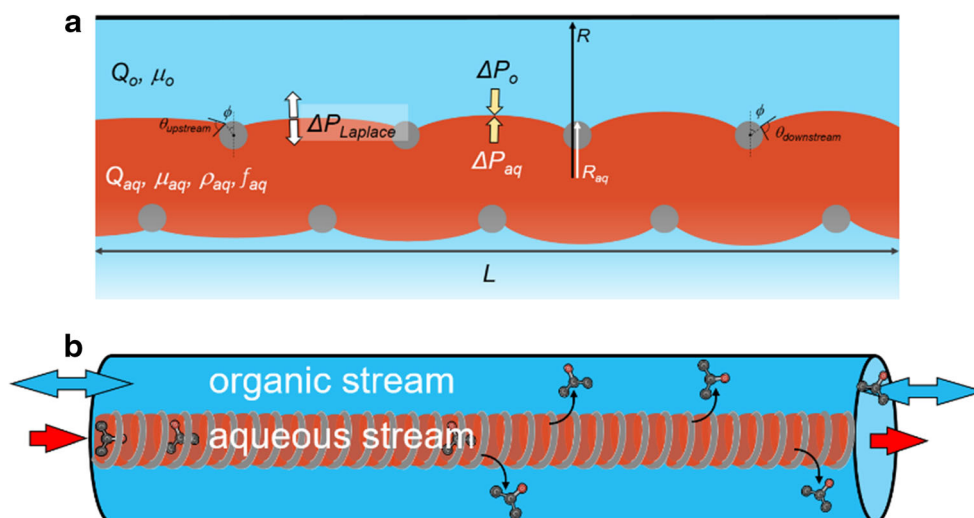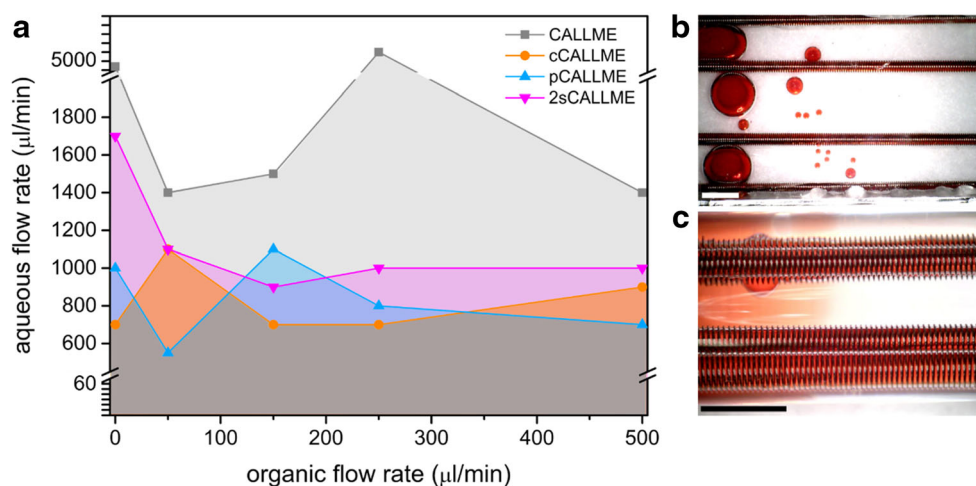
Fig. 3 Color-filled area showing stable interface for different aqueous and organic flow rate matches with all four CALLME configurations (**a**). Breakdown interfaces are observed at a fixed organic flow rate (150 µL/min) and with varying aqueous flow rates of 1200 µL/min (**b**) and 900 µL/min (**c**), respectively. Scale bar: 5 mm

unbalanced pressure caused by differences in the liquids' viscosity and density between streams. The pCALLME reached the maximum aqueous flow rate at 800 µL/min, and the 2sCALLME reached it at 1700 µL/min when the organic stream flowed slowly. Compared with CALLME, cCALLME, pCALLME and 2sCALLME have lower interface stability. A narrower input flow rate range (0.5–1700 µL/min for the aqueous and 0.5–500 µL/min for the organic streams) was observed. Nevertheless, all extractors can operate at 500 µL/min.

Determination of extraction efficiency and production rate

In the extraction experiment, 10 vol% acetone was extracted from the mixture solution (10 vol% acetone and 90 vol% water) to pure toluene solution. Two factors affecting the extraction efficiency are (1) the effective contact area of the two streams, which relates to the wire pitch configuration; and (2) the residence time, which is mainly determined by the aqueous flow rate. The wire configuration in both the cCALLME and 2sCALLME had pitches of 0.156 mm and 0.335 mm, which resulted in different effective contact areas of 0.254 and 247.5 mm^2, respectively. The same pitch

configuration (i.e., 0.156 mm and 0.335 mm) was applied in the pCALLME, resulting in an effective contact reaction area of 4.06 and 113.16 mm^2 because of the different wire length. Aqueous and organic streams were injected from the inlet with flow rates of 0.5–500 µL/min and 50–500 µL/min, respectively. A longer residual time resulted in higher efficiency because of the high reaction duration. Thus, a lower aqueous flow rate caused high extraction efficiencies of 15.4, 6.2, 3.1, 1.54, 0.62, and 0.31 min corresponding to aqueous flow rates of 10, 25, 50, 100, 250 and 500 µL/min in cCALLME and 2sCALLME. The aqueous stream was collected at the outlet separately and then examined with HPLC to determine the remaining acetone proportion.

We first examined the acetone concentration of the aqueous streams from individual wires in the scale-out systems, namely pCALLME and 2sCALLME. The results revealed no significant acetone concentration difference among the four wires (Fig. 4). Under residence time 15.4 min, only 0.56 ± 0.12 vol% and 0.2 ± 0.09 vol% of acetone remained in aqueous stream of pCALLME and 2sCALLME, respectively. The aqueous streams that flowed through the four wires underwent a similar extraction process. However, the results also suggested that wires #1 and #2 of the 2sCALLME had a lower extraction rate (the slope). This result might be because

Fig. 4 Concentration profiles of 10 % acetone after extraction from each wires: pCALLME (**a**) and 2sCALLME, N = 3 (**b**); several error bars are smaller than the size of the marker
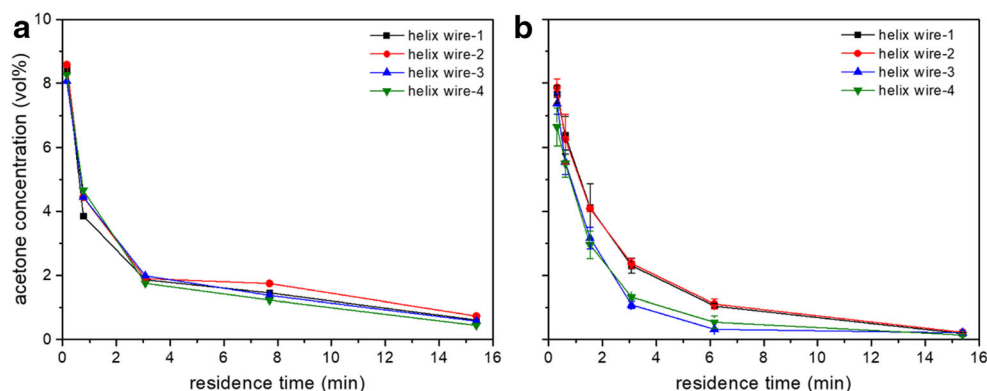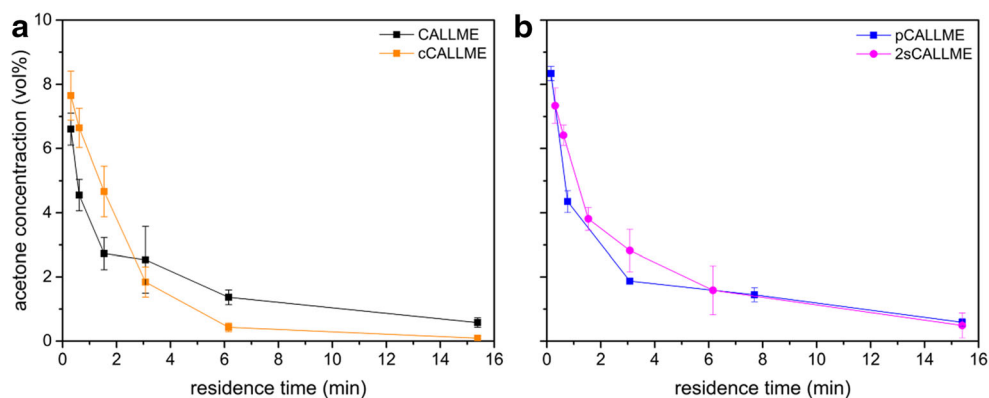
Fig. 5 Averaged concentration profiles of 10 % acetone after extraction for different CALLMEs. N = 3; several error bars are smaller than the size of the marker

of lower convection at the top of the glass tube (organic solvent flowed slower at the top of the glass tube) and because wires #1 and #2 are located at the upper part of the 2 × 2 square matrix.

Comparisons of the extraction efficiency of CALLME, cCALLME, pCALLME, and 2sCALLME under various aqueous flow rates are illustrated in Fig. 5. Comparing our previous work with cCALLME, with the same configuration but a different current direction, the CALLME extracted more than 5 vol% acetone within 1 min, but the cCALLME only extracted 3 vol% acetone. Nonetheless, at a longer residence time, > 15 min, the CALLME and cCALLME extracted 9.42 ± 0.15 vol% and 9.91 ± 0.003 vol% acetone and efficiency in both devices reached over 95.4 ± 1.2 % or even 99.7 ± 0.2 %, respectively. Although the CALLME had a higher extraction rate at higher input flow rates and a lower extraction rate at lower input flow rates than the cCALLME, the results suggested no significant differences in extraction efficiency in case of sufficient residence time. These data may also implied that the concentration profiles vary from different channel lengths: the extraction is marginally better for the countercurrent operation at longer channel configuration. Further investigation will present in our next study.

The pCALLME and 2sCALLME exhibited a similar trend. In the scale-up systems pCALLME and 2sCALLME, we tested two organic input flow rates, 150 µL/min and 500 µL/min, which both revealed that more than 90 % of the acetone was extracted during longer residence times (slower aqueous input flow rate). The 2sCALLME exhibited a higher extraction efficiency at higher aqueous input flow rates compared with the pCALLME. This might be because (1) the diffusion distance was smaller in 2sCALLME, and (2) the 2 × 2 matrix-like wire arrangement generated a faster flowing subcoannular organic stream in the center of the device causing higher mass transfer. However, this can only be determined using the velocimetry technique, which is not within the scope of this study.

The extraction efficiency of the pCALLME reached 90 % in 2 min, which is three times faster than that of the 2sCALLME did (Fig. 6). These results indicate that the pCALLME has a considerable potential to facilitate rapid process characterization. The 2sCALLME showed a higher production rate which is calculated by 10 % acetone multiplying the input flow rate and then extraction efficiency (in terms of how much acetone was extracted). For example, the extraction efficiency of pCALLME and 2sCALLME at Q_{aq} = 500 µl/min is 18.8 % and 27.2 %, and then results in 2.3 ml and 3.3 ml per hour acetone production (10 vol% x 500 µl/min x 18.8 or 27.2 % x 60 × 4). With the same 2sCALLME, 50 and 500 µl/min aqueous input flow rate conditions received 0.9

Fig. 6 Acetone extraction efficiency under different residence time in pCALLME (A) and 2sCALLME (B). Results are shown for a higher (500 µL/min, dark) and lower (150 µL/min, light) organic flow rate under while varying the aqueous stream. N = 3; several error bars are smaller than the size of the marker
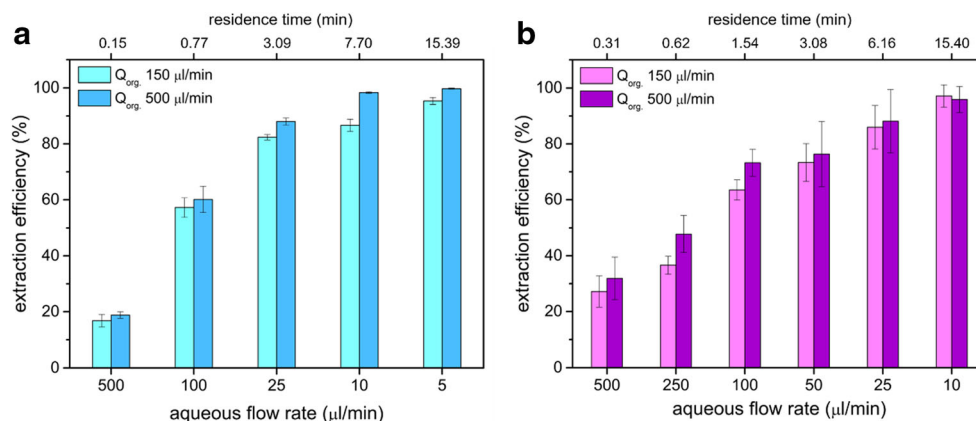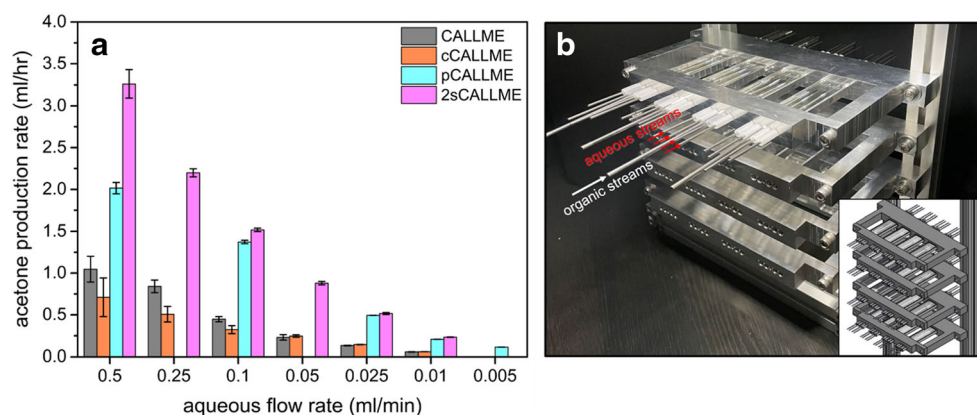
Fig. 7 Productivity of all four CALLMEs in an hour. N = 3; several error bars are smaller than the size of the marker (**a**). Four layers of pCALLME arrays comprised sixty-four CALLMEs to achieve high production rate (data does not show in this study)

and 3.3 ml acetone in an hour, respectively (Fig. 7a). It is seen that as we increase the input aqueous flow rare the improvement in performance becomes more significant. We also observed that the organic flow rates had a minor effect on the extraction efficiency in both configurations. This result also implies that by employing lower amounts of organic

Table 1 Comparison of Q_{aq}, Q_{org} and Q_{total} with droplet, counter-current and co-current flow microextractor

Author	Aqueous phase	Organic phase	Q_{aq} (μl/min)	Q_{org} (μl/min)	Q_{total} (μl/min)	
Droplet-based flow						
Yoshihito Okubo et al.	water	dodecane, phenol	2000	2000	4000	[4]
Lihua Zhang et al.	water, nickel sulfate, cobalt sulfate	Diisooctylphosphinic acid, kerosene	4000	4000	8000	[10]
Iris Vural Gürsel et al.	water, acetone	toluene	10000	10000	20000	[24]
	water, acetone	butylacetate	5000	5000	10000	
H.Breisig et al.	water	paraffin oil	150	500	650	[5]
Tingliang Xie et al.	water	sulfonated kerosene	30000	30000	60000	[25]
Tingliang Xie et al.	water	hydrogenated kerosene	20000	10000	30000	[26]
Nopphon Weeranoppanant et al.	water, acetone	toluene	2000	1000	3000	[27]
	water, acetic acid	ethyl acetate	500	2000	3000	
Safa Kutup Kurt et al.	water, acetone	butyl acetate	3900	3900	7800	[9]
Counter-current flow						
This study	water, acetone	toluene	800	500	1300	
Arata Aota et al.	water	butylacetate	3	5	8	[28]
Co-current flow						
This study	water, acetone	toluene	800-1700	500	2200	
Yu et al.	water, acetone	toluene	10000	1000	11000	[13]
Arata Aota et al.	water	butylacetate	15	5	20	[28]
Peyman Foroozan Jahromi et al.	water	n-butyl acetate	60	85	145	[29]
	water	1-octanol	100	13	113	
Polona Znidarsic-Plazl et al.	water	ethyl acetate flow	100	210	310	[7]
Osamu Tamagawa et al.	cesium nitrate, water	cyclohexane, phosphoric acid di(2-ethylhexyl) ester	96.67	96.67	193.34	[14]
Tatsuo Maruyama et al.	Tris-HCl buffer	n-heptane	9.9	14.66	24.56	[8]
Hajime Miyaguchi et al.	urine sample	1-chlorobutane	50	10	60	[30]
M.P.C. Marques et al.	phosphate buffer	n-heptane	72	154	226	[31]

solvent with the same efficiency as more organic solvent, organic solvent usage can be reduced. Higher production rate can be achieved using multiple array matrix strategy (Fig. 7b).

These developed devices have various advantages under different applications. With a lower product purity requirement, large quantities of the targeted compound can be obtained in a short period (the high aqueous input flow rate). For the final downstream purification process, the high extraction efficiency can be achieved in the low aqueous flow rate. This also implies that the plant-wide purify condition optimization and cost analysis of the production process can be simply done through the manipulation of flowrate and any permutation of CALLMEs (including cCALLME, pCALLME, 2sCALLME and other microoperators). Comprehensive flow dynamics predomination is required to achieve the large-scale production in micro- extractor for continuous biocatalysis. To our best knowledge there is very few literature studies on the device scale up (multiple devices). Most of the studies only demonstrated their scalability by increasing the input flow rate (Table 1).

However, difficulties persist for micro-extractor, especially liquid-liquid extractor, expanding from laboratory to industry due to the complex flow circuit. For example, membrane extractor or droplet-based extractor requires carefully back pressure control [32]. One failed extraction (phase separation unclear) will quickly build the pressure up in the flow circuit and causes domino effect of the failing of next and sequential membrane extractor. This leads to uncertainties in the extractor design and process optimization. The key advantages of scalability for continuous mass production using CALLME configuration is that the high surface and volume ratio was kept, large operating windows in terms of flow rate and flow ratio to adopt various extraction model systems in industrial production, and the productivity was evaluated by increasing the capacity of the reactor from microliter to milliliter by adjusting the number of wires (i.e., aqueous streams).

Conclusions

Experiments were performed to investigate the system stability, extraction efficiency and production rate in the countercurrent, parallel and square matrix CALLMEs for standard water-acetone-toluene systems. The cCALLME shows not significant difference in terms of extraction efficiency but less interface stability to CALLME. Cocurrent flow extraction eases further application and integration. The scale-out CALLMEs (pCALLME and 2sCALLME) provide larger specific interfacial areas in comparison with single CALLME and results in higher production rate. The pCALLME and 2sCALLME shows potential as a screening tool for various

two-phase extraction model systems and suitability for use at a production scale in biocatalysis and relevant application. A circulating flow scheme could be used for continuous and automatic manufacturing, thus making the scale-out CALLMEs suitable for bench-top production.

Experimental setup

The pCALLME comprised four 304 stainless steel helix wires (length, 2.0 cm; ID, 1.4 mm; wire diameter, 0.15 mm) and an aluminum metal trough (length, 75 mm; width, 124 mm; thickness, 7 mm) with two slide glasses (length, 74.8 mm; width, 24.8 mm; thickness, 1.1 mm). The transparent design facilitated the sequential investigation. The maximum stretching length for the four 2.0-cm-long helix wires was 5 cm, resulting in a pitch of 0.335 mm. The aqueous stream from the upstream reactant (red colored stream, as shown in Fig. 1) was surrounded by organic solvent; the interference between two liquids had to remain stable throughout the process. The 2sCALLME was composed of a straight glass tube (ID, 9.75 mm; thickness, 1.5 mm) and four 304 stainless steel helix wires (length, 4.0 cm; ID, 1.4 mm; wire diameter, 0.15 mm). The arrangement was a 2×2 square matrix inside the glass tube. To obtain the precise pitch of the stretching helix wires, we adopted a laser scanning microscope. The tube design of the device has two vital elements. First, the inlet and outlet tubes of the aqueous stream have different diameters (1.3 mm and 1.7 mm) and are made of peek and 304 stainless steel. The aim was to reduce any possible extra fluidic resistance caused by the smaller tube diameter. Second, the inlet tube of the organic solvent stream is designed for gradual enlargement instead of sudden expansion to avoid possible vortexes occurring. We performed all experiments at room temperature (24°C) except for the collection of the outlet product, which had to be preserved in a cold environment because of the volatility of the organic solvent. To study the molecular transport in the CALLMEs, we followed the standard testing system (toluene-acetone-water) of the European Federation of Chemistry Engineering [33] as our test model. The aqueous solution was 10 % (v/v) acetone dissolved in water, and pure toluene was used as an organic solvent for the experiment. Because of the high affinity and interfacial tension (36.1 mN/m) between acetone and toluene, the system is the perfect set for initial testing extraction. Moreover, red dye was added to the aqueous solution to facilitate interface observation.

Author contributions Cheng-Yan Lin: Investigation; Writing (original draft preparation); Methodology.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Conflicts of interest/Competing interests On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Cheng-Yan Lin joined Chiang's Lab in 2019 and worked on the novel liquid-liquid extraction strategy project. His research interest focuses on two-phase flow and biochemistry engineering, and flow chemistry.
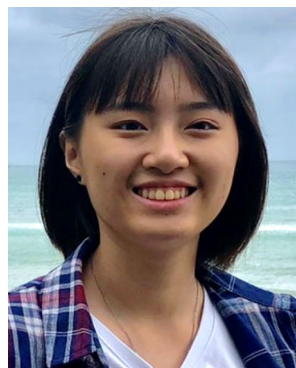
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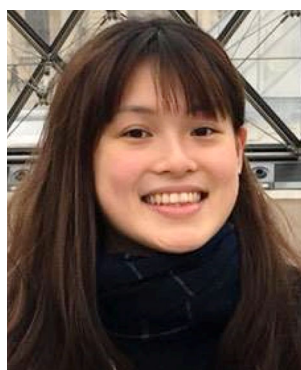
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