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► **To cite this version:**

Ange Maurice, Johannes Theisen, Jean Christophe Gabriel. Microfluidic lab-on-chip advances for liquid–liquid extraction process studies. *Current Opinion in Colloid & Interface Science*, 2020, 46, pp.20-35. 10.1016/j.cocis.2020.03.001 . hal-02865802

HAL Id: hal-02865802

<https://hal.science/hal-02865802>

Submitted on 22 Aug 2022

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Microfluidic Lab-on-Chip Advances for Liquid-Liquid Extraction Process Studies

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Keywords: Microfluidics | Liquid-liquid extraction | FTIR | SAXS | XRF | Lab-on-Chip | Integration | Phase diagram | Kinetics | Thermodynamics | Complex fluids

Abstract

The ever-increasing complexity of industrial products' recycling calls for more efficient purification processes such as liquid/liquid extraction. Because of the high complexity of liquid/liquid extraction, optimizing a large-scale extraction is both time and resource consuming and can only be justified to solve high volume and value purification problems. It is therefore difficult to apply to small scale and highly variable waste material influx. We believe that using a fully automated and integrated microfluidic approach will enable fast and cost-effective studies of liquid/liquid extraction processes. This review presents an overview of liquid/liquid metal extraction performed using microfluidics platforms. We first give an overview of the extraction methods. We then review the most relevant characterization methods that have been integrated with such platforms.

1. Introduction

Hydrometallurgy and more specifically liquid-liquid (L/L) extraction is a cornerstone of many metal extraction and purification processes. Formulation of such industrial processes are complex as they have many components, which interact at both molecular and mesoscale levels. Because of this high degree of complexity combined with the difficulty of studying liquid interfacial molecular phenomena, the field relies heavily on time consuming and labor-intensive phase diagram determinations. Complex fluid modelling and simulation in "lenaics"¹ have made lots of progress [1, 2], but these efforts often suffer from the lack of in-depth understanding of (i) interfacial mechanism [3], (ii) their thermodynamic and (iii) their kinetics [4]. This precludes process behavioral anticipation in the case of fluctuation of process parameters around the optimized functioning point. Firstly this can be expensive, for example, if a third and viscous phase appears which blocks the process flow and leads to plant stoppage for cleanup. Secondly, the recycling industry is facing new challenges when dealing with urban mining [5].² When treating mine ores, some composition fluctuations can be observed. They are handled by (i) a good understanding of each component's influence on the process; (ii) process simulation codes that are functional in a window close to normal experimental conditions. With urban mining, metal composition, contaminant and other materials concentrations

¹ lenaics, comprises the science and technologies associated to transfers of electrolytes between fluids in the absence of external electrical field, c.a. their flow, transportation, exchange and migration.

² Urban mining is the process of recovering rare metals from a stockpile of wastes (landfill).

can be radically different from one batch to the other depending on the source of the waste to be treated. With such high variations, B2B waste collection is the current preferred path to circumvent this issue as it assures consistency in the input waste. Beyond this, one will need much better understandings of liquid-liquid extraction processes, their mechanisms, their thermodynamics, their kinetics, as well as modelling tools and validation procedures, so that significant process adjustments or even development times can be drastically reduced. We are however still far from this. For example, most phase diagrams published are obtained using a batch approach in which macroscopic amount of leachate and solvent are used and analyzed for each data point explored. Not only is this time consuming, but it can prove to be expensive in terms of chemical waste management/treatment, especially when dealing with a newly developed, valuable and/or rare extractant molecule or the extraction of radioactive elements. Therefore, a fully automated and computer-controlled liquid-liquid extraction tool using a microfluidic platform integrated with necessary characterization methods would be a great tool to obtain faster phase diagrams. Indeed, it would allow extraction of the structural, thermodynamic and kinetics pieces of information that are necessary to explore the multi-dimensions phase diagram of the process under study. It would also allow to generate complementary data and enable process development based on big data analysis, as has been done in life science [6, 7]. This would therefore represent a significant advance in the field whether the objective is to determine a whole phase diagram, or just to rapidly evaluate process stability and/or performance in new conditions. It should also greatly reduced the amount of time required, the quantities of chemicals used and waste streams, therefore decreasing the cost of the study. It should be noted that in 2014, Ciceri *et al.* [8] stated, "A major area of future developments is envisaged to be the integration of traditional detections directly on chip." In the current review article, we therefore present our opinion on a selection of recent advances in liquid-liquid extraction of metals using a microfluidic platform together with associated efforts to automatize and integrate them with characterization methods. This includes original work performed in our group over the past six years to enable fast/cheap liquid-liquid metal extraction process investigation.

2. Approaches for liquid-liquid extraction using microfluidics

Several requirements must be met in order to fabricate a useful microfluidic device for liquid-liquid extraction:

- Feed and extraction phases should be kept separate or be separable after extraction for chemical analysis.
- Sufficient contact area between the two phases, with respect to sample volume, needs to be maintained to keep contact times in a reasonable order of magnitude and hence for extraction to take place.
- The contact area must be known when full kinetics study is the target.
- The device needs to function under a large flow rate window to vary contact time, thereby investigating reaction kinetics.
- Devices must be made of materials resistant to all chemicals used. Materials should not intervene with extraction and complex fluids.
- Finally, the devices must be leak-tight to a level well under the minimal flow rate.

Several device methodologies were developed since the early publications [9, 10]. Most recent relevant advances are presented in this section with respective advantages and drawbacks.

2.1. Devices using guide structures

Devices with guide structures are based on the principle of interfacial tension. Organic and aqueous liquids used in solvent extraction inherently have an interfacial tension, γ , keeping them from mixing. Nevertheless, in contact, they would at least form an emulsion. Hence, geometric barriers following Laplace pressure are required in order to prevent emulsification between aqueous and organic channels. Laplace pressure ΔP is connected to the radii R_1 and R_2 at the interface:

$$\Delta P = \gamma / (1/R_1 + 1/R_2) \quad \text{Equation 1}$$

Radii R_1 and R_2 are dependent on the extension of the contact area, whereas ΔP needs to compare to the hydrodynamic pressure which is related to channel sections, flow rates, and viscosities of the two phases.

There lies the crucial point: contact area and thus channel geometry needs to be very thin in order to maintain the interface. A nice example is given by Priest *et al.* for extraction of copper from an aqueous solution to a kerosene phase. Channels are in the order of some tens of micrometers with a guide height of 5 μm [11] (Figure 1).

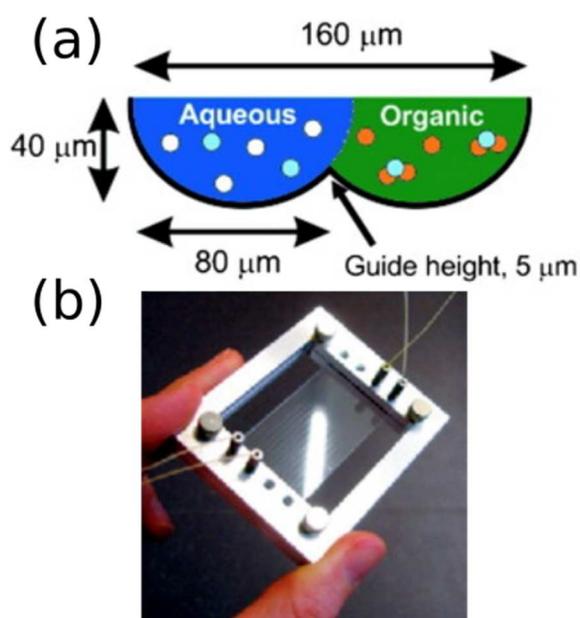


Figure 1: (a) channel geometry with guide separating phases by interfacial tension; (b) Complete glass device with macrofluidic interface. Adapted with permission from [11].

Such devices can now be found commercially and have recently been used for the study of liquid-liquid extraction (which used Y-Y geometry glass microchips from Dolomite® [12, 13]).

A further development was reported by Kikutani *et al.* [14] based on that principle but enhanced by selective surface modification of the glass channels. The organic channel is rendered hydrophobic by applying a thin film of octadecyl-dichloro-silane, whereas the aqueous channel stays hydrophilic (glass chip). This technique is called capillary-restricted modification by the authors: the 12 μm thin aqueous channel is not wet by the hydrophobizing agent, whereas the 59 μm thick organic channel is. Although the aqueous channel is very shallow, the hydrophobicity and hence augmented interfacial tension between the aqueous phase and the outer channel surface leads to efficient phase separation. The authors demonstrated the extraction of 3 μM methyl red into toluene (Figure 2).

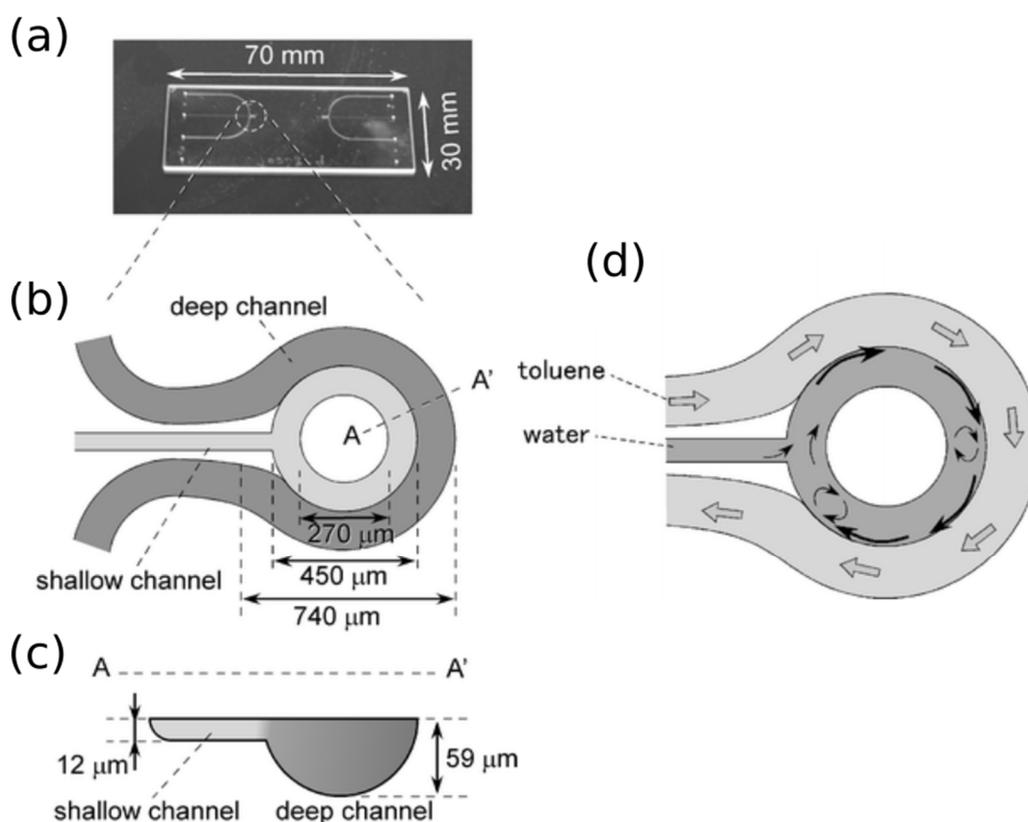


Figure 2: Complete glass device (a) with horizontal (b) and vertical (c) channel geometry. The outer solvent channel is hydrophobized, the inner aqueous channel remains hydrophilic. (d) Flow schematic for extraction: methyl red is extracted from the aqueous to the organic phase. Adapted with permission from [14].

A further approach on geometrically-assisted separation is given by Berthier *et al.* [15]. The channel interface is restricted and curved by periodically aligned separation geometries – pillars – of different shapes (Figure 3). Shape geometry is an important parameter for interface stability: since Laplace and hydrodynamic pressure tend to push onto the interface, a round cylindrical geometry can be less effective for interface stability than an edged geometry. This depends on the types of liquids and solids used. In this case, Berthier *et al.* demonstrated efficient extraction of lead ions from an aqueous phase into a chloroform/dithizone solution. The authors calculate interface and flow parameters extensively based on different methods. They can predict interface (in-)stability depending on flow parameters like viscosity and flow rate.

Overall, the main disadvantage of separation devices using guide structures is the limited functional window concerning flow rates (and hence kinetic window) and viscosity difference. Firstly, counter-flowing phases are proscribed, since immediate interface rupture would be the outcome. Secondly, even when working in co-flow regime, users need to dimension the device and the operating window in function of targeted functioning operating parameters. This can prove a difficult issue since viscosity might be changing in unpredictable ways when exploring new systems of complex fluids or unknown phase diagram windows. Indeed, since solvent chemistry implies complex fluid effects, many phases encounter viscosity alteration through molecular aggregation. This alters the required pressure to keep flow rates constant and may thus totally shift hydrodynamic pressure throughout extraction. For these reasons, most extraction systems will require different device approaches. This is particularly true for medium to highly concentrated systems.

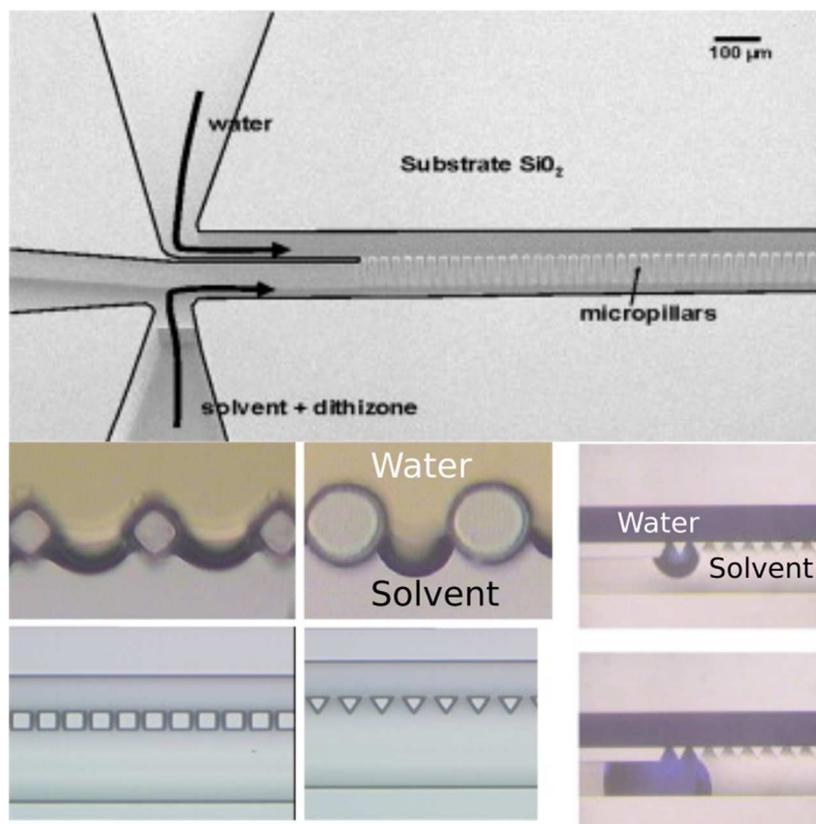


Figure 3: Top: Overview of a channel section with micropillars. Middle left: two examples of interface position depending on pillar geometry. Bottom left: two examples of pillar geometry. Bottom right: interface instability under co-flow. Adapted with permission from [15].

In addition, to reach fabrication resolution of less than 10 μm, device fabrication requires glass or silicon devices made using lithographic fabrication. This has two consequences: (i) fabrication processes required are more complex and costly than other examples discussed later in this section; (ii) inner channels volume is increasingly small compared to their surface, which can lead to different results from a bulk experiment due to interaction/adsorption of some of the components onto channel walls. This said, glass devices exhibit excellent chemical properties concerning chemical compatibility with all solvents and most acids, which is a major advantage over polymer-based microfluidic devices. Also, glass is very unlikely to interact with chemical reactions.

2.2. Membrane-based devices

Membrane-based liquid-liquid extraction microfluidic cartridges, can be related to pertraction in macroscopic solvent extraction [16]. It also relies on separation by capillary forces, like the examples described above, but with separating features related to the polymeric membranes topology which are orders of magnitude smaller than the microscopic features described above. Indeed, polymeric membranes are fabricated with pore sizes reaching sub-μm levels and can be made of various materials. Porosity can be adjusted from between 50% to 70% for most products, whereas thickness lies usually between 30 μm and 200 μm. For solvent extraction, mainly hydrophobic polymers such as PTFE or PVDF are useful, since the interface is then situated on the outer side of the membrane between the membrane and aqueous channel.

For co-flow or counter-flow membrane-based devices, as discussed in Theisen *et al.*, a membrane is introduced between two (e.g. polymeric or glass) plates containing milled or etched channels [17].

The membrane pores function as a physical separation between aqueous and organic channels (Figure 4).

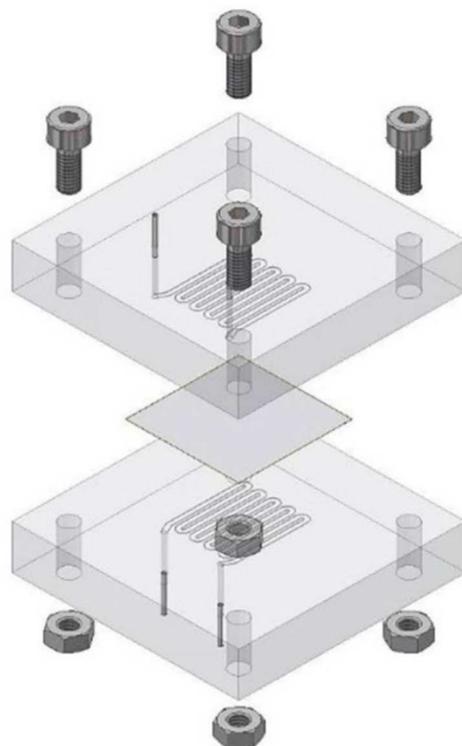


Figure 4: Microfluidic cartridge 3D-sketch with a porous polymer membrane (central square) mounted between two PMMA plates containing milled channels and micro-macrofluidic interfaces via stainless steel needles. Reprinted with permission from [17].

When using the device, it is necessary to introduce the aqueous phase prior to the organic phase to avoid wetting the aqueous side with organic liquid. This wetting, even partial, would build capillary bridges for the organic phase to leak into the aqueous channel. Also, to secure the interface within the membrane, a positive over-pressure of a few hundred Pa needs to be applied to the aqueous channel. Failure to do so would result in the same leakage of organic liquid into the aqueous channel [17].

Theisen *et al.* further demonstrated feasibility of solvent extraction studies over various time scales for rare earth extraction from an aqueous nitric phase to an organic phase of Isane[®], a mixed organic solvent formulation close to dodecane [17]. By simulating chemical transport, reaction rates could be estimated. Also, authors discuss the importance of membrane parameters as a kinetics-limiting factor, since it was the focus of some scientific discussions. Hence, this report shows that in some cases a well-chosen membrane is not the limiting factor and that furthermore and most importantly even interfacial mass transfer rate constants can therefore be measured using a very simple, easy to wash & re-use, microfluidic assembly and overall system.

Another membrane-based solvent extraction approach uses supported liquid membranes. This approach consists in soaking the hydrophobic membrane considered earlier with the organic phase used for extraction. In this case, both channels, above and below the membrane, are filled by the aqueous phase: a first phase contains the leachate to be extracted into the organic phase contained within the membrane. The second phase is used for de-extracting the extracted species from the

solvent into this second aqueous phase. Both aqueous phases must be adjusted in chemical potential so that studied species will be extracted into the organic phase and further be de-extracted into the second aqueous phase.

With such an approach, Wang *et al.* demonstrated the extraction of halo-acetic acid by TOPO from an aqueous solution into di-hexyl ether [18]. The polycarbonate device has a compact footprint of a few cm² using a 25 μ m thick polypropylene membrane facing, for example, a 0.75 mm deep feed channel and a 0.1 mm deep stripping channel of around 400 mm length and 0.75 mm width (Figure 5).

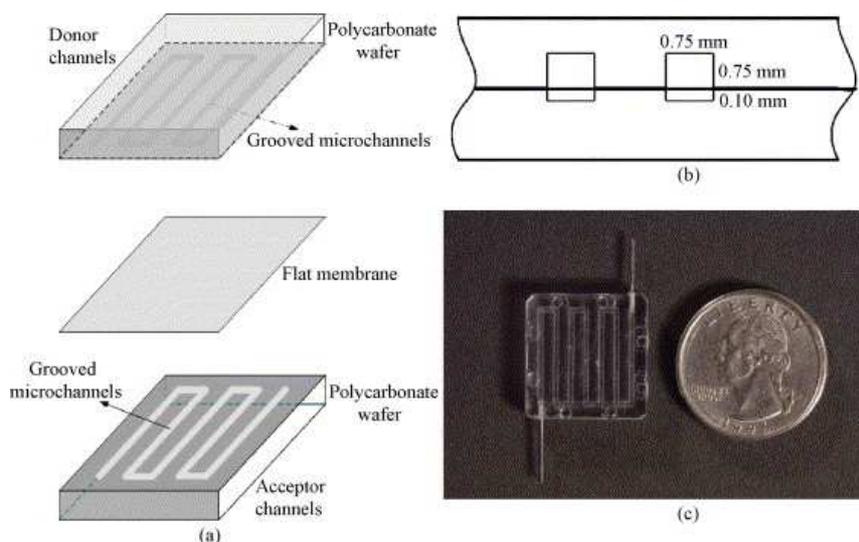


Figure 5: Polycarbonate microfluidic cartridge realizing a supported liquid membrane on a polypropylene basis. Reprinted with permission from [18].

This approach is very elegant, since the organic phase only interacts temporarily to bridge extraction and stripping phases and hence both steps are performed in one and the same device. However, some systems may co-extract water, acid or other reagents, which might impact on de-extraction efficiency. Hence, phase diagrams should be well known prior to using such a device.

2.3. Discrete microfluidics

Discrete microfluidics is mainly the usage of slug flows or bubble and droplet microfluidics. These approaches are inherently different from the examples discussed above. The main difference is that the extraction takes place in a single channel using a “controlled emulsion”. Flows are therefore compartmentalized in a slug flow, and laminar mixing due to wall friction plays an important role. Flows with a high Péclet number³ allow to speed up diffusional constraints and thus the interface reaction rate may be the controlling regime in these devices.

One prominent example in slug-flow devices for lanthanide extraction is demonstrated by Nichols *et al.* [4]. The authors developed a slug-flow device extracting rare earths by HDEHP from an aqueous solution into dodecane (Figure 6). The slug-flow-induced convection catapulted the kinetics into a reaction-limited regime. By varying flow rates, and using the known drop size and overall phase contact area, they could measure, for the first time, interfacial mass transfer rate constants.

³ The Péclet number is the dimensionless ratio of the advection of a physical quantity by the flow to the rate of diffusion of the same quantity in the presence of a gradient of said quantity [19].

The advantages of this elegant approach are: (i) the very well-known exchange surface area that can simply be calculated from droplet geometry, as well as (ii) the very large range of flow that can be addressed, reported to be two orders of magnitude wide (from 1 to 100 $\mu\text{L}/\text{min}$). Its main disadvantage is the complexity of the setup and of its fine tuning to separate both phases as realized here on-chip, once extraction is performed.

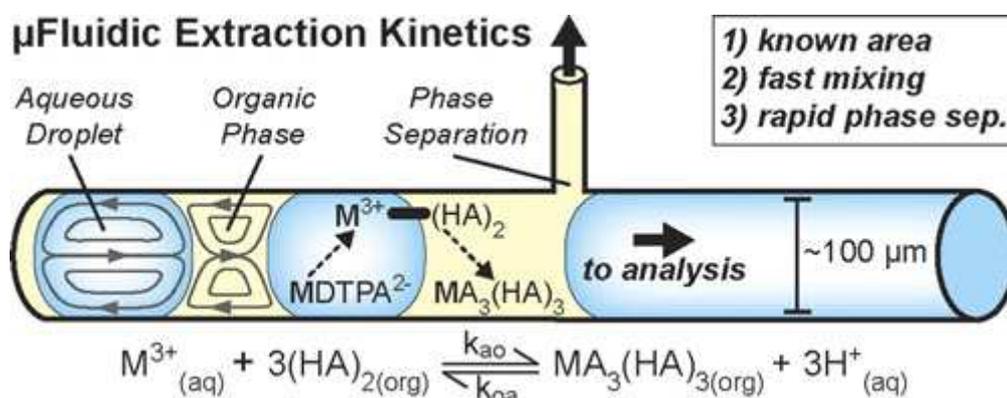


Figure 6: Sketch of the flow and mixing in the device prior to on-chip phase separation. Reprinted with permission from [4]

In a further approach, Wang *et al.* use air bubbles whose surface is covered with solvent [20] and that are generated and dispersed within an aqueous microfluidic channel. In other words, they created a gas–liquid–liquid double emulsion by dispersing a thin film of solvent around 0.5 μm to 4 μm thickness around the air bubble (Figure 7). With this, they demonstrated the extraction of Sudan IV from an aqueous solution into silicone oil. With such a small organic phase thickness, extraction kinetics are extremely short. However, in addition to disadvantages listed above regarding discrete microfluidics, it should be noted that the experiment described here uses PVA/SDS for interface stabilization. Depending on where these molecules are located, this additional layer could interfere with the kinetics of interfacial exchanges or extraction chemistry. Special attention to the validation procedure should therefore be taken when using such an approach for kinetic studies.

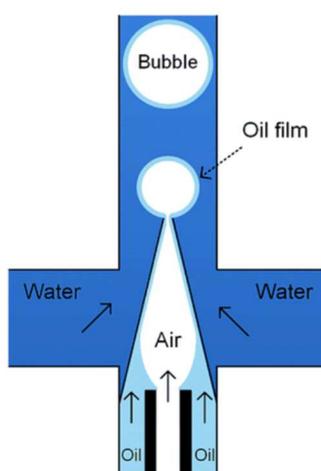


Figure 7: Sketch of the system for generation of a solvent-coated air bubble in aqueous medium. The generated solvent film is of the order of 0.5 to 4 μm thin. Adapted with permission from [20].

For all techniques using discrete microfluidics, an issue is that it is necessary to separate aqueous and organic droplets after extraction. This stops the process of extraction and contributes to proper on-chip or post-experimental analysis. One way of doing this, which was mentioned earlier in the case of Nichols *et al.* [4], requires finely tuned orifices to remove the solvent phase by capillary forces.

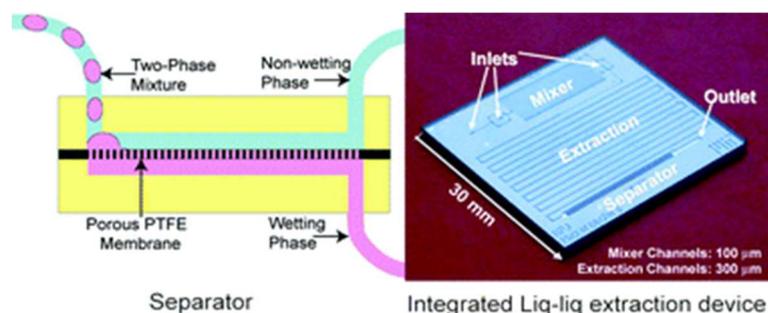


Figure 8 : Droplet phases separation using a porous membrane, Reprinted with permission from [21].

A different approach is to lead the mixed flow through a separator device which is composed of two channels sandwiching a hydrophobic membrane [21]. By applying high-enough backpressure to the extraction side, either through long tubing or through a pressurized sample vial, the organic phase is squeezed through the hydrophobic membrane, while the aqueous phase continues to the sample vial (Figure 8). Back pressure must not be higher than Laplace pressure given by the pore size and liquid-liquid interfacial tension. This last condition gives an idea about the maximum pore size to be used for the membrane.

3. Fully automated approach

In an ideal instrumented micro-extraction study, one would need to vary all parameters in a controlled and automatic manner: temperature, concentrations, flow rate and mixing ratio. With modern tools, most instruments can be computer controlled. Thus, simple programs can run a micro-extraction experiment. Yet, it is very challenging to accurately tune and assess the variation of these parameters. For example, the flows can be unstable because of poor injection, or pressure drops within the tubing/channels. These challenges can be overcome using precise flow control systems, shorter tubing, geometry optimization, flow sensors and efficient micro-mixers [22].

To develop experimental automation and enable screenings, we also must be able to vary the sampling, for example if we want to perform a combinatorial study to determine the best extractant. One way is to simply prepare many solutions (one for each extractant) connected with automated valves to dispense the correct samples in sequence. However, this approach requires fastidious preparations and dissolutions of all molecules prior to the experiment. Ideally, the dissolution should occur within the microsystem. In this case, the biggest obstacle is to achieve consistent concentrations over time.

In a recent article, Gökçe *et al.* described a simple microfluidic device that allows controlled dissolution of reagents with precise control of the concentration [23]. They call the device a “self-coalescent module” (SCM, Figure 9 (a)). The device is a straight microfluidics channel split in half by a capillary pinning line acting as a leading barrier. The simplicity of this system is that the capillary pinning line is just a 5 μm trench. The reagents are positioned at the bottom part while the inlet is at the top. Figure 9(b) shows a time series images of the process. The barrier leads the liquid until the top part is filled. When it reaches the diversion barrier, self-coalescence occurs, and the bottom parts fill up. This results in homogeneous dissolution of the reagents along the channel. By

comparison, a control device without the capillary line is shown in Figure 9(c). In this example, the resulting concentration profile is highly heterogeneous (Figure 9(d)). With its simple structure, the SCM yields a very consistent concentration profile.

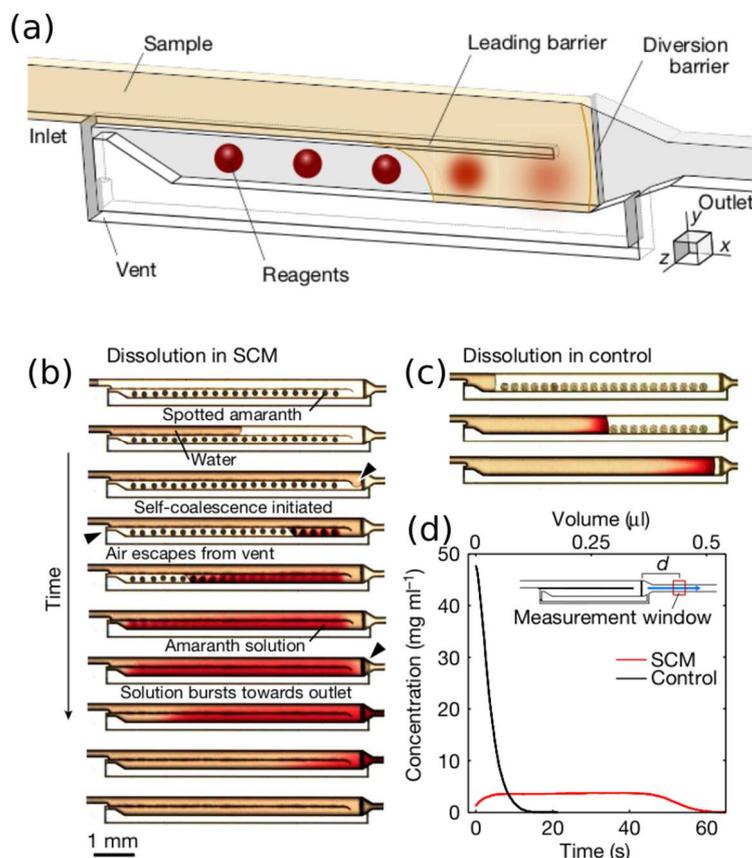


Figure 9: (a) Schematic view of the Self-coalescent module (SCM); (b) Time series of bright-field microscope images showing the reconstitution of amaranth in an SCM filled with water; (c) Control experiment using a channel without capillary pinning line; (d) Concentration profiles of obtained with an SCM (red) and the control device (black). Adapted with permission from [23]

When carrying out automated L/L extraction, these findings could improve combinatorial screening where several extracting compounds would be tested within the same automated experiment.

4. Integration with characterization methods

For characterizing L/L extraction processes, the methods need to yield either quantitative (e.g. concentration) or thermodynamic information (e.g. chemical activity). In addition, the techniques must be interfaced and non-invasive. Ideally, it must allow measurements in both the aqueous and organic phase. In this section, we review the characterization methods that could be integrated on-line with a microfluidic L/L extraction experiment. For a more general listing of characterization methods used in microfluidics, beyond hydrometallurgy, the reader can also refer to a recent review by Rizkin *et al.* [24]. Furthermore, Gavaille *et al.* describe thoroughly recent methods to measure thermophysical properties of fluids (viscosity, density etc.) using microfluidics approaches [25]. Lastly, Kocot *et al.* review the characterization methods that are used to detect metal species after micro-extraction [26].

4.1. Infrared spectroscopy: an enabler to measure the chemical activity of volatile molecules, including solvents

With modern optics, Infrared (IR) technology can be scaled down to microfluidics level. Thus, by using an IR-transparent microfluidic chip, absorption of the species yields concentration. This approach has been widely used to perform in-situ imaging of microfluidic flows and thoroughly reviewed by Perro *et al.* [27]. To measure concentration, the chip is often used in transmission mode. However, a major challenge is to avoid a total loss of signal due to the high absorption of liquids. To solve this problem, channels must be as shallow as possible which, in turn, induces pressure issues. Another trending solution is to use the very intense synchrotron infrared light sources [28-30]. The main drawback of a synchrotron source is the availability of the beam, the experimental cost and the synchrotron's size. An alternative strategy would be to use quantum cascade lasers for infrared spectroscopy [31]. Indeed, they are compact with very high-power throughput, although their wavenumber range is usually narrow which limits its universal use. Hence, only a few studies report the use of QCLs integrated with microfluidics [32, 33].

For integration with L/L extraction, we selected some recent innovative approaches. Since quantification is important, we note that IR spectroscopy enables concentration measurements in the organic phase. An example can be found in the work of Chan *et al.* where the concentration of benzoic acid in decanol is quantified [34]. We also note the new technological advancement by Sriram *et al.* describing a 10 nm-deep channel combined with ATR-FTIR [35]. These nanofluidic solutions will greatly improve the response time of the systems but the detection of small amounts of species may become extremely challenging.

Apart from concentration measurements, the accurate determination of thermodynamic parameters is a major challenge. Another drawback of previous IR approaches is that they do not allow for the measurement of the solvent's chemical activity, which is a key entry for ionic modelling, as molecular aggregation and solvent interaction translate directly into solvent's activity [1]. Indeed, microfluidic processes tend to become more and more complex involving the use of complex fluids, mesophases and aggregations. We are therefore far from diluted systems of non-interacting molecules, for which the convention is to define the solvent's chemical activity to be equal to unity. This is not applicable when dealing with complex fluids such as those used in L/L extraction.

An innovative approach to this problem is to measure the chemical activity of the liquids in the mixture by looking at their vapor phases. Indeed, the chemical activities of the species are related to their vapor pressures (modified Raoult's Law [36]) and, in turn, their molar fraction in the vapor phase considering fugacity is close to unity. This was demonstrated by Kokoric *et al.* using a fully integrated infrared hollow waveguide system to measure chemical activity and validated using water/ethanol mixtures [37] (Figure 10(a)). In this design, the liquid sample is injected through a liquid channel of which one wall is made of an oleophobic membrane [38]. The volatile components present in the sample evaporate through the membrane and diffuse into an infrared waveguide. This membrane permeation feature is common in membrane vapor extraction processes ([38, 39]. Figure 10 b) shows that the time needed to reach vapor pressure equilibrium is $t_{90} = 134$ s. From the absorbance of both ethanol and water, the activity can be measured. Calculated activity values are consistent with the data from the literature (Figure 10(b)). We note that this system was later applied for measuring water activity in NaCl/H₂O mixtures [40].

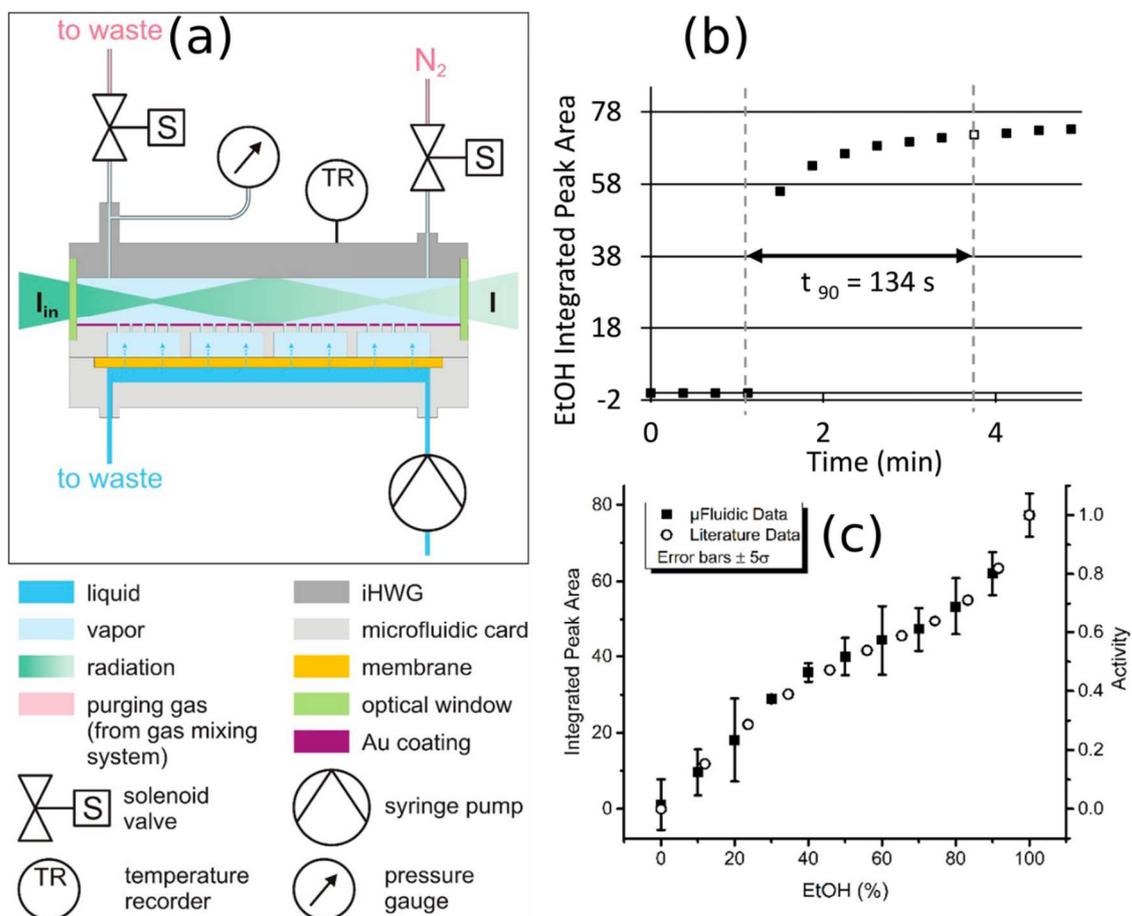


Figure 10: (a) Schematic cross-sectional view of the integrated infrared hollow waveguide; (b) Integrative absorbance of ethanol vs time; (c) Multiple y-axis diagram showing the integrated peak areas of ethanol absorption at equilibrium and the calculated activity values. The data is compared with literature. Adapted with permission from [37]

4.2. Raman spectroscopy

Like infrared techniques, Raman spectroscopy is vibrational, therefore it provides information regarding chemical bonds. Raman spectroscopy has been used heavily in microfluidics because it is practical to implement with existing Raman microscopes. Both quantitative and qualitative information can be retrieved, so is compatible with a micro-extraction study. However, it is worth reminding that Raman spectroscopy measures only molecules. In L/L extraction, the technique would be ineffective at measuring pure ions being extracted from an aqueous phase.

For studying thermodynamic parameters, we note a recent study dealing with the characterization of aqueous/organic interfaces with Raman spectroscopy [41]. The authors obtain high resolution concentration profiles at the aqueous/organic interface. These findings provide useful thermodynamic data for studying diffusion phenomena occurring at the interface during L/L extraction. However, from an on-line analysis perspective, it is still unclear how this type of characterization can be integrated in a micro-extraction system.

Several reviews have been published on Raman Spectroscopy and microfluidics [42]. Because Raman signal intensity is inherently low (inelastic scattering), researchers are shifting towards surface enhanced Raman scattering (SERS [43, 44]). This is more compatible with the small sampling

volumes involved in microfluidics. The principle is to add metallic nanoparticles (typically Ag or Au) to increase the Raman signal using plasmonic resonance phenomena. However, this can add unwanted contamination in the fluidic system and create clogging or aggregates. To solve this problem, researchers use stationary targets (or SERS substrate) such as silver nanopillars or nanoporous gold structures. These structures are embedded in the chip design and should be reusable. However, a so-called memory effect causes irreversible adsorption of the compounds to the targets. To improve reproducibility, the objective is to regenerate the SERS substrate.

In a recent study, Höhn *et al.* demonstrated an electrochemical approach to regenerate a SERS substrate using a chip-integrated silver electrode [45]. Figure 11 (a) shows their experimental setup. They use a porous silver wire as the SERS substrate and a copper counter-electrode as the anode. After measuring an organic analyte (Crystal violet), the chip is flushed with an electrolyte solution. By applying a voltage, the SERS substrate can be efficiently regenerated and reused. Figure 11 (b) shows a plot of the Raman intensity of the analyte vs time. At 20s, a voltage is applied and the signal decreases thus regenerating the SERS substrate within seconds.

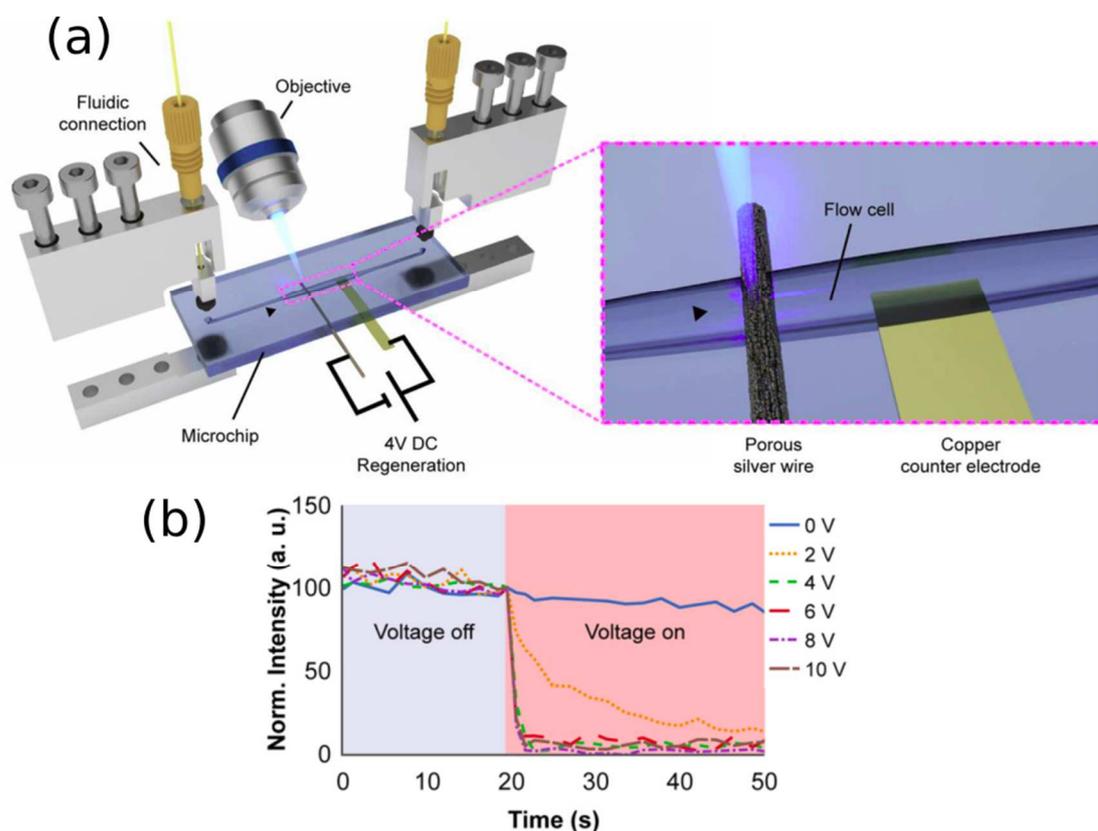


Figure 11: (a) Illustrated view of the SERS-microfluidic experimental setup; (b) Raman intensity vs time showing the SERS substrate regeneration after applying a voltage at 20s. Adapted with permission from [45]

Höhn *et al.* explain that the desorption of the analytes occurs because of the electrolytic decomposition of the solvent. They demonstrated the robustness of their setup using an automated approach with more than 18 regeneration cycles. They can also alternate analytes. These advances make SERS an attractive technique to perform on-line characterisation of analytes being extracted within a micro-extraction experiment.

4.3. Small angle X-ray diffraction spectroscopy (SAXS)

Using facilities such as X-ray labs or synchrotron radiation sources might seem paradoxical, since the surrounding experimental support outweighs, at first glance, any space gain of the miniaturization of extraction processes. However, the significant advantage in using miniaturization over classical approaches lies in the time gains produced by automated mixing and on-line integration of characterization methods.

SAXS is particularly popular with microfluidics because it uses a collimated X-ray beam that is compatible with the scale of the channels. It enables precise characterisation of nanostructures present in the liquids and can be used both in aqueous and organic phases. In liquid-liquid extraction, complex formulations often contain micelles, emulsions, aggregates and mesophases, therefore we believe that SAXS is an interesting characterisation method to study extraction processes [46-49]. The technique has already been thoroughly reviewed in previous works [50-53], so we will not detail these approaches here.

It should however be noted that the main limitation of SAXS is that it is not easy to extract elemental information which is important when dealing with L/L extraction. One must indeed be able to determine the extraction efficiency. An interesting strategy would be to combine it with X-ray fluorescence (XRF) to retrieve elemental analysis. Thus, phase aggregation (SAXS analysis) can be combined with values for extraction efficiency (XRF analysis) on a single device. This would require a single X-Ray source and two detectors yielding elemental and structural information, respectively.

4.4. X-ray fluorescence (XRF): Elemental analysis

Compared to SAXS, a handful of studies combine X-ray fluorescence and microfluidics. In the view of studying extraction processes, XRF enables the detection of a very broad range of chemical elements. With accurate calibration, XRF can be used for both qualitative and quantitative measurements. Additionally, XRF can be selective if multiple elements must be detected simultaneously. Another advantage, especially when compared to ICP, is that measurements can just as be performed in both aqueous and organic phases, although with proper calibrations. In terms of chip design, transparency to X-rays only needs to be achieved on one side of the chip thus simplifying fabrication processes and costs compared to SAXS.

In a recent study, Nagasaka *et al.* use narrow synchrotron radiation beams to perform soft micro-XRF mappings of Pyridine and water flows merging in a T-mixer [54]. The main downside of spatial measurements in XRF is that the experiment times are lengthy. Indeed, the instrument must scan every pixel in order to complete the image. This could be incompatible with on-line measurements aimed at studying extraction processes.

Other studies describe more quantitative approaches. Researchers performed XRF on single tubing/capillaries [55-57] or custom-made chips [58]. In these studies, the X-ray beam excites the total sample volume to maximize the signal. More than twenty-two different elements were detected and quantified with limits of detection as low as $\approx 10^{-4}$ mole/L. Thus, only one spectrum is taken but the measurements can be repeated over time. This strategy is fully compatible with on-line measurements that could be integrated with L/L extraction. It is worth noting that Macintosh *et al.* measure strontium in both aqueous and organic phases (synthetic fuel) [58]).

In his PhD work, C. Penisson presents preliminary results obtained with a homemade XRF apparatus (Christophe Penisson, PhD thesis, Institut de Chimie Séparative de Marcoule, 2018). Figure 12(a) shows a photograph of the apparatus. The detector and X-ray tube point towards a commercial microfluidics chip (From ChipShop). Figure 12(b) shows the spectrum obtained when a nitric acid

leachate CPU (Central processing Unit) is injected. As expected for a CPU, the solution contains large amounts of copper and even small amounts of lead and nickel.

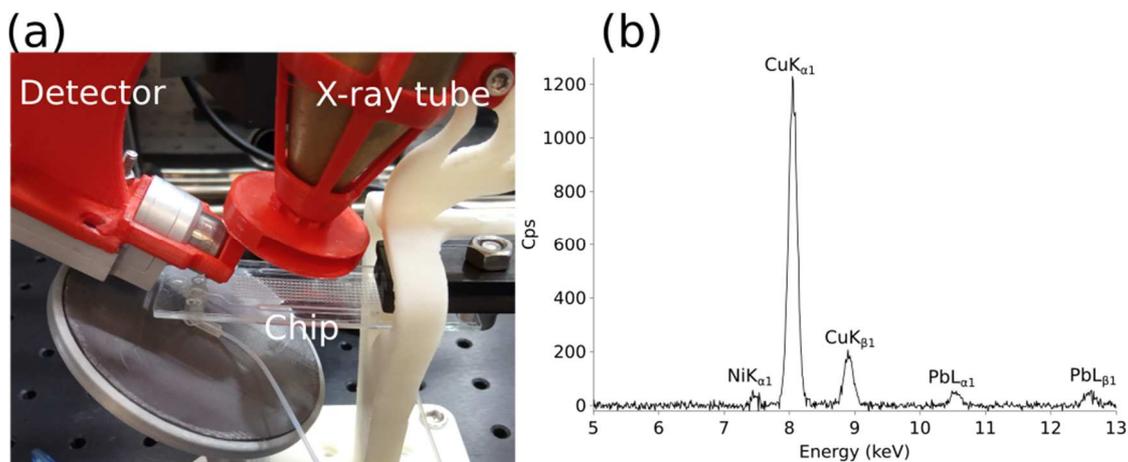


Figure 12: (a) Photograph of the apparatus showing the X-ray tube and the detector directed towards a commercially available microfluidics chip. (b) XRF spectrum obtained with dissolved CPU in HNO_3 ; [Christophe Penisson, PhD thesis, Institut de Chimie Séparative de Marcoule, 2018].

This experiment highlights the potential of using XRF as an online characterization tool. We can use both commercial and custom-made chips.

The main limitation of the XRF method is the fluorescence signal that inherently decreases with the volume of liquid. This goes against the microfluidics approach as we need smaller volumes for faster response times, therefore a compromise must be found between liquid volume and limit of detection depending on the applications. Additionally, the intrinsic design of the chip must be considered (surface area, thickness etc.) to minimize scattering and increase the X-ray fluorescence signal.

4.5. Other methods

Among other promising methods, there are the end-of-line (EOL) methods. They differ from on-line methods because they destroy the sample in order to obtain data. Hence, they are usually implemented at the end of the microfluidic line. In addition, there can be only one EOL method within a given microfluidic line, while there can be multiple on-line methods (e.g. XRF and Raman).

For accurate quantification, inductively coupled plasma (ICP) systems are very attractive [59, 60]. We notably emphasize the research of Hellé *et al.* who performed the first online measurements of co-flow L/L extraction integrated with ICP-MS [61], using a commercial glass microfluidic chip. By doing so, they could optimize the liquid/liquid extraction of uranium for various experimental conditions such as flow rate or contact time. These results illustrate the potential of using a characterization technique integrated with micro-extraction approach. Nevertheless, the authors note that the integration of the ICP-MS system induces changes in hydrodynamic conditions (pressure drops, flow instability). Although located at the outlet of the microsystem, the measurement remains indirectly invasive. We also highlight recent interests in similar integrated approaches such as high performance liquid chromatography (HPLC) [18, 62, 63] or liquid chromatography with mass spectrometry (LC-MS) [64]. For in-depth details on mass spectrometry integrated with microfluidics, we refer the reader to a recent review by Lin *et al.* [65]. Most of these approaches however have a limited range of functioning concentration which may require additional steps of dilution or concentration.

Among other optical techniques, UV-visible spectroscopy is widely reported and can measure ions concentration [66]. Yet, we believe that this approach often lacks the selectivity required when measuring mixtures of elements in the same sample, especially for both aqueous and organic phases. Also, the optical path and concentration required to reach limit of quantification is often not compatible with microfluidic devices. Finally, quantitative analysis requires in depth analysis of emitting species, which can prove difficult when various aggregates of extractant molecules and ions are mixed. It can become very difficult to analyze and interpret data.

Ultimately, researchers integrate different characterisation methods in the same microfluidic apparatus [67]. This strategy is costly but potentially yields powerful data. On the one hand, the more techniques that are used, the more information are retrieved. On the other hand, if two different techniques yield overlapping information, the level of confidence associated with the results is greater.

Conclusions

This review highlights that Instrumented microfluidics could soon be a fast and efficient way to study L/L extraction processes with lower environmental impact than classic methods (e.g. Lewis cell). It will require accurate mixing and injection capacities as well as suitable combinations of various characterization techniques. For instance, for inorganic species X-ray techniques would be preferred, while infrared/Raman spectroscopy will be used for organic species; the use of combined SAXS and XRF will also represent an innovative and fruitful approach for the automated study of L/L extraction of rare earth, metals and heavy metals.

Hence, we therefore anticipate that automatically produced phase diagrams of complex formulations should be published in scientific literature within a couple of years. From an industrial point of view, one will need to study the correlation between results obtained using a microfluidic approach with those obtained in their process plant. Some improvements are still required such as more compatible materials for the microchip (such as glass).

Other methods might also get integrated in the future which could prove useful and complementary to those presented here, as for example UV-vis spectroscopy, although its use to measure absolute concentrations will be particularly difficult to perform especially in the case of mixtures of various elements and variable extractants. Another one would be the use of ultrasounds that could accelerate significantly the kinetics or enable new separation methods [68-71].

Some of the modules developed in the framework of L/L extraction could also have a significant impact beyond this field as they give access to universal data in kinetics and thermodynamic. The most prominent example being the possibility to measure water or solvent chemical activity [72-74], for the study of the membranes [75] or to quantify mixing quality, especially when dealing with microfluidics. Indeed, mixing fluids down to the molecular level and its quantification is far from easy to perform when using microfluidics where creating turbulence or strong shearing can be challenging [76]. Currently, most methods to check if the mixing is done properly rely on macroscopic/microscopic optical observations. These are however not enough to ensure homogeneous mixing at molecular level, as it has been proven that such a mixture can be separated back to its original constituents by using acoustic fields [77, 78]. A good signature of molecular mixing could be found in the measurement of the solvent activity.

Regarding the market potential of integrated liquid-liquid extraction microfluidic chips, this technology has currently reached Technological Readiness Level (TRL)⁴ of 4 to 5, depending on the module considered, which is the threshold that provokes momentum and industrial interest. It should be noted that overall, a recent study by Grand View Research, Inc. on the worldwide microfluidics market size projects that it will reach USD 63.05 billion by 2023 from an estimated USD 12.33 billion in 2019 (hence with a staggering Compound Annual Growth Rate of 22.6%) [79]. We therefore anticipate industrial adoption of these technologies once they are made commercially available, probably within the next few years.

Aknowledgements

AM acknowledge financial support from SCARCE project, which is supported by the National Research Foundation, Prime Minister's Office, Singapore, the Ministry of National Development, Singapore, and National Environment Agency, Ministry of the Environment and Water Resource, Singapore under the Closing the Waste Loop R&D Initiative as part of the Urban Solutions & Sustainability – Integration Fund (Award No. USS-IF-2018-4). The literature search performed for section 2, as well as first generation of integrated XRF device presented for the first time in this review, was made possible thanks to funding from the European Research Council under the European Union's 7th Framework Program (FP/2007-2013)/ERC Grant Agreement N° [320915] "REE-CYCLE": Rare Earth Element reCYCling with Low harmful Emissions.

Declaration

The authors declare no conflicts of interests.

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