Review on microfluidic device applications for fluids separation and water treatment processes

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Abstract

This review deals with a particular application of microfluidic devices such as fluids separation and water treatment. Through the different sections of the document, the reader can find not only a state of the art of specific applications related with fluids separation but also how this kind of micro-technology is being efficiently used by designing novel devices to carry out specific tasks of separation and water purification. In particular, this work has focused in three important processes: liquid-liquid separation; separation of biological samples; and water purification. After reading the document, the reader will have a clear view of how different microfluidic devices and technologies can be efficiently used in separation processes.

Keywords: Microfluidic devices, Separation processes, Liquid-liquid, Biological samples, Water purification.

1 Introduction

Microfluidics is the science and technology of system handling low amount of fluids, using structures from tens to hundreds of micrometres (Whitesides, 2006). Microfluidics allow obtaining great advantages from microscale regarding macroscopic methods. These advantages, together with many usual examples one can find in industrial processes, will be discussed in this review focused on two particular applications: fluids separation and water purification. The three next sections are dedicated to three different kinds of fluid-involved processes where separation steps or chemical treatment must be conducted.

2 Liquid-liquid extraction

2.1 Introduction

Liquid-liquid extraction or solvent extraction is an important purification or separation process in which the components of a solution, separate from the primary liquid by contacting another immiscible liquid. This process has at least three components, and all components are present in the immiscible phases. The driving force of mass transfer is the chemical differences between the two phases, which distributes the components between the two phases and the relative separation of the components (Blumberg, 1988). This process, as a possible alternative to distillation, can be used for separation due to the low both relative volatility of the components and sensitivity to the separation heat of components.

In the selection of the extraction phase, a wide range of liquids can be used, but the following should be taken into account in their selection (Hanson, 2013):

1. Selectivity; 2. Distribution coefficient; 3. Solubility; 4. Recoverability; 5. Density; 6. Surface tension; 7. Chemical activity.

This operation was successively used in chemical, oil and petrochemical processes in the separation of aromatics, aliphatic materials or hydrocarbons (Li et al., 2009, Habaki et al., 2018). For many decades, the solvent extraction was used to separate biological compounds from fermentation media, isolate the antibiotics or recovery the proteins by researchers (Liang et al., 2016, Pahlavanzadeh et al., 2012, Grossmann et al., 2018). Additionally, the operation has several applications in nuclear and mineral industries for the extraction of radioactive salts (Zhao et al., 2014), and in environmental processes for the treatment of wastewater (Razmara et al., 2011) and industrial waste from the

hydrometallurgy, electroplating and electrochemical industries containing heavy, toxic and non-degradable heavy metal cation (Mafi et al., 2016, Seyfi and Abdi, 2009).

2.2 Challenges and future

Due to the high demand, the use of this method has increased dramatically over recent years. So, many types of research have been conducted by authors to improve mass transfer between the immiscible liquid phases by faster internal recirculation. Based on previous studies, the efficiency of extraction can be maximized by increasing the interface area and reducing the mass transfer resistance (Burns and C. Ramshaw, 2001, Assmann et al., 2013).

As an example, the surface area of the interface between the immiscible phases can be increased by creating smaller droplets of the dispersed phase. However, by changing the droplets size, a balance should be considered between increasing the efficiency and formation of emulsions, because, smaller droplets create a balanced emulsion which makes it difficult to separate the phases (Berthier et al., 2009). The mass transfer resistance also decreases with increasing temperature as a result of reduced viscosity of the fluid. This behaviour arises from the balance of viscous forces and surface tension which against each other (Gu et al., 2011).

Development of liquid-liquid extraction processes has made progress in the production of various extractors to increase the efficiency in different industries. These extractors can be divided into the following categories: Mixer-Settlers, centrifugal extractors, and columns (Coulson and Richardson, 2002). Although the conventional liquid-liquid extraction with high volumes of fluid has advantages, the post-separation stage requires a costly and time-consuming operation. Also, extraction processes use a lot of raw materials/solvents and energy to achieve chemical equilibrium state (Schweitzer, 1988).

To overcome the impact of the toxic organic phase, waste materials and more control in liquid-liquid extraction devices, miniaturization were suggested by different researchers (Marsousi et al., 2019, Novak et al., 2012, Kralj et al., 2007). Microfluidic technology is one of the novel technologies most widely used in micro-scale for accurate and controlled experiments on fluids, due to low residence time and favourable conditions.

By application of these devices, many advantages, inherently linked to the operation in micro dimensions, will arise over conventional type extractors as: (i) the flow is laminar

with lack of turbulence (Sia and Whitesides, 2003); (ii) smaller space occupation on demand (Voloshin et al., 2007); (iii) high surface-to-volume ratio; (iv) efficient and less energy consumption by-products (Lawal et al., 2010); and (v) effective process control for toxic or hazardous chemicals which are difficult to handle with traditional technologies (Geyer et al., 2006).

Moreover, extensive research is ongoing to develop microfluidic applications in many areas as biology, microbiology, pharmacy, tissue engineering, biotechnology, nanotechnology, chemical engineering, and medical engineering (Miura and Yokokawa, 2016, Jiang et al., 2014).

Generally, these devices consist of the following parts: 1) microfluidic device; 2) pressure-driven devices, like syringes or peristaltic pumps; 3) connections system between the devices; and 4) detection tools for the analyse. Considering the specific structure, it is possible to found these devices with channel lengths below 900 μm, commonly in the range of 10 to 500 μm.

The first attempt to use the extraction with microfluidic was by Brody and Yager (1997). They used the mixture of water with small fluorescent dye carboxyfluorescein (CF) and fluorescent spheres (0.5 μm diameter) in an H-shaped microchannel. Mary et al. investigated mass transfer between moving water droplets and octanol as an external phase in a rectangular microchannel which was 250 μm wide and between 30 and 95 μm for the height (Mary et al., 2008). They examined the influence of many parameters as flow rates, channel dimensions, viscosities, droplet spacing, and drop size.

Regarding the materials the microfluidic devices are made of, they are usually quartz, silicon, glass, metals, PDMS (Polydimethylsiloxane) or PMMA (poly methyl methacrylate) (Tabeling, 2005, Fries et al., 2008, Whitesides, 2006). However, the use of the material strongly depends on costs, compatibility of the devices with reagents and solvents, and detection techniques. The most common polymer used is PDMS because it is chemically inert and transparent, flexible and has a low cost.

The extraction of orange (II) + methyl blue into ionic liquid droplets ([EMIm][NTf2]) has been recently reviewed by Barikbin et al. (2010). Their PDMS microfluidic device has a rectangular shape with a width, height, and length of 300 μm, 155 μm and 0.45 m, respectively. In another study described by Maruyama et al. (2003), p-chlorophenol was extracted with isooctane/laccase and succinic acid buffer in a glass microchannel.

These devices can be classified into different groups based on the shape or type of junction such as X, H, T, Ψ, and Y/S shaped (Nandagopal et al., 2016, Novak et al., 2015, Jiang et al., 2018, Wang and Luo, 2017). However, the two most common shapes in microfluidic devices are T and Y-Y.

Dessimoz et al. (2008) studied the mass transfer performance and flow patterns between two immiscible liquids (deionized water and dyed toluene (or hexane)) in T- and Y-shaped rectangular glass microchannels. For the Y-shaped glass microfluidic devices with a guideline structure, the same study was performed by Tagawa et al. (2007). In this study hydrolysis of benzoyl chloride was selected as a model for performing organic–aqueous reactions.

2.3 Usual applications

The liquid-liquid extraction process using microfluidic devices is a well-explored method. Because of the importance of this subject and its applications, several articles have been published. So that, from the beginning of the 20th century, more than 200 articles have been published applying microfluidic devices to improve the liquid-liquid extraction. Some applications of this process can be summarized as follows:

1. To prevent the thermal decomposition of materials; in which, extraction can be a good alternative to distillation or evaporation, e.g., in the Biological and Pharmaceutical industries.
2. To separate metal ions from dilute solutions, which can even compete with other chemical methods in the mineral industry.
3. In cases where the vapour pressure of the components is close to each other (volatility coefficient near 1), e.g., in separation of chemical products.
4. In processes where separation by conventional liquid-liquid extraction methods are performed with difficulties by choosing a suitable and novel solvent e.g., in ionic liquids (IL) or aqueous two-phase systems (ATPS) it leads to relative separation of the material.

2.3.1 Pharmaceutical and biological application:

With regards to versatility and efficiency of these devices, much effort has been put into the extraction of compounds from biological media. For example, they have been applied in the separations of organic molecules, cells and dyes (Mu et al., 2010, SooHoo and

Walker, 2009, Nichols et al., 2011, Kamat et al., 2018, Sun et al., 2006). In particular, Miyaguchi et al. (2006) have described the liquid-liquid extraction for gas-chromatography analysis of amphetamine-type stimulants in a microchip-based in a 1-chlorobutane/ alkalinized urine (complex matrix) system for forensic toxicology, see Figure 1.

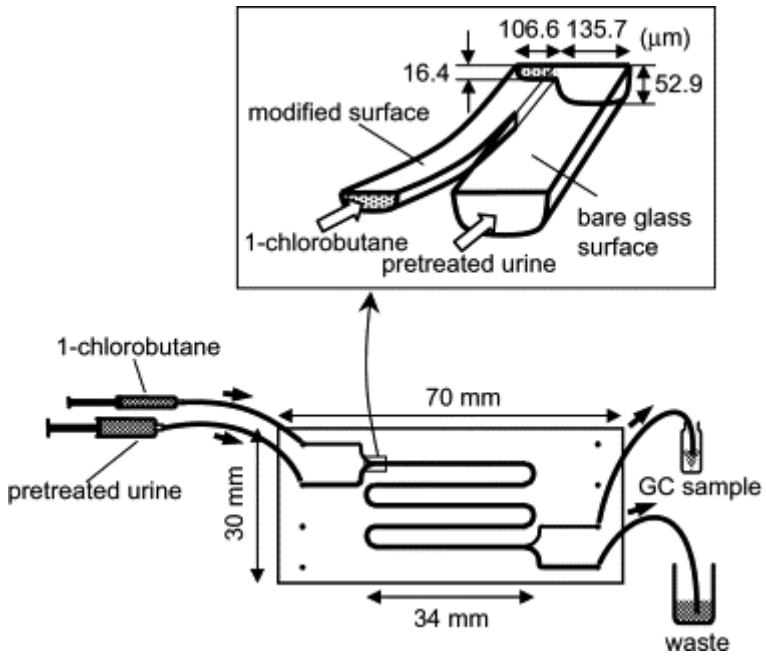

Figure 1. Sketch of a microchip for liquid-liquid extraction. Reprinted with permission from Miyaguchi et al. (2006).

The same extraction was studied by using serpentine microchannels by Hu et al. (2011) to purify membrane proteins from crude cell extract. To evaluate this method, different separation and detection methods were applied with an aqueous polyethylene glycol/detergent two-phase system.

2.3.2 Separation of metal ions

The most important applications of liquid-liquid extraction using microfluidic devices have done in the separation of metal ions. As a practical application, these devices have been applied to the extraction of cobalt, copper, nickel, iron, or rare earth metal ions (Dai et al., 2017, Jiang et al., 2018, Luo et al., 2017, Ciceriet al., 2014, Xie et al., 2019).

Kurniawan et al. (2018) reported on the selectivity of the diethylamide derivative as an extraction reagent to extraction Pb(II) ion over several other metal ions. Their results show that using a microfluidic reactor (see Figure 2), an extraction time of around

2 seconds can be achieved. Another illustration of extraction was given by Minagawa et al. (2001), who combined a wet analysis on a glass chip with m-xylene/2-nitroso-1-naphthol chelates system to extract Co(II) ions.

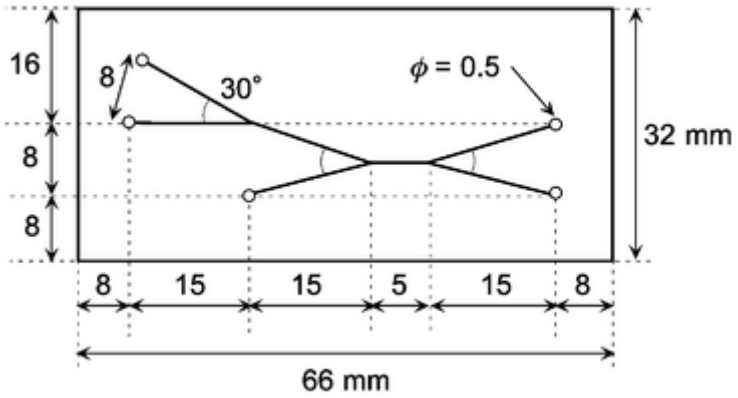

Figure 2. Sketch and dimensions of the microdevice used in Minagawa et al. (2001). The microchannels are 100 µm deep and 250 µm wide. Reprinted with permission.

2.3.3 Separation of chemical products

In the context of traditional liquid-liquid extraction, this process has been done using microfluidics devices by many researchers (Kashid et al., 2010, Kashid et al., 2007, Zhao et al., 2007). Up to now, different extraction systems in microchannels have been investigated. In particular, Das et al. (2015) showed that to improve the liquid-liquid extraction efficiency of phenol from silicone oil to water in multiphase droplet-based microfluidic reactors (as the one shown in Figure 3), the relative effect of flow rates of the external continuous phase to dispersed oil phase is higher than others.

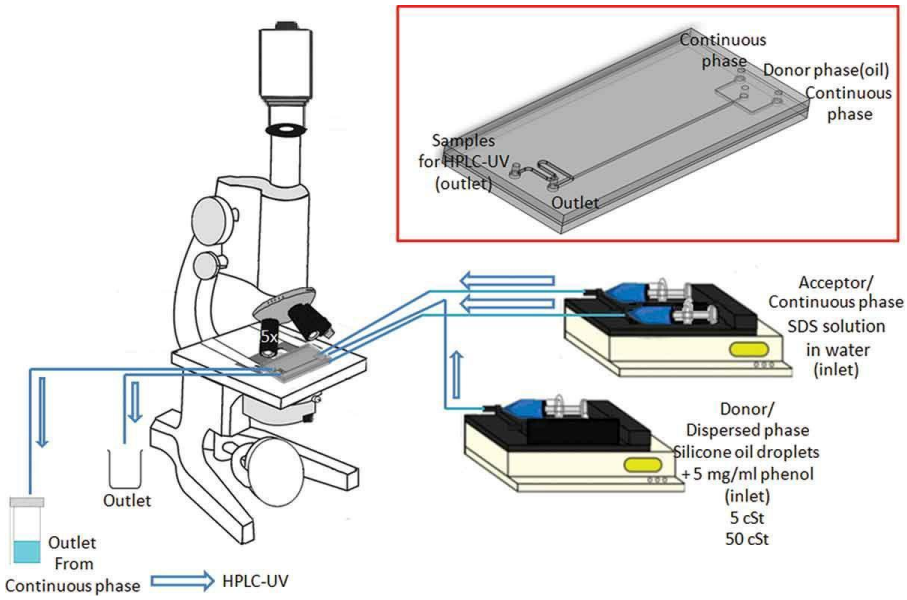

Figure 3. Experimental set-up used in Das et al. (2015). The inset shows the microdevice made of PMMA. Reprinted with permission.

The comparison of microchannels and conventional stage-wise extractors for liquid-liquid extraction using a water/succinic acid/n-butanol system was studied by Singh et al. (2015). Furthermore, they showed that maximum volumetric mass transfer coefficient and specific extraction rates could be easily achieved.

2.3.4 Separation by novel solvent systems

In recent years, to meet environmental sustainability goals, novel and greener solvents have been proposed. Among them, ATPS ionic liquids (IL), and supercritical fluids (SCF) can be found in extensive works on liquid-liquid extraction (Tsaoulidis et al., 2013, Abbasi et al., 2018, Soares et al., 2017).

The concept of using ATPS to separate and purify bovine serum albumin (BSA) from polyethylene glycol 4000 and ammonium sulfate in a coaxial capillary microfluidic device has been presented by Huang et al. (2014) (see Figure 4). They showed that with just three cycles to extract BSA, a recovery yield of around 70% can be achieved in just 3.6 s.

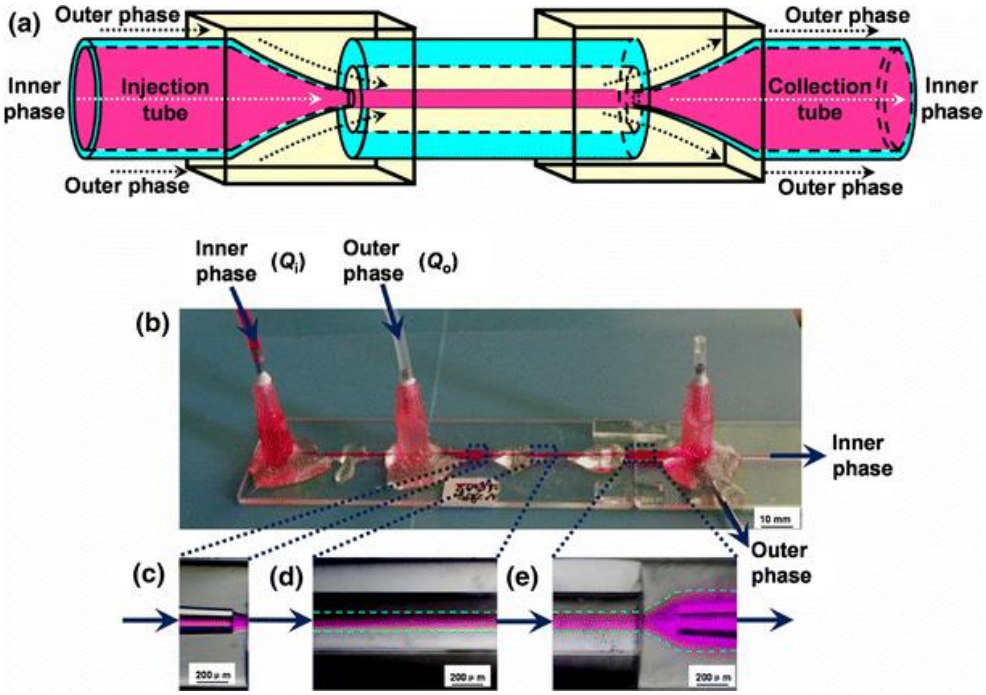

Figure 4. (a) Sketch of the coaxial capillary microfluidic device. (b) Photo of the microdevice: Q_i is the inner phase flow rate and Q_o is the outer one. (c)-(e) represent, respectively, the injection tube, the cylindrical glass capillary tube, and collection tube. Reprinted with permission from Huang et al. (2014).

On the other hand, Fukuyama et al. (2009) studied the radical-based carbonylation reaction of alkyl halides via tributyltin hydride, or tris(trimethylsilyl)silane (TTMSS), under pressurized carbon monoxide gas in a T-shaped microfluidic system.

3 Microdevices for separation of biological samples

3.1 Introduction

Biotechnology applications are one of the most outstanding areas of Microfluidics. The capacity of scale reduction of biological systems jointly with the accomplishment of multiple experiments in a single chip is a very attractive concept, arising great interest of academic community.

This section is devoted to present different techniques and microfluidic devices to deal with separation of biological samples usually present in processes related with deoxyribonucleic acid (DNA), ribonucleic acid (RNA), acid drugs, parallel genetic analysis, blood samples, disease diagnosis or blood plasma, among others.

3.2 Usual applications

Gumuscu et al. (2017) developed a low cost and easy manufacturing microdevice made of glass, for ultrafast separation and purification of DNA. The new chip was capable to perform DNA fragmentation in only few minutes, while conventional approaches could take hours. The microfluidic device also presents high resolution and fragment purification, removing salts from the DNA sample. Low amounts of DNA, as used in medical diagnosis and forensic medicine, are sufficient. Figure 5 presents a description of the microfluidic chip. The support chip consisted in three main parts: The bottom part, that includes a glass window allowing to observe the DNA fragmentation in epifluorescent inverted microscopes. The medium part presents slits acting as buffer reservoirs directly contacted to the buffer reservoirs in the microchip. These reservoirs are filled with buffer solution to allow contact with platinum wires. The top part has orifices to align the platinum wires with the centre reservoirs. The wires are connected to an electric source.

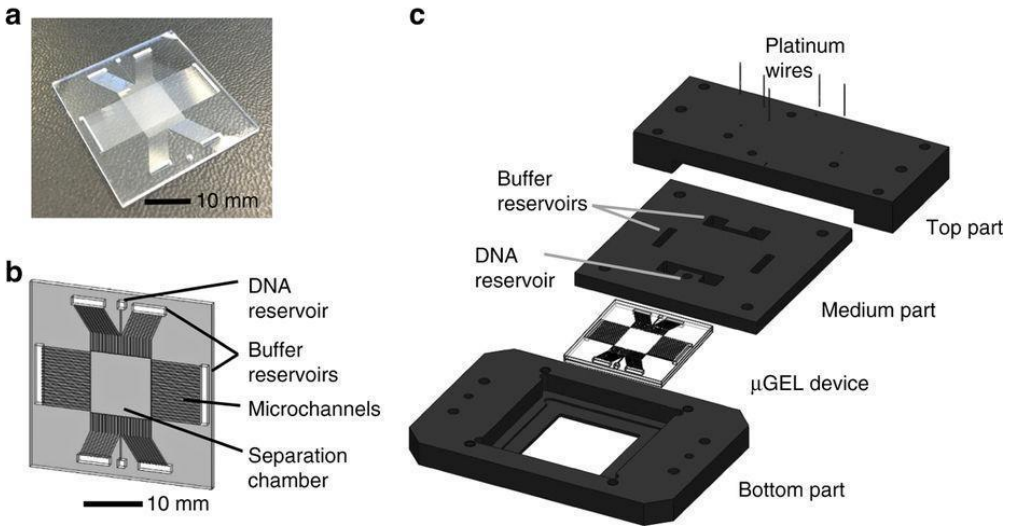

Figure 5. Microdevice design used to separate and fragmentate DNA samples: (a) glass microdevice, (b) microchip layout (reservoirs indicated), (c) support made of Delrin and its schematics. Reprinted from Gumuscu et al., 2017.

Ramos-Payan et al. (2016) studied extraction and determination of acid drugs using a microfluidic-based liquid-phase microextraction device. The liquid-phase microextraction was combined with high performance liquid chromatography procedure. The developed devices exhibited extraction efficiencies higher than 87% and 72% for all tested acid drugs in urine and environmental samples, respectively. The microdevices consisted in two symmetric plates of polymethacrylate with inlets and outlets. The front

side contained a channel with donor solution (sample). The rear side was employed as the acceptor channel. The channels were 13 mm long, 80 µm deep and 2 mm wide.

A common technique used in biological separation is the electrophoresis. According to Fritsch and Krause (2003), electrophoresis is a general term used to describe migration and separation of charged particles (ions) under the influence of an electric field, i.e. this technique can be used to separate charged particles based on the difference of their migration velocities.

Pan et al. (2010) developed a simple integrated microdevice (Figure 6) with multiples polymerase chain reaction (PCR) chambers and multiple separation channels based on chip electrophoresis (CE) for parallel genetics analysis. The microdevice presented temperature control. The PCR product was introduced in the CE channels, where the electric field promoted separation and detection. According to the authors, using parallel channels allows easy determination of the exact size of the PCR products adding DNA markers and semi-quantitatively measuring of DNA sample concentration. The results suggested the potential application for qualitative DNA analysis.

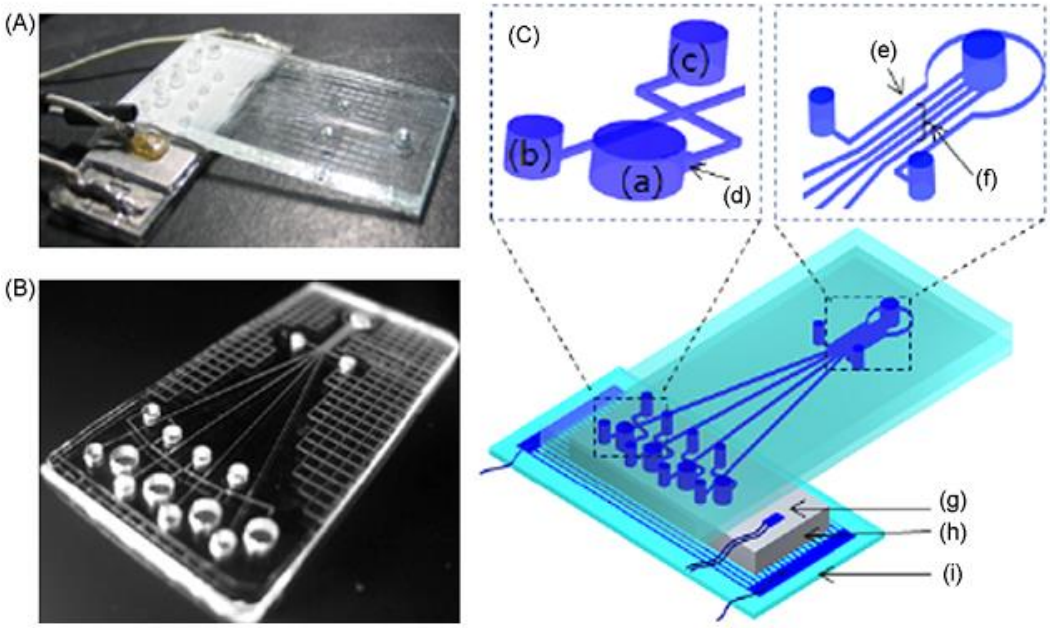

Figure 6. Integrated microdevice with multiple PCR chambers and multiple electrophoresis-based separation channels. Reprinted with permission from Pan et al., (2010).

Li and Bashir (2002) using dielectrophoresis (DEP, i.e. dielectric particles motion in a non-uniform electric field) to develop a separation system for live and heat-treated *L.*

innocua cells in water. The efficiency was 90% applying a signal of 1 V at 50 kHz. The authors manufactured interdigitated microelectrodes in a glass surface. The electrodes width and spacing between adjacent electrodes were 15 µm (Figure 7). Bisceglia et al. (2010) proposed a microdevice for bacteria (*Escherichia coli*) and yeast (*Candida albicans*) separation from blood samples. These microorganisms can be handled in the microdevice and consequently separated from red and with globules using dielectrophoresis in low conductivity media (deionized water). The results showed that for a signal frequency of 20 MHz, 92% of the microorganisms experienced a DEP+ force, being concentrated at the electrodes edges. Simultaneously, altered red globules experienced a DEP- force and were grouped at the microdevice centre, above the electrodes centre. The microdevice consisted in an assembly of interdigitated electrodes, coated with an isolation layer and a microfluidic chamber. The electrodes arrangement consisted in 5 electrodes pairs (width = 90 µm and gap = 10 µm), coated by silica (isolation) to minimize the electrochemical reaction occurrence with the electrolyte and to allow the maximization of microdevice service lifetime.

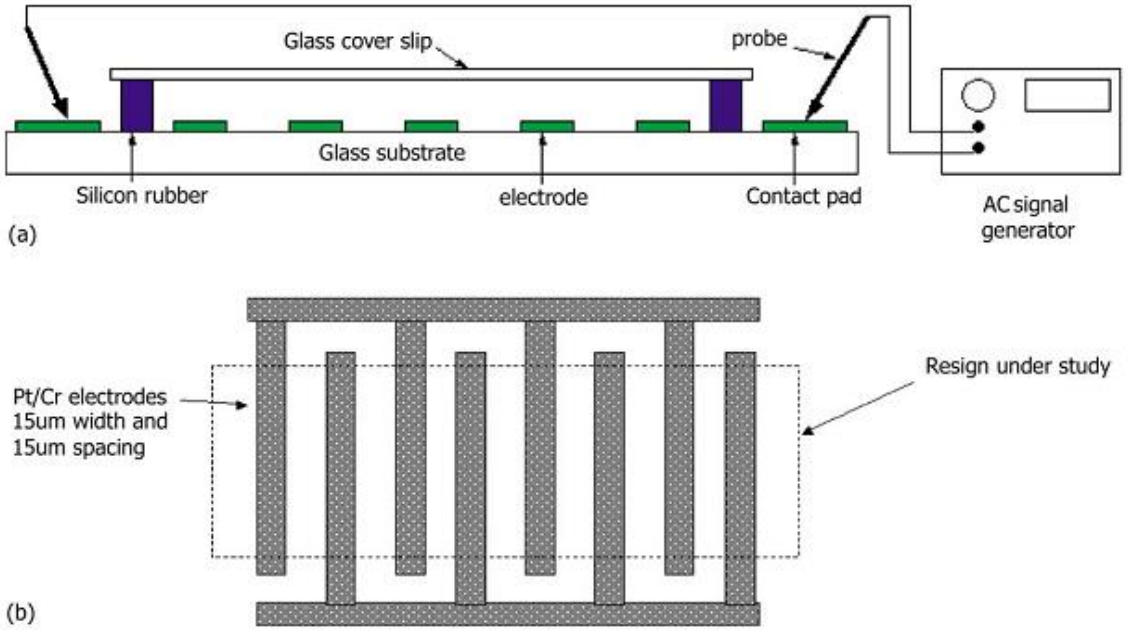

Figure 7. (a) Microdevice developed by Li and Bashir (2002), (b) superior view of the interdigitated electrodes. Reprinted with permission.

The human blood plasma provides crucial information about disease diagnosis. The plasma is the liquid portion of the blood, being about 55% of overall blood content and it

plays a critical role in several health problem treatments. Accordingly, various researchers proposed microdevices to perform blood plasma separation. Tripathi et al. (2013) highlighted some advantages of portable devices including a faster analysis, requirement of low amounts of samples and reactants and ensuring an *in loco*, real time monitoring of the patient.

Chen et al. (2014) developed a microdevice for blood plasma separation based on a gradual filtration process using a two-layer cell-capture/back-end filters arrangement. The first layer has pillars to provide small gaps between the second layer and a glass layer. The plasma flowed through the spacing, while the blood cells were retained due to the larger volume. The authors tested two filter configurations (straight line filter and square wave filter, with widths of 22 µm and 5 µm, respectively – Figure 8). The square wave filter exhibited superior performance. The microdevice was made of PDMS (polydimethylsiloxane) via soft lithography. The blood was dilute at different factors (10, 20, 50) to evaluate the separation efficiency. The plasma separation efficiency increased with the dilution factor, decreasing with the gap height increment and being the separation efficiency close to 100%.

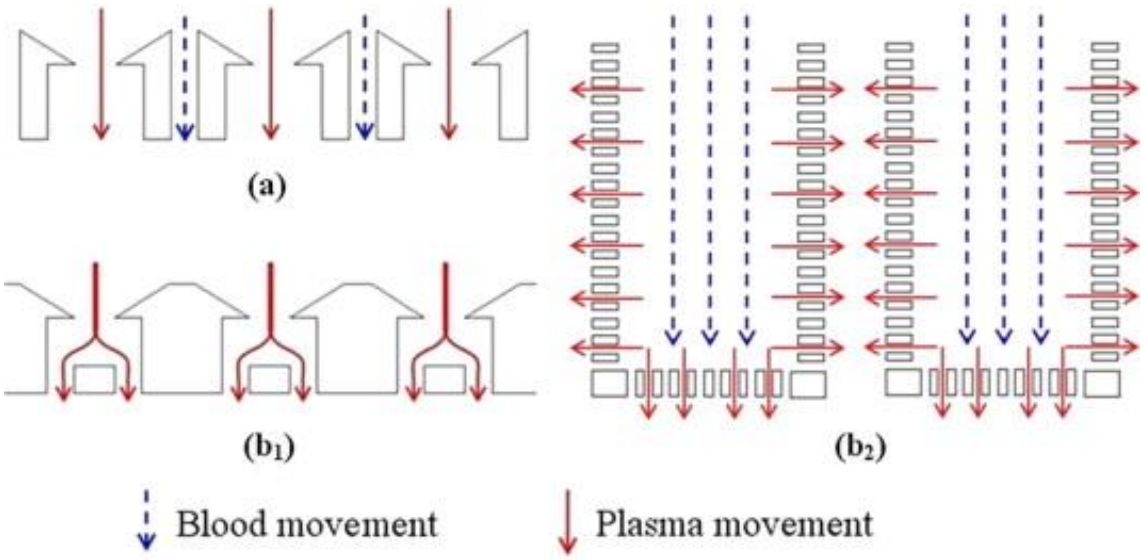

Figure 8. Design of the: (a) cell-capture structures, (b_1) straight line filter, (b_2) square wave filter. Reprinted with permission from Chen et al., (2014).

Rodrígues-Villareal et al. (2010) proposed a microfluidic separation device to work under high flow rates of blood. The device uses fluidic focusing and particle dispersion in the separation (Figure 9). Also, the design employed a channel cross section reduction, narrowing the blood flow stream, enhancing the blood cell deformability. The narrow

stream of blood cells flows from the wider channel to a lateral channel where the plasma was collected. The superior result, 97.05% of cell separation, was observed at higher flow rate (200 µL min^{-1}) at 37 ºC. All channels have a depth of 40 µm. The width of inlet and outlet was 400 µm, while the lateral channel presented an inlet zone 65 µm wide and 800 µm long and an outlet section 200 µm wide and 2000 µm long.

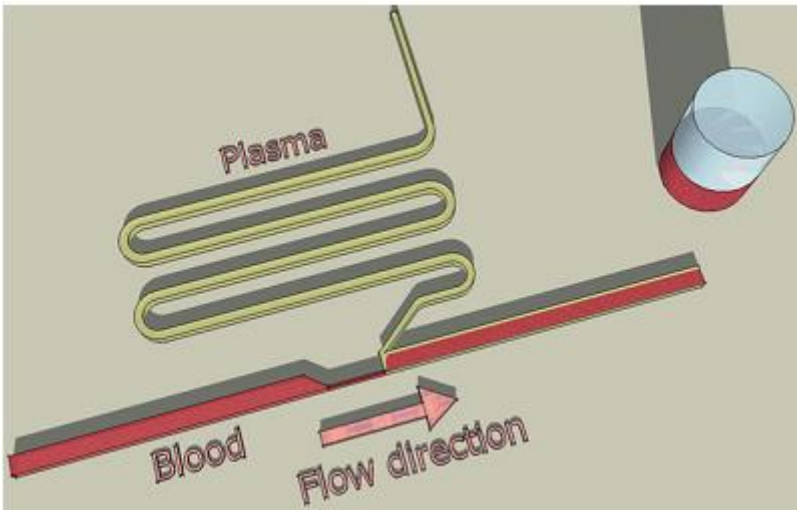

Figure 9. Sketch of the microdevice. Blood direction and plasma separation after the channel constriction. Reprinted with permission from Rodrígues-Villareal et al., (2010).

Vaghi et al. (2016) applied surface functionalization in microchannels for viral RNA purification. The plane surfaces made of PDMS were modified to adsorb RNA. Careful chemical and morphological analyses were carried out in the modified surfaces, and the functionalization protocol that provided superior RNA adsorption was employed in the PDMS microdevices. Nam et al. (2011) proposed a microdevice based on standing surface acoustic waves (SSAWs) for high purity separation of platelets from blood using whole blood without dilution. The device (Figure 10) was composed by interdigitated transducers (IDTs), microchannels and hydrodynamic focusing technique. The sample and sheath flow rates were 0.25 µL min^{-1} and 5 µL min^{-1}, respectively. The platelets purity at outlet (A) reached 98%.

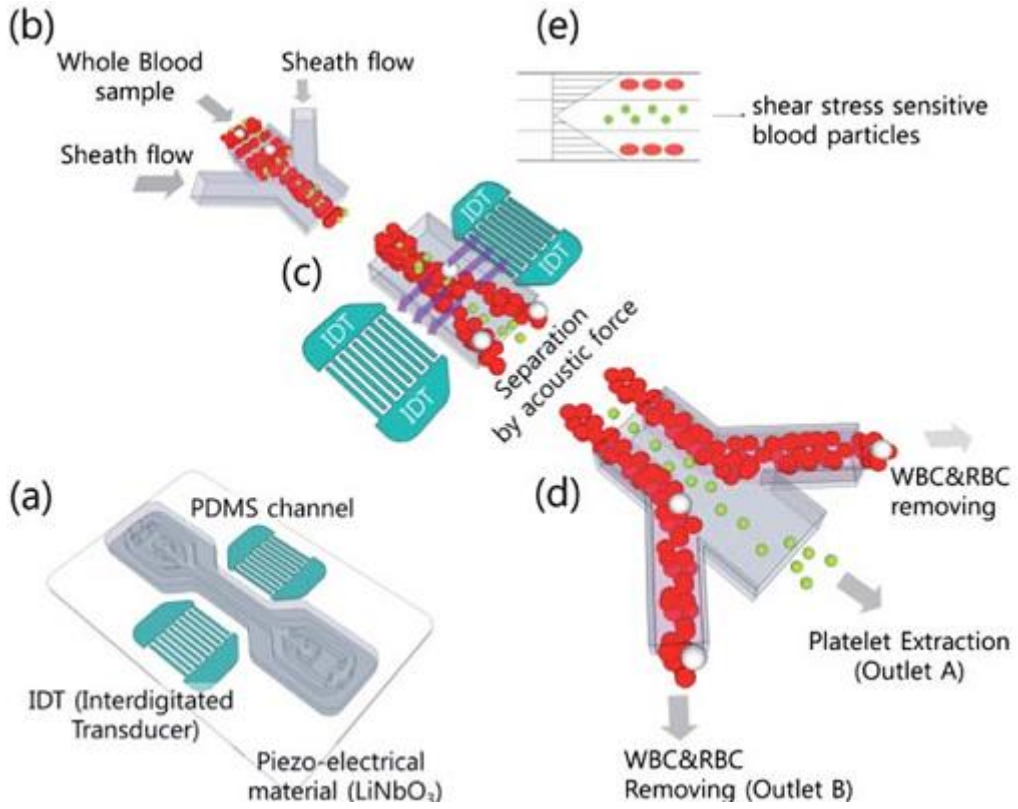

Figure 10. Platelet separation from whole blood in a microdevice with acoustic system: (a) schematics of the acoustic device with a pair of IDTs, (b) whole blood sample is injected and hydrodynamically focused by two sheath flow layers, (c) separation of blood particles in the working region of SSAWs by means of a size-gradient manner - large particles (red and white blood corpuscles) are driven to the side of the channel instead of the small particles, (d) platelets are mainly sorted and collected through the center outlet, (e) platelets are designed to flow in the middle of the channel, where the shear effect is minimized. Reprinted with permission from Nam et al., (2011).

Tripathi et al. (2013) demonstrated the plasma separation using hydrodynamic separation in microchannels with size scale orders of mm. The authors demonstrated an interesting application of the Zweifach-Fung bifurcation law in length scales much superior than the suspended particle size. The microdevice worked under a constant flow rate of 0.15 mL min^{-1}. The authors evaluated the haematocrit level and the flow rate distributions. The results demonstrated a separation efficiency increment with the increase on flow rate and the dilution of the blood samples (i.e., the separation efficiency increased with the decrease on haematocrit level), achieving 100% of separation efficiency at low haematocrit levels. Figure 11 presents the process separation and the design of the T-shape microchannel. The device has a blood sample inlet and two outlets for plasma and

concentrated blood cells. The authors used higher Peclet numbers to provide the formation of blood cell clustering. The cell agglomeration flowing near the microchannel bifurcation promoted the high efficiency separation.

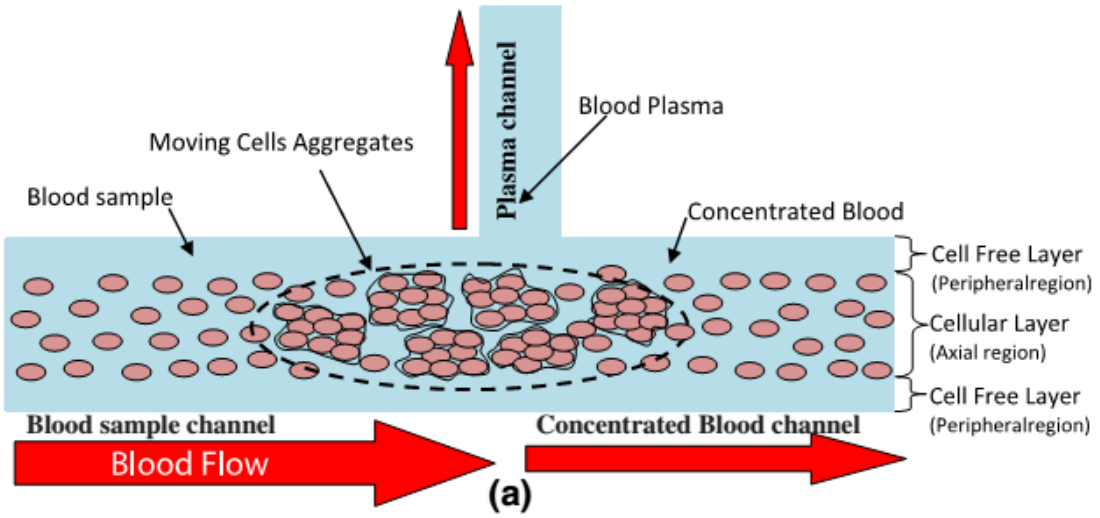

Figure 11. Blood plasma separation process in a T-shape microchannel. Reprinted with permission from Tripathi et al., (2013).

Forchelet et al. (2018) have developed a device for separating blood micro-samples using a basic microfluidic principle: laminar flow. The device allowed the separation of 25 μL of undiluted blood samples in complete passive manner, without requiring additional or external equipment: both separation and pumping are passive mechanisms. Whole blood is separated into liquid and waste cells by using a separation principle which is based on viscosity differences. They, the viscosity differences, are promoted by sedimentation and simultaneous capillary driven laminar flow. The manufacture of the microfluidic device was based on standard lithographic processes. The device consists of two parts: the top one contains the impression of the structure, while the bottom one is flat which is modified with surfactant in order to obtain adequate capillary pressure in the device. Each area performs a specific function: separation of blood samples and ejection of a sample free of output cells with volume measurement, respectively. When flowing in the separation area, the cells present in the sample, thanks to the action of gravitational forces, sediment towards the bottom part of the channel, which does not present any complex structure.

4 Water Purification

This section approaches recent advances in water treatment and desalination using membrane technology and electrochemical and photocatalytic microreactors.

4.1 Membrane Technology

Membrane technology has been widely used in water purification and desalination. The great advantage of membrane technologies is the achievement of high-quality water without requiring relative less chemical treatment or energy consumption regarding traditional distillation methods. Membrane separation can be divided in low pressure operation: Microfiltration (MF) and Ultrafiltration (UF), and high pressure operation: Nanofiltration, (NF) and Reverse Osmosis (RO). The main characteristics of these membranes are summarized in Table 1.

Table 1. Main characteristics of membrane technologies with representative ranges.

Process	Driving Force Range[a]	Membrane type, pore size range	Molecular Weight Cut-Off, MWCO (Da)*
MF	0.5-2 bar	Porous, 0.1-0.8 μm[a]	> 100,000[c]
UF	2-6 bar	Porous, 1-10 nm[a]	> 1,000[a]
NF	5-15 bar	Semipermeable, ≤ 1 nm[b]	200-500[a,b]
RO	10-60 bar	Semipermeable	< 200[c]
* The MWCO represents the chemical species molecular weight rejected (or retained) by the membrane. a: Petrus and Tessaro (2016); b: Mohhamad et al. (2015); c: Prudich et al. (2008).			

Low pressure-driven processes (MF and UF) are performed in porous membranes and are usually employed as pre-treatment stages to remove suspended particles and macromolecules. Convective transport and size exclusion mechanisms prevails in MF and UF. In MF, small particulate solids, microbial cells and large colloids are retained. UF membranes reject colloids, emulsion, proteins and macromolecules (Petrus and Tessaro, 2016). In NF and RO membranes, molecular diffusion transport and solute-membrane matrix interactions occurs, including size and charge exclusion, approaching separation at molecular and ionic levels (Malaeb and Ayoub, 2011). The scope of this section was to present the main features of high pressure-driven membranes.

Fouling is a main limiting factor in NF and RO applications and can be divided in surface and internal fouling. The fouling mechanism differs from low pressure-driven to high pressure-driven membranes. For MF and UF, pore clogging or adsorption are more common. For NF and RO, surface fouling is more frequent due to the dense nature of the

membranes (Malaeb and Ayoub 2011). Depending on feed water composition and their interactions with the membrane, fouling can be irreversible (Jiang et al. 2017). Accordingly, feed water pre-treatment is necessary to prolong membrane lifetime and prevent its fouling. Pre-treatment usually consists of chemical coagulation, filtration (including UF and MF) and scaling control. Membrane fouling can occur due to inorganic or mineral scaling, organic fouling, microbial growth and colloidal and particulate deposition (Badruzzaman et al., 2019, Malaeb and Ayoub, 2011). Anti-fouling pre-treatment strategies are widely discussed by Mohammad et al. (2015) for NF and by Badruzzaman et al. (2019) and Jiang et al. (2017) for RO. Several metal and metal oxide nanoparticles (zeolites, titanium dioxide) have been incorporated into polymeric matrix of NF membranes, improving mechanical and thermal characteristics, anti-fouling and anti-bacterial properties. Titanium dioxide has been widely used as antifouling in membrane preparation, due to its hydrophilicity, repeling hydrophobic foulants (Damodar et al., 2009) and photocatalytic behavior, aiding the degradation of organic compounds from water. Carbon-based nanomaterials (e.g., carbon nanotubes, CNTs and graphene) are also employed in NF membranes. These materials present hydrophobic and excellent water transport characteristics due to smooth inner walls. Mixed matrix membranes prepared by CNT addition exhibit enhanced separation and antifouling characteristics. Borg et al. (2018) and Majumder et al. (2005) performed molecular dynamics (MD) simulations in CNT with diameters below 10 nm. Both researches observed water fluxes about 2-5 orders of magnitude greater than Hagen-Poiseuille predictions. Recently, metal-organic frameworks (MOF) emerged as potential nanoporous material for NF membrane preparation. The main characteristics are high surface area-to-pore volume ratio, tunable chemical structure and surface properties. Sorribas et al. (2013) observed an increment in the solvent permeance into MOF membrane regarding a conventional polymeric membrane without sacrificing the rejection due to preferential flow paths. However, structural stability and species separation performance should be further improved.

Traditionally, water desalination is carried out using Multistage Flash (MSF) or RO. The two main issues related to RO membranes are the membrane fouling and the energy consumption (about 44% of the produced water cost) related to the high operating pressure. Recently, hybrid process using NF as a pre-stage for RO desalination allowed an increment about 60% in water production and costs reduction around 30% regarding traditional RO and MSF processes (Mohammad et al., 2015). Song et al. (2012) used UF-

NF pre-treatment process for total organic carbon (TOC) removal, removing 96.3% of the TOC. Membrane fouling was observed even after chemical cleaning. A dual stage NF process was investigated by Harrison et al. (2007) using bench and pilot scales by Long Beach Water Department to produce potable water, resulting in the reduction of energy consumption regarding a NF-RO unit. The energy consumption in RO process can also be reduced using energy recovery systems, such as Pelton wheel or pressure exchangers using the brine stream (Malaeb and Ayoub, 2011). Khawaji et al. (2006) reported an energy consumption reduction from 6-8 to 4-5 kWh/m^3 and a potential optimization to 2 kWh/m^3 when using energy recovery systems. Furthermore, hybrid system using renewable energy sources have been used. Latorre et al. (2015) observed a power input reduction 20% lower than the original RO plant when using a wind turbine. Murat (2018) evaluated a hybrid system composed by a wind-photovoltaic-diesel-battery in a small-scale RO. The results showed an effective method for production of potable water in remote areas with good wind and solar power characteristics.

Despite the advances in membrane technology, further developments are required in membrane fouling control, brine disposal and new materials for membrane, e.g. the use of titanium dioxide allows a synergetic effect of photo-degradation of organic compounds from water, or the use of CNTs improving the permeate flux across the membrane. The use of hybrid systems, including mechanical energy recovery devices and renewable energy sources, presents great potential aiming costs reduction in water treatment. Numerical simulations appear as fundamental tools for development and analyses of such systems, approaching from molecular dynamics to macroscopic energy and exergy analyses.

4.2 Electrochemical Technology

Electrochemical technologies appear as a promising technique for wastewater treatment. The main challenge is to reduce the energy consumption, especially in the purification of low-conductive affluents. The energy consumption is directly related to the overall electrical circuit ohmic resistance, or ohmic drop, and it strongly depends on the electrode cell design. The ohmic drop is due to energy dissipation, deprecating the cell performance and it is directly related to the inter-electrode (IE) gap – the spacing between the electrodes. The main contribution to ohmic drop increment is the low conductivity of electrolytes regarding other system components. The electrolyte conductivity can be

largely increased, by the increment in electrolyte concentration. However, this leads to secondary pollution, since the inorganic compounds were carried out in effluent resulting in operational costs increment (Perez et al., 2018, Scialdone et al., 2014a). Recently, the use of microfluidic devices allowed the use of small IE gaps, usually below 1000 μm resulting in superior performance. Microfluidic devices also present higher current efficiencies in oxidation processes due to the mass transfer enhancement (Scialdone et al., 2014a-b, 2013).

Continuous electrochemical reactors present two main flow arrangements (Figure 12): Flow-By (FB) and Flow-Through (FT). In the FB configuration, the electrolyte fluid flows between parallel-plate electrodes. The reduction of IE gap increases the pressure drop, limiting the flow rate. Moreover, this configuration could present clogging problems when working under high current densities and gas evolution reactions (Bouzek et al., 2010). In the FT configuration, the electrolyte fluid flows across 3D electrodes (meshes, foams or packings). This configuration allows advantages of simultaneous minimization of ohmic drop and maximization of mass transfer, avoiding the operational problems observed in the FB. Moreover, the addition of activated carbon or metal particles inside the IE gap contributes to the enhancement in conductivity, mass transfer and adsorption of the pollutants, allowing superior removal performance (Zhang et al., 2013, Wei et al., 2010). The electrochemical oxidation of pollutants is generally divided in two categories: direct and indirect oxidation. In the first, the electron is directly transferred on the anode. In the indirect mechanism, radical species are generated from water electrolysis, as for example, the electro-Fenton process (Zhang et al., 2013).

In 3D electrodes, three mechanisms could act in the electrochemical oxidation: adsorption/electrosorption, catalytic degradation by oxidation and electrocoagulation. Adsorption and electrosorption occur due to the packing high specific area combined with the electric charge. Catalytic degradation by oxidation is due to the formation of polarized microelectrodes, comprehending direct and indirect oxidation. The addition of some metals, e.g., Fe^{2+}, induces electro-Fenton reactions (indirect oxidation), enhancing the catalytic degradation performance. Electrocoagulation is used to remove macromolecular hydrophobic substances. It is based on the use of iron or stainless steel anodes or particle electrode producing iron hydroxide. The major drawback is the iron sludge generation, requiring a final disposition.

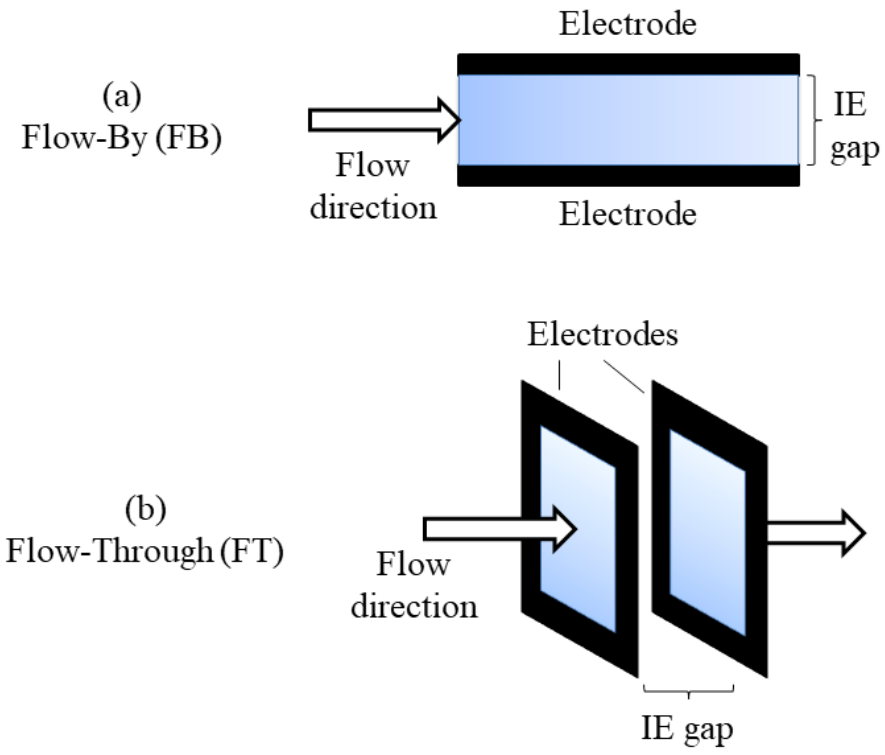

Figure 12. Electrochemical reactor configuration: (a) Flow-By; (b) Flow-Through.

The anode material plays a fundamental role affecting the catalyst activity and selectivity and the current efficiency. Thin oxide films (PbO_2, SnO_2) experience activity loss due to surface fouling or relative short service lifetime (Bagastyo et al., 2011). Metal oxides, including RuO_2, IrO_2, present long service life, good activity and are relatively inexpensive. Boron-doped diamond (BDD) appears as an ideal anode for wastewater oxidation, due to its long lifetime, stability and mechanical characteristic; however, it is more expensive than metal oxides (Zhang et al., 2013). The cathode is usually composed by metals or carbon materials, including stainless steel, activated carbon fibre and graphite. Granular activated carbon (GAC) is the most frequently used particle electrode due to its advantages of large specific area, pore structures and adsorption loading capacity (Berenguer et al., 2010). The use of GAC in wastewater treatment promotes a synergetic combination of adsorption and electrosorption, promoting high removal of organics. Future perspectives include supported catalysts. Common catalyst support includes alumina, molecular sieves, zeolites and ion-exchange resins. Heterogeneous Fenton catalyst solves the drawback of iron sludge disposal after treatment, eliminating additional separation steps (Zhang et al., 2013). Arena et al. (2017) manufactured a 3D-printed, highly ordered porous electrode, made of a nickel-coated stainless steel. The

printed electrode was used in electrochemical cell applications. Its performance was evaluated by optical microscopy, electrochemical and mass transport characteristics. The 3D-printed electrode mesh exhibited tailored composition, good characteristics of catalytic activity, active surface area, fluid flow and mass transfer. The authors highlighted the potential use of multi-material additive manufacturing, opening a possibility of a versatile fabrication of specific designed electrochemical reactors.

Scialdone et al. (2011) listed some advantages of microdevices over macroscale reactors, including easier scale-up procedure using parallelization, fast operating conditions optimization, due to the small IE gaps and relative short residence times, potentially use of multistage system with two or more electrochemical cells arranged in series working under optimal current densities and consequently minimizing the treatment time. Scialdone et al. (2011) also proposed a micro-electrochemical cell composed by two plate electrodes of BDD/Nb (anode) and nickel (cathode). The IE gap was ranged from 50-75 μm. The oxidation of formic acid (FA) was performed. High levels of FA oxidation were observed for low flow rates (long residence times) and high current densities. An abatement level of 99% of formic acid was obtained at 13.3 $mAcm^{-2}$, 0,05 mL min^{-1} for a IE gap of 50 μm.

Scialdone et al. (2014) employed macro- and micro-fluidic cells for the electrochemical abatement of chloroacetic acid (CAA) using direct and indirect oxidation pathways. The system I was composed by a stirred batch glass cell with electrodes plates of 3 cm^2 (Pt sheet or BDD thin-film anode and a carbon-PTFE-air diffusion cathode, where PTFE stands for Polytetrafluoroethylene) with an IE gap of 1 cm. The system II consisted in undivided filter-press reactor (ElectroCell AB, Tarm, Denmark) working in continuous regime. The electrode plates have 10 cm^2 of area. Ti/IrO_2-Ta_2O_5 or BDD anode and compact graphite, Ag, Cu or stainless steel (AISI 304) cathode were used. The IE gap was 4 mm. Also, a single-pass microreactor (System III) was used, operating under 0.05 – 0.6 mL min^{-1}, equipped with the ElectroCell AB jointly with PTFE spacer providing IE gaps ranging between 50-100 μm. The electrode working areas were 5 cm^2. A superior CAA abatement was observed in the microfluidic cell for the indirect oxidation, even in the absence of supporting electrode (an essential key in the macro-cells to obtain a significant abatement). The direct oxidation path provided high abatement levels in macro and micro-cells. Coupled oxidation processes were evaluated, leading to superior CAA abatement performances regarding single processes. The coupled process using a BDD

anode and graphite cathode with iron sulfate resulted in faster and higher abatement level (above 90%) under low current densities (< 5 $mAcm^{-2}$) in the microfluidic reactor with a IE gap of 100 μm.

Perez et al. (2018, 2017) proposed a flow-through microreactor (FTMR) (Figure 13) with different IE gaps (6,000-1,000 and 400 μm) using electrolyte conductivity ranging from 0.7 to 40.1 mS cm^{-1}. The microreactor was composed by RuO_2/IrO_2 coated titanium-mesh cathode of total size 8 x 9.5 cm. The surface area was 52.8 cm^2. The anode was composed by a thin-film BDD electrode supported in a niobium mesh with total size of 8 x 9.5 cm. The estimated anode surface area was 49.5 cm^2. The FTMR performance was compared with a stirred tank (ST) reactor with parallel plate electrodes (IE gaps of 25,000-6,000 and 1,000 μm) working with similar electrolyte concentrations. The FTMR required a lower cell voltage regarding the ST. The IE gap reduction did not influence the pressure drop. The electric charge was 4-10 times lower and the energy consumption was 6-15 times lower for the mineralization of 100 ppm of the clopyralid. The estimated mass transfer coefficient was 70% higher than in a conventional reactor. The ohmic resistance in the 0.7 mS cm^{-1} solution was 6 Ω at 400 μm, against 346 Ω for the ST at 25,000 μm (a common gap in lab-scale reactor). For similar IE gap of 1000 μm, the ohmic resistances for FTMR and ST were 11 Ω and 61 Ω, respectively.

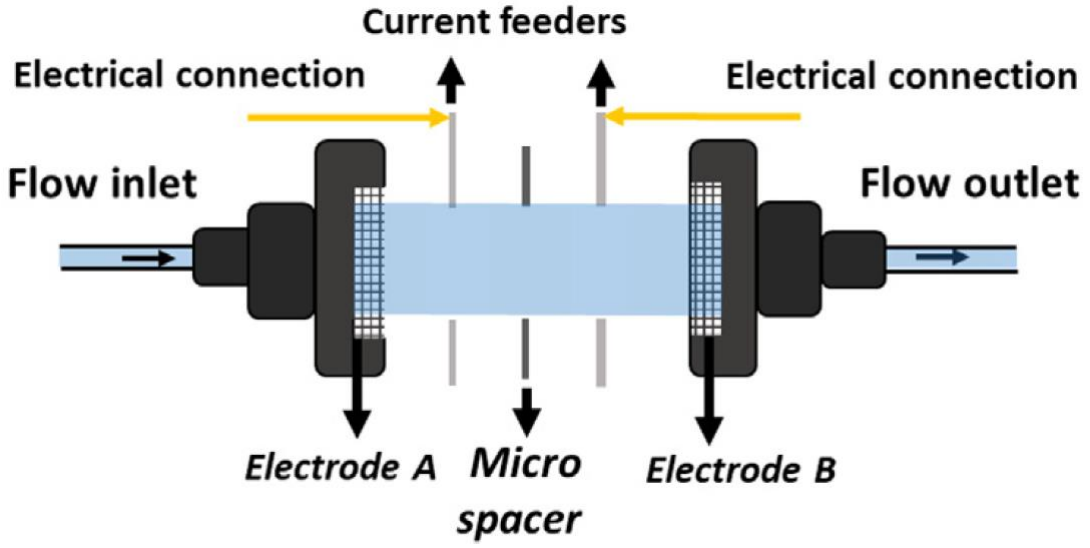

Figure 13. FT microfluidic reactor configuration proposed by Pérez et al. (2018). Reprinted with permission.

Electrochemical microreactors appear as promising technology for water treatment. The FT design represents a feasible configuration for scaling-up to achieve high throughputs. The combination of continuous FTMRs operating in series could allow the operation under superior electric performance. The use of combined oxidative process provides superior organic abatement, appearing as an interesting strategy. These features combined with the numbering-up could lead to large throughput and efficient modular plants. Moreover, the advancement of 3D printing techniques lined up with numerical simulations to obtain optimized devices and flow distributors appears as promising tools in the field of electrochemical microreactors.

4.3 Photocatalytic Technologies

Photocatalytic processes have been receiving great attention in the fields of water treatment, chemical synthesis and medicine (Van Gerven et al., 2007). Photocatalysis is a series of oxidation-reduction reactions, driven by photo-excited electron, that are activated by photon absorption carrying energy equal, or higher than, the band-gap energy of the catalyst (Wang et al., 2014; Van Gerven et al., 2007). Two main oxidation pathways were observed experimentally: the hole-driven and the electron-driven. In the hole-drive pathway, oxidized products are obtained from the generation of a hole in the valence band promoted by the photon carrying an energy amount greater than the semiconductor photocatalyst bandgap. The electron-driven oxidation is carried out by excited electrons captured by the dissolved oxygen, resulting in a sequence of oxidation and reduction reactions, producing as intermediate peroxide hydrogen, and consequently providing more hydroxyl radicals. The most used photocatalyst is the titanium dioxide (TiO_2), since it is chemically and biologically inert, high efficient and stable, safe and nontoxic (Carp et al., 2004). As irradiation source, UV light-emitting diode (LED), UV lamp and also solar light can be used (Wang et al., 2014).

Photocatalytic reactors stand out as a promising technology due to the decomposition of a wide range of organic compounds into innocuous products by the use of ultraviolet (UV) or sunlight irradiation (Wang et al., 2014). The photocatalytic efficiency depends on mass transfer and photon transfer limitations, recombination of photo-excited electrons and holes, and the oxygen available for oxidation. Often, these limitations are observed in conventional bulk reactors. In order to overcome these issues, optical microdevices have been developed. They lie on Optofluidics, an emerging area aiming the synergetic exploitation of optics, photonics and microfluidics.

Three major issues are related to the photocatalytic process efficiency: mass transfer – related to the contaminant particles motion to the catalytic surface, directly related to the surface area-to-volume ratio (A/V); photon transfer – the delivery of the photon to the catalytic sites, ideally the catalytic surface requires uniform radiation; and the available dissolved oxygen. The major limitations and design details of photocatalytic reactors are widely discussed in Heggo and Ookawara (2017) and Van Gerven et al. (2007).

Currently, the photocatalytic purification of water is performed in two classes of conventional bulk reactors: Slurry reactors (SR) - suspended nanoparticles of photocatalysts in the liquid, resulting in large A/V and good mass transfer rates, but this configuration experiences light scattering and absorption by the suspended particles, resulting in low photon transfer and the necessity of nanoparticles filtration; Immobilized Reactors (IR) - the photocatalyst is immobilized on substrates forming a wall coated surface. Good photon transfer rates and no requirement of additional filtration are the main advantages, although, low A/V results in poor mass transfer. Other reactor configurations were proposed by using optical fibre and oxygen/oxygen peroxide feed, however, none of the proposed design succeed all three major limitation issues.

Photocatalytic microreactors (MRs) present advantages over bulk reactors including large surface area-to-volume ratio, diffusion path reduction, uniform residence time and irradiation, short residence time and enhancement of photocatalyst life cycle. The large A/V results in more effective contact among reactants and catalysts. The magnitude order of A/V for microdevices range from 10,000 – 300,000 $m^2 m^{-3}$ to < 600 $m^2 m^{-3}$ from bulk reactors (Wang et al., 2012). Also, the use of porous nanoparticles could enlarge even more the A/V. The short residence time is a consequence of the large A/V and short diffusion path, resulting in enhancement of reaction rate constant up to 10,000 times the conventional reactors (Leblebici et al., 2015). Significant pollutant degradation levels (over 90%) were observed (Wang et al., 2012; Lei et al., 2010) in MR operating in order of tens of seconds against several hours required by bulk reactors (Oelgemöller, 2012). In MRs the photocatalyst is usually immobilized as a coated film and the fluid feed flows over this layer. This layout allows a uniform irradiation and high illumination efficiency. Furthermore, the own flow stream refreshes the coated surface, improving the catalyst life cycle. Wang et al. (2012) reported that photocatalyst can lasts for several hundreds of runs against only 10 runs of bulk reactors. Accordingly, the use of optimal microdevices could treat the most of pollutants in only one run, without the need of multiple passes

through the reactor, a common strategy used in bulk reactors (Wang et al., 2014; Van Gerven et al. 2007).

Lei et al. (2010) manufactured a planar microreactor (PMR) to study the degradation of methylene blue using solar radiation using three setups: traditional microreactor and two TiO_2-coated PMR (single and dual coating, Figure 14). Planar microreactors consist in a rectangular reaction chamber with two coatings, placed in superior and inferior walls, separated by the liquid layer height. The degradation efficiency experimentally observed was 94% for a residence time of 36 s. The reaction rate constant increased over 100 times regarding conventional reactors. The reaction rate decrease with the residence time increment. This behaviour can be attributed to mass transfer efficiency and oxygen availability. The TiO_2 coating thickness was also investigated. For the single coat, the degradation performance increased with the film thickness from 0.5 to 2.0 µm. For the dual-layer TiO_2 coating the degradation performance reached a maximum for a 1.0 µm film thickness. Despite the good performance of the PMR, the main limitations were the oxygen deficiency and the low light utilization efficiency. In order to overcome the irradiation issues another PMR was proposed by Wang et al. (2012) (Figure 15) using at the chamber bottom a nanoporous coating of $BiVO_4$/Indium-Tin Oxide (ITO). The $BiVO_4$ has high photocatalytic activity, enhancing the solar irradiation usage. In the superior chamber wall an ITO glass was used and electric coupled bottom ITO coating by a voltage source. A polarity bias voltage scheme was used, enabling the control of the oxidation pathway (electron or hole-driven). Furthermore, the synergistic effect of photo- and electro-catalysis overcame the oxygen deficiency. The proposed photo-electrocatalytic microreactor showed potentiality to be scaled up for high-performance water purification.

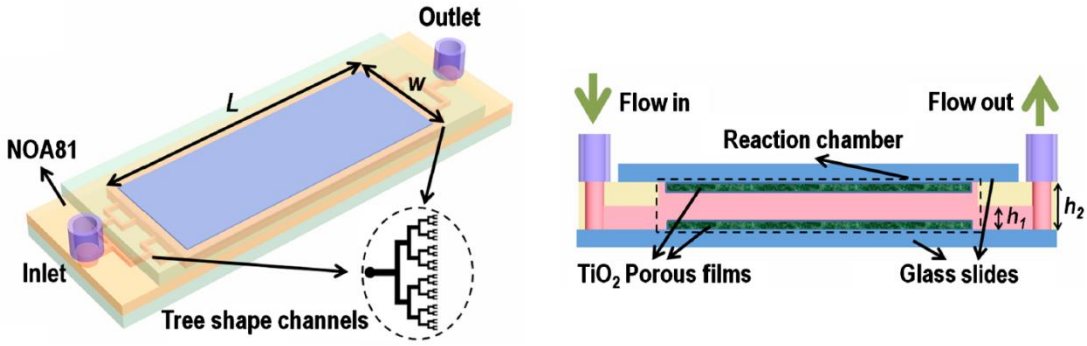

Figure 14. Planar microreactor configuration proposed by Lei et al. (2010). Reprinted with permission.

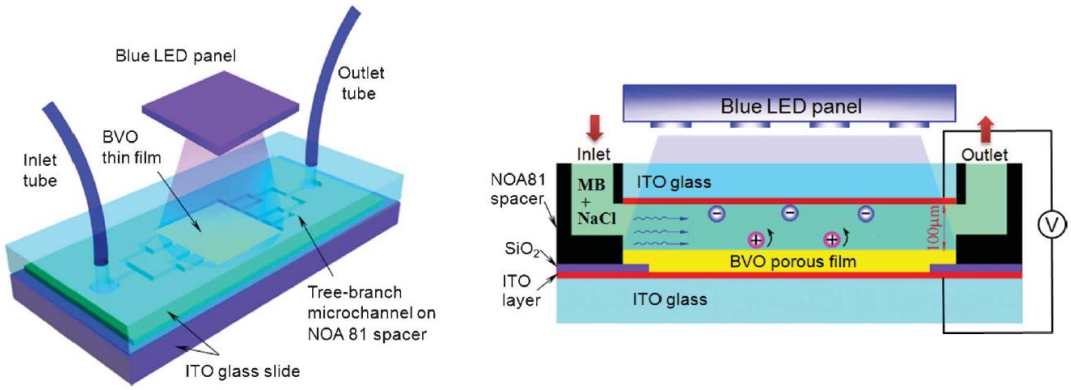

Figure 15. Planar photocatalytic microreactor proposed by Wang et al. (2012). Reprinted with permission.

Meng et al. (2013) presented a photocatalytic microreactor by using electrospun nanofibrous TiO_2. The proposed design has the advantages of shorter diffusion distance, high photocatalytic activity mostly due to the higher A/V compared to TiO_2 films. The degradation performance was evaluated for a residence time range from 12 s to 53 s. For a residence time of 53 s, the degradation rate observed for fiber and film microreactors were > 99% and ≈ 40%, respectively. Furthermore, the specific reaction rate constant increased with the residence time (from 4.06 to 5.20 min^{-1}) in fiber microreactor, in contrast with the reduction observed in film microreactor (from 1.5 to 0.54 min^{-1}).

Leblebici et al. (2015) compared the performance of 12 photocatalytic reactor designs including a microreactor. The authors proposed a benchmark based on the photocatalytic space-time yield, PSTY (m^3 water day^{-1} m^{-3} reactor kW^{-1} lamp), that relates the main operating parameters, as the rate of wastewater processed, the reactor volume, the apparent reaction rate and the lamp power. The overall superior performance was noticed for the tubular slurry reactor, scoring a PSTY of 0.72, due to the plug flow behaviour and the good mass transfer characteristic from slurry systems. The best performances of the immobilized reactors were the Spinning Disc Reactor (PSTY of 0.0149) and the microreactor (PSTY = 0.0108). The authors emphasized that with a lamp power optimization (e.g., use of a LED arrays), the MR could result in a PSTY of 13 (over 20 times the superior PSTY observed), standing out the great potential of the microdevice. The MR scale-up procedure for photocatalytic application must include an efficient light

distribution that addresses a major challenge in numbering-up. Another aspect to be mentioned is the reaction rate, *k*, provided by the different reactor designs. The MR exhibited *k* of magnitude order of 10^6 day^{-1} against 10^1 to 10^2 day^{-1} of the other reactors. Also, the lamp power per volume unit of the MR was about 1000 times greater than the other designs.

Optimal photocatalytic microreactors must encompass enhanced mass and photon transfer mechanisms, high efficiency irradiation usage and oxygen supply approaches. The numbering-up could be used as a smart scale-up strategy to achieve large rates for water treatment, therefore, uniform distribution schemes for flow and irradiation through all microdevices must be considered. New combinations of nanoporous and nanofibrous catalyst coating and integration of electro-photon catalysis jointly with high efficiency UV-LED arrays stand out as promising technologies for the development of high performance scalable microdevices.

5 Conclusions

As demonstrated in this review, intensification of liquid-liquid extraction can take advantage from the small dimensions of microfluidic devices. These advantages are intrinsically related to the short path lengths, thus high interfacial area between the phases can improve efficiency of extraction which reduce chemical waste produced. It should be noted, despite the benefits in microfluidic devices, some limitation could be found such as difficulty phase separation, restricted methods for analysis and the limited range of flow.

Regarding the area of biotechnology, it is one of the most successful applications of microfluidics. In this review, it is shown that microfluidic devices can be used in the efficient separation of biological samples usually present in processes related to, among others, DNA, RNA, acid drugs, parallel genetic analysis, blood samples, disease diagnosis or blood plasma. For separation of biological samples, techniques such as extraction, electrophoresis and hydrodynamics can be used together with simple microchannel design. The channels can range from micrometric to millimeter scale, which facilitates the manufacturing process of microfluidic devices and their use.

Finally, micro and nanotechnology has substantiated the development and optimization of water purification processes including membrane technology, electrochemical and photocatalytic treatments. Further developments in membrane technology are required to

control membrane fouling and to manufacture new membrane materials. The use of smart materials appears as an interesting alternative, including membrane coating with titanium dioxide promoting a synergetic photo-degradation effect of organic species, or the use of carbon nanotubes to enhance the permeate flux. Electrochemical microreactors with flow-through configuration are feasible for scaling-up to achieve high throughputs. The use of combined oxidative processes is an interesting strategy. The advances in additive manufacturing (3D printing) emerges as promising tool in the field of electrochemical microreactors, allowing the fabrication of optimized and customized microdevices and also, the design and assembly of efficient modular plants based on the numbering-up concept. Optofluidic devices allowed the combination of the key factors for an efficient photocatalytic process: enhanced mass and photon transfer, high efficiency irradiation usage and oxygen supply. The combination of new nanocatalysts and the integration of electro-photon process and high efficiency UV-LED appears as potential technology for usage in high performance microreactors.

List of Abbreviations

ATPS	Aqueous two-phase systems.
A/V	Area-to-volume ratio.
BDD	Boron-doped diamond.
BSA	Bovine serum albumin.
CAA	Chloroacetic acid.
CE	Chip electrophoresis.
CNT	Carbon nanotube.
DEP	Dielectrophoresis.
DNA	Deoxyribonucleic acid.
FB	Flow-by.
FA	Formic acid.
FT	Flow-through.
FTMR	Flow-through microreactor.
GAC	Granular activated carbon.
IDT	Interdigitated transducer.
IE	Inter-electrode.
IL	Ionic liquids.
IR	Immobilized reactors.
ITO	Indium-tin oxide.
LED	Light-emitting diode.
MD	Molecular dynamics.
MF	Microfiltration.
MOF	Metal-organic frameworks.
MR	Microreactor.
MSF	Multistage flash.
MWCO	Molecular weight cut-off.

NF	Nanofiltration.
PCR	polymerase chain reaction.
PDMS	Polydimethylsiloxane.
PMMA	Poly methyl methacrylate.
PMR	Planar microreactor.
PSTY	Photocatalytic space-time yield.
PTFE	Polytetrafluoroethylene.
RNA	Ribonucleic acid.
RO	Reverse osmosis.
SCF	Super critical fluids.
SR	Slurry reactors.
SSAW	Standing surface acoustic wave.
TOC	Total organic carbon.
TTMSS	Tris(trimethylsilyl)silane.
UF	Ultrafiltration.
UV	Ultraviolet.

Declarations

Availability of data and supporting materials section

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

HSS was in charge of writing Sections 3 and 5. JLSJ was in charge of writing Sections 4 and 5. BA was in charge of writing Sections 2 and 5. JOC was in charge of writing the Abstract, Sections 1 and 5, and asked for permission for reprinting the corresponding figures. All authors read and approved the final manuscript.

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