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ARE MICROREACTORS THE FUTURE OF BIODIESEL SYNTHESIS?

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ABSTRACT

Microfluidic devices or microdevices refer to systems with a characteristic length in the micrometer range. Systems in this size allow handling small quantities of reagents and samples, with reduced residence time, better control of chemical species concentration, high heat and mass transfers, and high surface/volume ratio. These characteristics led to the application of these microdevices in several areas, such as biological systems, energy, liquid-liquid extraction, food, agricultural sectors, pharmaceuticals, flow chemistry, microreactors, and biodiesel synthesis. Microreactors are devices that have interconnected microchannels, in which small amounts of reagents are manipulated and react for a certain period of time. The traditional characteristics of microreactors are less quantities of reagents and samples, high surface area in relation to volume (10000 m^2 m^{-3}), reduction of resistance to heat and mass transfer, reduced reaction times, and narrower residence time distributions. In recent years, several studies have been carried out on biodiesel production in microreactors that explore the influence of operating conditions, mixing and reaction yield, numbering, and especially the microdevices design. Despite all the advantages of microreactors, the literature shows that there are only a few applications on an industrial scale. Two main reasons that hinder the adoption of this technology are the scale-up to a large enough volume to deliver the necessary production capacity and the costs related to industrial manufacturing microreactors. It is often stated that large-scale production of microreactors can be easily achieved by numbering-up. However, researches show that an incredibly high number of microdevices would be needed, which results in a technical unfeasibility and a strong impact on the construction costs of the industrial system. The present review aims to show whether microreactors can replace conventional biodiesel production processes and how this replacement technology could be carried out. The current chapter was divided into the following sections: Introduction, Synthesis and Purification of Biodiesel in Microreactors, Fundamentals of CFD, and Fundamentals of Scale-up. Finally, conclusions and future perspectives are exposed.

Keywords: biodiesel, microreactor, transesterification, Computational Fluid Dynamics.

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INTRODUCTION

The main energy source for power and transportation comes from fossil fuels. The increasing energy demand has resulted in the extensive reduction of oil reserves. In addition, the use of fossil fuels produces a large emission of CO_2, which exacerbates global warming and accentuates negative climate change. As an eco-friendly option, biodiesel has been considered a promising substitute for fossil fuel. Global biodiesel production increased from 6 billion liters per year in 2005 to 46 billion liters per year in 2020 (Ogunkunle and Ahmed 2019). It has advantages such as being four times easier to degrade (Demirbaş *et al.* 2008), emitting 86% fewer greenhouses gases (Voegele 2020), obtaining from renewable sources, such as crude vegetable oils, waste cooking oil (WCO), or animal fat (ASTM D6751–15, 2015). Biodiesel is a mixture of long-chain fatty acid alkyl ester (FAAE) produced by esterification and/or transesterification. Esterification occurs between free fatty acid and methanol in the presence of a catalyst, such as strong acid, having FAAE and water. Transesterification, the most common reaction, occurs between triglycerides and alcohol in the presence of a catalyst such as strong acid or alkali, producing FAAE and glycerol. The reactions usually happen on a macroscale by a continuous reactor or, more often, by a batch reactor; and take several hours to achieve high conversion requiring huge excess of alcohol, consuming extensive energy, and producing a large volume of residues (Bashir *et al*. 2022; Jachuck *et al*. 2009). These issues increase the process costs and hamper biodiesel's commercialization. Thus, improved processes are required to overcome these gaps. The microchemical plant has been shown as one of the most promising technologies.

A microchemical plant refers to a system with internal dimensions of 10-1000 μm (Balbino *et al.* 2016; Dimov *et al*. 2008; Santana *et al.* 2018a). According to Bannatham et al., (2021), the microscale process can require a residence time 720 shorter than a batch reactor because the microchannels' interfacial area is 32 times larger. The same reaction developed by batch reactor and microreactor showed a yield of 94.1% in 180 minutes against 95.8% in 1 minute, respectively (Santana *et al.* 2016). The process enlargement can be carried out by parallel or series arrangement of the micro/millireactor, by the modular scale-up concept, in combination with a slight increment in the channel dimensions (scale-out), as, for example, from micro to milliscale (Santana *et al*. 2018b; Zhang *et al*. 2017). These slight increment of the channel dimensions aims to increase the operating flow rate without missing the advantages of microscale's enhanced transport phenomena. This strategy can be performed for any type of microreactor, and each specific reaction process will have an optimal channel dimension. Microplants have been shown promising results, such as those obtained by Billo et al., (2015). He produced 2.47 L.min-1 of biodiesel by multiplying 14.000 microreactors. The plant had 35 manifolds with 8 modules, and each module with 50 microdevices. The whole fabrication process took 3 months (Billo *et al.* 2015). In addition to overcoming the macroscale plant issues aforementioned, the

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microscale configuration has advantages such as higher process security and control, large surface contact area, low shear stress, easy management of thermal exchange and reaction kinetics, easy maintenance, and repairability without completely stopping production (Budžaki *et al.* 2017; Sun *et al.* 2008a, 2008b; Wirth 2013). However, strategies to intensify heat and mass transfer rates are the key factor to achieving high efficiency.

Contrary to the conventional processes, by using microdevices, the heat and mass transfer are more homogeneous without spots that can compromise the reaction development. One strategy is the use of micromixers and/or complex geometry to promote turbulent mixing spots or chaotic advection. Martínez Arias et al., (2012), evaluated the transesterification of castor oil and ethanol catalyzed by NaOH. The shape that fomented chaotic flows (Tesla-shape) favored turbulent mixing and resulted in higher conversion (92%). In comparison, the shape that fomented laminar flow (T-shape) resulted in lower conversion (73%). Hence, studying the fluid flow is essential to optimize the process, and it can be developed using Computational Fluid Dynamics (CFD) techniques. CFD provides complete and detailed process information for a given fluid flow. Variables such as velocity, density, viscosity, temperature, species concentrations, and reaction rates may be acquired for all computed points in the flow domain. Moreover, beyond CFD being used for process design, it can complement experiments in process analysis (Chung 2002). The use of microscale allied to CFD can also be adopted for biodiesel purification, considering that the separation of the reaction products is a fundamental key in the process feasibility. Thus, the microscale plant can efficiently contemplate the entire process of biodiesel production, and the purpose of this chapter is to provide a comprehensive summary of these technologies.

LITERATURE REVIEW

Biodiesel Synthesis in Microreactors

Biodiesel refers to a fatty acid alkyl ester (FAAE) obtained from renewable sources. The feedstock (i.e. canola oil, waste cooking oil, and soybean oil) reacts with short-chain alcohol (i.e. methanol, ethanol, and isopropanol) in the presence of a homogeneous or heterogeneous catalyst (i.e. sulphuric acid, potassium hydroxide, and lipases), resulting in FAAE. Two reactions routes are the most common: esterification (Reaction 1) by using free fatty acid (FFA), and transesterification (Reaction 2) by using triglycerides (TGL). High yields are achieved by optimizing feedstock properties, alcohol, catalyst, temperature, mixing, and reactor shape and size. The batch reactor is frequently used, but it takes several hours for high yield (Yeh *et al.* 2016). By using microreactors, it is possible to achieve superior efficiency in a short time. The same reaction developed by batch reactor and microreactor showed a yield of 94.1% in 180 minutes against 95.8% in 1 minute,

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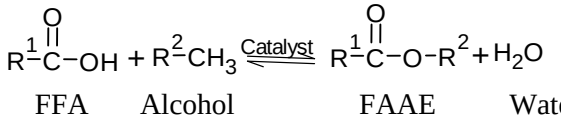
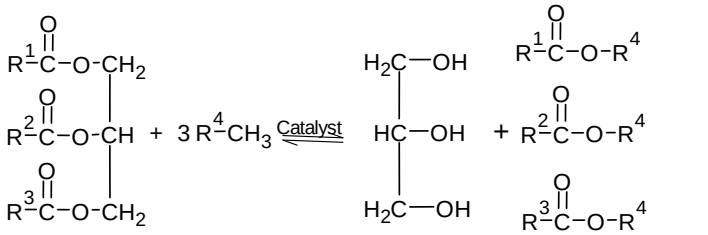
respectively (Santana *et al.* 2016). According to Bannatham et al., (2021), the microscale process requires a residence time 720 shorter than a batch reactor because the microchannels' interfacial area was 32 times larger. The most significant gap of this process is the reactants' miscibility. It can be overcome by using high alcohol content and temperatures higher than 50ºC (Bonet 2014; Silva *et al.* 2015) or increasing the interfacial surface (i.e., ultrasound, supercritical conditions, co-solvents, and microscale reactors). Microreactors have a high surface area relative to the volume (Kobayashi *et al.* 2009), easier control of operating conditions, and better heating performance, i.e., superior homogeneous distribution (no heating spots) than macroscale devices. Moreover, microreactors processes can be quail and quantitatively optimized mainly by microdevices design, operating conditions (i.e. temperature, molar ratio, and flow rate), and catalyst.



(1)

FFA Alcohol FAAE Water



(2)

TGL Alcohol Glycerin Mixture of FAAE

Microdevices design

Different designs for microreactors have been evaluated to carry out biodiesel reactions. The major aspect of a higher yield is to obtain a better reactants' contact and mass transfer. Lukić and Vrsaljko, (2021), observed that the two reactants form segmented interspersed flow and the reaction occurs between both reactants' borders. Thus, smaller reactants' segments result in a larger conversion. Two artifices are frequently used for that: (1) reduction of the channel cross-sectional area and (2) use of complex channels geometry.

Firstly, smaller cross-sections increase the reactants' area contact, although it also accentuates the pressure drop. In contrast, a larger cross-sectional area, which requires low pressure, results in a lower conversion. As observed by Guan et al., (2010), the reaction yield obtained by microchannels with 0.96 mm and 0.46 mm is similar (89.2% and 91.7%, respectively) for a residence time of 252 s. In contrast, for a residence time of 112 s, a significant difference in the conversion was observed (43% and 80%, respectively).

Secondly, the microdevice geometry influences the reaction yield because it improves the reactants mixture. The mixing improvement often occurs by a micromixer adapted to the microreactor inlets or by turbulent mixing spots, or chaotic advection, inside the reactor

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developed by complex microchannels designs. The micromixer design was evaluated by Rahimi et al., (2016), for soybean and methanol transesterification catalyzed by NaOH. Three designs with confluence angles of 45º, 90º, and 135º, respectively, were compared and the first one resulted in higher conversion (98.8%). Martínez Arias et al., (2012), evaluated the transesterification of castor oil and ethanol (1:9 molar ratio) catalyzed by NaOH (1 wt%) at 50ºC. The shape that fomented chaotic flows (Tesla-shape) favored turbulent mixing and resulted in higher conversion (92%). In comparison, the shape that fomented laminar flow (T-shape) resulted in lower conversion (73%). Moreover, designs that fomented turbulent mixing require low alcohol content (Martínez Arias *et al.* 2012). Turbulent mixing yielded a similar conversion for 1:9 and 1:24 molar ratios (92% and 97%, respectively). At the same time, a higher difference was observed for laminar flow (73% and 94%, respectively). Rahimi et al., (2014), searched for the use of different microdevices designs for soybean oil and methanol (1:9 molar ratio) transesterification catalyzed by KOH (1.2% w/wt) at constant temperature (~60ºC). A circular microtube with a T-shaped micromixer achieved a conversion of 89% with a residence time of 180 s (Rahimi *et al.* 2014). In comparison, an optimized zigzag micro-channel reactor with a T-shape inlet with a three-way junction achieved a conversion of 99.5% with a residence time of 28s (Wen *et al.* 2009).

Moreover, although unexplored for microscale, the use of microwave, ultrasound and coil, for example, could improve the mass transfer (Bucciol *et al.* 2020; Chipurici *et al.* 2019; Thangarasu *et al.* 2020). Palm fatty acid distillate (PFAD) feedstock consisting of >90% free fatty acid and methanol (1:9 molar ratio) catalyzed by sulfonated glucose (2.5 wt%) was carried out in an oscillation flow microreactor (OFR) (60◦C, residence time of 50 minutes, and oscillation frequency of 6Hz) resulting in a biodiesel yield of 94% (Kefas *et al.* 2019). The OFR is a continuous oscillatory flow tubular reactor adaptable for homogeneous and heterogeneous catalysts (Eze *et al.* 2013; Kefas *et al.* 2019). A mixture of oils and methanol (1:9 molar ratio) catalyzed by KOH was carried out in a helical coil microreactor by single flow (SFHR) and reverse flow (RFHR). At the same operational conditions (2g of catalyst, 65◦C, and residence time of 5 minutes), both reactors resulted respectively in 91% and 99% of biodiesel production. The difference occurred because the RFHR operates by a reverse turn coil. It results in a secondary flow with a dipole-like velocity field development; further, the flow near the inner surface of the coil generates large eddies. Both behaviors help to improve the reactants mixture, resulting in an 8-9 times higher reaction efficiency than a batch reactor (Gupta *et al.* 2019). Therefore, the microdevices design can be explored in different ways to achieve high efficiency by focusing, for example, on mild operational conditions and low-cost catalysts.

Operational conditions

Esterification and transesterification usually require high temperature and alcohol content to promote efficient mixing. The conventional processes, by using acid and alkali,

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almost use temperatures higher than 100°C (Georgogianni *et al.* 2009; Stacy *et al.* 2014; Tabatabaei *et al.* 2019). On the contrary, using a microreactor, temperatures higher than 50°C are frequently desirable, but lower alcohol (3 mols of alcohol for 1 FAAE mol) content is required (Billo *et al.* 2015; Guan *et al.* 2010; Martínez Arias *et al.* 2012; Mohadesi *et al.* 2020a; Rahimi *et al.* 2014; Wen *et al.* 2009). However, the microdevices design impacts both operating conditions. Martínez Arias et al., (2012), evaluated the temperature influence in different microdevices shapes for castor oil and ethanol transesterification. The Tesla shape, which fosters turbulent spots and better mixing, achieved 75%, 93%, and 93% for 30, 50, and 70°C, respectively. In contrast, T-shape, which fosters laminar flow and poor mixing, achieved 66%, 73%, and 88% for 30, 50, and 70°C, respectively. These results are in agreement with Lukić and Vrsaljko, (2021), study. They observed the formation of segmented interspersed flows between both reactants. The reaction occurred between both reactants' borders, and the higher the temperature, the smaller each reactant segment. At a temperature higher than the alcohol boiling point, the mixture stops being a liquid-liquid interface to becomes a gas-liquid interface, resulting in convective mixing and consequently improving the FAAE conversion. Therefore, microdevices that foment better mixing require temperatures higher than 50°C with liquid-liquid interfaces. Meanwhile, microdevices that cannot develop a good mix require temperatures higher than the alcohol boiling point to achieve higher conversions.

The molar ratio required for esterification is 1 mol of FFA for 1 mol of alcohol (Reaction 1). For transesterification, 1 mol of TGL is required for 3 mols of alcohol (Reaction 2). However, the alcohol excess is usually considered, as it helps to obtain a superior mixing between the reactants. By using acid or alkali, the traditional processes require 50-300 mols of alcohol for each FFA/TGL mol (Gopi *et al.* 2022). In contrast, microdevices, which foment better mixture, require a range between 3 to 30 molar alcohol for 1 TGL or FFA (Billo *et al.* 2015; Guan *et al.* 2009a; Martínez Arias *et al.* 2012; Mohadesi *et al.* 2020a; Rahimi *et al.* 2014; Wen *et al.* 2009). For example, castor oil transesterification resulted in a conversion of 93% for 1:9 molar ratio and a constant conversion value of 97% for 1:12, 1:18, and 1:24 molar ratio by carrying out the reaction in a reactor shape that improves the reactant mixing. In comparison, a result of 76%, 83%, 92%, and 93% were achieved for 1:9, 1:12, 1:18, and 1:24 molar ratio, respectively, by carrying out the reaction in a reactor shape that promotes lower reactant mixing (Martínez Arias *et al.* 2012). Even so, the microscale process requires a lower alcohol content than the conventional processes.

Catalyst

Homogeneous catalysts, such as strong acid or alkalis, are mostly used for biodiesel production on microscales and industrial scales (Gopi *et al.* 2022). Strong acids can be used for esterification and transesterification. However, the reaction is slow, and the reactors demand a non-corrosive material finish. Anyhow, damages to the reactor can occur and

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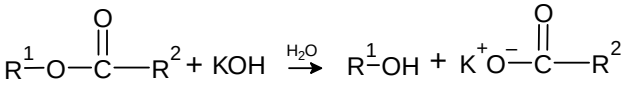
need to be repaired. For an industrial scale reactor, it is necessary to stop a large reaction volume. At the same time, on a microscale, the process continues, requiring the replacement of a few units by cheaper maintenance. The alkalis catalyze just transesterification; however, by a faster reaction than a strong acid. Moreover, the alkali reaction requires free water feedstock; otherwise, saponification may occur as described by reaction (3). Considering that saponification may occur, a large volume of water and reactants in an industrial-scale reactor is necessary to solve it. Although, in a microscale reactor, it would probably happen in sparse units, and the problem would be solved with less volume of reactants and water, without stopping production.



(3)

Heterogeneous catalysts have advantages such as easier catalyst recovery and reuse, and higher purified product (Ebiura *et al.* 2005; Essamlali *et al.* 2017; Xie *et al.* 2006; Zabeti *et al.* 2009; Zhang *et al.* 2010). Gojun et al., (2021), achieved 94% of biodiesel conversion from sunflower oil and methanol (1:10 molar ratio) catalyzed by a lipase from *Thermomyces lanuginosus* (723.34 ± 19.19 U/mg) in a microdevice (40ºC and residence time of 20 minutes). The oil+enzyme and methanol entered the microreactor by a T-shaped micromixer. Mohadesi et al., (2020b), achieved 97% of biodiesel conversion from WCO and methanol (1:2.25 molar ratio) catalyzed by KOH/Clinoptilolite (8.1 wt%) in a micro-tube reactor (65ºC and residence time of 13.4 minutes). The oil+catalyst and alcohol entered the reactor by a T-shaped micromixer. Mohadesi et al., (2020a), achieved 97% of biodiesel conversion from WCO and methanol (2.15:5 molar ratio) catalyzed by kettle limescale deposit (15 wt%) and acetone as co-solvent (13.95 wt% methanol) in a microreactor (60 ºC and residence time of 12.5 minutes) with T-shaped micromixer entered.

Low-cost material as a catalyst has been evaluated. Mohadesi et al., (2021), achieve 99% of biodiesel conversion from WCO and methanol (1:2.5 volume ratio) catalyzed by cow bone (8.5 wt%) in microdevice (63ºC and residence time of 60 s). The WCO+cow bone and the methanol entered to microreactor by a T-shaped micromixer into a microchannel's diameter of 0.8 mm. Pavlović et al., (2021), achieved 51% of biodiesel conversion from sunflower oil and methanol (1:2.5 volume ratio) catalyzed by chicken bone (10 wt%) in microdevice (60 ºC and residence time of 10 minutes). The oil+chicken bone and methanol entered to microreactor by a T-shaped three-way micromixer into a microchannel's diameter of 0.8 mm.

Packed micro-channel reactors for continuous biodiesel production have also been explored. Palm oil and methanol in the presence of calcium oxide pretreated with methanol as catalyst resulted in a conversion of 99% by using 65°C, 1:24, and residence time of 8.9 min. The catalyst was stable for an operating time of more than 24 hours (Chueluecha *et*

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al. 2017). According to Mohadesi et al., (2020a), residence time, temperature, and molar ratio are the most important operational conditions for biodiesel production by heterogeneous catalysis in microdevices.

Enzymes, frequently lipases, are one of the most common heterogeneous catalysts which have been evaluated for biodiesel production. They have been used in microreactors by edible and non-edible oils (Budžaki *et al.* 2017). This process has the potential for sustainable industrial biodiesel production (Budžaki *et al.* 2017). However, it presents three challenges: efficient immobilization, catalyst cost, and reactants mixing (Budžaki *et al.* 2017; Rossetti 2018). By using a microscale reactor, the mild operating conditions reduce the enzyme demobilization and loss. However, low flow rate or poor mixing can affect the enzyme efficiency, considering that glycerol can impregnate the channels and catalyst surfaces, therefore requiring additional removal operation. For an industrial scale reactor, a process involving a large volume of reactants is necessary to solve it. Although, in a microscale reactor, it would probably occur in sparse units, and the problem would be solved with less volume of reactants without stopping production.

Biodiesel can also be produced by non-catalyst methodologies, such as supercritical conditions (Kusdiana & Saka 2001; Qadeer *et al.* 2021; Saka & Kusdiana 2001), electrolysis (Fereidooni *et al.* 2021; Guan & Kusakabe 2009), or plasma (Buchori *et al.* 2016; Oliveira Palm *et al.* 2022). An advantage of the non-catalyzed reaction is that is not required a catalyst recovery, reducing cost and wastewater production. However, these technologies are unexplored by microdevices. Although it can be successfully applied as observed by Akkarawatkhoosith et al., (2021), who achieved 97% of rice bran oil conversion using supercritical conditions (360ºC, 1:11 oil to alcohol molar ratio and residence time of 35 minutes) in a microreactor.

Biodiesel Purification in Microdevices

Transesterification of oils with short-chain alcohol leads to the formation of biodiesel and the co-product glycerol, in addition to the excess alcohol. The separation of these three compounds is a fundamental key in the process's feasibility. In addition, the reactor downstream can also contain impurities from feedstock, unsaponifiable materials, residues from catalyst and water (Gopi *et al.* 2022). Post-treatment stages of biodiesel are available, including distillation, membrane filtration, liquid-liquid extraction, and wet and dry washing, being the last two the most common methods currently used to achieve the biodiesel standards (Fonseca *et al.* 2019).

Usually, for traditional batch processes, the reacted mixture follows a gravitational separation process due to the density difference of the resulting phases. This separation also experiences an emulsion formation, making the separation relatively slow and hard to accomplish (Tiwari *et al.* 2018). In microscale, the driving force of density difference is very reduced, and then gravitational separation is not possible. In contrast, other driving

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forces can be intensified in microscales, such as the centrifugal forces and secondary vortex generation (Dean flow) employed in inertial focused devices to separate biological particles (Nasiri *et al.* 2020).

Process intensification strategies include the use of integrated operations, e.g., reaction and separation in the same equipment. Membrane reactor appears as an interesting alternative for biodiesel production (Gao *et al.* 2017; Reyes *et al.* 2012; Xu *et al.* 2015; Maia *et al.* 2016). The two-phase membrane reactor performs the transesterification and separation of the biodiesel in a single continuous operation (Gao *et al.* 2017). The continuous separation of the products from the feed stream (reactants mixture) allows a high mass transfer rate between the immiscible phases (Baroutian *et al.* 2011; Cao *et al.* 2009).It is a flexible alternative since the most usual transesterification routes (i.e., acid, alkali, and enzymatic, homogeneous, or heterogeneous media), can be coupled to the microfilter membrane (Atadashi *et al.* 2012; Baroutian *et al.* 2012). These characteristics produce an oil-free biodiesel stream at the membrane reactor outlet, thus resulting in simple downstream processing and lower energy demand (Shuit *et al.* 2012; Kiss *et al.* 2012).

There are few studies in biodiesel separation and purification in microdevices, such a the use of Liquid-Liquid extraction performed by Crawford et al., (2008). The authors used an integrated reactor-extractor system made by a Syrris 250 µL microchannel reactor arranged in series with a Flow Liquid-Liquid Extraction (FLLEX) module, which was composed by a polytetrafluoroethylene (PTFE) membrane (Kralj *et al.* 2007). The continuous separation of glycerol from biodiesel was achieved by the introduction of water in the stream, where the hydrophobic biodiesel phase was able to flow across the membrane, in contrast to the hydrophilic aqueous/glycerol phase. An in-line mass spectrum system was coupled to the micro-plant, allowing the biodiesel quantification in real-time. A residence time of 2.5 minutes was enough to provide a complete conversion of the vegetable oil at ambient temperature.

Recently, Bacic et al., (2021), proposed an integrated continuous process for biodiesel synthesis and purification by using Deep eutectic solvents (DESs) with lipase catalyst. The performance was assessed for batch system and microreactor. The microsystem was composed of a Y-shaped input with a tubular channel of an inner diameter of 500 µm and 1.2 m long made by polytetrafluoroethylene (PTFE). At the optimal conditions, the batch reactor provided 43.5% of biodiesel yield and extraction of 99.54% of glycerol after 2 h (w_G = 0.027% wt of glycerol); however, it did not achieve the international standards for glycerol content. The microsystem provided a similar performance, 45.33% of biodiesel yield and 99.56% of glycerol removal, for a residence time of 2 h, w_G = 0.019% wt of glycerol content, achieving the international standards (w_G = < 0.02%). The authors concluded that the microsystem can be considered a starting point for further development of integrated production/purification biodiesel synthesis in a single-stage.

The excess alcohol also can be recovered in the downstream stages. Santana et al., (2017a), designed and fabricated a micro-heat exchanger (MHE) to perform the excess

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ethanol evaporation from the biodiesel stream. The MHE consisted in a multichannel (15 channels of 500 µm of hydraulic diameter) microdevice with a Peltier plate to provide the heat required for ethanol evaporation. The microdevice was manufactured by poly(dimethylsiloxane) (PDMS) using soft lithography. The excess ethanol was evaporated and recovered at one of the two outlets of the device. The operating variables' effect in the ethanol recovery were assessed by ranging the ethanol/biodiesel molar ration from 2 to 11, temperature from 80 ºC to 120 ºC, and flow rate from 0.1 mL/min to 1.2 mL/min. The superior performance of the MHE was a recovery efficiency of 82% for ethanol/biodiesel molar ratio of 2, at 100 ºC and 0.6 mL/min for a single pass through the microdevice. The MHE design was also evaluated by numerical simulations using CFD by Silva Jr. et al., (2017). These results testify to the potential usage of the MHE in continuous modular plants.

Introduction to Computational Fluid Dynamics (CFD) concepts

Computational Fluid Dynamics

Computational Fluid Dynamics (CFD) is the area of fluid mechanics based on applying computational tools to solve mathematical models that describe fluid flows. It is a heavily used approach to analyze two- or three-dimensional flows, whose analytical solution is too difficult to obtain. Hence, computers are used to speed up this process through numerical solutions.

There are three basic laws that determine a fluid flow: mass conservation, Newton's second law, and energy conservation. Therefore, flows are represented in terms of mathematical equations described in partial differential equations. CFD techniques are applied in order to transform these equations, which represent a continuum behavior, in algebraic equations, interpretable and solvable by computers by appropriate algorithms (Bhatti *et al.* 2020).

Advantages of applying CFD in process analysis

Computational fluid dynamics techniques are nowadays well established and applied in many technology fields. Some heavy CFD users are manufacturers of aircraft, cars, ships, and turbomachinery. Besides these, such a design approach has been adopted to solve problems in oceanography, meteorology, astrophysics, and others (Moukalled *et al.* 2016).

Cost-saving is by far the main advantage of applying CFD in process and equipment design when compared to experimental investigations. Studying a process through a proper set of simulation runs based on a validated model saves financial, human, and material resources than the same set of experiments in a pilot plant. Furthermore, undetermined and human errors that may influence lab tests are eliminated, while well-conducted numerical solutions always tend to provide accurate results.

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CFD analysis also provides information difficult to obtain via experiments. On the one hand, it is possible to obtain flow details as velocity field throw particle image velocimetry (PIV) with resolution limitations. On the other hand, a simulation provides a velocity field which resolution only depends on the available computational resources. Besides that, real-time experimental data on reactive flows is not easily accessible. Although techniques like Raman spectrometry allow such data acquisition, they are limited by few samples for a given flow domain. On the contrary, CFD analysis provides results as species concentration fields, i.e., throughout the flow domain, in real-time when considering a transient process (Anderson, 1995).

Summarizing, CFD provides complete and detailed process information for a given fluid flow. Variables such as velocity, density, viscosity, temperature, species concentrations, and reaction rates may be acquired for all computed points in the flow domain. Furthermore, not only CFD can be used in process design but it also can complement experiments in process analysis (Chung, 2002).

CFD analysis workflow

The steps to analyze a problem using CFD are represented in the flowchart shown in Figure 1.

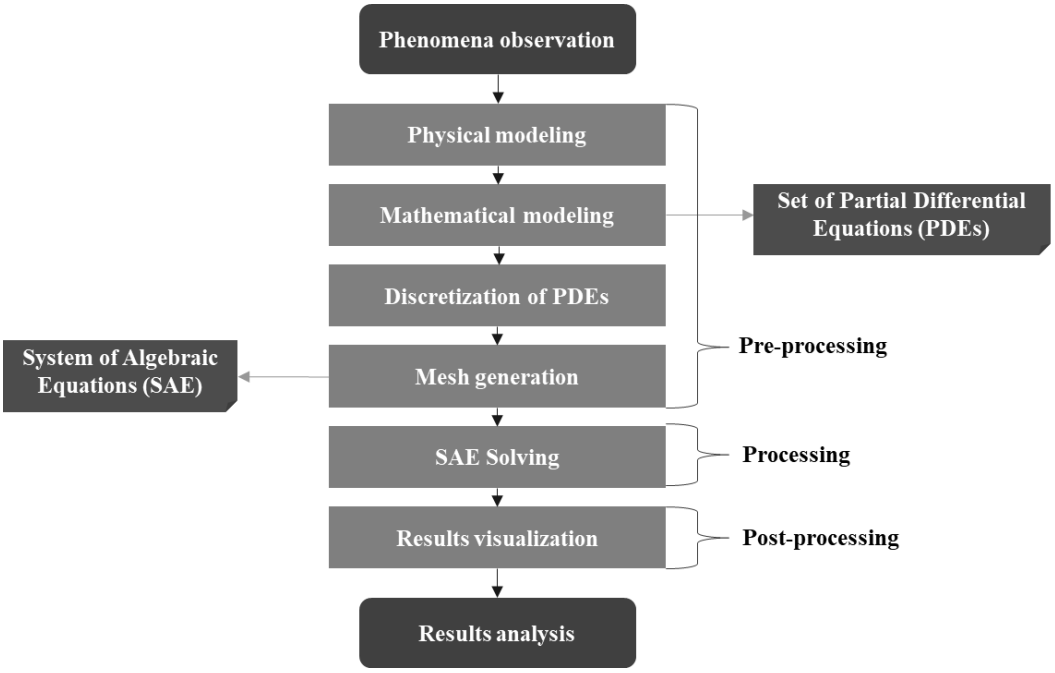

Figure 1: CFD analysis basic steps.

The starter step when developing a CFD model is the observation of a given process. This consists not only of phenomena investigation but also of assumptions survey, based on observer's experience. The next step is physical modeling, which consists in establishing

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a control volume for the fluid flow by imposing control surfaces. This basically means representing the flow domain using a geometry, usually developed in a CAD software.

Thereon, a mathematical modeling is applied in order to represent how the flow parameters vary throughout the domain. This consists of applying basic conservations laws to the control volume, so there are dependent field variables that describe the flow. This step results in a set of partial differential equations (PDEs) where, e.g., pressure and velocity are dependent field variables, and independent field variables are dimensions and time in a transient problem.

Subsequently, PDEs are discretized. This step is needed for adequate implemented algorithms to solve the fluid flow through a digital computer. Such discretization step can be done using methods such as finite differences (FDM), finite elements (FEM), or finite volumes (FVM). Conversely, mesh generation means the spatial discretization of the physical domain. In this step, an inherently continuous geometry is transformed into a domain composed of a finite number of points, elements, or cells, the so-called mesh or grid. PDEs discretization and mesh generation then result in a system of algebraic equations (SAE) for each domain element, where the field variables are now discrete variables. The set of PDEs that was then applicable to the whole domain is now represented by a SAE for each mesh element (Moukalled *et al.* 2016).

The steps described above are called pre-processing steps, i.e., the needed steps to prepare a fluid flow case for a computer algorithm to solve it by transforming a continuous into a discrete domain. The simulation run is the processing step. It consists of the SAE solution for each element of the domain. There are many well-established numerical methods which allows the solution of linear and non-linear problems. Such nonlinearities usually appear in reacting flows, e.g., when reaction rates are described by second or high order kinetics. Once the numerical simulation converges, the subsequent steps are post-processing. This can be done by an adequate software to obtain flow details graphically for any computed field variable (Moukalled *et al.* 2016). A few more details about pre-processing, processing, and post-processing steps of a CFD analysis are given in the subsequent sections.

Physical modeling

In CFD analysis, physical modeling is the development of a geometry that represents the control volume to be analyzed. There are commercial and free CAD software, such as SALOME, Gmsh, SketchUp, and others that allow geometry design. This step is critical both in process design and analysis. In a process analysis, it is important to assure that the control volume represents, e.g., the needed length for a fully developed outflow. In a process design, geometry design is determinant to assure, e.g., reactants mixing effectiveness in a microreactor. Figure 2 represents a micromixer which geometry was developed in such a way that reactants mixing is enhanced by obstacles (Santana *et al.* 2021).

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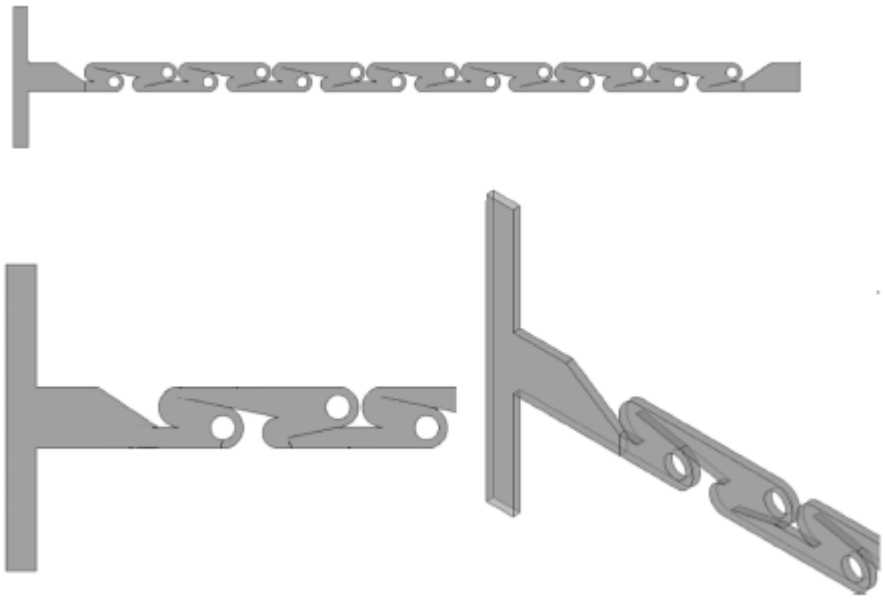

Figure 2: Design of the micromixer "Elis", developed for enhanced fluid mixing and organic reactions.

Mathematical modeling

There are two different approaches to describe a fluid flow. The Lagrangian approach is based on describing the path of a given particle throughout a flow domain. On the other hand, the Eulerian approach is based on describing how field variables vary throughout a given domain where all points are specified. From this point on, the fluid dynamics concepts are described based on the Eulerian approach.

Developing a mathematical model consists of applying the conservation equations for the control volume that represents a given flow domain. The starter step is to apply the proper conservation equations to an infinitesimal control volume. Thus, such equations are represented in a set of PDEs. The solution of these PDEs gives fluid flow details by fields of velocity, pressure, density, etc.

In a three-dimensional flow, independent variables are scalar variables, such as dimensions and time. The field variables to be calculated can be pressure and velocity. In this, as in all other cases, there are vector field variables, as velocity, and scalar field variables, as pressure, by definition (Moukalled *et al.* 2016).

The simpler three-dimensional flow to be solved can be described by a set of two differential equations, those for mass and momentum conservation. The mass conservation equation is a scalar equation given as:

$$\frac{\partial \rho}{\partial t} + \nabla . (\rho \vec{u}) = 0 \qquad (1)$$

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Where ρ is fluid density and $\vec{u}$ is velocity. Equation 1 is also called the continuity equation, since its formulation is based on the *continuum* hypothesis. This assumption considers that all flow properties vary continuously in space and time. The first term on the left side of the equation represents the mass variation in the control volume, while the second term represents the balance of mass flux across control surfaces.

The momentum conservation equation is derived from Newton's second law of motion. When this law is applied to a case of incompressible, isothermal, and laminar flow of a Newtonian fluid, the resulting equation is known as the Navier-Stokes Equation. This is a vectorial equation given as:

$$\frac{D\vec{u}}{Dt} = \rho\vec{g} - \nabla P + \nabla.\left[\mu\left(\nabla\vec{u} + {}^{t}\nabla\vec{u}\right)\right] \quad (2)$$

Where the term on the left side of equation represents the material derivative, which can be understood as the advective term. On the other hand, $\nabla.\left[\mu\left(\nabla\vec{u} + {}^{t}\nabla\vec{u}\right)\right]$ is the momentum diffusion term for a Newtonian fluid, ∇P is the pressure gradient, which gives the flow direction, and $\rho\vec{g}$ is the term of gravitational force, the most usually field force present in flow cases.

Here, we presented the concept of advection and diffusion of transport variables. Advection is the transport due to a bulk fluid motion, and diffusion is the transport mechanism due to molecular interaction. Additional terms would be needed to describe momentum transport if there was turbulent shear stress (Bird *et al.* 2006).

In chemical processes, it is also critical to describe species conservation. Biofuel synthesis eminently involves the transfer, generation, and consumption of chemical species. Thus, we must emphasize that, as momentum transport, species transport is represented by equations composed by advective and diffusive terms. Generally, conservation of a given species can be described as:

$$\frac{\partial C}{\partial t} + \nabla.(\vec{u}C) = \nabla.[\mu(\nabla C)] + r \quad (3)$$

Where is $\frac{\partial C}{\partial t}$ the concentration of a species variation with time, $\nabla.(\vec{u}C)$ is the advective term, $\nabla.[\mu(\nabla C)]$ is the diffusive term, and r represents the balance of this species concentration when there is a reactive flow, expressed by the reaction kinetics, given as:

$$r_i = r_{generation} - r_{consumption} \quad (3)$$

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These governing equations are naturally coupled, so all equations need to be solved simultaneously. In transient processes, the obtained solution express variables that vary not only with space, but also with time.

The relation between physical and mathematical models is established by boundary conditions. They are constraints presented in the problem adopted at the control surfaces, always represented as equations. Such equations are requirements for solving the set of PDEs (Chung, 2002).

Discretization of a mathematical model

A digital computer can solve a mathematical model problem only if the set of PDEs are described into systems of algebraic equations. The three main methods used to discretize equations in a CFD model are: finite-difference (FDM), finite-element (FEM), and finite-volume methods (FVM).

Basically, the finite-difference method consists of assuming a point in space where the *continuum* hypothesis can be considered for the original set of PDEs, and then these equations are turned into discrete equations, the so-called finite-difference equations. It is a quite suitable discretization option if there is a regular domain shape, like rectangular or box-shaped. On the other hand, this method does not handle well with variables discontinuities due to geometry. Also, it is too difficult for implementation in complex shapes.

Finite-element methods are based on subdividing the physical model in small parts of simple shape, that form a mesh of finite elements. The set of PDEs are formulated not only for the entire domain, but for each element. Thus, this method consists of approximate field variables in simple low-degree polynomial functions, such as linear or quadratic. This procedure results in a local approximation into an SAE for each element. When this formulation is extrapolated for all domain elements, then an SAE is obtained, represented by a sparse matrix that can be solved through any well-known sparse matrix solver. This method allows to increase results accuracy in specific regions of a domain, as corners, by increasing the number of elements, i.e., refining the mesh. However, finite-element methods require relatively advanced mathematical expertise for their implementation, and transient cases are even more complex (Pulliam *et al.* 1999).

Finite-volume methods are based in applying conservation laws to elements of a domain called cells. Thus, finite-volume methods are similar to finite-elements since both are based on dividing a geometry in small shape elements, although the adopted approaches over governing equations are quite different. In FVM, a flux variable that enters in a cell's face has to leave the other side's face of the same cell. Therefore, implementing these methods results in a set of flux conservation equations defined for mean variables at the cells. Since most of governing equations of a fluid flow are based on conservation laws, FVM is successful to solve such problems. As in FEM, this method provides more accurate results if a mesh is locally refined (Hirt and Nichols, 1981; Pulliam, *et al.* 1999).

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Mesh generation

Meshing consists of discretizing the physical model in space, i.e., generating a discrete representation of a fluid domain geometry. This mesh unfolds which are the points to which the equations will be solved, and which points belong to the interior and to the boundaries of the domain. A mesh strongly influences convergence rate or even the lack of convergence, accuracy of the results, and time required for a computer to solve a simulation. Hence, CFD designers attempt mesh quality parameters towards reasonable simulation results.

Volume elements of a mesh are usually called cells, which constitute each control volume of a 3D grid. These elements may be tetrahedrons, hexahedrons, or polyhedrons. Vertices are called nodes, and a centroid is a point referring to the center of a cell, to which flow properties are computed during a simulation run. Lines are called edges, which constitute the boundaries of a face. So, a face is a boundary of a cell. Nodes, faces, and cells may be part of a zone. Finally, a flow domain is made of nodes, faces, and cell zones (Bakker, 2006). The described mesh terminology is represented in Figure 3.

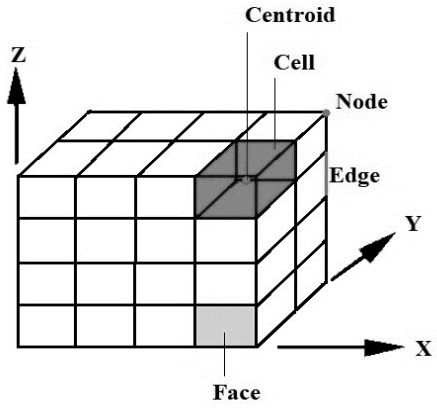

Figure 3: Representation of mesh terminology concepts.

Regarding to the mesh types, there are structured and unstructured meshes. A structured mesh is one where there is cell indexing in order to locate nearing cells of one for which the problem is being solved. Thus, structured meshes can only be applied in simple geometries, so that all cells of a 3D domain may be addressed by three index variables, e.g., *i*, *j*, and *k*. An unstructured mesh is composed of elements arranged without indexing, so there is no limitation concerning geometry shape (Moukalled *et al.* 2016). However, this type of mesh implies in memory and CPU overhead due cells referencing. There are a few mesh quality parameters, as mesh density, skewness, smoothness, and aspect ratio, whose definitions may be well comprehended in the literature.

Simulation runs

As above mentioned, a simulation run consists of solving SAE for each element of discretized flow domain. There are well-known established numerical methods for this

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purpose implemented in commercial and free software. A few examples of available CFD commercial software are COMSOL, Ansys CFX, Ansys Fluent, and Siemens StarCCM+. Open-source CFD solutions are also available as OpenFOAM.

Post-processing

Results of a simulation run can be visualized using a proper post-processing software. Field variables can be expressed graphically so that process variables can be seen for the entire flow domain. Figure 4 expresses how the oil mass fraction varies in a biodiesel synthesis in a simulation run applied to microreactor design from Figure 2 (Santana *et al.* 2021).

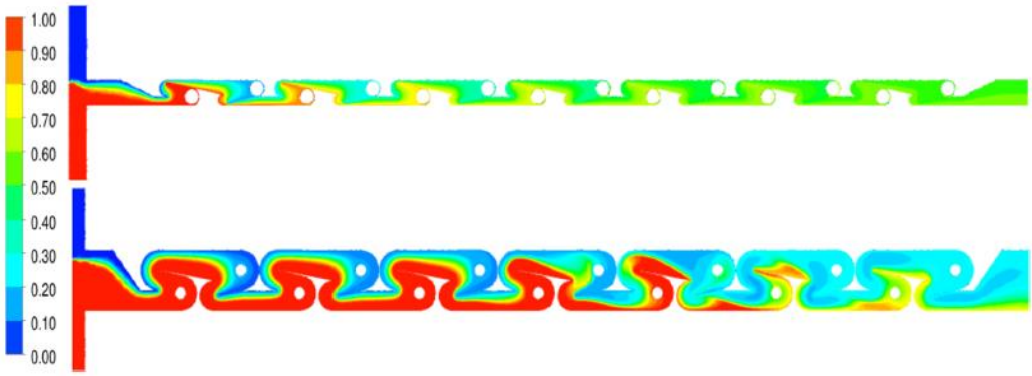

Figure 4: Vegetable oil mass fraction distributions for different operating conditions simulated in Elis microreactor for biodiesel synthesis.

Numerical Simulation of Biodiesel Synthesis in Microreactors

Biodiesel production has been increasing with the demand of reducing fossil fuels consumption. This way, engineers also have been investigating how to design a rapid and safe production process to supply such demand. Since biodiesel synthesis is a multiphase transesterification reaction, slow mass transfer impacts overall reaction time and continuous reactors have been developed to overcome this issue (Quiroz-Pérez *et al.* 2019). To implement this production process at industrial scale, mass and heat transfer must be enhanced. In this context, microfluidic devices provide some major advantages like a higher area to volume ratio, which enhances mass and heat transfer and smaller reaction times (Zhang *et al.* 2006).

Since CFD modeling is a powerful tool in process design, the improvement of biodiesel production via microreactors has been explored through simulation in recent years. One of the first CFD investigations was conducted by (Han *et al.* 2011), which studied biodiesel synthesis in a capillary microreactor by the transesterification of soybean oil and methanol. Research on biodiesel production by experiments and numerical simulations were also conducted using a tubular microreactor (López-Guajardo *et al.* 2017). However, through intense research, it was observed that one of the key parameters that influence oil conversion is the reactants mixing. Usually, increasing flow velocities provide an efficient

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mixing degree in microreactors, but this can also be obtained by modifying the reactor design.

Further investigations indicated the effects of static obstacles in oil conversion. It was found that a reactor design with a cross-shape promoted the highest mixing index, since internal obstructions in the microchannel split and recombined the flow stream, which enhances mixing between chemical species (Santana *et al.* 2017b).

Through CFD results such as velocity profile, as seen in Figure 5, it was found that a design with obstacles in an alternating pattern result in a level of flow perturbation that increases the contact surface area between reactants. It was also found that baffles promote the flow direction changes and the formation of vortexes, resulting in higher mixing, thus enhancing mass transfer and oil conversion, as in Figure 6.

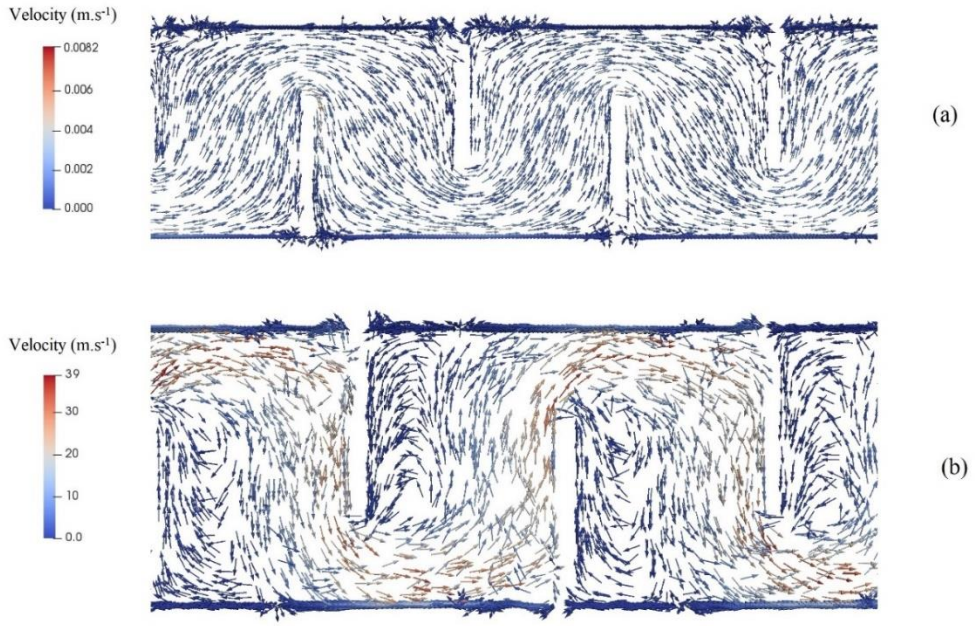

Figure 5: Velocity profiles in a microreactor with deflecting obstacles, or baffles, in different configurations of biodiesel synthesis: (a) Re = 0.01; (b) Re = 100. Reprinted from International Journal of Multiphase Flow, 132, Marcos R.P. de Sousa,Harrson S. Santana,Osvaldir P. Taranto, Modeling and simulation using OpenFOAM of biodiesel synthesis in structured microreactor, 103435, (2020), with permission from Elsevier.

Mixing enhancement in a microreactor for biodiesel production has also been studied by (Mohd Laziz *et al.* 2020). This investigation, based on experiments and simulation, resulted in a continuous production of biodiesel from palm oil and methanol with a reaction time of 40 s and oil conversion of 98.6% using a slug flow of methanol.

Research has also been focused on approaches alternative to alkaline catalysis in biodiesel synthesis in microreactors. Some studies are based on ultrasound technology, supercritical solvents or the use of catalytic enzymes for the transesterification process

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(Akkarawatkhoosith *et al.* 2020; Basiri *et al.* 2016). These approaches result in lower energy consumption, while avoiding the formation of undesirable products. (Gojun *et al.* 2019) validated a model in COMSOL to investigate biodiesel reaction yield enhancement and found that fatty acids methyl esters yield was 30% higher in a microreactor than a batch reactor.

Fundamentals of Scale-up and Scale-up of Microfluidic Devices

Microfluidics systems present high yield and selectivity due to the reduction in mass and heat transfer resistances inherent from the higher surface to volume ratio, allowing superior process performance in short times regarding traditional macroscale equipment (Wirth 2013; Whitesides 2006). Furthermore, microdevices consume lower amounts of reactants and samples and can also be manufactured by 3D printing, reducing the costs and facilitating the design optimization and validation procedures.

Despite these advantages, the main issue lies on the very reduced throughput of the microdevice regarding the industrial scale demand. According to Zhang et al., (2017), to make feasible the use of microdevices, some challenges must be overcome, such as the use of thousands of microreactor units, the guarantee of uniform flow distribution among these units, and the total costs of fabrication of the microreactors and the assembly of the microchemical plant. Accordingly, the scale-up strategy is a fundamental point to make feasible the introduction of microfluidic devices in industrial processes.

Dr. Björn Mathes, in his article "Future Production Concepts in the Chemical Industry" argues that the scale-up of micro and millidevices can be employed to overcome the disadvantages of batch processes. In order to establish a batch process, there are some tests in pilot plants considering the adequation of chemical reaction performance on a large scale. This time of process development and adaptation is even more critical in the pharmaceutical industry, which usually needs fast responses to the market demand, for example, in a pandemic. In addition, the continuous production using scaled-up micro and millidevices allows a relative reduction in reactants amount due to the higher yield, easier handling and automation, and low operational costs.

The scale-up can be carried out by the parallel or series arrangement of the micro/millireactor, by the modular scale-up concept, in combination with a slight increment in the channel dimensions (scale-out), such as, for example, from micro to milliscale (Zhang *et al.* 2017; Santana *et al.* 2018). These slight increment of the channel dimensions aims to increase the operating flow rate without missing the enhanced transport phenomena advantages from microscale. This strategy can be performed for any type of microreactor, and each specific reaction process will have an optimal channel dimension.

Vankayala et al., (2007), developed Falling Film Microreactors (FFMR) for the oxidation of organic compounds and CO_2 absorption with sodium hydroxide solution. The study evaluated the channel dimensions effects in the reaction performance. One

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microreactor has 16 channels of 1200 µm x 400 µm (width x depth), while the other configuration was a 32 channels reactor with dimensions of 600 µm x 300 µm (width x depth). The superior yield was noticed for the larger microreactor, a surprising result, since both reactors possessed the same wetted area.

Lin et al., (2021), applied the scale-out process in a liquid-liquid micro-extractor and obtained an extraction efficiency above 90% in 10 min. The applied strategy was effective in overcoming the low production rate. Kang and Tseng, (2007), developed a micro-heat exchanger and evaluated the effect of channel dimensions increment in the pressure drop and heat transfer rates and efficiency. The authors observed that for the same heat transfer rate and efficiency, the dimensions increment considerably reduced the pressure drop. The optimal operating conditions of the scaled-up heat exchanger were defined as the efficiency below 0.4, marked by a very reduced pressure drop. However, the authors concluded that the scale increment should be evaluated specifically according to the main application goal.

Mohammad et al., (2021), aiming the intensification of the Fischer-Tropsch process with microreactors, tested three scale-up arrangements: the use of parallel units (numbering-up), the use of units in series and the increment of channel dimensions (scale-out). The scaled-up channels consisted of 7 channels of 1000 µm x 1000 µm against the initial 11 channels of 500 µm x 500 µm. After the synthesis in the microreactors, the authors observed no significant effects of the increase in the channel width in the reactor performance.

A successful case of scale-up was presented by the company Ehrfeld Mikrotechnik BTS, which designed and manufactured a scaled-up millireactor with a production capacity of 10.000 ton/year. The MIPROWA millireactor, presented in Figure 6, was firstly designed in the micrometric scale. After the size scale increment, the millireactor presented a total width of 400 mm and length of 7 m with 150 rectangular channels with static mixers, achieving an operating condition of 1 m^3/h. The millireactor, when continuously operated, can replace up to 20 batch reactors. The investment in the millireactor development was motivated by the final product quality. The reaction yield was optimized, and the company achieved a quick return on the invested capital.

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Figure 6. Milirreator MIPROWA. Adapted from Millireactor in Production (2016).

The scale-up can also be performed by the modular concept. Han et al., (2017), presented a multidimensional expansion strategy based on the modular integration, as illustrated in Figure 7. The throughput enlargement is carried out firstly by parallelizing N microchannels in a bidimensional matrixes. These M matrixes are then pilled to form a module. Finally, the integration of Q modules creates the system with a production flow rate proportional to the scale N x M x Q.

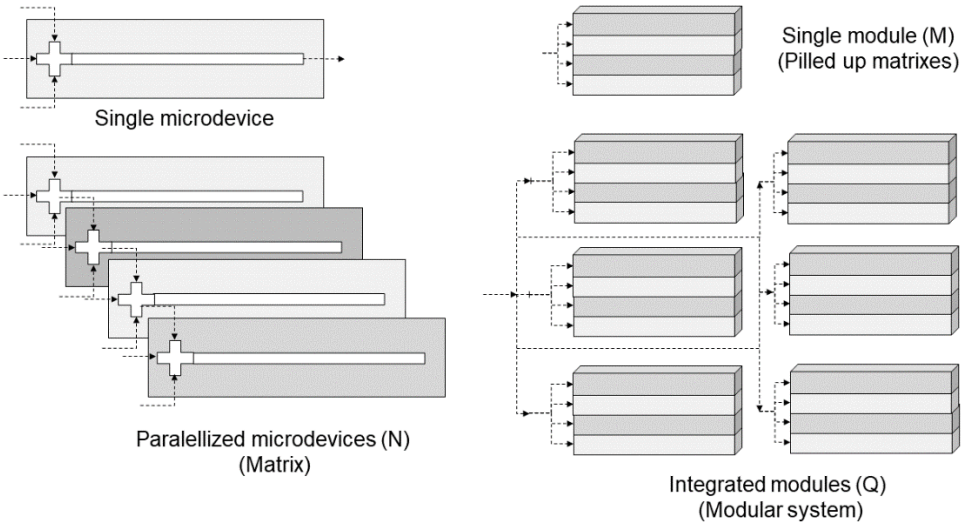

Figure 7. Multidimensional scale-up strategy for modular plant assembly from a single device. Adapted from Han et al. (2017) conceptualization.

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Tonkovich et al., (2005), developed a microchannel system for hydrogen generation on commercial scale. The system was composed by modules with 72 rectangular microchannels in parallel arrangement with dimensions of 4 mm of width and 0.5 mm of height. The modules with the grouped matrixes presented the dimensions of 45 cm (width) x 30 cm (length). The authors highlighted the importance of the uniform flow among the microdevices to ensure the efficient production. For the studied case, flow maldistribution below 20%, i.e., the mass flow rate ranging by about 20% at each reactor inlet, did not present significant effects in the system performance.

One of the major challenges is to ensure the uniform flow distribution in each of the microdevice units. The reactants maldistribution can reduce the microdevice performance, once the optimal reactant proportion could be incorrect, deprecating the reactor performance. Wang et al., (2016), approached the difficulty of keeping the transport characteristics, and reaction performance observed in a single microreactor when the numbering-up is performed. The authors highlighted the importance of an adequate design for the flow distributor. Accordingly, the flow distributors have the main goal of providing flow uniformity along all microdevices, contributing to keeping the high performance of the parallelized unit, similar to the observed in a single microreactor (Saber *et al.*, 2010).

Shen et al., (2018), pointed out the importance of the uniform flow in several scaled-up systems, including single-phase and two-phase flows and multiphase flows with bubbles and droplets generation. For a specific situation, it is mandatory to evaluate the flow distribution to achieve an efficient scaled-up system. The studies about the flow distribution must be extended to contemplate a wider range of fluids, including viscous and non-Newtonian, for future applications in microchannels and scale-up procedures. Vladisavljević et al., (2013), reviewed industrial applications of lab-on-chip devices, presenting the parallelization as an efficient method to be applied in reactive systems. However, in this arrangement, the inlet flow must be equally distributed at all microdevice units. Although, the microchannels can present some imperfections at the surface walls, and the hydraulic resistance can be different among these channels, also contributing to flow maldistribution. In this context, the flow distribution is a key parameter related to the system efficiency. Dong et al., (2021), grouped the flow distributors in internal and external. An external flow distributor is an independent unit, where the reactants fluids are distributed before entering the microreactor channels. The internal distributor is manufactured coupled to the microchannels. In addition, these two approaches can be combined to increase the reaction performance.

A study of biodiesel production in a scaled-up microplant was performed by Lopes et al., (2019). Different conical flow distributors were evaluated. After the initial tests, two distributors with flow deviations below 1% were selected to perform the ethanol and vegetable oil feed in the millidevices. Each reactant flow stream with its specific transport properties (dynamic viscosity) requires an optimal distributor design, aiming for the

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minimization of flow maldistribution. An integrated system, i.e., a micro-chemical plant, was evaluated. The ethanol flow deviation increased to 4.2% due to the pressure drop of the system. The scaled-up system was capable to achieve a biodiesel production rate of 126.4 mL min^{-1} with a yield of 83.3%.

Bannatham et al., (2021), carried out an experimental study of the transesterification in a microreactor with an inner diameter of 0.508 mm and length of 1.2 m. The reaction performance was evaluated at 52 ºC and 60 ºC for a methanol-oil molar ration of 6:1. The droplet-base microfluidics technique was used to feed the methanol in the continuous oil stream. The methanol droplet diameter was about 0.04 mm. The amount of methyl ester increased with temperature, flow rate, and reactor length. According to the authors, the increase in the reactor length caused the reduction of droplets sizes, resulting in an increment of the interfacial area and higher yield. In order to achieve a yield of over 97%, the microreactor length should be at least 1.2 m.

Lukić and Vrsaljko, (2020), developed millireactors to produce biodiesel. The conversion of sunflower oil in methyl esters of fatty acids was evaluated in channels with diameters from 1.5 mm to 3.5 mm. The millireactors of smaller diameters at higher temperatures achieved superior biodiesel yield with shorter times, regarding conventional batch reactors. As expected, the evaluated millireactor presented a larger production volume and smaller pressure drop concerning microreactors.

In this context, the study of scale-up strategies using micro/millireactors is of fundamental importance to enable its usage in an industrial scale. The microfluidic advantages are well known and established in the scientific community; however, there is still a necessity for studies focusing on the production throughput increment using microdevices and the particularities at each reactive process, including single and multiphase flows.

CONCLUSION AND FUTURE PERSPECTIVES

In the recent decades, microfluidic devices received great attention due to their inherent advantages of enhanced microscale transport phenomena is distinct technology fields, including chemical and biochemical process intensification. The need for renewable and sustainable energy sources on a global scale demands the development of innovative and efficient synthesis of biofuels. All these issues contributed to the development of microfluidic-based biodiesel processes. Major advances were achieved in fluid mixing and reaction performance, especially for biodiesel synthesis. However, there is still a lack in the effective and practical scale-up of the microfluidics devices to the industrial scale demand. The combination of different scale-up strategies, keeping the intensified heat and mass transfer rates, is a key-factor, since the process performance parameters, including selectivity and yield are directly affected by the transport phenomena. The coupling of scale-out and numbering-up concepts appears as an interesting alternative for a large

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throughput increment from a single optimized device, i.e., bringing together the best of both approaches. The scale-out from micro- to milli-scale, jointly with the use of optimal design static micromixers, allows the increment of operational flow rate, reducing the pressure drop and keeping the optimal mixing and reaction performance from the microscale. The numbering-up provides a prompt increase in the total throughput by a factor proportional to the microchemical plant construction, i.e. multiple by the number of parallelized microdevices, the pilled matrixes, and the integrated modules. Despite this smart and flexible strategy, a uniform flow distribution must be ensured along with all devices, minimizing variances among the microreactors. In all these steps, detailed CFD simulation can be employed for the devices design and optimization, appearing as an economical method, prior to the physical prototyping. Also, 3D printing can be used along CFD to manufacture microchemical plants. In this context, there are several advantages of the use of micro and millidevices in the continuous production of biodiesel, employing modern tools of Computer Aided Engineering and Industry 4.0. Future efforts must be spent in the scale-up and low-cost manufacturing strategies of integrated and automated modular plants, including mixing, reaction, and purification stages. These integrated plants will allow the continuous and flexible production of biodiesel, achieving the required demand.

REFERENCES

Akkarawatkhoosith, N., Kaewchada, A. and Jaree, A. (2020). Continuous catalyst-free biodiesel synthesis from rice bran oil fatty acid distillate in a microreactor. *Energy Reports*, 545–549.

Akkarawatkhoosith, N., Tongtummachat, T., Kaewchada, A. and & Jaree, A. (2021). Non-catalytic and glycerol-free biodiesel production from rice bran oil fatty acid distillate in a microreactor. *Energy Conversion and Management: X*, 100096.

Anderson, J.D.J. (1995). Computational Fluid Dynamics, 1st ed. McGraw-Hill, New York.

ASTM, & D6751–15. (2015). D6751–15. Standard, specification for biodiesel fuel blend stock (B100) for middle distillate fuels. West Conshohocken, PA: ASTM.

Atadashi, I.M., Aroua, M.K., Aziz, A.R.A. and Sulaiman, N.M.N. (2012). High quality biodiesel obtained through membrane technology, *Journal of Membrane Science*, 154-164.

Bacic, M., Ljubic, A., Gojun, M., Salic, A., Tusek, A.J. and Zelic, B. (2021). Continuous Integrated Process of Biodiesel Production and Purification—The End of the Conventional Two-Stage Batch Process? *Energies*, 403.

Bakker, A, (2006). Lecture 7 - Meshing. Available at: http://www.bakker.org/dartmouth06/engs150/07-mesh.pdf. Accessed December 14, 2021.

Balbino, T. A., Serafin, J. M., Malfatti-Gasperini, A. A. and de La Torre, L. G. (2016). Microfluidic Assembly of pDNA/Cationic Liposome Lipoplexes with High pDNA Loading for Gene Delivery. *Langmuir*, 1799–1807.

Bannatham, P., Banthaothook, C., Limtrakul, S., Vatanatham, T., Jaree, A., and & Ramachandran, P.A. (2021). Two-Scale Model for Kinetics, Design, and Scale-Up of Biodiesel Production. *Industrial & Engineering Chemistry Research*, 15972–15988.

Baroutian, S., Aroua, M.K., Raman, A.A.A. and Sulaiman, N.M.N. (2011). A packed bed membrane reactor for production of biodiesel using activated carbon supported catalyst, *Bioresource Technology*, 1095–1102.

Baroutian, S., Aroua, M.K., Aziz, A.R.A. and Sulaiman, N.M.N. (2012). TiO_2/Al_2O_3 membrane reactor equipped with a methanol recovery unit to produce palm oil biodiesel, *International Journal of Energy Research*, 120–129.

Bashir, M. A., Wu, S., Zhu, J., Krosuri, A., Khan, M. U., and Ndeddy Aka, R. J. (2022). Recent development of advanced processing technologies for biodiesel production: A critical review. *Fuel Processing Technology*, 227, 107120.

Basiri, M., Rahimi, M. and Mohammadi, H.B. (2016). Ultrasound-Assisted Biodiesel Production in Micro Reactors. *Iranian Journal of Chemistry and Chemical Engineering*, 22-32.

Bhatti, M.M., Marin, M., Zeeshan, A. and Abdelsalam, S.I. (2020). Editorial: Recent Trends in Computational Fluid Dynamics. *Frontiers in Physics*, 1–4.

Billo, R. E., Oliver, C. R., Charoenwat, R., Dennis, B.H., Wilson, P.A., Priest, J.W. and Beardsley, H. (2015). A cellular manufacturing process for a full-scale biodiesel microreactor. *Journal of Manufacturing Systems*, 409–416.

Bird, R.B., Stewart, W.E. and Lightfoot, E.N. (2006). *Transport Phenomena*, Revised 2nd Edition. Vol. 1, John Wiley Sons, Inc.

Bonet, J., Valentin, P., Ruiz, A.E.B., Petrica, I. and Llorens, J. (2014). Thermodynamic Study of Batch Reactor Biodiesel Synthesis. *Revista de Chimie*, 358–361.

Bucciol, F., Colia, M., Calcio Gaudino, E. and & Cravotto, G. (2020). Enabling Technologies and Sustainable Catalysis in Biodiesel Preparation. *Catalysts*, 988.

Buchori, L., Istadi, I. and Purwanto, P. (2016). Advanced chemical reactor technologies for biodiesel production from vegetable oils - A review. *Bulletin of Chemical Reaction Engineering, Catalysis*, 406–430.

Budžaki, S., Miljić, G., Tišma, M., Sundaram, S. and Hessel, V. (2017). Is there a future for enzymatic biodiesel industrial production in microreactors? *Applied Energy*, 124–134.

Cao, P.G., Tremblay, A.Y. and Dube, M.A. (2009). Kinetics of canola oil transesterification in a membrane reactor, *Industrial & Engineering Chemistry Research*, 2533-2541.

Chipurici, P., Vlaicu, A., Calinescu, I., Vinatoru, M., Vasilescu, M., Ignat, N.D. and Mason, T.J. (2019). Ultrasonic, hydrodynamic and microwave biodiesel synthesis – A comparative study for continuous process. *Ultrasonics Sonochemistry*, 38–47.

Chueluecha, N., Kaewchada, A. and & Jaree, A. (2017). Biodiesel synthesis using heterogeneous catalyst in a packed-microchannel. *Energy Conversion and Management*, 145–154.

Chung, T.J. (2002). Computational fluid dynamics. *Cambridge University Press*, Cambridge.

Crawford, E., Duquette, D., Grant, D., Gray, R., Musselman, B., Peacock, M. and Petersen, J. (2008). Continuous biodiesel production with continuous liquid-liquid extraction and online MS analysis. Available at: https://www.syrris.com/wp-content/uploads/2017/10/Continuous-Biodiesel-Production.pdf . Accessed January 12, 2022.

Demirbas, A., Demirba¸s, A. and Demirbas, D. (2008). Biodegradability of Biodiesel and Petrodiesel Fuels, *Energy Sources, Part A: Recovery, Utilization, and Environmental Effects Biodegradability of Biodiesel and Petrodiesel Fuels*, 169–174.

Dimov, I. K., Garcia-Cordero, J. L., O'grady, J. and O'kennedy, R. (2008). Integrated microfluidic tmRNA purification and real-time NASBA device for molecular diagnostics. *Lab on a Chip*, 2071–2078.

Dong, Z., Wen, Z., Zhao, F., Kuhn, S. and Noël, T. (2021). Scale-up of micro- and milli-reactors: An overview of strategies, design principles and applications. *Chemical Engineering Science: X*, 100097.

Ebiura, T., Echizen, T., Ishikawa, A., Murai, K. and Baba, T. (2005). Selective transesterification of triolein with methanol to methyl oleate and glycerol using alumina loaded with alkali metal salt as a solid-base catalyst. *Applied Catalysis A: General*, 111–116.

Essamlali, Y., Amadine, O., Larzek, M., Len, C. and Zahouily, M. (2017). Sodium modified hydroxyapatite: Highly efficient and stable solid-base catalyst for biodiesel production. *Energy Conversion and Management*, 355–367.

Eze, V. C., Phan, A. N., Pirez, C., Harvey, A. P., Lee, A. F. and Wilson, K. (2013). Heterogeneous catalysis in an oscillatory baffled flow reactor. *Catalysis Science & Technology*, 2373.

Fereidooni, L., Abbaspourrad, A. and Enayati, M. (2021). Electrolytic transesterification of waste frying oil using Na^+/zeolite–chitosan biocomposite for biodiesel production. *Waste Management*, 48–62.

Fonseca, J.M., Teleken J.G., de Cinque Almeida V. and da Silva, C. (2019). Biodiesel from waste frying oils: methods of production and purification. *Energy Convers Manage*, 205-218.

Georgogianni, K. G., Katsoulidis, A. K., Pomonis, P. J., Manos, G. and Kontominas, M. G. (2009). Transesterification of rapeseed oil for the production of biodiesel using homogeneous and heterogeneous catalysis. *Fuel Processing Technology*, 1016–1022.

Gojun, M., Šalić, A. and Zelić, B. (2021). Integrated microsystems for lipase-catalyzed biodiesel production and glycerol removal by extraction or ultrafiltration. *Renewable Energy*, 213–221.

Gojun, M., Pustahija, L., Tušek, A.J., Šalić, A., Valinger, D. and Zelić, B. (2019). Kinetic Parameter Estimation and Mathematical Modelling of Lipase Catalysed Biodiesel Synthesis in a Microreactor. *Micromachines*, 759.

Gopi, R., Thangarasu, V., Vinayakaselvi M, A. and Ramanathan, A. (2022). A critical review of recent advancements in continuous flow reactors and prominent integrated microreactors for biodiesel production. *Renewable and Sustainable Energy Reviews*, 111869.

Guan, G. and Kusakabe, K. (2009). Synthesis of biodiesel fuel using an electrolysis method. *Chemical Engineering Journal*, 159–163.

Guan, G., Kusakabe, K. and Yamasaki, S. (2009). Tri-potassium phosphate as a solid catalyst for biodiesel production from waste cooking oil. *Fuel Processing Technology*, 520–524.

Guan, G., Teshima, M., Sato, C., Son, S.M., Irfan, M.F., Kusakabe, K., Ikeda, N. and Lin, T.-J. (2010). Two-phase flow behavior in microtube reactors during biodiesel production from waste cooking oil. *AIChE Journal*, 1383–1390.

Gupta, J., Agarwal, M. and Dalai, A. K. (2019). Intensified transesterification of mixture of edible and non-edible oils in reverse flow helical coil reactor for biodiesel production. *Renewable Energy*, 509–525.

Han, W., Charoenwat, R. and Dennis, B.H. (2011). Numerical investigation of biodiesel production in capillary microreactor, in: Proceedings of the ASME Design Engineering Technical Conference. *American Society of Mechanical Engineers Digital Collection*, 253–258.

Han, T., Zhang, L., Xu, H. and Xuan, J. (2017). Factory-on-chip: Modularised microfluidic reactors for continuous mass production of functional materials. *Chemical Engineering Journal*, 765-773.

Hirt, C. W. and Nichols, B. D. (1981). Volume of Fluid (VOF) Method for the Dynamics of Free Boundaries. *Journal of Computational Physics*, 201-225.

Jachuck, R., Pherwani, G., & Gorton, S. M. (2009). Green engineering: continuous production of biodiesel using an alkaline catalyst in an intensified narrow channel reactor. *Journal of Environmental Monitoring*, 642-647.

Kang, S. W. and Tseng, S. C. (2007). Analysis of effectiveness and pressure drop in microcross-flow heat exchanger. *Applied Thermal Engineering*, 877–885.

Kefas, H. M., Yunus, R., Rashid, U. and Taufiq-Yap, Y. H. (2019). Enhanced biodiesel synthesis from palm fatty acid distillate and modified sulfonated glucose catalyst via

an oscillation flow reactor system. *Journal of Environmental Chemical Engineering*, 102993.

Kiss, A. A. and Bildea, C. S. (2012). A review of biodiesel production by integrated reactive separation technologies, *Journal of Chemical Technology & Biotechnology*. 861-879.

Kobayashi, I., Neves, M. A., Yokota, T., Uemura, K. and Nakajima, M. (2009). Generation of Geometrically Confined Droplets Using Microchannel Arrays: Effects of Channel and Step Structure. *Industrial & Engineering Chemistry Research*, 8848–8855.

Kralj, J. G., Sahoo, H. R. and Jensen, K. F. 2007. Integrated continuous microfluidic liquid–liquid extraction. *Lab Chip*, 256-263.

Kusdiana, D. and Saka, S. (2001). Kinetics of transesterification in rapeseed oil to biodiesel fuel as treated in supercritical methanol. *Fuel*, 693–698.

Laziz, M., KuShaari, A., Azeem, K.Z., Yusup, B., Chin, S. and Denecke, J. (2020). Rapid production of biodiesel in a microchannel reactor at room temperature by enhancement of mixing behaviour in methanol phase using volume of fluid model. *Chemical Engineering Science*, 115532.

Lin, C. Y., Chen, Y. Y., Chen, P. Y., Chen, M. C., Su, T. F. and Chiang, Y. Y. (2021). Scale-out production in core-annular liquid–liquid microextractor. *Journal of Flow Chemistry*, 569–577.

Lomax, H., Pulliam, T. H. and Zingg, D. W. (1999). *Fundamentals of Computational Fluid Dynamics*. University of Toronto Institute for Aerospace Studies.

Lopes, M.G.M., Santana, H.S., Andolphato, V.F., Russo, F.N., Silva Jr., J.L. and Taranto, O.P. (2019). 3D printed micro-chemical plant for biodiesel synthesis in millireactors. *Energy Conversion and Management*, 475-487.

López-Guajardo, E., Ortiz-Nadal, E., Montesinos-Castellanos, A. and Nigam, K.D.P. (2017). Process Intensification of Biodiesel Production Using a Tubular Micro-Reactor (TMR): Experimental and Numerical Assessment. *Chemical Engineering Communications*. 467–475.

Lukić, M. and Vrsaljko, D. (2021). Effect of channel dimension on biodiesel yield in millireactors produced by stereolithography. *International Journal of Green Energy*, 156–165.

Maia, D.C., Salim, V.M.M. and Borges, C.P. (2016). Membrane contactor reactor for transesterification of triglycerides heterogeneously catalyzed, *Chemical Engineering and Processing*, 220-225.

Martínez Arias, E. L., Fazzio Martins, P., Jardini Munhoz, A. L., Gutierrez-Rivera, L. and Maciel Filho, R. (2012). Continuous Synthesis and in Situ Monitoring of Biodiesel Production in Different Microfluidic Devices. *Industrial & Engineering Chemistry Research*, 10755–10767.

Mathes, B. (2016). Future Production Concepts in the Chemical Industry. Available at: https://www.chemanager-online.com/en/topics/production/future-production-concepts-chemical-industr. Accessed: January 16, 2022.

Mohadesi, M., Aghel, B., Maleki, M. and Ansari, A. (2020a). Study of the transesterification of waste cooking oil for the production of biodiesel in a microreactor pilot: The effect of acetone as the co-solvent. *Fuel*, 117736.

Mohadesi, M., Aghel, B., Maleki, M. and Ansari, A. (2020b). The use of KOH/Clinoptilolite catalyst in pilot of microreactor for biodiesel production from waste cooking oil. *Fuel*, 116659.

Mohadesi, M., Gouran, A. and Dehghan Dehnavi, A. (2021). Biodiesel production using low cost material as high effective catalyst in a microreactor. *Energy*, 119671.

Mohammad, N., Chukwudoro, C., Bepari, S. And Basha, O., Aravamudhan, S. and Kuila, D. (2021). Scale-up of high-pressure F-T synthesis in 3D printed stainless steel microchannel microreactors: Experiments and modeling. *Catalysis Today*.

Moukalled, F., Mangani, L. and Darwish, M., (2016). *The Finite Volume Method in Computational Fluid Dynamics: An Advanced Introduction with OpenFOAM and Matlab*, *Fluid Mechanics and its Applications.* 1 edition, Vol. 1, Springer, Switzerland.

Nasiri, R., Shamloo, A., Akbari, J., Tebon, P., R. Dokmeci, M. and Ahadian, S. (2020). Design and Simulation of an Integrated Centrifugal Microfluidic Device for CTCs Separation and Cell Lysis. *Micromachines*, 699.

Ogunkunle, O. and Ahmed, N. A. (2019). A review of global current scenario of biodiesel adoption and combustion in vehicular diesel engines. *Energy Reports*, 1560–1579.

Palm, O. M., Barbosa, S. L. A. F., Gonçalves, M. W., Duarte, D. A., Catapan, R. C. and Pinto, C. R. S. C. (2022). Plasma-assisted catalytic route for transesterification reactions at room temperature. *Fuel*, 121740.

Pavlović, S., Šelo, G., Marinković, D., Planinić, M., Tišma, M. and Stanković, M. (2021). Transesterification of Sunflower Oil over Waste Chicken Eggshell-Based Catalyst in a Microreactor: An Optimization Study. *Micromachines*, 120.

Qadeer, M. U., Ayoub, M., Komiyama, M., Daulatzai, M. U. K., Mukhtar, A., Saqib, S., Ullah, S., Qyyum, M. A., Asif, S. and Bokhari, A. (2021). Review of biodiesel synthesis technologies, current trends, yield influencing factors and economical analysis of supercritical process. *Journal of Cleaner Production*, 127388.

Quiroz-Pérez, E., Gutiérrez-Antonio, C. and Vázquez-Román, R. (2019). Modelling of production processes for liquid biofuels through CFD: A review of conventional and intensified technologies. *Chemical Engineering and Processing: Process Intensification*, 107629.

Rahimi, M., Aghel, B., Alitabar, M., Sepahvand, A. and Ghasempour, H. R. (2014). Optimization of biodiesel production from soybean oil in a microreactor. *Energy Conversion and Management*, 599–605.

Rahimi, M., Mohammadi, F., Basiri, M., Parsamoghadam, M. A. and Masahi, M. M. (2016). Transesterification of soybean oil in four-way micromixers for biodiesel production using a cosolvent. *Journal of the Taiwan Institute of Chemical Engineers*, 203–210.

Reyes, I., Ciudad, G., Misra, M., Mohanty, A., Jeison, D. and Navia, R. (2012). Novel sequential batch membrane reactor to increase fatty acid methyl esters quality at low methanol to oil molar ratio, *Chemical Engineering Journal*, 459-467.

Rossetti, I. (2018). Continuous flow (micro-)reactors for heterogeneously catalyzed reactions: Main design and modelling issues. *Catalysis Today*, 20–31.

Saber, M., Commenge, J. M. and Laurent, F. (2010). Microreactor numbering-up in multi-scale networks for industrial-scale applications: Impact of flow maldistribution on the reactor performances. *Chemical Engineering Science*, 372-379.

Saka, S., and Kusdiana, D. (2001). Biodiesel fuel from rapeseed oil as prepared in supercritical methanol. *Fuel*, 225–231.

Santana, H. S., Lopes, M. G. M., Silva Jr., J. L. and Taranto, O. P. (2018a). Application of microfluidics in process intensification. *International Journal of Chemical Reactor Engineering*, 16(12).

Santana, H. S., Sanchez, G. B. and Taranto, O. P. (2017a). Evaporation of excess alcohol in biodiesel in a microchannel heat exchanger with Peltier module. *Chemical Engineering Research and Design*, 20-28.

Santana, H. S., Silva, J. L., Da Silva, A. G. P., Rodrigues, A. C., Amaral, R. D. L., Noriler, D. and Taranto, O.P. (2021). Development of a New Micromixer "elis" for Fluid Mixing and Organic Reactions in Millidevices. *Industrial & Engineering Chemistry Research*, 9216–9230.

Santana, H. S., Silva, J. L., Tortola, D. S., & Taranto, O. P. (2018b). Transesterification of sunflower oil in microchannels with circular obstructions. *Chinese Journal of Chemical Engineering*, 852–863.

Santana, H. S., Tortola, D. S., Reis, É. M., Silva, J. L. and Taranto, O. P. (2016). Transesterification reaction of sunflower oil and ethanol for biodiesel synthesis in microchannel reactor: Experimental and simulation studies. *Chemical Engineering Journal*, 752–762.

Santana, H. S., Tortola, D. S., Silva, J. L. and Taranto, O.P. (2017b). Biodiesel synthesis in micromixer with static elements. *Energy Conversion and Management*, 28–39.

Silva, M. V. D., Hori, C. E. and Reis, M. H. M. (2015). Thermochemical data of the oleic acid esterification reaction: A quantum mechanics approach. *Fluid Phase Equilibria*, 168–174.

Shen, Q., Zhang, C., Tahir, M. F., Jiang, S., Zhu, C., Ma, Y. and Fu, T. (2018). Numbering-up strategies of micro-chemical process: Uniformity of distribution of multiphase flow in parallel microchannels. *Chemical Engineering & Processing: Process Intensification*, 148-159.

Shuit, S. H., Ong, Y. T., Lee, K. T., Subhash, B. and Tan, S. H. (2012). Membrane technology as a promising alternative in biodiesel production: a review, *Biotechnology Advances*, 1364-1380.

Stacy, C. J., Melick, C. A. and Cairncross, R. A. (2014). Esterification of free fatty acids to fatty acid alkyl esters in a bubble column reactor for use as biodiesel. *Fuel Processing Technology*, 70–77.

Sun, J., Ju, J., Ji, L., Zhang, L., and Xu, N. (2008). Synthesis of Biodiesel in Capillary Microreactors. *Industrial & Engineering Chemistry Research*, 1398–1403.

Tabatabaei, M., Aghbashlo, M., Dehhaghi, M., Panahi, H. S. P., Mollahosseini, A., Hosseini, M. and Soufiyan, M. M. (2019). Reactor technologies for biodiesel production and processing: A review. *Progress in Energy and Combustion Science*, 239–303.

Thangarasu, V., Siddharth, R. and Ramanathan, A. (2020). Modeling of process intensification of biodiesel production from Aegle Marmelos Correa seed oil using microreactor assisted with ultrasonic mixing. *Ultrasonics Sonochemistry*, 104764.

Tiwari, A., Rajesh, V. M. and Yadav, S. (2018). Biodiesel production in micro-reactors: a review. *Energy for Sustainable Development*, 143-161.

Tonkovich, A., Kuhlmann, D., Rogers, A., Mcdaniel, J., Fitzgerald, S., Arora, R. and Yuschak, T. (2005). Microchannel technology scale-up to commercial capacity. *Chemical Engineering Research and Design*, 634-639.

Vankayala, B. K., Lob, P., Hessel, V., Menges, G., Hofmann, C., Metzke, D., Krtschil, U. and Kost, H. J. (2007). Scale-up of process intensifying falling film microreactors to pilot production scale. *International Journal of Chemical Reactor Engineering*, A91.

Vladisavljević, G. T., Khalid, N., Neves, M. A., Kuroiwa, T., Nakajima, M., Uemura, K., Ichikawa, S. and Kobayashi, I. (2013). Industrial lab-on-a-chip: Design, applications and scale-up for drug discovery and delivery. *Advanced Drug Delivery Reviews*, 1626-1663.

Voegele, E. (2020). NBB: Biodiesel can help meet USDA's AIA goals. Biodiesel Magazine. Available at: http://www.biodieselmagazine.com/articles/2517256/nbb-biodiesel-can-help-meet-usdaundefineds-aia-goals. Accessed October 15, 2021.

Wang, L., Kong, X. and Qi, Y. (2016). Optimal design for split-and-recombine-type flow distributors of microreactors based on blockage detection. *Chinese Journal of Chemical Engineering*, 897-903.

Wen, Z., Yu, X., Tu, S. T., Yan, J. and Dahlquist, E. (2009). Intensification of biodiesel synthesis using zigzag micro-channel reactors. *Bioresource Technology*, 3054–3060.

Wirth, T. (2013). *Microreactors in Organic Chemistry and Catalysis*. (T. Wirth, Ed.), 2nd edition, Vol. 1, Wiley-VCH.

Whitesides, G. M. (2006). The origins and the future of microfluidics. *Nature*, 368-373.

 doi:10.20944/preprints202202.0257.v1

Xie, W., Peng, H. and Chen, L. (2006). Transesterification of soybean oil catalyzed by potassium loaded on alumina as a solid-base catalyst. *Applied Catalysis A: General*, 67–74.

Xu, W., Gao, L. J., Xiao, G. M. (2015). Biodiesel production optimization using monolithic catalyst in a fixed-bed membrane reactor, *Fuel*, 484-490.

Yeh, S. I., Huang, Y. C., Cheng, C. H., Cheng, C. M. and Yang, J. T. (2016). Development of a millimetrically scaled biodiesel transesterification device that relies on droplet-based co-axial fluidics. *Scientific Reports*, 29288.

Zabeti, M., Wan Daud, W. M. A. and Aroua, M. K. (2009). Activity of solid catalysts for biodiesel production: A review. *Fuel Processing Technology*, 770–777.

Zhang, B., Ren, J., Liu, X., Guo, Y., Guo, Y., Lu, G. and Wang, Y. (2010). Novel sulfonated carbonaceous materials from p-toluenesulfonic acid/glucose as a high-performance solid-acid catalyst. *Catalysis Communications*, 629–632.

Zhang, J., Wang, K., Teixeira, A. R., Jensen, K. F. and Luo, G. (2017). Design and scaling up of microchemical systems: A review. *The Annual Review of Chemical and Biomolecular Engineering*, 285-305.

Zhang, X., Wiles, C., Painter, S. L., Watts, P. and Haswell, S. J. (2006). Microreactors as tools for chemical research. *Chimica Oggi*, 43–45.