



HAL
open science

Production of oil in water emulsions in microchannels at high throughput: Evaluation of emulsions in view of cosmetic, nutraceutical or pharmaceutical applications

Ralph Nehme, Walid Blel, Agnès Montillet, Jérôme Bellettre, Luc Marchal

► To cite this version:

Ralph Nehme, Walid Blel, Agnès Montillet, Jérôme Bellettre, Luc Marchal. Production of oil in water emulsions in microchannels at high throughput: Evaluation of emulsions in view of cosmetic, nutraceutical or pharmaceutical applications. *Chemical Engineering and Processing: Process Intensification*, 2021, 161, pp.108301. 10.1016/j.cep.2021.108301 . hal-03148346

HAL Id: hal-03148346

<https://hal.science/hal-03148346v1>

Submitted on 23 Mar 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Journal: Chemical Engineering Processing – Process intensification

Production of oil in water emulsions in microchannels at high throughput: evaluation of emulsions in view of cosmetic, nutraceutical or pharmaceutical applications.

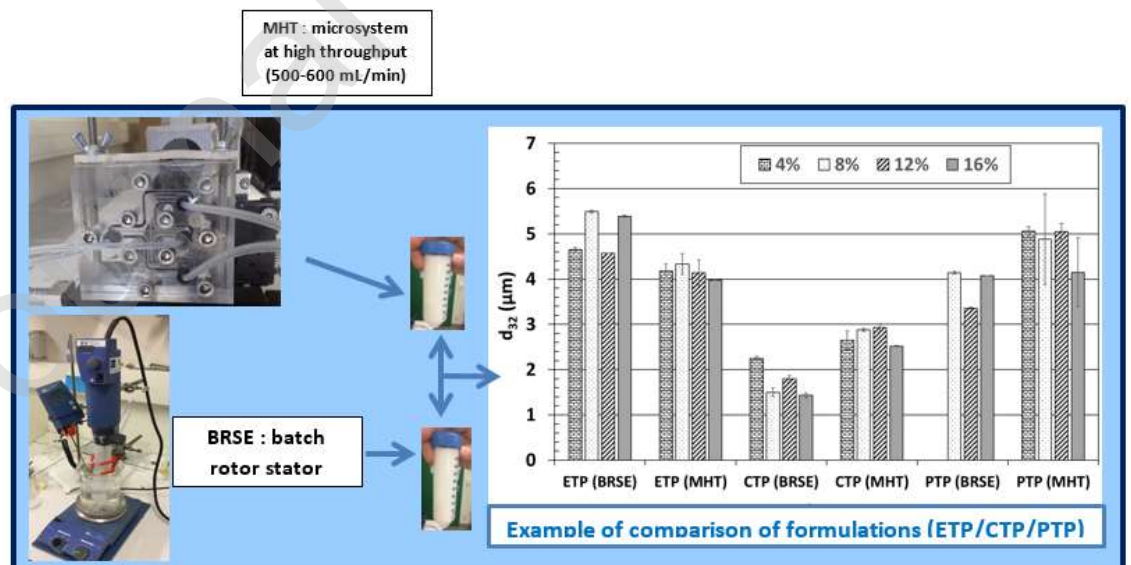
Ralph NEHME¹, Walid BLEL¹, A. MONTILLET^{1,*}, Jérôme BELLETTRE², Luc MARCHAL¹

¹ Université de Nantes, CNRS, GEPEA, UMR6144, BP 406, 44602 Saint-Nazaire (France),

² Université de Nantes, CNRS, LTeN, UMR6607, BP 50609, 44306 Nantes (France)

**Corresponding author: agnes.montillet@univ-nantes.fr,*

Graphical abstract



Highlights

- Evaluation of an emulsifier based on a cross-slot microsystem at high flowrate
- Use of 3 formulations related to cosmetics, nutraceuticals or pharmaceuticals
- Comparison of emulsions to those made with a laboratory rotor-stator device
- Characteristics of emulsions from microsystem are close to those from rotor-stator

Abstract

This work investigates the quality of emulsions obtained from fast emulsification in a microsystem implemented at high throughput. The aim is to manufacture oil in water (O/W) emulsions in which bioactive ingredients could be encapsulated. These emulsions may be of interest for cosmetic, nutraceutical and/or pharmaceutical applications. A microsystem based on an improved cross-slot configuration is tested for production of emulsions with various formulations in a range of flow rate comprised in 100-600 mL/min. Dispersed lipid phase consists mainly in sunflower oil. The continuous aqueous phase is a Non-Newtonian fluid as it includes xanthan in order to stabilize the emulsions. Several commercial surfactants are also used to stabilize the emulsions. Their stability is examined during a storage period of approximately 30 days. For most tests, the evaluation of emulsions is based on a comparison with emulsions produced from a commercial laboratory rotor stator emulsifier. The results show only a few slight differences between the characteristics of emulsions generated in continuous in the microsystem and those obtained from the batch rotor-stator emulsifier. The results are therefore mostly comparable, which leads to the conclusion that microsystems can offer an interesting alternative to the small-scale production of emulsions.

Keywords

Microsystems, oil-in-water emulsion, continuous emulsification, physical stability, size distribution.

Introduction

Cosmetic and nutraceutical fields are particularly concerned by emulsification processes. Depending on applications, specific characteristics of emulsions are targeted. Emulsions can be characterized as a function of many parameters such as: the nature of the dispersed and continuous phases, the volume content of the dispersed phase, the particle size distribution of droplets, the stability... (**Tadros, 2016**). Concerning the droplet size distribution, mean droplet size and size distribution are the main parameters that allow classifying the emulsions. Three main kinds of emulsions are therefore described in the literature with the following respective size range: micro-emulsions (10-100 nm), mini or nano-emulsions (200-1000 nm) and macro-emulsions ($>1 \mu\text{m}$) (**Brochette, 2013**). Macro-emulsions are opaque, like milk, while micro and nano emulsions are rather transparent. Based on smaller droplets, micro-emulsions are thermodynamically more stable.

Recent publications show a keen interest in the effect of encapsulation of bioactive molecules in micro and nano-emulsions for nutraceuticals and cosmetics. However, many common cosmetics like milks and creams are based on macro-emulsions (**Arrieta-Escobar et al., 2019**). On the other hand, macro-emulsions are still of interest in food science technology (**Kan et al. 2020**). Concerning nutraceutical applications, macro-emulsions are also of interest; knowing that emulsion based delivery systems can involve many functional ingredients including hydrophilic or hydrophobic molecules.

Macro-emulsions are usually prepared at a large scale in batch mode, using tanks equipped with ad-hoc stirring mobiles or rotor-stator devices (**Poux and Canselier, 2004, Arrieta-Escobar et al., 2019, Binder et al., 2019**). Continuous processes are also available in the market; they are mainly based on the use of high pressure devices, like homogenizers (**Brochette, 2013**). More seldom is the use of static mixers for these kinds of applications.

One drawback observed with some commonly used techniques such as high-pressure homogenizers, particularly when several passes are implemented, as well as microfluidizers and rotor-stator devices is the risk of denaturation of sensitive compounds by undesired dissipated heat (**Khalid et al., 2017**). Another possible concern is the necessity of limiting the exposure of fluids to dioxygen, particularly when compounds such as antioxidant substances and unsaturated fat are involved in the formulation. These two kinds of risks may be easily avoided by using a fast and confined continuous emulsifying process. The development of

microsystems is mainly based on the possibility of intensifying the mass and momentum transfer; they are well known to offer the possibility of mixing and dispersing liquid/liquid phases or gas/liquid ones at a very small scale, in a very tiny confined volume and at a very short time scale. However, as a drawback, microfluidics is often associated to very small treated fluxes, which is usually the case. This is a fact that, in most of published works concerning the emulsification in microchannels, flow conditions are such that very narrow distributions of size of droplets are obtained. Implementation of Microsystems at High Throughput (MHT), i.e. at the order of half a liter per minute, has however already been successfully investigated, in particular in the case of water in oil (W/O) emulsification with diesel (**Marchitto et al., 2018**) in order to improve the combustion.

MHT may have an interest as a versatile tool for small scale productions as well as for research and development. Unlike tanks equipped with rotor-stator systems, no development of scale-up is necessary with a MHT device between the trials at laboratory scale (2-3 L) and a small-scale production (i.e. 300-800 L/day). MHT also could be integrated in compact processes as a continuous mixing device. In the present work, the objective is to test a recently designed MHT (Bellettre et al., 2017) in the case of oil in water (O/W) emulsions with different formulations that may approach potential applications in nutraceutical and cosmetic fields. The idea is to explore the potential of MHT, based on the characteristics of the obtained fresh emulsions, such as mean size of droplets and size distribution, as well as on their physical stability at middle time scale (about 30 days). Obtained emulsions are compared to those prepared using a classical laboratory-scale rotor-stator device as a reference. Several formulations are implemented, including xanthan as stabilizing agent and various commercial surfactants. Some formulations are inspired from the work of **Rodriguez-Ruiz et al. (2018)** who investigated astaxanthin loading in lipid carriers at a very small batch level. **Khalid et al. (2017)**, used MicroChannel Emulsification (MCE) for a similar objective. Their device is based on a microchannel array plates; droplets are formed through circular micro-holes with diameter 10 μ m. The principle of this process is close to membrane emulsification, giving rise to the generation of rather monodisperse droplets. In the work of **Khalid et al. (2017)**, the range of flow rates of the dispersed phase tested was approximately 1 to 6 mL/h, while that of continuous phase was 250 to 500 mL/h. The Sauter diameter of the droplets ranged between 20-40 μ m, depending on the dispersed phase flow rate. The same device was used by **Ma et al. (2020)** to make a comparative study with High Pressure Homogenization (HPH) on oil-in-water emulsions encapsulating fucoxanthin. It was pointed out that the MCE device provides

stable monodispersed emulsions but the Sauter diameter (about 30-40 μm) obtained is much higher than that from HPH (about 0.1 μm). The chemical stability of emulsion was shown to be better using the MCE device than HPH. The authors attribute the poorer performance of PHP to the particularly high energy input. On the other hand, bio accessibility of fucoxanthin was better with emulsions obtained from HPH, due to the higher specific surface area in the emulsions. In conclusion, the MCE device used by these authors has the major advantage of providing rather monodisperse size distributions, but the Sauter diameter of the droplets is rather high, which is expected due to the principle of the device. A second drawback is the flow rate of emulsion that can be produced with MCE. It is 60 times lower than those that can be implemented with the presently tested MHT. Then, as explained, the major challenge of the present work lies in investigating the potential of MHT in terms of size distribution and size dispersion of droplets. Considering previous works based on W/O emulsions (Marchitto, 2018), this device is intended to produce emulsions with lower Sauter diameters than MCE. On the other hand, it may involve less energy input compared to HPH. Thus, energy dissipation rate of the flow in MHT emulsifier and energy consumption of process are also evaluated and discussed in this work.

Materials and methods

Chemicals

As explained in the introduction, the objective of this work is to get an insight on the potential of MHT as an alternative kind of emulsifier for cosmetic, nutraceutical or even pharmaceutical applications. Therefore, some of the tested formulations are inspired from works done on the encapsulation of antioxidant such as that of **Rodriguez-Ruiz et al. (2018)**, and some other are simplified formulations based on various surfactants that are commercially available for cosmetic, pharmaceutical and/or food fields. This work doesn't intend to analyze thoroughly the physicochemical effects of surfactants, nor to optimize formulations, but to test fairly simple and standard ones in order to characterize the quality of emulsions obtained with MHT, in terms of droplet size and physical stability, and to compare them with emulsions obtained from a classical rotor-stator device.

The main mass component of the continuous phase of oil in water emulsions prepared in this work is tap water, while the main mass ingredient used in dispersed phase is commercial sunflower oil. This vegetal oil has been selected as it is a suitable and usual

diluent for carotenoids such as astaxanthin, for example. It is itself rich in antioxidants such as vitamin E (440-1520 mg/kg) and phytosterols (2400-5000 mg/kg). These molecules can help in preserving the antioxidant activity of beta-carotene (**Rodriguez-Ruiz et al., 2018**). As explained, various surfactants and additives have been selected for their respective ability in obtaining emulsions complying for use in pharmaceutical, nutraceutical or cosmetic fields; they are included in the dispersed and continuous phases in this work, depending on the tested formulations. Their main characteristics are briefly described in **Table 1**.

Concerning the applications of the three surfactants respectively used in the oily dispersed phase, according to the manufacturers:

- Labrafac™ (Gattefosse, France) can be used for oily and self-emulsifying lipid formulation for oral applications. It can also be included in topical ointment, emulsions, microemulsions, and foams as well as in parenteral lipid-based solution.
- Peceol™ (Gattefosse, France) is an oily vehicle used as a solubilizer for lipophilic Active Pharmaceutical Ingredients (APIs) in oral and topical formulations. Easynov™ (Seppic, France) is a non-ionic liquid emulsifier destined to cosmetic W/O emulsions.
- Precirol® ATO 5 is a glyceride with an intermediate melting point that can be used for different pharmaceutical applications, such as lubricant and flow aid in powder blends for capsule filling and as a coating agent for taste masking. It is presently added in the dispersed phase to help its stabilization at ambient temperature.

Concerning the two surfactants used in the aqueous continuous phase:

- Poloxamer™ 407 (Sigma Aldrich, Germany) is a hydrophilic synthetic polymer which is non-ionic surfactant. It can be used for cosmetic applications and in personal care products, or for some pharmaceutical formulations like oral gels (**Basha et al., 2013**).
- Tween80™, i.e. polysorbate 80, is approved as a texture agent (emulsifier and stabilizer) according to its codification E433 in the *Codex Alimentarius*. It can be added to many foods at maximum doses between 10 mg/kg (salt) and 5,000 mg/kg (seasonings and condiments, clear sauces, etc.), or even 25,000 mg/kg in food supplements. The European Association of Emulsifier Manufacturers (EFEMA) also lists polysorbate 80 in pharmaceuticals and cosmetics. Seppic (France) indicates that it can be used for injection or oral and topical pharmaceutical applications.

Xanthan gum (XG) is a well-known thickening agent of industrial relevance that is approved for food application with codification E415. For such an application, it is generally added

with an amount of 0.1 to 0.5% (w/w). The use of this microbial gum is widespread: from personal care products and cosmetics to enhancement of oil recovery. Regarding the application of the xanthan gum in cosmetics, the properties induced by this gum in solutions are still under study; for their part, **Dubuisson et al. (2018)** reports that concentration of xanthan in solutions has a great impact on end-use properties all over the life of the product, i.e. before, during and after its application on skin. These authors also point out that a relationship links the involved amount of xanthan with several paramount qualities expected from cosmetics: “integrity of shape, penetration force, wetness, ease of spreading and gloss” **Dubuisson et al. (2018)**. Concerning the targeted applications in this work, the use of xanthan in aqueous solutions has a major advantage. Added as stabilizer, it ensures a large viscosity to the produced emulsion at rest. Furthermore, aqueous solutions of xanthan gum exhibit a very shear thinning behavior. According to **Sworn (2009)**, the rheology of these solutions is characterized by a second levelling off of the viscosity, so-called lower Newtonian region, which is located at high shear rates (upper than 10^5 s^{-1}). So, they present a low apparent viscosity at high shear rates. This is a key point that explains why it is feasible to inject and handle aqueous xanthan solutions in MHT. Another key point is the ability of xanthan to limit oxygen consumption. The antioxidative effect of xanthan has been studied by **Shimada et al. (1996)**. According to these authors, its high antioxidative effect, compared to other polysaccharides like pectin, guar gum and tragacanth gum, may be mostly accounted for by its high metal-binding ability. Its viscous behavior may also be determinant. Finally, an interesting result of their contribution is the fact that, in the range of mean droplet size 7 to 21 μm , the average droplet size and the time for 50% consumption of dissolved oxygen show no correlation.

A commercial xanthan, Ketrol AP (Kelco), is used in this work. It is sold as a powder that can be dissolved in aqueous solutions at ambient.

Designation	Supplier	Generic name	Component / or main components	HLB	aspect	phase
Precirol TM ATO 5	Gattefosse (France)	glyceryl palmitostearate	esters of palmitic (C16) and stearic acids (C18), the diester fraction being the predominant	2	Powder that can be dissolved at 50-60 $^{\circ}\text{C}$	D

Peceol	Gattefosse (France)	Monoleate glycerol		1	Liquid at ambient	D
EasyNov™	Seppic (France)	octyldodecanol	Octyldodecanol, Octyldodecyl Xyloside, PEG-30 Dipolyhydroxystearate	?	Liquid at ambient	D
Labrafac™ Lipophile WL 1349	Gattefosse (France)	Medium chain triglycerides	triglyceride with medium chain size (caprylic (C8) and capric (C10) acids)	1	Liquid at ambient	D
Keltrol AP™	Kelco	xanthan	extracellular polysaccharide secreted by a bacteria (<i>Xanthomonas campestris</i>)		Powder	C
Poloxamer 407™	Sigma Alrich (Germany)		Nonionic synthetic copolymer made of hydrophobic residue of polyoxypropylene (POP) between two hydrophilic polyoxyethylene (POE) units.	22	Powder that can be dissolved at ambient	C
Tween 80™	Sigma Alrich (Germany)	polysorbate 80 (E433)	Polyoxyethylene sorbitan monooleate	15	Liquid at ambient	C

Table 1: Surfactants and additives used in dispersed (D) and continuous (C) phases, depending on the tested formulations.

Formulations and preparation of continuous and dispersed phases

As a starting point, a formulation proposed by **Rodriguez-Ruiz et al. (2018)** is selected. These authors have investigated ‘encapsulating’ of an antioxidant, Astaxanthin, in a dispersed oily phase. Their formulation encountered a mixture of poloxamer™ 407 and Tween 80 in water as the continuous phase, and a mixture of Precirol™ ATO5 and sunflower oil as the dispersed phase. The volume fraction of lipid phase was fixed at 8.4%. They have managed to produce stable astaxanthin loaded nanostructured lipid carriers (~60 nm) thanks to a batch procedure implemented at small scale (i.e. a volume of few mL). It is currently planned to transpose their protocol into a continuous mode one, using MHT. The implementation of MHT is intended to limit the contact between atmosphere and liquid phases as well as

reducing the residence time of the fluids in the emulsifier thanks to the intensification of mixing. On the other hand, the system can be implemented up to 60-70 degrees Celsius (°C). This is useful for handling dispersed phases that contain lipid compounds characterized by a high melting temperature, such as Precirol™.

Due to the use of Precirol™, the formulation proposed by **Rodriguez-Ruiz et al. (2018)** needs to be implemented at a relatively high temperature (about 75 degrees Celsius (°C) in their work) which, in our opinion, may be not favorable concerning the encapsulation of thermosensitive molecules. Then, in order to offer the possibility of reducing the temperature of emulsification, other surfactants, respectively Peceol™, Labrafac™ and Easynov™ (Table 1), have been investigated as possible alternative for Precirol™. These three commercial surfactants can be handled at ambient temperature and are compatible with the targeted applications. It should be kept in mind that Precirol™, being solid at ambient temperature, presents the major advantage of helping in stabilizing emulsions. Then, in the present work xanthan gum is selected to be added in the aqueous phase in order to increase the viscosity of the emulsions at rest, so as to slow coalescence phenomenon, which is particularly important in the case of formulations free of Precirol™.

The different formulations tested in the present work are recapped in Table 2. The volume fraction of dispersed phase is varied between 4 and 16% in all the tested formulations and even up to 24% in the case of formulation containing Precirol™. Only the volume fraction of dispersed phase is investigated, as this work doesn't intend to optimize formulations (i.e. composition and contents of components in each phase). The contents of components have been usually fixed following the guidelines of suppliers. However, in the case of Easynov™, preliminary tests have outlined that a content of 30 mg/mL of the dispersed phase gives better results. It should be emphasized that no preservative agent was added in the formulations, so the samples were kept in a fridge at 4 degrees Celsius (°C) after their production.

Name and Reference of the formulation (% of the oily phase)	Dispersed oily phase		Continuous aqueous phase		
	Sunflower oil added in sufficient quantity for (mL)	Mass content per volume of dispersed phase	Water added in sufficient quantity for (mL)	Mass content per volume of continuous phase	
Tween 80 (mg/mL)		Precirol™ (mg/mL)		Poloxamer (mg/mL)	Xanthan (mg/mL)

PTP / 4	4	7.12	53.2	96	4.91	2
PTP / 8	8			92		
PTP / 12	12			88		
PTP / 16	16			84		
PTP / 20	20			80		
PTP / 24	24			76		
		Tween 80 (mg/mL)	Peceol TM (mg/mL)		Poloxamer (mg/mL)	Xanthan (mg/mL)
CTP / 4	4	7.12	53.4	96	4.91	2
CTP / 8	8			92		
CTP / 12	12			88		
CTP / 16	16			84		
		Tween 80 (mg/mL)	Easynov TM (mg/mL)		Poloxamer (mg/mL)	Xanthan (mg/mL)
ETP / 4	4	7.12	30	96	4.91	2
ETP / 8	8			92		
ETP / 12	12			88		
ETP / 16	16			84		
		Tween 80 (mg/mL)	Labrafac TM (mg/mL)		Poloxamer (mg/mL)	Xanthan (mg/mL)
LTP / 4	4	7.12	53.2	96	4.91	2
LTP / 8	8			92		
LTP / 12	12			88		
LTP / 16	16			84		

Table 2: Details on the tested formulations. Different fractions of dispersed phases are tested. The volumes of oil and water (i.e. dispersed and continuous phases) are given for a total volume of emulsion of 100 mL.

The formulation of the aqueous phase in the four types of emulsions is the same. To prepare a batch of 1 liter of this solution, water is pre-heated at 50 degrees Celsius (°C) in order to dissolve easily Poloxamer and xanthan gum using a magnetic stirrer. After complete dissolution (i.e. after about one hour), the solution is cooled and stored at 4 degrees Celsius (°C).

Batches of 40 mL of each lipid phase are prepared separately. Emulsifiers of oily phase are dissolved in oil at 50 degrees Celsius (°C).

Emulsification procedure with a rotor stator system

A laboratory scale batch rotor-stator emulsifier, **BRSE**, is used in this work as a reference system for emulsification. An Ultra-TurraxTM device manufactured by IKA (reference T18 – mixing tool S18D-10 G- ks) is implemented in this work. In this system, the dispersion of the to be dispersed phase into the continuous one is ensured by a very high circumferential speed that strains the fluid between the mobile and fixed parts of the device. The fluid undergoes a strong shear. In this process, the recirculation of the fluid must be done during a set period of time. The number of revolution per time represents the second parameter to select; it determines the velocity of the mobile part. The operator must indeed select them keeping in mind that an equilibrium must be insured, allowing a thin emulsion to be formed while avoiding breaking and/or over-heating it. Heating the solution is particularly problematic if one or both phases include a thermosensitive compound like vitamin E, for example.

Therefore, a preliminary study has been developed with PTP formulation in order to determine the influence of the speed of the rotor and that of the duration of its rotation. The emulsions are obtained by slowly introducing a pre-heated oily phase into a pre-heated water phase while operating the rotor-stator.

Experimental device based on MHT microsystem

As mentioned in the introduction, the MHT (**Bellettre et al., 2017**) used in this work has been primarily developed for a project targeting energy applications, for which a continuous production of specific water in oil emulsions was required. Its objective was to improve combustion in boilers and engines by feeding them in a continuous way with a fresh W/O emulsion (water in gas-oil or water in vegetable oil). Using a fresh emulsion, i.e. made on demand, may avoid the use of surfactant, which is better for several reasons such as not altering the carbon balance in the process and not producing extra hazardous molecules. Then, specifications which led to its development encountered different constraints like: the fraction of water in oil (about 5-15%), the average diameter of droplets (~4 μm ideally), the flow rate of produced emulsion (300-600 mL/min). The improvement of the design of microsystems made specifically for this topic had led to the development of an emulsifier (Fig. 1) based on cross slot geometry including a step, favoring impingement of two different fluxes of fluids, and an elbow in each inlet branch to intensify the break-up of droplets (**Belkadi et al., 2018**). The microsystem encounters four microchannels with square cross sections that are engraved in a plate of PMMA. An upper plate of PMMA acts as a cover. The plates are sealed thanks to

screws and a seal. In the present work, the dispersed phase is admitted in the $300\ \mu\text{m}$ in width microchannel (fig. 1). The continuous phase enters in the opposite channel, which is $600\ \mu\text{m}$ in width. Both inlet channels being off-centered, a swirl motion is given to the fluids in the impact zone. The emulsion is formed and collected through two $600\ \mu\text{m}$ in width microchannels. Concerning the particular flow pattern and droplet break-up mechanisms occurring in such a system, the reader can refer to several publications (Belkadi et al., 2015, Belkadi et al., 2016, Ji et al., 2020). The specific design of the microsystem enhances a swirl flow in the impinging area, associated with a dead zone. At the entrance of the outlet channels, flow structures are highly stretched and elongated, leading to multiple breakages of fluid filaments into droplets as well as of droplets into smaller ones.

The continuous and dispersed phases are pumped using two tri-pistons pumps (AP Trix 500, Armen, France). Preliminary tests made with xanthan aqueous solutions and sunflower oil have allowed verifying the values of the flowrate's values set on the pump's software. The volume fraction of the dispersed phase in the emulsion is fixed by setting the ratio of the flow rate of the dispersed phase on the sum of flow rates of the dispersed and continuous phases.

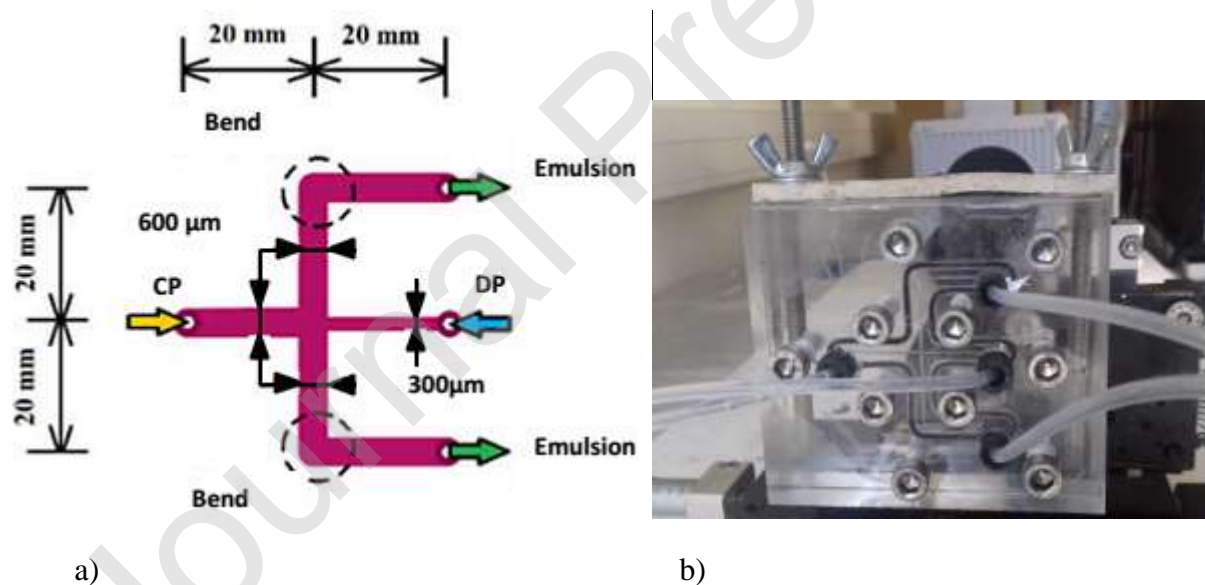


Figure 1: a) schematic representation of the microsystem (MHT) used. CP designates the continuous phase and DP the dispersed one. b) Image of the microsystem in use.

Characterization of droplets size distribution in emulsions

In this study, two techniques have been used in order to characterize the size dispersion of droplets in emulsions: optical microscopy (Axio scope A1, Zeiss), **OM**, and laser diffraction

particle size analysis, **LDPSA**, (Mastersizer 3000, Malvern). Both techniques present advantages and drawbacks. To be representative, optical microscopy needs to analyze a large number of droplets. The convenient number of droplets is set based on getting a convergence of standard deviation versus the number of measured droplets. Two drawbacks have to be cited for this technique: the limitation of accurate measurement of droplets, as there is a physical cut-off at about $1\ \mu\text{m}$, and the time needed for getting each size distribution. Concerning laser diffraction particle size analysis, a prior setting of various parameters is necessary to get a reliable use of this technique. Once this condition is achieved, many samples can be analyzed in a very limited time, which is the main advantage of this technique. A second advantage is, in theory, the range of particle size that can be detected by the device. Due to its physical principle, this technique gets access to the volume distribution of droplets; this is the distribution of the probability in terms droplet volume expressed as a function of the diameter of the droplets. The software of the device can convert this volume distribution into ones based on the surface of particles or number of particles. However, it should be emphasized that the conversion may amplify errors. Among the drawbacks presented by this technique, a part from using a special module which has not been available in this study, droplets presented in aggregates are not recognized as identities but analyzed as a single particle. This has been observed for some of our emulsions when comparing size distributions obtained from the two techniques. Indeed, applying a cut-off at $1\ \mu\text{m}$ in the case of **LDPSA** and comparing the volume density distributions obtained from the two techniques, points out a significant more spread dispersion with **LDPSA**. This is due to the presence of aggregates of droplets, proved by the images captured with the microscope.

The methodology that had been followed in this study is to favor the use of **LDPSA** for time saving, knowing that the main objective of this study is to compare the use of **MHT** versus **BRSE**.

As explained above, **LDPSA** provides a volume distribution. Such distribution attributes a high weight to large droplets, even if they are present in small numbers. Inversely, distributions that are based on the number of particles per range of size of droplets rub out the eventual presence of a few large droplets. It is usually recommended to use a distribution that has a meaning to the targeted application. In the present case, surface distribution is more relevant as interfacial phenomena govern the life time of emulsions. Thus, the distributions will be described using Sauter diameter, d_{32} , as the mean characteristic diameter (Eq. 2). A second parameter, called span (Eq. 3), is used to characterize the size dispersion.

$$d_{32} = \frac{\sum_{i=1}^n f_i d_i^3}{\sum_{i=1}^n f_i d_i^2} \quad \text{Eq. (2)}$$

$$\text{Span} = \frac{d_{90} - d_{10}}{d_{50}} \quad \text{Eq. (3)}$$

Where d_{10} , d_{50} and d_{90} are respectively the diameters corresponding to a cumulative probability density of 10, 50 and 90%.

Physical stability:

Since no preservative agent was added in the tested formulations, samples were stored in a fridge (4 degrees Celsius ($^{\circ}\text{C}$)) over a period of 30 days to evaluate the long-term emulsions stability. A slight or more pronounced creaming was observed, depending on the formulations, in emulsions. Then, the samples were gently manually re-dispersed before evaluating their characteristics: droplet size distribution, mean droplet size and span as explained above for fresh emulsions.

Rheology

Some rheological measurements were carried out at 20 degrees Celsius ($^{\circ}\text{C}$) (temperature maintained by Peltier effect) using a rotational rheometer (AR1000, TA Instruments) with smooth cone-plane geometry (60 mm diameter flat cone system with a 2° angle). The rheological measurements were carried out respectively on the aqueous phase, lipid phase and on emulsions made with CTP formulation only. Concerning emulsions, the measurements were tested on emulsions for which the 8% and 16% respective percentage of volume fraction of oily phase. Emulsions from BRSE and MHT emulsifiers were compared.

Results and discussion

Setting of the parameters for batch rotor stator emulsifier (BRSE)

As formerly explained, two parameters, speed of rotation of rotor and duration of dispersion respectively, have to be set. This was done using the PTP formulation. Moreover, a third parameter, the volume fraction of dispersed phase, was also varied in these trials. For each trial, the diameter of Sauter, d_{32} , is determined using **LDPSA** technique. The results are presented in Figure 2. Two durations for mixing, respectively 2 and 5 minutes, and two speeds of rotation of the rotor have been tested (15,000 and 20,000 rpm). At 15,000 rpm the

duration of mixing influences the final value of the Sauter diameter which is smaller at 5 min., whereas the tested duration of mixing shows no significant influence at 20,000 rpm, meaning that a full efficiency of the BRSE is reached at a smaller time at high speed of rotation. This observation is rather trivial as the speed of rotation conditions the number of passes of the fluid in the device and thus the probability of break-up of larger droplets, as well as the shear rate in the device ports. But, as already said, these tests are necessary to select parameters that are convenient for the present kinds of formulations. On the other hand, when using 20,000 rpm as the speed of rotation, the value of the Sauter diameter increases rather monotonically with the volume fraction of dispersed phase. The breakage of droplets may be limited by the energy brought by the system at high volume fractions; i.e. when a higher fraction of viscous fluid is introduced in the device. Another possible explanation may be that using a high fraction of oily phase favors coalescence; this phenomenon may be due to the higher specific surface area of created droplets and a possible lack of surfactant to cover them. At 15,000 rpm the value of the Sauter diameter is less sensitive to the volume fraction of dispersed phase, showing no clear relationship with it. The breakage of droplets is less efficient at this speed of rotation, then they are rougher, independently of the volume fraction of dispersed phase.

Despite a better breakage at 20,000 rpm, the couple of parameters [15,000 rpm, 5 min.] was selected in this study for the following experiments in order to avoid over-heating of emulsions during their formation. According to the literature, these conditions rather correspond to the production of coarse emulsions or dispersions (**Verkempinck et al., 2018**). It should be emphasized that many products from cosmetic companies corresponds to coarse emulsions, like milks for example. Experimental works usually report that finer emulsions are obtained either using a higher speed rotation in a single step or as a second one (**Vassaux et al., 2019**) or even using in a second step a high-pressure homogenizer (**Verkempinck et al., 2018**).

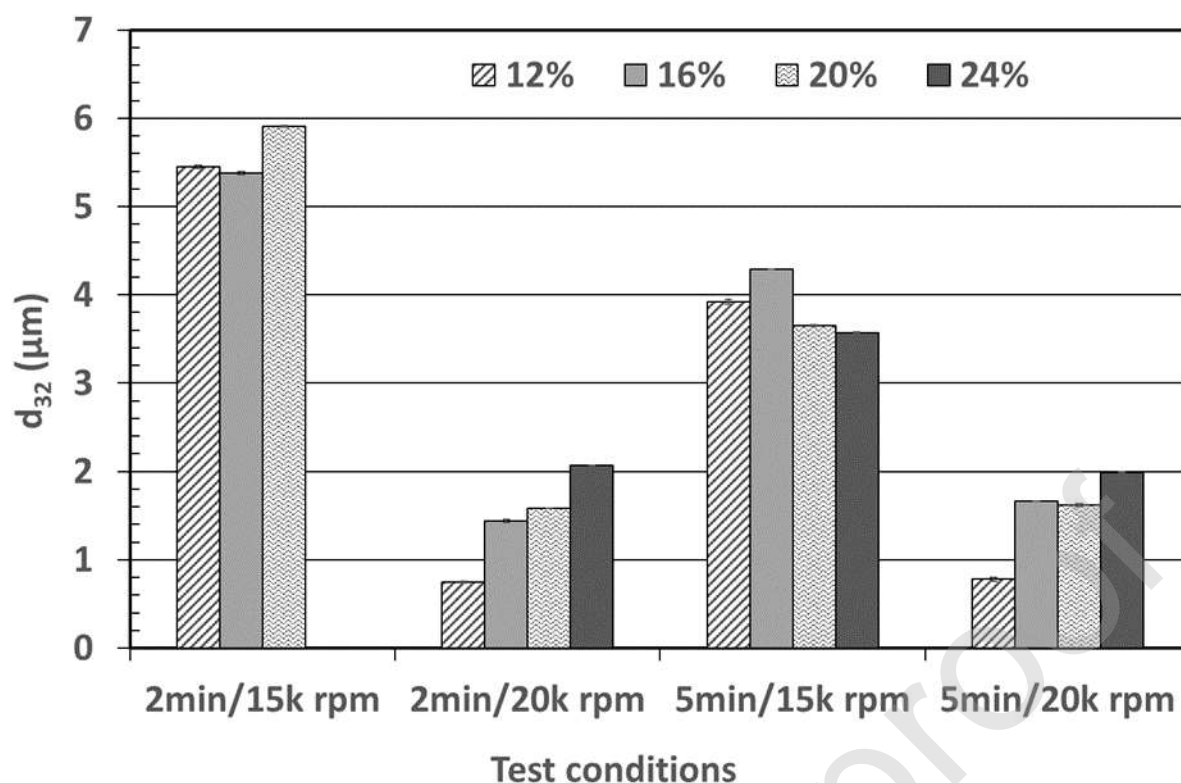


Figure 2: Determination of conditions of use of rotor stator system, BRSE, based on the formulation PCP (Table 2): variation of the Sauter diameter, d_{32} , as a function of speed rotation of stator, duration of mixing and volume fraction of dispersed phase in emulsions (in %).

Preliminary tests of the formulations with batch rotor stator emulsifier (BRSE)

Preliminary tests of the formulations that are presented in Table 2 have been performed using **BRSE**, for the sake of a quick screening of the formulations, as smaller volumes of solutions are necessary with this device than with the MHT. The results obtained with the four formulations are presented in Figure 3. Anova and T tests with a confidence level of 95% confirm that a significant difference of Sauter diameter is observed between these formulations. LTP formulation clearly gives the worse results in terms of Sauter diameter, compared to the other ones. It has then not been selected for the further tests involving **MHT** emulsifier.

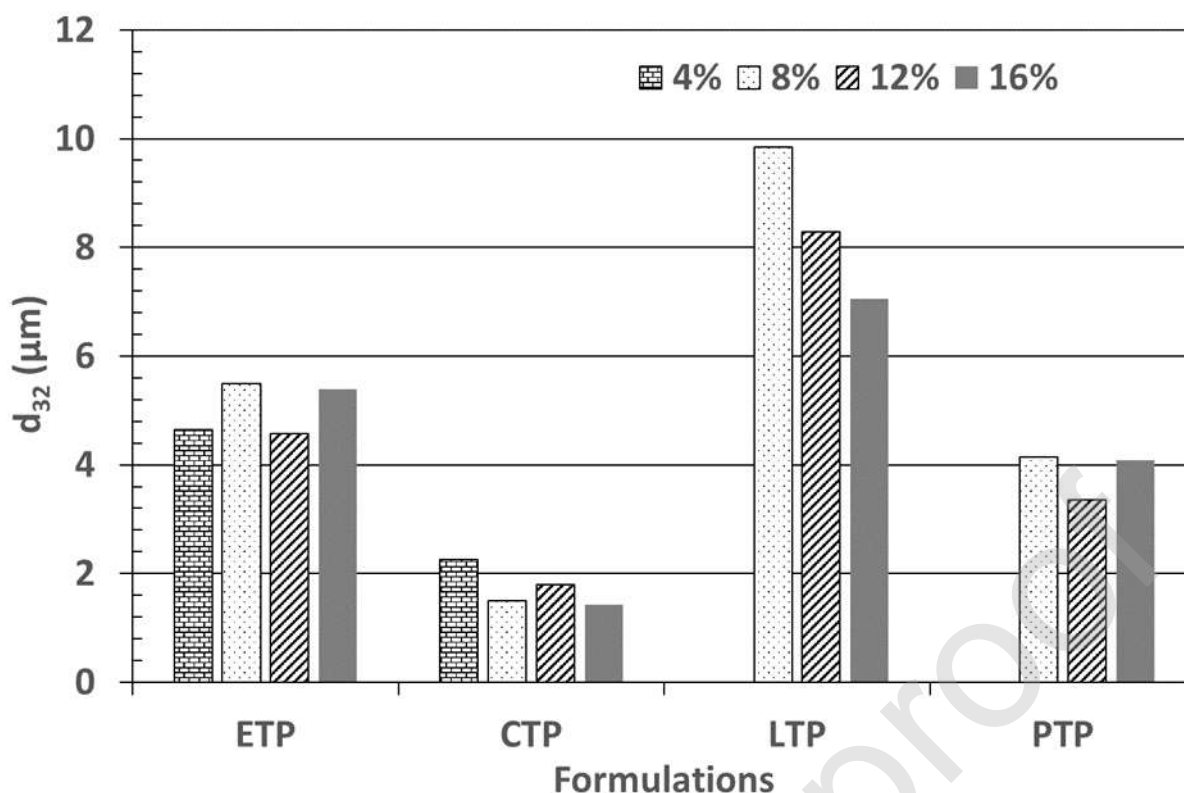


Figure 3: Sauter diameter, d_{32} , (in μm) obtained with 4 formulations (see Table 2) and various oil fractions (in %) after 5 min. at 15,000 rpm using the BRSE.

Investigation of the MHT emulsifier:

The MHT emulsifier was investigated with the three retained formulations, i.e. previously designated as PTP, ETP and CTP. The experimental conditions are recapped in Table 2. Experiments were performed at ambient temperature, except with PTP formulation (60 degrees Celsius ($^{\circ}\text{C}$)) due to the necessity of maintaining PrecirolTM at a temperature higher to the melting one, which is about 50°C . The flowrate of continuous phase was fixed at the maximal value available by the pump, i.e. 500 mL/min, whereas the flow rate of the dispersed phase was set according to the desired volume fraction of dispersed phase in the emulsion. The pressure measured at each pump is also given in Table 3. When a pressure variation was observed at different times, a range of values of the pressure is given. Fluctuations observed were usually very limited around an average value. These ones are mainly due to the course of the three pistons of the pump, i.e. reciprocation in the movements of these pistons. Trials have been implemented twice and samples of each trial have been analyzed.

Figure 4 recaps the results in term of Sauter diameter and Figure 5 gives the corresponding calculated spans. The values of the Sauter diameter obtained using BRSE and MHT emulsifiers are of the same order of magnitude. Slight variations are observed but they do not appear to be significant. It should be emphasized that the residence time of the fluids in the MHT itself, i.e. were the emulsion is formed, is about 0.04 s, while it is about 7 s for the whole process (i.e. from the pumping point of fluids to the collection of the emulsion). A similar level of breakage is obtained using the BRSE device in the selected conditions, but with needing longer shear time of the mixture between the rotor and stator and corresponding to many passes of the fluid in the device. In the present study an operating time of 5 minutes is applied with BRSE for a volume of 100 mL of fluid. The time required for the MHT system to produce a similar volume of emulsion does not exceed 12 s.

In the case of MHT emulsifier, there is no monotonous relation between the Sauter diameter and the content of dispersed phase. It means that despite the fact that the total flow rate is presently increased with the dispersed phase content, it does not increase in a sufficient extent to reduce significantly the Sauter diameter of fresh emulsions for any formulation.

Concerning the size distributions of droplets in obtained emulsions, the values of the span are presented in Fig.5. It can be observed that the values of the span obtained with the MHT emulsifier are higher; their values are about twice than those of emulsions from BRSE, showing that dispersions are more spread out. The order of magnitude of the span of emulsions obtained from both emulsifiers is rather high. Another observation that can be reported is that the value of the span tends to diminish with the total flow rate using MHT in the case of the ETP and CTP formulations. Indeed, increasing the total flowrate in MHT allows the increase of the breakage, as formerly observed by several authors in microchannels of different geometries and under different regimes of formation of droplets (**Fan et al., 2006, Belkadi et al., 2015**). However, the effect of flowrate on the value of the span is not significant in the case of the PTP formulation, which may be explained by the more viscous nature of the dispersed phase, due to the content of Precirol™.

It can also be mentioned that the values of the span obtained with MHT proves that the breakage mechanisms occurring at high throughput are very different from those observed in microchannels implemented at low flow rates. Indeed, as stated by **Zhao and Middleberg (2011)** and many other authors, size dispersion of droplets in microfluidic devices is usually intended to be very small, i.e. characterized with a coefficient of variation, i. e. ratio of the

standard variation on the mean, less than 10% with membranes and even currently less than 5% with other systems like T-junction, for instance. But it might be emphasized that it is mainly the case if the break-up is dominated by capillary effects, which is not the case in the conditions implemented using MHT in the present work (**Belkadi et al., 2015, Ji et al., 2020**).

The smaller values of the span obtained with BRSE may be due to the fact that the fluid undergoes many passes in the system, between the rotor and the stator, which tends to make the dispersion more uniform. This phenomenon is well known concerning high pressure homogenizers for which several passes are generally implemented. Recirculation in MHT has not been presently been investigated. However, a previous work (**Belkadi et al., 2016**) has shown that using two microsystems implemented in series allows, in some different situations, to reduce the mean droplet size and to refine the droplets distribution.

Characteristics of our emulsions can also be compared to these obtained in the work of Khalid et al. (2017) or that of Ma et al. (2020) which implemented a microchannel emulsifier (MCE). This system, as explained in the introduction, was used to produce emulsions for encapsulation of antioxidants. Even if the formulations used by these authors are somewhat different from ours, it can be observed that the Sauter diameter of emulsions from MHT are about 10 times smaller than those from MCE, for a flowrate that is 60 times higher. This is not surprising, knowing that flow conditions are very different. The values of the span are, on the other hand, about 7-11 times higher with MHT, compared to MCE. This result is also coherent. Thus, MHT may produce finer emulsions, offering a better bio accessibility than emulsions from MCE. As a drawback, due to the inertial flow conditions in MHT leading to multiple breakage of droplets, their size dispersion is much larger.

Formulation	Volume fraction of oily phase (%)	Flow rate of aqueous phase (mL/min)	Flow rate of oily phase (mL/min)	Pressure of injection at the pump of oily phase (bar)	Pressure of injection at the pump of aqueous phase (bar)	Energy dissipation rate (kW/kg) Eq. (4)
PTP	4.1	500	20.8	[21-22], 25	[9-10], [9-10]	7480
	8	500	43.5	[39-42], [33-37]	[9-10], 12,5	7230

	12	500	68.2	[61-66], [55-60]	[12-15], [10-11]	7080
	16	500	95.2	[80-85], [66-69]	[10-11], [10-11]	7220
	18	500	110	[51-52], [66-69]	12, 10	7460
ETP	4	500	20.8	[26-27], 26	12, 12.5	7480
	8	500	43.5	[38-43], [8-42]	12.5, 13	7230
	12	500	68.2	[12-56], [43-59]	13.5, 12.5	7080
	16	500	95.2	[13-90], [13-99]	12.5, 14	7220
CTP	4	500	20.8	[25-26], 26	13, 13	7480
	8	500	43.5	[44-47], [45-47]	14, 12	7230
	12	500	68.2	[66-68], [62-70]	13, 14	7080
	16	500	95.2	[79-85], [83-96]	14, 14	7220

Table 3: Experimental conditions of trials performed with MHT emulsifier. The pressure is given by the pump (pressure of injection); the two numbers or ranges of values provided for a pump are corresponding to two successive trials performed in the same conditions.

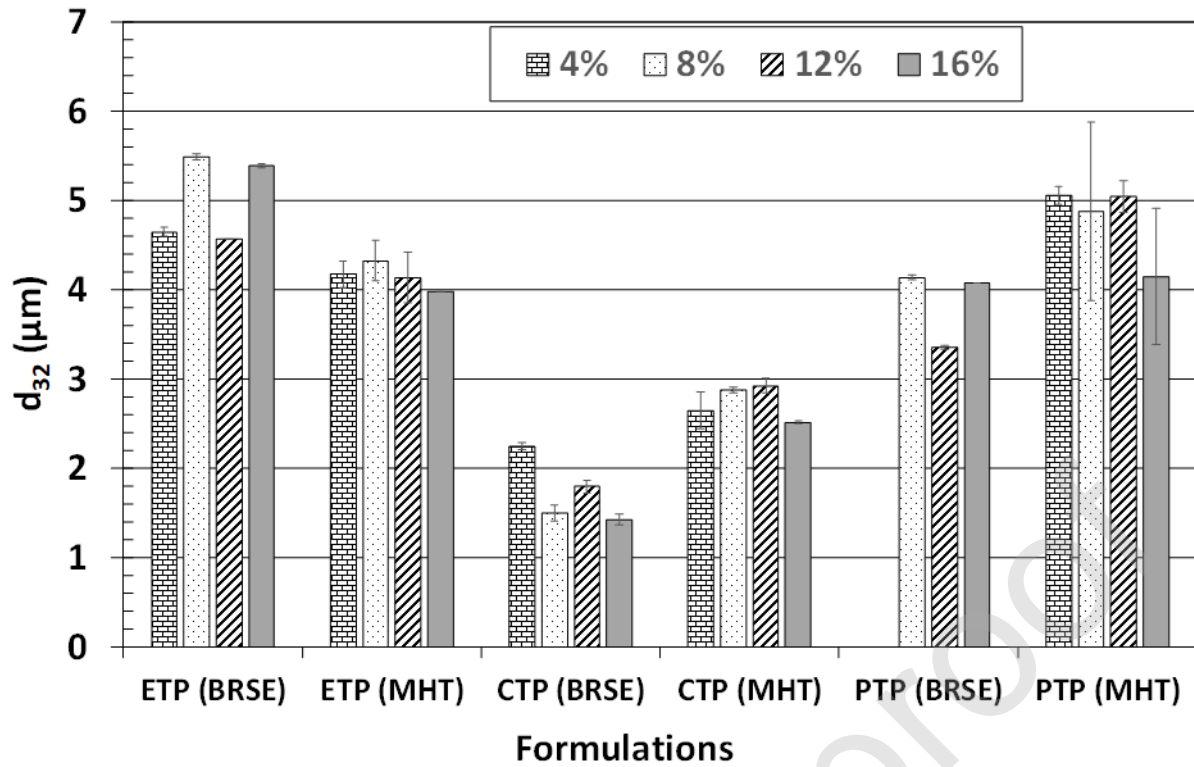


Figure 4: Comparison of values of Sauter diameter obtained with ETP, CTP and PTP formulations using MHT emulsifier versus BRSE.

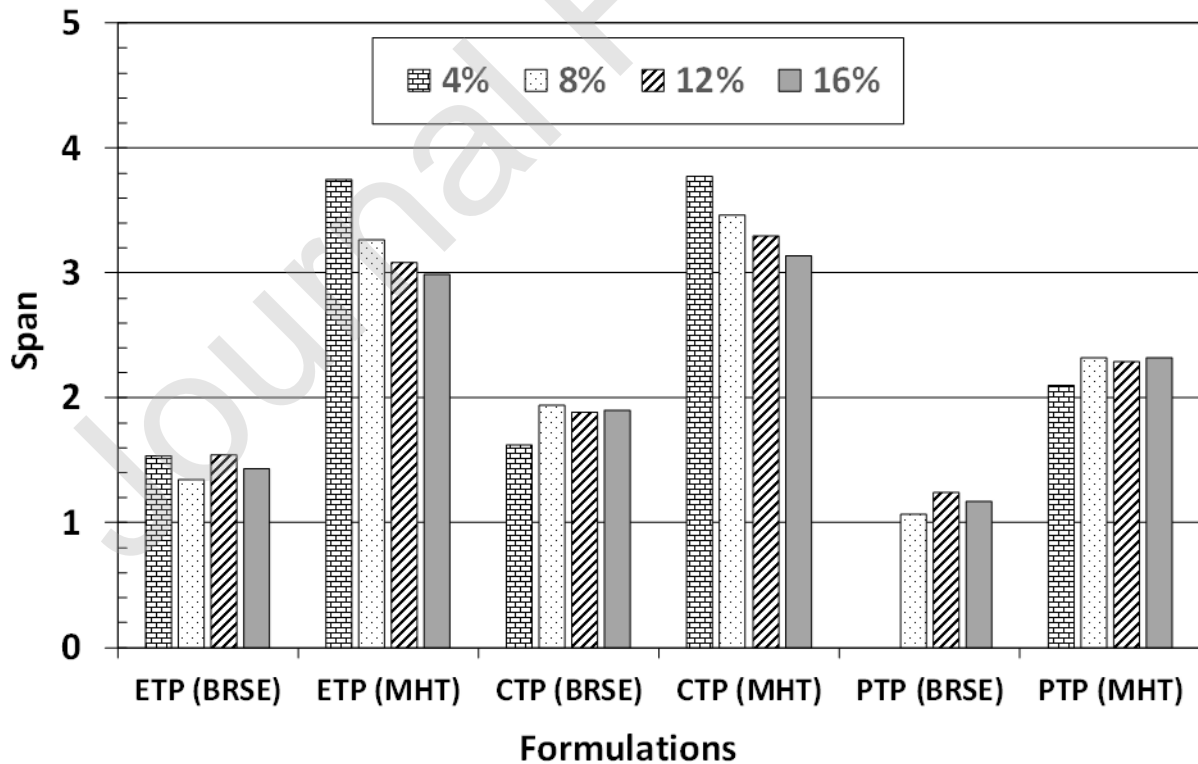


Figure 5: Comparison of the values of the span obtained with ETP, CTP and PTP formulations using MHT emulsifier versus BRSE. Each symbol corresponds to a given volume fraction of the dispersed phase (in %).

Rheology of CTP formulation.

As stated in the Materials & Methods section, CTP emulsions only are investigated in this section; in particular those with respective volume fraction 8% and 16% of oily phase. Samples of two different emulsions made using MHT and one obtained with BRSE were tested and compared. The oily phase of CTP formulation has also been tested. Corresponding data and related experimental details are provided as a supplementary material. The oily phase has a purely Newtonian character and its viscosity is 67 mPa s. The global rheological behavior of the CTP emulsions is independent on the emulsification method. On the other hand, the volume fraction of oily phase modifies, in a very limited extent, the value of the apparent viscosity; this later being globally similar to that of the aqueous phase. The rheological behavior of CTP emulsions is clearly dominated by the non-Newtonian character of xanthan. With a volume fraction of 16% of the oil phase and for shear rates higher than about 20 s⁻¹, the apparent viscosity of CTP emulsion tends to be slightly higher than that of the aqueous phase. This shear rate coincides with a value of apparent viscosity that is equal to that of the oily phase. For higher shear rates, the oily phase content has then an impact on the apparent viscosity of the emulsion. This is coherent with Taylor's law (1932).

Energy dissipation rate of the flow in MHT emulsifier and energy consumption of process:

The energy dissipation rate for the head-on collision presently involved in the micromixer can be estimated as follows (**Johnson and Prud'homme, 2003; Siddiqui et al., 2009**):

$$\epsilon = \left(\frac{Qm_c U_c^2}{2} + \frac{Qm_d U_d^2}{2} - \frac{Qm_e U_e^2}{2} \right) / \rho_e V \quad \text{Eq.(4)}$$

Where Qm_c , Qm_d and Qm_e respectively designate the mass flow rate of continuous phase, dispersed phase and outlet emulsion flow. ρ_e designates the density of emulsion, U_c , U_d and U_e are respectively the superficial velocities of continuous phase, dispersed phase and outlet emulsion flow.

They are calculated considering the respective surface sections of the concerned microchannels. V denotes the estimated volume of mixing zone, i.e. the junction area between

the two inlet microchannels where the collision of the two liquid phases occurs. It is assumed to be $600\ \mu\text{m} \times 600\ \mu\text{m} \times 600\ \mu\text{m}$. The energy dissipation rate corresponds to the net kinetic energy carried by the two impinging jets into the mixing zone utilized for emulsion production per mass emulsion and per time. Its estimated value is given in Table 3 as a function of the different tested conditions; its order of magnitude is about $4.4\ \text{kW/kg}$.

A comparison of this dissipation rate with those reported, for example by **Kockmann (2008)** for different mixing microsystems needs to estimate the level of involved Reynolds number. This is rather delicate in our case as the emulsions have the characteristics of shear thinning fluids, due to the use of xanthan. Combined with the fact that conventional rheometers do not allow the reach of the level of shear rates involved in our trials, only a raw estimation of Reynolds number can be proposed here. In the case of CTP formulations, i.e. those based on Peceol™, rheology of both phases as well as that of emulsions have been investigated up to a shear rate of $10^3\ \text{s}^{-1}$ (see the previous section). For this shear rate, the apparent viscosity of emulsions is about $0.010\ \text{Pa}\ \text{s}^{-1}$. As a matter of fact, as previously mentioned, it was observed that the rheology of CTP emulsions has the same behavior as that of the aqueous phase. Thus, xanthan gum has a dominant effect on their rheology. Considering for this value leads to an underestimated value of the Reynolds number as the wall shear rate estimated in the outlet square microchannels is about $7\ 10^3\ \text{s}^{-1}$ which means that the apparent viscosity is actually much lower, at least at the vicinity of the walls. The underestimated value of the Reynolds number may be comprised in the range 700-800, taking into account for the range of flowrates tested. According to **Sworn (2009)**, the second Newtonian plateau of xanthan solutions occurs for shear rates of about $10^5\ \text{s}^{-1}$ and, in this condition, with an aqueous solution with 0.5 % xanthan content the apparent viscosity is about $0.002\ \text{Pa}\ \text{s}^{-1}$. This means that this estimation of the Reynolds number may be underestimated with a factor up to about 5. **Kockmann (2008)** reports values of mean specific energy of different mixing elements of same scale that are, at $\text{Re}=1000$, comprised in the range $16.6\ \text{kW/kg}$ for a T-mixer to $640\ \text{kW/kg}$ for a tangential mixer. The level of energy dissipation rate involved with the head-on collision in the MHT tested seems to be higher as its value varied between $7100\text{-}7500\ \text{kW/kg}$ during the trials (Table 3).

The energy consumption is a parameter often used to characterize the level of energy involved in a process; it can be estimated using the following equation:

$$E = \Delta P / \rho_{emulsion} \quad \text{Eq. (5)}$$

Where ΔP is the pressure drop through the system and ρ_{emulsion} is the density of the emulsion. ΔP is presently roughly estimated using the pressure at the inlet of the pump admitting the more viscous phase. Considering the maximal head pressure observed during these trials, i.e. 100 bar, the corresponding maximal energy consumption involved during these trials would be 2.8 kWh/ton.

As a comparison, the energy consumption of the BRSE used in this study can be estimated using the following equation that can be applied for calculating the power of rotor-stator systems:

$$P = N_p \rho N^3 d^5 \quad \text{Eq. (6)}$$

with N the speed of the rotor and d its diameter (**Roustan et al. 2015**).

Taking into account for a value of 2.3 for the power number, N_p , and the experimental conditions of use of the BRSE, its energy consumption is estimated as being 3.0 kWh/ton. Thus, the maximal energy consumption of MHT observed in this study has the same order of magnitude than the regular one of BRSE.

Physical stability of emulsions:

Figure 6 shows the time evolution of the Sauter diameter in emulsions obtained with various volume fraction of oil phase. The stability has been followed between the day of their formation (D0) and 30 days of storage (D30) at 4°C. No significant difference was detected (T test, $\alpha = 5\%$) with ETP and PTP formations, with whatever used emulsifier, as well as with most CTP emulsions obtained from the rotor-stator system. Only CTP emulsions produced with the MHT system exhibit a systematic and significant increase of the Sauter diameter. It might be noticed that the CTP emulsion obtained with BRSE with a content of 4% of dispersed phase also presents a bad stability in time. The particular behavior of CTP emulsions would need further investigations, i.e. an analysis of physico-chemical effects and their interactions. Monoleate glycerol (Peceol™) is used in these formulations. Despite its low HLB, it may not be adequate to stabilize emulsions. LTP formulation, containing Labrafac™, was not retained for investigations with MHT, due to the high Sauter diameter obtained using BRSE as emulsifier. Indeed, Labrafac™ and Peceol™ share several characteristics. Among them, are their liquid character at ambient temperature and their rather

simple composition. Surfactants that are solid at ambient temperature generally favor the stabilization of emulsions; this is much less the case with surfactants that are liquid at ambient temperature. Added to that, emulsions made with CTP using MHT are characterized by a higher dispersion of droplet size than these made with BRSE (Figure 7). This may explain that CTP emulsions from MHT are more likely to present a bad physical stability.

To analyze more thoroughly the physical evolution of emulsions, the volume distribution of their droplets is respectively presented with a volume fraction of the oil phase of 8% and 16% in Figure 8. The particle size distributions tend to become more extensive over time, showing an increase in the value of the Span, excepted with ETP emulsions.

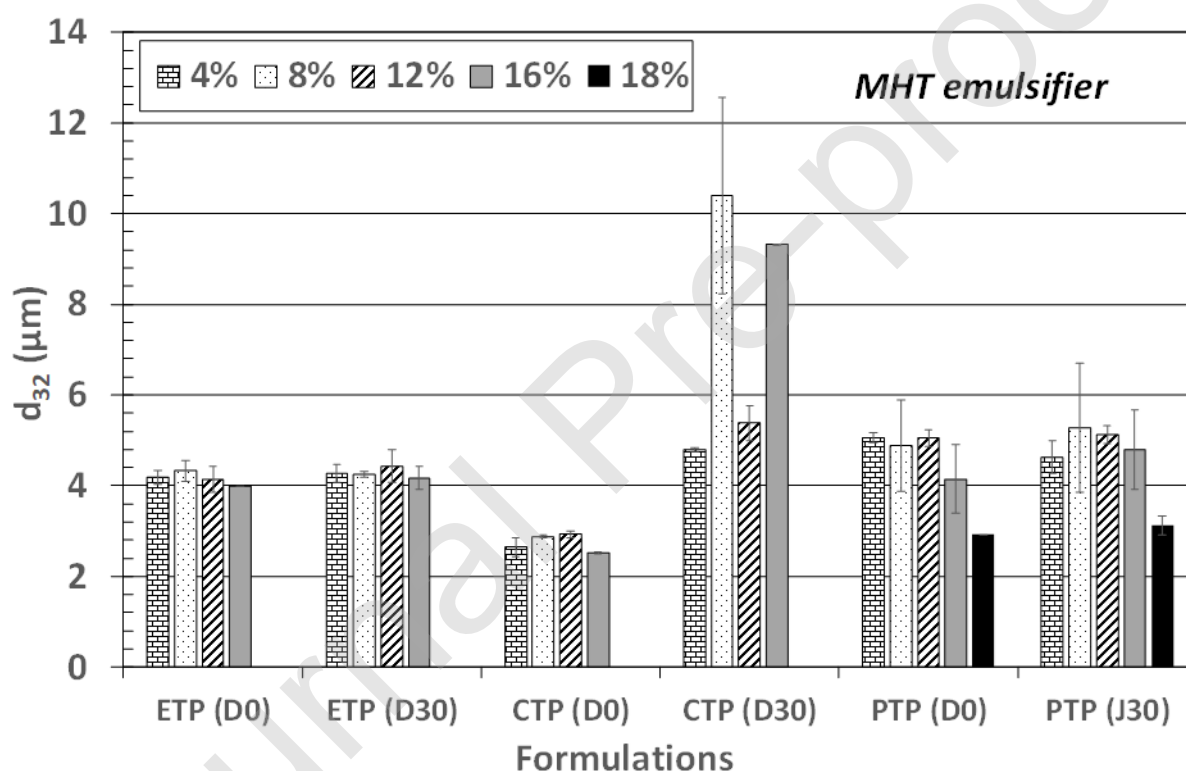


Figure 6: Comparison of the values of the Sauter diameter corresponding to fresh emulsions (D0) and emulsions after 30 days of storage (D30). Emulsions were obtained with ETP, CTP and PTP formulations using MHT emulsifier. The volume fraction of the dispersed phase is indicated in %. All trials have been repeated twice (the scatter is indicated with an error bar).

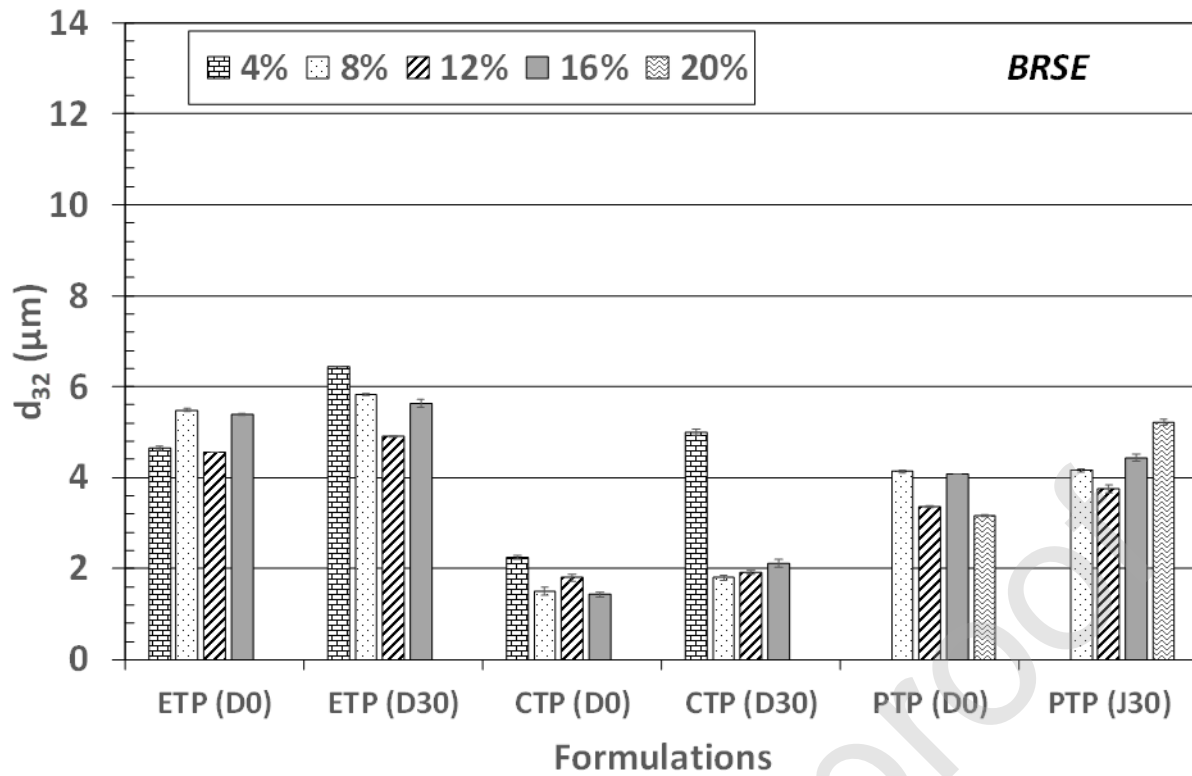
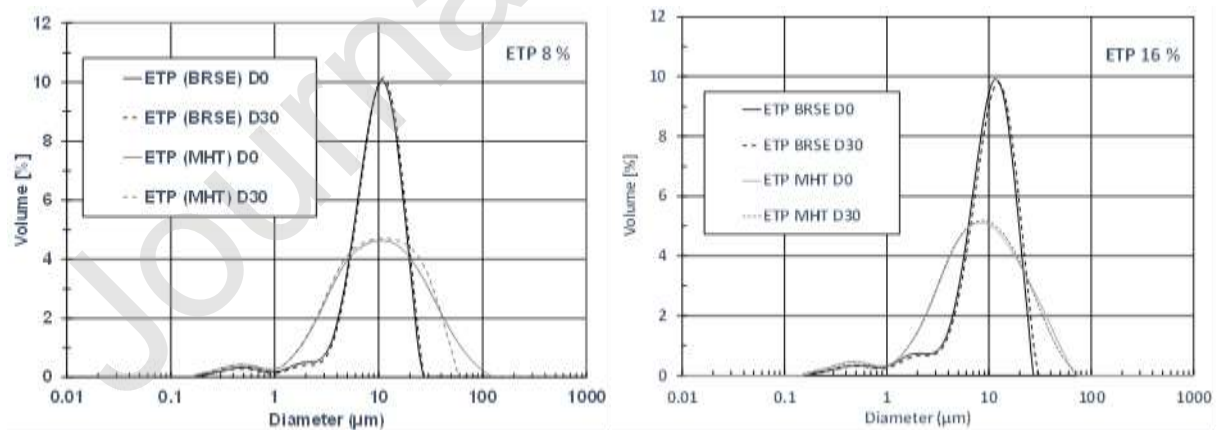


Figure 7: Comparison of the values of the Sauter diameter corresponding to fresh emulsions (D0) and emulsions after 30 days of storage (D30). Emulsions were obtained with ETP, CTP and PTP formulations using BRSE. The volume fraction of the dispersed phase is indicated in %. All trials have been repeated twice (the scatter is indicated with an error bar).



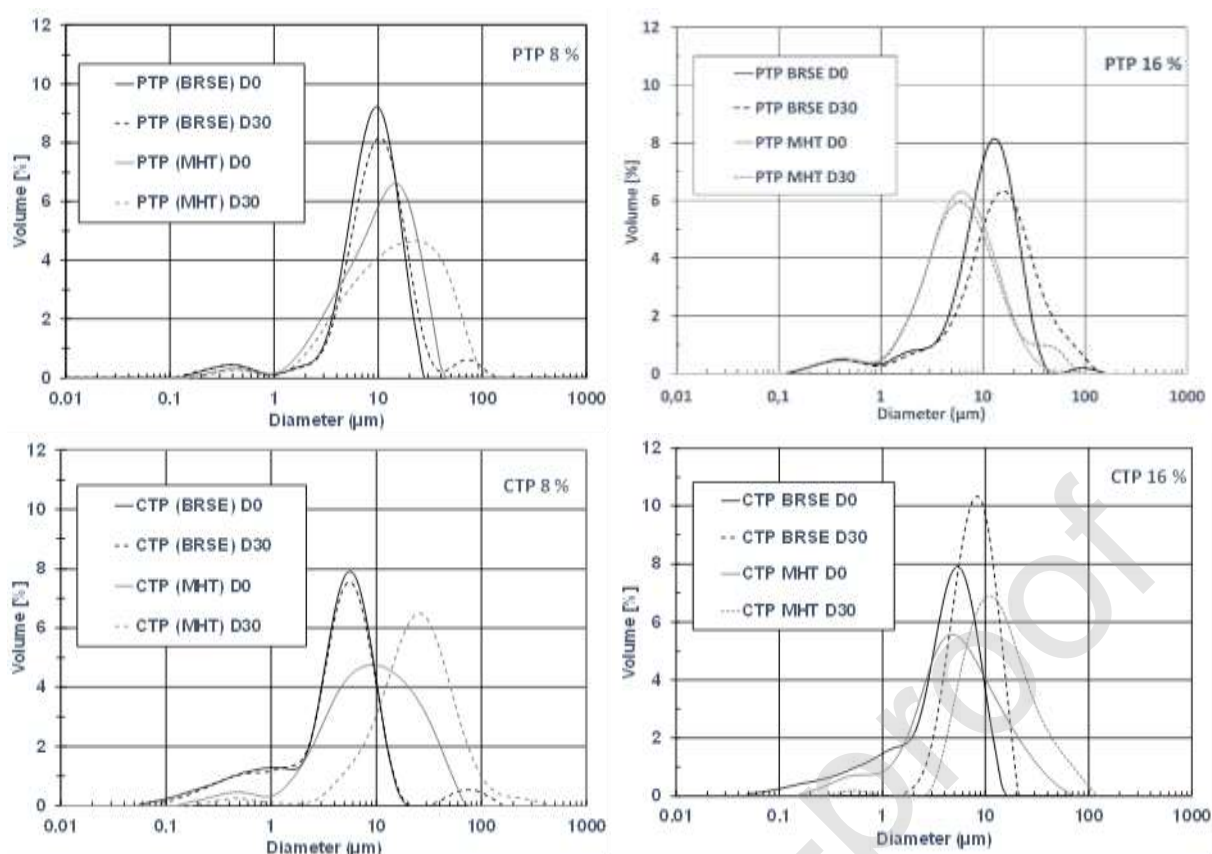
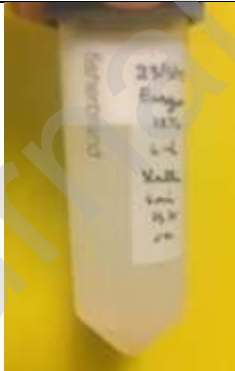




Figure 8: Comparison of the volume distribution of droplets in emulsions made with 8 % and 16 % of volume fraction of oil phase.

Size dispersions of droplets in emulsions obtained from MHT are generally more spread at D0 than those obtained with BRSE (Figure 8). This point was formerly discussed when comparing initial values of Span. It is well known that the higher the droplet dispersion is, the more unstable is the emulsion, which can be verified from the observation of the evolution of droplets size dispersions between D0 and D30 in Figure 8. The initial dispersion of droplets size may compromise the stability at a scale of few months of emulsions produced with MHT. This suggests that successive microsystems should be implemented to refine the dispersion of droplets. On the other hand, Figure 8 reveals that dispersions in emulsions obtained with MHT are less spread and that emulsions are more stable with an oil content of 16 % (in volume). This can be explained by the higher total flowrate involved in MHT with 16% volume fractions of oil phase (Table 3). It then confirms that dispersions of emulsions are relatively sensitive to the total flowrate as well as to the characteristics of the oily phase; the flow-rate of aqueous phase being invariant in the tested formulations.

At the end, it can be noticed that, independently of the emulsifying device used, ETP is the formulation that provides more stable emulsions based on the criterion of evolution of size dispersion. ETP is based on EasynovTM as the emulsifying agent of the lipid phase. This one is liquid at ambient temperature but it results from the mixing of different compounds; among them is PEG-30 Dipolyhydroxystearate. This synthetic compound is able to emulsify many vegetable oils, polar and not polar ones. Therefore, EasynovTM has a more complex composition than LabrafacTM and PeceolTM. Its own formulation may explain its particular ability to stabilize ETP emulsions. However, considering now the visual aspect of these emulsions and their corresponding creaming index, emulsions made with ETP formulation exhibit a higher level of creaming. The creaming index is presently estimated from the ratio of the height of white opaque part of emulsion on the height of the more translucent one. The opaque part of emulsion is richer in oily droplets due to their smaller density. It is recalled that the mean size and size dispersion have been determined at D30 after manually and gently overturning the emulsions in order to re-homogenize them. Photos of emulsions at D30 and values of the corresponding creaming index are presented in Figure 9 for emulsions with a volume fraction of the oil phase equal to 12%. PTP formulation ensures a more stable visual aspect of the obtained emulsions. This may be explained by the content in glyceryl palmitostearate (from PrecirolTM) in the oily phase; this compound being solid at ambient temperature.

Formulation:	ETP	PTP	CTP
BRSE / D30			
Creaming index (%)	72	5	27



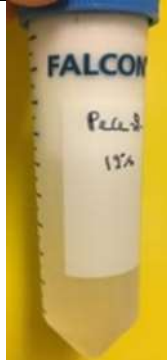
MHT / D30			
Creaming index (%)	87	13	55

Figure 9: Photos at D30 of emulsions made with 12 % of volume fraction of oil phase and values of their corresponding creaming index.

Conclusion:

The objective of this work was to test a micromixer (MHT) as a possible alternative for continuous emulsification. This device is based on a cross slot geometry and an impinging of the two phases to be dispersed. Previous works have demonstrated that it is particularly efficient in conditions of high throughput (up to about 600 mL/min). Multiple breakage of droplets is expected, leading to smaller Sauter diameters of emulsions than with many more classical microsystems. Targeted applications in this work concern various industrial fields such as cosmetics, nutraceuticals or pharmaceuticals, for which stable emulsions are required. Several formulations for oil-in-water emulsions have then been selected and tested in this objective. A classical laboratory rotor-stator emulsifier, Ultra-Turrax™ (BRSE), was used as a reference, in conditions corresponding to the production of rather coarse emulsions.

Globally, emulsions produced with MHT have characteristics which are comparable to those produced with BRSE. Sauter diameter are very close, but size dispersion is generally more spread with MHT than with BRSE, suggesting that a second micromixer should be used in series in order to reduce size dispersion. Otherwise, energy dissipation rate of the flow in MHT emulsifier has been evaluated and a comparison has been attempted with other microdevices; the energy dissipation rate of MHT seems to be rather higher which confirms the involvement of a more intensified fluid mixing. In the same kind of idea, energy consumption of process has been calculated in the case of MHT and BRSE. Their values are similar.

The study of physical stability of emulsions after 30 days of storage also confirms a slight advantage of BRSE. Indeed, this could be expected as a smaller dispersion of droplet size at D0 generally favors its stability in time.

However, these conclusions can be modulated considering the nature of formulations. This one has a significant influence on the obtained size dispersion at D0 and its evolution over time. Different features and evolutions in time are observed depending on the formulation. Emulsions made with ETP formulation exhibit a higher creaming index at D30 but the size dispersion of droplets is not significantly modified during this period, whatever the emulsifier used. Moreover, the larger size dispersion obtained with MHT does not induce coalescence with this formulation. In the case of use of PrecirolTM, a compound which is solid at ambient temperature, the emulsions have a more homogeneous aspect at D30, i.e. a small creaming index, but a slight variation of the droplet size dispersion is noticed. A specific analysis of the physico-chemical effects of the compounds used in the formulations would be needed to deepen the conclusions on their respective roles. This was not targeted in this prospective work.

This work provides a clear insight on performances that can be expected from microsystems at high throughput as possible continuous compact emulsifiers. MHT is a complementary tool in the range of available emulsifiers. Due to its working mode, it avoids overheating of fluids and limits contacts with atmosphere; therefore, as already mentioned it is a good candidate for nutraceutical, pharmaceutical or cosmetics applications. It could represent a versatile and very handle tool to be integrated in complex continuous processes. A possible application could be its integration in small production units or automated modules for “on demand” orders. This study suggests that further efforts should focus on the design of MHT so as to target finer dispersions of droplets size. Perspectives are opened as previous experiments have shown that two successive impingements of the flow allow to reduce the droplet size dispersion. Another challenge is the scale-up of the flux that can be presently treated in such systems. This implies to design a device based on parallelized microsystems. On a more fundamental point of view, more efforts should also be made towards a fine characterization of dispersion and mixing phenomena at high Reynolds numbers and at the scale of the droplets in such microsystems.

Credit authorship contribution statement:

Jerôme Bellettre: resources, participation to experimental investigation

Walib Blel: supervision, resources, methodology, validation, formal analysis, participation to experimental investigation

Luc Marchal: resources, review

Agnès Montillet: supervision, resources, conceptualization, methodology, validation, formal analysis, participation to experimental investigation, writing - original draft, writing - review & editing.

Ralph Nehme: methodology, experimental investigation, formal analysis.

Declaration of interests

None

Journal Pre-proof

References:

- Arrieta-Escobar, J.A., Bernardo, F.P., Orjuela, A., Camargo, M., Morel, L. Incorporation of heuristic knowledge in the optimal design of formulated products: Application to a cosmetic emulsion. *Computers and Chemical Engineering*, 122 (2019) 265–274.
<https://doi.org/10.1016/j.compchemeng.2018.08.032>
- Bhasha, S.A., Khalid, S. A., Duraive, S., Bhowmik, D., Kumar, K. P. S. Recent trends in usage of polymers in the formulation of dermatological gels. *Indian Journal of Research in Pharmacy and Biotechnology*. Volume 1(2), March-April 2013, 161-168.
- Belkadi, A., Tarlet, D., Montillet, A., Bellettre, J., Massoli, P. Water-in-oil emulsification in a microfluidic impinging flow at high capillary numbers. *International Journal of Multiphase Flow* 72 (2015) 11–23.
- Belkadi, A, Tarlet, D., Montillet, A., Bellettre, J., Massoli, P., Study of two impinging flow microsystems arranged in series. Application to emulsified biofuel production. *Fuel* 170 (2016) 185–196
- Belkadi, A., Montillet, A., Bellettre, J., Biofuel emulsifier using high velocity impinging flows and singularities in micro-channels. *Journal of Energy Resources Technology (ASME)*, Vol 140 (2018) 012202 1-8.
- Bellettre, J., Belkadi, A., Montillet, A., Dispositif et procédé pour réaliser une émulsion en continu de deux liquides immiscibles, Patent WO2017103498, 2017.
- Binder, L., Klang, V., Sheikh Rezaei, S., Neuer, O., Zhang, Z., Jasmin Lunter, D., Wolzt, M., Valenta, C. Topical application of highly concentrated water-in-oil emulsions: Physiological skin parameters and skin penetration in vivo - A pilot study. *International Journal of Pharmaceutics* 571 (2019) 118694. <https://doi.org/10.1016/j.ijpharm.2019.118694>
- Brochette, P., Émulsification – Élaboration et étude des émulsions, in *Techniques de l'Ingénieur*, 2013, J2150 V2, 1-5.
- Dubuisson, P., Picard, C., Grisel, M., Savary, G. How does composition influence the texture of cosmetic emulsions? *Colloids and Surfaces A* 536 (2018) 38–46.
<http://dx.doi.org/10.1016/j.colsurfa.2017.08.001>

- Ji Y., Bellettre J., Montillet A., Massoli P. Fast oil-in-water emulsification in microchannel using head-on impinging configuration: Effect of swirl motion. *Int J Multiphase Flow* 131 (2020) 103402. <https://doi.org/10.1016/j.ijmultiphaseflow.2020.103402>
- Johnson, B.K., Prud'homme, R.K., 2003. Chemical processing and micromixing in confined impinging jets. *AIChE J.*, 49, 2264-2282.
- Kan, X., Yan, Y., Ran, L., Lu, L., Mi, J., Zhang, Z., Li, X., Zeng, X., Cao, Y., Evaluation of bioaccessibility of zeaxanthin dipalmitate from the fruits of *Lycium barbarum* in oil-in-water emulsions. *Food Hydrocolloids*, 105 (2020) 105781, <https://doi.org/10.1016/j.foodhyd.2020.105781>.
- Khalid, N., Shu, G., Kobayashi, I., Nakajima, M., Barrow, C. J., Formulation and characterization of monodisperse O/W emulsions encapsulating astaxanthin extracts using microchannel emulsification: Insights of formulation and stability evaluation. *Colloids and Surfaces B: Biointerfaces*, 157 (2017) 355–365.
- Kockmann, N., *Transport phenomena in micro process engineering*, Springer, 2008.
- Ma, Z., Zhao, Y., Khalid, N., Shu, G., Neves, M., Kobayashi, I., Nakajima, M., Comparative study of oil-in-water emulsions encapsulating fucoxanthin formulated by microchannel emulsification and high-pressure homogenization. *Food Hydrocolloids* 108 (2020) 105977. <https://doi.org/10.1016/j.foodhyd.2020.105977>
- Marchitto, R. Calabria, C. Tornatore, J. Bellettre, P. Massoli, A. Montillet, G. Valentino Optical investigations in a CI engine fueled with water in diesel emulsion produced through microchannels. *Experimental Thermal and Fluid Science* Vol. 95, July 2018, Pages 96-103
- Poux, M., Canselier, J.-P., *Procédés d'émulsification, Techniques et Appareillage*, (2004) J2153, 1-14.
- Rodriguez-Ruiz, V., Salatti-Dorado, J.A., Barzegari, A., Nicolas-Boluda, A., Houaoui, A., Caballo, C., Caballero-Casero, N., Sicilia, D., Venegas, J. B., Pauthe, E., Omidi, Y., Letourneur, D., Rubio, S., Gueguen, V., Pavon-Djavid, G., Astaxanthin-Loaded Nanostructured Lipid Carriers for Preservation of Antioxidant Activity, *Molecules*, 23 (2018) 2601- 2612.

Roustan, M., Pharamond, J.M., Line, A., Agitation. Mélange -Concepts théoriques de base. Techniques de L'ingénieur, J3008 (2015) 1-22.

Siddiqui, S.W., Zhao, Y., Kukukova, A., Kresta, S.M., Characteristics of a confined impinging jet reactor: energy dissipation, homogeneous and heterogeneous reaction products, and effect of unequal flow. *Ind. Eng. Chem. Res.* 48 (2009) 7945-7958.

Shimada, K., Okada, H., Matsuo, K., Yoshioka, S. Involvement of Chelating Action and Viscosity in the Antioxidative Effect of Xanthan in an Oil/Water Emulsion, *Bioscience, Biotechnology, and Biochemistry*, 60:1 (1996) 125-127, DOI: 10.1271/bbb.60.125

Sworn G., Xanthan gum, in *Handbook of Hydrocolloids (Second edition)*, Woodhead Publishing Series in Food Science, Technology and Nutrition (2009) 186-203

Tan, Y. C., Cristini, V., Lee, A. P., Monodispersed microfluidic droplet generation by shear focusing microfluidic device. *Sensors and Actuators B: Chemical*. Volume 114, Issue 1, 30 March 2006, 350-356. <https://doi.org/10.1016/j.snb.2005.06.008>

Tadros, T., F. Emulsions: Formation, Stability, Industrial Applications (De Gruyter Textbook) 2016, DOI: <https://doi.org/10.1515/9783110452242>

Vassaux,S., Savary,G., Le Pluart, L., Grisel, M. On the key role of process parameters to control stability and properties of Pickering emulsions stabilized by montmorillonite. *Colloids and Surfaces A* 583 (2019) 123952. <https://doi.org/10.1016/j.colsurfa.2019.123952>

Verkempinck, S.H.E., Salvia-Trujillo,L., Denis, A., Van Loey, A. M., Hendrickx, M., E., Grauwet, T., Pectin influences the kinetics of in vitro lipid digestion in oil-in-water emulsions. *Food Chemistry* 262 (2018) 150–161. <https://doi.org/10.1016/j.foodchem.2018.04.082>

Zhao, C.X., Middelberg, A.P.J. Two-phase microfluidic flows. *Chem. Eng. Sci.* 66, (2011) 1394-1411.