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Microfluidics as a tool to assess and induce emulsion destabilization

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Microfluidic technology enables a judicious control of the process parameters on a small length scale, which in turn allows speeding up the destabilization of emulsion droplets interface in microfluidic devices. In this light, microfluidic channels can be used as an efficient tool to assess emulsion stability and to observe the behavior of the droplets immediately after their formation, enabling to determine whether or not they are prone to re-coalescence. Observation of the droplets after emulsifier adsorption also allows the investigation of emulsion stability over time. Both evaluations would contribute to determine emulsion stability aiming at specific applications in food and pharmaceutical industries. Furthermore, emulsion coalescence can also be performed under extremely controlled conditions within the microfluidic devices in order to explore emulsion droplets as micro-reactors (for regulated biological and chemical assays). Such microfluidic procedures can be performed either in confined environments or under dynamic flow conditions. Under confined environments, droplets are observed in fixed positions simulating different environmental conditions. On the other hand, with the scrutiny of emulsions under dynamic flow processes, it is possible to determine the behavior of the droplets when subjected to shear forces, comparable to those experienced in conventional emulsification techniques or even in pumping operations. Given the above, this paper reviews different microfluidic techniques (such as changing channel geometry or wettability) hitherto used to destabilize emulsions, mainly focusing on the specificities of each study, whether the droplets are destabilized in confined or dynamic flow processes. Thereby, by going deeper into this review, readers will be able to identify different strategies for emulsion destabilization (in order to understand stabilizing mechanisms or even to apply these droplets as micro-reactors), as this paper shows the particularities of the most recent studies and elucidates the current state-of-the-art of this microfluidic-related application.

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Contents

1 Introduction

Microfluidics is defined as the science and technology of designing, manufacturing, and operating either processes or devices with small quantities of fluids (10^{-9} to 10^{-18} liters), with typical dimensions ranging from tens to hundreds of micrometers (or even a few millimeters), but it must exhibit at least one dimension smaller than 1mm [1–3]. This technique presents several advantages, but the most important are related to the application of devices with small sizes, reduced sampling, low energy consumption and dissipation and, consequently, relatively low cost. Such advantages arise from an interplay of unique features related to laminar and diffusive flow, such as very small molecular diffusion distances, large surface areas, high-performance heat transfer, precise control of flow conditions and so on [4]. Thus, microfluidics provides a powerful strategy for exploring the behavior of small-scale fluids, where diffusion, viscous, and interfacial forces predominate [5]. These characteristics steer the technique towards industrial and research applications, which has led to its swift development in recent years [6].

The use of microfluidics in multiphase systems enhances the precise control of the formation of a defined interface between fluids [2]. Indeed, emulsion droplets produced in microfluidic devices have a highly monodisperse size distribution because they are not only formed one-by-one, but also generated under milder conditions when compared to high-energy techniques [7,8]. Overall, the mean size of droplets formed in shear-based geometries (micro-capillaries and planar) is in the range of tens to hundreds of micrometers [8–11]. Nevertheless, depending on the composition, some emulsions may exhibit complex rheological behavior that can cause channel obstruction and difficulties in both fluid injection and flow stabilization. In addition, different components of the emulsions (such as oil and surfactants) can interact with the surface of the channels [12], impairing the formation of the droplets. Therewith, the development and application of microfluidic devices that can operate in high-throughput conditions remain a major challenge for expanding the use of this technology. To overcome such drawback, different techniques (laser ablation, micromachining and soft lithography), materials (glass, polydimethylsiloxane (PDMS) and thermoplastic) and surface wall treatments (plasma and covalent modifications) have been used to produce a wide range of microfluidic devices [12,13]. The choice of approaches to be applied depends on whether the objective is to assess and/or produce an oil-in-water (O/W) or a water-in-oil (W/O) emulsion.

In addition to droplets production and development of emulsions, microfluidic technology is growing in other fields in the study of multiphase systems. Particularly, microfluidic platforms have been used either to promote the separation of emulsion phases or to trigger the merge of the emulsion droplets for a better understanding of the droplet coalescence mechanism. Generally, to foster droplets coalescence, the instability of their interface must be induced. It is interesting to study the stability or to induce the fusion of the droplets within microfluidic channels, as these devices can provide visualization of the droplet interface and the precise control of the droplet formation and destabilization process. Microfluidics also operates at high shear rates due to their reduced length-scale [14], which can positively influence droplet destabilization. Therefore, microfluidic tools can be applied to induce droplet coalescence, which is especially important considering many facets, such as:

(i) Evaluation of emulsion (in)stability using lab-scale experiments - The performance of systematic studies using different components to improve emulsion stability is a growing demand in many industries [15], which can be achieved by observing emulsion droplets and their respective destabilization within microfluidic devices. However, the application of different conditions to investigate emulsion stability will provide specific information. Observing the coalescence immediately after droplets formation provides insights on the probability of re-coalescence in classic shear emulsification processes [16], which is paramount because it usually defines the final droplet size [17]. On the other hand, the destabilization study performed after a period of time has elapsed since the emulsion production [12] can be used to identify long-term kinetic stability of droplets under specific conditions (e.g., during storage or in contact with different matrices as

well as wall materials) or even during simulated gastrointestinal environment.

(ii) Application of the droplets as micro-reactors, when the process of droplet fusion triggers chemical or biological reactions - Due to the short time-scales and the efficient heat and mass transfer typically involved in microfluidic systems, the droplets can be used as micro-reactors. However, in this specific case, a judicious control of the droplet coalescence is targeted to allow a proper mixture of reagents [6,18–20]. In this light, microfluidics can be applied as a miniaturized platform to modulate both reactions and product synthesis [21].

(iii) Phase-inversion induction - The study of concentrated droplets using in situ analysis is fundamental to understand the origin of the shear-induced phase inversion and to determine which factors can drive the triggering of this phenomenon [22].

(iv) Study of interaction of emulsion droplets with different components - Observation of droplets inside microfluidic devices when other compounds are also added inside the channel is of paramount interest to observe real-time kinetics and specific changes on emulsion droplets [12,23] in different processes and formulations.

Overall, droplet destabilization is triggered in microfluidic devices by applying two different approaches: active and passive methods. Passive methods are associated with changes in microchannel structure and wettability, while active methods include external energy (e.g., electric or magnetic fields) to induce interfacial instability [6,19]. Normally, passive methods are more feasible due to their simplicity and reduced inter-droplet contamination, but they require the design of the microchannel network and the adjustment of flow conditions based on the properties of the fluids to increase separation efficiency [6,19]. In this sense, this review sheds light on the fundamentals of droplet destabilization in microfluidic devices as well as the passive strategies currently applied to promote such phenomenon, systematically showing an overview of the main advances, the specificities of each study and the challenges to be overcome. With this set of information, we intend to show the gaps and the current state-of-the-art of the subject, aiming at the implementation of these microfluidic platforms in both fundamental and applied research.

2 Mechanisms to promote droplet destabilization in passive microfluidic devices

Passive strategies present remarkable advantages (ease of production, use of different materials, low cost, amongst others) when compared to active methods, in addition to being directly associated with changes in the microfluidic channels themselves. The liquid film drainage model is usually used to describe the process of passive fusion between two spherical droplets in contact within microfluidic channels. Typically, when two spherical droplets come into contact, they initially slide one over each other, rotating so that the line connecting the droplet centers is no longer parallel to the flow axis. In the meantime, the membrane between the droplets (constituted by the continuous phase) begins to drain, favored by the excess of capillary pressure between the films [6,24]. When the liquid film is thin enough, the interfacial tension is unbalanced (if there is a surfactant) and van der Waals forces, as well as other interactions, start to play a fundamental role in the membrane disruption, leading to the fusion of the droplets. Therefore, in an ideal scenario, droplet coalescence mechanism in microfluidic channels includes three main steps, as illustrated in Figure 1: (i) two droplets approach, collision and deformation, (ii) drainage of the film constituted by the continuous phase, and (iii) rupture of the interfacial film and fusion of the droplets [6,24,25].

In general, several factors affect droplet destabilization in microfluidics devices, including the inlet velocity and viscosity of the phases, as well as the presence and absence of surfactants. However, surface wall wettability and design of the channels can definitely play a fundamental role on droplet destabilization [12]. Droplet coalescence in microfluidic devices is more suitable for surfactant-free dispersions and despite many efforts; it is still a challenge to induce the coalescence of an emulsion stabilized with surface-active compounds [19]. In these surfactant-based systems, the Marangoni effect can occur, hindering the drainage of the continuous phase and, thereby, increasing the coalescence time [6]. In view of the numerous attempts to induce destabilization of emulsion droplets within microfluidic devices, the following sections (Section 2.1 and its subsections) show the fundamentals of passive strategies and the respective studies based on this approach.

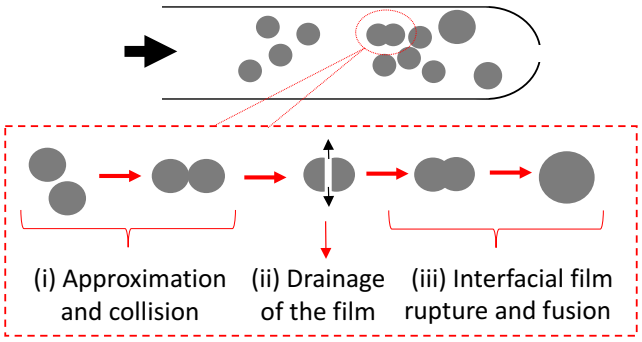

Fig. 1 Illustration of the main steps of the coalescence process within microfluidic devices (based on [26,27]).

2.1 Passive strategies to induce droplet destabilization

Passive methods can be divided into two different approaches: i) changing fluid dynamics based on channel configurations and ii) modifying channel surface properties. According to the literature, changing the channel configuration includes, for instance, manipulating the path or inserting an expansion chamber [6] to increase the collision of the droplets, reducing the amount of continuous phase between them. Changes in the surface properties of the channels, on the other hand, can compromise the stability of the droplets due to repulsive/attractive forces between the walls and either the continuous or the dispersed phase of the emulsion [12,28]. As a result, the wall can immobilize the continuous phase, triggering droplets collision, or even attract the dispersed phase, inducing the droplet to "burst" onto the wall [12,28]. Despite

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progress in understanding the different mechanisms and ways of achieving emulsion destabilization, promoting the coalescence of kinetically stable emulsions still remains a major challenge as previously mentioned. In this sense, several studies have emerged showing different techniques to induce emulsion destabilization, also seeking to identify the role of each parameter in driving the droplet coalescence or the separation of emulsion phases.

Considering these approaches, in this review, we divide passive methods into two different group-concepts (confined and dynamic flow processes). Techniques based on flow-induced coalescence were classified as dynamic flow processes (DFP), wherein the droplets are in constant flow while different strategies are applied to allow their merge/destabilization (Table 1). In general, the coalescence of droplets in this type of process can be hampered by the relatively "long film drainage times" compared to the "short residence times" experienced in microfluidic devices. Thus, it is clear that coalescence happens easily in microfluidic devices if there is enough spatial time for droplet collisions to occur[6,29]. However, the effect of the intrinsic emulsion properties must also be taken into account, especially because coalescence time can be influenced by droplet size and deformation, viscosity ratio and interfacial tension between the phases [6,24]. Therefore, such information can be interesting indicators of the stability of emulsions within microfluidic devices.

Confined processes (CP) have also emerged as a pivotal strategy to induce emulsion destabilization and coalescence, but, unlike DFP techniques, they are still scarcely explored. However, application of CP techniques can be a rational strategy to manipulate the residence time of the droplets in microfluidic devices. In such cases, the droplets are usually confined within either a small trap/anchor or a reservoir and destabilization is observed over time (Table 2)[18,22,23,30–32]. As they are confined systems, the effect of the channel surface or external components on the droplets has also been evaluated[12,18,23,32].

Table 1 and Table 2 summarize and illustrate different passive strategies to destabilize emulsion droplets that have been proposed in recent years. DFP strategies were classified as (1) single direction of droplets approach, (2) multiple directions of droplets approach, (3) insertion of other microstructures and (4) tailoring the wettability. CP studies, on the other hand, were classified as (1) droplets confinement, (2) reservoir and also (3) tailoring the wettability. Regardless of the flow conditions, both strategies (DFP and CP) are typically associated with modifying the design and/or the surface of the channels. However, a direct comparison between the different techniques presented in Tables 1 and 2 is not possible because the materials used either to compose the emulsions or to manufacture the devices were different. Notwithstanding, these outcomes allowed to better elucidate the process of droplet destabilization, providing important details of each approach and specific information about the different studies.

2.1.1 Dynamic Flow Processes (DFP)

The processes in which the emulsions are destabilized during the continuous flow of the droplets are denominated in this review as *Dynamic Flow Processes* (DFP). In such circumstances, droplets generally experience shear stresses that can be compared to those applied in conventional emulsification processes, due to the reduction in the length-scale of the devices[14]. As aforementioned, we divide these processes in different approaches. In the first strategy - (1) single direction of droplets approach - the droplets flow only on the "x" axis (i.e., in the main direction of the flow) throughout the observation process, colliding with each other and potentially experiencing coalescence. On the other hand, in the second perspective - (2) multiple directions of droplets approach -, instead of flowing on the same "x" axis, droplets flow coming from multiple directions and a forced head-on faced collision of the droplets is usually observed. In the latter, either a T- or a Y-junction is typically applied. Considering the (3) insertion of other microstructures and (4) tailoring the wettability, a scarce number of studies have emerged. For instance, in the former case, we can point to an example related to the addition of a tip inside the channel to induce local instabilities on the surface of the droplets[21]. On the other hand, in the strategy related to the manipulation of channel wettability, specific regions are created to immobilize the droplets[28,29]. In the next section, we pinpoint some examples of these techniques, and the main characteristics related to the emulsion coalescence. In addition, Table 1 shows the strategies (either channel geometry or wettability modification) and fundamental information considering each study.

2.1.1.1 Single direction of droplets approach

The single direction of droplets approach is the most widely used concept for studying droplet coalescence in microfluidic devices. In this strategy, a flow resistance is introduced along the channel, which can be any type of flow perturbation occurring over a one-dimensional flow. Therefore, based on the premise that fluid must be removed from between the two colliding droplets, different techniques have been proposed (Table 1). Examples of such techniques include an increase in the area of the microchannel section[15,16,25,33–35] or the addition of a geometrical constriction for a single droplet[36]. In this context, Tan *et al*[33] investigated the fusion of water droplets (W/O emulsion) using three different geometries, including straight and tapered expansions as well as a flow rectifying design. In both expansions, the configuration of the channels allowed to decrease the distance separating the droplets, leading to their approach and consequent collision. In the tapered expansion, undesired multiple coalescence was triggered, while the flow rectifying design enabled a more controlled fusion of the droplets, which was associated to the regulated drainage of the continuous phase imposed by the insertion of an upper and a lower channel with identical resistances (Table 1)[33]. Therefore, it is possible to modulate judiciously the number of merged droplets using a flow-rectifying structure. Overall, one can affirm that if the aim is to coalesce and determine the stability of the droplets, these strategies are quite interesting. However, when the objective is to collide only two droplets (for their application as micro-reactors); especially the geometries based on expansions leave much to be desired due to the difficulty in controlling flow conditions[20]. Similarly, Tan *et al*[34] applied a rectifying geometry, but testing a trifurcating channel with varied width dimension in order to guarantee an even more controlled fusion of water droplets, emphasizing that the platform can be applied

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to either study coalescence rate or perform the mixing of chemicals. In the same vein of the successful principle above, Gunes *et al*[35] implemented a main channel containing several channels on both lateral walls (see Table 1). By properly controlling the flow conditions in these vertical (lateral) channels, the drainage of the oil film (in W/O emulsions) could be manipulated and the coalescence of droplets achieved as desired. The main advantage of this strategy is the adaptation of the separation of the droplets by playing only with the influx and outflux of the lateral channels.

Resembling the straight geometry used by Tan *et al*[33], Baret *et al*[16] proposed a microfluidic strategy based on a collision chamber to observe the coalescence of W/O emulsions. In summary, they studied the droplet re-coalescence and quantitatively determined the influence of the adsorption dynamics of the surfactant at the water-oil interface on the emulsion stabilization. Using the same approach, Krebs *et al*[15] evaluated the demulsification kinetics by applying a simple experimental setup that consisted of a microfluidic chamber, but testing an O/W emulsion. They cautiously analyzed the interactions and trajectories of the droplets, which allowed measuring the coalescence rate under varying flow conditions, suggesting that the method could provide an easy-to-use tool to determine the stability of emulsions. Furthermore, they also pointed out that although the applied glass chips are only suitable for analyzing oil-in-water emulsions, these same devices can also be treated with alkylsilanes to evaluate water-in-oil emulsion systems (as in native PDMS material). Ultimately, Dudek *et al*[37] also used the concept of coalescence chamber, but with a design capable of evaluating the contact time as well as the speed of approach of the colliding droplets. The geometry consisted of a straight chamber similar to that used in other studies[26,37–41] but with an additional division separating the droplets into two streams. After separation, these droplets were subsequently introduced into a square channel, where the coalescence of even thousands of droplets could be evaluated.

Another solid strategy that contradicted expectations was performed by Bremond *et al*[25], who demonstrated that coalescence of W/O emulsions could not take place with droplets impact in the expansion channel, but only occurred during droplets separation due to instantaneous instability and the formation of two-facing nipples. They also showed that in a compact system (with a train of droplets), once destabilization was triggered, a cascade of coalescence could be achieved even in surfactant-stabilized emulsions (with Span 80)[25]. To explain better the results, Lai *et al*[42] performed, in a later study, an in-depth characterization of the phenomenon and concluded that the nipple formation led to an increase of local contact area, which unleashed momentary instabilities.

Another flow-controlled method was applied by Chen *et al*[43], where the authors used an interesting strategy to produce and subsequently evaluate the coalescence of emulsions inside microcapillary devices. In this case, double emulsions with two inner cores were fabricated and a hydrodynamic method was investigated to control the coalescence of such internal droplets. As a result, a flow regime to induce the internal coalescence of the droplets was established. However, since the internal coalescence within double emulsions is out of the scope of this paper, additional details can be found in the reference cited. Finally, in addition to the chamber-related strategies, this section also encompasses the addition of geometrical constrictions for the fusion of the droplets. In such structures, a droplet is immobilized and instabilities are promoted on its surface meanwhile a rear droplet flows towards it. Chokkalingam *et al*[36] applied this strategy for sol-gel reactions, triggering chemical synthesis from the precise synchronization and coalescence of the droplets.

2.1.1.2 Multiple directions of droplets approach In multiple directions of droplets approach, a junction structure is usually proposed, but unlike the one direction strategy, most of these designs need meticulous synchronization of the droplets to allow their contact at the junction, which is a challenge[6]. However, as with unidirectional flow strategies, coalescence takes place when the continuous phase is drained, enabling droplets fusion. Therefore, the controlled pattern of these structures allows the droplets to be efficiently merged one-by-one[19], while inducing a coalescence cascade is difficult in these microfluidic systems. As a result, the droplets can be used as micro-reactors in which reactions are triggered once the droplets are merged. Nevertheless, the physicochemical properties of the droplets and the process parameters, mainly the viscosity and the flow rate of the phases, seem to play a pivotal role in either improving or preventing the fusion of the droplets[6].

Considering the junction strategy, Christopher *et al*[24] analyzed the role of droplet size and flow rate in triggering the coalescence of a pair of droplets in a perpendicular T-junction. Within these channels, the authors observed the transition between different mechanisms (coalescence, splitting, slipping, late coalescence, multiple splitting, and late splitting), which depended on the applied variables (droplet size and flow rate). In general, coalescence occurred easily using slow collision speeds, while splitting and slipping of the droplets could be visualized when faster velocities were established. Therefore, they concluded that the local velocity and droplet curvature were the control parameters, since both typically influence the drainage time of the liquid film. However, although the aforementioned study was able to induce coalescence, it indeed presented an inherent issue related to droplets synchronization. To overcome this impasse, Shen *et al*[44] developed a T-junction geometry coupled with a rectangular microgroove, which enabled a better coalescence efficiency of water-in-oil emulsion droplets. Moreover, in addition to the perpendicular-based structures, Liu *et al*[45] and Wang *et al*[46] also tested other angles (30°, 60°, 120°, 150° and 180° for the former and 60°, 120° and 180° for the latter) and both found that, by reducing the junction angle, coalescence efficiency could be improved. Liu *et al*[45] further corroborated the fact that, when droplets are in conditions of low flow rate, they easily undergo coalescence.

Simone[47] also used the shock-induced approach to promote droplet coalescence, but an extra "shuffling element" (or "coalescence element") was inserted into the channel, which allowed the process to be independent of both the phases of the emulsions and the synchronization of the droplets. In order to prove the versatility of the channel, she also applied this "lab-on a-chip" to fuse

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the droplets and mix different components. Later, Simone *et al*[48] applied a similar geometry to investigate the effect of the rheological and physical properties of the phases on the occurrence of coalescence, concluding that the viscosity ratio of the phases has a direct influence on the coalescence dynamics. Ultimately, Mazutis & Griffiths [19] implemented a different approach based on the hydrodynamic flow to trigger coalescence. In addition to the T-junction strategy, where two droplets collide in a widening channel, they also applied droplets with different sizes (playing with droplet polydispersity). In this scenario, the droplets did not coalesce during the collision. Instead, a more spontaneous fusion was reproduced due to the flow field that induced the smaller droplet to rotate on the surface of the larger droplet, which consequently changed the shape of the smaller droplet, unbalancing the interfacial tension and triggering coalescence.

2.1.1.3 Insertion of other microstructures In DFP methods, another different approach is to insert other classes of structures within the microchannels in order to induce local-points of instability on the surface of the droplets. Deng *et al*[21] classified their study as a surgery-like strategy, in which they explored structures called micro-lancets, manipulating their shape and hydrophilicity. The authors found that adequate wettability can make these lancets able to scratch the droplets and, consequently, unbalance the surfactants deposited at the water-oil interface. Such phenomenon may have led to a local scattering of surfactants in two contacting droplets, inducing their destabilization. As expected, hydrophilic structures and sharp tips easily induced coalescence of water-in-oil emulsions, while when using hydrophobic tips, the droplets did not fuse. In fact, hydrophilic tips triggered an easier droplet destabilization because the oil phase did not wet the surface and the water droplets could be scratched. The main advantage of this technique is the independence of droplet synchronization, since the tip has the capacity to partially immobilize the first droplet until the other arrives, allowing long-term processing.

Another practical study was performed by Li *et al*[49] using double emulsions (W/O/W) as model systems. Here, they produced the emulsions using a capillary device, collected the droplets, following by their reinjection inside another microfluidic device containing a tapered nozzle with different tilt angles. From modeling the system and confirming with experiments, they observed that the breakup of droplets could not be visualized with an angle larger than 9°. Therefore, it is clear that the manipulation of such a parameter can be used to prevent the breakup of droplets and consequently the release of the emulsion core. In the same line, Chen *et al*[50] applied the same colloidal system (double emulsion with the same phases) to study the effect of the droplet size on their breakup when flowing through constrictions with varied sizes. Interestingly, a complex phenomenon involving the formation of two daughter droplets, and release of inner water into the outer continuous phase was responsible for the complete burst of the double emulsion. In the end, they concluded that although the size of the droplets is important to manipulate the droplet breakup, the flow conditions as well as the size of the nozzle are also controlling parameters. Therefore, a phase diagram containing the capillary number and the ratio of the diameter of the inner droplets and the size of the constriction was generated.

2.1.1.4 Tailoring the wettability Another method that has been studied is the change on the wettability of the channel surface. This technique is based on the surface energy pattern that initially induces droplets entrapment (in regions where the continuous phase of the emulsion has no affinity with the surface of the channel), followed by the detachment of droplets in a region of easy flow. The droplet entering the modified region is expected to slow down and even stop until another droplet reaches the "surface-inducing trap." As soon as the drag force exceeds the surface energy, immobilized droplets are released[20,28]. In a first study[28] the authors observed the behavior of W/O emulsions in a patterned PDMS produced with hydrophilic poly (acrylic acid), which was grafted via UV-induced photo-polymerization. A second study[29], on the other hand, observed O/W emulsions in a glass capillary device with a heterogeneous surface-pattern, presenting a segment of hydrophobic wall. Interestingly, this latter work demonstrated how to control the stability of the emulsions within the microfluidic device. Hence, it is clear that the change in wettability, including heterogeneous surfaces (different hydrophilicity), improves droplet destabilization under flow conditions.

In addition to droplet coalescence, Chen *et al*[51] also observed the breakup of droplets induced by their adhesion inside a microfluidic channel. For this, O/W emulsions were flowed within a glass capillary device with patterned surface and adhesion of the droplets was observed in the hydrophobic region, leading to droplets breakup. However, they concluded that such an adhesion was directly related to the speed and size of droplets and, more broadly, to the capillary number.

2.1.2 Confined Processes (CP)

We define as Confined Processes (CP) the conditions in which emulsion droplets are destabilized within a confined environment. As observed in the literature, confined processes were developed primarily for three purposes: (i) to observe the behavior of the droplets over time in a packed system[22], (ii) to evaluate the effect of adding external components to the colloidal system[23,32] and (iii) to observe the droplets while playing with their surface properties in order to have controlled fusion[18]. Herein, we divide the different approaches used in this type of destabilization (CP) in (1) droplets confinement, (2) reservoirs and (3) tailoring the wettability (Table 2). In the former case, either individual or a small number of droplets is captured within a structure in the devices (trap/anchors). Next, different components are added within the microchannel and the behavior of the droplets is monitored to provide information on the stability of the emulsions in contact with different compounds. Another strategy is the use of reservoirs, which collect hundreds or even thousands of droplets to allow the observation of their behavior when in contact with each other over time. Finally, in this same chamber, other approaches can be incorporated, such as modifying the channel wall wettability to also take into account the influence of this variable.

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2.1.2.1 Droplets confinement In a first scenario, Marze *et al*[23] developed a microfluidic device containing traps to confine oil droplets (O/W emulsions). Later, Nguyen *et al*[30,31] applied this same geometry, but instead of using plasma-treated PDMS, they modified the surface wettability by applying a UV-based polymerization technique, to maintain channel hydrophilicity for longer periods than that typically offered by plasma treatment. Regardless of the case, they used the system to observe the behavior of immobilized droplets when facing the continuous injection of digestive fluids (simulating intestinal biochemical environment). Firstly, they produced the droplets and continuously injected them into the microfluidic traps. Therewith, they were able to evaluate the behavior of the emulsions by measuring the increase/decrease on droplets diameter over time. Scheuble *et al*[32] applied the same approach to study emulsion digestibility, but using glass channels fabricated by the wet-etching technique. These experiments were carried out after stabilizing the droplet interface overnight, while the studies mentioned previously[23,30,31] were performed immediately after emulsion formation. In fact, other technical details differ when comparing the two set of experiments, but it is beyond the scope of this review.

Similar to the traps, Tullis *et al*[18] suggested another strategy for efficiently capturing and fusing pairs of water droplets under stationary conditions using anchors. On this platform, the coalescence of water-in-oil emulsions was achieved by injecting an external flow of surfactant-free oil into the device, leading to the dilution of the surfactant in the continuous phase. As expected, they also found that emulsions made with surfactant-free oil showed faster coalescence. However, this absence of surfactant resulted in an uncontrolled destabilization and, therefore, would not be indicated for processes that require controlled fusion. They also observed that, by manipulating the flow conditions, different patterns of coalescence and selective droplet fusion could be achieved, enlightening that this methodology can be considered an interesting tool to study surfactant absorption/desorption onto droplet surface.

2.1.2.2 Reservoirs In the reservoir-based strategy, only the effect of droplet compaction is normally studied. In this context, Bremond *et al*[22] investigated the coalescence propagation inside a microfluidic chamber and concluded that the phase inversion of the emulsion could be favored by the existence of a droplet size distribution (polydispersity). The authors also suggested that two main physico-chemical mechanisms may govern the destabilization of concentrated emulsion systems: the diffusion of the dispersed phase through the continuous phase and the coalescence of neighboring droplets. Taking advantage of this geometry, they studied the propagation and the probability of coalescence for different sizes and organization of droplets.

2.1.2.3 Tailoring the wettability The surface walls of a confined environment can be tailored to induce droplet destabilization. Studies typically use the same combination of emulsions and channel surface treatment, where the continuous phase perfectly wets the channel surface, i.e. O/W emulsions in hydrophilic channels and W/O emulsions in hydrophobic devices. A recent study[12], demonstrated the effect of opposite channel surface treatments on inducing emulsion instability, where O/W emulsions were destabilized in hydrophobic as well as in hydrophilic channels. This simple modification in the surface properties has been shown to generate other subtle destabilization mechanisms (in addition to coalescence) such as emulsion "bursts," defined as the rupture of the droplet interfacial layer. When the droplet interfacial layer ruptures, the dispersed phase wets the surface of the channel wall. This is different from the coalescence destabilization mechanism, where the dispersed phase still remains confined within the droplet regardless of the growth in the size of the droplet. Qualitatively, this can be distinguished from the morphology of the droplet structure.

Another interesting destabilization mechanism recently reported is fracture, where adhesion between emulsions is strong enough such that the packing moves globally as a solid[12]. Here, the destabilization mechanism is linked to displacement of the local emulsion structure that results to strain (similar to the appearance of a "crack" in a solid structure). Emulsion destabilization via fracture is the primary mechanism at early times. However, at longer time scales and as more points of local strain continue to appear, the destabilization mechanism transitions to an emulsion burst/coalescence[12] or, depending on parameters, a complex combination of other mechanisms.

These destabilization mechanisms are linked to different conditions, including surface energy between the droplet interface and the channel wall. Moreover, the role of surface charges (zeta potential) on both the channel walls and droplet interfaces has proved to be equally important, depending on the nature of the surfactant used. For instance, emulsions stabilized by positively charged surfactants do not adhere to the positively charged surface walls due to inherent repulsion. By modifying the charge, destabilization can be induced by introducing non-negligible attractive forces between the emulsion droplets and the channel surface wall, thereby allowing the emulsion to break. Understanding the role of wettability is crucial to understand emulsion behavior during storage, because surface properties may change over time, depending on conditions, which can have adverse effects on emulsion stability.

3 Conclusions

This paper provides an overview of relevant studies in the field of droplet destabilization and coalescence in microfluidic channels, presenting their outcomes and highlighting their important aspects and specificities. Overall, one can observe that although recent studies have been published in the area, the facets that influence droplet destabilization are still being investigated, especially due to the complexity of the subject. In any case, in this paper we present fundamental insights and premises on how to induce droplet destabilization according to the application, in addition to showing the feasibility of implementation of each class of strategy. Furthermore, evaluating these studies, we were able to point out some challenges that still need to be overcome in order to properly promote emulsion coalescence within these microsystems.

- **(i)** In the case of droplets acting as micro-reactors, a more

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precise control of the process conditions must be implemented, as well as experiments with different compounds and multiple droplets.

- (**ii**) A wide range of materials must be tested and their efficiency compared, mainly because a direct correlation between the different techniques is hitherto not possible, since the materials used either to compose emulsions or to manufacture microfluidic devices are different.

- (**iii**) The influence of the wall material should be further exploited, especially for oil-in-water emulsions, in which surfactants can be highly charged and attraction to the surface can play a key role in promoting destabilization of the droplets. For instance, the wall material can be explored to induce emulsion burst on the surface of the channel, which may be a trigger to promote emulsion destabilization and phase separation. Generally, emulsion burst can be generated by either inducing "attraction" between the channel surface and the dispersed phase of the emulsion (e.g., using hydrophobic surfaces and oil as a dispersed phase) or even by applying attractive charges between the channel walls and the surfactants stabilizing the emulsion droplets.

We believe that, by studying these different approaches, information of paramount importance can be obtained, improving the exploitation of microfluidics in the fields of emulsion development, droplets as micro-reactors or even separation of multiphase systems. Finally, since we were able to distinguish the effect of channel geometry, insertion of additional structures and surface wetting on the destabilization of emulsion droplets, we can rationalize that these strategies can be implemented for different purposes i.e., study droplet destabilization and/or use droplets as micro-reactors. However, especially for micro-reactor applications, the coalescence should be extremely controlled and therefore, the contact of a limited number of droplets is usually proposed. For instance, in DFP, collision of droplets using the strategy of Multiple directions of droplets approach as well as Tailoring the wettability are highly recommended. Of course, the insertion of microstructures such as the microlancets is also a rational strategy to allow the collision of a pre-determined number of droplets. On the other hand, in CP, Droplets confinement using traps and anchors would be the most suitable strategy to control the amount of contacting droplets. For the study of droplet destabilization, more broad strategies can be applied depending on the focus of the study. For example, a train of flowing droplets or even hundreds of static droplets in contact are very interesting approaches to understand real production or processing of emulsion systems. However, for more fundamental studies, comprehension on how the droplet interface changes is also pivotal and therefore, focusing on two (or a limited amount) of droplets could be a more interesting strategy, permitting valid use of the approaches suggested for micro-reactors.

Author Contributions

All three authors equally contributed to the paper, in terms of literature review, writing, and editing the paper.

Conflicts of interest

There are no conflicts of interests to declare.

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4 Tables

In the following tables, we show simplified schematics of the channel layout, with a characteristic length scale, based on the appropriate references. The blue arrows indicate the direction of the aqueous phase (either in droplet form or the continuous phase in the case of O/W emulsions) while the yellow arrows indicate the direction of the oil phase (either in droplet form or the continuous phase in the case of W/O emulsions).

- Table 1: Strategies based on Dynamic Flow Processes (DFP) that aim to promote droplet destabilization.
- Table 2: Strategies based on Confined Processes (CP) that aim to promote droplet destabilization.

Table 1: Strategies based on Dynamic Flow Processes (DFP) that aim to promote droplet destabilization.

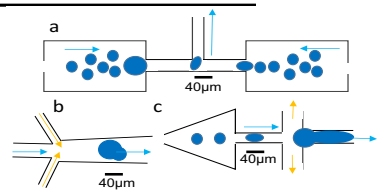
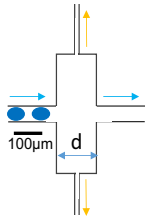
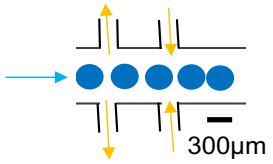
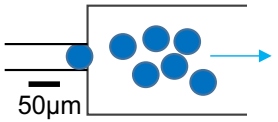
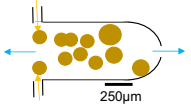
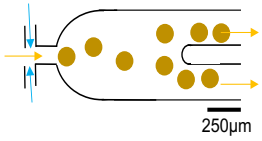
DFP	Ref.	Emulsion nature	Aqueous phase	Oil phase	Emulsifier	Channel strategy	Device characteristics	Simpified scheme of the channel layout
Single direction of droplets approach	Tan et al. 2004[33]	W/O	Water	Oleic acid	Span 80	**Geometry:** a) Straight expansion b) Tapered expansion c) Flow rectifying design	PDMS bonded to a glass slide	
	Tan et al. 2007[34]	W/O	Water	Oleic acid	-	**Geometry:** Addition of a trifurcating junction with different (d) dimension	PDMS bonded to a glass slide	
	Gunes et al. 2013[35]	W/O	Water	PDMS MCT	Tween 20 PGPR	**Geometry:** Lateral channels on both sides of the main channel to manage the amount of fluid between droplets	TOPAS COC resin	
	Baret et al. 2009[16]	W/O	Buffered solution (10mM Tris-HCl)	Fluorinated oil (FC40)	Amphiphilic molecule Krytox FHS+DMP	**Geometry:** Coalescence chamber - abrupt expansion of the channel	PDMS bonded to a glass slide and treated with aquapel	
	Krebs et al. 2012[15]	O/W	Water	Hexadecane	-	**Geometry:** Collision chamber	Glass	
	Dudek et al. 2020[37]	O/W	Water Saline solution	Heptane Xylene Dodecane	Span 85	**Geometry:** Split channel + square chamber	Glass	

Table 1: Strategies based on dynamic flow processes (DFP) that aim to promote droplet destabilization. - continued

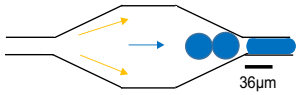
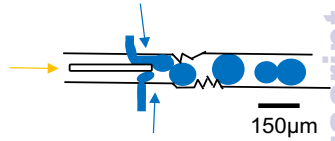
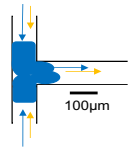
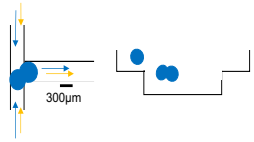
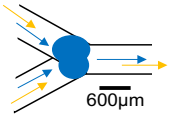
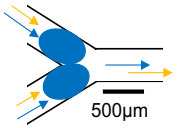
DFP	Ref.	Emulsion nature	Aqueous phase	Oil phase	Emulsifier	Channel strategy	Device characteristics	Simplified scheme of the channel layout
Single direction of droplets approach	Bremond et al. 2008 [25]	W/O	Water	Hexadecane	Span 80	**Geometry:** Expansion and contraction of the channel width	PDMS bonded to a glass slide spincoated with PDMS	
	Chokkalingam et al. 2010 [36]	W/O	Water + different materials	Perfluorodecalin	$C_8H_3F_{15}O$	**Geometry:** Geometrical constriction	PDMS bonded to a glass slide	
Mutiple directions of droplets approach	Christopher et al. 2009 [24]	W/O	Water Glycerol solution	Silicone oil	-	**Geometry:** Droplets collision at a T-junction	PDMS bonded to a glass slide spincoated with PDMS	
	Shen et al. 2017 [44]	W/O	Water Ethanol	Sunflower oil	-	**Geometry:** Droplets collision at a T-junction coupled with a rectangular microgroove	PDMS	
	Wang et al. 2013 [46]	W/O	Water Ethanol	Pentanol Octanol Decanol	-	**Geometry:** Droplets collision at a Y-junction (60°, 120°, 180°)	polymethyl methacrylate (PMMA)	
	Liu et al. 2015 [45]	W/O	Water	Liquid paraffin Silicone oil	-	**Geometry:** Droplets collision at a Y-junction and T-junction (30°, 60°, 90°, 120°, 150°,180°)	-	

Table 1: Strategies based on dynamic flow processes (DFP) that aim to promote droplet destabilization. - continued

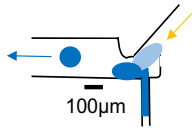
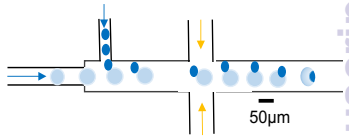
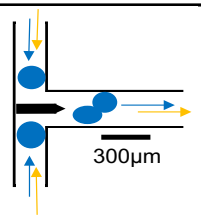
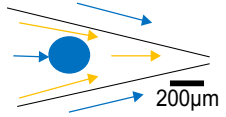
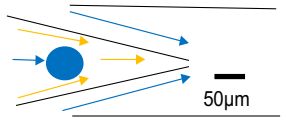
DFP	Ref.	Emulsion nature	Aqueous phase	Oil phase	Emulsifier	Channel strategy	Device characteristics	Simplified scheme of the channel layout
Multiple direction of droplets approach	Simone 2015 [47]	W/O	Water Gelatin solution	Fluorinated oil	-	**Geometry:** Shuffling element	PDMS-glass composite	
	Mazutis & Griffths 2012 [19]	W/O	Water Sodium phosphate Tris-HCl NaCl solution	FC-40 FC-77 Galden-HT135	EA-Surfactant	**Geometry:** Droplets collision at a junction	PDMS bonded to a glass slide and treated with aquapel	
Insertion of other structures	Deng et al. 2013 [21]	(1) W/O (2) O/W/O	Water	Silicone oil Soybean oil Benzyl benzoate	Dow Corning 749, PGPR nanoparticles and SDS	**Structures:** Micro-lancets with different wettability and shapes (sharp and flat tips)	Micro-lancets (plastic, copper and aluminum wire) hydrophilic or hydrophobic	
	Li et al. 2011 [49]	W/O/W	Water and Water + PVA	PDMS	Dow Corning 749,	**Structures:** Injection through tapered nozzle	Two different nozzles (6.5° and 9°)	
	Chen et al. 2011 [50]	W/O/W	Water and Water + PVA	PDMS	Dow Corning 749,	**Structures:** Injection through tapered nozzle	Tapered tip diameters 0-120μm	

Table 1: Strategies based on dynamic flow processes (DFP) that aim to promote droplet destabilization. - continued

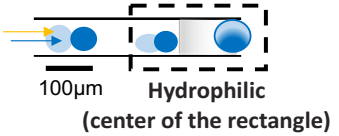
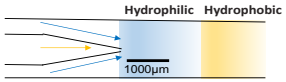
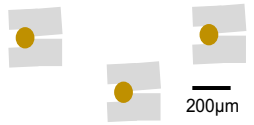
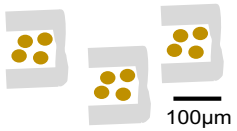
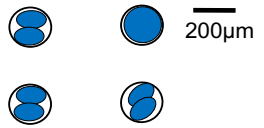
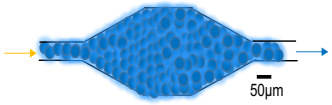
DFP	Ref.	Emulsion nature	Aqueous phase	Oil phase	Emulsifier	Channel strategy	Device characteristics	Simplified scheme of the channel layout
Tailoring the wettability	Fidalgo et al. 2007[28]	W/O	Water	Fluorous phase	-	**Surface Wettability**	PDMS patterned with hydrophilic poly(acrylic acid)	
	Meng et al. 2016[29]	O/W	Water + polyvinyl alcohol (PVA)	Paraffin oil	-	**Surface Wettability**	Glass capillary patterned with octyltriethoxysilane (OTES) coating	
	Chen et al. 2013[51]	O/W	Water + PVA alcohol (PVA)	Liquid paraffin	-	**Surface Wettability**	Glass capillary patterned with octadecyltrichlorosilane OTS) coating	

Table 2: Strategies based on confined processes (CP) that aim to promote droplet destabilization.

DFP	Ref.	Emulsion nature	Aqueous phase	Oil phase	Emulsifier	Channel strategy	Device characteristics	Simplified scheme of the channel layout
Droplets confinement (traps and anchors)	Marze et al. 2014[23]	O/W	Water	Tricaprylin Triolein Olive oil Fish oil	β-lactoglobulin	Traps	PDMS used immediately after plasma treatment	
	Scheuble et al. 2017[32]	O/W	Phosphate buffer solution	MCT oil	β-lactoglobulin	Traps	Glass prepared by wet-etching	
	Tullis et al. 2014[18]	W/O	Water with FeCl and KSCN	Fluorinated oil Novec 7500	QX100 Pluronic F-68	Anchors	PDMS with Novec 1720 coating	
Reservoirs	Bremond et al. 2011[22]	W/O	Water	Hexadecane	Span80	Chamber with concentrated droplets	PDMS bonded to a glass slide spincoated with PDMS	
Tailoring the wettability and reservoir	Santos et al. 2021[12]	O/W	Water	Light mineral oil Hexadecane	SDS, LDS, TTAB, DTAB, Tween 80	Microchamber with packed concentrated droplets	PDMS bonded to a glass slide spincoated with PDMS used after plasma treatment immediately after plasma treatment, after transition to hydrophobic conditions or even chemically treated with APTES