Review

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Droplets-Based Microfluidics as a Platform to Design Food-Grade Delivery Systems Based on the Entrapped Compound Type

Jhonatan Rafael de Oliveira Bianchi [1], Lucimara Gaziola de la Torre [2] and Ana Leticia Rodrigues Costa [1,2,*]

[1] Department of Materials and Bioprocess Engineering, School of Chemical Engineering, University of Campinas, Av. Albert Einstein, 500, Campinas, SP CEP: 13083-852, Brazil
[2] Institute of Exact and Technological Sciences, Federal University of Viçosa (UFV) – Campus Florestal, Florestal, MG CEP: 35690-000, Brazil
* Correspondence: author: ana.leticia@ufv.br

Abstract: Microfluidic technology has become a powerful tool for several applications in chemistry, physics, biology, and engineering. Benefiting from the advantages of flowing fluids in the laminar regime, droplet-based microfluidics enable the development of various delivery systems based on food-grade emulsions, such as multiple emulsions, microgels, microcapsules, solid lipid microparticles, and giant liposomes. Besides, by manipulating fluids on a micrometer scale with low-energy demand, it is possible to control the size, shape, and dispersity of droplets generated, which makes microfluidic emulsification an excellent strategy to modulate delivery system properties depending on the entrapped compound type. Thus, this review points out the most current advances in droplet-based microfluidic processes, in which food-grade materials were successfully utilized to develop simple and complex delivery systems. In that context, we summarized the principles of droplet-based microfluidics, introducing the most common microdevices geometries, manufacturing materials, and forces involved in the different droplet generation processes within the microchannels. Subsequently, the encapsulated compound type, classified as lipophilic or hydrophilic functional compounds, was used as a starting point to present current advances in delivery systems based on food-grade emulsions and assembly using microfluidic technologies. Finally, we discuss the limitations and perspectives of scale-up in droplet-based microfluidic approaches, including the challenges that have limited the transition of microfluidic processes from lab-scale to industrial-scale.

Keywords: microchannels; droplet; hydrophilic compound; hydrophobic compound; drug delivery; emulsion

1. Introduction

Microfluidics is defined as the science and technology that investigates and manipulates fluids in micrometer-scale channels [1]. It is a multidisciplinary technology that involves fundamental concepts from several fields, including chemistry, physics, biology, and engineering [2]. Microfluidics equally allows a diverse array of applications within these fields, including chemical analysis [3] diagnostics [4], microreactors [5], drug scanning [6], and delivery systems [7].

Droplet-based microfluidics is a branch of microfluidics in which small droplets are generated one by one under the effect of balanced forces between immiscible fluid phases, usually oil and water [2,8,9], generated from the dispersion of droplets of one fluid (disperse phase) in another immiscible one (continuous phase) are called emulsions. Emulsions are present in several products from the cosmetic, pharmaceutical, and food industries to improve sensory and functional attributes, provide protection and stability to functional compounds susceptible to oxidation or hydrolysis, and currently control and sustain their release [10–12].

In conventional emulsification methods, non-uniform mechanical forces (shear or/and cavitation forces) involved in the droplet breakup lead to emulsions with high droplet size polydispersity [13,14]. Polydisperse droplets affect the compound's release profile, making sustained and controlled

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delivery a major challenge. Difficulties associated with localizing compound delivery and generating carriers loaded with multiple therapeutic agents are also limitations of conventional emulsification methods [7]. In addition, the high energy applied in these methods can increase the system's temperature, making the addition of temperature-sensitive compounds unfeasible [14]. The low encapsulation efficiency and very low-energy efficiency of these processes also result in higher costs for the industry [14,15].

Droplet-based microfluidics provides a novel approach to overcoming these problems through a rational design of delivery systems with precise control of emulsification processes [16,17]. Benefiting from the advantages of manipulating fluids in laminar flow with low-energy demand, highly monodisperse droplets can be generated into microchannels and used as templates for developing complex multiphase and multicomponent microcarriers, such as multiple emulsions, microgels, microcapsules, solid lipid particles, and giant liposomes [18–21]. Thus, unlike emulsions produced by conventional methods, droplet-based microfluidic systems allow for the controlled and sustained delivery of multiple therapeutic agents and temperature-sensitive compounds to target sites.

Safety-related aspects have driven the development of new strategies that aim to minimize toxicity and increase the specificity of delivery systems through more efficient processes, such as microfluidics, and more biocompatible materials. Biocompatible carrier materials can be used as delivery systems in a variety of applications, including fields of regenerative medicine, disease treatment and prevention, food and cosmetics industries [15,22–24]. In general, desirable characteristics in delivery systems are associated with their loading capacity and retention; the delivery mechanism and type of protection provided for the functional compound; the commercial viability and safety aspects of the carrier materials [11]. Synthetic materials have been widely explored as carriers in microfluidic-assembled delivery systems, while few are food-grade [25]. However, the assembly of food-grade delivery systems using microfluidic approaches has been the subject of interest in many studies since several food-grade materials emerge as viable options for this proposal [26–29]. For example, in oral administration applications, the delivery system must be produced entirely from food-grade ingredients using processing operations that have regulatory approval. Food-grade ingredients, such as carbohydrates, proteins, and lipids, are typically inexpensive, available, biodegradable, and highly biocompatible [30]. Therefore, some studies already report the development of food-grade systems for delivery by other routes, such as local injection [31].

It is currently known that microfluidic techniques also allowed, through the choice of ingredients and the emulsification process parameters, to precisely modulate properties of the carrier systems to suit the type of entrapped functional compound and its final application. It is of great interest to design delivery systems suited to the specific encapsulated compound in order to improve its bioavailability, therapeutic efficacy, and sustained delivery to target sites. Accordingly, this review points out the most current advances in droplet-based microfluidic processes, in which food-grade materials were successfully utilized to develop several delivery systems, including single/multiple emulsions, microgels, microcapsules, solid lipid microcapsules, and giant liposomes. In addition, the entrapped compound type, classified as lipophilic or hydrophilic functional compound, was used as a starting point to present current advances in delivery systems based on food-grade emulsions and assembly using microfluidic technologies.

Figure 1 is a schematic representation of the main topics covered in this review on microfluidic assembly for the design of food-grade emulsion-based delivery systems with a focus on the entrapped compound type, which are: (i) microfluidic approaches, (ii) food-grade ingredients, and (iii) emulsion-based delivery systems.

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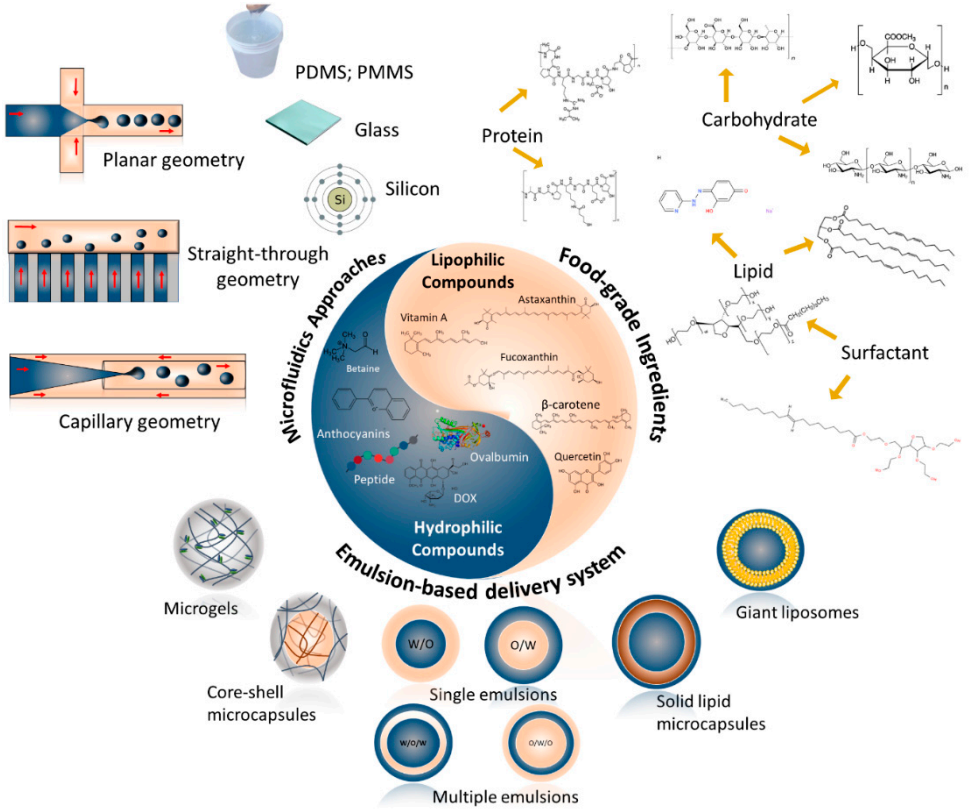

Figure 1. Schematic representation of the main topics on microfluidic assembly for the design of food-grade emulsion-based delivery systems with a focus on the entrapped compound type.

2. Principles of droplets-based microfluidics

Understanding the fluid dynamics behind microfluidic devices is essential for successfully developing droplet-based systems. Droplets generation by microfluid techniques introduces nonlinear laws into the otherwise linear Stokes flows, which are related to the complexity of fluid dynamic events during droplet formation and breakup into the microchannels [32]. Besides, since liquids flow in tiny channels, surface effects become more important than macroscale [33]. Thus, when two mutually immiscible fluids flowing in microchannels come into contact, the forces (e.g., interfacial, viscous, or inertial) involved in the droplet formation process act immediately on the fluids [33,34]. In these droplet generation methods, called passive, positive displacement pumps (syringes pumps) control the fluid flow into the channels, and the droplet formation and breakup are strongly affected by the microchannel properties (such as material, design, wettability, and roughness) and fluid properties (such as density, viscosity, emulsifier type, and concentration) [20,29].

Several techniques (soft lithography, micromachining, and laser ablation) and materials (silicon, glass, and polydimethylsiloxane-PDMS) are used to manufacture microfluidic devices with different geometries. In general, the choice of microdevice type will depend on the desired droplet-based system. Droplet generation devices are based on shear-induced geometries and interfacial tension-induced ones. The droplet formation process in shear-induced geometries occurs under the effect of balanced forces (interfacial, viscous, and inertial), while in interfacial tension-induced geometries, the droplet is generated spontaneously as only a function of the interfacial tension between immiscible fluid phases. The most used interfacial tension- and shear-induced geometries in obtaining food-grade emulsions are oblong straight-through geometry and capillaries assemblies or planar geometries, respectively [35–37]. In addition, due to the hydrophilic nature of silica and glass, these materials are mainly used to produce oil droplets dispersed in water (O/W emulsions), whereas PDMS, a hydrophobic polymer, is primarily used to disperse water droplets in oil (W/O emulsions).

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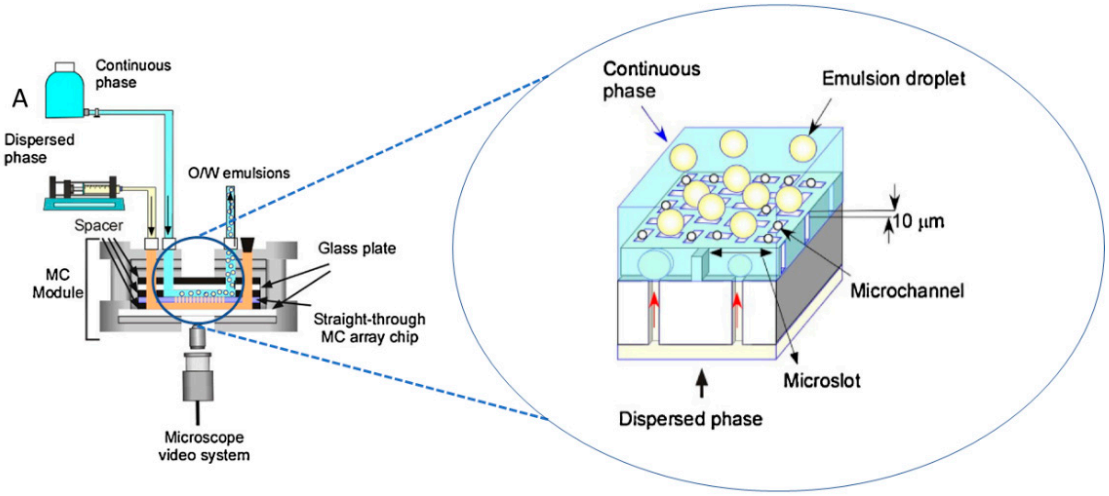
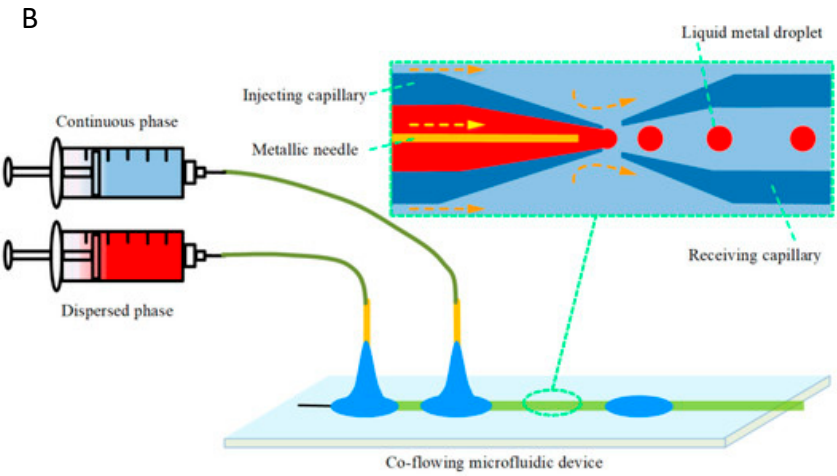
However, in order to design more complex droplet-based systems, some strategies for modifying the surface of microchannels obtained from these materials are proposed, such as layer-by-layer deposition and covalent surface modification via graft photopolymerization [24,37,38].

Currently, most microdevices based on the oblong straight-through geometry used to produce emulsion-based carrier systems are commercial silicon chips microfabricated using the repeated deep-reactive-ion etching (DRIE) process and photolithography [15,39–41]. The silicon chip is tightly held between two rubber spacers in the microfluidic module (MC module), and the droplet formation behavior is directly observed on the microscope video system (Figure 2). The dispersed phase is forced to pass through the microchannel in a controlled flux, provided by syringe pumps, to an area previously filled with a continuous phase, which is supplied from a reservoir elevated to the chip (Figure 2) [15,39]. The droplet generation process occurs when the fluid interface near the tip of the channel is forced to elongate during the droplet growth across the channel (highlighted in Figure 2). Then, the force to restore the interface-tension gradient of the elongated interface spontaneously shears the droplet from the tip of the channel [35].





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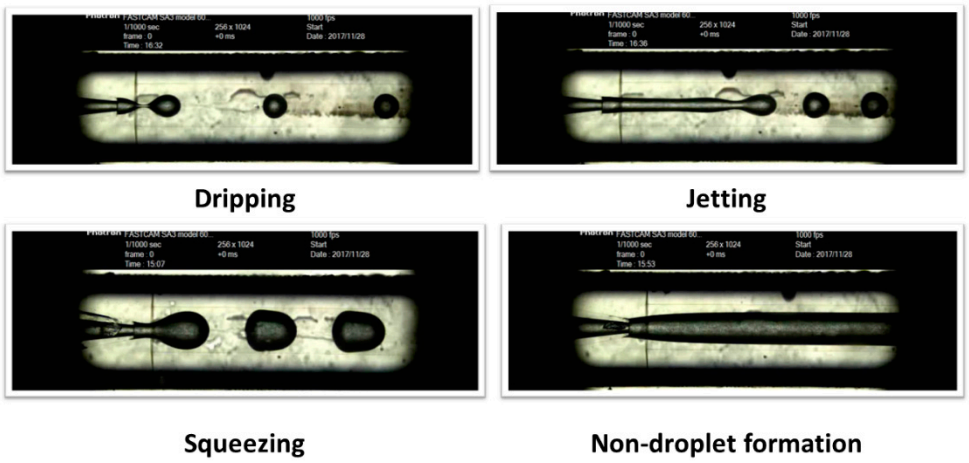

Figure 2. (A) Graphical representation of a straight-through microfluidic device setup and droplet generation representation through oblong straight-through geometry (adapted from: [42]) (B) Graphical representation of a shear-induced microfluidic devices setup. (C) Droplet formation regimes of shear-induced geometries [43].

Shear-induced geometries are based on planar geometries and capillaries assemblies [37]. Capillary microfluidic devices are coaxial assemblies of square and cylindrical glass capillaries [44]. Typically, the cylindrical capillary is inserted inside a square one with a large diameter and placed on a glass slide. Hypodermic needles attached to the devices allow fluid injection into the microchannel through plastic tubing connected to syringes pumps [43]. Usually, the dispersed phase flowing inside the cylindrical capillary is constricted by the continuous phase that flows between the capillaries to generate single emulsion droplets (Figure 2B). Despite all the advantages associated with the production of emulsion-based carrier systems using capillary devices (Table 1), the intensive labor involved in the manufacture and alignment of the tubes [44] drives the use of alternative devices.

Table 1. Advantages and limitations of different geometry droplet-based microfluidic devices.

geometry	Advantages	Limitations
Planar	- Can be manufactured in different geometries (T- and Y- junction) - Easy to modulate and can be made with different materials (e.g., PDMS, PMMA, and other polymers) - Allow manufacturing more complex configurations chips	- Complex structures for industrial production - For multiple emulsions is necessary complex structure - Some based materials are not compatible with organic solvent - Rather sample microchannels structure
Capillary	- Good for multiple emulsions in one step. - Commonly manufactured of glass which has high transparency, high chemical resistance, inertness to most substances, biocompatibility	- Complex structures for industrial production - Difficult reproducibility and manufacture - Low reproducibility - High cost - High time-consuming for fabricated
Straight-through	- droplet generation independent of flow rate. - good monodispersity - low energy consumption	- Specific configuration

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- easy amplification of the device - non-dead volume - reduced cost of chip design, processing, and operation.

Planar devices are microchannels with rectangular cross-sections produced primarily with flexible PDMS by the soft lithography technique [45]. In this technique, a master produced by photolithography is used to create a mold. PDMS or another elastomer precursor with a curing agent is poured into the mold and cured. The device is then peeled off and closed with a glass or PDMS coverslip. This easy and simple method of designing and manufacturing planar devices overcomes some of the challenges associated with capillary ones, allowing for more elaborate design configurations [46,47]. The configuration of planar devices is defined according to the type of junction between the microchannels, generally classified as T-, Y-, and cross-junctions. Unlike interfacial tension-induced geometry, the droplet formation in planar geometries is mainly a result of the shear force promoted by the continuous phase on the dispersed phase. The continuous phase flowing on either side of the dispersed phase stream at the cross-junction causes higher shear than at the T- or Y-junctions. This configuration, known as hydrodynamic flow-focusing, has been widely used to produce emulsion-based carrier systems since it leads to the generation of small and uniform droplets [37,48,49].

In both shear-induced geometries, process parameters and fluid properties regulate the velocity of droplets detachment, which in turn defines the three regimes of droplet formation, namely, dripping, squeezing, or jetting (Figure 2C) [50,51]. The jetting regime occurs when forces related to the interfacial tension dominate the continuous phase shear forces. Thus, the dispersed phase forms a long neck along the main channel, and droplet breakup occurs downstream based on the Rayleigh–Plateau uncertainty principle [52,53]. In the squeezing regime, the dispersed phase accumulates for a short period, occupying almost the entire transversal area of the main channel until the droplet pinch-off is triggered by the pressure differential behind and in front of a confined extension of the fluid interface [43,54]. In the dripping regime, the viscous dragging forces quickly overcome interfacial ones. Thus, the dispersed phase is broken before filling the entire cross-section area of the main channel, generating droplets smaller than those produced in the squeezing regime. The compound's more efficient and controlled release to the target site is usually achieved with smaller droplets; therefore, the dripping regime is desired in most droplet-based microfluidic processes [55]. No droplets are formed if the velocity of the dispersed phase is greater than that of the continuous phase. Under these flow conditions, highly viscous dispersed phases can hamper the action of shear forces, preventing droplet formation [56].

Flow patterns and droplet formation regimes can be predicted based on dimensionless numbers. The Capillary number (Ca) is often used to parametrize droplet breaking processes when viscous effects are more important than inertial ones, while Weber number (We) is used when inertial stresses dominate viscous ones [32]. The Ca (Eq. 1) and We (Eq. 2) numbers relate the viscous and inertial stresses in the flow to the interfacial stresses, respectively.

$$Ca = \frac{\mu U}{\gamma} \quad (1)$$

$$We = \frac{\rho U^2 l}{\gamma} \quad (2)$$

where, μ is the dynamic viscosity (Pa·s), U is the characteristic velocity of the fluid (m/s), ρ is the density (kg/m^3), l is the characteristic dimension of the channel (m), and γ is the interfacial tension (J/m^2).

Critical transition values between droplet formation regimes are not standardized in the literature since these numbers can be strongly influenced by the microchannels' geometry and the fluids' actual flow rates. However, microfluidic droplet formations are known to have typically Ca number values ranging from ~ 10^{-3} to 10^{1} for flow rates accessible using syringe pumps [57]. In

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addition, as the Ca number increases, a gradual transition from squeezing to dripping and jetting is observed [57].

The advantages and disadvantages of planar, capillary, and straight-through microfluidic devices are presented in Table 1. Each of them can enhance or limit the application of the microfluidic device in the development of emulsion-based delivery systems, including in large-scale processes. Commercial devices are an important part of recent advances in droplet-based microfluidic processes as they have been used successfully to design carrier systems based on food-grade emulsions. Table S1 (supplementary material) summarizes the main technical specifications of commercial devices, as knowing them can expand their use in a range of applications (*i.e.*, food, biology, and chemical) and encourage further studies related to new processes and products.

3. Microfluidic assembly of food-grade delivery systems based on entrapped compound type

3.1. Lipophilic functional compounds

The food, pharmaceutical, cosmetic and medical industries need to deliver a range of lipophilic functional components, including bioactive lipids, nutraceuticals, therapeutic agents, and drugs. However, many of these compounds are prone to degradation and crystallization upon exposure to environmental conditions, poor water solubility, unpleasant odor, and low bioavailability [11,58,59]. Emulsion-based delivery systems have been reported to overcome most of these drawbacks, including the improvement in their solubility and chemical stability [60–62].

The single oil-in-water (O/W) emulsions are the simplest delivery systems for encapsulating lipophilic functional compounds. These systems ensure protection and target delivery by dispersing oil droplets containing the lipophilic compound in an aqueous phase containing an emulsifier or surfactant [55,63,64]. Emulsifiers are amphiphilic molecules that act at the oil-water interface reducing the tension between the phases, favoring the droplet breakup and preventing the recoalescence of the droplets during the emulsification process [65]. The type and concentration of the emulsifiers, as well as the droplet size polydispersity, are the main factors that govern the kinetic stability of these systems against the main destabilization mechanisms (i.e., flocculation, coalescence, creaming, and Ostwald ripening) [11]. There are a significant number of emulsifiers classified as food-grade ingredients, including low molecular weight surfactants (polyoxyethylene sorbitan fatty acid esters (Tweens), polyglycerol polyricinoleate (PGPR), and sorbitan fatty acid esters (Spans)), phospholipids (soybean lecithin), and biopolymers (proteins and carbohydrates) [63,66].

Khalid et al., (2016) [42] investigated the effects of emulsifier type, bovine serum albumin (BSA) and polyoxyethylene (20) sorbitan monolaurate (Tween 20) on droplet formation characteristics and stability of emulsions encapsulating quercetin produced in straight-through microfluidic devices. Both emulsifying molecules have non-attractive interaction with the chip surface; thus, uniform-sized droplets could be generated regardless of the type of emulsifier. However, more stable droplet generation and smaller droplet size were observed with Tween 20 (nonionic emulsifier) in comparison to BSA (protein emulsifier). After optimizing microfluidic process parameters (J_d = 20 L/m^2 h^1 and Q_c = 250 ml/h) and ingredient formulations (1% w/w Tween 20 and 0.4 mg/ml quercetin in MCT oil), the delivery systems showed encapsulation efficiency superior to conventional emulsification methods, exceeding 70% after 30 days of storage at 4 and 25 °C. In a similar study, Khalid, Shu, et al., (2017) [39] showed that the purity of the lipophilic compound could also influence the droplet generation process in straight-through microfluidic devices. Typically, low-purity commercial compounds have stabilizing ingredients that disfavor emulsification. In these cases, optimized process conditions and suitable emulsifiers are key factors for successful encapsulation. Different emulsifiers (1% w/w sodium dodecyl sulfate (SDS), decaglycerol monooleate (MO-7S), decaglycerol monolaurate (ML-750), modified lecithin (ML), and sodium caseinate (Na-Cs)) with different stabilizing mechanisms were used to stabilize O/W emulsions encapsulating astaxanthin (AXT) extracts in two purity degree, Zanthin® (ZA, purity 10%) and AstaReal® (AR, purity 20%). All emulsifiers, except Na-Cs, promoted the production of uniform droplets of MCT oil with ZA extract into the microchannels. The same behavior was observed during the generation of oil droplets with

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AR extract stabilized by polyglycerol fatty acid esters (ML-750 and MO-7S) and the ionic emulsifier (SDS). In contrast, broad size distribution curves confirmed the unstable generation of oil droplets with AR extract stabilized by protein-based emulsifiers (Na-Cs and ML). These results showed that the chemical composition of the lipophilic compound could directly affect the ability of the emulsifier to reduce the interfacial tension between the oil-water phases, which may or may not favor the process of forming stable droplets in straight-through microfluidic devices.

Straight-through microfluidic devices were also used to assess the effect of different concentrations of two different lipophilic compounds, γ-oz and β-st, on droplet formation characteristics of emulsions [42]. At low concentrations (0.5 - 1% (w/w) each) of γ-oz and β-st and Q_d between 1–5 mL/h, small droplets (diameters between 26.5 and 28.5 μm) could be formed uniformly with no signal of wetting by the dispersed phase on the chip surfaces. Besides, very small Ca numbers (1.0×10^{-3} - 1.4×10^{-3}) indicated a smooth droplet generation into microchannels without the influence of different flow rates on the droplet size. On the other hand, at high concentrations γ-oz and β-st (1.0 - 4% (w/w) each), an increase in droplet size and polydispersity was observed, which may be associated with the crystallization of the lipophilic compounds in the dispersed phase. The emulsions formulated with γ-oz and β-st (1% w/w Tween 20 and Q_d = 2 mL/h) maintained the encapsulation efficiency of more than 80% during 30 days of storage period at room and refrigerated temperatures. Besides, the γ-oz and β-st retention values in O/W emulsions (14 μg/mL and 53 μg/mL, respectively) correlated well with the recommended daily intake values.

In a more recent study, fucoxanthin's chemical stability and bioaccessibility during *in vitro* digestion of O/W emulsions produced by straight-through microchannel emulsification and high-pressure homogenization were compared [40]. The chemical stability of fucoxanthin in emulsions produced by microfluidics was significantly higher than those produced by high-pressure homogenization. In contrast, the free fatty acids released and fucoxanthin bioaccessibility in emulsions using microfluidics (around 10%) were significantly lower than using a high-pressure homogenizer (around 60%). The high-energy emulsification process caused degradation of fucoxanthin but led to significantly smaller droplet generation than microfluidics (0.14 μm and 33.7 μm, respectively). Large oil droplets reduced the number of triacylglycerol molecules exposed to the lipase action; thus, only a small amount of fucoxanthin could be released from emulsions produced by straight-through microchannel emulsification.

As lipid digestion is an interfacial process, the oil droplet size and the nature of carrier ingredients play an important role in the lipid hydrolysis (lipolysis) rate of O/W emulsions [63,67,68]. Most food-grade emulsions are produced with medium-chain triglycerides (MCT) or long-chain triglycerides (LCT), such as soybean oil, rapeseed oil, and sunflower oil [40,41,69,70]. The LCT oil is formed by unsaturated fatty acids, which makes its molecular structure more complex and bent, whereas the MCT oil is saturated with a linear molecular structure [64]. These structural differences affect the hydrophobicity, solubility of the lipophilic compound, and lipolysis rate of O/W emulsions during digestion. In general, long-chain free fatty acids accumulate at the oil-in-water interface, while medium-chain ones tend to move towards the aqueous phase due to their lower hydrophobicity [71]. Thus, LCT systems offer lipophilic compounds higher bioaccessibility and protection during digestion than MCT systems [64]. Furthermore, considering that many lipophilic compounds must be absorbed in the intestine to promote health benefits, they must pass the gastric digestion step intact, resisting the stomach acid pH [72]. Some gelling biopolymers, such as gelatin, alginate, kappa-carrageenan, and pectin, are resistant to gastric conditions and can protect the bioactive until it reaches the small intestine to be absorbed [28,72–74]. These biopolymers can form three-dimensional (3D) networks composed of crosslinked hydrophilic chains that allow the encapsulation of hydrophilic compounds. The encapsulation of lipophilic compounds can be accomplished by creating a core surrounded by the polymer matrix [43], which makes emulsions ideal templates for obtaining these systems. (J. Zhang, Zhang, et al., 2021) [75] designed a simple method to prepare O/W emulsion encapsulating vitamin A using a microscale 3D printed microfluidic device. Sodium alginate, gelatin, and ethylenediaminetetraacetic acid calcium disodium salt hydrate (EDTA-Ca) were used as the continuous phase, while vitamin A mixed with tert-butyl hydroquinone (ratio of

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4:1) were used as dispersed phase. The emulsion droplets were collected in an acid environment similar to the gastric fluid to generate microgels since the acid caused calcium ions (Ca^{2+}) leakage from the EDTA-Ca and crosslinking with sodium alginate. The low vitamin A concentration in the simulated gastric fluid (about 20%) indicated that the microgels were stable, preventing the release of bioactive. However, the polymeric matrix of the microgels was destroyed in simulated intestinal fluid, allowing the release of vitamin A (around 75%) within 2.5 h.

Unlike highly hydrophilic biopolymers, synthetic polymers can be built from different monomers that, depending on original features and proportions in the polymer chain, define the chemical and physical properties of the synthesized material [76]. Some synthetic polymers have already been classified as food-grade, such as poly-lactic-co-glycolic acid (PLGA), polymethyl methacrylate (PMMA), polyethyleneimine (PEI), poly (vinyl alcohol) (PVA), and polyethylene glycol (PEG) [25,77,78]. PLGA is the most commonly used synthetic polymer for microfluidic assembly as a carrier material [26,27,79]. It is a copolymer constituting of PGA (polyglycolic acid) and PLA (polylactic acid) that decomposes into non-toxic byproducts through the Krebs cycle. Besides, by changing the proportions of PGA (hydrophobic compound) and PLA (hydrophilic compound), the degree of hydrophilicity and lipophilicity can be modulated to encapsulate both lipophilic or hydrophilic drugs [80,81].

Finasteride, a highly lipophilic compound, was encapsulated in PLGA microspheres using a microfluidic chip containing 7 parallel microchannels (Inventage Lab Inc. Precision Particle Fabrication). PLGA 5050A (acid-terminated with a lactide/glycolide ratio of 50/50) or PLGA 7525A (acid-terminated with a lactide/glycolide ratio of 75/25) were dissolved in dichloromethane (DCM) followed by the addition of finasteride (28 mg) to compose the dispersed phase, while the aqueous solution of PVA (0.25% w/v) was used as the continuous phase [26,27]. The dispersed and continuous phases were inserted into the microfluidic chip with a pressure of 1,100 mbar and 2,200 mbar, respectively. Finasteride-added PLGA droplets generated within the channels were polymerized after DC evaporation, lyophilized, and injected subcutaneously into healthy male beagle dogs to assess their drug release and pharmacokinetics *in vivo*. The microspheres generated by parallelized microchannels showed high encapsulation efficiency (96.5% - 101.2%) and particle sizes within the recommended range for injectable dosage forms (all smaller than 50 μm). Microspheres produced with PLGA 7502A (75:25 copolymer) exhibited lower initial drug release and more extended-release (about 1 month) in beagle dogs than microspheres based on PLGA 5002A (50:50 copolymer). Besides, the *in vivo* drug release profile was proportionally related to the amount of drug loading.

PLGA has also been used to synthesize drug-carrying nanoparticles using the nanoprecipitation method by droplet-based microfluidic approaches [79,82,83]. Nanoparticles are widely studied as potential strategies to improve solubility, bioavailability, circulation time, and delivery efficiency of functional compounds due to their high specific surface area [84,85]. Within the microchannels, the formation of polymeric nanoparticles begins when the droplet of the polymer dissolved in an organic solvent has its solubility reduced by mixing the water-miscible organic solvent with an aqueous solution [79]. However, mixing efficiency may be a limiting factor of using the nanoprecipitation method in microchannels due to the laminar flow regime of the fluids. Staggered herringbone mixers (SHM) are passive mixers inserted into channel walls to destabilize laminar flow and increase mixing efficiency [86]. Rutin-loaded PLGA nanoparticles were generated in microfluidic devices with SHM using rutin (10 mg/mL) in methanol and PLGA (14.9 mg/mL) in acetonitrile as the dispersed phase (or organic solvent phase) and PVA (1% w/v) as continuous phase (or aqueous phase) [79]. The optimal formulation of rutin-loaded PLGA nanoparticles prepared by the microfluidics method showed entrapment efficiency of 34 ± 1%, size of 123 ± 4 nm, and drug loading of 0.015 ± 0.001%. Rutin-loaded PLGA nanoparticles produced in the microfluidic devices exhibited a faster release of rutin with higher burst release than those produced in the bulk method. Similar studies applied droplet-based microfluidics using glass and stainless-steel metal devices to obtain nanoparticles of itraconazole and fenofibrate by nanoprecipitation methods. Metal cross-junction channel provided a good mixing environment to generate smaller and more uniform particles of itraconazole, while glass

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microfluidic devices provided an inert and stable platform for preparing highly monodisperse fenofibrate nanoparticles [82,83].

The high manipulating fluids control provided by droplet-based microfluidic devices at the laminar regime allows the design of more elaborate structures using double or multiple emulsions as templates, such as oil-in-water-in-oil (O/W/O) and water-in-oil-in-water (W/O/W) [37]. For example, a glass capillary microfluidic device with two emulsion generators and one adjusting unit was designed to prepare O/W/O double emulsions [70]. From O/W/O emulsion templates, alginate core-shell microcapsules were produced by gelling the middle aqueous phase with calcium ions - released from the water-soluble calcium complex after mixing with acidified oil solution (Figure 3A). Alginate shells had their thickness little affected by alginate concentration and their strength was improved by post-crosslinking in polyetherimide, calcium chloride ($CaCl_2$), or chitosan solution. The proposed microfluidic approach allowed the precise control of the proportion between different oil droplets (thyme and lavender essential oils) and the number of the oil cores in alginate microcapsules by manipulating flow rates in the microfluidic device [70]. In another study, a similar glass microfluidic device was manufactured for producing giant unilamellar liposomes from W/O/W emulsions templates using low-cost, food-grade phospholipids (soybean lecithin powder) and FDA-approved toxicological class III solvents (ethyl acetate and pentane) [87]. Giant unilamellar liposomes are defined as aqueous volumes surrounded by layers of phospholipid molecules. Thus, the oil middle phase consisted of a mixture of soybean lecithin (0.5% w/v) and β-carotene (0.125% w/v) dissolved in different mixtures of organic solvent, while the innermost aqueous phase and the continuous phase contained PVA (1% w/v) mixed with dextran (9% w/v) and only PVA (10% w/v), respectively. After collecting double emulsions, giant liposomes were generated by dewetting and evaporating the organic solvents forming the oil middle phase (Figure 3B). The giant unilamellar liposomes loaded with β-carotene presented diameters varying between 100 μm and 180 μm, and stability of approximately 7 days. Besides, the presence of β-carotene inside the oil shell did not significantly affect the stability, mean diameter, and coefficient of variation of liposomes compared to those without β-carotene [87]. Thus, all of the described microfluidic approaches for manufacturing high-performance delivery systems from food-grade emulsions are potentially useful for many applications in the protection, controlled, and sustained delivery of lipophilic functional compounds.

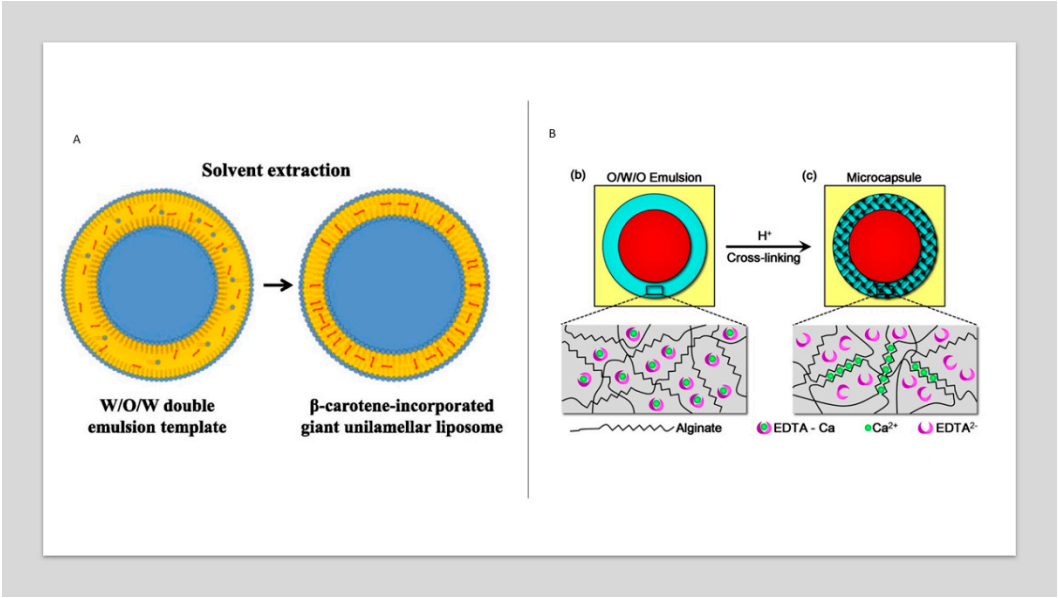

Figure 3. (A) Schematic illustration of obtaining alginate core microcapsules from O/W/O emulsion generated in glass microfluidic devices. After collecting the O/W/O emulsions, the aqueous middle phase was gelled with calcium ions released from the water-soluble calcium complex after mixing with an acidified oil solution [70]. (B) Diagram of the organic solvent extraction process to form giant unilamellar liposomes from W/O/W emulsion templates generated in glass microfluidic devices [87].

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3.2. Hydrophilic functional compounds

Many pharmaceutical, cosmetic, and food industries require delivery systems for hydrophilic functional compounds, including vitamins, enzymes, proteins, bioactive peptides, and drugs. These applications include the need to mask the bitter taste of drugs and minimize their side effects [88,89]; improve the bioavailability of functional molecules and control-sustain their release at target sites [23,90,91], flavors and water-soluble colors during storage [41]. While lipophilic functional compounds can be carried in O/W emulsions, hydrophilic ones are more adequately protected in water-in-oil (W/O) systems. Besides, with the addition of gelling polymers in the dispersed phase, a more efficient protection system can be achieved by gelling the emulsion droplets [13,24] .The process of gelling emulsion droplets in microfluidic approaches occurs in two steps. In the emulsification step, the droplet is generated in the microchannels (section 2), followed by the gelation step, which is the solidification of the emulsion droplets induced by a chemical or physical crosslinking agent [92]. The main gelation methods applied in droplet-based microfluidics (e.g., external, internal, coalescence-induced gelation, and *in situ* mixing) differ among them by the location of the biopolymer and crosslinking agent in the different phases and by the triggering mechanism for gelation External and internal gelation are the most popular methods. In the first one, crosslinking agent ions diffuse to the droplet interface from the continuous phase or a bath located outside the channel. In the second, the biopolymer and the crosslinking agent in the inactive form are inserted together into the channel; the release of ions for gelling is triggered by an additional substance dispersed in the continuous phase (*e.g.,* acetic acid) [13,92].

As aforementioned, the 3D network formed by hydrophilic polymers allows the encapsulation of hydrophilic compounds in the polymer matrix. Natural biopolymers derived from animals (*e.g.,* gelatin and chitosan), plants (*e.g.,* pectin), algae (*e.g.,* alginate), and microorganisms (*e.g.,* gellan gum) have become important carrier materials motivated by their excellent biocompatibility, reproducibility, biodegradability, and ability to form gels easily [93]. Ogończyk et al., (2011) [94] produced pectin microgels from W/O emulsions using flow-focusing microfluidic devices. The pectin droplets (0.5 - 1% w/w) were solidified by the external gelation method, in which hydrogen and Ca^{2+} were delivered from the continuous phase composed of rapeseed oil, acetic acid (1 - 10% w/w), and calcium carbonate ($CaCO_3$; 0.05 - 2% w/w). This method allowed the encapsulation of gold nanoparticles in pectin microgels and the control of their release rate. Gellan gum microgels incorporated with *jabuticaba* extract, a fruit rich in anthocyanins, were also produced from W/O emulsions by the external gelation method using capillary microfluidic devices [24]. The emulsions droplets generated by the dripping regime were solidified into gellan microgels induced by Ca^{2+} present in the continuous phase (composed of soybean oil, PGPR (4% w/w), and calcium acetate (1% w/w)). However, *jabuticaba* extract-loaded gellan microgels (0.2% w/w) showed an irregular structure, a flocculated state with an elliptical shape, and low stability, which was mainly associated with the osmotic pressure difference during the storage and the low gellan gum concentrations. The flow of gellan gum at high concentrations (i.e., high viscosity fluid) into microchannels was a process limitation since Ca^{2+} in the *jabuticaba* extract triggered gellan gelation, which resulted in an uneasy-flowing material prior to microchannel inlet [24]. In general, microgels produced from natural polymers have low mechanical performance. However, strategies associated with chemical modification and blending of biopolymers to form hybrid or layer-by-layer hydrogels can overcome this limitation once each polymer's physical and chemical advantages are integrated [95].

L. Yu et al., (2019) [96] combined the internal and external gelation methods to control the morphology of the protein-core alginate-shell microgels. In the PDMS microfluidic devices, protein ovalbumin aqueous solution co-flowed with alginate solution (2% w/v) containing $CaCO_3$ (200 mM) to form a core-shell stream, which was further sheared off by the continuous phase mineral oil containing Span 80 (3% w/w). In general, mineral oil can be safely used in food, and having residue trace amounts would not be a safety concern [96]. The internal gelation process started with the release of calcium ions from $CaCO_3$ in the alginate shell due to the insertion of an extra continuous phase composed of mineral oil with Span 80 (3% w/w) and acetic acid (0.2% v/v). The external gelation process was completed in a collecting bath containing $CaCl_2$ (0.27 M) aqueous solution

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located outside the device, which ensured the microgels' spherical structure. Furthermore, two approaches were applied to improve the retention of the model protein ovalbumin. In the first one, the alginate microgels were coated with a layer of oppositely charged polymer (poly(ethyleneimine) (PEI) or chitosan). In the second, small particles (inulin microparticles adjuvant) were added inside the water core to block the pores of the polymeric network. The percentage of encapsulation efficiency and protein release of the PEI-coated alginate microgels were 88% e 62% (at 24 h), respectively, while for the chitosan-coated alginate microgels, these values were 80% and 100% (at 48 h), respectively. The highest encapsulation efficiency and sustained-controlled protein delivery were achieved when the two strategies were combined; PEI-coated ovalbumin-delta inulin-encapsulated alginate microgels achieved up to 90% encapsulation efficiency and 20% protein release after 7 days.

Some proteins with intracellular activity have significant potential to treat Crohn's disease and ulcerative colitis [23]. In these applications, ensuring the protection and controlled-sustained delivery of protein to the specific target is essential, especially for delivering protein therapeutics via the oral route. However, these proteins still need to be internalized into cells and penetrated into natural mucus to exert their therapeutic functions [23]. Compared to soluble proteins, protein nanoparticles have been shown more capacity to reach inflamed tissue, penetrate the mucosa, and increase cellular internalization [97,98]. Using a PDMS microfluidic device, Ling et al., (2019) [23] produced alginate microgels encapsulating protein (AvrA enzyme) from W/O emulsions by external gelation method. Alginate droplets were gelled in a collecting bath containing $CaCl_2$ and simultaneously coated with chitosan. Chitosan-coated alginate microgels protected and retained protein activity against harsh gastric conditions *in vitro*, whereas its release was induced only in simulated intestinal fluid. In addition, oral administration of protein nanoparticles encapsulated into alginate/chitosan microgels reduced clinical symptoms and histological inflammation scores in a murine dextran sulfate sodium (DSS)-induced colitis pre/co-treatment model.

Encapsulation of multifunctional compounds in oil droplet-templated microgels is also a fascinating strategy for medical and pharmaceutical applications, especially in multidrug treatments with high frequencies of administration [99]. Mineral oil droplets added with both quercetin nanoparticles and retinyl palmitate were generated inside the PDMS microfluidic devices in an aqueous phase composed of pectin (1 wt%) and Tween 80 (1 wt%). An extra continuous phase composed of water, ethanol (40 wt%), and calcium chloride (1 wt%) was mixed with the O/W emulsion to solidify pectin on the oil droplets' surface based on the pectin's precipitating properties in ethanol and its ionic crosslinking with calcium ions. By changing the flow rate of the phases, the oil core and the shape of the pectin shell were easily controllable. Besides, core-shell microgels could protect quercetin nanoparticles and retinyl palmitate from degradation and oxidation by exposure to water and oxygen [99].

Similar to lipophilic compounds, the design of more elaborate structures using double emulsions as templates may also be suitable for encapsulating hydrophilic functional compounds [10,41,69,91,100]. Pagano et al., (2018) [41] described the encapsulation of three different sources of betanin, E162 (mixture of beetroot extract and maltodextrin; 0.4% w/w betanin), pure betanin, and spray-dried beetroot juice, in W/O/W emulsions prepared using a straight-through microfluidic device. W/O single emulsions were previously prepared using betanin (0.1 - 1.0% w/w) and D-glucose (1% w/w) as the dispersed aqueous phase, while soybean oil and tetraglycerin monolaurate condensed ricinoleic acid ester emulsifier (CR-310; 1% w/w) were used as the continuous oil phase. These emulsions were inserted into the microfluidic device in a controlled flux (from 5 to 100 L/m^2 h) and broken up into droplets in the outer aqueous phase (aqueous solution of Tween 20, 1 - 3% w/w). Increasing the flux from 5 to 20 L/m^2 h did not affect droplet size. However, droplet size and polydispersity increased when the flux was higher than 100 L/m^2 h. The W/O/W emulsion encapsulating pure betanin showed smaller droplets, higher stability, and droplet size distribution when compared to the emulsions containing betanin from other sources and negative control (without pigment), probably due to the higher electrostatic repulsion observed between these droplets.

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While W/O single emulsions are widely used as templates to prepare microgels, O/W/O and W/O/W double emulsions are generally used to fabricate microcapsules (Shah et al., 2008), including solid lipid microcapsules and core-shell microcapsules. Comunian et al., (2014) [10] used W/O/W emulsions generated into the capillary microfluidic devices as templates to design solid lipid microcapsules (SLMs) loaded with ascorbic acid. SLMs consist of a matrix made of solid lipids stabilized in an aqueous dispersion by surfactants or polymers [101]. Thus, melted palm fat was used as the middle phase, while the innermost aqueous phase and the continuous phase contained ascorbic acid solution (3 - 20% w/w) with or without the presence of salt (Na_2CO_3) or/and chitosan (0.25% w/w) and only PVA (10% w/v), respectively. The W/O/W emulsion was collected in an ice bath to rapidly solidify the oil droplets to form a shell. The encapsulation efficiency of ascorbic acid increased from 73% to about 90% when salt and chitosan were added to the SLMs. Two different mechanisms to increase ascorbic acid's encapsulation efficiency and stability were described: (1) the clogging of the pores generated during the lipid solidification process at high salt concentrations and (2) the presence of chitosan inside the core, acting with a micromolecule-chelating agent (Figure 4) [10].

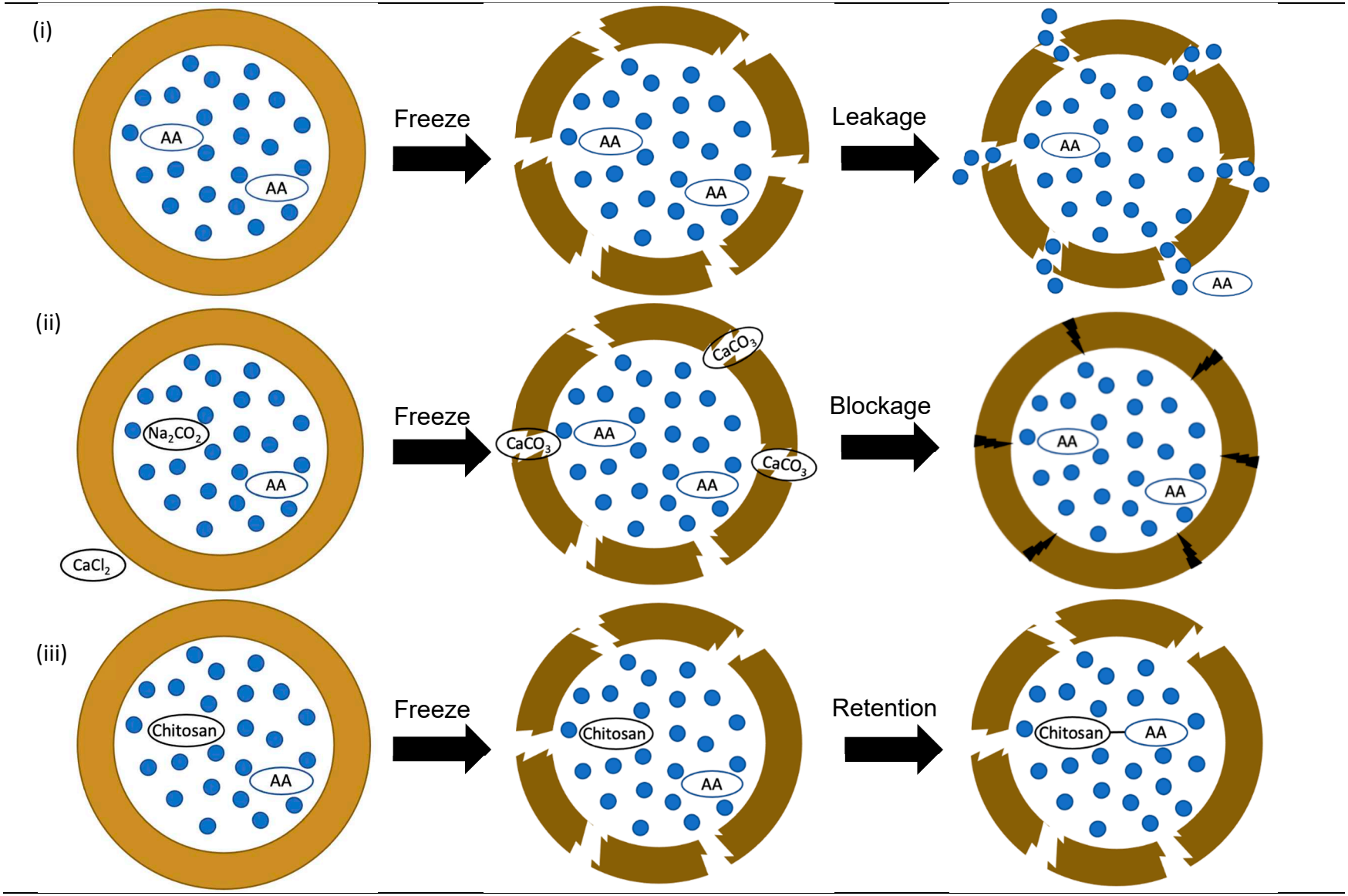

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Figure 4. Schematic representation of the mechanisms involved in the release or retention of ascorbic acid (AA) in the core of solid lipid microcapsules (SLMs): (i) AA release through pores formed during lipid solidification, (ii) AA retention due to clogging of lipid pores at high salt concentrations (Na2CO3), and (iii) AA retention due to the chelating action of chitosan [10].

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Although many studies point to core-shell microcapsules as candidates for drug delivery systems, most of the materials used for producing these systems by microfluidic techniques are synthetic polymers, including food-grade ones (*e.g.*, PLGA) [69,91,100,102]. PLGA microcapsules encapsulating mesoporous silica nanoparticles (MSNs) were generated from W/O/W emulsion via capillary microfluidic devices to obtain further, more specific control over drug release kinetics. MSNs can penetrate tissues through capillaries and be absorbed by cells, improving drug delivery to injury sites in the body. To generate W/O/W emulsions in microchannels, the innermost aqueous phase was composed of MSN solution, while PLGA solution (0.6 wt% in DCM) was injected into the microchannel as the middle oil phase. The PVA aqueous solution (outermost phase) flows through the square capillary from the opposite direction of the inner and middle phases. After double emulsion generation, the PLGA microcapsules were solidified by the evaporation of DCM. The mean diameter of MSNs-loaded PLGA microcapsules was 56 μm (CV= 4.91%). Furthermore, the release of a model dye from these microcapsules was sustained for 4 months without any observable burst release [91].

H. Chen et al., (2018) [100] used the same microfluidic approach to produce PLGA microcapsules loaded with 2-[[(4-phenoxyphenyl)sulfonyl]methyl]-thiirane (SB-3CT) for traumatic-brain-injury (TBI) pharmacological therapy. The PLGA-SB-3CT microcapsules with sizes ranging from 35 to 65 μm and encapsulation efficiency of 99% presented an SB-3CT releasing duration of around 50 days. Then, PLGA-SB-3CT microcapsules injected in rats at the trauma site after TBI showed preliminary neuronal protection efficacy by accelerating behavioral recovery and reducing neuronal cell apoptosis in CA2, hilus hippocampus, and cortical injury region. In another study, core-shell microparticles were produced from W/O/W emulsion templates using gelatin-methacryloyl (GelMa) as the core and PLGA oil solution as the shell for synergistic and sustained drug delivery applications [102]. GelMa is a semi-synthetic material obtained from the reaction of gelatin with methacrylic anhydride, which results in the modification of hydroxyl and lysine residues with methacrylate and methacrylamide side groups [103]. The GelMa core added with doxorubicin hydrochloride (DOX, hydrophilic drug) was photopolymerized under UV illumination downstream from the capillary microfluidic channel, while the PLGA shell added with camptothecine (CPT, hydrophobic drug) was solidified after DCM evaporation. Drug release from core-shell microcapsules initially occurred by diffusion of DOX from the GelMa core and delivery of DOX and CPT to the external environment through pores throughout the PLGA shell. With the degradation of the PLGA shell, the DOX and CPT drugs were also gradually released. Furthermore, liver cancer cells (HCT116 and HepG2) treated with GelMa-PLGA core-shell microcapsules loaded with DOX and CPT showed reduced viability (less than 20% for HCT116 cells and 10% for HepG2 cells), which confirmed the high therapeutic efficacy of these microcapsules in treating liver cancer cells [102].

Table S2 summarizes the technological approaches and properties of the delivery systems based on food-grade emulsions assembled by microfluidic techniques, including microfluidic device type, emulsification process conditions, functional compound type, and delivery system characteristics (*e.g.*, size, polydispersity, and encapsulation efficiency). Other recent studies have also pointed to microfluidics as an excellent tool for obtaining delivery systems based on food-grade emulsions. In general, these works aimed to evaluate droplet formation process parameters using complex fluids and/or the development of new geometries or microfluidic devices without effective encapsulation of a functional compound. Considering their technological potential to act as delivery systems, Table S3 presents the most recent droplet-based microfluidics approaches to obtain emulsified systems, including the phase compositions, emulsification process conditions, and microfluidic device type.

4. Limitations and perspectives of scale-up in droplet-based microfluidic approaches

As aforementioned, many studies reported and supported the advantages of using droplet-based microfluidics to encapsulate both lipophilic and hydrophilic functional compounds. However, the path from proof-of-concept in developing delivery systems via microfluidic technologies to their practical application on an industrial scale presents some problems that limit this transition. Although microfluidic techniques allow the manipulation of a small volume of fluids and the precise

control of droplet generation into the microchannels, their production efficiency cannot satisfy industrial productivity. On a laboratory scale, about milliliters of material can be generated per hour; however, the industrial-scale demands many tons of material per year, leading scientists and researchers to seek solutions.

As an alternative to industrial-scale, parallel microchannels in different configurations have been developed to solve the microdevices scalability issue. The most common scale-up devices are based on parallelization (2D scale-up) and/or stacking (3D scale-up) of microchannels. In 2D scale-up, multiple channels with several identical junctions are designed on a single chip for simultaneous droplet generation. These chips can also be stacked to form a parallel multichip system. As an alternative to industrial-scale, parallel microchannels in different configurations have been developed to solve the microdevices scalability issue. The most common scale-up devices are based on parallelization (2D scale-up) and/or stacking (3D scale-up) of microchannels. In 2D scale-up, multiple channels with several identical junctions are designed on a single chip for simultaneous droplet generation. These chips can also be stacked to form a parallel multichip system. (Mulligan & Rothstein, (2012) [104] developed a PDMS microfluidic device composed of 6 flow-focusing junctions operating in parallel to generate W/O single emulsions. The continuous phase composed of mineral oil was pumped at a flow rate (Qc) of 20 μL/min, while the dispersed aqueous phase, composed of surfactant solution and 5 mM cetylpyridinium chloride (CPyCL), was pumped at a varied flow rate (Qd = 2 - 20 μL/min). All microchannels were fed with only two inlets, one for each phase, and the effects of flow rates on the droplet generation process were analyzed. The emulsion droplets had sizes varying from 155 to 179 μm and a coefficient of variation (CV) of 5%, which was slightly higher than emulsions produced in only one channel junction (CV ~ 2%). Probably, the fluid distribution affected the pressure inside microchannels, disfavoring the formation of more uniform droplets (Z. Liu et al., 2020). In another study, Gelin et al. (2020) designed a 3D PMMA microdevice with 4 parallel droplet generators to produce O/W single emulsions (Figure 5A). In this system, the flow rate of the continuous phase (aqueous solution of PVA 2%wt) and the dispersed phase (mixture of hexane and Span 80 20% wt) varied between 1 and 4 mL/h (Qd = Qc). At low flow rates, large droplets with high polydispersity were generated. By increasing the flow rates to 4 mL/h, smaller and monodisperse droplets could be produced in the parallelized microchannels.

Some companies have also been looking to develop novel microfluidic devices based on parallelization and stacking of microchannels in order to turn them into commercially successful products. For example, Dolomite has developed Telos® Chips (Table S1), a glass microfluidic device with 7 parallel junctions which assist in achieving higher throughput for various applications. This chip can be stacked with 10 more ones, resulting in 70 droplet generators [105]. In addition, Microfluidic ChipShop designs the Fluidic 912 (Table S1), a droplet generation chip made of Topas® COC (cyclic olefin copolymer) or polycarbonate (PC) that consists of 8 parallel flow-focusing junctions. The company also has a smaller microchip with 3 droplet generators (Fluidic 536), which could be combined into a 3-dimensional model to increase droplet production [106].

The straight-through microfluidic devices and their variations, called step emulsification, have also been great alternatives in simultaneous droplet generation processes [107]. Besides, more complex configurations of parallel microfluidic devices have been designed to obtain multiple emulsions [108]. As mentioned before, multiple emulsions such as O/W/O and W/O/W emulsions can be widely exploited in pharmaceutical and medical applications, including for multidrug delivery. Using 3D printing and acrylic monomer, (Jans et al., (2019) created a microfluidic device with 4 identical parallel structures for high-throughput synthesis of W/O/W and O/W/O (diameter 500 μm) emulsions (Figure 5B). The 3D-printing microdevice combined lithography patterning and capillary geometry with good resolution for generating small and monodisperse droplets with low dead volume and high productivity (production rate of 12 L/h, 10^7 monodisperse microgels per hour). Although all these approaches can be helpful to design emulsions by microfluidic techniques on an industrial scale, the manufacturing, cleaning, and maintenance of the devices are still a challenge to overcome. For example, if only one channel clogs, the entire device becomes inoperative until

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maintenance. Thus, developing high-throughput droplet generating devices with independent maintenance and cleaning may be exciting alternatives to be addressed in future applications.

A unique high-throughput droplet generation microchip is desirable because scalability is related to droplet production, not just scaling microchannel size or chip quantity. Thus, the main issue in scaling-up droplet-based microchips is to produce monodisperse droplets in an easy operation and faster generation. This challenge can be overcome by using a step-emulsion microfluidic with many parallelized microchannels that generate droplets simultaneously [109,110]. Basically, one phase flows into a hundred identical microchannels, intersecting an upper reservoir channel containing another phase. (e Rutte et al., (2019) [109] developed a step-emulsion microdevice, in which the droplet generation was induced by geometry and facilitated by sudden expansion at channel height at the end of each channel. This microchip operates with flow rates between 5 and 10 mL/h; in contrast, a flow-focusing device operates at the magnitude of microliter per hour. Furthermore, the droplets produced presented sizes around 50 and 90 μm (CV 3%), determined by the microchannel dimensions. The droplets were gelled and used for tissue engineering purposes; however, this microchip also has the potential to be used for generating previously unexplored food-grade droplets.

Lastly, the parallelization of microchannels in non-spontaneous droplet generation methods, called active, has been explored as potential alternatives to passive ones for developing food-grade emulsions on an industrial scale. In active methods, the droplet formation process within the microchannels occurs under external forces such as magnetic field, electric field, centrifuge forces, and acoustic waves [111–113]. Using a multi-channel rotating system, J. Li et al., (2022) [112] produced alginate microgels (Figure 5C). In this system, the rotational cylinder is a core component that contains many glass capillary nozzles distributed like spikes on the periphery. The rotating cylinder serves as a reservoir for the dispersed phase and can rotate under the drive of a motor. Besides, an outer container serves the rotor with the continuous phase. When the rotor is active during the centrifugation, the dispersed phase is thrown out to form pendant droplets through the capillary nozzle tips. The droplets detach from the tips when the centrifuge forces exceed the counteracting drawing force due to interfacial tension. These droplets then move until they fall into the continuous phase in the outer container [112]. The multi-channel rotating system is an alternative for large-scale droplet production since it can be adjusted to generate different emulsions with desired dispersity and size at a production rate that can supply the needs of the industry.

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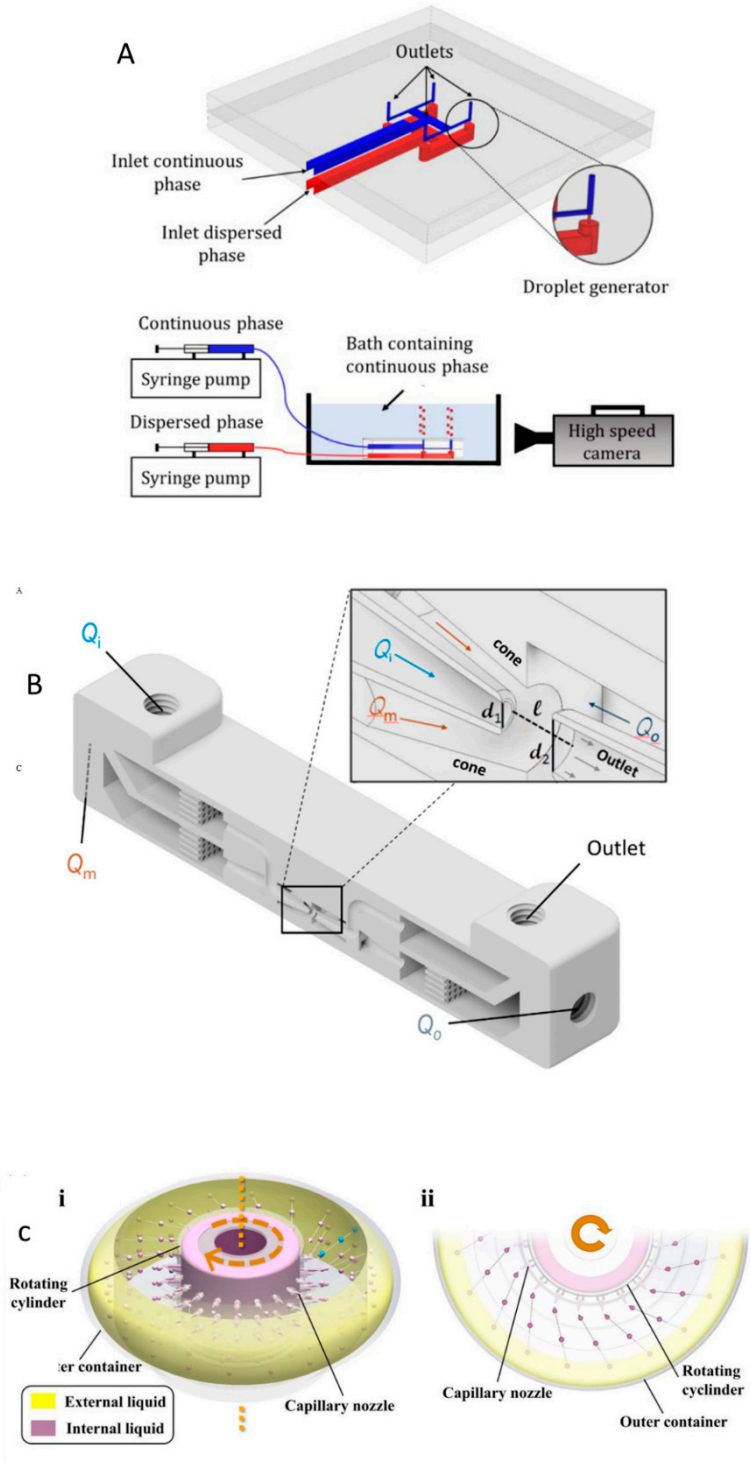

Figure 5. (A) Overall view of the 3D PMMA microdevice containing 4 nozzles and a magnification of a droplet generator, and schematic representation of the microfluidic setup [114] (Gelin et al., 2020). (B) Lateral cut view on a 3D rendering of the parallelized device with one of the 4 double emulsion droplet makers and the respective distribution channels for 3 inlets and a collection channel. Q_i shows the inlet of the inner phase, Q_m of the middle phase, Q_o of the continuous outer phase, and finally, the outlet for collecting the double emulsions is indicated [108]. (C) Multi-channel rotating system [112].

5. Conclusions

Assembling delivery systems based on food-grade emulsions in microfluidic platforms requires extensive research for effective implementation in food, pharmaceutical, medical, and cosmetics

applications. Therefore, this review discussed the state-of-the-art of droplet-based microfluidics for producing food-grade emulsions due to their importance as templates for developing more complex delivery systems and designing the properties of these systems depending on the entrapped compound type. As described, several types of microfluidic devices (*e.g.*, planar, capillary, and straight-through) were successfully used for fabricating these systems with specific designs and characteristics from food-grade materials, which can be either natural or synthetic. Microfluidic techniques also allowed, through the choice of ingredients and the emulsification process parameters, to precisely modulate properties of the carrier systems to suit the type of encapsulated functional compound and its final application. Despite these advantages, some challenges associated with the mass production, cleaning, and maintenance of the devices have limited the transition of microfluidic processes from lab-scale to industrial-scale. Thus, future studies focusing on developing high-throughput droplet generating devices with independent maintenance and cleaning are needed, especially because complex fluids, such as biopolymers, are uneasy-flowing materials at high viscosities and very prone to cause microchannel clogging.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Figure S1: title; Table S1: title; Video S1: title.

Author Contributions: Jhonatan Rafael de Oliveira Bianchi: Investigation, Writing – original draft. Lucimara Gaziola de la Torre: Resources, Funding acquisition, Conceptualization, Writing – review & editing, Supervision. Ana Letícia Rodrigues Costa: Conceptualization, Investigation, Writing – original draft, review & editing, Supervision

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