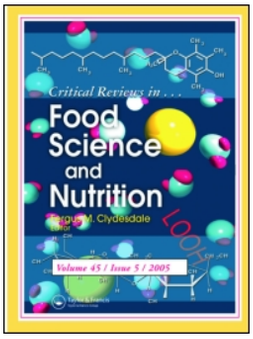

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Microchannel emulsification: A promising technique towards encapsulation of functional compounds

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ABSTRACT

This review provides an overview of microchannel emulsification (MCE) for production of functional monodispersed emulsion droplets. The main emphasis has been put on functional bioactives encapsulation using grooved-type and straight-through microchannel array plates. MCE successfully encapsulates the bioactives like β-carotene, oleuropein, γ-oryzanol, β-sitosterol, L-ascorbic acid and ascorbic acid derivatives, vitamin D and quercetin. These bioactives were encapsulated in a variety of delivery systems like simple and multiple emulsions, polymeric particles, microgels, solid lipid particles and functional vesicles. The droplet generation process in MCE is based upon spontaneous transformation of interfaces rather than high energy shear stress systems. The scale-up of MCE can increase the productivity of monodispersed droplets >100 L h^{-1} and makes it a promising tool at industrial level.

KEYWORDS

Microchannel emulsification; delivery systems; encapsulation; emulsification; functional bioactives; monodisperse emulsion droplets; spontaneous transformation

Introduction

The deficiency of essential nutrients is regarded as "hidden hunger" and it effects almost every segment of world population. These nutrient deficiencies post devastating consequences in developing countries and affect both social development and public health. Omega-3-fatty acids, phytochemicals, proteins and antioxidants are common functional compounds that can be added to food to improve its palatability and nutritional profile. These value-added foods in turn prevent diseases like heart diseases, micronutrient deficiencies, cancer and many others. However, the major challenges in incorporating these functional compounds in food matrix are their susceptibility towards oxidative deterioration, unpleasant odor, hydrophobicity and many more. These factors affect the organoleptic and sensory properties of the foods in which they are incorporated.

The recent trends in food and nutritional science proves that diet plays a significant role in maintaining health and homeostasis of body. The term "functional food" itself was first used in Japan, in the 1980s, for food products fortified with special constituents that possess advantageous physiological effects (Siro et al., 2008). Functional foods not only satisfy hunger but also provide vital nutrients for mitigation of many diseases. However, there is no clear definition of functional foods. Technically, these are defined as foods that have a potentially positive effect on health beyond basic nutrition (Siro et al., 2008). In last decade (Fig. 1), there was more than 50,000 publications that describes functional attributes of these functional foods. The global market of functional food is estimated to at least 33 billion US$ (Hilliam, 2000). Other experts like Sloan (2002) has calculated the global functional food market to be 47.6 billion US$, being the United States the largest market segment, followed by Europe and Japan. Some estimations report even more global market value (nearly 61 billion US$) (Benkouider, 2004).

Different nutrient delivery systems like emulsification and encapsulation are prime tools to deliver these important nutrients in different food and pharmaceutical systems with good efficiencies. These systems encapsulates vital nutrients in form of emulsions, microspheres, solid lipid nanoparticles, polymeric nanoparticles, nanocomplexes and many more (McClements, 2010). In recent decade numerous emulsification devices have been developed to encapsulate functional nutrients, each of these devices has numerous advantages and disadvantages (McClements, 2010). The choice of particular device depends upon production method, volume of materials to be homogenized, droplet size distribution and required physicochemical properties of final products (Santana et al., 2013). Recently, microfluidic devices have getting more popularity in comparison to conventional devices on the basis of energy and encapsulation efficiencies. Microfluidic devices produce monodisperse emulsions and limits the process of Ostward ripening and flocculation (Taylor, 1998). The better stability and physicochemical properties of monodisperse emulsions have attracted various industries to produce valuable emulsion products like functional microparticles, nanoparticles and multiple emulsions (Shah et al., 2008). Various microfluidic and microstructure devices are there for production of monodisperse

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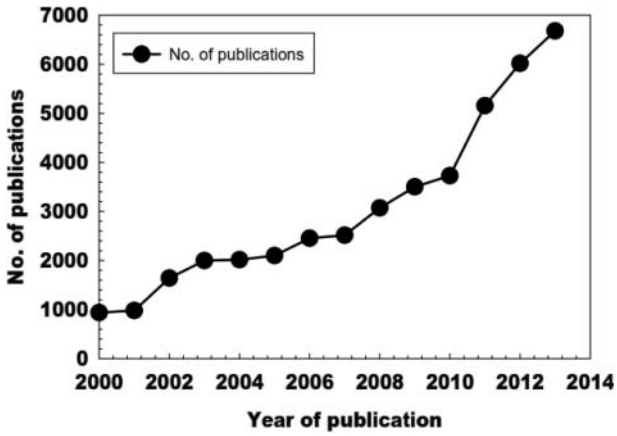

Figure 1. The functional foods development in terms of scientific publications from 2000 to 2013. The values are obtained from Thomson Reuters "ISI Web of Knowledge" search engine.

emulsion droplets. These includes T- or Y-shaped junctions (Steegmans et al., 2009; Wehking et al., 2014), flow focusing devices (Anna et al., 2003), step emulsification (Li et al., 2015), edge-based droplet generation (EDGE) emulsification system (van Dijke et al., 2009), and microchannel emulsification (MCE) system (Vladisavljevic et al., 2012).

These microfluidic devices have their own merits and demerits. T- and Y-junctions are easy to fabricate and as well as operate. They allow synchronized droplet production but monodipsersity is not well maintained with time together with productivity (Seemann et al., 2011). The flow focusing geometry can be manipulated by adjusting the flow rates of dispersed and continuous phases, hence droplet sizes with greater flexibility can easily be obtained in flow focusing devices (Gañán-Calvo, 1998). The step emulsification is the modified version of coflowing geometry, in which T-and Y-junctions are sealed into a high aspect ratio. Step emulsification has many desirable properties, like droplet homogeneity, worked at relatively high dispersed phase volume ratios typically up to 96% (Priest et al., 2006; Saeki et al., 2008). The EDGE based emulsification involves the combination of geometrical step with T-junction geometry (van Dijke et al., 2009). The EDGE based emulsification produce monodisperse emulsions with good production rates, however, the coefficient of variation (CV) among produced droplets is slightly higher than 8% (van Dijke et al., 2010a). In comparison these microfluidic devices, MCE

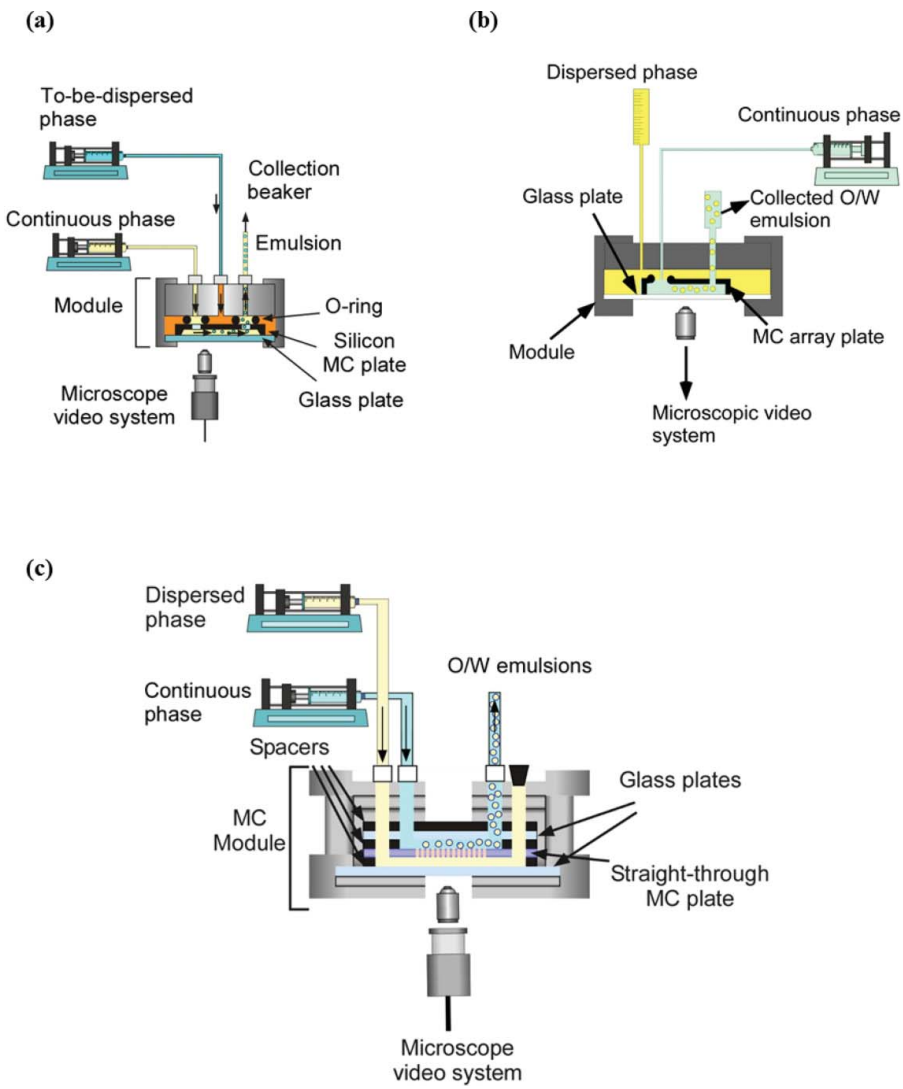

Figure 2. Schematic presentation of MCE setups. (a) Dead-end type MCE, (b) cross-flow type MCE, and (c) straight-through MCE used for encapsulating bioactives.

produce extremely monodispersed droplets with CV <5% with higher productivity of >100 L h^{-1}. Moreover, monodispersity is well maintained even with less viscous fluids (Vladisavljevic et al., 2012). The detail of production mechanism and as well as merits and demerits are described in later sections.

This detailed review focuses on the functionality of monodisperse emulsions produced from MCE. The production of functional monodisperse emulsions using MCE is reviewed and its applications in functional food development is described in detail.

Microchannel emulsification

The MCE was firstly proposed by Kawakatsu et al. (1997). It is an emulsification technique that have ability to produce monodispersed emulsion droplets with extremely small CV and it is typically less than 5% as standard CV in many MCE studies (Vladisavljevic et al., 2012). The typical setups of MCE are presented in Fig. 2. The setup is technically called as module comprises of various stainless parts, glass plates for visualizing the flow of phases and variety of O-rings and spacers for holding dispersed and continuous phases. Moreover, these modules also contain MCE plates (reviewed in later section). Typically, the MCE has ability to produce monodisperse emulsion droplets ranging from few microns to 550 μm (Vladisavljevic et al., 2012, 2013).

Microfabrication technology is used to fabricate micrometre-sized channels on a microfluidic array plates. These plates enable the formulation of emulsions with size controlled droplets at high encapsulation and energy efficiencies (Ushikubo et al., 2015). Variety of encapsulated products can be produced using MCE ranging from single to multiple emulsions, microspheres, lipid vesicles, microcapsules, gel microbeads, giant vesicles and many others (Boom and Schroen, 2011; Neethirajan et al., 2011; Vladisavljevic et al., 2013; Wang et al., 2015). The other advantage of MCE is very narrow size droplet distribution normally in order of less than 1% (Boom and Schroen, 2011). In comparison, the tradition emulsification devices use intense forces to disrupt the droplets into smaller sizes and produces polydisperse droplets in the emulsion system. However, these traditional devices are favorable at industrial level due to easy scale up methodologies and homogeneity in products in comparison to microfluidic devices (Neves et al., 2015).

In MCE, droplets are generated via MC arrays with a unique and precise geometry (Kobayashi and Nakajima, 2006; Vladisavljevic et al., 2012) with spontaneous transformation of an oil–water interface (Sugiura et al., 2001a). The mild droplet generation in MCE with no involvement of energy makes it preferable system to prevent denaturation of sensitive bioactive compounds (Maan et al., 2011, 2015). MCE array plates have been fabricated on a variety of substrates like single silicon crystal, silicon-on-insulator, stainless steel and polymeric substrates (Fig. 3). The surface and material properties of different substrates are presented in Table 1. Mostly silicon crystal and silicon-on-insulator is used to fabricate grooved and straight-through MC arrays, since the surface properties can easily be modified using hydrophobic and hydrophilic treatments (Kobayashi et al., 2008a, 2010, 2012b). Due to spontaneous droplet generation process, the MCE is highly energy efficient with typical energy input less than 10^3–10^4 J/m^3 (Kobayashi et al., 2008b; Sugiura et al., 2001a).

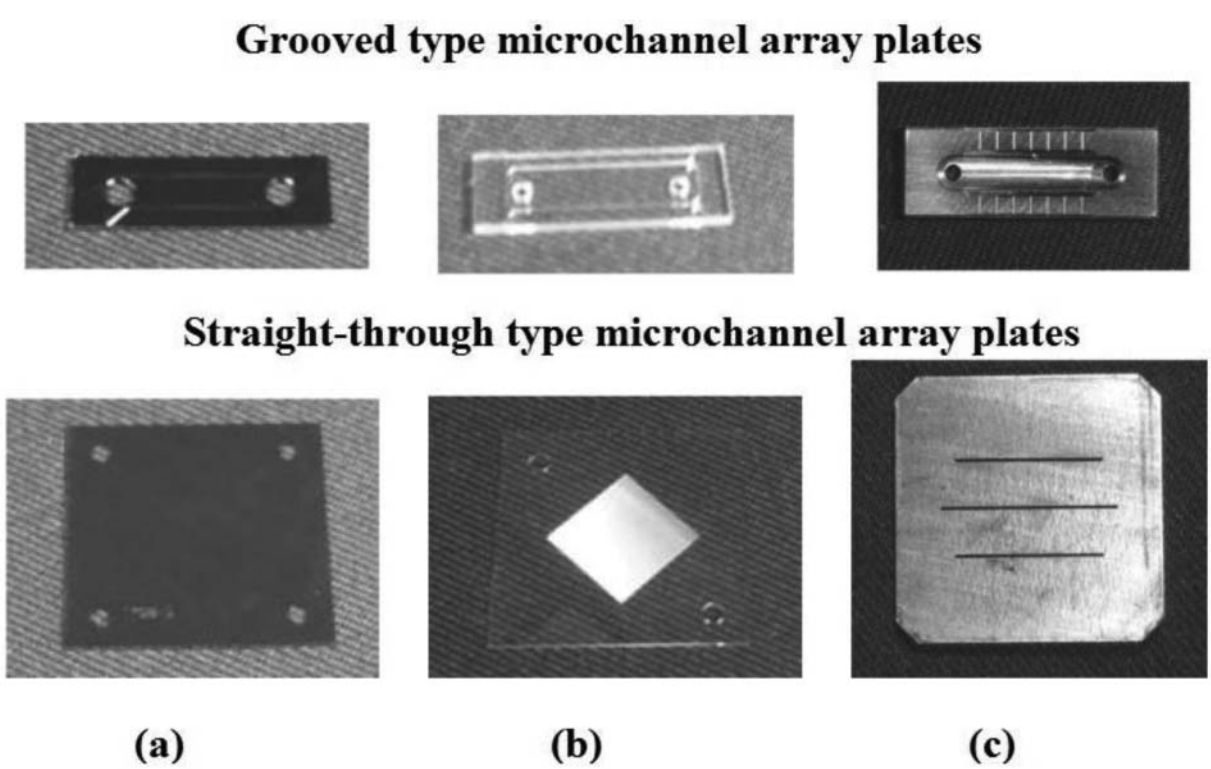

Figure 3. Photographic view of different type of microchannel array plates: (a) silicon, (b) poly(methyl methacrylate, (PMMA)), and (c) stainless steel MC array plates.

Table 1. Physicochemical properties of different substrates used for fabrication of MC array plates.

Substrate	Fabrication techniques	Surface properties	References
Silicon	Anisotropic wet etching, chemical dry etching	Hydrophilic but can be changed to hydrophobic after treatment with different saline coupler reagents	Kobayashi et al. (2005b); Kawakatsu et al. (1997); Kobayashi et al. (2009b)
PMMA	Injection moulding, synchrotron lithography	Hydrophobic	Liu et al. (2004); Kobayashi et al. (2008a)
Stainless steel	Mechanical dicing and end milling	Hydrophilic	(Tong et al., 2001); (Kobayashi et al., 2012b)

MCE devices

The MCE is divided into two major types depending up the arrangement of MCs on the surface of MC array plates. These are either grooved type or straight-through type. In grooved type MCE, the MCs are fabricated parallel to the plate surface (Kawakatsu et al., 1997) and in straight-through, the MCs are located on the surface of plate (Kobayashi et al., 2002, 2008b). The different MCE types have its own merits and demerits. The droplet generation characteristics can easily be observed in grooved type MCE, while droplet productivity can easily be scale up in straight-though MCE. This section briefly describes the geometry and characteristics of different MCE types.

Grooved MCE devices

Grooved MCE devices are made of single-crystal silicon and are fabricated using photolithography techniques coupled with anisotropic wet etching (Vladisavljevic et al., 2012). Grooved MCE devices are further categorized into dead- end and cross-flow types (Fig. 4). Currently available grooved MC devices can produce monodisperse emulsions with droplet sizes of 1–550 μm (Kobayashi et al., 2007b, 2010).

The simplest geometry of grooved MCE contains at least two grooved MC arrays positioned on MCE array surface. The other geometries includes four grooved MC arrays arranged on all four sides of a array (Kawakatsu et al., 1997). The dead-end type MC arrays provide better understanding of droplet

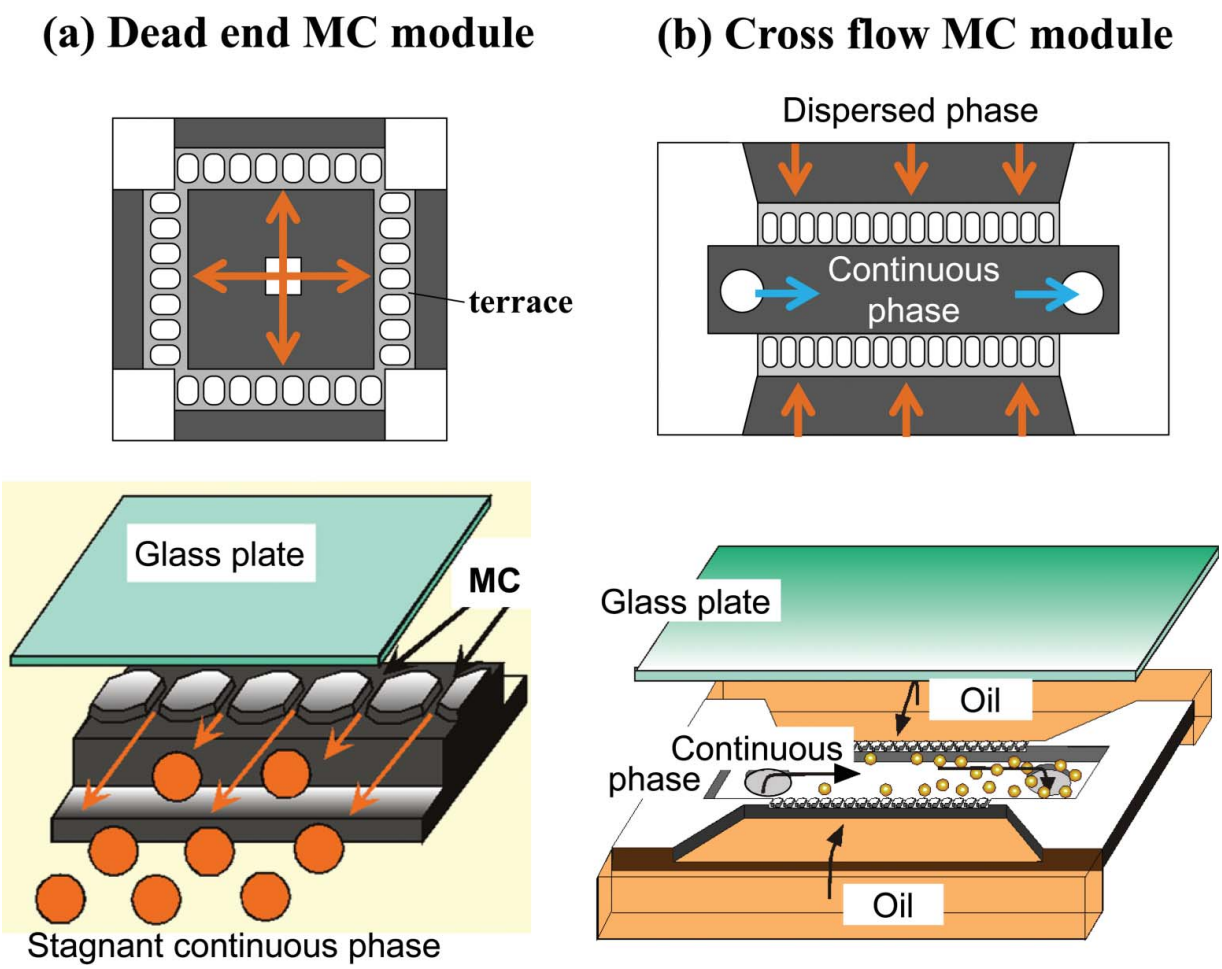

Figure 4. Grooved-type MC array plates: (a) dead-end plate with motionless continuous phase, (b) simple cross flow type MC array plate with recirculating continuous phase. Reprinted with permission from (Vladisavljevic et al., 2013).

generation characteristics visually. The grooved MCE with dead end type structure had a major drawback in collecting the formed droplets. To solve this problem, Kawakatsu et al. (1999) and Kobayashi et al. (2007b) developed a cross flow type grooved MCE arrays. The simplest cross-flow array, contains two grooved MC arrays arranged at both longitudinal sides, while the central well was used as the cross-flow channel. The cross-flow type devices have capacity to produced micron scale droplets over longer period of time. To evaluate the long term production strategy, Zhang et al. (2013) demonstrated a successful long-term production of monodisperse oil-in-water (O/W) emulsions for seven days using a cross-flow grooved MC array array. The monodispersity of micron-sized droplets can be controlled using an appropriate MC depth (Kobayashi et al., 2001). It is worth to mention that, the greater the channel length/depth ratio, the higher the pressure drop in the dispersed phase flowing in the channel and a result more monodisperse droplets can be generated in MCE devices (Sugiura et al., 2002).

The grooved MC devices typically have 8.3 channels/mm^2, such low number of channels depict low productivity as major drawback. The typical dispersed phase flow rate in grooved MCE is typically less than 0.1 mL/h (Kawakatsu et al., 1999). The productivity can be increased in cross flow MCE by using many parallel MC arrays on a single MC plate. Recently, Kobayashi et al. (2010) designed large cross-flow MCE device, each consisting of 14 parallel MC arrays with a total of 11,900 channels and have a channel depth of 1–2 μm (Fig. 5a). The new design can produce uniform oil droplets with average droplet size of 10 μm at maximum dispersed phase flow rate of 1.5 mL/h (Fig. 5b). The productivity of droplets was although increased in large cross-type MCE but collecting the formed droplet is the still limiting factor in cross flow type MCE.

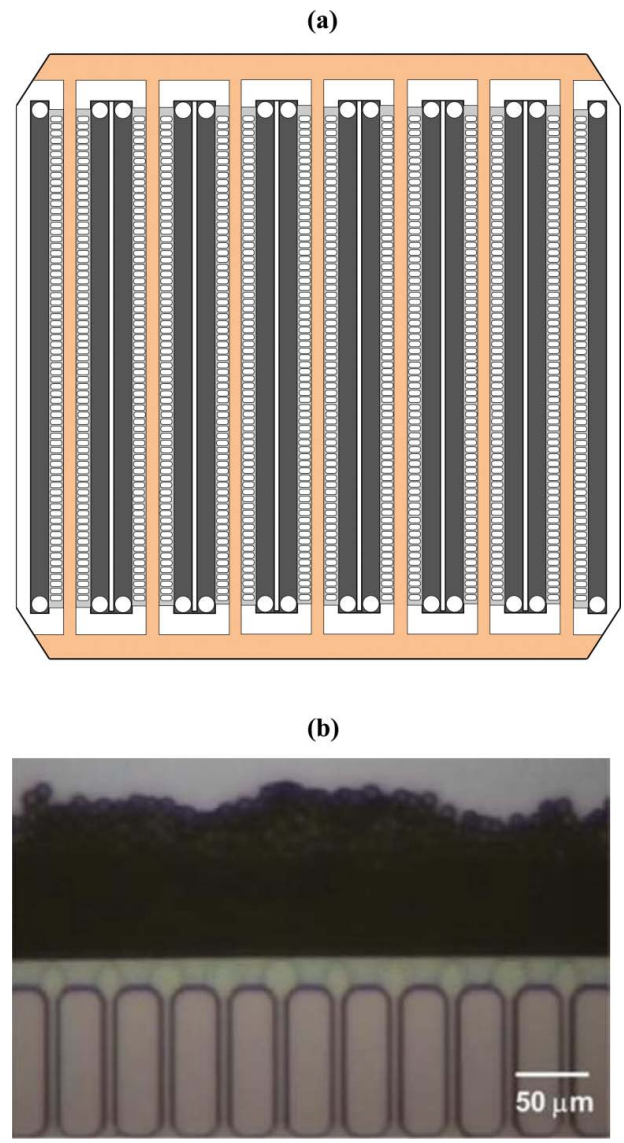

Figure 5. (a) Schematic diagram of scale-up grooved MC array plate from cross flow type MCE. Each MC array consisting of 850 MCs. (b) Optical micrograph showing droplet productivity at dispersed phase (soybean oil) flow rate of 1.5 mL h^{-1}. 1.0 wt% SDS in Milli-Q water was used as continuous phase. Reprinted with permission (Kobayashi et al., 2010; Vladisavljevic et al., 2013).

Straight-through MCE devices

The throughput capacity of MCE can be increased using straight-though MC array plates since these allows integration of hundreds and thousands of MCs on a single plate (Kobayashi et al., 2002). The straight-through devices are fabricated by a process including deep reactive-ion etching and a latticed support layer on the bottom side of a silicon-on-insulator plate to protect and reinforce the delicate straight-through holes (Kobayashi et al., 2002). The straight-through MC devices typically have 47 to 411 channels/mm^2 to increase the throughput capacity of emulsion system. The straight-through array plates (Fig. 6) comprises of either symmetric to asymmetric design with numerous circular and oblong channels and micronozzles (MNs) that are compactly arranged on the surface of array plate (Kobayashi et al., 2008b).

Most of the studies in MCE was conducted with asymmetric design with circular channels since the rectangular (oblong) channels cannot perform well with low viscosities fluids having viscosities less than 1 mPas. In asymmetric straight- through MCE, the circular channel are located on the upstream side, while the microslot on the downstream side (Kobayashi et al., 2005b). The use of these arrays enabled the stable production of monodisperse emulsions having viscosities less than 1 mPa s (Kobayashi et al., 2005b; Kobayashi et al., 2009b). The straight-though MCE arrays depicted in Fig. 7 produced uniform *n*-tetradecane droplets with dispersed phase flux over 2700 L/(m^2 h) indicating throughput capacity of 3.2 million droplets per second. The summary of straight-thought MCE is presented in Table 2. Recently, Kobayashi et al. (2012a) developed a scale-up model for asymmetric straight-through MC array plates containing four MCs arrays with total active cross-sectional area of 484 mm^2. This scale-up version increased the productivity of *n*-tetradecane monodisperse emulsions up to 1.4 L/h.

Droplet generation process in MCE

The droplet generation process in MCE have been evaluated using variety of techniques ranging from experimental approach using high speed microscopy (Sugiura et al., 2001a; Sugiura et al., 2001b) or numerical simulation and modelling like Lattice Boltzmann methods (van der Zwan et al., 2009; van

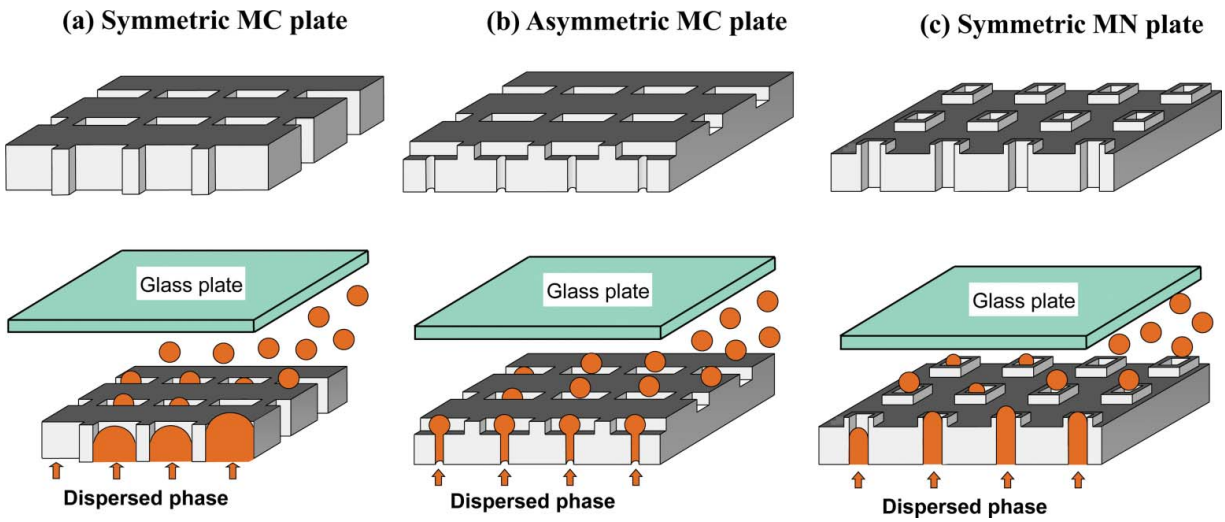

Figure 6. Straight-through MC array plates: (a) symmetric plate with microslots on both sides, (b) asymmetric plate with circular channels on the upstream side and slots on the downstream side, and (c) Symmetric plate with MNs. Reproduced with permission (Vladisavljevic et al., 2012).

Dijke et al., 2008) and computational fluid dynamics (CFD) (Kobayashi et al., 2004, 2006, 2007a, 2011; van Dijke et al., 2008). These simulation methods depicted spontaneous change of dispersed phase in droplets on the microchannel surface, which was further depended upon interfacial tension on a micron scale. Figure 8 shows the droplet-generation mechanism in MCE. The droplet-generation process begins when the dispersed phase (Fig. 8a) starts to expand in the terrace (grooved MCE) or microslot (straight-through MCE). This expansion process ends, when the expanding dispersed phase reaches the outlet of microslot or terrace (Fig. 8b) and then leading the expansion phase to detachment phase. In the initial stage of the detachment process, the dispersed phase slowly expands over the microslot outlet or terrace surface, as the internal pressure of the dispersed phase over the microslot outlet is higher than inwards (Fig. 8c). The difference in pressure corresponds to Laplace pressure difference between the two phases. The difference in pressure continues until the pressure balance becomes opposite and a neck is formed (Figs. 8d and 8e) in the microslot due to rapid flow of the dispersed phase. In this stage, the dispersed-phase flux at the neck exceeds than that present in the front of the neck leading to the instantaneous pinch-off of the neck and the completion of the detachment process (Figs. 8e and 8f) (Kobayashi et al., 2011).

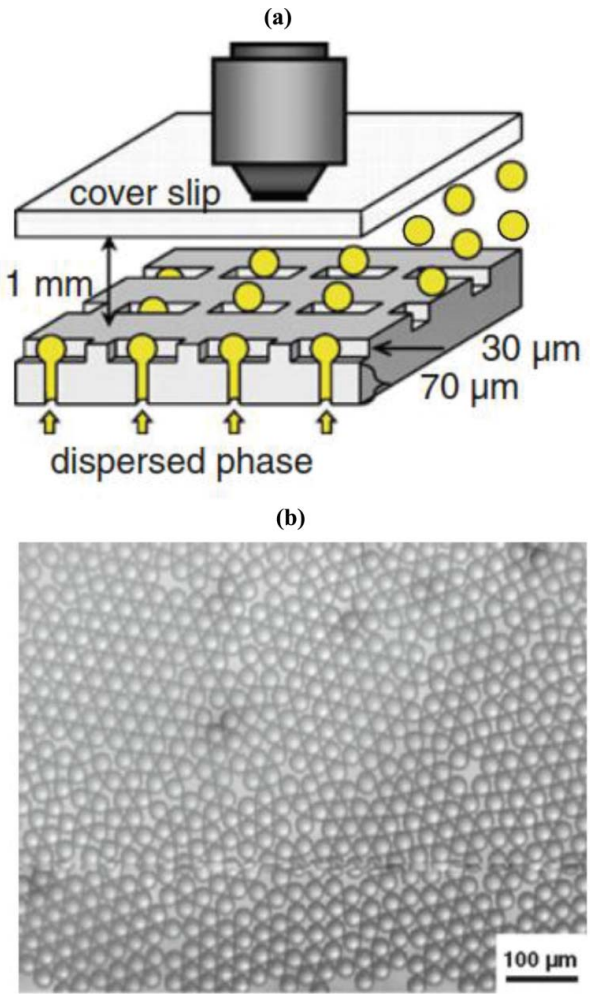

Figure 7. (a) Typical droplet generation in asymmetrical straight-through MCE. (b) Optical micrograph of *n*-tetradecane droplets with Sauter mean droplet diameter of 27 μm at 900 L m^{-2} h^{-1}. Reprinted with permission (Vladisavljevic et al., 2011).

Operating factors effecting droplet generation in MCE

The droplet generation process in MCE is extremely selective and is influence by variety of factors that ensure stability of different emulsion systems. The droplet generation mechanism in MCE is effected by temperature (Fujiu et al., 2011a, 2011b, 2012), composition of different dispersed and continuous phases, flow velocities and viscosities of different phases (van Dijke et al., 2010b; Vladisavljevic et al., 2011) and also electrolyte composition (Kobayashi et al., 2014). Besides these physiochemical parameters, optimization of processing conditions, mixing of different ingredients and choice of emulsifiers are important parameters for obtaining monodispersity and stability in MCE (Neves et al., 2015).

Temperature controlled emulsification is needed to produced solid lipid microparticles, microparticles and high melting point dispersions. MCE enables production of these emulsion systems with monodispersity (Iwamoto et al., 2002;

Table 2. Overview of straight-though MCE array plates. The droplet diameter, coefficient of variation and throughputs capacities were presented from previously published research works.

MC array plate	Code name	Channel number	Droplet size and (CV)	Throughput capacity	Maximum dispersed phase flow rate	References
24 × 24 mm (symmetric)	—	4,300 MCs	39.1 μm (2.5%)	5.3×10^4 s^{-1}	6 mL h^{-1}	Kobayashi et al. (2003)
24 × 24 mm (symmetric)	—	10,000 MCs	41.9 μm (1.9%)	—	—	Kobayashi et al. (2004b)
40 × 40 mm (symmetric)	—	211,248 MCs	31–32 μm (<10%)	$3.2\text{-}5.3 \times 10^5$ s^{-1}	20–30 mL h^{-1}	Kobayashi et al. (2005c)
15 × 15 mm (symmetric)	—	23,548 MCs	6.7 μm (3.9%)	8.8×10^4 s^{-1}	0.05 mL h^{-1}	Kobayashi et al. (2008b)
15 × 15 mm (symmetric)	—	92,575 MCs	4.4 μm (5.5%)	2.8×10^4 s^{-1}	0.004 mL h^{-1}	Kobayashi et al. (2008b)
24 × 24 mm (asymmetric)	WMS 1-2	10,313 MCs	35 μm (1.9%)	10 droplets s^{-1} per active MC	—	Kobayashi et al. (2005b)
24 × 24 mm (asymmetric)	WMS 1-3	23,348 MCs	26–35 μm (<3%)	250 droplets s^{-1} per active MC	100–2700 mL h^{-1}	Vladisavljevic et al. (2011); Kobayashi et al. (2014)
24 × 24 mm (asymmetric-stainless steel)	SUS-304	7 MCs	1.43 mm (4.4%)	0.11 droplets s^{-1} per active MC	—	Kobayashi et al. (2008c)

Sugiura et al., 2000). The formulation of different emulsion systems containing functional compounds at high temperature will be discussed in later section. Monodisperse O/W emulsions were produced in MCE that were independent of the temperature applied and the type of emulsifier used. Moreover, at high temperature the droplet size decreased to a slight extend (Fujiu et al., 2011a, 2011b). Similarly, in case with W/O emulsions the droplet diameter remains constant below the dispersed phase critical flow velocity. On the other hand, the droplet generation frequency increased with increasing operating temperature, probably due to reduction in velocities of the operating fluids (Fujiu et al., 2012).

Viscosity of different phases is one of the critical parameter in MCE. van Dijke et al. (2010b) evaluated the effect of the viscosities in MCE using sodium dodecyl sulfate (SDS), polyethylene glycol (PEG) and their mixtures as continuous phase in MCE. They found that the droplet size was constant at higher viscosity ratio (defined as the ratio of the dispersed phase viscosity over the continuous phase viscosity) in comparison to low viscosity ratio. At lower viscosity ratio, the

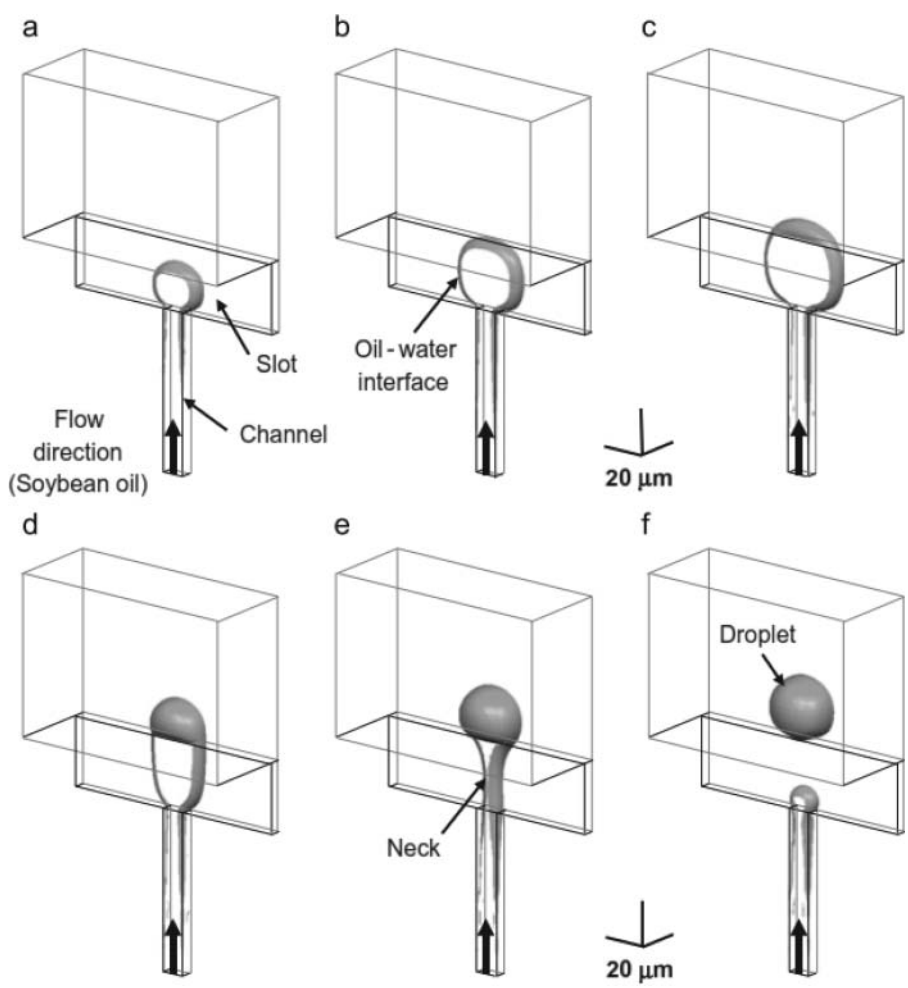

Figure 8. CFD-ACE+ simulation results for successful droplet generation in asymmetrical straight-though MCE. (a) $t_d = -40.0$ ms, (b) $t_d = -0.0$ ms, (c) $t_d = -35.3$ ms, (d) $t_d = -41.8$ ms, (e) $t_d = -48.7$ ms, and (f) $t_d = -51.9$ ms. t_d corresponds to detachment time. CFD-ACE-GUI software with a finite volume code was used to set the equations and parameters. Reproduced with permission (Kobayashi et al., 2011).

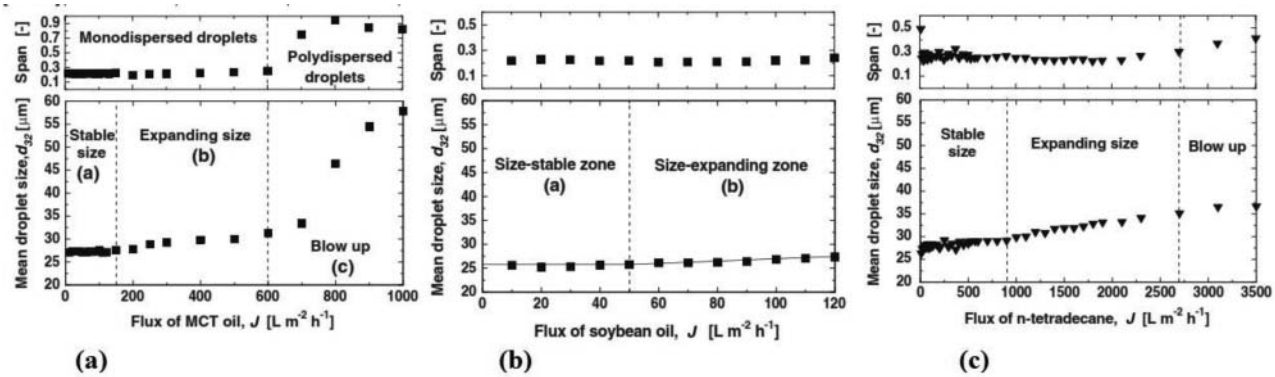

Figure 9. Effect of viscosities of dispersed phases on droplet generation in microchannel emulsification. The droplet generation regime is divided into stable, expanding and blow up regime in relation to dispersed phase flux. Three oil types (medium chain triglycerides (MCT), soybean oil and *n*-tetradecane) are evaluated) in relation to dispersed phase flux. Reproduced with permission (Vladisavljevic et al., 2011).

droplet size increased until a critical viscosity ratio is reached, where there is no more formation of droplets from MCs. Moreover, the viscosity effect was further depends upon MCE geometry and design. The droplet generation is possible even at low viscosity ratio, if longer MCs will be used, since in longer MCs there is a higher hydrodynamic flow resistance, which slows down the flow from channel to the terrace during droplet formation. The frequency of droplet generation in MCE is depended upon viscosity of the fluids. Vladisavljevic et al. (2011) studied the effect of dispersed phase viscosity on the droplet generation frequency in asymmetric straight-through MCE. They divided the droplet generation with different dispersed phase viscosities into three regimes: the stable generation regime, the expanding and blow up regime (Fig. 9). The dispersed phase with lowest viscosity perform well, even at higher dispersed phase flux.

Kobayashi et al. (2014) studied the effect of table salt (NaCl) on generation of O/W droplets in straight-through MCE. They mentioned the threshold concentration of 0.3–0.5 mol L^{-1} of NaCl in SDS and Tween 20 stabilized emulsions. Moreover, the droplet generation was slower and less stable, when the concentration of NaCl was increased, indicating the sensitivity of MCE towards electrolyte concentration.

Encapsulation of lipophilic compounds using MCE

Variety of food grade materials were used in MCE for production of, O/W emulsions. These includes vegetable oils (e.g., sunflower oil, safflower oil, soybean oil, and olive oil). Most of the studies were also conducted with MCT oil, that contain mixture of 75% caprylic acid and 25% capric acid (Kawakatsu et al., 1997; Neves et al., 2015; Vladisavljevic et al., 2012). Similarly, variety of food grade emulsifiers were used for encapsulation, including non-ionic emulsifiers and protein based emulsifiers (Kobayashi and Nakajima, 2002; Saito et al., 2005, 2006). The results of various studies showed that hydrophilic–lipophilic balance (HLB) greater than 10 is necessary for generating monodisperse emulsion droplets in MCE. Recently, Souilem

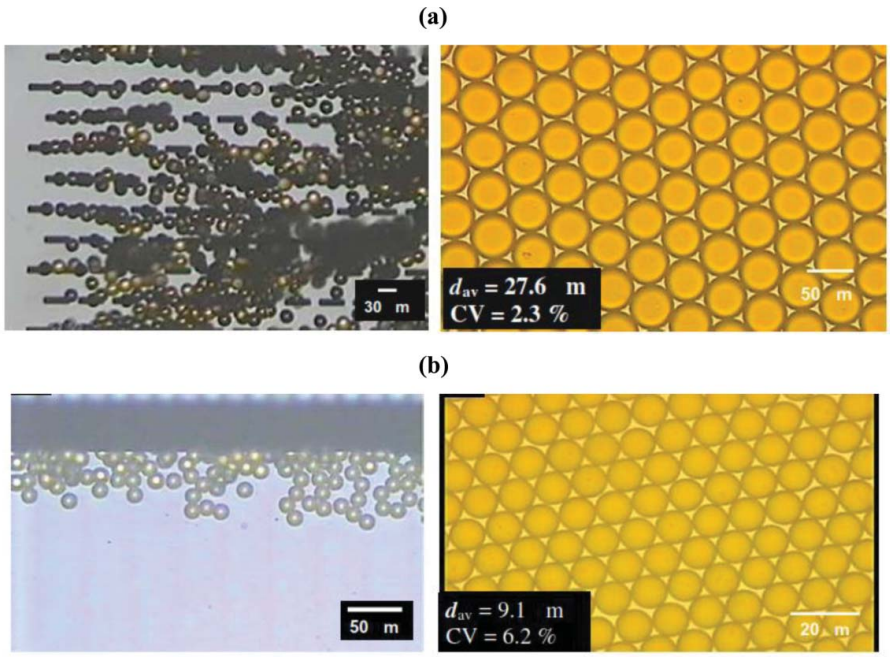

Figure 10. Micrographs of a β-carotene loaded O/W emulsions. (a) Obtained from straight-though microchannel emulsification and (b) obtained from grooved type microchannel emulsification. Reproduced with permission from (Neves et al., 2008b).

et al. (2014a) investigated the emulsifying ability of oleuropein and olive leaf extracted oleuropein (a natural polypenolic compound extracted from olives) using MCE. Successful MCE was conducted with refined soybean oil, refined olive oil and extra virgin oil olive oil with d_{av} of 25 μm and CV of <5%. The continuous phase in all of these emulsion systems constitute 0.6 wt% oleuropein in Milli-Q water (Souilem et al., 2014a).

Various lipophilic compounds have been encapsulated in O/W emulsions using MCE. These include β-carotene (Neves et al., 2008a; Neves et al., 2008b), γ-oryzanol (Neves et al., 2008b), ergocalciferol (Khalid et al., 2015c), mixture of cholcalciferol and ergocalciferol (Khalid et al., 2015d), quercetin (Khalid et al., 2016), β-sitosterol together with γ-oryzanol (Khalid et al., 2017) and various functional oils like argan oil (El-Abbassi et al., 2013) and clove oil (Purwanti et al., 2015). The important production characteristics and functionality is described in this section.

Various model studies have been conducted with MCE to check the stability and generation characteristics of O/W emulsions containing various oils like soybean oil, MCT and olive oil. MCT oil was encapsulated in O/W microspheres using MCE, the produced microspheres were well stable and have d_{av} of 3.7–3.8 μm with CV of 6–7% (Kobayashi et al., 2001). Olive oil was encapsulated in monodisperse O/W emulsions using straight-through MCE using 1 wt% polyglycerol monooleate as emulsifier. The monodisperse emulsion droplets exhibit good stability and the droplet size was independent of the continuous phase flow rate (Neves et al., 2009).

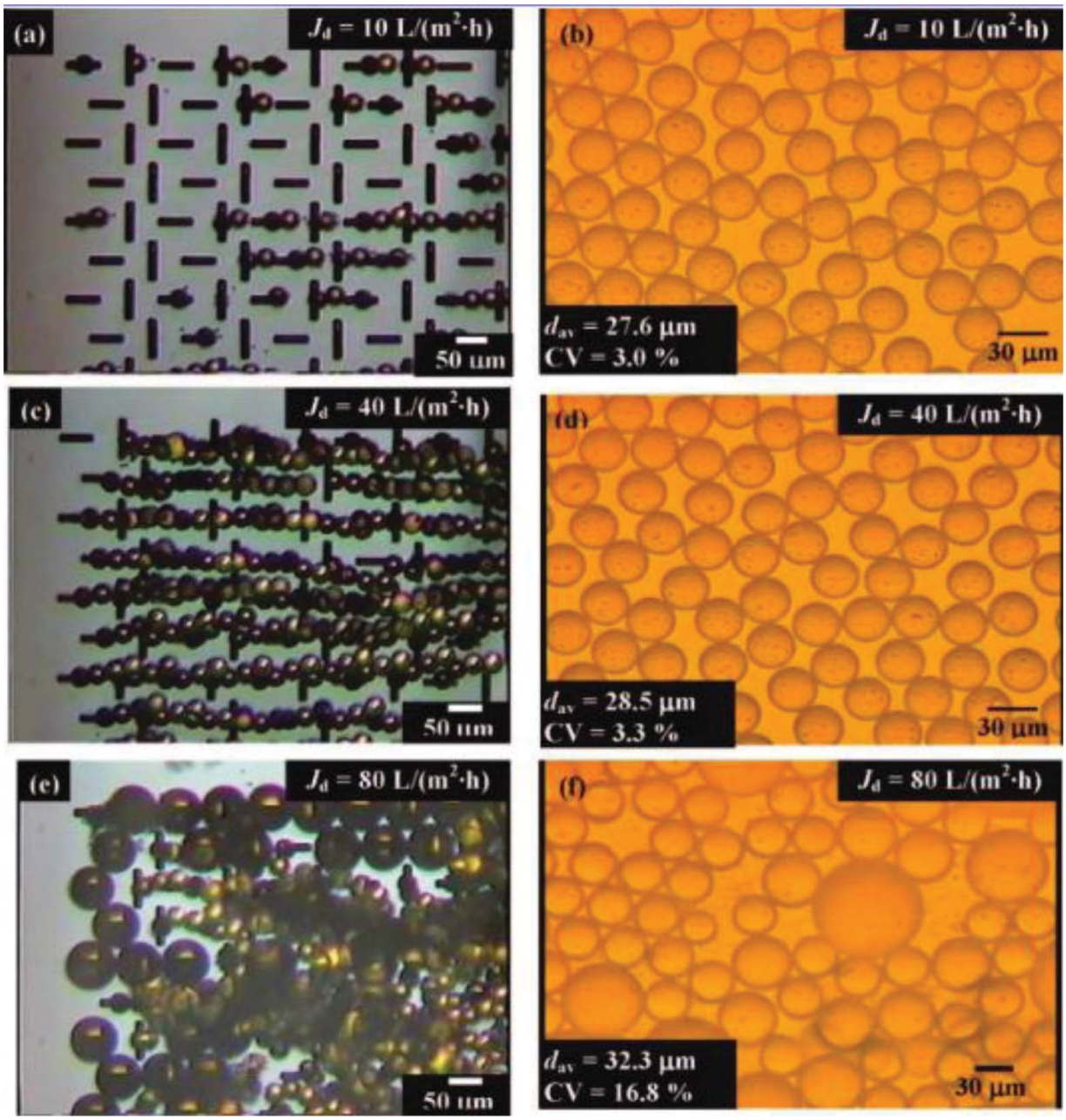

Figure 11. Optical micrographs showing droplet generation of PUFAs loaded O/W emulsions at various dispersed phase fluxes. The monodisperity can be visualized at low dispersed phase flux (a to d), while polydispersity can be observed at higher dispersed phase flux (e and f). Adopted with permission (Neves et al., 2008a) American Chemical Society.

Encapsulation of antioxidants

Antioxidants compounds like β-carotene, γ-oryzanol and quercetin play an important role in maintaining healthy life, these compounds protect the body against various aliments like cancer, cardiovascular diseases, immune functions and also reducing risks of obesity (Pisoschi and Pop, 2015). These antioxidants are very sensitive towards light, heat and oxidation, moreover the solubility of these compounds is very low in food grade materials (Shahidi and Ambigaipalan, 2015). β-carotene and other carotenoids are very sparingly soluble in oil (~0.2 g/L), quercetin ((~0.2–0.4 g/L), the solubility can be increased with increasing temperature. However, the bioaccessibility and bioavailability of these bio-active in gastro-intestinal fluids are quite low even after production from MCE. β-carotene is the precursor of vitamin A and have functionality in numerous food products like beverages, bakery products and dietary supplements. In order to increase the functionality Neves et al. (2008b) formulated O/W emulsions containing 3.2 g β-carotene/L oil using grooved type and straight-through MCE. The β-carotene was dissolved in refined soybean oil, while the continuous phase constitutes 1 wt% gelatin or sucrose monolaurate. Successful MCE was conducted with average droplet diameter (d_{av}) of 27.6 μm and a CV of 2.3% (Fig. 10). The β-carotene encapsulated emulsions remained stable for 4 month and resist polydispersity when stored in dark conditions at 5°C. The O/W emulsions containing γ-oryzanol were stabilized by 1 wt% gelatin or sucrose monolaurate with d_{av} of 28.8 μm and a CV of 3.8% (Neves et al., 2008b). The MCE array plate used in this study have 23, 348 MCs, each having a circular channels of 10 μm in diameter with depth of about 70 μm.

Encapsulation of polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFAs) play an important role in maintaining blood cholesterol levels, brain functionality and in maintaining lipid membranes (Calder, 2015). These PUFAs are prone to oxidation that limit their functionality in numerous food products. Moreover, encapsulation of PUFAs in different systems also increased the absorption *in vitro* (Yonekura and Nagao, 2007). PUFAs were also encapsulated in sized controlled O/W emulsions by Neves et al. (2008a) using straight-

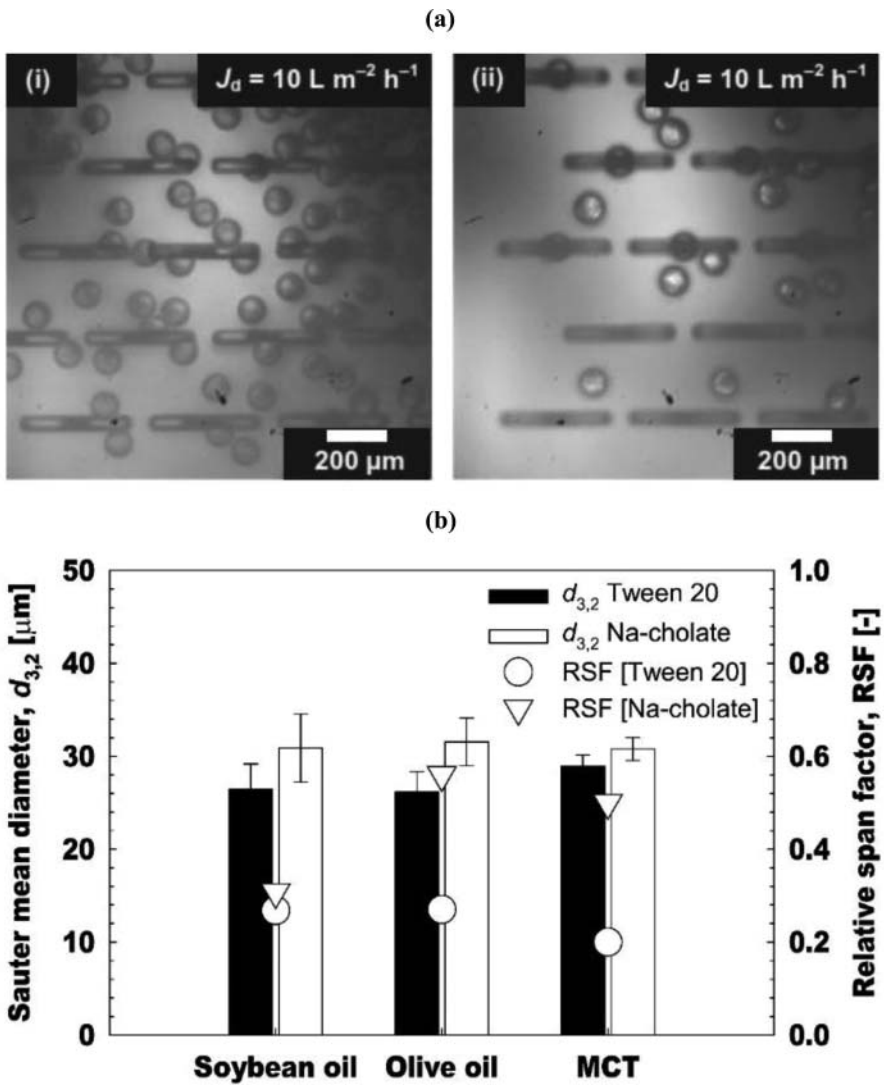

Figure 12. Droplet generation of O/W emulsions encapsulating mixture of vitamin D_2 and D_3 from MC arrays (i) Tween 20 stabilized emulsions (ii) sodium cholate stabilized emulsions. (b) Droplet sizes of O/W emulsions suing different oil types. Reproduced with permission (Khalid et al., 2015d).

through MCE (Fig. 11). The continuous phase include mixture of β-lactoglobulin and sucrose monolaurate, while the dispersed phase composed of β-carotene enriched palm oil loaded with 45 g/L PUFAs. The monodispersed O/W emulsion droplets were collected by regulating the flow of continuous and dispersed phases. The monodispersity of emulsion droplets varied with dispersed phase flux (J_d). Monodisperse droplets with d_{av} of 28.5 μm and a CV of >3.3% was obtained at $J_d < 40$ L m^{-2} h^{-1}, the higher J_d leads to polydispersity in the emulsion system (Fig. 11). However, the continuous phase flow rate has no pronounced effect on monodispersity in MCE.

Encapsulation of vitamin D

There are an estimated one billion people worldwide who are either vitamin D deficient or have insufficient vitamin D intake (Holick, 2007). Vitamin D is a seco-steroid hormone with two active forms, cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2) (Gonnet et al., 2010). Vitamin D_3 is produced in the skin upon exposure to sun-light (Lund and DeLuca, 1966), while vitamin D_2 is formed by the irradiation of ergosterol (Rosenheim and Webster, 1928).

Most dietary products are poor source of vitamin D, including breast milk (Wagner et al., 2006). Moreover, the high phytate and fibre content of vegetarian diets may also reduce the vitamin D absorption. The deficiency of this important vitamin can be corrected by using supplementation and fortification techniques. The fortifying foods with vitamin D can be difficult due to its hydrophobicity in food systems (Loftsson and Hreinsdottir, 2006), variable oral bioavailability (Haham et al., 2012), degradability at high temperatures (Grady and Thakker, 1980), narrow pH range (Markman and Livney, 2012) and oxidation (DeRitter, 1982). We recently encapsulated vitamin D in various emulsion systems using MCE. The brief overview of encapsulation system is described below.

Khalid et al. (2015d) encapsulated mixture of vitamin D_2 and D_3 using straight-through MCE. The dispersed phase contains 0.5% (w/w) vitamin D_2 and D_3 in soybean oil, olive oil and MCT. While, the continuous phase comprises either 1% (w/w) sodium cholate or Tween 20 in Milli-Q water. Monodisperse emulsion droplets were generated using all type of continuous and dispersed phases under optimized conditions (Fig. 12). The optimized conditions include dispersed phase flow rate of 2 mL h^{-1} with continuous phase flow rate of 250 mL h^{-1}. The O/W emulsions have Sauter mean diameter ($d_{3,2}$) of 28 to 32 μm and relative span factor (RSF, the width of the droplet size distribution) below 0.3. The vitamin D loaded emulsions have physical stability of more than 30 days at 25°C with both emulsifiers, but have stability of more than 30 days at 4°C with only Tween 20. The reduced stability with sodium cholate at low temperature might be due the aggregation of sodium cholate at low temperature (Calabresi et al., 2007; Jojart et al., 2014). The O/W emulsions stabilized by Tween 20 have encapsulation efficiencies (EEs) over 70% at 4 and 25°C after 30 days of storage period. In contrast, those stabilized by sodium cholate have EE of 70% only at 25°C (Fig. 13) after 30 days of storage period.

Vitamin D_2 was encapsulated in O/W emulsions using both grooved type and straight-through MCE by (Khalid et al., 2015c). They used variety of food grade oils (MCT, soybean oil, olive oil and safflower oil) with varying concentration of vitamin D_2 as dispersed phase while continuous phase contains either 1% (w/w) decaglycerol monolaurate (Sunsoft A-12), Tween 20 or β-lactoglobulin. The optimized composition includes 0.5% (w/w) vitamin D_2 in soybean oil with 1% (w/w) Tween 20 in Milli-Q water as continuous phase. Monodisperse emulsion droplets were generated from straight-though MCs with $d_{3,2}$ of 34 μm with a RSF of less than 0.2. The vitamin D_2 emulsion droplets were stable for more than 15 days with EE of over 75% during storage period.

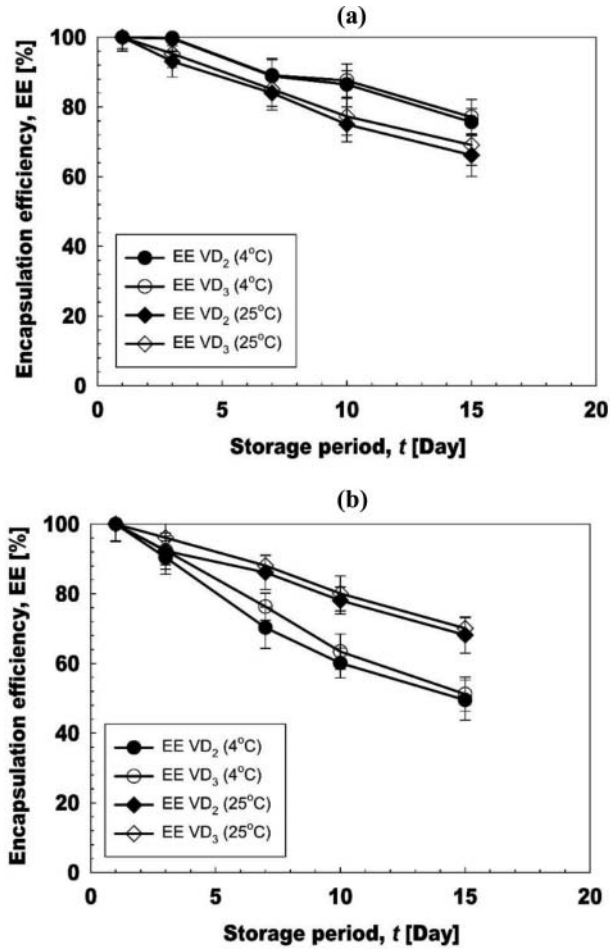

Figure 13. Encapsulation efficiencies of O/W emulsions encapsulating mixture of vitamin D_2 and D_3 (a) Tween 20 stabilized emulsions (b) sodium cholate stabilized emulsions. Reproduced with permission (Khalid et al., 2015d).

Encapsulation of functional oils

The use of essential oils as functional material in food, drinks, cosmetics and toiletries are getting popularity due to their flavor and fragrance aspects, health promoting properties and generally having safe status in food products (ALi et al., 2015; Vergis et al., 2015). The argan tree is an endemic tree in Morocco and traditionally well known for its cardioprotective and antioxidant properties (El Abbassi et al., 2014). The argan oil has a specific fatty acid composition that make it, as an excellent nutraceutical ingredient in food, pharmaceutical and cosmetic products. However, the self-life of argan oil is quite small and can be prolonged using encapsulation techniques

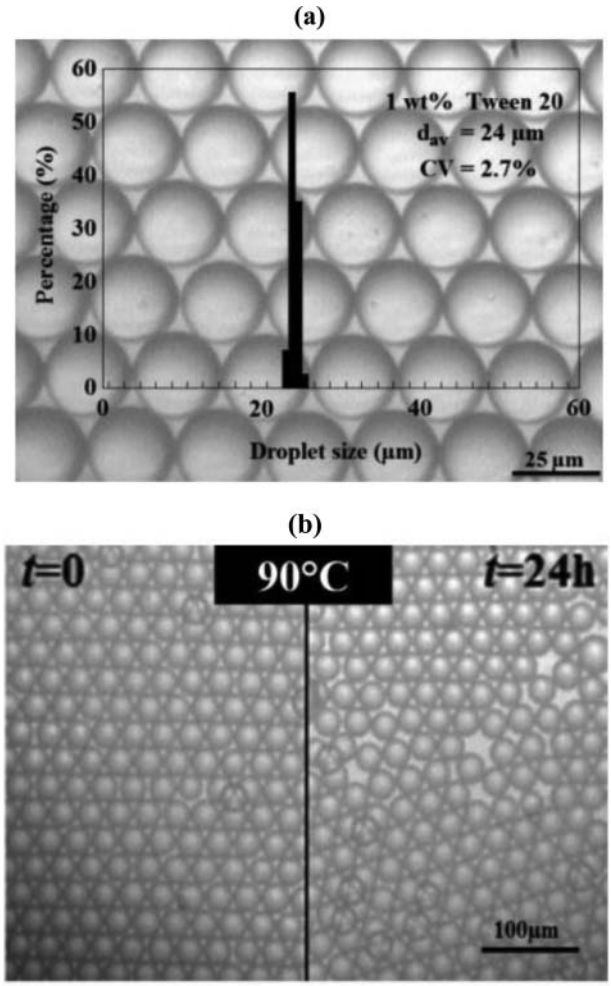

Figure 14. (a) Droplet size distribution of argan O/W emulsion stabilized by 1wt% Tween 20. (b) Optical micrographs showing argan O/W emulsion stability at 90°C with function of time at 0 and 24 h after formulation. The emulsion was stabilized using 0.25 wt% Tween 20. Reproduced with permission (El-Abbassi et al., 2013).

(El-Abbassi et al., 2013). El-Abbassi et al. (2013) formulated argan O/W emulsions using straight-through MCE (Fig. 14a). They check the effect of different non-ionic emulsifiers and processing temperature on droplet size and distribution of O/W emulsions. In terms of stability, the argan O/W emulsions were stabilized with 0.5–3 wt% Tween 20 and the temperature was increased to 90°C, even at low emulsifier concentration of 0.25 wt%, the O/W emulsions show stability against coalescence even after 24 h of formulation (Fig. 14b). The emulsions stabilized by 1 wt% Tween 20 remained stable of more than 4 months at room temperature without showing any creaming or phase separation. The results of their study highlighted that emulsifier concentration and temperature are the major factors that affect the droplet size and distribution of O/W emulsions.

Clove oil is widely used in fragrance, flavor, and pharmaceutical industries. The clove oil has many functional properties ranging from antioxidant, anti-inflammatory, analgesic, and many others (Sarfraz and Shahid, 2015). In many applications clove oil is encapsulation or formulated in order to preserve the functionalities over period of time. Numerous delivery systems have been developed to preserve the essence and functionality of clove oil including polymer matrixes, solid lipid particles, and O/W emulsions. However, the stability of clove oil in formulated system is still a challenging task (Purwanti et al., 2015; Sarfraz and Shahid, 2015; Shahavi et al., 2015). Monodisperse O/W emulsions encapsulating clove oil was successful formulated using MCE (Liu et al., 2001; Purwanti et al., 2015). The continuous phase constitutes different concentrations of sodium dodecyl sulfate (SDS) in Milli-Q water as emulsifier. Monodisperse clove oil droplets of 20 μm size were successfully generated from MCs and the monodispersity was depended upon SDS concentration. The SDS concentration above critical micelle concentration (CMC) results in formulation of polydisperse oil droplets that broke up with time (Liu et al., 2001). The droplet instability mechanism in MCE at high SDS concentration was recently proposed by Purwanti et al. (2015), they proposed diffusion driven, spontaneous emulsification and reverse micelle formation (Fig. 15) as main instability mechanism of clove oil encapsulation during MCE. Moreover, they proposed that the instability mechanism can be suppressed by saturating the continuous and dispersed phases prior to emulsification.

Encapsulation of hydrophilic compounds using MCE

MCE methods are also applicable for production of microspheres, monodisperse water-in-oil (W/O) and water-in-oil-in-water (W/O/W). However, surface modification of MC array plate is necessary for production of W/O emulsions and microspheres. The surface modification of MC array of plate can be performed using silicon coupler reagents like octadecyltriethoxysilane and hexamethyldisilazane with different treatment protocols (Chuah et al., 2009; Fujiu et al., 2012). The hydrophobic treatment produces an uncharged surface on silicon MC plate and create no strong repulsive interaction between the hydrophobic surfactant molecules and MC plate surface (Kobayashi et al., 2009b). Premix homogenization is needed for production of W/O/W emulsions from MCE. The premix homogenization is performed using either rotor-stator homogenizer (RSH) or high pressure homogenizer (HPH). In some cases, a combination of both RSH and HPH was utilized to produce fine W/O emulsion droplets before conducting MCE (Kobayashi et al., 2005a; Sugiura et al., 2004).

Many fundamental studies were conducted to formulate and characterize W/O emulsions, giant vesicles (GVs) and microspheres using silicon and polymer based MCE. Kobayashi et al. (2009b) formulated W/O emulsions using triglyceride oils by straight-though MCE. There was successful production of monodisperse W/O emulsions but the generation of droplets were highly depended upon operation conditions and viscosities of dispersed and continuous phases. Moreover, the droplet productivity of W/O emulsions increased exponentially with increasing temperature without effecting droplet sizes of W/O emulsions (Fujiu et al., 2012). Acrylic polymer based MC array plates were used to produce W/O emulsions using tetraglycerin condensed ricinoleic acid esters (CR-310) as emulsifiers. Monodisperse W/O droplets were generated having d_{av} of 40–98 μm with CV $<$ 10% (Liu et al., 2004; Liu et al., 2005). MCE is also a useful technology for production of monodisperse microspheres and microbeads. Chuah et al. (2009) produces alginate microspheres with narrow size droplet distribution using combine operation of MCE and external gelation method. These microspheres have d_{av} of 18–22 μm with CV $<$ 5-26%. The

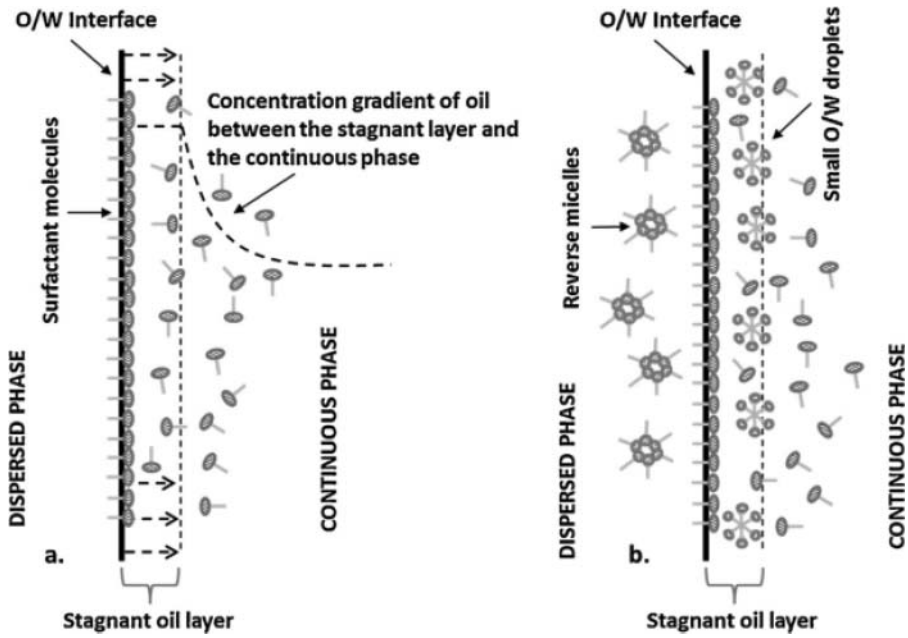

Figure 15. Droplet instability mechanism depiction for clove oil encapsulation in MCE. The clove oil was encapsulated in O/W emulsions using different concentrations of SDS in Milli-Q water. Reproduced with permission (Purwanti et al., 2015).

gelation of these microspheres shrinks the d_{av} to 6.2 μm with CV < 10%.

Kobayashi et al. (2005) formulated W/O/W emulsions using combined operation of microfluidizer and MCE. They use tetraglycerin monolaurate condensed ricinoleic acid esters (TGCR) or polyglycerin polycondensed ricinoleic acid esters (PGPR) in soybean oil as emulsifiers in the continuous phase of the W/O emulsions. The high-pressure homogenizer produced W/O emulsions with d_{av} of 0.15–0.25 μm for PGPR-stabilized system and 0.16–0.26 μm for the TGCR-containing system. Monodisperse W/O/W emulsions with an d_{av} of 39.0–41.0 μm and a CV < 5% were formulated using an oblong straight-through MCE and with polyoxyethylene (20) sorbitan monoleate (Tween 80) as hydrophilic emulsifier to stabilize the other aqueous phase. Similarly, Sugiura et al. (2004) formulated W/O/W emulsions using different oil types (MCT, ethyl oleate, decane, and triolein). They used 5% CR-310 as emulsifier in the oil phase and Tris–HCl buffer as aqueous (dispersed) phase. Successful MCE was conducted with different oil types (Fig. 16). Monodisperse oil droplets with d_{av} ranging between 32.6 and 35.7 μm with CVs of 5–8% were successfully prepared using different oil types. The entrapment efficiency was over 91% with different oil types.

In another study Kawakatsu et al. (2001) formulated monodispersed W/O/W emulsions using different lipophilic emulsifiers and oil types. They noticed that lipophilic emulsifiers had effect on stability and monodispersity of W/O/W emulsions. Similarly, they also formulated solid-in-oil-in-water (S/O/W) microcapsules using calcium solution and Tween 20 as external water phase (outer aqueous phase). The results indicate that it is possible to change the texture of W/O/W emulsion after using appropriate gelation agents. The above mention fundamental studies do not encapsulate any functional hydrophilic agents but provide valuable information regarding generation characteristics and stability profiles using MCE. This section briefly explains the encapsulation of hydrophilic functional compounds using MCE.

Encapsulation of L-ascorbic acid in different emulsion systems

L-ascorbic acid (AA) is a powerful antioxidant and have variety of applications and functions in a living body. It has the capacity to regulate the immune system, provide efficient protection against various type of cancers and also regulates the heart function. Besides numerous health benefits, it is prone to heat, light and oxidation. These agents limit it functionality in living bodies. The positive aspect of this vital compound is the no-toxicity even at high concentrations (Grosso et al., 2013). In the last two decades variety of encapsulation strategies was devised to encapsulate AA, each of these has its own limitation and positive values (Abbas et al., 2012). We used MCE to encapsulate high concentration of AA in numerous delivery systems like W/O, W/O/W emulsions and microspheres (Khalid et al., 2014b, 2015a, b).

Khalid et al. (2014b) encapsulated high concentration of AA in W/O/W emulsions using two step homogenization. The first step involves encapsulation of AA in W/O emulsions using rotor-stator homogenizer and the second step re-homogenize the W/O emulsion droplets into W/O/W emulsions using straight-through MCE. The dispersed phase comprises of 1% (w/w) gelatin, 10–30% (w/w) AA and 1% (w/w) magnesium sulfate as stabilizer in Milli-Q water. The continuous phase contains 4–8% (w/w) CR-310 in soybean oil. The W/O emulsion droplets had d_{av} of 2.6–2.9 μm with CV > 15%. The W/O was re-homogenized by using outer aqueous phase containing 1% (w/w) decaglycerol monolaurate and 10–30% (w/v) glucose to counter the osmotic pressure. The second homogenization using MCE produced W/O/W emulsion droplets with d_{av} of 26–31.5 μm and CV < 10%. They also mentioned that

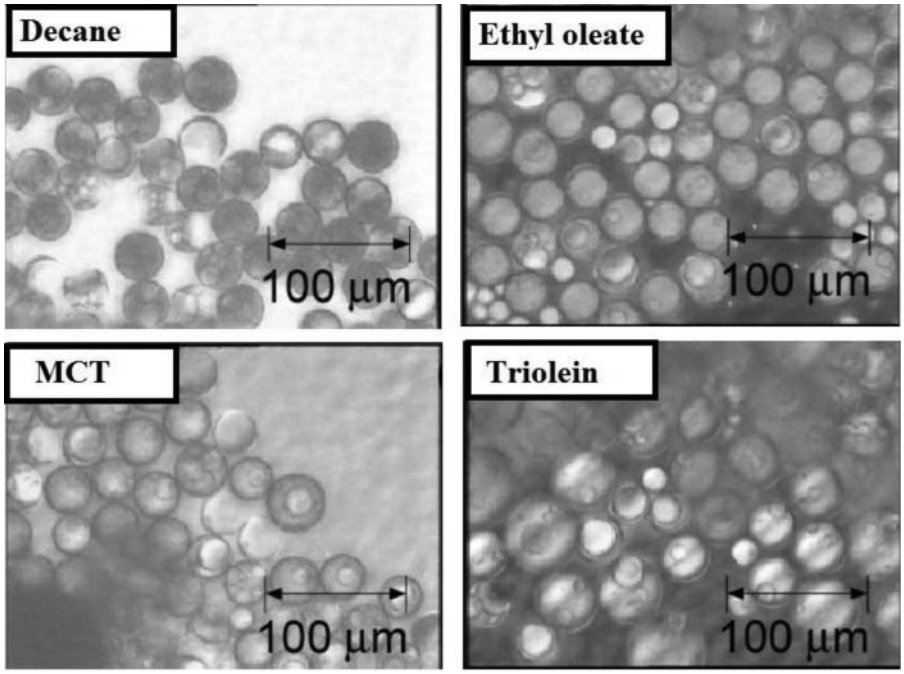

Figure 16. Optical micrographs of W/O/W emulsions from MCE. Differential interference contrast (DIC) microscopy was used to detect the oil phase. Reproduced with permission (Sugiura et al., 2001).

concentration of CR-310 as a critical parameter for successful droplet generation in MCE (Fig. 17). The higher CR-310 (6–8% (w/w) concentration resulted in formation of unstable droplets probably due to rapid adsorption of CR-310 molecules at the newly created interface. The monodisperse W/O/W emulsions had EE of over 80% during evaluated storage period. The similar dispersed and continuous phase composition had EE of less than 50% in W/O and W/O/W emulsions formulated by conventional devices (Khalid et al., 2013a, b). The higher EE of emulsion system formulated by MCE clearly demonstrate its advantage over conventional devices.

Khalid et al. (2015b) formulated aqueous microspheres containing high concentration of AA using different concentration of sodium alginate (Na-ALG) in grooved type MCE. The oil phase contain water saturated decane and 5% (w/w) CR-310 or Span 85. The optimized condition for obtaining monodisperse aqueous microspheres include 2% (w/w) Na-ALG and 1% (w/w) magnesium sulfate together with varying concentration of AA. At optimized conditions, the MCE produces aqueous microspheres with d_{av} of 14–16 μm and CV $<$ 8%. The higher Na-ALG reduces the droplet generation frequency and subsequently produces polydisperse microspheres. Similarly, lower magnesium sulfate concentration results in unstable microsphere production (Fig. 18), while high concentration results in bursting of microspheres due to high osmotic potential (Khalid et al., 2015b).

The optimized conditions for Na-ALG containing aqueous microspheres were used in straight-through MCE for analyzing physical and chemical stability of 20% (w/w) AA. The monodisperse aqueous microspheres with d_{av} of 18.7–20.7 μm and CV $<$ 6% were generated from straight-through MCs (Khalid et al., 2015a). The produced microspheres remained stable for more than 10 days with EE $>$70% at 40°C storage temperature (Fig. 19a). Moreover, the d_{av} of microspheres increased with increasing J_d, the monodisperse aqueous microspheres were produced under J_d of 5–10 L m^{-2} h^{-1} (Fig. 19b and c). The further increased in J_d results in out flow of dispersed phase from MCs (Khalid et al., 2015a).

Encapsulation of ascorbic acid derivatives

Ascorbic acid derivatives have been used as additivities in numerous food and pharmaceutical industries. Ascorbic acid derivatives also possess strong antioxidant activity just like ascorbic acid. These derivatives are added in different formulations to prevent oxidation of the loaded drugs or sensitive food components (Fočo et al., 2005; Moribe et al., 2011). MCE was used to encapsulate calcium ascorbate (Ca-As) and ascorbic acid 2-glycoside (AA-2G) in W/O emulsions (Khalid et al., 2014a). The continuous phase constitutes 5% (w/w) CR-310 or Span 85 in different oil types like soybean oil, decane and equal mixture of decane and soybean oil. Dead end type MCE was used to encapsulate ascorbic acid derivatives. Successful emulsification was conducted with both Ca-As and AA-2G. The W/O emulsions have d_{av} of 17-28 μm and CV $<$ 7%. The d_{av} of the W/O emulsions increased with increasing dispersed phase viscosities but maintaining monodispersity. It was also observed that the d_{av} of W/O emulsions remain unaffected by the dispersed phase flow rate below the critical values (Fig. 20). The critical flow rate of dispersed phase ranged between 1.2 and 1.6 mL h^{-1}. The results also indicated that emulsifier type have stronger effect on the stability of W/O emulsions. The AA-2G have long chain structure with no ion involvement and helps in better penetration of emulsifier at the interface of W/O emulsions in comparison to Ca-As that have ionic structure and hinders the absorbance at emulsifier at nearly created interface (Khalid et al., 2014a).

Encapsulation of oleuropein

Oleuropein is a major phenol compound extracted from olive leaves, privet's leaves and olive oil. Oleuropein in a specified

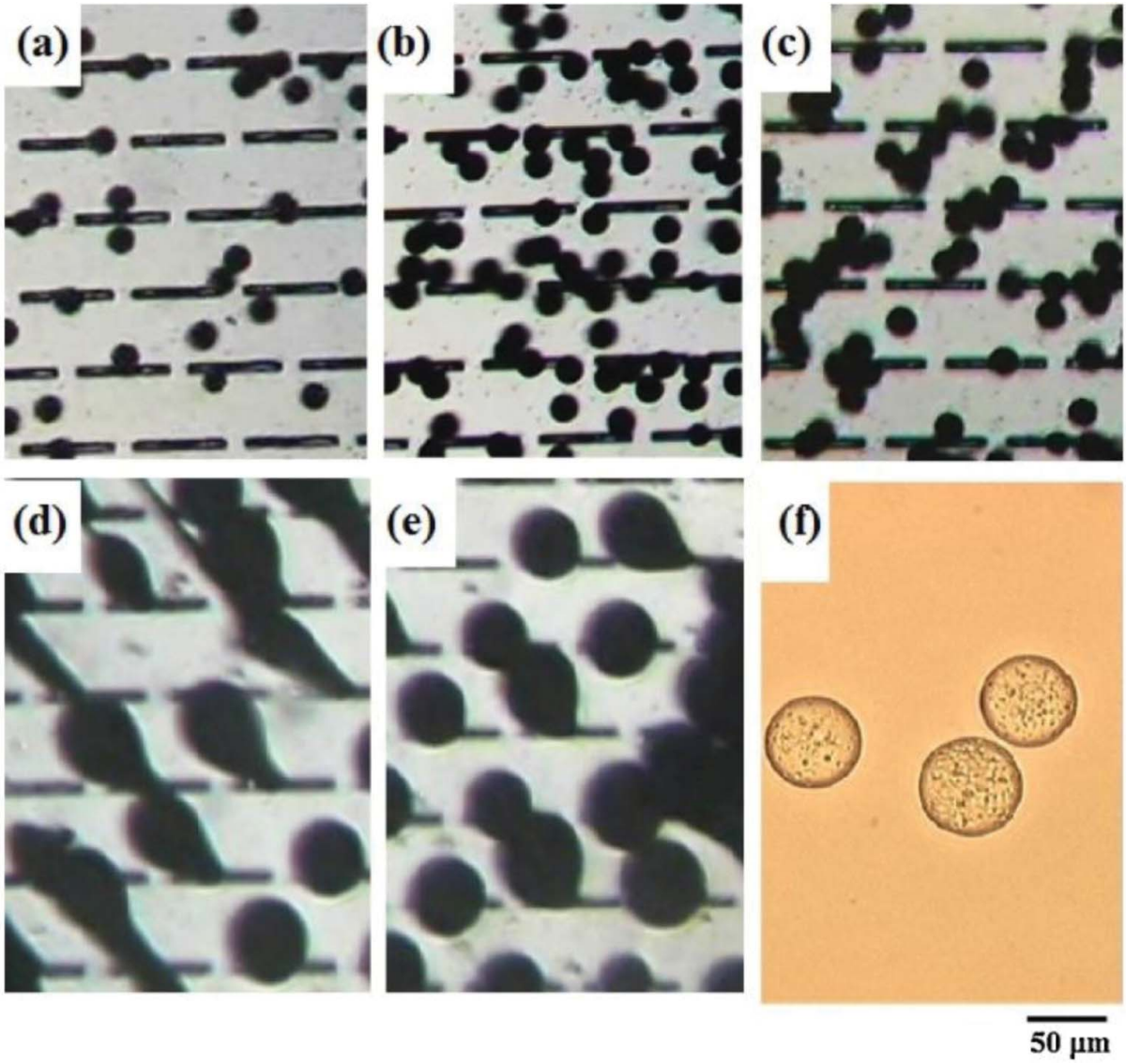

Figure 17. Encapsulation of L-ascorbic acid in W/O/W emulsions using straight-through MCE. (a) Droplet generation containing 4% (w/w) CR-310 and with 10% (w/w) AA, (b) 4% (w/w) CR-310 and with 20% (w/w) AA, (c) 4% (w/w) CR-310 and with 30% (w/w) AA, (d) 6% (w/w) CR-310 and with 30% (w/w) AA, (e) 8% (w/w) CR-310 and with 30% (w/w) AA and (f) Optical micrograph of W/O/W emulsions containing 30% (w/w) AA. Reproduced with permission (Khalid et al., 2014b).

quantity have great functional attributes like antioxidant, antidiabetic, anticancer, antibacterial and many others (Khan et al., 2007; Vissers et al., 2004). Despite of its great functional attributes, the bitter taste, prone to oxidation and enzymatic degradation limits it usage in food and pharmaceutical products (Fang and Bhandari, 2010). Moreover, oleuropein is easily degraded in small intestine and hence have poor solubility (Fang and Bhandari, 2010). In order to overcome these limitations, oleuropein is encapsulated in numerous emulsions systems (Mourtzinos et al., 2007; Souilem et al., 2014b).

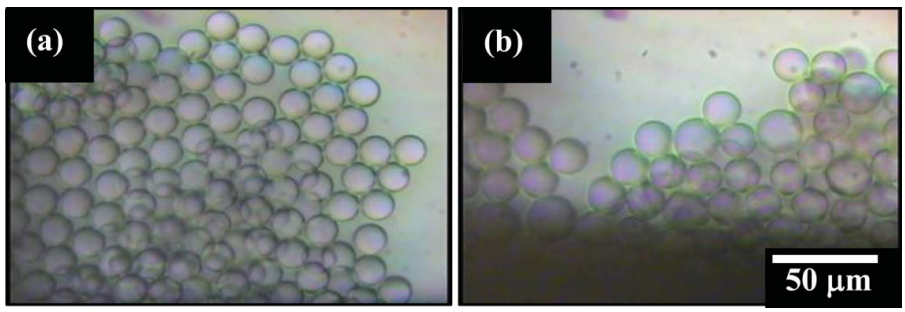

Figure 18. Optical micrographs showing aqueous microspheres containing 30% (w/w) L-ascorbic acid. (a) 1% (w/w) magnesium sulphate and (b) No addition of magnesium sulphate. Reproduced with permission (Khalid et al., 2015b).

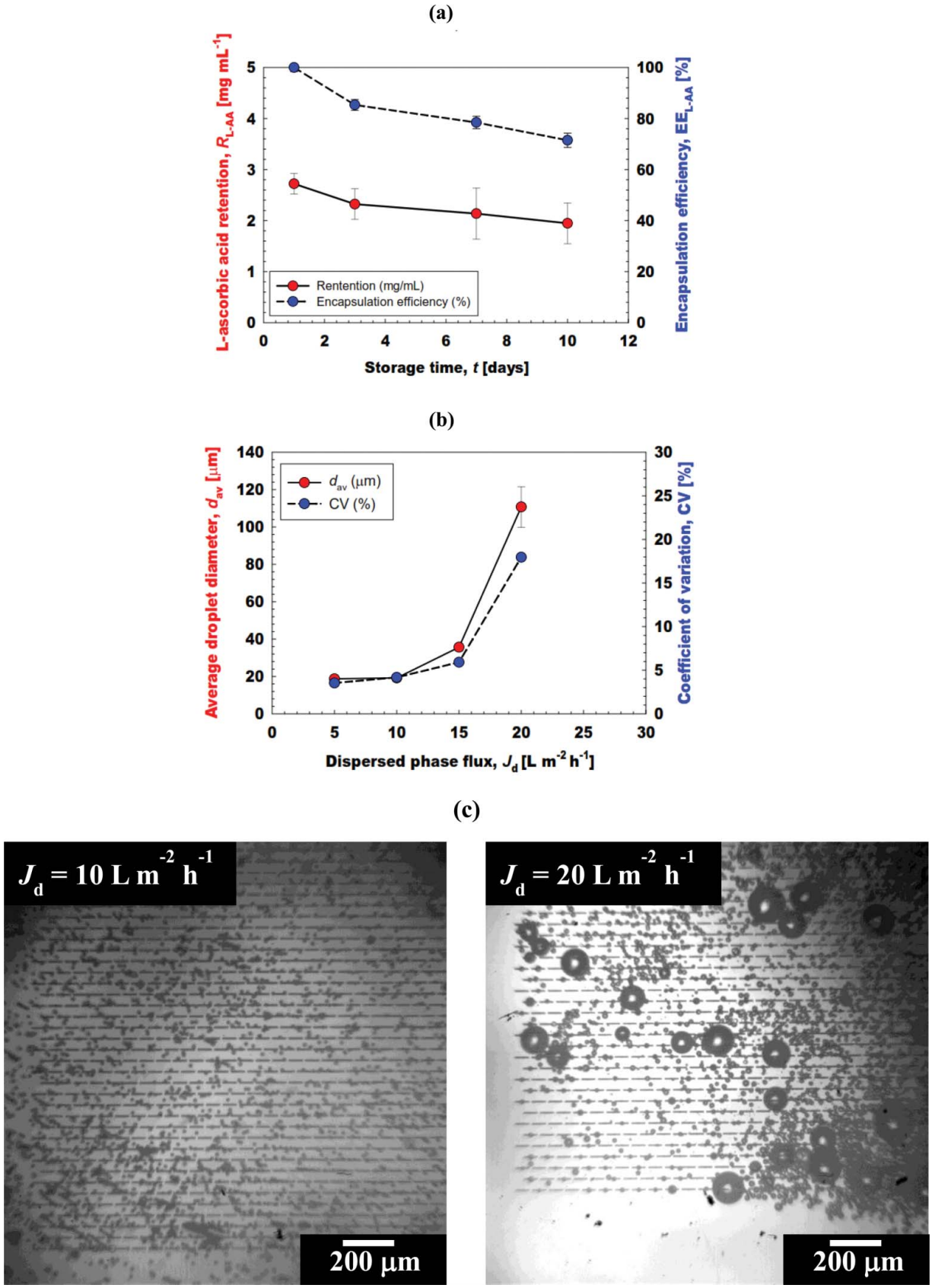

Figure 19. (a) Encapsulation and retention profile of 20% (w/w) L-ascorbic acid in aqueous microspheres produced from MCE. (b) Effect of dispersed phase flux on microspheres d_{av} and CV and (c) optical micrographs showing effect of dispersed phase flux on microsphere generation from MCs. Reproduced with permission (Khalid et al., 2015a).

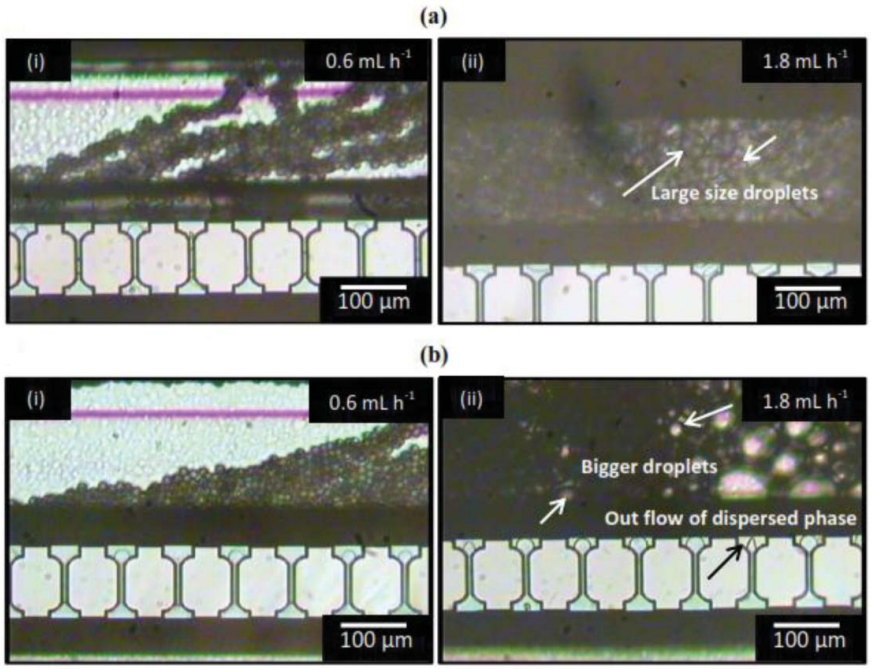

Figure 20. Droplet generation of W/O emulsions in microchannel emulsification encapsulating calcium ascorbate. (a) Stabilized by CR-310 and (b) stabilized by Span 85. (i) Below critical flow rate, (ii) above critical flow. The arrows indicate unstable W/O droplets. Reproduced with permission (Khalid et al., 2014a).

Recently, Souilem et al. (2014b) encapsulated oleuropein in food grade W/O/W emulsions using combined operation of HPH and MCE. The dispersed phase constitute 5 wt% glucose and 0.1–0.7 wt% oleuropein in 5 mM phosphate buffer, while the continuous phase contain 3–8 wt% CR-310 in soybean oil. The primary W/O emulsions had d_{av} of 0.15 μm with monomodal droplet size distribution. The W/O emulsion droplets were re-emulsified in outer aqueous phase containing 5 wt% glucose and 1 wt% decaglycerol monolaurate in 5 mM phosphate buffer using grooved type MCE. Monodisperse oil droplets were produced with d_{av} of 27 μm with CV $<$ 5%. The droplet generation was further depended upon MC dimensions (Fig. 21). The MC array plate having channel depth of 5 μm and width of 18 μm (CMS 6-2) produces more monodisperse oil droplets in comparison to narrow width of 8 μm (CMS 6-1). Moreover, their study concluded that higher hydrophobic emulsifier concentration and low oleuropein concentration stabilized emulsions were stable for more than 40 days of storage in comparison to emulsions stabilized by low concentration of hydrophobic emulsifier or emulsions containing high concentration of oleuropein (Souilem et al., 2014b).

Encapsulation of enzymes and polysaccharides in giant vesicles

MCE was also used to produce GVs (Fig. 22a), the production method involves the preparation of W/O emulsions by keeping water droplets in frozen state. Afterwards, the emulsifier was replaced by a lipid bilayer mixture and then oil phase was evaporated. Later on, the lipid bilayer was hydrated that surrounds

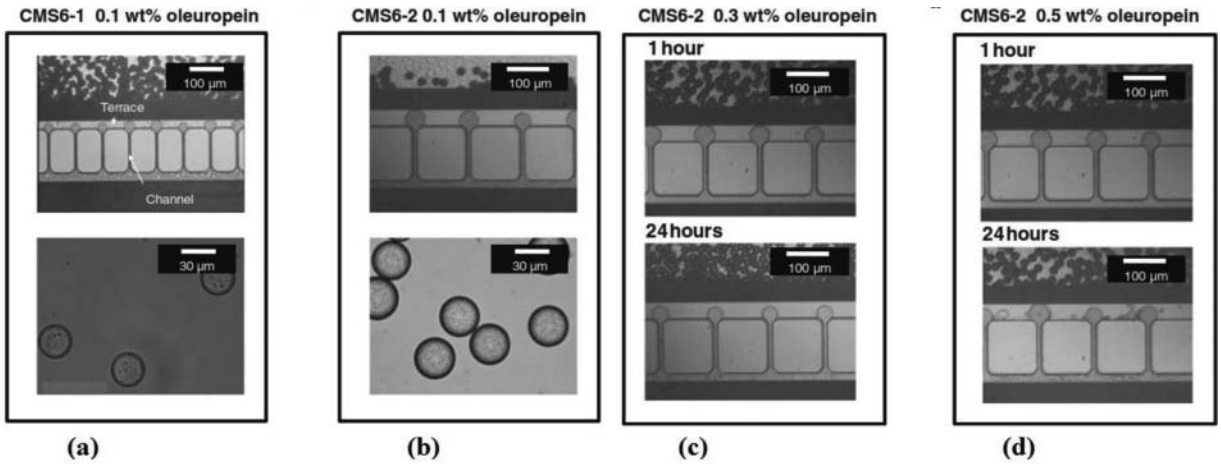

Figure 21. Effect of MC array plates dimensions on droplet generation characteristics of W/O/W emulsions encapsulating oleuropein. (a) Droplet generation together with optical micrograph of W/O/W emulsions produced in MCE with channel width of 8 μm. (b) W/O/W emulsions produced in MCE with channel width of 18 μm. (c) Effect of oleuropein concentration as function of time during droplet in MCE. Reproduced with permission (Souilem et al., 2014b).

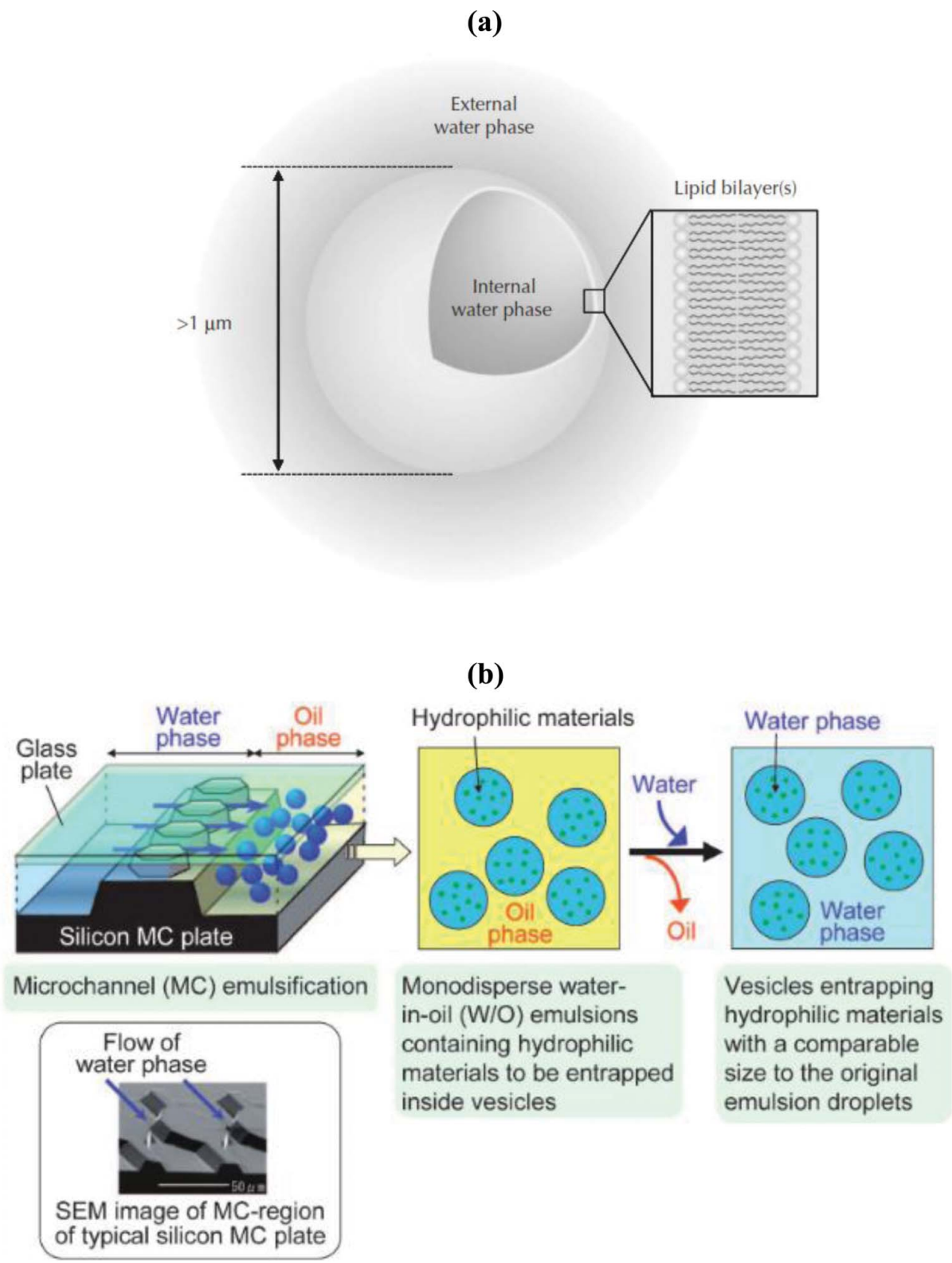

Figure 22. (a) Schematic presentation of giant vesicles. (b) Schematic presentation of "Lipid-coated Ice Droplet Hydration Method" for preparing giant vesicles from a monodisperse W/O emulsion with controllable size and high encapsulation efficiency (Ichikawa and Kuroiwa, 2008).

the water droplets. This production method was also called as "lipid-coated ice droplet hydration method" (Fig. 22b). The size of the GVs can be controlled by controlling the size of water droplets in W/O emulsions (Ichikawa and Kuroiwa, 2008, Kuroiwa et al., 2009, 2012, Kuroiwa et al., 2009). The structure of GVs formulated from MCE can be observed using water-soluble fluorescent dyes like calcein in the inner part of GVs. The optical microscopic observations confirmed structure ranging from oligolamellar to multilamellar (Sugiura et al., 2008). MCE successfully formulated GVs having d_{av} ranging from 7 to 40 μm (Kobayashi et al., 2009a; Kuroiwa et al., 2009, 2012; Sugiura et al., 2008).

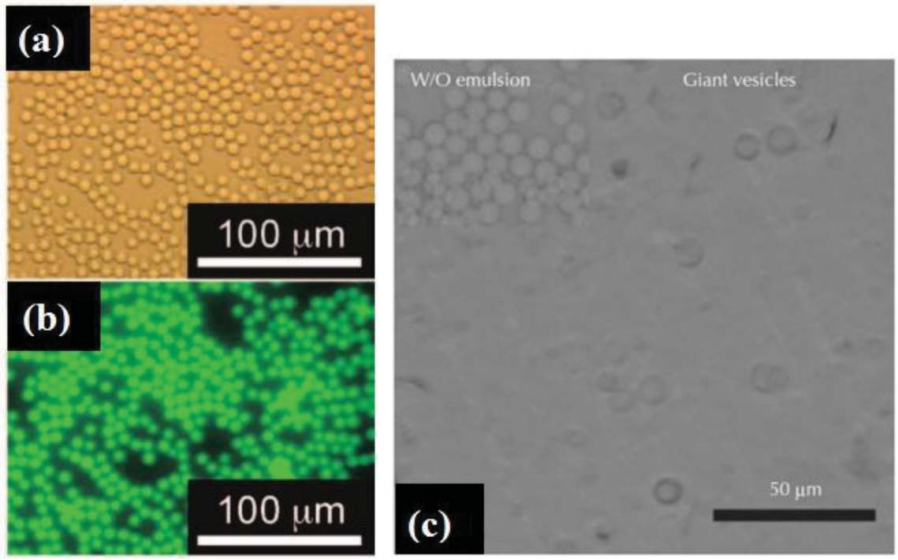

Figure 23. Monodisperse W/O emulsions produced for formulating giant vesicles (a) optical micrograph of emulsion (b) fluorescent micrograph of emulsion and (c) giant vesicle encapsulating carboxylesterase in W/O emulsion (Kuroiwa and Ichikawa, 2008).

Variety of hydrophilic compounds like fluorescent markers (calcein and FTIC (fluorescein isothiocyanate), biopolymers like enzymes and polysaccharides were entrapped in the inner water phase of GVs (Kobayashi et al., 2009a; Kuroiwa et al., 2009, 2012; Sugiura et al., 2008). The EE of encapsulated compounds is depended upon the droplet size of water droplets, the composition of external water phase, type of solvent used and other operating conditions in MCE. The optimized conditions produced GVs with EE ranging from 20% to 50% of encapsulated compounds (Kuroiwa et al., 2009; Sugiura et al., 2008).

Encapsulated enzymes in its active state can be used as compartments for microbioreaction system. Fig. 23 shows GVs encapsulating carboxylesterase and α-chymotrypsin using MCE. The encapsulation activates the activity of carboxylesterase and α-chymotrypsin by transporting substrate molecules via permeation through the lipid bilayer in the GVs. The efficiency of enzymatic reactions can be increased using appropriate substrate molecule (Kuroiwa and Ichikawa, 2008).

Conclusion and outlook

This review has outlined the recent developments in encapsulation of functional ingredients using MCE. MCE is a useful technology to produce monodisperse emulsion droplets using precisely fabricated microchannels with well-defined geometry. The MCE is capable of producing micro-emulsions with narrow size distribution in comparison to conventional homogenization devices. Recently, the development of nanochannel emulsification by our group leads to the formulation of nanoemulsions, however the fabrication of nanochannel emulsification is still in development stage. The production of emulsion droplets in MCE is much gentle with no involvement of high shear forces. Moreover, variety of emulsified products can be obtained in MCE ranging from simple to multiple emulsions.

The development of straight-through MCE enable the mass scale-up production of emulsion droplets. MCE enable formulation of emulsion droplets with average droplet sizes from 1 to 550 μm. Moreover, this emulsification technology is highly energy efficient in comparison to traditional homogenization processes. The production efficiency in MCE is highly depended upon choice of dispersed and continuous phases, type of emulsifiers and physicochemical properties of functional compound. The further scale-up of MCE following channel parallelization principle can enable production of encapsulated nutraceuticals at industrial level in near future.

References

Abbas, S., Da Wei, C., Hayat, K. and Xiaoming, Z. (2012). Ascorbic acid: microencapsulation techniques and trends—a review. *Food Rev. Int.* **28**:343–374.

Ali, B., Al-Wabel, N. A., Shams, S., Ahamad, A., Khan, S. A. and Anwar, F. (2015). Essential oils used in aromatherapy: a systemic review. *Asian Pacific J. Trop. Biomed.* **5**:601–611.

Anna, S. L., Bontoux, N. and Stone, H. A. (2003). Formation of dispersions using "flow focusing" in microchannels. *Appl. Phys. Lett.* **82**:364–366.

Benkouider, C. (2004). Functional foods: a global overview. *Int. Food Ingredients.* **5**:66–68.

Boom, R. M. and Schroen, C. G. P. H. (2011). Emulsification with microstructured membranes and micro-engineered systems. In: Bubble and Drop Interfaces, pp. 481–502. Miller, R. and Liggieri, L., (Eds.).

Calabresi, M., Andreozzi, P. and La Mesa, C. (2007). Supra-molecular association and polymorphic behaviour in systems containing bile acid salts. *Molecules.* **12**:1731–1754.

Calder, P. C. (2015). Marine omega-3 fatty acids and inflammatory processes: effects, mechanisms and clinical relevance. *Biochim. Biophys. Acta (BBA)-Mol. Cell Biol. Lipids.* **1851**:469–484.

Chuah, A. M., Kuroiwa, T., Kobayashi, I., Zhang, X. and Nakajima, M. (2009). Preparation of uniformly sized alginate microspheres using the novel combined methods of microchannel emulsification and external gelation. *Colloids Surf. a-Physicochemical Eng. Aspects.* **351**:9–17.

DeRitter, E. (1982). Vitamins in pharmaceutical formulations. *J. Pharm. Sci.* **71**:1073–1096.

El-Abbassi, A., Neves, M. A., Kobayashi, I., Hafidi, A. and Nakajima, M. (2013). Preparation and characterization of highly stable monodisperse argan oil-in-water emulsions using microchannel emulsification. *Eur. J. Lipid Sci. Technol.* **115**:224–231.

El Abbassi, A., Khalid, N., Zbakh, H. and Ahmad, A. (2014). Physicochemical characteristics, nutritional properties, and health benefits of argan oil: a review. *Crit. Rev. Food Sci. Nutr.* **54**:1401–1414.

Fang, Z. and Bhandari, B. (2010). Encapsulation of polyphenols–a review. *Trends Food Sci. Technol.* **21**:510–523.

Fočo, A., Gašperlin, M. and Kristl, J. (2005). Investigation of liposomes as carriers of sodium ascorbyl phosphate for cutaneous photoprotection. *Int. J. Pharm.* **291**:21–29.

Fujiu, K. B., Kobayashi, I., Neves, M. A., Uemura, K. and Nakajima, M. (2011a). Effect of temperature on production of soybean oil-in-water emulsions by microchannel emulsification using different emulsifiers. *Food Sci. Technol. Res.* **17**:77–86.

Fujiu, K. B., Kobayashi, I., Neves, M. A., Uemura, K. and Nakajima, M. (2012). Influence of temperature on production of water-in-oil emulsions by microchannel emulsification. *Colloids Surf. a-Physicochemical Eng. Aspects.* **411**:50–59.

Fujiu, K. B., Kobayashi, I., Uemura, K. and Nakajima, M. (2011b). Temperature effect on microchannel oil-in-water emulsification. *Microfluidics Nanofluidics.* **10**:773–783.

Gañán-Calvo, A. M. (1998). Generation of steady liquid microthreads and micron-sized monodisperse sprays in gas streams. *Phys. Rev. Lett.* **80**:285.

Gonnet, M., Lethuaut, L. and Boury, F. (2010). New trends in encapsulation of liposoluble vitamins. *J. Control Release.* **146**:276–290.

Grady, L. T. and Thakker, K. D. (1980). Stability of solid drugs: degradation of ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) at high humidities and elevated temperatures. *J. Pharm. Sci.* **69**:1099–1102.

Grosso, G., Bei, R., Mistretta, A., Marventano, S., Calabrese, G., Masuelli, L., Giganti, M. G., Modesti, A., Galvano, F. and Gazzolo, D. (2013). Effects of vitamin C on health: a review of evidence. *Front Biosci. (Landmark Ed).* **18**:1017–1029.

Haham, M., Ish-Shalom, S., Nodelman, M., Duek, I., Segal, E., Kustanovich, M. and Livney, Y. D. (2012). Stability and bioavailability of vitamin D nanoencapsulated in casein micelles. *Food Funct.* **3**:737–744.

Hilliam, M. (2000). Functional food-how big is the market?. *World Food Ingredients.* **12**:50–52.

Holick, M. F. (2007). Vitamin D deficiency. *N. Engl. J. Med.* **357**:266–281.

Ichikawa, S. and Kuroiwa, T. (2008). Novel method for preparing vesicles from a monodisperse emulsion aimed at controlling the size and improving the entrapment yield. *Yakugaku Zasshi-J. Pharm. Soc. Japan.* **128**:681–686.

Iwamoto, S., Nakagawa, K., Sugiura, S. and Nakajima, M. (2002). Preparation of gelatin microbeads with a narrow size distribution using microchannel emulsification. *AAPS Pharm. Sci. Tech.* **3**:E25–E25.

Jojart, B., Posa, M., Fiser, B., Szori, M., Farkas, Z. and Viskolcz, B. (2014). Mixed micelles of sodium cholate and sodium dodecylsulphate 1:1 binary mixture at different temperatures–experimental and theoretical investigations. *PLoS One.* **9**:e102114.

Kawakatsu, T., Kikuchi, Y. and Nakajima, M. (1997). Regular-sized cell creation in microchannel emulsification by visual microprocessing method. *J. Am. Oil Chem. Soci.* **74**:317–321.

Kawakatsu, T., Komori, H., Nakajima, M., Kikuchi, Y. and Yonemoto, T. (1999). Production of monodispersed oil-in-water emulsion using crossflow-type silicon microchannel plate. *J. Chem. Eng. Japan.* **32**:241–244.

Kawakatsu, T., Tragardh, G. and Tragardh, C. (2001). Production of W/O/W emulsions and S/O/W pectin microcapsules by microchannel emulsification. *Colloids Surf. a-Physicochemical Eng. Aspects.* **189**:257–264.

Khalid, N., Kobayashi, I., Neves, M. A., Uemura, K. and Nakajima, M. (2013a). Preparation and characterization of water-in-oil-in-water emulsions containing a high concentration of L-ascorbic acid. *Biosci., Biotechnol. Biochem.* **77**:1171–1178.

Khalid, N., Kobayashi, I., Neves, M. A., Uemura, K. and Nakajima, M. (2013b). Preparation and characterization of water-in-oil emulsions loaded with high concentration of l-ascorbic acid. *LWT - Food Sci. Technol.* **51**:448–454.

Khalid, N., Kobayashi, I., Neves, M. A., Uemura, K., Nakajima, M. and Nabetani, H. (2014a). Formulation of monodisperse water-in-oil emulsions encapsulating calcium ascorbate and ascorbic acid 2-glucoside by microchannel emulsification. *Colloids Surf. a-Physicochemical Eng. Aspects.* **459**:247–253.

Khalid, N., Kobayashi, I., Neves, M. A., Uemura, K., Nakajima, M. and Nabetani, H. (2014b). Monodisperse W/O/W emulsions encapsulating L-ascorbic acid: Insights on their formulation using microchannel emulsification and stability studies. *Colloids Surf. a-Physicochemical Eng. Aspects.* **458**:69–77.

Khalid, N., Kobayashi, I., Neves, M. A., Uemura, K., Nakajima, M. and Nabetani, H. (2015a). Monodisperse aqueous microspheres encapsulating high concentration of l-ascorbic acid: insights of preparation and stability evaluation from straight-through microchannel emulsification. *Biosci., Biotechnol., Biochem.* **79**:1852–1859.

Khalid, N., Kobayashi, I., Neves, M. A., Uemura, K., Nakajima, M. and Nabetani, H. (2015b). Preparation of monodisperse aqueous microspheres containing high concentration of L-ascorbic acid by microchannel emulsification. *J. Microencapsulation.* **32**:570–577.

Khalid, N., Kobayashi, I., Neves, M. A., Uemura, K., Nakajima, M. and Nabetani, H. (2016). Microchannel emulsification study on formulation and stability characterization of monodisperse oil-in-water emulsions encapsulating quercetin. *Food Chem.* **212**:27–34.

Khalid, N., Kobayashi, I., Neves, M. A., Uemura, K., Nakajima, M. and Nabetani, H. (2017). Encapsulation of β-sitosterol plus γ-oryzanol in O/W emulsions: Formulation characteristics and stability evaluation with microchannel emulsification. *Food Bioproducts Process.* **102**:222–232.

Khalid, N., Kobayashi, I., Wang, Z., Neves, M. A., Uemura, K., Nakajima, M. and Nabetani, H. (2015c). Formulation characteristics of triacylglycerol oil-in-water emulsions loaded with ergocalciferol using microchannel emulsification. *Rsc Adv.* **5**:97151–97162.

Khalid, N., Kobayashi, I., Wang, Z., Neves, M. A., Uemura, K., Nakajima, M. and Nabetani, H. (2015d). Formulation of monodisperse oil-in-water emulsions loaded with ergocalciferol and cholecalciferol by microchannel emulsification: insights of production characteristics and stability. *Int. J. Food Sci. Technol.* **50**:1807–1814.

Khan, Y., Panchal, S., Vyas, N., Butani, A. and Kumar, V. (2007). Olea europaea: a phyto-pharmacological review. *Pharmacogn Rev.* **1**:114–118.

Kobayashi, H., Fujita, R., Kuroiwa, T., Nakajima, M., Uemura, K., Sato, S. and Ichikawa, S. (2009a). Flow cytometric analysis and sorting of giant vesicles containing enzyme prepared by lipid-coated ice droplet hydration method. *J. Biosci. Bioeng.* **108**:S73–S74.

Kobayashi, I., Hirose, S., Katoh, T., Zhang, Y., Uemura, K. and Nakajima, M. (2008a). High-aspect-ratio through-hole array microfabricated in a PMMA plate for monodisperse emulsion production. *Microsystem Technol.-Micro- Nanosystems-Inf. Storage Process. Syst.* **14**:1349–1357.

Kobayashi, I., Lou, X. F., Mukataka, S. and Nakajima, M. (2005a). Preparation of monodisperse water-in-oil-in-water emulsions using microfluidization and straight-through microchannel emulsification. *J. Am. Oil Chem. Soc.* **82**:65–71.

Kobayashi, I., Mukataka, S. and Nakajima, M. (2004). CFD simulation and analysis of emulsion droplet formation from straight-through microchannels. *Langmuir.* **20**:9868–9877.

Kobayashi, I., Mukataka, S. and Nakajima, M. (2005b). Novel asymmetric through-hole array microfabricated on a silicon plate for formulating monodisperse emulsions. *Langmuir.* **21**:7629–7632.

Kobayashi, I., Murayama, Y., Kuroiwa, T., Uemura, K. and Nakajima, M. (2009b). Production of monodisperse water-in-oil emulsions consisting of highly uniform droplets using asymmetric straight-through microchannel arrays. *Microfluidics Nanofluidics.* **7**:107–119.

Kobayashi, I. and Nakajima, M. (2002). Effect of emulsifiers on the preparation of food-grade oil-in-water emulsions using a straight-through extrusion filter. *Eur. J. Lipid Sci. Technol.* **104**:720–727.

Kobayashi, I. and Nakajima, M. (2006). Microchannel emulsification technology: Formulation and application of monodisperse emulsions. *J. Japanese Soc. Food Sci. Technol.-Nippon Shokuhin Kagaku Kogaku Kaishi.* **53**:317–326.

Kobayashi, I., Nakajima, M., Chun, K., Kikuchi, Y. and Fukita, H. (2002). Silicon array of elongated through-holes for monodisperse emulsion droplets. *Aiche J.* **48**:1639–1644.

Kobayashi, I., Nakajima, M., Nabetani, H., Kikuchi, Y., Shohno, A. and Satoh, K. (2001). Preparation of micron-scale monodisperse oil-in-water microspheres by microchannel emulsification. *J. Am. Oil Chem. Soc.* **78**:797–802.

Kobayashi, I., Neves, M. A., Wada, Y., Uemura, K. and Nakajima, M. (2012a). Large microchannel emulsification device for mass producing uniformly sized droplets on a liter per hour scale. *Green Process. Synth.* **1**:353–362.

Kobayashi, I., Takano, T., Maeda, R., Wada, Y., Uemura, K. and Nakajima, M. (2008b). Straight-through microchannel devices for generating monodisperse emulsion droplets several microns in size. *Microfluidics Nanofluidics.* **4**:167–177.

Kobayashi, I., Uemura, K. and Nakajima, M. (2006). CFD study of the effect of a fluid flow in a channel on generation of oil-in-water emulsion droplets in straight-through microchannel emulsification. *J. Chem. Eng. Jpn.* **39**:855–863.

Kobayashi, I., Uemura, K. and Nakajima, M. (2007a). CFD analysis of generation of soybean oil-in-water emulsion droplets using rectangular straight-through microchannels. *Food Sci. Technol. Res.* **13**:187–192.

Kobayashi, I., Uemura, K. and Nakajima, M. (2007b). Formulation of monodisperse emulsions using submicron-channel arrays. *Colloids Surf. a-Physicochemical Eng. Aspects.* **296**:285–289.

Kobayashi, I., Vladisavljevic, G. T., Uemura, K. and Nakajima, M. (2011). CFD analysis of microchannel emulsification: Droplet generation process and size effect of asymmetric straight flow-through microchannels. *Chem. Eng. Sci.* **66**:5556–5565.

Kobayashi, I., Wada, Y., Hori, Y., Neves, M. A., Uemura, K. and Nakajima, M. (2012b). Microchannel emulsification using stainless-steel chips: oil droplet generation characteristics. *Chem. Eng. Technol.* **35**:1865–1871.

Kobayashi, I., Wada, Y., Uemura, K. and Nakajima, M. (2010). Microchannel emulsification for mass production of uniform fine droplets: integration of microchannel arrays on a chip. *Microfluidics Nanofluidics.* **8**:255–262.

Kobayashi, I., Zhang, Y., Neves, M. A., Hori, Y., Uemura, K. and Nakajima, M. (2014). Influence of electrolyte concentration on microchannel oil-in-water emulsification using differently charged surfactants. *Colloids Surf. a-Physicochemical Eng. Aspects.* **440**:79–86.

Kuroiwa, T., Fujita, R., Kobayashi, I., Uemura, K., Nakajima, M., Sato, S., Walde, P. and Ichikawa, S. (2012). Efficient preparation of giant vesicles as biomimetic compartment systems with high entrapment yields for biomacromolecules. *Chem. Biodiversity.* **9**:2453–2472.

Kuroiwa, T. and Ichikawa, S. (2008). Efficient preparation of material–encapsulating giant vesicles and their utilization for developing intravesicular microbioreaction systems (In Japanese). *MEMBRANE.* **33**:294–299.

Kuroiwa, T., Kiuchi, H., Noda, K., Kobayashi, I., Nakajima, M., Uemura, K., Sato, S., Mukataka, S. and Ichikawa, S. (2009). Controlled preparation of giant vesicles from uniform water droplets obtained by microchannel emulsification with bilayer-forming lipids as emulsifiers. *Microfluidics Nanofluidics.* **6**:811–821.

Li, Z., Leshansky, A., Pismen, L. and Tabeling, P. (2015). Step-emulsification in a microfluidic device. *Lab Chip.* **15**:1023–1031.

Liu, H. J., Nakajima, M. and Kimura, T. (2004). Production of monodispersed water-in-oil emulsions using polymer microchannels. *J. Am. Oil Chem. Soc.* **81**:705–711.

Liu, H. J., Nakajima, M., Nishi, T. and Kimura, T. (2005). Effect of channel structure on preparation of a water-in-oil emulsion by polymer microchannels. *Eur. J. Lipid Sci. Technol.* **107**:481–487.

Liu, X. Q., Nakajima, M., Nabetani, H., Xu, Q. Y., Ichikawa, S. and Sano, Y. (2001). Stability characteristics of dispersed oil droplets prepared by the microchannel emulsification method. *J. Colloid Interface Sci.* **233**:23–30.

Loftsson, T. and Hreinsdottir, D. (2006). Determination of aqueous solubility by heating and equilibration: a technical note. *AAPS Pharm. Sci. Tech.* **7**:E4.

Lund, J. and DeLuca, H. F. (1966). Biologically active metabolite of vitamin D3 from bone, liver, and blood serum. *J. Lipid Res.* **7**:739–744.

Maan, A. A., Schroen, K. and Boom, R. (2011). Spontaneous droplet formation techniques for monodisperse emulsions preparation - Perspectives for food applications. *J. Food Eng.* **107**:334–346.

Maan, A. A. L., Nazir, A., Khan, M. K. L., Boom, R. and Schroen, K. (2015). Microfluidic emulsification in food processing. *J. Food Eng.* **147**:1–7.

Markman, G. and Livney, Y. D. (2012). Maillard-conjugate based core-shell co-assemblies for nanoencapsulation of hydrophobic nutraceuticals in clear beverages. *Food Funct.* **3**:262–270.

McClements, D. J. (2010). Emulsion design to improve the delivery of functional lipophilic components. *Annu. Rev. Food Sci. Technol.* **1**:241–269.

Moribe, K., Limwikrant, W., Higashi, K. and Yamamoto, K. (2011). Drug nanoparticle formulation using ascorbic Acid derivatives. *J. Drug Deliv.* **2011**.

Mourtzinos, I., Salta, F., Yannakopoulou, K., Chiou, A. and Karathanos, V. T. (2007). Encapsulation of olive leaf extract in beta-cyclodextrin. *J. Agric. Food Chem.* **55**:8088–8094.

Neethirajan, S., Kobayashi, I., Nakajima, M., Wu, D., Nandagopal, S. and Lin, F. (2011). Microfluidics for food, agriculture and biosystems industries. *Lab Chip.* **11**:1574–1586.

Neves, M., Kobayashi, I. and Nakajima, M. (2009). Development of microchannel emulsification technology for monodispersed soybean and olive oil-in water emulsion. *J. Arid Land Stud.* **19**:97–100.

Neves, M. A., Hashemi, J. and Prentice, C. (2015). Development of novel bioactives delivery systems by micro/nanotechnology. *Curr. Opin. Food Sci.* **1**:7–12.

Neves, M. A., Ribeiro, H. S., Fujiu, K. B., Kobayashi, I. and Nakajima, M. (2008a). Formulation of controlled size PUFA-loaded oil-in-water emulsions by microchannel emulsification using beta-carotene-rich palm oil. *Ind. Eng. Chem. Res.* **47**:6405–6411.

Neves, M. A., Ribeiro, H. S., Kobayashi, I. and Nakajima, M. (2008b). Encapsulation of lipophilic bioactive molecules by microchannel emulsification. *Food Biophys.* **3**:126–131.

Pisoschi, A. M. and Pop, A. (2015). The role of antioxidants in the chemistry of oxidative stress: a review. *Eur. J. Med. Chem.* **97**:55–74.

Priest, C., Herminghaus, S. and Seemann, R. (2006). Generation of monodisperse gel emulsions in a microfluidic device. *Appl. Phys. Lett.* **88**:024106.

Purwanti, N., Neves, M. A., Uemura, K., Nakajima, M. and Kobayashi, I. (2015). Stability of monodisperse clove oil droplets prepared by microchannel emulsification. *Colloids Surf. a-Physicochemical Eng. Aspects.* **466**:66–74.

Rosenheim, O. and Webster, T. A. (1928). The specificity of ergosterol as parent substance of vitamin D. *Biochem. J..* **22**:762–766.

Saeki, D., Sugiura, S., Kanamori, T., Sato, S., Mukataka, S. and Ichikawa, S. (2008). Highly productive droplet formation by anisotropic elongation of a thread flow in a microchannel. *Langmuir.* **24**:13809–13813.

Saito, M., Yin, L.-J., Kobayashi, I. and Nakajima, M. (2006). Comparison of stability of bovine serum albumin-stabilized emulsions prepared by microchannel emulsification and homogenization. *Food Hydrocolloids.* **20**:1020–1028.

Saito, M., Yin, L. J., Kobayashi, I. and Nakajima, M. (2005). Preparation characteristics of monodispersed oil-in-water emulsions with large particles stabilized by proteins in straight-through microchannel emulsification. *Food Hydrocolloids.* **19**:745–751.

Santana, R. C., Perrechil, F. A. and Cunha, R. L. (2013). High- and low-energy emulsifications for food applications: a focus on process parameters. *Food Eng. Rev.* **5**:107–122.

Sarfraz, R. A. and Shahid, T. (2015). Biological activity-based assessment of essential oil emulsions. *J. Food Process. Preservation.* **39**:1452–1456.

Seemann, R., Brinkmann, M., Pfohl, T. and Herminghaus, S. (2011). Droplet based microfluidics. *Rep. Prog. Phys.* **75**:016601.

Shah, R. K., Shum, H. C., Rowat, A. C., Lee, D., Agresti, J. J., Utada, A. S., Chu, L.-Y., Kim, J.-W., Fernandez-Nieves, A., Martinez, C. J. and

Weitz, D. A. (2008). Designer emulsions using microfluidics. *Mater. Today.* **11**:18–27.

Shahavi, M. H., Hosseini, M., Jahanshahi, M., Meyer, R. L. and Darzi, G. N. (2015). Evaluation of critical parameters for preparation of stable clove oil nanoemulsion. *Arabian J. Chem.* In Press. doi:10.1016/j.arabjc.2015.1008.1024.

Shahidi, F. and Ambigaipalan, P. (2015). Phenolics and polyphenolics in foods, beverages and spices: antioxidant activity and health effects—a review. *J. Funct. Foods.* **18**:820–897.

Siro, I., Kapolna, E., Kapolna, B. and Lugasi, A. (2008). Functional food. Product development, marketing and consumer acceptance—a review. *Appetite.* **51**:456–467.

Sloan, E. (2002). The top 10 functional food trends. The next generation. *Food Technol.* **56**:32–57.

Souilem, S., Kobayashi, I., Neves, M. A., Jlaiel, L., Isoda, H., Sayadi, S. and Nakajima, M. (2014a). Interfacial characteristics and microchannel emulsification of oleuropein-containing triglyceride oil-water systems. *Food Res. Int.* **62**:467–475.

Souilem, S., Kobayashi, I., Neves, M. A., Sayadi, S., Ichikawa, S. and Nakajima, M. (2014b). Preparation of monodisperse food-grade oleuropein-loaded W/O/W emulsions using microchannel emulsification and evaluation of their storage stability. *Food Bioprocess Technol.* **7**:2014–2027.

Steegmans, M. L., Schroën, K. G. and Boom, R. M. (2009). Characterization of emulsification at flat microchannel Y junctions. *Langmuir.* **25**:3396–3401.

Sugiura, S., Kuroiwa, T., Kagota, T., Nakajima, M., Sato, S., Mukataka, S., Walde, P. and Ichikawa, S. (2008). Novel method for obtaining homogeneous giant vesicles from a monodisperse water-in-oil emulsion prepared with a microfluidic device. *Langmuir.* **24**:4581–4588.

Sugiura, S., Nakajima, M., Iwamoto, S. and Seki, M. (2001a). Interfacial tension driven monodispersed droplet formation from microfabricated channel array. *Langmuir.* **17**:5562–5566.

Sugiura, S., Nakajima, M. and Seki, M. (2001b). Monodispersed droplet formation caused by interfacial tension from microfabricated channel array.

Sugiura, S., Nakajima, M. and Seki, M. (2002). Effect of channel structure on microchannel emulsification. *Langmuir.* **18**:5708–5712.

Sugiura, S., Nakajima, M., Tong, J. H., Nabetani, H. and Seki, M. (2000). Preparation of monodispersed solid lipid microspheres using a microchannel emulsification technique. *J. Colloid Interface Sci.* **227**:95–103.

Sugiura, S., Nakajima, M., Ushijima, H., Yamamoto, K. and Seki, M. (2003). Preparation characteristics of monodispersed water-in-oil emulsions using microchannel emulsification. *J. Chem. Eng. Jpn.* **34**:757–765.

Sugiura, S., Nakajima, M., Yamamoto, K., Iwamoto, S., Oda, T., Satake, M. and Seki, M. (2004). Preparation characteristics of water-in-oil-in-water multiple emulsions using microchannel emulsification. *J. Colloid Interface Sci.* **270**:221–228.

Taylor, P. (1998). Ostwald ripening in emulsions. *Adv. Colloid Interface Sci.* **75**:107–163.

Ushikubo, F. Y., Oliveira, D. R. B., Michelon, M. and Cunha, R. L. (2015). Designing food structure using microfluidics. *Food Eng. Rev.* **7**:393–416.

van der Zwan, E., Schroen, K. and Boom, R. (2009). A geometric model for the dynamics of microchannel emulsification. *Langmuir.* **25**:7320–7327.

van Dijke, K., de Ruiter, R., Schroën, K. and Boom, R. (2010a). The mechanism of droplet formation in microfluidic EDGE systems. *Soft Matter.* **6**:321–330.

van Dijke, K., Kobayashi, I., Schroen, K., Uemura, K., Nakajima, M. and Boom, R. (2010b). Effect of viscosities of dispersed and continuous phases in microchannel oil-in-water emulsification. *Microfluidics Nanofluidics.* **9**:77–85.

van Dijke, K., Veldhuis, G., Schroën, K. and Boom, R. (2009). Parallelized edge-based droplet generation (EDGE) devices. *Lab Chip.* **9**:2824–2830.

van Dijke, K. C., Schroen, K. C. P. G. H. and Boom, R. M. (2008). Microchannel emulsification: From computational fluid dynamics to predictive analytical model. *Langmuir.* **24**:10107–10115.

Vergis, J., Gokulakrishnan, P., Agarwal, R. and Kumar, A. (2015). Essential oils as natural food antimicrobial agents: a review. *Crit. Rev. Food. Sci. Nutr.* **55**:1320–1323.

Vissers, M., Zock, P. and Katan, M. (2004). Bioavailability and antioxidant effects of olive oil phenols in humans: a review. *Eur. J. Clin. Nutr.* **58**:955–965.

Vladisavljevic, G. T., Khalid, N., Neves, M. A., Kuroiwa, T., Nakajima, M., Uemura, K., Ichikawa, S. and Kobayashi, I. (2013). Industrial lab-on-a-chip: Design, applications and scale-up for drug discovery and delivery. *Adv. Drug Deliv. Rev.* **65**:1626–1663.

Vladisavljevic, G. T., Kobayashi, I. and Nakajima, M. (2011). Effect of dispersed phase viscosity on maximum droplet generation frequency in microchannel emulsification using asymmetric straight-through channels. *Microfluidics Nanofluidics.* **10**:1199–1209.

Vladisavljevic, G. T., Kobayashi, I. and Nakajima, M. (2012). Production of uniform droplets using membrane, microchannel and microfluidic emulsification devices. *Microfluidics Nanofluidics.* **13**:151–178.

Wagner, C. L., Hulsey, T. C., Fanning, D., Ebeling, M. and Hollis, B. W. (2006). High-dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: a 6-month follow-up pilot study. *Breastfeed Med.* **1**:59–70.

Wang, Z., Neves, M. A., Kobayashi, I. and Nakajima, M. (2015). Controlling properties of micro- to nano-sized dispersions using emulsification devices. In Nanotechnology and Functional Foods: Effective Delivery of Bioactive Ingredients (Eds. Sabliov, M. C., Chen, H. and Yada, Y. R.), John Wiley & Sons, Ltd, Chichester, UK. doi:10.1002/9781118462157.ch5

Wehking, J. D., Gabany, M., Chew, L. and Kumar, R. (2014). Effects of viscosity, interfacial tension, and flow geometry on droplet formation in a microfluidic T-junction. *Microfluidics Nanofluidics.* **16**:441–453.

Yonekura, L. and Nagao, A. (2007). Intestinal absorption of dietary carotenoids. *Mol. Nutr. Food Res.* **51**:107–115.

Zhang, Y., Kobayashi, I., Neves, M. A., Uemura, K. and Nakajima, M. (2013). Long-term continuous production of soybean oil-in-water emulsions by micro channel emulsification. *Food Sci. Technol. Res.* **19**:995–1001.