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Partitioned EDGE devices for high throughput production of monodisperse emulsion droplets with two distinct sizes

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We present a novel microfluidic EDGE (Edge based Droplet GEneration) device with regularly spaced micron-sized partitions, which is aimed at upscaling of o/w emulsion preparation. By this means, remarkably higher pressure stability was obtained, and two orders of magnitude higher droplet formation frequency was achieved compared to regular EDGE devices. Interestingly, we observed two different monodisperse droplet formation regimes for plateaus that were 2 micrometres in height, and to the best of our knowledge no other microfluidic device has this ability. The average diameters of the droplets were 9 and 28 µm, both with a coefficient of variation (CV) below 5%.

Based on the experimental throughput and a plausible mass parallelization scenario, the amount of hexadecane that can be emulsified is estimated to be between 6 and 25 m³ m⁻² h⁻¹ depending on the required droplet size. With its high throughput potential and ability to produce uniform droplets of two different sizes, the partitioned EDGE device is promising for industrial emulsion production.

Introduction

Emulsions are the basis of many products ranging from food to pharmaceuticals, cosmetics and chemicals amongst others. In general, conventional emulsification technologies can produce emulsions at high throughput but utilize brute force and can degrade heat and shear sensitive formulations. They are highly energy inefficient; energy utilization for droplet formation is reported to be as low as 1-5%, and have poor control over the droplet size and size distribution.

In comparison, microstructured emulsion systems (i.e., membranes and microfluidic devices) are very mild, have outstanding control on droplet size and distribution and offer great potential for the design of new products with unique features and/or functionality. To be complete, we like to mention that microfluidics can also be used to investigate other aspects related to emulsification such as the (dynamic) interfacial tension, which is linked with the droplet size, and emulsion stability.

For emulsion production, most of these microstructured systems, maybe with the exception of membranes, have not been used at large scale. In order for a new emulsification technology to be accepted it needs to be able to handle considerable product flows, and droplet diameters need to be smaller than 10 µm in most applications. Therefore, various efforts have been made to upscale microfluidic devices capable of producing monodisperse emulsions; here we summarize these attempts, and refer the interested reader to some recent reviews for a broader overview.

Shear-based systems (T-, Y- junctions, and flow focusing devices) allow very high frequencies from a single unit, however mass parallelization of these systems is complex due to the necessity of very precise control over both phases at single droplet formation unit level in order to achieve uniform droplet size. Besides, when operating in parallel, cross-talk between neighbouring droplet formation units may occur, in particular for the preparation of droplets smaller than 10 µm in diameter. This greatly influences productivity and droplet monodispersity.

Interfacial tension driven spontaneous emulsification devices (grooved and straight-through microchannels, and EDGE systems) require the control of dispersed phase only, and are relatively easy to scale up through mass parallelization (in spite of their lower frequency per droplet formation unit compared to shear-based systems). Lab scale parallelization of microchannels (MCs) was realized for 10 µm droplets and larger ones up to 300 µm However, preparation of smaller droplets, which requires smaller channels, could not be scaled out that successfully; the percentage of active MCs dropped dramatically and could be as low as few percent. This is a consequence of local pressure differences and consequent interplay between the active and inactive channels, as described earlier by Abrahamse et al. for microsieve emulsification.

The fraction of active pores or microchannels is influenced by a number of factors, such as porosity, channel geometry and dispersed phase viscosity. Reducing the porosity helps to increase the fraction of active pores albeit at the expense of larger sieve areas; alternatively, the devices can be made thicker to improve pore activation, though higher pressures are needed to produce emulsions. Considering the effect of channel geometry, symmetric straight-through oblong MCs outperform the circular ones, but require a minimum aspect ratio of 3 for successful preparation of monodisperse droplets. Moreover, asymmetric straight-through MCs (with a slit connected to a circular channel) outperform the symmetric ones and allow emulsification of low viscosity oils; although, the proportion of active channels is higher for higher dispersed phase viscosity. These authors attributed this to the higher upstream pressure induced by higher viscosity, which is more likely to overcome the capillary pressure; but it could also be explained as an additional resistance against flow in higher viscosity liquids which leads to better pore activation following the argument of Abrahamse and co-workers.

As compared to MCs, microfluidic EDGE systems introduced by the authors’ group are less sensitive to pressure fluctuations due to the inherent geometry of this droplet formation unit, the so-called plateau which is able to produce multiple monodisperse droplets simultaneously. The system was parallelized successfully in
on a chip with 100% efficiency of 196 droplet formation units, which was a promising start. Increasing the number of droplet formation points and overall droplet formation frequency are possible ways to increase the system productivity. This frequency increases with increased pressure stability on the plateau, which can be achieved by imparting extra resistance on the plateau, as was seen by Maan and co-workers for the preparation of o/w and w/o emulsions using semi-metal EDGE systems. They observed fingering behaviour of the dispersed phase flowing on the plateau, which added to the overall resistance and resulted in a wider pressure range. This was an important finding from an operational stability perspective; however, from a productivity point of view, the higher pressure stability was only relevant if it did not reduce the number of droplet formation points.

The best results that were obtained by Maan and colleagues did show an increase in overall productivity, but it also left room for improvement. This inspired us to look into new plateau designs with engineered partitions to distribute and direct the flow on the plateau more evenly aiming at higher number of droplet formation points, and ideally higher droplet formation frequency. We tested this experimentally for the preparation of oil-in-water emulsions with droplets < 10 µm. In particular, we investigated the flow behaviour on the plateau, and the characteristics of droplet formation. In addition, we checked whether the partitioned plateau design is suitable for the emulsification of low viscosity oils (< 1 mPa·s). Finally, the results obtained from partitioned EDGE devices were compared with regular EDGE devices and other spontaneous emulsification systems, from which design suggestions for a large scale device were made.

Experimental

Chemicals

For the preparation of o/w emulsions, MilliQ ultrapure water with 0.5 wt% sodium dodecyl sulphate (SDS, Merck, Hohenbrunn, Germany) was used as continuous phase. As the dispersed phase, hexadecane (C16H34, ReagentPlus®, 99%) from Sigma-Aldrich (Germany) and decane (C10H22, ≥95%) from Fluka (Germany) were used. The viscosity of hexadecane and decane at 20 °C are 3.47 and 0.92 mPa·s, respectively. Unless otherwise mentioned, all experiments were conducted with hexadecane.

Chip design

The EDGE microchips were constructed on glass substrates using deep reactive ion etching (DRIE) technique (Micronit Microfluidics, Enschede, The Netherlands). Figure 1 shows the layout of the microchips used in our experiments: five plateaus (black rectangles) are positioned in between the dispersed phase and continuous phase (meandering) channels.

Fig. 1 The layout of EDGE microchips used, consisting of five shallow plateaus of 2 µm deep (black rectangles) placed between the dispersed and meandering continuous phase channels that are 175 µm deep and 400 µm wide.
Fig. 2 Impression of the regular, EDGE-R (left) and partitioned, EDGE-P (right) microchips and their constituent elements. (a) Channels, 175 µm deep and 400 µm wide, were etched in the bottom plate, (b) plateaus, 2µm deep, were etched in the top plate, after which (c) the bottom and top plates were bonded together. In the figure, the dimensions are not drawn to scale.
**Table 1** Characteristics of (partitioned) plateaus and supply channels.

<table>
<thead>
<tr>
<th>Plateau designs</th>
<th>Number of micro-plateaus [-]</th>
<th>Micro-plateau [L×W×H]</th>
<th>Main plateau [L×W×H]</th>
<th>Channels [W×H]</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDGE-R</td>
<td>0</td>
<td>-</td>
<td>200×500×2</td>
<td>400×175</td>
</tr>
<tr>
<td>EDGE-P</td>
<td>33</td>
<td>30×5×2</td>
<td>200×500×2</td>
<td>400×175</td>
</tr>
</tbody>
</table>

**Peripherals and emulsification procedure**

The microchip was placed in a Fluidic Connect PRO chip holder (Micronit Microfluidics, Enschede, The Netherlands) and all four holes of the chip (inlets and outlets of both phases, see Figure 1) were connected to the outside world through 1/16" OD PEEK tubing with an inner diameter of 0.030". First the continuous phase was fed into the chip through the respective channel, and afterwards the oil was pushed through the dispersed phase channel. When the dispersed phase channel was filled and a steady flow developed, the channel outlet was blocked. By blocking the dispersed phase outlet, oil flowed continuously through the dispersed phase channel onto the plateau and ended up in the continuous phase channel in the form of droplets. For the injection of both phases into the chip, liquids in the respective reservoirs were pressurized through a digital pressure controller (Elveflow®, Paris, France), which was operated by Elveflow® Smart Interface software (Elveflow®, Paris, France). The accuracy of the set pressures was as low as 0.1 mbar. Depending on the dispersed phase pressure, the typical applied pressure for the continuous phase channel was between 1 and 8 mbar, enabling adequate flow inside the channel that removes the generated droplets.

During emulsification, the microchip was placed under a microscope that was equipped with a set of objectives up to 100x, and an optivar with the factors of 1x, 1.6x and 2.5x (Axiovert 200 MAT, Carl Zeiss b.v., Sliedrecht, The Netherlands). The droplet formation process was monitored via a high-speed camera (MotionPro HS-4, IDT Inc., Tallahassee, FL, USA) connected to the microscope. The high-speed camera was able to deliver images at up to 5130 fps at the maximum resolution of 512×512. The combination of frame rate and magnification was limited by the amount of the light reaching the high-speed camera, so the best combination of both was sought. Before acquiring the images, the process was run for 5-10 minutes under the set conditions to ensure a stable operation. The acquired images were then analysed to characterize the droplet formation process.

**Chip cleaning**

Before their first use, chips were placed in a furnace and baked at 550 °C for 2 hours. To clean the chips after use, they were flushed with ethanol first and sonicated for an hour in piranha solution (H₂SO₄ and H₂O₂ solution in 3:1 v/v ratio).

**Droplet size and size distribution**

The size distribution of the droplets was expressed in the form of coefficient of variation, CV, which is defined as:

\[
CV = \frac{\sigma}{d_{dr}} \times 100
\]

where \(\sigma\) is the standard deviation of the droplet diameters and \(d_{dr}\) is the number-average droplet diameter. The droplet diameters were measured using an image analysis software. For the analysis of very monodisperse droplets, 50 droplets were analysed for every determination (i.e., each process condition), which is an established procedure in our lab. For similarly sized droplets, the images were acquired at the same magnification to eliminate measurement errors inherent to pixel distribution.

**Results and discussion**

We premier the characteristics of the EDGE chips with partitioned plateau designs in this work. Among others, we investigated the filling behaviour of the plateaus, pressure stability, number of droplet formation points and frequencies, and eventually compared the overall performance to that of regular plateaus. We round off by discussing an upscaling strategy.

**Visualisation of various droplet formation phases**

1. **Invasion of the plateau and formation of small droplets**

Having launched the experiment as described earlier, the dispersed phase pressure was increased gradually, and the entire droplet formation process was monitored as function of this pressure; Figure 3 shows different stages, from the moment oil invaded the plateau, to monodisperse droplet formation and the inception of blow-up.

The dispersed phase entered the main plateau at 55 mbar, the so-called invasion pressure (Figure 3a). Upon slight increase in the applied pressure, the interface moved ahead evenly on the main plateau and reached the beginning of the micro-plateaus at 60 mbar, leading to complete filling of the main plateau including the far corners (Figure 3b), unlike standard EDGE chips in which this area is not well used, and semi-metal EDGE systems that were not uniformly filled. 25, 26 The reason for complete oil filling of our partitioned plateau, prior to droplet formation from any of the micro-plateaus, was the higher flow resistance in the micro-plateaus compared to the rest of the plateau. The first droplets formed from a few micro-plateaus situated in the middle at 115 mbar, the so-called breakthrough pressure (Figure 3c). Please note that droplet formation takes place at the dark black line; the actual partition walls are a bit longer than the actual plateau for construction reasons. With increasing applied pressure, the number of micro-plateaus generating droplets increased gradually and eventually all became active at 400 mbar (Figure 3d). As expected, upon further increase in pressure, productivity of the micro-plateaus increased significantly (Figure 3e). The produced droplets remained uniform until 1000 mbar, above which blow-up occurred (Figure 3f). At even higher pressures other interesting phenomena occurred that we discuss later, but first we describe the filling behaviour of the plateau in more detail.
Fig. 3 Invasion of the partitioned plateau and droplet formation; (a) Hexadecane entered the plateau, (b) the main plateau was filled further and eventually filled completely with hexadecane, (c) droplet formation started from few micro-plateaus at the dark black line which signifies the change from shallow to deep channel, (d) all micro-plateaus were involved in droplet formation, (e) many monodisperse droplets formed at high frequency below the blow-up pressure, (f) some micro-plateaus blew up above 1000 mbar, resulting in polydispersity.

Figure 4 shows a detailed analysis of the activation of the micro-plateaus as function of the applied pressure on the dispersed phase. When certain micro-plateaus were activated at breakthrough pressure (115 mbar), they remained active while neighbouring micro-plateaus became active at higher pressures. Most probably, the active micro-plateaus created a pressure gradient leading to gradual
activation of all micro-plateaus at 400 mbar. Thereafter all micro-plateaus operated stably until the so-called blow-up pressure was reached at 1000 mbar. The remarkable pressure stability was due to the higher flow resistance induced by the micro-plateaus, which allowed initially non-active micro-plateaus to be activated at higher pressures without blowing up the already active ones. This is also in line with the findings of Gijsbertsen-Abrahamse, et al. who reported that more pores become active with increasing microsieve pore resistance in shear-based emulsification, albeit that the fraction of active pores was very low compared to what is found here. The 100% micro-plateau activation was also much higher as reported for straight-through MCs that produce similar-sized droplets. In addition, when compared to straight-through MCs that require a minimum aspect ratio of 3 for stable monodisperse droplet formation, the micro-plateaus with a markedly lower aspect ratio of 2.5 were capable of producing monodisperse droplets. Unlike straight-through MCs, the micro-plateaus are connected to the oil supply through a wide plateau, and we think that this creates a buffering zone that levels pressure fluctuations, preventing a preferential flow to certain micro-plateaus, therewith leading to stable operation.

**ii. Blow-up and formation of large uniform droplets**

Above the blow-up pressure (1000 mbar), some of the micro-plateaus started producing approximately three times larger droplets (Figure 3f). Additional increase of few hundred mbar in pressure resulted in blow-up of the remaining micro-plateaus but not in continuous outflow of the oil phase, unlike MCs. All micro-plateaus eventually blew up at 1400 mbar, but surprisingly produced equal-sized larger droplets (Figure 5a) for a wide pressure range up till 2100 mbar; neighbouring droplets did not hinder each other, deform or coalesce. At even higher pressures that we investigated (up to 4000 mbar), the droplets became and stayed polydisperse (Figure 5b).

![Fig. 4](image_url) Position of active micro-plateaus as function of applied pressure. The filled symbols on the y-axis indicate the position of micro-plateaus.

![Fig. 5](image_url) Blow-up regime and formation of large uniform droplets: (a) all micro-plateaus blew up at 1400 mbar producing larger uniform droplets until 2100 mbar; droplets on the left side were out of focus, but they were the same size, and (b) uniformity of large droplets was impaired above 2100 mbar.
In literature, the so-called balloon regime was reported by Tarchichi, et al. for droplet formation in T-junctions, where they also found large uniform droplets at low dispersed phase velocities (<6 mms⁻¹). These authors associated this with the structural stability of the growing droplet’s circular shape coupled with the high interfacial tension they used, and suggested that the droplet formation mechanism in the balloon regime is similar to the capillary instability phenomenon. Although our observations may at first glance seem similar to the balloon regime, we believe that these larger uniform droplets were also formed spontaneously by interfacial tension effects. In comparison with the small droplets in the first monodisperse regime, the high applied pressure may have kept the neck from collapsing, thereby allowing the droplet to grow larger before it detached. To elucidate this to some extent, we performed a series of preliminary experiments using different microplateau dimensions and viscosities of both phases. With decreasing viscosity ratio, the droplet size increased as found in the first regime, and as expected in spontaneous droplet formation processes such as MC and EDGE emulsification. At high continuous phase viscosity, the second monodisperse regime was not found. This can be attributed to higher flow resistance for a more viscous continuous phase that needs to invade the plateau area around the neck, in combination with droplet formation points that are so close together that they influence each other, leading to polydispersity. Upon increasing the width of the micro-plateaus, the second monodisperse regime was found as described earlier, indicating that the resistance against flow of the continuous phase does effect the second stable regime, and that also hints at spontaneous droplet formation. We hope to reveal the actual mechanism in a follow-up publication.

**Droplet size (distribution) as function of applied pressure**

Figure 6 shows the effect of applied pressure on droplet size and size distribution for partitioned (6a-b) and regular plateaus (6c-d). As shown in Figure 6a, the diameter of the very first droplets that formed at the breakthrough pressure of 115 mbar was 8 µm; their size only increased very marginally to 8.9 µm at 300 mbar, and remained constant until 800 mbar. The coefficient of variation remained below 3% from breakthrough pressure to 800 mbar. With further increase in pressure, the average droplet diameter increased to 9.2 µm (at 900 mbar) and 9.3 µm (1000 mbar) which also resulted in an increase in the coefficient of variation; please keep in mind that the actual value was still below 5%.

As shown in figure 6c, EDGE devices with regular plateaus had a stable pressure range of 55-115 mbar, which is much narrower as for partitioned devices. The formed droplet diameters were 12 µm leading to a scaling factor of 6 between the droplet diameter and plateau height, as previously reported. When compared to EDGE chips with regular plateaus of the same height, the partitioned EDGE system produced smaller droplets (9 µm), resulting in a scaling factor of 4.5, which would position them at the high end of the spectrum reported for microchannel emulsification (i.e., 2.5-4 times the smallest dimension). It seems that the lower scaling factor compared to regular EDGE is analogous to that of MCs and related to the geometry of the micro-plateaus. We currently investigate this in a follow-up research through variation of the dimensions of the micro-plateaus.
The diameter of large droplets produced from 1400 to 2100 mbar was 28 micrometres, which corresponds to a scaling factor of 14, which is much higher as found for regular plateaus and other microfluidic devices. But it does show that it is possible to have two rather wide pressure ranges in one chip that allow the production of two completely different sized emulsions, and this is a unique feature of the partitioned EDGE chips. Whether that is beneficial is to be seen; some thoughts on the productivity are shared in the last section.

**Pressure stability and system productivity**

Table 2 summarizes the pressure stability and productivity of regular and partitioned plateaus. Compared to regular ones, the partitioned plateau has remarkably wider pressure stability in the first monodisperse droplet formation regime (115-1000 mbar). Also, a similarly wide pressure stability was observed for the second monodisperse droplet formation region obtained at higher pressures (1400-2100 mbar). This increased pressure stability led to significantly improved droplet formation frequencies. At the maximum pressure at which droplets were still monodisperse, a regular plateau of 500 µm wide produced 160 droplets of 12 µm per second, and a partitioned plateau of the same width, with 33 microplateaus, produced about 35000 small and 4500 larger uniform droplets per second. Interestingly, we observed that the droplet formation frequency per micro-plateau did not vary a lot among the micro-plateaus and was almost identical. The average frequency for 9 µm droplets was 1049 Hz with minimum and maximum values of 909 and 1250 Hz, respectively. Similarly, the average frequency for 28 µm droplets was 137 Hz with minimum and maximum values of 9 and 28 µm.

Table 2 Comparison of the pressure stability and productivity of the EDGE devices with regular and partitioned plateaus.

<table>
<thead>
<tr>
<th>Plateau design</th>
<th>Pressure stability [mbar]</th>
<th>Droplet diameter [µm]</th>
<th>Per 500 µm plateau length</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maximum frequency [Hz]</td>
</tr>
<tr>
<td>EDGE-R</td>
<td>55-115</td>
<td>12</td>
<td>160</td>
</tr>
<tr>
<td>EDGE-P [I]</td>
<td>115-1000</td>
<td>9</td>
<td>35000</td>
</tr>
<tr>
<td>EDGE-P [II]</td>
<td>1400-2100</td>
<td>28</td>
<td>4500</td>
</tr>
</tbody>
</table>

The frequency values for the partitioned plateau were calculated from the analysis of randomly selected individual micro-plateaus.

**Process robustness**

The partitioned plateaus were tested for longer times to check whether they are prone to any operational instability that might develop in time. Without any cleaning procedure between the consecutive days, an experiment was run for a week albeit that we only could run during working hours. All micro-plateaus were active and worked regularly at the same frequency reported earlier. This indicates the robustness of the process, which is essential when upscaling a system.

The system was also checked for its ability to disperse low viscosity liquids using decane. As was the case for hexadecane, two stable monodisperse droplet formation regimes were observed, and all micro-plateaus were active. The maintained high micro-plateau efficiency differs from that of straight-through MCs, in which the fraction of active channels decreases with decreasing oil viscosity.

**An upscaling scenario for partitioned EDGE device**

Although various options for upscaling of partitioned EDGE devices have been considered, the best option, in our opinion, would be the sieve design that is shown in Figure 7. The plateaus could be etched in a single plane in such a way that it resembles straight-through MCs or microsieves. This can be realized by two directional etching of the target surface; micro-plateaus can be etched from one surface and the main plateaus can be etched from the other surface.
In this design, we assumed that the distance between the main plateaus is 15 µm as is the distance between neighbouring micro-plateaus on the same plateau. Therefore, the distance between the centres of a micro-plateau and any surrounding micro-plateau would be 15 µm. The micro-plateaus were assumed to have the same dimensions as presented in Table 1 for the microchips used in this work (L×W×H; 30×5×2). According to the micromachining industry experts we consulted, the intended dimensions are realistic and can be achieved using silicon based substrates. These dimensions will result in a surface porosity of 4.4% on the micro-plateau side and 13.2% on the main plateau side, which is reasonable from a mechanical stability perspective. The feeding of the plateaus with oil and the collection of the formed droplets can be arranged through placing the chip into a standard module.

Table 3 shows the amount of oil that theoretically can be emulsified using this device was calculated to be in the order of several cubic meters per hour per square meter device area. We believe that if built, the proposed device can be well suited for large scale emulsification.

Table 3 Calculated productivity of the suggested upscaled EDGE-sieve device with a surface area of 1 m².

<table>
<thead>
<tr>
<th>Oil type</th>
<th>Droplet diameter [µm]</th>
<th>Productivity [m³ h⁻¹]</th>
</tr>
</thead>
<tbody>
<tr>
<td>hexadecane</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>25</td>
</tr>
</tbody>
</table>

* Calculation based on the experiments conducted with hexadecane.

Conclusions

The partitioned EDGE device, has two orders of magnitude higher productivity than the regular EDGE devices. The design has shown a wide pressure stability at 100% micro-plateau activation and high monodispersity, also during long term operation. Interestingly, we found two size ranges in which monodisperse droplets were formed, and this occurred for oils of different viscosities. All in all, the partitioned EDGE device combines high productivity with the advantages of other spontaneous emulsification devices such as high monodispersity and ease of control.

Based on our findings, we proposed a design strategy for a large scale device. The amount of (vegetable) oil that can theoretically be emulsified using this device was calculated to be in the order of several cubic meters per hour per square meter device area. We believe that if built, the proposed device can be well suited for large scale emulsification.

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Notes and references

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