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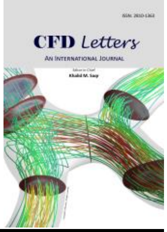

Numerical Investigation of Double Emulsion Droplets using Modified Flow Focusing Microfluidic Device for Drug Delivery

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ABSTRACT

Double emulsion droplets generation is convenient for drug delivery applications since the core-shell template has the ability to increase the success of the target and release of the drug. In this study, the modified flow-focusing microfluidics device is proposed to generate double emulsion droplets with high monodispersity and high throughput, satisfying industrial needs. The W/O/W (water-in-oil-in-water) encapsulation template is a common combination in drug delivery. The research aims to analyze double emulsion droplets generation using the 2D Volume of Fluid (VoF) VoF approach, which is able to visualize flow regime, droplets average diameter, Coefficient of Variation (CoV), and droplets generation rate. Combination of water-in-olive oil-in-water was used as the working fluids. The diameter of the droplets, CoV, and generation rate was obtained using image processing. The simulation results showed that the injection model and the sudden expansion in the modified flow-focusing device successfully produced double emulsion droplets with two dripping instabilities. The narrowing jetting flow regime is obtained, including its droplets evolution. The average diameter for both outer and inner droplets were achieved with their CoV, including the generation rate. The outer and inner droplet's diameter generated can potentially be implemented for drug delivery, although the inner droplet's monodispersity must be further investigated. Nevertheless, the proposed device and the flow control were able to generate high-throughput double emulsion droplets.

1. Introduction

Recently, microfluidic technology has developed rapidly as a multidisciplinary field, attracting many researchers to investigate and expand its functionality. Microfluidics is able to control fluid flow precisely in the microchannel that usually presents in multiphase flow [1]. This technology has been successfully implemented in several fields as follows: lab on a chip [2], drug delivery [3], bio-medical [4], digital polymerase chain reaction (ddPCR) procedure [5], cell sorting [6], food industry [7] and chemical [8]. Although microfluidics plays an essential role in many sectors, the current development of this technology focuses on drug delivery since the world has been impinged by the Covid-19 pandemic for the last two years. Zhuo *et al.,* [3], were able to form double emulsion droplets for drug delivery using two anticancer

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drugs: water-soluble drug as the shell and oil-soluble drug as the core, controlled by a magnetic field. On the other side, according to current Covid-19 issues, microfluidics also has been conducted for Covid-19 study, especially in diagnosing and therapeutics. Ramachandran *et al.,* [9] have studied the SARS-coronavirus 2 (SARS-CoV-2) exposure using rapid detection of 35 minutes after receiving a test sample of raw nasopharyngeal swab using a microfluidic chip. Furthermore, Ramezankhani *et al.,* [10] stated the potential of microfluidic devices for studying SARS CoV-2 and drug development to overcome this issue.

To prepare droplets for drug delivery, choosing a double emulsion template to protect the droplet's core or drug is more convenient. The double emulsion droplets are mainly used due to their capability of encapsulating multiple components simultaneously. Moreover, it can also be used as templates for fabricating microcapsules and microparticles with core-shell structures, especially for pharmaceutical applications [11, 12]. Dao Tong *et al.,* [11] append that double emulsion droplets can be used to encapsulate specific compounds such as nutrient composition, drug, and cell released at a proper condition in these applications. The microfluidic device used to generate droplets will consider the channel-based method since its geometry is more straightforward than the surface-based method. Some devices are mainly developed to produce double emulsions such as T-junction, Co-flowing, and Flow Focusing. Siqueira *et al.,* [13] developed a double T-junction microchannel for generating double emulsion with the use of styrene-in-sodium lauryl sulfate-in-distilled water in their microreactor system. Liu *et al.,* [14] have been successful in generating 5% (*w/w*) glycerol in a water-in-mixed solution of PDMS and silicone oil-in-5% (*w/w*) aqueous of polyvinyl alcohol using a double co-flowing device. Yandrapalli *et al.,* [15] conducted research to produce liposomes using an inner aqueous solution-in-oil phase containing lipids-in-outer-aqueous solution using a double cross-junction. A study by Tan *et al.,* [16] investigated a novel six-way junction as a sub-division of a flow-focusing device for preparing stable double emulsion droplets. This six-way junction is the potential for preparing double emulsion droplets such that Tan *et al.,* device will be adopted as a fundamental idea in developing microfluidic devices for drug delivery which requires very stable droplets in the current research. The six-way junction later in this research will be called a modified flow-focusing microfluidic device.

The flow behavior of microfluidic devices can be investigated through experimental or numerical methods. The numerical CFD (Computational Fluid Dynamics) is a powerful tool to estimate flow in the microchannel [17]. Numerical studies have been applied in many sectors, which can evaluate system performance [18]. Several CFD investigations have been successful in predicting droplet generation. Raad *et al.,* [19] have investigated droplets splitting in branched T-junction using a numerical approach using a two-phase level-set model. Yousofvand *et al.,*[20] implemented Lattice Boltzmann Method (LBM) to analyze double emulsion droplets generation in the novel simultaneous co-flow and flow-focusing device. Liu *et al.,* [14] conducted a numerical investigation using the VOF (Volume of Fluid) model to visualize double emulsion generation in a double co-flowing device. Sattari *et al.,* [21] conducted numerical investigation using VoF-CSF (Continuum Surface Force) model to visualize double emulsion production using dual-coaxial device which combines with DOE (Design of Experiments) to optimize the number of simulation running and Response Surface Methodology to predict the inner and outer droplets. Then, Tan *et al.,* [16] carried out research using the VoF model to predict double emulsion production in their six-way junction. In this study, a modified flow-focusing microfluidic device will utilize injection and sudden expansion geometry to support the break-up mechanism in the double emulsion. Sudden expansion geometry has the ability to delay the break-up mechanism after the second junction, which ensures the inner phase inserting into a double emulsion, as reported by Shin *et al.,* [12] and Tan *et al.,* [16]. Through the utilization of the sudden expansion geometry, it is expected that the size and the monodispersity of the double-emulsion droplets to be controllable.

The VoF modeling is advantageous in giving insight into the multiphase flow phenomenon. However, there are few numerical investigations and study resources in VoF modeling of double emulsion droplets generation, especially in drug delivery applications. This research highlights double emulsion droplets generation using a modified microfluidic device that utilizes VoF modeling in two-phase flow for two-dimensional (2D) analysis. The device utilizes injection and sudden expansion in its geometry. The current study aims to study the double emulsion droplets generation, visualizing flow regime, droplets average diameter, Coefficient of Variation (CoV), and droplets generation rate.

2. Methodology

2.1 Geometrical Model and Material

The microfluidics device utilized in this research is based on the Tan *et al.,* [16] model and further adjusted by adding additional features such as an injection model before the first junction. The injection model ensures that the inner phase can enter the middle phase. Then, the geometry dimension is adjusted for drug delivery implementation, as depicted in Figure 1.

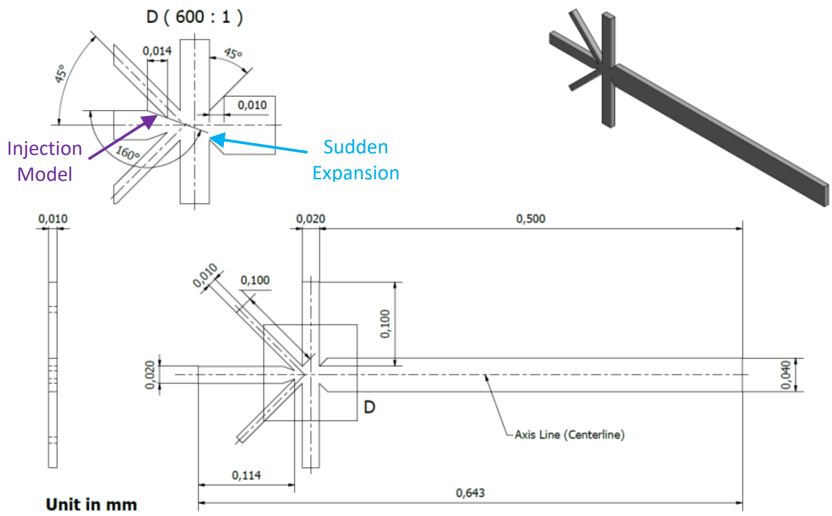

Fig. 1. The modified flow focusing device

The double emulsions consist of three sections: the inner phase, middle phase, and outer phase, which will be used to form a W/O/W (water-in-oil-in-water) template. The working fluids in this study are based on that of Raad *et al.,* [19] since the fluids are suitable for drug delivery. Water is used as the inner phase (core), while olive oil is used as the middle phase (shell). Then, water is also used as the outer phase. Moreover, the fluid properties are available in Table 1.

Table 1
Working fluid properties adopted from Raad *et al.,* [19]

Fluid Properties	Inner Phase	Middle Phase	Outer Phase
	Water	Olive Oil	Water
Density	998.2 kg/m^3	908.9 kg/m^3	998.2 kg/m^3
Dynamic Viscosity	0.00093 Pa s	0.068 Pa s	0.00093 Pa s
Surface Tension	0.02774 N/m		

2.2 Numerical Modeling

This study used a 2D axisymmetric geometry with a double-precision and transient model. As the velocity inside the microchannel was low, the flow can be referred to as laminar. Moreover, the gravitational effect in the fluid flow is negligible, as reported by Liu *et al.,* [14]. The VoF is chosen for multiphase flow modeling since it has the ability to model two or more immiscible fluids by solving a single set of momentum equations and tracking the volume fraction of each fluid throughout the domain [22]. The governing equations in the 2D VoF consist of several equations, namely: conservation of mass (continuity) in Eq. (1) and momentum in Eq. (2) – (3).

$$\frac{\partial \rho}{\partial t} + \rho\left(\frac{\partial u}{\partial x} + \frac{\partial v}{\partial y}\right) = 0 \tag{1}$$

$$\rho\left(\frac{\partial u}{\partial t} + u\frac{\partial u}{\partial x} + v\frac{\partial u}{\partial y}\right) = -\frac{\partial p}{\partial x} + \mu\left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2}\right) + F_{\gamma_x} \tag{2}$$

$$\rho\left(\frac{\partial v}{\partial t} + u\frac{\partial v}{\partial x} + v\frac{\partial v}{\partial y}\right) = -\frac{\partial p}{\partial y} + \mu\left(\frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2}\right) + F_{\gamma_y} \tag{3}$$

Furthermore, the VoF model used volume fractions to capture the interface in the elements or cells. The volume fraction for two-phase flow in this research consists of inner phase volume fraction or outer phase volume fraction ($\alpha_i = \alpha_o$) and middle phase volume fraction ($\alpha_m = 1 - \alpha_i$). The computation method in the cell with a two-phase flow will consider the volume fraction of each phase. The density and the dynamic viscosity in the mass and momentum equation is presented in Eq. (4) and Eq. (5), respectively.

$$\rho = \alpha_i \rho_i + (1 - \alpha_i)\rho_m \tag{4}$$

$$\mu = \alpha_i \mu_i + (1 - \alpha_i)\mu_m \tag{5}$$

A combination of volume fraction α_c ($c = i, m$) is used in the transport equation in 2D VoF modeling, as shown in Eq. (6). Brackbill's continuum surface force (CSF) model is used to obtain the interfacial surface force term (F_γ) at the free surface according to the combined volume fraction [23] as represented in Eq. (7). Moreover, the considered variables presented in the interfacial surface force term are available in Eq. (8) – (9).

$$\frac{\partial \alpha_c}{\partial t} + \frac{\partial (u\alpha_c)}{\partial x} + \frac{\partial (v\alpha_c)}{\partial y} = 0 \tag{6}$$

$$F_\gamma = \gamma \kappa \nabla \alpha_c \tag{7}$$

$$\kappa = \nabla . \hat{n} \tag{8}$$

$$\hat{n} = \frac{\nabla \alpha_c}{|\nabla \alpha_c|} \tag{9}$$

Furthermore, the boundary conditions are given in Table 2, and the scheme is available in Figure 2. The solution methods solve the velocity-pressure coupling by the Coupled scheme with the second-order implicit transient formulation.

Table 2
Boundary conditions

Description	Value
Velocity inlet of the inner phase	0.001 m/s
Velocity inlet of the middle phase	0.003 m/s
Velocity inlet of outer phase	0.009 m/s
Pressure outlet (gauge pressure)	0 Pa
Symmetry axis	Axis
Wall shear condition	No-slip
Contact angle	180°

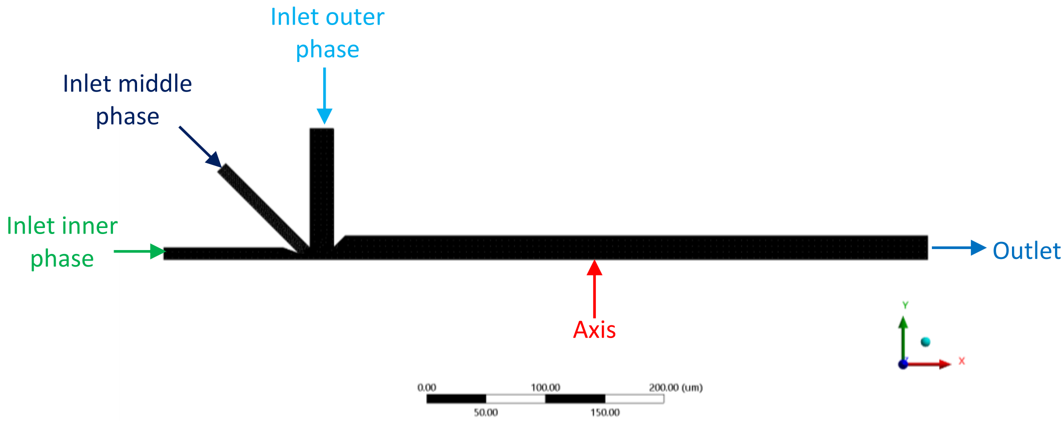

Fig. 2. Scheme of boundary conditions in the pre-CFD process

The numerical investigation is conducted using ANSYS Fluent which the two-phase flow is analyzed utilizing a two-dimensional (2D) mesh. The mesh is treated by wall inflation near the wall region, and it has a 1 µm element size for preliminary analysis. Then, mesh independency analysis is conducted, and the results are available in Fig. 3. Since the mesh with a minimum 1 µm element size and the minimum 0.5 µm element size have the lowest relative error compared to other element sizes, thus 0.5 µm element size with 67,079 nodes and 65,356 elements will be chosen for further simulations. Moreover, the 0.5 µm element size obtained a better visualization of the interface between two-phase when compared to that of the 1 µm element size.

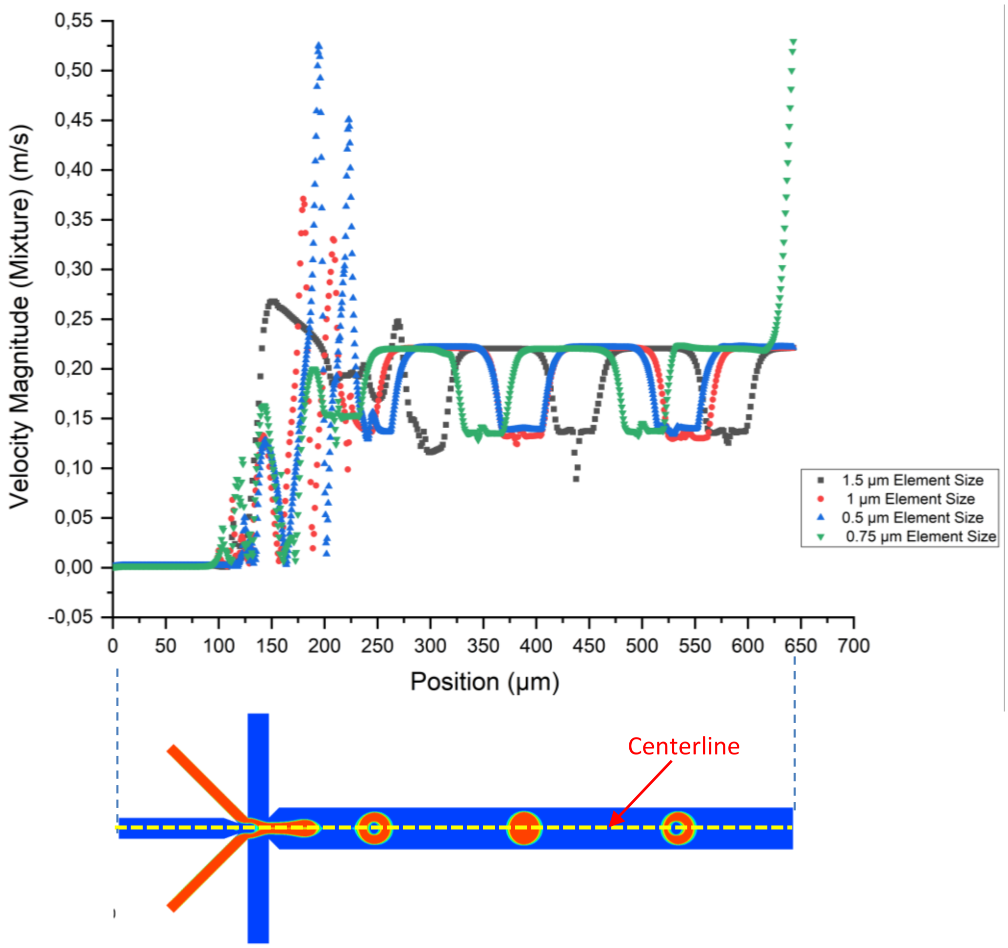

Fig. 3. Mesh independency analysis with the use of velocity magnitude profile along centerline vs. position along the x-axis

2.3 Non-Dimensional Number

Non-dimensional numbers utilized in this study are the Weber number (*We*) and Capillary number (*Ca*). These dimensionless groups were used to analyze the break-up mechanism and can be found in Table 3.

Table 3
Group of dimensionless numbers

Description	Capillary number	Weber number
Inner phase		$We_i = \frac{\rho_i D_{hi} {u_i}^2}{\gamma_{im}}$
Middle phase	$Ca_m = \frac{\mu_m u_m}{\gamma_{im}}$	$We_m = \frac{\rho_m D_{hm} {u_m}^2}{\gamma_{mo}}$
Outer phase	$Ca_o = \frac{\mu_o u_o}{\gamma_{mo}}$	

2.4 Image Processing

To further analyze the simulation results, the droplets diameter, coefficient of variation (CoV), and droplets generation rate are estimated using open-source software, ImageJ. Image data acquisition is conducted using grayscale video obtained from post-CFD results. The video is transformed into image sequences for analyzing the requirement procedure in ImageJ and turned into threshold visualization for the droplets estimation process. These processes are depicted in Figure 4 and Figure 5, respectively.

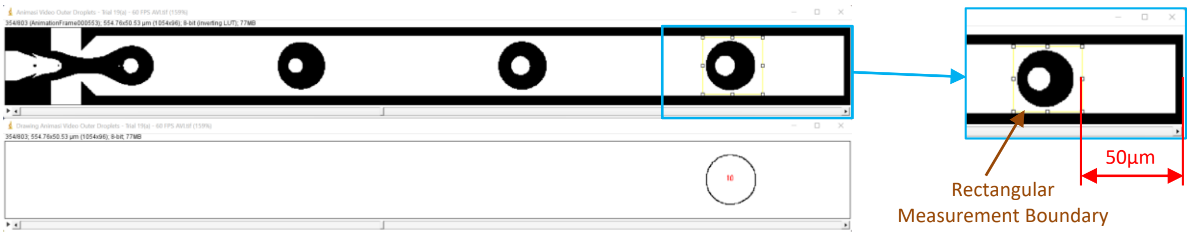

Fig. 4. Outer droplets diameter estimation

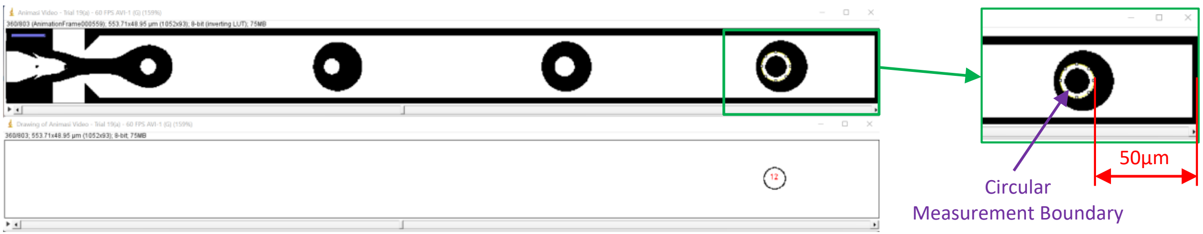

Fig. 5. Inner droplets diameter estimation

The measurement limit for outer and inner droplets is set to 50 µm from the outlet to avoid the effect of outlet boundary conditions. Furthermore, the boundary for the two cases is then determined according to the biggest droplets measured from the image sequence. Thus, the droplets diameter and the droplets generation rate of the recorded image sequence can be acquired.

3. Results and Discussion

3.1 CFD Simulation Results

The modified flow-focusing microfluidics device was able to generate double emulsion by adjusting the flow rate of the inner, middle, and outer phases appropriately. The flow rate of the phases was as follows: 0.72 µL/h for the inner phase, 2.16 µL/h for the middle phase, and 12.96 µL/h for the outer phase. These flow rate combinations are implemented in this study to evaluate the microfluidic device's ability to generate double emulsion droplets. Furthermore, the CFD simulation result for the evolution of the droplet-based on oil (olive oil) volume fraction is depicted in Figure 6, while the pressure distribution in droplet generation is available in Figure 7.

Figure 6 represents the time-series image of droplet generation in the modified flow-focusing device, which has a narrow jetting flow regime after the second junction. The phenomenon is caused by the effects of *Ca* and *We* which the *Ca* represents the shear force of the continuous phase acting on the dispersed phase to induce a break-up mechanism in relation to interfacial tension [24]. Moreover, the *We* represents the inertial force that pushes the dispersed phase in relation to its surface tension [24].

Furthermore, Figure 6 shows two dripping instabilities in double emulsion droplets generation since the generation is started by inner droplets after the first junction and then outer droplets after the second junction. The first dripping instability occurs when We_i and Ca_m are lower than 1 at the first junction. The second dripping instability happens when both or either We_m and Ca_o are lower than 1 at the second junction. As the narrowing jetting occurs after the second junction, the inertial force is more dominant than the shear force before the break-up mechanism occurs. The phenomenon in current research has good agreement with the previous research conducted by Utada *et al.,* [25], Nabavi *et al.,* [23] and Seiffert and Thiele [24].

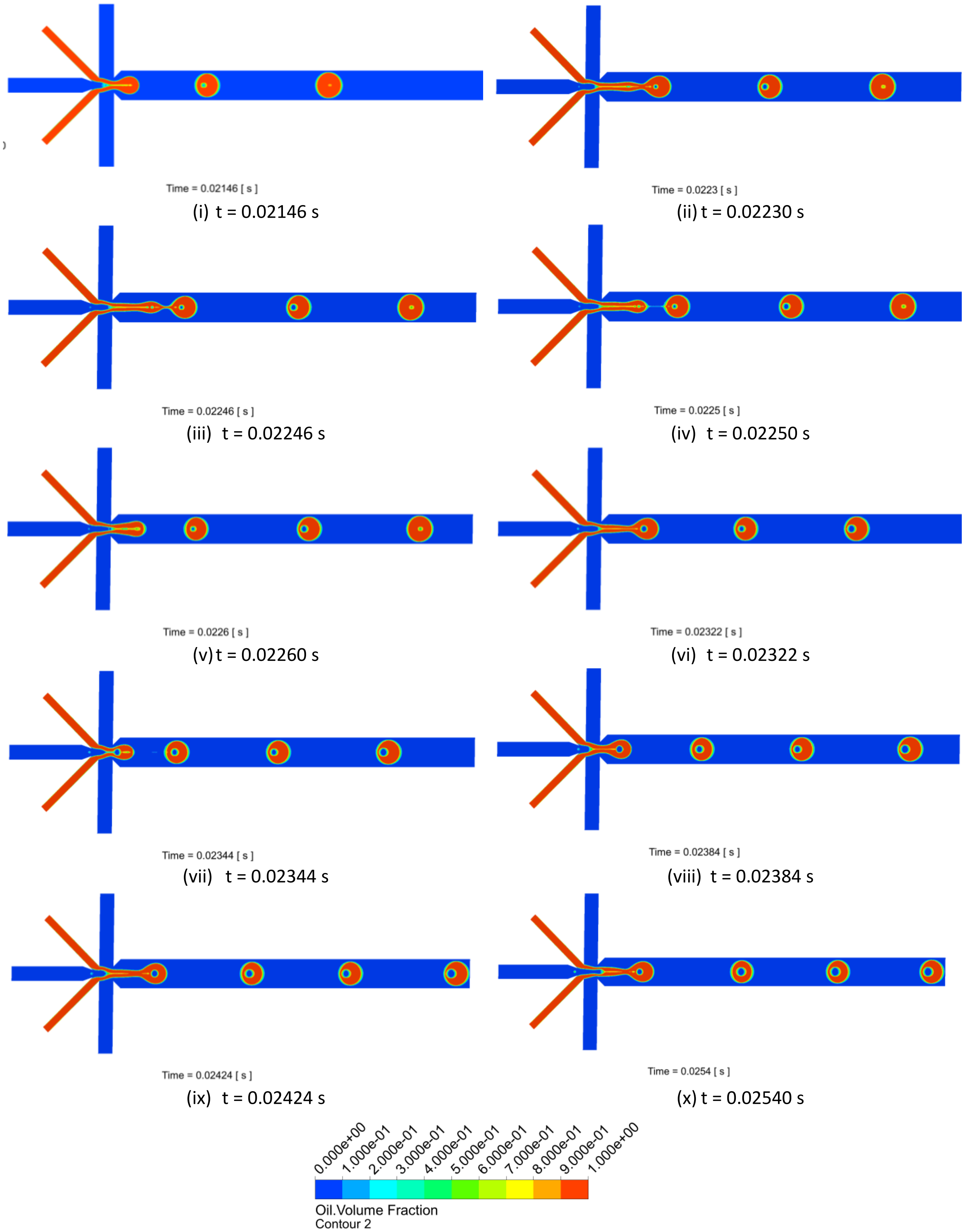

Fig. 6. Droplets evolution based on olive oil volume fraction

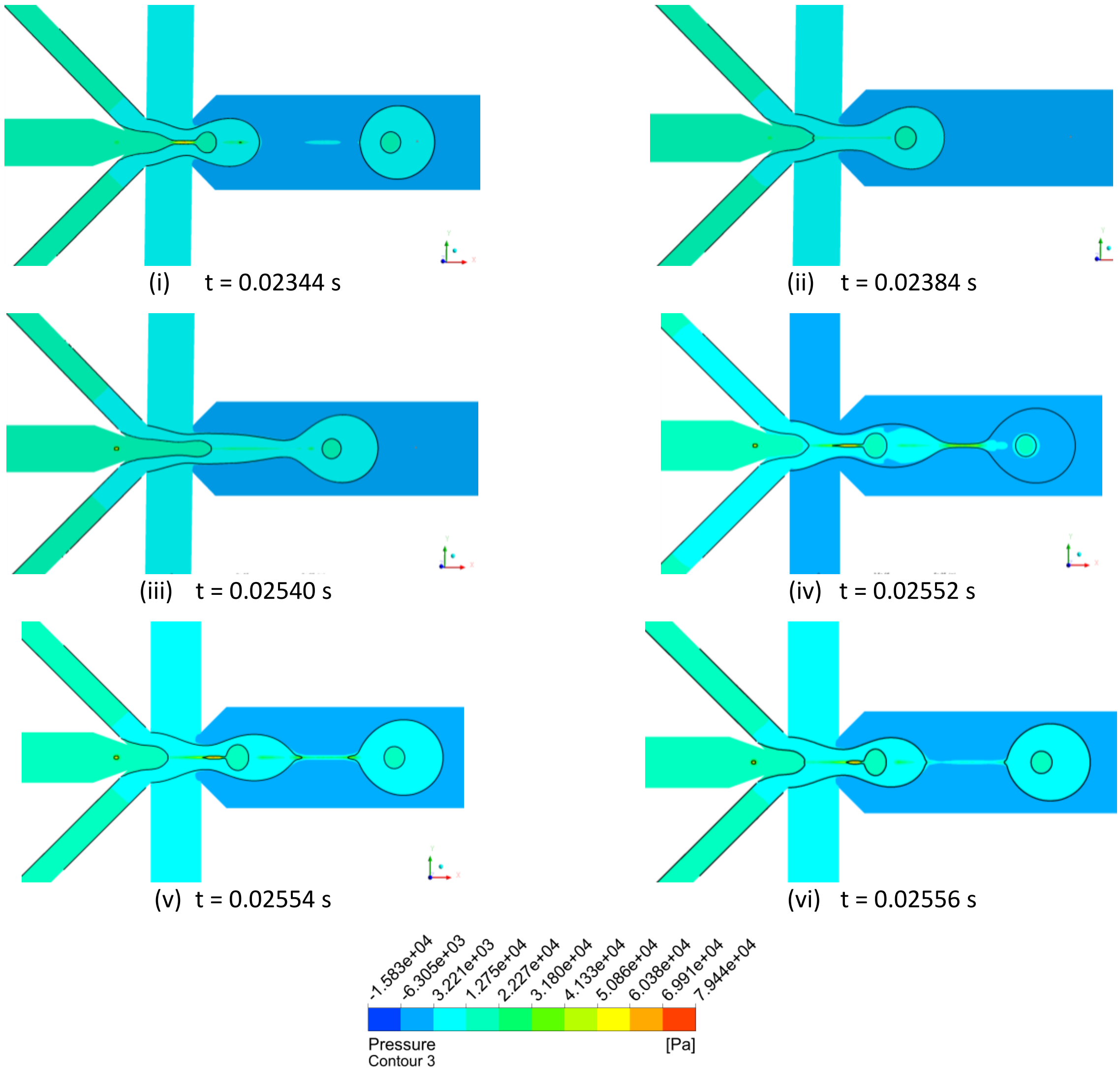

Fig. 7. Pressure contour on droplets evolution at the junction

Furthermore, the pressure distribution in Figure 7 visualizes the pressure dominated in the double emulsion droplets formation. Figure 7(i) shows the pressure rise at the inner droplets since both the inner phase and middle phase block the channel and cause the inner droplets to pinch off from their rear thread after exceeding the respective interfacial tension. Then, the next step is the middle phase flow containing inner droplets that will decelerate after passing sudden expansion in Figure 7(ii) which the middle phase develops into a bigger size to ensure the shell can be formed properly for encapsulating the inner phase. The combination of the adjacent two junctions and the sudden expansion can form the double emulsion droplets with exact timing. Figure 7(iii) indicates the narrowing jetting formation in which the break-up mechanism is started slightly downstream in Figure 7(iv). The rear tip of the double emulsion propagates into the main double emulsion droplets after the break-up mechanism in Figure 7(v) and will be stable in Figure 7(vi).

3.2 Microfluidics Device Assessment

The assessment of device performance can be considered from the droplets generation samples obtained from the image processing. The estimation results and statistical analysis of the outer droplets and the inner droplets are shown in Table 4.

Table 4
Measurements results of the outer droplets and the inner droplets

Measurements Description	Outer Droplets	Inner Droplets
Average droplet diameter	32.736 µm	12.765 µm
Coefficient of Variation (CoV)	2.242%	10.404%
Droplets generation rate	978.995 Hz	857.843 Hz

The average diameter for outer droplets is still capable of a shell for encapsulating the inner droplets since the diameter is close to 30 µm. Then, the inner droplets as the core of drug delivery have an average droplet diameter of around 10 µm which is suitable for preparing the drug. Furthermore, the outer droplets' CoV is acceptable when the variation is still lower than 5%. On the other hand, the CoV of the inner droplets is about 10%, which implies that the variation is still large enough. However, the droplet generation rate for the outer and inner droplets represents that the high-throughput droplets generation is successfully achieved. Thus, the design of the microfluidic device and the combination of inner phase, middle phase, and outer phase flow rate proposed are potential for further developments, and it can be used as a reference for generating double emulsion droplets for drug delivery applications.

4. Conclusion

The VOF modeling in this numerical investigation has successfully been implemented to analyze the phenomenon in the double emulsion droplets generation for drug delivery application. The flow rate combination of the inner, middle, and outer phases in the amount of 0.72 µL/h, 2.16 µL/h, and 12.96 µL/h, respectively, can produce double emulsion droplets in the narrowing jetting regime. The current flow control in the modified flow-focusing device was able to obtain high-throughput droplets generation. The analyzed flow rates result in 32.736 µm outer droplets diameter and 12.765 µm inner droplets diameter, which are potential for drug delivery application. Thus, the modified flow-focusing device can be implemented for this application.

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