Quantitative Modeling of Oil-in-Water Microemulsion for Assay and Therapy in Aerospace Medicine

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ABSTRACT

The miniaturization of biological and chemical processes is generally believed to be useful in designing airspace medicine recently. Like a lab-on-a-chip, a microchip performing multiphase material synthesis operations with integrated transducers leads to a wide use of microfluidics, creating the controllability of investigation in mass transport process that becomes more and more crucial along with increasing demand for microfluidic designs with low pressure drop. This study presents a quantitative analysis of an oil-in-water (O/W) microemulsion flow in a microfluidic T-junction for improving its formation mechanism. The experiment is based on an adjustment of flow rates that forms O/W microemulsions with different constituent ratios, resulting in changes of flow patterns. In response to the pressure drops, demonstrated periodic fluctuations are consistently shown and deeply related to the regularity of microemulsion dynamics. The response surface methodology (RSM) introduced in the modeling of microemulsion formations demonstrates well predicted results with measurement. Accordingly, the microemulsion quality and quantity can be precisely controlled by inspecting the flow properties.

Keywords: Microemulsion, Microfluidic, Resonance, Pressure drop, Response surface methodology

應用於航太醫療之水油微型乳液定量模型研究

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摘　　要

微型生醫元件適用於航太醫學檢測與治療，故藉由整合多種感測裝置於單一晶片，發展微流體量化技術已是研究趨勢。在高度侷限環境中，微流體可控機制及其靈敏度對於醫療效率提升尤其重要。鑒此，本研究旨在發展可精確操控微流體之量化模型，提供合理可行之水油混合微型乳液操作依據，進以藉由設計參數改善其成型機理。經分析，流量造成乳液不同成分比，導致流譜與壓降改變，且其成型品質與流場規律性密切相關，證明模型可用性。

關鍵詞：微型乳液，共振，壓降，響應曲面法

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I. INTRODUCTION

Medical detection of nucleic acids using polymerase chain reaction (PCR) takes lots of time to frame the reactions and obtain the results from a purified product [1-2]. This time-consuming process is unsuitable for public use, especially in high mobility or long-term transportation. The point is that at a lab-scale of submilliliter reaction volumes, PCR assays are not available for laboratories without professional facilities and human resources. In the light of this, novel methods in biomedical tests have been completely self-contained, minimize, portable, single-use, or rule out sample preparation, and were complete instantly due to tiny reaction sizes are in development [3]. To airspace medical application, the above-mentioned revolutions using micro-and nano-technology improved the physical test by: 1) obtaining accurate assay of the physical condition of a pilot; 2) confirming the harmful gene mutations that affect the efficacy of prescription drugs; 3) accurate assessment of the adaptation status of aviation professionals on duty, and; 4)testing for toxic substances in the cabin environment. As a group, these assays are often referred to as lab-on-a-chip [4-6].

Versatile designs of microchannel system have been developed for micromedical applications. Determining the therapeutic target, a suitable medicine with specific formation and delivery should be prudently designed. Micromedicines were often consistently quantitatized and used for long-term therapies [7-8]. The purpose of drug delivery is to ensure that the therapeutic molecule reaches the target organ or tissue, such that the effectiveness of the drug is maximized. Basically, the efficiency of a drug delivery system depends on the design of carrier. Micro- and nanofibers have been increasingly used for this purpose [9-11]. Reasons for increasing interest include simplification of manufacture, the large surface area to volume ratio of micro- and nanofibers, well mechanical properties, and ideal drug release profiles. To reach the therapeutic target, a micro sized-medicine must make its way into the blood vessels and across the vessel wall into the interstitium and finally migrate through the interstitium. A precisely quantitative technique is the key to development of micro fluidic devices for the medicine delivery. Due to the specific ratio of medicines, microemulsions with different phases are often used as mediums. Through complicated processes of assembling, different types of medical emulsions are formed. Emulsions consist of small liquid droplets evenly immersed in another liquid, typically oil in water or water in oil [12-13]. When the shear stress from the continuous phase is large enough to affect momentum, it leads to the interfacial instability of the forefront portion of coming liquid stream to be dispersed.

Microchannels have great potential in intensification of flow reactions, which has been validated by using such as mixing or convergence of multi-phase flow. To illustrate the performance of emulsion formation, one often uses liquid–oil system to investigate the hydrodynamics and mass transfer of such systems in a microchannel with T-junctions [14-16]. Through the channel design, segmented flows are formed with inlet sequences and the size law of the dispersed phase is obtained. The mechanism responsible for the formation of dispersed oil/water droplets is identified, including squeeze by the oil phase and cut by interface between water–oil/gas–oil phases [17-19].

In this study, a quantitive investigation based on the response surface methodology (RSM) is used to investigate into the effects of design variables for forming emulsions. The RSM is associated with the regression analysis and the statistical design of experiments for constructing the total optimization [20-22]. Based on RSM approach, the cause-and-effect relationship can be determined and represented between true mean responses and input control variables influencing the responses as a two or three dimensional hyper surface. This, the interactions of design variables such as input flow rate, total pressure drop, and formation period can be established as polynomials by means of RSM analysis. When transferring the formation period into frequency domain, the quality of of emulsions was determined. Thus, a better volume control in slug flow of a microfluid can be obtained through analyzing the effect of design variables.

II. GOVERNING EQUATIONS FOR A O/W MICROEMULSION FLOW

The governing equations used at interface of disperse and continuous phases consist of a continuity equation, a momentum transport equation, and a level set equation for the advection of the level set function ϕ [23].

$$\nabla \cdot u = 0 \tag{1}$$

$$\rho \frac{\partial u}{\partial t} + \rho(u \cdot \nabla)u = \nabla \cdot \left(-pI + \mu\left(\nabla u + (\nabla u)^T\right)\right) + f_{st}$$

, where $f_{st} = -\sigma(\nabla \cdot n)\delta n$ (2)

$$\frac{\partial \phi}{\partial t} + u \cdot \nabla \phi = \gamma \nabla \cdot \left(-\phi(1-\phi)\frac{\nabla \phi}{|\nabla \phi|} + \varepsilon \nabla \phi\right) \tag{3}$$

where ρ is the density, u is the velocity, t is time, μ is the dynamic viscosity, p is the pressure, and f_{st} the surface tension force. Furthermore, ϕ is the level set function, and γ and ε are stabilization variables. For the formation of emulsions, the continuous phase commonly consists of oils or water-immiscible organic solvents, which tends to be naturally more viscous than water. The density and viscosity of emulsion can be calculated by

$$\rho = \rho_w + (\rho_o - \rho_w)\phi \tag{4}$$

$$\mu = \mu_w + (\mu_o - \mu_w)\phi \tag{5}$$

where the subscripts *o* and *w* represent oil and water phase solutions, respectively.

III. EXPERIMENTAL

A schematic diagram of the experiment setup is shown in Fig. 1. The T-junction was fabricated on a polydimethylsiloxane (PDMS) chip using soft lithography technology [24]. In the T-junction configuration, the inlet channel B containing the dispersed phase perpendicularly intersects the main channel which contains the continuous phase. The dispersed phase, a water phase solution, used was DI water, and the continuous phase, an oil phase solution, used was glycerol (SD Tech Co., Ltd., Taiwan). The physical properties of these two phases are listed in Table 1.

The aspect ratio of inlet and main channels are 0.5 (100 μm/200 μm), Tween 20 was used as the addition to change the PDMS surface into an oleophobic surface, and the wettability of the modified surface was determined by a contact angle measuring instrument (FTA1000B Class, First Ten Angstroms, Inc. Canada). Two differential pressure transmitters (XCS-062-10D, Kulite, France) with ± 0.17% uncertainty set at both ends of main channel were used to measure the pressure variations with a sampling rate of 100 Hz. Thus, the total pressure drop of the main channel can be derived by

$$\nabla P = P_i - P_o \tag{6}$$

where the subscript "*i*" and "*o*" represent inlet and outlet, respectively. A dimensionless variable for discussion of the variation of pressure with flow rates can then be represented as

$$\nabla P^* = \frac{P_t - P_o}{P_i - P_o} \tag{7}$$

where the subscript "*t*" represents any time during the measurements, and the superscript "*" represents normalization, a transient value normalized by the maximum value of variations.

Two syringe pumps (YSP-301, YMC Co., Ltd., Taiwan) were used to control the flow rates filled into channels, 30μl/hr for inlet A and ranged from 10 ~ 150 μl/hr for inlet B. Here, the flow rate of dispersed phase, Q_B, was only adjusted for changing the flow pattern of emulsion at a constant continuous phase.

The process of emulsion fromation was observed by a CCD camera (C8000-30, Hamamatsu Photonics, Japan).

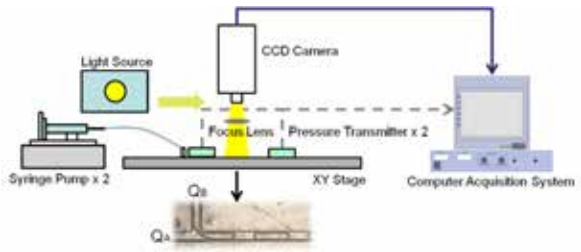

Fig.1. Schematic of experimental setup.

Table 1 Physical properties of test fluids.

property (25 °C, 100 kPa)	water	glycerol
density (kg/m^3)	1000	1261.6
viscosity (Pa·s)	8.9×10^{-4}	0.945
surface tension (N/m)	7.275×10^{-2}	6.33×10^{-2}

IV. METHODOLOGY

The thorough understanding of the internal hydrodynamic phenomena is an essential prerequisite resulting in formulating the mathematical models describing the formation of emulsions. In the emulsion flow, there exist multiple variables that influence its forming quality, like channel geometry, fluid properties, flow rate, pressure drop etc. These variables coupled each other to change the flow pattern and compounding ratio, but it is rare to find a combination of which to manipulate the quality and quantity of emulsions. Thus, the issue of a mathematical modeling of emulsion formation has to be dealt with only after experimental measurements were conducted.

The response surface methodology (RSM) based on statistics is introduced into this modeling strategy. A response surface used represents the relationships between the design variables u_i and the response y. This relationship can be presented by

$$y = F\left(u_1, u_2, \cdots u_n\right) + \varepsilon, \tag{8}$$

where ε is an error term. If the function F is a polynomial 1 that exactly describes the physical process being modeled, ε may be considered to represent random errors from experimental noises. In this study, the function F is normally a quadratic form of polynomial with n design variables can be written as

$$y = p_0 + \sum_{i=1}^{n} p_i u_i + \sum_{i=1, j\geq i}^{n} p_{ij} u_i u_j + \varepsilon, \tag{9}$$

where p are unknown coefficients. For employing two variables, the response surface is expressed as

$$y = p_0 + p_1 u_1 + p_2 u_2 + p_3 u_1^2 + p_4 u_2^2 + p_5 u_1 u_2 + \varepsilon, \tag{10}$$

To begin with linear terms (i.e. $u_3 = u_1^2$, $u_4 = u_2^2$, and $u_5 = u_1 u_2$) by replacing the quadratic terms, then Eq. (10) can be expressed as

$$y = p_0 + p_1 u_1 + p_2 u_2 + p_3 u_3 + p_4 u_4 + p_5 u_5 + \varepsilon, \tag{11}$$

The coefficients in Eq. (11) are estimated by a linear multiple regression which can be rewritten in a matrix form as

$$Y = UP + E, \tag{12}$$

where $Y = \begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{bmatrix}$, $U = \begin{bmatrix} 1 & u_{11} & u_{12} & \cdots u_{1k} \\ 1 & u_{21} & u_{22} & \cdots u_{2k} \\ \vdots & \vdots & \vdots & \ddots \vdots \\ 1 & u_{n1} & u_{n2} & \cdots u_{nk} \end{bmatrix}$, $P = \begin{bmatrix} p_1 \\ p_2 \\ \vdots \\ p_k \end{bmatrix}$,

and $E = \begin{bmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \vdots \\ \varepsilon_n \end{bmatrix}$, (13)

The unbiased estimator b of the coefficient vector P is obtained through the least square error method as

$$b = \left(U^T U\right)^{-1} U^T Y, \tag{14}$$

The variance–covariance matrix of b is obtained by

$$\operatorname{cov}\left(b_i, b_j\right) = C_{ij} = \sigma^2 \left(U^T X\right)^{-1} \tag{15}$$

where σ is the error of Y. The estimated value of σ is

$$\sigma^2 = \frac{SS_E}{n - k - 1}, \tag{16}$$

where SS_E is the squared sum of errors expressed as

$$SS_E = Y^T Y - b^T U^T Y, \tag{17}$$

The adjusted coefficient of multiple determinations R_{adj}^2 (R-square-adjusted) is used to evaluate the performance of the approximation of the response surface as

$$R_{adj}^2 = 1 - \frac{SS_E / \left(n - k - 1\right)}{S_{yy}\left(n - 1\right)}, \tag{18}$$

where S_{yy} is the sum of squares. It is calculated by

$$S_{yy} = Y^T Y - \frac{\left(\sum_{i=1}^{n} y_i\right)^2}{n} \tag{19}$$

In the modeling, each coefficient of the response surface can be tested using the t-statistic. The t-statistic of the coefficient b_j is

$$t_0 = \frac{b_j}{\sqrt{\sigma^2 C_{jj}}}, \tag{20}$$

where C_{jj} is the element of number jj of the variance–covariance matrix of Eq. (15).

The RSM uses quantitative data from the related experiment to determine regression model and to optimize a response which is influenced by several independent variables. In our experimental set-up, $Q_{B/A}$ and $V_{B/A}$ were

considered as the control variables, and both of which were respectively set 5 changes. Thus, a total of 25 responses were obtained. By the modeling procedures, the causality between variables and target performance (i.e. response) were precisely built as a polynomial. In addition, The response model is validated by the deviation analysis [25], defined as measurement of the absolute difference between any one number in a set and the mean of the set. Here, the deviation is evaluated by the correlation of predicted and measured results.

V. RESULTS AND DISCUSSION

From the observation on flow patterns with different fill conditions, there are four main processes in emulsion formation can be categorized, including penetrating, blocking, squeezing, and breakup (Fig. 2). When these two phases form an interface at the junction, the tip of the dispersed phase enters the main channel. It entails that the shear forces generated by the continuous phase and the subsequent pressure gradient cause the head of the dispersed phase to elongate into the main channel until the neck of the dispersed phase thins and eventually breaks the stream into a droplet.

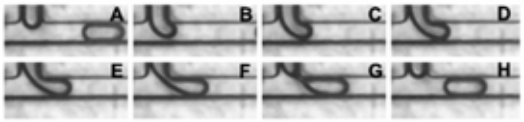

Fig.2. Flow patterns of droplet formation in a T-junction. These sequences illustrate (A) the dispersed phase penetrates into the main channel and (B - D) it gradually blocks the channel. Then, (E - F) the emerging droplet elongates downstream into the main channel and (G - H) finally separates from the inlet stream.

To quantify the fractions of phases in emulsion, a flow rate of dispersed phase, Q_B, was adjusted for changing the formation of emulsion at a constant continuous phase. Fig. 3 shows the droplet size was changed by altering Q_B, causing the fraction of dispersed phase in the O/W micro-emulsion flow was also changed. The breakup of dispersed phase was expanded and the droplet sizes are elongated with flow rate ratios of dispersed phase to continuous phase ($Q_{B/A}$). In this figure, L_c is the mean length of the combination of dispersed and continuous phases, and L_d is the mean length of the dispersed phase droplet size. The experiment indicates L_d increases in proportion to $Q_{B/A}$, an index of fill conditions, which can be designed as a quantified control used in fabrication of O/W micro emulsions. Moreover, the volume fraction of dispersed phase in emulsion ($V_{B/A} = L_d/L_c$) can also be regarded as a quantitative control used in fabrication of emulsions.

It is difficult to analyze its physical properties and related dimensionless variables for a chaotic system of this microfluidic design through the conventional methods including numerical solution and semi-empirical model. Thus, the RSM was used to model the relationship between variables and the responses. In this study, three variables were used to build a practical model for quantitative prediction of emulsion: $\overline{\nabla P^*}$, $Q_{B/A}$, and f.

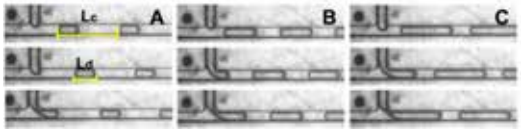

Fig.3. Comparisons of dispersed phase droplets in a micro-emulsion flow at different fill conditions: (A) $Q_{B/A} = 0.33$, (B) $Q_{B/A} = 1.67$, and (C) $Q_{B/A} = 2.67$.

With increasing $Q_{B/A}$, droplet sizes were increased. $V_{B/A}$ also increased with $Q_{B/A}$ and followed an increasing trend, shown in Fig. 4. A saturated value of $V_{B/A}$ can be found around 0.69~0.70 at a $Q_{B/A}$ ranging from 2.00 to 2.67, where the fraction of dispersed phase was tiny affected by $Q_{B/A}$. When $Q_{B/A}$ up to 3.00, a distinct value of $V_{B/A}$ prompt to 0.85, showing the emulsion slug achieves the critical forming condition.

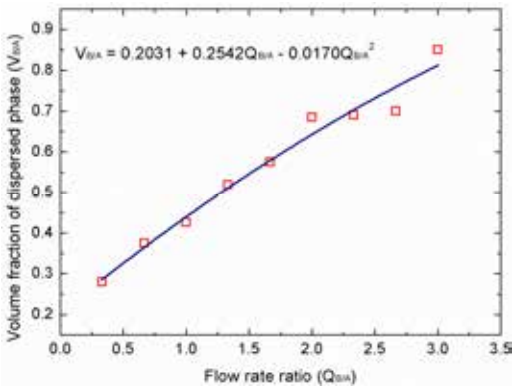

Fig.4. Volume fractions of dispersed phase in a micro-emulsion flow at different fill conditions.

Pressure drop occurs when frictional forces, caused by the resistance to flow, act on the fluid as it flows through the microchannel. Because pressure drop deeply affects the flow dynamics in a microchannel, it can be used to evaluate the formation of emulsion. The main determinants of resistance to fluid flow are fluid velocity through the channel and fluid viscosity. Pressure drop increases proportionally with the frictional shear forces within the flow and channel wall. It indicates high flow velocities or high fluid viscosities could result in a larger pressure drop across the channel. Because the emulsion forms periodically, the flow fluctuates following a similar trend. The mean value of normalized pressure drop, $\overline{\nabla P^*}$, is regarded as an index for emulsion formation. Fig. 5 shows the variation of pressure drops with different fill conditions, where two slow variation trends can be found as the ratio at 0.333-0.667 and 2.0-2.75. Noted that when $Q_{B/A}$ achieves 3.0, an obvious large pressure drop of 0.876 can be measured. This indicates the total flow rate of phases causes high flow frustrations and would lead imprecisely emulsion formation.

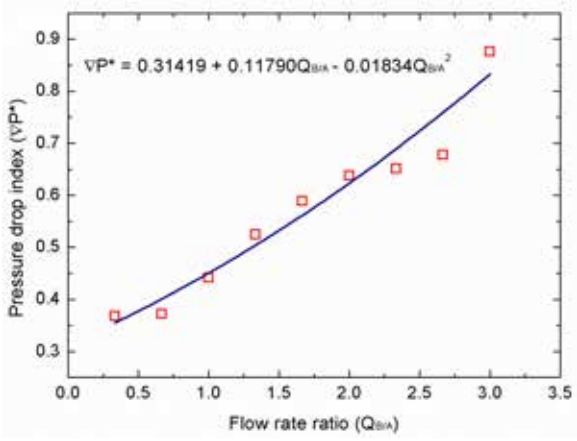

Fig.5. Pressure drops of a micro-emulsion flow in the main channel at different fill conditions.

Corresponding to the measurement of pressure drops, demonstrated periodic fluctuations are consistently appeared and deeply related to the regularity of emulsion dynamics. Thus, the emulsion quality can be controlled by inspecting the flow resonances. Fig. 6 shows the transient $\overline{\nabla P^*}$ of a micro-emulsion flow in the main channel at different $Q_{B/A}$. It is shown that the range of the pressure drop fluctuates during the formation process of emulsion. Moreover, these quasi-periodic fluctuations can be corresponded to the formation time of emulsions, implying the emulsion is formed regularly while the volume fractions of phases in emulsion is kept constant. The fluctuation periods for these fill conditions can be measured from 0.11 to 0.42 s. (Fig. 7), and then the formation frequency (F) of emulsion can be obtained.

When the emulsion volume, formation period, and flow pressure drop were modelled by experimental data as a function of flow rate ratio, well quality of emulsions can then be quantifiably controlled. The formation frequency of emulsions can be derived from the formation period and modeled by the normalized variables (i.e. $V_{B/A}$, Q*) for general use, fitted with a 2nd-order polynomial as

$$F=10.743-3.643Q^*-8.486V_{B/A}+3.862\ Q^*V_{B/A} \quad (21)$$

where F represents the formation frequency of emulsion, Q* is the ratio of $Q_{B/A}$/ $Q_{B/A,\ max}$.

Fig. 8 shows the variation trend of emulsion quantity with volume fraction and flow rate ratio. A nonlinear curve on this figure illustrates the lowest formation frequency was occurred at a condition of the largest $V_{B/A}$ and the smallest $Q_{B/A}$, and whereas the highest frequency was at both the smallest $V_{B/A}$ and $Q_{B/A}$. However, the formation frequency should be modulated if control an emulsion formation with a medium $V_{B/A}$ and $Q_{B/A}$. thus, a suitable formation for different applications can be obtained by the model. Practically, volumetric and quantitative control is commonly used to evaluate the quality of emulsion formation of a two-phase microfluidic channel. A trend line in all figures represents an idealized situation for stable variation with design variables, which is a good indicator for determining the optimal operational condition.

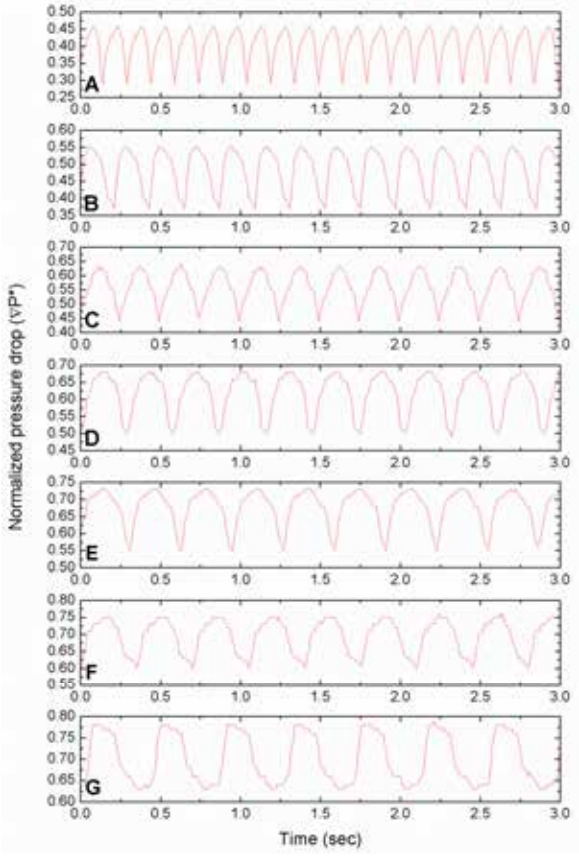

Fig.6. Transient pressure drops of a micro-emulsion flow in the main channel at different fill conditions: (A) $Q_{B/A}$ = 0.667, (B) $Q_{B/A}$ = 1.000, (C) $Q_{B/A}$ = 1.333, (D) $Q_{B/A}$ = 1.667, (E) $Q_{B/A}$ = 2.000, (F) $Q_{B/A}$ = 2.333, and (G) $Q_{B/A}$ = 2.667. These periodic fluctuations related to flow behaviors can be used to ensure the quantification of emulsion.

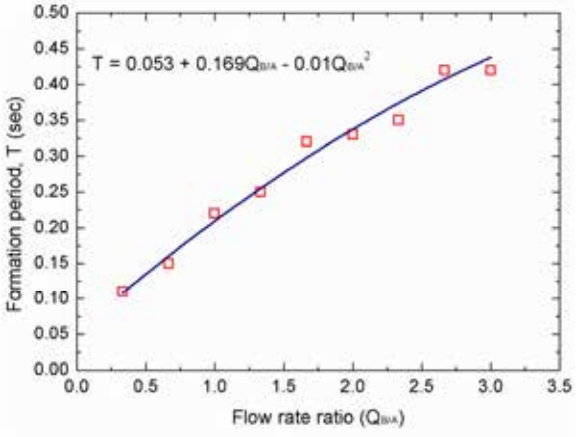

Fig.7. Periods of pressure fluctuations in the main channel at different fill conditions.

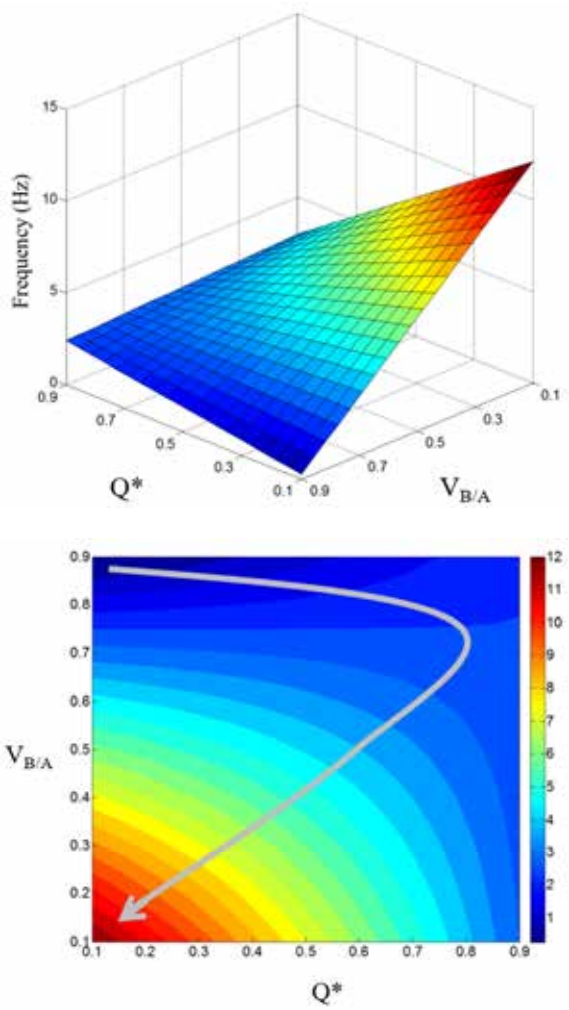

Fig.8. Variation of formation frequency for emulsions with design parameters.

As mentioned above, the variable design of a non-linear emulsion dynamical system can be accomplished by means of RSM approach. Simultaneously, this modeling approach reveals a different exploration in the linkage between design variables and system characteristics.

VI. CONCLUSION

Based on the flow rate, the mass of emulsion segment was calculated. It is found that water droplet can significantly enhance the transfer of oil droplet initially. When oil-water cluster was formed downstream the microchannel, pressure drop will retard the mass transfer. Other characteristics such as inlet velocity and formation rate are also discussed. The information is beneficial for microreactor design when applying oil-water flow reactions.

The quantitative prediction model for oil-water emulsion formation in a microfluidic channel was proposed in this study. Through the RSM approach, the responses of a micro-emulsion flow at different operational conditions is reasonably predicted, which could provide an optimal emulsion design. The proposed model revealed that the quantity of emulsion was inversely proportional to $Q_{B/A}$ and $V_{B/A}$, respectively. The conjugate effect of both parameters resulted in nonlinear variation in emulsion formation. Not only the manipulation range but the limitation of the emulsion performance for specific purposes can further be obtained resulting from this RSM model. Accordingly, the quality and quantity of a micro-emulsion flow can be identified by formation frequency and can be actually controlled by suggested the RSM model.

VII. ACKNOWLEDGMENTS

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