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Micromixer as a Continuous Flow Reactor for the Synthesis of a Pharmaceutical Intermediate

Jaehoon Choe, Youngwoon Kwon, Yeongdae Kim, Hyun-Seob Song and Kwang Ho Song[†]

LG Chem, Ltd./Research Park, 104-1 Moonji-dong, Yuseong-gu, Daejeon 305-380, Korea

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Abstract−A mixing device composed of a micron scale flow channel was applied as a continuous reactor to control exothermic reaction heat and to increase the product yield, in a synthesis of a pharmaceutical intermediate of quinolone antibiotics. The model reaction featured a fast reaction rate, high heat generation, and impurity formation due to a prolonged contact time between reactants and products. Using the micromixer reactor, the reaction heat was efficiently removed so that virtually no impurities were produced during the reaction. A product yield comparable to the theoretical value was achieved in a single micromixer unit. Optimum operating conditions were acquired from a statistical method by using factorial design, which was also verified by a CFD calculation.

Key words: Micromixer, Microreactor, Boc, Response Surface Method, Exothermic Reaction

INTRODUCTION

Recent advances in process intensification, such as the development of micron-sized chemical production equipment, make it possible to utilize some exceptionally useful features for chemical processes in micro scale. These features include extremely fast heat and/or mass transfer rates due to a high surface to volume ratio, rapid mixing by inter-digitized micro flows, inherently safe process operations through strictly controlled conditions and the small amount of chemicals involved. Several successful applications of micro unit operations to commercial or pilot scale production have been reported [Kusakabe et al., 2001], including a production of hazardous materials [Ajmera et al., 2001], improvement in molecular weight distribution of polymers by mixing monomer and initiator in a micromixer [Bayer et al., 2000] and quality enhancement of pigment using a micromixer as a reactor [Wille et al., 2002].

One of the high potential applications of the micromixer is that of changing a batch synthesis of a chemical to continuous reaction. Most active pharmaceutical ingredients are generally produced by batch processes because they are typically high value added, small volume products. Batch processes have many advantages, such as simplicity of operation, flexibility for various kinds of products, etc. However, they also have some disadvantages, such as difficulties in precise control of reaction temperature as the scale becomes large, and the requirement for good mixing devices. Moreover, when the reaction shows highly exothermic behavior and a side reaction occurs resulting from the reaction heat, the product yield in a batch operation greatly decreases. The reaction of *t*-Boc_2O as a protective group for primary amines in a pharmaceutical intermediate is a good example of a fast, exothermic reaction.

In this study, the performance of the micromixer reactor was tested with various reaction conditions. The optimal conditions for production yield were determined by using the statistical method, design of experiments. A computational fluid dynamics (CFD) analysis of the micromixer was performed as well, to compare flow patterns in an optimal reaction condition with those reactions having low product yields.

EXPERIMENTAL

1. Micromixer and Reaction Conditions

The micromixer, which was manufactured by IMM (Mainz, Germany), consists of a mixing element, two inlets and one outlet. The feed flows are introduced to a mixing element inside the micromixer via the two inlets, from opposite directions. The mixing element consists of 2×15 interdigital channels with corrugated walls. The two fluids flow through the interdigital channels and then flow upwards into a slit, which is perpendicular to the interdigital structure. Here, the mixing takes place, after which the mixed fluid is discharged. The width of the interdigital channels used in this experiment is 25 μm and that of the discharge slit is 60 μm. Photographs of the micromixer are shown elsewhere [Ehrfeld et al., 2000].

LC pumps were used to feed the two fluids. One was fluid A, composed of 4-(N-(tert-butoxycarbonyl)-4-aminomethylene-pyrrolidine-3-one (**1**) (61.6 g, 290 mmol), isopropyl alcohol (338.4 g, 81.8% solution in water) and di-*tert*-butyl dicarbonate (*t*-Boc_2O) (76 g, 348 mmol). The other was KOH (50% solution in water). The reaction scheme is shown in Fig. 1. The micromixer was immersed in a temperature controlled bath, where the temperature of the bath was set at 15 °C. The discharged product was quenched with an acid, and samples were taken for HPLC analysis.

The reaction mixture shows two phase behavior at certain mixture compositions since *t*-Boc_2O and water are immiscible. The solubil-

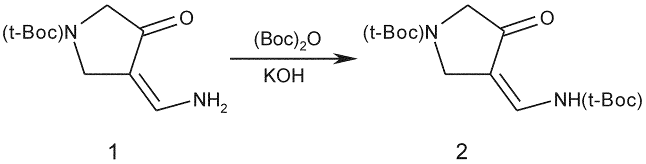

Fig. 1. Reaction scheme.

[†] To whom correspondence should be addressed.
E-mail: khsong@lgchem.com

Table 1. Coded factor levels corresponding to real values for factorial design (α=1.4142)

Coded level	Flow rate of fluid A (mL/min)	KOH equivalency to R-NH_2
Level+α	9.99	12.98
Level+1	9.70	12.40
Central point (0)	9.00	11.00
Level−1	8.29	9.60
Level−α	8.00	9.02

ity of the ternary system of *t*-Boc_2O, water, and isopropyl alcohol was measured with an RC1 reaction calorimeter (Mettler-Toledo, Switzerland) equipped with an RD10 dosing controller and an FSC402 process turbidity meter. The binary mixture of *t*-Boc_2O and isopropyl alcohol was prepared by mass with a precision of 0.01 g, on a Mettler PB4002-S balance. The temperature of the jacket was controlled to maintain the reactor contents at a constant temperature of 25 °C. Cloud points were determined by a turbidity meter, while water and isopropyl alcohol were added in turn by mass with an RD10 dosing controller.

2. Experimental Design and Statistical Analysis

The flow rate of fluid A and the equivalency of KOH to compound **1** were determined to be the main factors, after experiments of the 2^3 factorial analysis of three factors were performed, including KOH concentration. A central composite design was applied to find the optimum operating conditions of the micromixer. The factors and their levels are shown in Table 1. The experiment was conducted by changing the flow rates of fluid A and the aqueous KOH feed. The running order of the experiment was randomly generated from the statistical software package MINITAB™ Release 13 and is described in Table 2, with the corresponding experimental results.

Table 3. Estimated regression parameters of central composite designed experiment (R^2=0.944)

Parameter	Parameter estimate (coded unit)	Standard error coefficient	T-ratio	Probability
Intercept	94.760	0.4040	254.540	0.000
X_A	1.041	0.3194	3.258	0.014
X_B	2.969	0.3194	9.295	0.000
X_A^2	−0.136	0.3425	−0.398	0.703
X_B^2	−1.211	0.3425	−3.536	0.010
$X_A^*X_B$	−1.300	0.4517	−2.878	0.024

Table 4. Analysis of variance (ANOVA)

Source	Degree of freedom	Sum of squares	Mean square	F value	Probability
Model	5	96.154	19.2309	23.56	0.000
Linear	2	79.185	39.5925	48.51	0.000
Square	2	10.209	5.1047	6.25	0.028
Interaction	1	6.760	6.7600	8.28	0.024
Residual error	7	5.713	0.8162		
Lack of fit	3	1.161	0.3871	0.34	0.799
Pure error	4	4.552	1.1380		
Total	12	101.868			

Multiple regression analysis was applied to fit the experimental data of the central composite design to a second-order polynomial equation. The regression coefficients for the second-order polynomial equation, expressed in Eq. (1), are also listed in Table 3.

$$Y=94.76+1.041X_A+2.969X_B-0.136X_A^2-1.211X_B^2-1.3X_AX_B \qquad (1)$$

The regression coefficients and results of a T-test, in Table 3, show that two linear terms, the flow rate of fluid A (X_A) and KOH equivalency (X_B), one interaction term (X_AX_B), and the quadratic term of X_B exert a significant effect on the production yield ($p<0.05$). The fit of the model can be assessed by a coefficient of determination R^2, which was calculated to be 0.944, indicating that 94.4% of the

Table 2. Central composite design matrix with the response

Actual levels		Coded levels		Observed conversion (%)
Flow rate of fluid A (mL/min)	KOH equivalency to R-NH_2	Flow rate of fluid A (mL/min)	KOH equivalency to R-NH_2	
		X_A	X_B	Y
8.00	11.00	−1.414	0	92.7
9.70	12.40	1	1	95.9
8.29	9.60	−1	−1	88.7
9.00	12.98	0	1.414	96.8
9.70	9.60	1	−1	93.2
9.00	9.02	0	−1.414	87.5
9.00	11.00	0	0	95.7
9.00	11.00	0	0	94.3
9.00	11.00	0	0	94.6
8.29	12.40	−1	1	96.6
9.00	11.00	0	0	93.3
9.99	11.00	1.414	0	95.9
9.00	11.00	0	0	95.9

variability in the response could be explained by the model. The analysis of variance in Table 4 also indicates the regression model is adequate for this set of data. This is evident from the probability value of ≅0.000 for the overall regression model. The test statistics F values for linear, square and interaction terms are significant at the upper 5% level. The lack of fit test was also used to determine whether the constructed model was adequate to describe the experimental data. The estimated probability value for the lack of fit is larger than 0.05 indicating the non-significant lack of fit at the 95% confidence level, which further supports that the model represents the data adequately.

3. Computational Fluid Dynamics Analysis

The mixing patterns of the two feeds in the micromixer were calculated and graphically presented by the commercial CFD code FLUENT 6 at various reaction conditions. The number of meshes used was approximately 100,000, which were generated using the software GAMBIT 2. In order to effectively visualize the mixing patterns in the micromixer, the two feed fluids were treated as different phases in the calculation. Among the various multiphase models available in FLUENT 6, a mixture model was employed to predict the micromixer performance. The volume fraction equation for each phase was solved together with the continuity and momentum equations. Chemical reactions were not considered in this calculation, due to the limitation of the multiphase models in FLUENT. The cold flow simulation provided an insight into the mixing pattern in the micromixer.

RESULTS AND DISCUSSION

Analysis of the response surface methodology was conducted to identify how a production yield is affected by a set of variable changes, as well as to determine the optimum operating conditions. Fig. 2 shows the contour plot of the production yield versus the two main factors, calculated by using Eq. (1). The maximum yield achieved in the experiment was found to be 97%, when the flow rate of fluid A was 8.9 ml/min and KOH equivalency to compound **1** was 13. It also shows that the product yield was improved with an increase in the feed flow rate and an increase in KOH equivalency. For example, an increase in the flow rate of fluid A led to increased product yield when the KOH equivalency was fixed at a value below 12.0. These results are consistent with the work of Haverkamp et al. [Haverkamp et al., 1999]. They reported that the dispersion of two immiscible fluids was improved with an increased total flow rate in the micromixer. The energy per unit volume increased with an increase in the flow rate, which was then used to disperse two fluids. They also found that increasing the ratio of flow rates of water to silicon oil led to improved dispersion of two fluids. These results were also highly consistent with the experimental results under discussion here. The high KOH equivalency implied both the high ratio of aqueous KOH to the compound **1** in the fluid A and a high flow rate of aqueous KOH, which also led to a higher production yield. An excess of aqueous KOH solution helps compound **1** and *t*-Boc$_2$O to disperse well in the solution.

However, a reduction of the yield was observed in the region where the flow rate of both feeds was high. The increase of the flow rate

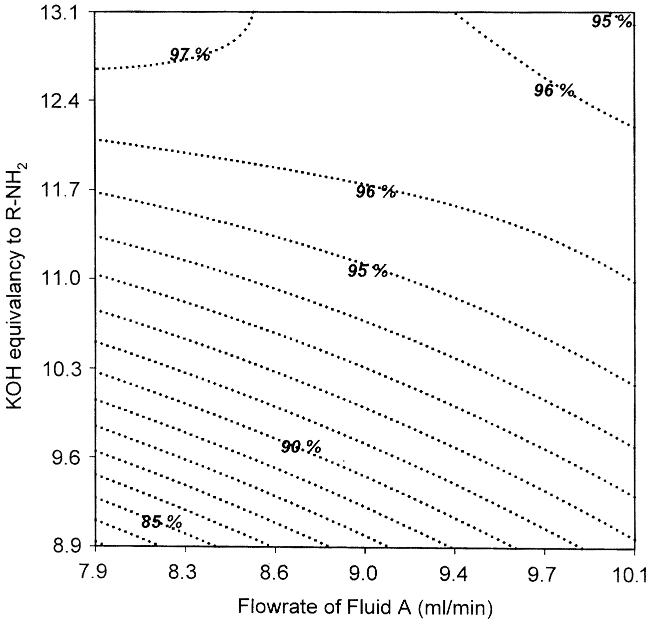

Fig. 2. Contour plot of production yield versus flow rate and KOH equivalency.

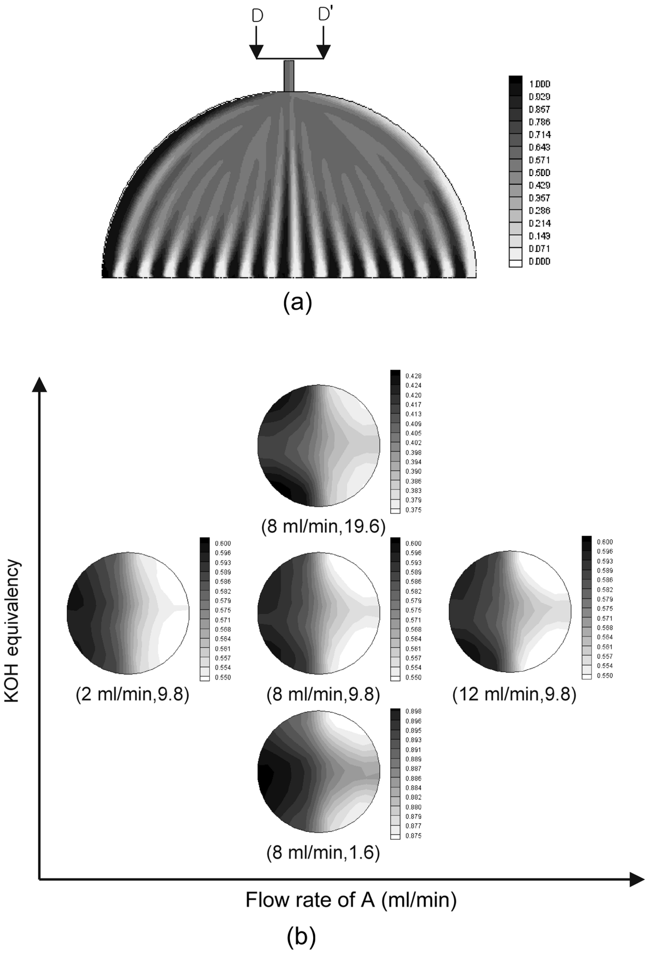

Fig. 3. CFD results on mixing and segregation of two fluids in the micromixer: the darker shades denote the higher the volume fraction of fluid A as shown in the color scale at the right. (a) lateral view (b) cross-sectional view : operation condition (x ml/min, KOH equivalency of y).

of fluid A, for example, resulted in a product yield reduction when the KOH equivalency was around 13, as shown in Fig. 2. This is because the product yield could be affected by the residence time, as well as mixing power. If the residence time in the micromixer is too short (<20 μsec, residence time equals micromixer volume over flow rate), the reaction cannot be completed, so that the unreacted feed lowers the product yield.

CFD calculations provided a clear picture of the mixing pattern in the micromixer, which explains the effects of the feed flow rates on the production yield. In Fig. 3(a), the black area represents the fluid A and the white area represents the aqueous KOH. Both fluids interdigitally flowed out of the silt from the bottom of the chamber. The streams then mixed in the chamber as shown in Fig. 3(a). The basis of calculation was that the flow rate of fluid A is 8 ml/min and the flow rate of aqueous KOH (50%) is 6 ml/min, which is equal to the KOH equivalency 9.8. A product yield of 88% was achieved experimentally by using the aforementioned condition. A cross-sectional view of the outlet taken on plane DD' is depicted in Fig. 3(b) at the center. The dark color at the left half of the circle indicates a higher fluid A concentration and the white at the right half of circle indicates a higher aqueous KOH concentration. This can be explained by the structure of the micromixer. The micromixer has 30 interdigital channels. When both fluids flow upward into the slit, the left half of the mixing chamber consists of 15 channels having 8 channels for fluid A and 7 channels for the aqueous KOH. The right half of the mixing chamber also consists of 15 channels, but 7 channels are for fluid A and 8 channels are for the aqueous KOH. Therefore, the left half of chamber will presumably have a higher concentration of fluid A than the right and vice versa.

As indicated earlier, the micromixer exhibited the tendency to enhance the product yield as the flow rate of fluid A or the KOH equivalency increased. These cases correspond to the three figures aligned along the horizontal and vertical axis of Fig. 3(b), respectively. When the KOH equivalency was the lowest (i.e., 1.6), an island of fluid A was observed at the left corner of the circle indicating unreacted compound **1**. However, it separated into two smaller concentrations as the KOH equivalency increased, resulting in a better mixing of the reactants. The enhancement of the yield with an increased flow rate of A can also be explained by the three central figures along the horizontal axis in Fig. 3(b).

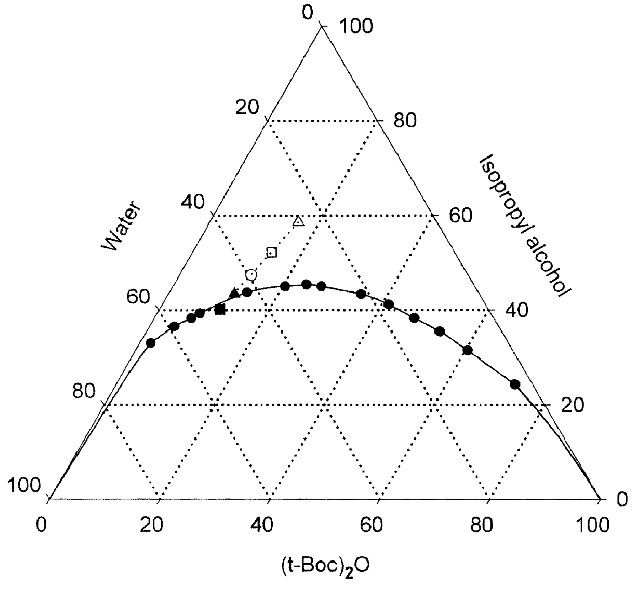

Fig. 4. Phase diagram for the ternary system of Boc$_2$O, Isopropyl alcohol (IPA) and Water. ●: measured solubility, △: 9 equivalency of KOH, □: 10 equivalency of KOH, ○: 11 equivalency of KOH, ▲: 12 equivalency of KOH, ■: 13 equivalency of KOH.

Aside from the mixing power and the residence time, the phase separation would be another important factor affecting the mixing of the liquid reactants. The solubility diagram shown in Fig. 4 determines whether a mixture exists in a single phase or in two phases. The reaction in a micromixer favors a high value of KOH equivalency, as discussed above. The phase diagram reveals that the phase of the mixture, along the operating curve in Fig. 4, changes from two phases to a homogeneous phase at a value of KOH equivalency over 12. The increased water content with increasing KOH equivalency changed the composition of the ternary mixture so that it became miscible. Over a KOH equivalency of about 12, phase separation between the Boc$_2$O and the aqueous phase was not observed. The miscibility of the reactant fluids will enhance the mixing performance of the micromixer, resulting in a drastic increase in yield with a high KOH equivalency value.

Reaction kinetics studies show that impurities are formed when the reaction temperature is over 20 °C [Choe et al., 2003]. The adiabatic temperature rise was estimated to be 33 °C and the heat of reaction was −213.2 KJ/mol [Choe et al., 2003]. In this experiment, the bath temperature was controlled at 15 °C and the measured micromixer outlet temperature was the same as the bath temperature. A high yield of 97% was reached at a total flow rate of 13 ml/min without impurities when the molar ratio of aqueous KOH and compound **1** was 13 at the bath temperature of 15 °C.

CONCLUSION

A micromixer was successfully applied to a fast exothermic reaction step for continuous production of a pharmaceutical intermediate, which consisted of a primary amine group with *t*-Boc. Theoretical maximum yields may be achieved by avoiding a side reaction, which is a positive feature of the micromixer. The experimental results show that the maximum yield requires aqueous KOH and compound **1** in a molar ratio of 13 and a total flow rate of 13 ml/min in the micromixer. Efficient heat removal is possible due to the extremely large surface to volume ratio and effective mixing, within a short residence time. In batch reactions, impurities are readily generated by side reactions due to a high reaction temperature and a long contact time between products and reactants. In this case, a further purification step, such as crystallization, can be skipped, which was inevitable and caused significant yield loss in a batch process. The productivity of the micromixer is superior to that of batch process. Only 25 parallel units of the micromixer can replace a commercial 10 m^3 scale batch reaction vessel, which also means a dramatic decrease in capital and operational cost.

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