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High Performance Liquid Chromatograph Nexera™ FV

Application News

On-Line Monitoring of Flow Synthesis Reactions Using Nexera FV

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User Benefits

- On-line monitoring of flow synthesis reactions can be performed.
- Simple operation with dedicated software allows automatic execution of analysis at specific sampling intervals and automatic report generation.
- Reliable experimental system setup can be established using HPLC as a part of flow synthesis system.

■ Introduction

In the pharmaceutical and fine chemical industries, there is an increasing demand to switch from conventional batch manufacturing for the sake of improvement of efficiency (labor and manpower savings), quality and safety, and reduction of environmental load.

ICH-Q13 guidelines for continuous production of drug substances and drug products recommend the application of Process Analytical Technology (PAT) for the purpose of maintaining controlled conditions for manufacturing. Consequently, the demand for PAT is increasing.

Nexera FV is an HPLC system setup for on-line analysis equipped with a flow through vial in the autosampler (Fig. 1). The system enables automated processes from continuous delivery of reaction solution into the flow through vial to resulting report creation of HPLC analysis.

This article introduces an on-line monitoring of flow synthesis reactions using Nexera FV, taking an example of the esterification of carboxylic acid.

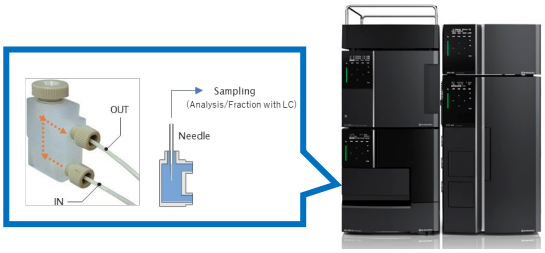

Fig. 1 Nexera FV (for flow synthesis) and flow through vial

■ Analytical conditions

An esterification reaction under acidic condition was investigated. Esterification by dehydration-condensation is a process in which a carboxylic acid reacts with an alcohol to form an ester, which is catalyzed by an acid. 3-phenylpropionic acid was used as the reactant of carboxylic acid and methanol as the alcohol, and AmberLyst™ 36WET, a strong acid catalyst, was packed in the reaction column and used for the reaction (Fig, 2).

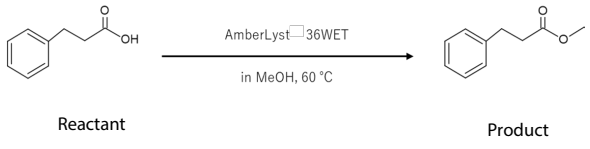

Fig. 2 Esterification reaction of phenylpropionic acid

In this study, on-line monitoring of the esterified reaction solution was performed by delivering 50 mmol/L phenylpropionic acid methanol solution through the reaction column (AmberLyst 36WET) heated to 60 ℃ at the flow rate of 0.1 mL/min (Fig. 3).

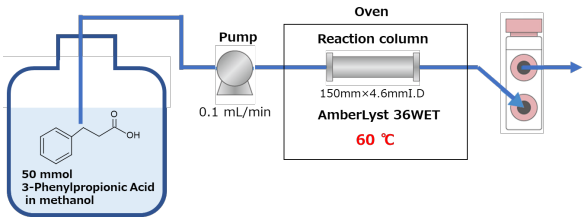

Fig. 3 Flow path diagram of flow synthesis monitoring

■ On-line monitoring with Nexera FV

Nexera FV introduces the reaction solution delivered from the flow synthesizer into the flow through vial for sampling. In this case, LC-40D pump and CTO-40C column oven of Shimadzu Nexera Series were used as the flow synthesizer and were connected to Nexera FV to introduce the reaction solution from the reaction column into the flow through vial (Fig. 4). The reaction solution was automatically injected from the flow through vial to HPLC according to the created analytical batch.

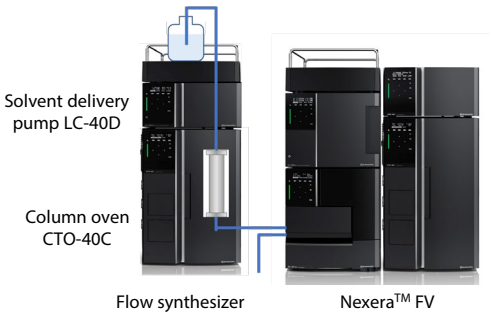

Fig. 4 System setup of flow synthesizer and Nexera FV

■ LabSolutions™ FV for easy creation of analytical batch

LabSolutions FV, a dedicated on-line monitoring software, allows users to easily perform complicated procedures such as creating an analytical batch and entering operational settings during reaction monitoring (Fig. 5). The analytical batch is automatically created by simply entering information such as HPLC conditions and sampling interval, allowing to start on-line HPLC analysis without any difficulties. It also supports input of external signals and start of sampling at a specified time, making it possible to link with other systems.

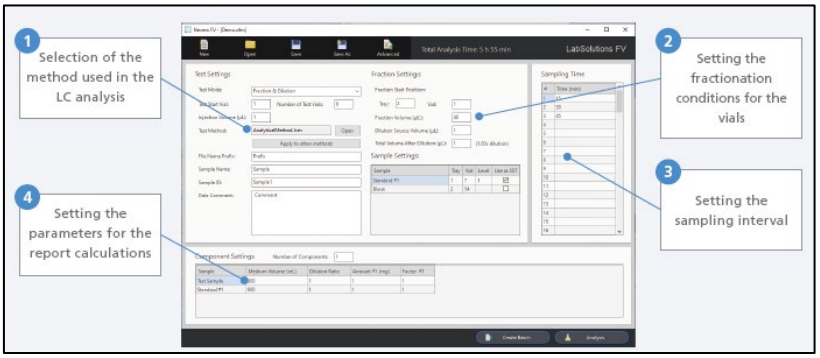

Fig. 5 Setting screen of LabSolution FV

■ Analysis of reaction solution

In this monitoring of the flow synthesis reaction, measurements were performed using the direct injection method, in which the reaction solution was injected directly from the flow through vial into the HPLC. Table 1 shows the HPLC analytical conditions, and Fig, 6(a) shows the chromatogram of the reaction solution (at 0 min) and Fig, 6(b) shows the chromatogram of the reaction solution (at 300 min). Phenylpropionic acid and product peaks were detected at 0.49 min and 1.15 min, respectively. Reaction monitoring was conducted from 20 to 960 minutes after the start of pumping, and it was confirmed that under these conditions, the esterified product was obtained constantly at 95~96% purity after 120 min.

Table1 HPLC conditions

Column	:	Shim-pack™ Velox C18 *1 (50 mm×2.1 mm I.D., 1.8 µm)
Mobile phase A	:	0.5% Formic acid in Water
Mobile phase B		Acetonitrile
Time program (%B)	:	30% (0 min)→95% (0.45-1.40 min)→ 30% (1.41-3.5 min)
Flow rate	:	0.8 mL/min
Column temp.	:	40 °C
Injection vol.	:	1 µL
Detection	:	UV 254 nm

*1 P/N : 227-32001-02

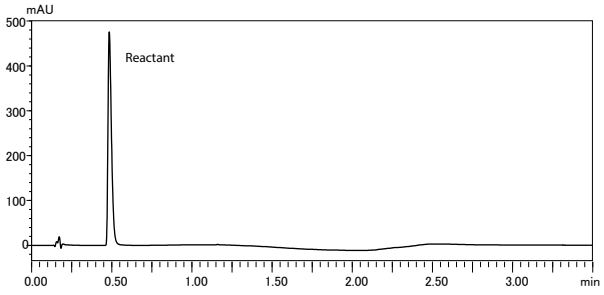

Fig. 6(a) Chromatogram of reaction solution (0 min)

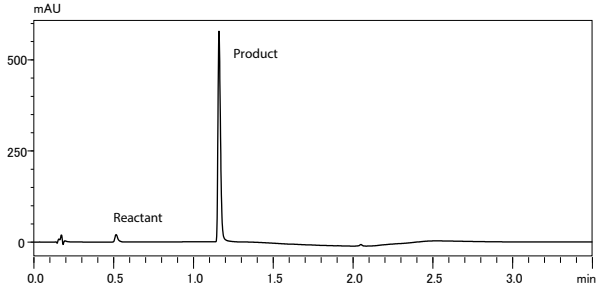

Fig. 6(b) Chromatogram of reaction solution (After 300 min)

■ Reaction product tracking using trend plot

A trend plot of the variations in the peak areas of phenylpropionic acid and the reaction product based on the reaction monitoring results is shown in Fig.7, created using LabSolutions' Multi-Data Report*2 function. Using the multi-data report function, a report (Fig. 8) can be automatically created after all analyses are complete, allowing visualized confirmation of the yield and the variation of intermediate in the synthesis process.

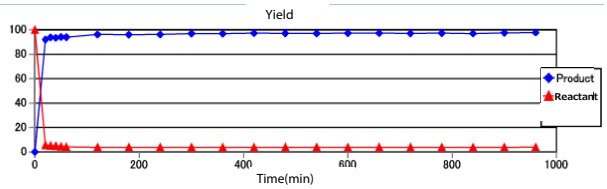

Fig. 7 Trend plot for phenylpropionic acid(reactant) and product

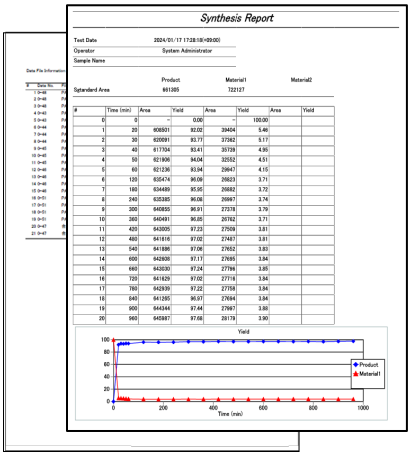

Fig. 8 Multi data report*2

*2 Multi data report is a function equipped in LabSolutions DB/CS

■ Conclusion

On-line monitoring of the esterification reaction of phenylpropionic acid by flow synthesis was performed using Nexera FV. Connecting the reaction system and the flow through vial, sampling and analysis was able to be performed automatically according to the analytical batch. In addition, the multi-data reporting function allowed reaction tracking on reactant and product by automatic generation of trend plot after analysis. Nexera FV and LabSolutions FV simplified analytical batch creation, automated sampling, and reporting. It results in a reduction of working time and increase of efficiency.

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