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Case study:

Accelerated reaction exploration in continuous flow with real-time UV-Vis Process Analytical Technology (PAT)

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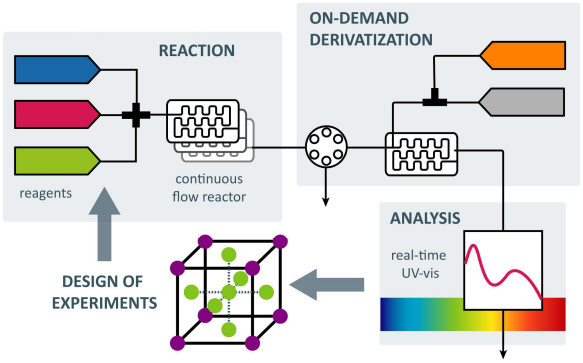
ABSTRACT. This short note presents an internal case study highlighting how real-time analytical tools combined with flow chemistry can accelerate the rational development and optimization of chemical processes. Using a proprietary representative chemical transformation, we demonstrate here the beneficial integration of continuous flow reaction, Process Analytical Technologies (PAT) and Design of Experiments (DoE) approaches.



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1. Introduction

Global challenges such as climate change, resource and energy constraints are reshaping priorities in chemical manufacturing. Addressing these challenges requires the development of chemical processes that are not only more efficient and safer, but also aligned with sustainable pathways, delivering both societal, environmental and economic benefits.

This paradigm shift calls for rethinking how chemical products and processes are conceived, developed, and scaled – from discovery to industrialization. Approaches such as the Safe and Sustainable by Design (SSbD) framework, green chemistry principles, and circular economy strategies provide guidelines, regulatory reference points, and directions for designing safer, more sustainable chemical processes.[1-3] In this context, process intensification, continuous manufacturing, advanced automation and digitalization technologies emerge as powerful enablers for accelerated and sustainable innovation.[4,5]

Process Analytical Technology (PAT) – initially introduced by the United States Food and Drug Administration (US FDA) in the pharmaceutical industry and defined as "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during

processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality"[6] – plays a pivotal role in this direction and has become increasingly important in the development and operation of continuous flow processes, whether in the context of R&D or manufacturing activities. [7-10]

PAT tools provide real-time (or near-real-time) insights into reaction progress, enabling the monitoring of key indicators such as product quality and productivity. These extended capabilities facilitate the implementation of advanced automation and digitalization strategies to enhance process efficiency, sustainability, and robustness. For example, data from PAT devices allow the implementation of active process control strategies (such as feedback loops) to automatically and rapidly detect disturbances and adjust, in real time, the process accordingly (comprising the timely diversion of non-conforming materials), thus ensuring operational stability and consistency, as well as facilitating product release validation. In R&D, PAT has become instrumental in accelerating reaction discovery, understanding, and optimization through for instance combination of PAT-integrated flow reaction platforms, automation, self-optimization algorithms and artificial intelligence.[11, 12]

Overall, PAT tools can be classified based on their level of integration with the process stream: in-line, where analysis occurs directly in the main flow; on-line, where a sample is diverted from the flow for analysis before being reintroduced; and at-line, where a sample is removed and analyzed externally, without being reinjected. A variety of PAT solutions have been commercially developed for "real-time" process monitoring, including spectroscopic (FTIR, Raman, UV-Vis, NMR), mass spectrometric (MS) and chromatographic (GC, LC, SEC) techniques, each offering distinct level of qualitative and quantitative information, as well as advantages in terms of resolution, sensitivity, response time, and susceptibility to spectral overlap. Yet, no single PAT tool is universally applicable.

In this case study, we describe the development of a custom flow reactor platform equipped with real-time (at-line) UV-Vis monitoring, designed to enable rapid reaction exploration and optimization.

2. Discussion

2.1. Real-time UV-vis reaction analysis

Ultraviolet-visible (UV-Vis) absorption spectroscopy is based on the ability of certain molecules to absorb light in the ultraviolet (100-400 nm) and visible (400-750 nm) regions. According to the Beer-Lambert law, absorbance (A) is directly proportional to the molar absorption coefficient (ε), optical path length (l), and solute concentration (c), i.e., $A = \varepsilon lc$. This proportionality provides the foundation for quantitative analysis, provided that the measurements remain within the linear dynamic range of the detector.

Because of its high sensitivity, straightforward implementation and relatively low cost, UV-Vis spectroscopy is widely used as a detection method in analytical techniques such as HPLC. However, this same sensitivity often becomes a limiting factor in PAT applications, where chemical processes often operate at high concentrations. Under such conditions, the process stream must therefore undergo controlled dilution, optical path adjustment, or other fractionation strategies to obtain meaningful measurements. Additionally, when UV-Vis spectroscopy is applied in standalone mode (i.e., without chromatographic separation), challenges arise when two or more absorbing species are present in the reaction mixture. In such cases, quantification is only possible if their spectral features are sufficiently distinct to enable selective tracking. These intrinsic limitations greatly restrict the applicability of standalone UV-Vis spectroscopy PAT in complex or concentrated reaction systems.

These limitations were particularly evident in the model reaction studied here, where the chromophoric reactant and product exhibited identical absorption spectra, preventing direct reaction monitoring. Moreover, the reaction was intended to be carried out at relatively high concentrations to achieve rapid kinetics compatible with continuous flow operation, further complicating direct analysis. To overcome these challenges, a simple and robust dilution/derivatization method was developed prior to investigating the reaction in flow. This creative approach generated spectroscopically distinct chromophores from prepared mixtures simulating different extents of reaction, enabling quantification of reaction yield. Calibration curves established in parallel using both our benchtop and inline UV-Vis instruments exhibited excellent linearity and repeatability, confirming the accuracy of the method and prompting its integration in a continuous flow setup.

2.2. Continuous flow setup and reaction exploration

The continuous flow exploration platform consisted of a reaction module built from a Corning® Low Flow reactor, a custom-made fractionation/derivatization module, and an UV-Vis detector (Ocean Optics) (see Figure 1 and Graphical Abstract). Particularly, the developed fractionation/derivatization module enables on-demand UV-Vis analysis of the reaction mixture (e.g., at each residence time) by diverting only a small fraction of the flow stream when needed. The diverted stream is then automatically diluted, mixed with the derivatization medium, and directed towards the UV–Vis flow cell for analysis; the whole continuous process providing instant analytical results following equilibration.

Temperature, pressure, and flow sensors enabled monitoring and control of key process parameters, as well as ensuring operational safety. Following validation of critical reactor control parameters (temperatures, flow rates, and process volumes), a central composite design DoE was established using JMP® for exploration of the model reaction, considering the following key factors: reaction temperature, residence time, concentration and stoichiometry.

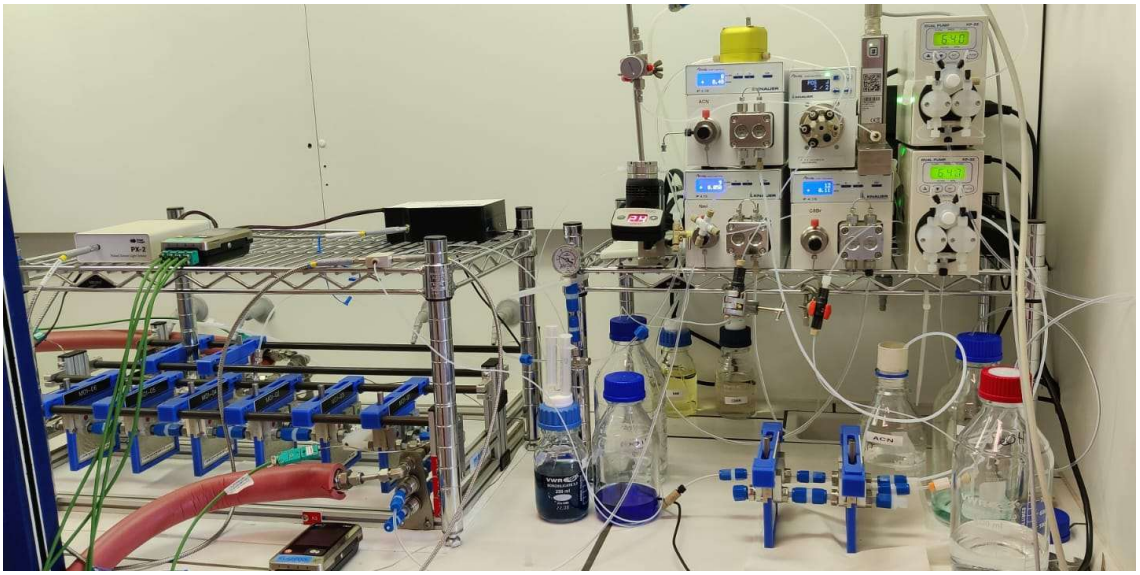

Figure 1. Experimental set-up developed for accelerated reaction exploration in continuous flow with real-time UV-Vis PAT.

A total of 30 experiments were conducted to systematically explore the chemical design space and assess the predictive accuracy of the model. Beyond the conventional goal of yield maximization, which often drives processes toward unsustainable extremes (e.g., high temperatures and stoichiometries), the study also considered productivity (space-time yield, STY), mass efficiency, and energy efficiency as complementary objectives, evaluated under both single- and multi-objective optimization.

The resulting models identified optimal conditions for each single-objective case, as well as conditions for different multi-objective optimizations, revealing clear trade-offs between performance criteria. For example, maximizing yield resulted in quantitative product formation but only moderate productivity. In contrast, optimizing both yield and STY slightly reduced yield (about 20% lower) while substantially increasing productivity by nearly 4-fold.

Process optimization is inherently multivariate, and the objective function – whether single or a (weighted) combination of multiple objectives – must be carefully defined to align with the desired goals.

3. Conclusion

These preliminary results highlight how integrating continuous flow chemistry with PAT tools can accelerate reaction exploration and optimization. Particularly, real-time UV-Vis analysis was combined here with a custom on-demand fractionation/derivatization module to enable reliable quantification and screening of a model reaction run in a continuous flow reactor, within a DoE framework. This approach illustrates how digitalized, data-rich experimentation can support more efficient and sustainable process development in modern chemistry. Future efforts will focus on integrating other PAT tools to gain deeper insights into structural features, as well as on automating the platform towards fully autonomous operation and extending its application to other relevant reactions. Artificial intelligence could also be leveraged to enhance data analysis, deepen process understanding, and support decision-making.

For more information on these topics and implementation of continuous flow and digital technologies in chemistry, please contact us.

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Certech's mission is to provide innovative solutions for the improvement or development of products and processes, in agreement with the principles of sustainable chemistry and circular economy to meet industrial and societal needs.

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Certech's key activities in the development of (bio)chemical processes are closely linked to process intensification, with a strong focus on continuous flow technologies at both micro- and mesofluidic scales.

Whenever significant gains in process efficiency, sustainability, and safety can be achieved – or when developing new innovative processes – transitioning from batch to flow operation becomes a strategic choice.

Certech offers a full range of services to support this transition, from preliminary evaluations of process intensification routes - covering both the core chemistry and chemical engineering aspects - to conceptual flow reactor design, prototype construction, proof-of-concept studies, up to technology transfer. All these activities are executed according to detailed specifications and requirements, in close collaboration with the customer throughout the process.

Such services may thus include the complete design of flow reactors, from early experimental reaction data, initial fluid dynamics simulations, to final engineering deliverables (P&ID diagram, equipment list, material of construction, PAT, etc.) and prototype construction. A particular attention is given to the optimal design of critical mixing and reaction zones to maximize performances and fully leverage the benefits of intensified reactor technologies. From this stage, systematic experimental studies and optimization campaigns may be conducted to rationally optimize process design and reaction conditions, for example through DoE methodologies.

In addition to these unique capabilities, Certech provides a comprehensive range of analytical services for detailed product characterization, spanning both organic and inorganic materials.