Pharma and biopharma

Leveraging a Vanquish UHPLC system and Chromeleon CDS to optimize the manufacturing process

Sanofi advances in drug substances manufacturing through flow chemistry and automation

sanofi

Keywords
HPLC, UHPLC, high-performance liquid chromatography, Chromeleon CDS, pharmaceutical manufacturing, lab automation, flow chemistry, productivity

Traditional manual vs. modern automated approach for a flow chemistry workflow

Optimizing the manufacturing process of raw materials for small molecule drugs is crucial for pharmaceutical companies to deliver drugs efficiently and cost-effectively. Traditionally, this process is labor-intensive and variable. Recently, automation has enhanced efficiency, consistency, and scalability, but it also presents challenges in lab integration and customization. Flow chemistry, or continuous flow chemistry, offers improved control over reaction conditions, safety, and efficiency compared to traditional batch processing. It allows precise control of parameters like temperature and pressure, efficient mixing, heat transfer, and easy scalability, making it ideal for rapid optimization and large-scale production. Decision time and productivity are also improved using flow chemistry.

In the realm of flow chemistry, a variety of detection methods can be employed, each presenting unique benefits and limitations. Techniques such as Raman and near-infrared (NIR) spectroscopy are notable for their ability to deliver rapid analytical results. Despite this advantage, Raman and NIR spectroscopy primarily offer insights into one or two specific molecules within the reaction mix, rather than providing a comprehensive overview of the entire reaction environment. Conversely, liquid chromatography presents a different set of attributes. While it requires a longer analysis time, it compensates

> "Thanks to Thermo Fisher's technical support efficiency and understanding of our needs, today we can optimize and quickly develop a robust processes of flow chemistry."
>
> –Richard Flacher (Senior Scientist, Automation Engineer) and Jérôme Cezerac (Senior Scientist, Process Engineering)

by offering a holistic view of the chemical reaction. This comprehensive approach allows for a detailed understanding of the reaction components and their interactions, which is crucial for thorough chemical analysis. The complementary nature of these technologies provides phase appropriate tools aligning with the requirements of each stage of drug development and enabling the ability to make timely decisions.

Intelligent automation for process optimization

Implementing an automated system for continuous process optimization is a complex task that demands a thorough understanding of both scientific and technical elements. It involves numerous steps and interactions between software and equipment to ensure the entire setup meets laboratory requirements and operates efficiently. The goal is to create a virtuous cycle that allows for optimization in a reduced time frame (Figure 1). Each step included in this cycle is closely linked to the subsequent ones. They are designed to ensure precision, accuracy, and efficiency, ultimately leading to enhanced productivity.

Experimental conditions

The initial setup of experimental conditions is critical, as it sets the foundation for all subsequent steps. This involves careful calibration of the reactor and precise control of the flow chemistry parameters such as proportion of reagent and temperature. These parameters are monitored by third-party software.

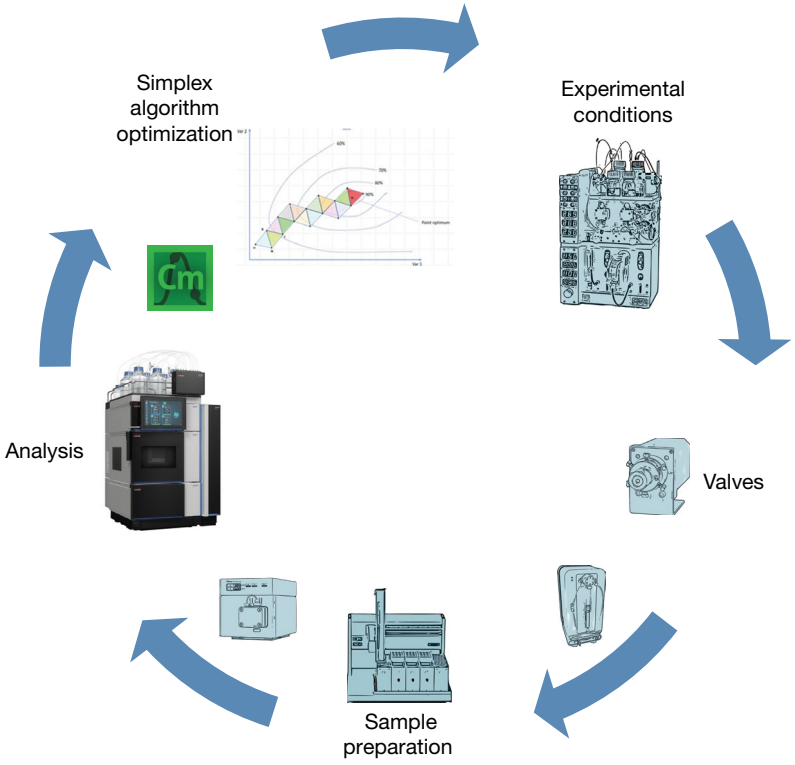


Figure 1. Optimization life cycle

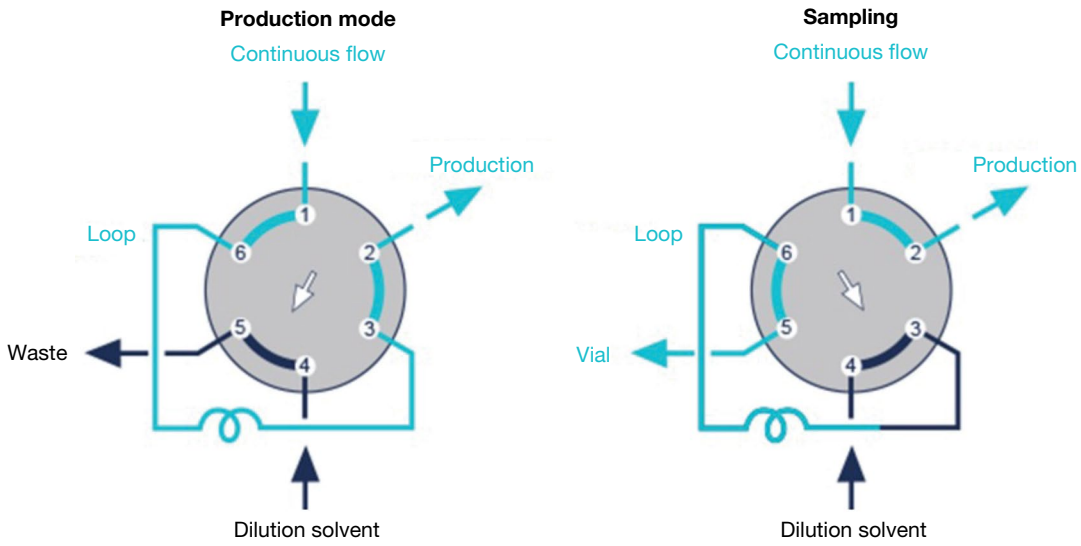


Figure 2. 2-position/6-port valve flow paths

Valves

The use of a 2-position/6-port valve provides the flexibility needed to seamlessly integrate the sample into the automated workflow (Figure 2). The sample can be collected directly from the reactor at any time without any human intervention. A Valco™ valve was chosen as it could be connected using ⅛ inch tubing.

Sample preparation

The compatibility of the sample obtained directly from the reaction medium for ultra-high performance liquid chromatography (UHPLC) analysis conditions is essential to ensure accurate and reproducible results without matrix effects and without compromising instrument performance. As an example, the solvent used to perform the synthetic reaction may not be compatible with the mobile phase or the stationary phase of the column.

Here, the use of an automatic diluter not only streamlines the process but also minimizes the risk of human error, thereby enhancing the reliability of the analyses.

Simplex algorithm

A simplex algorithm is used by Sanofi to find the best solution between three defined parameters. The internal optimization algorithm uses the data obtained by Thermo Scientific™ Chromeleon™ Chromatography Data System (CDS). The simplex algorithm is the linchpin of the entire process, driving continuous improvement and refinement of synthesis conditions. By leveraging real-time analytical data, the algorithm iteratively identifies the parameters to be adjusted such as the reaction temperature and reagents proportion to achieve the optimal synthesis conditions. These new parameters are shared with the third-party software to perform the modification. This iterative process not only accelerates the optimization cycle but also ensures that the results are consistently aligned with the desired outcome of generating the maximum synthesis yield.

Difference between the manual and the automated approach

The traditional manual system necessarily requires human intervention to transport the collected sample from the synthesis reactor to the autosampler. All the different steps mentioned above can be used separately without direct connection limiting the number and pace of injections.

Boosting efficiency

The Thermo Scientific™ Vanquish™ Flex UHPLC system and Chromeleon CDS set new standards in analytical chemistry by combining modern technology with user-friendly design and operation, making them an ideal combination for automated setups. Chromeleon software can support 21 CFR Part 11 and GxP regulations and allows simultaneous integration with control for different components like pumps, valves, and detectors. It facilitates seamless data sharing, enhancing overall efficiency and laboratory interoperability.

Here, the signal from the Valco valve is received by Chromeleon CDS, which then issues a command, via an added line to the instrument method script, to the additional switching valve integrated in the Vanquish system and initiates the eWorkflow procedure. A cable with a DIN connector facilitates communication between the programmable logic controller (PLC), sending an analog signal to the third-party software and the Vanquish UHPLC system. The ultraviolet (UV)-visible detection method is particularly advantageous due to its sensitivity and simplicity, which are crucial for detecting various analytes with chromophores in complex matrices.

> “Without the ease of access to the script command lines in Chromeleon CDS, we would not have been able to seamlessly integrate external systems into our analysis sequences."
>
> –Salomé Soulier (Analytical Engineer) and Grégoire Mathieu (Senior Scientist, Prep Chromatography Expert)

Benefits of the Vanquish Flex UHPLC system and Chromeleon CDS

The Vanquish Flex UHPLC system offers several significant benefits for this application. It is designed for easy and efficient connection with external valves, which minimizes setup time and reduces potential connection issues. Additionally, the Vanquish Flex system is built to maintain high performance and reliability over extended periods, ensuring consistent operation and minimizing maintenance requirements. Furthermore, it supports ultra-high performance liquid chromatography, allowing for the development of shorter analytical methods, typically around five minutes or less. This capability enhances productivity and throughput in laboratory settings. One key feature is the use of triggers, which enable anticipatory actions of the equipment based on predefined instructions within the instrument method. For instance, triggers can automate tasks such as valve switching, module operations, and relay activation, ensuring precise and timely execution of analytical workflow steps.

Intelligent Run Control

Intelligent Run Control (IRC) in Chromeleon CDS is a feature that enables the system to automatically respond by either proceeding with the next injection, re-injecting the current solution, or aborting the sequence.[1-3] IRC dynamically influences subsequent processes based on chromatographic results, automatically initiating calculations or additional processes and optimizing workflow efficiency.

eWorkflow procedure

The Chromeleon software eWorkflow procedure provides instrument, processing, and reporting methods while standardizing the sequence format to be used. This automation of the entire chromatographic analysis ensures consistency and reproducibility. It allows for automated method setup, standardized procedures, and improved data integrity.

Custom variables

Custom variables enable users to customize methods, adapt to different sample types, and streamline data analysis, making the systems versatile. For application, it is possible to create a custom variable within the sequence to add a theoretical concentration. This value can then be compared to the measured mass and used in yield calculations. Automating complex tasks, providing customizable options, and ensuring robust performance, the Vanquish UHPLC system and Chromeleon CDS reduce manual intervention and potential errors, leading to faster data acquisition and more reliable, reproducible results. Streamlined operations allow laboratory personnel to focus on critical decision-making and overall system progress.

Overcome setup challenges

Such an experimental setup is not without its challenges. The first major challenge involves the programming and automation of the various software and equipment involved. This requires them to communicate effectively using a common data format. While this may seem like a straightforward task, it necessitates a deep understanding of both the software and hardware components to ensure compatibility and synchronization. The process of programming a fully automated system is intricate and demands high precision, which can be both painstaking and time-consuming. Each line of code must be meticulously written and tested to ensure that the system functions flawlessly under various conditions. Chromeleon software ensures a smooth communication process by allowing multiple brands and modules, including third-party brands, to be connected simultaneously, as exemplified by the valve automation required in the presented setup. The second challenge pertains to the customization complexity of the entire system. Each laboratory has unique requirements and specifications, making it imperative to design a setup that is not only efficient but also adaptable to changing needs. This involves strategic planning and a thorough understanding of the laboratory's workflow to create a system that can be easily modified or upgraded as needed. Chromeleon CDS addresses these challenges with its robust customization features, such as triggers, eWorkflow procedures, and IRC functionality. These features provide unparalleled flexibility and adaptability.

The proof of concept

As proof of concept, a comparison was conducted between the traditional manual and the fully automated approach with the Valco valve on a calibration curve of a pharmaceutical product. The results obtained are presented in Figure 3.

The comparative analysis revealed no significant impact on internal calibration or on the peak area repeatability (Tables 1 and 2), indicating that the difference between the two approaches is negligible to quantify the compounds of interest. The difference between peak areas can be explained by using different samples. Furthermore, during the routine analysis of samples, the entire sequence (including standards, samples, etc.) will be analyzed under identical analytical conditions. Consequently, the results obtained will be comparable, making it a valuable tool for high-throughput environments and fast decision-making environments, such as drug manufacturing.

This comparison demonstrates that the fully automated approach performs comparably to the traditional manual approach, ensuring reliable and consistent results while enhancing efficiency, reducing potential human error, and allowing a better responsiveness. Optimizing the process through this automated approach is revolutionizing efficiency at Sanofi. Not only does it eliminate the need for constant human monitoring, but it also enables 24/7 operations. The automated approach, capable of functioning without interruption, significantly increases the number of tests conducted each day, thereby maximizing their productivity and accelerating the achievement of results.

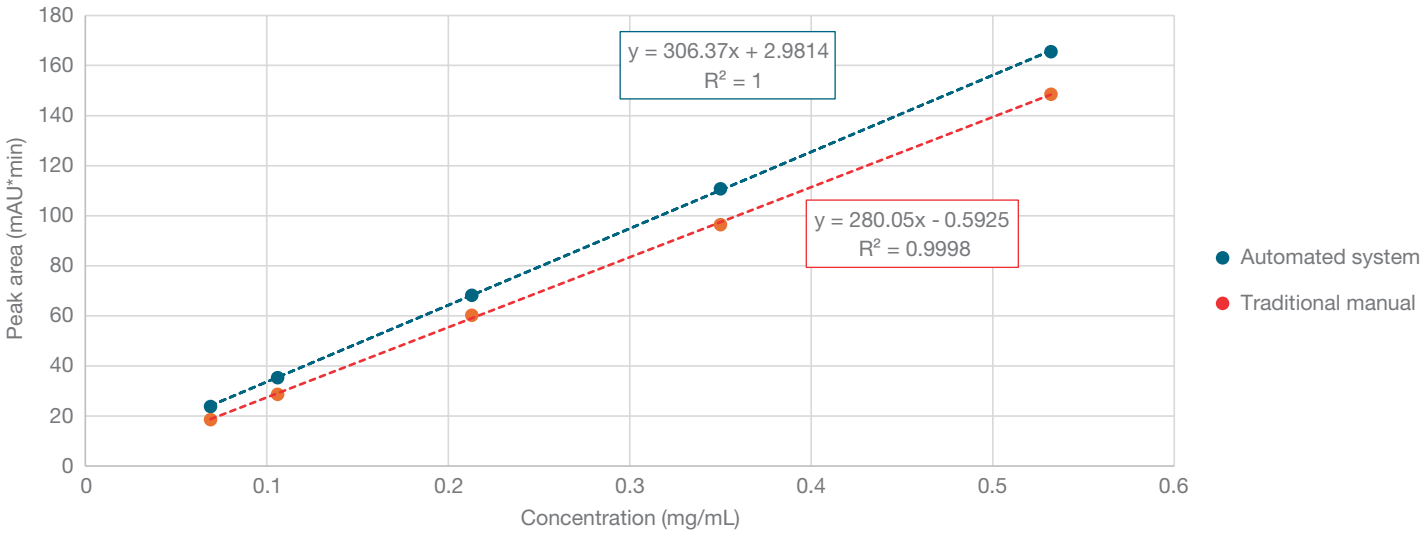


Figure 3. Linearity comparison between the traditional manual and the fully automated approach

Table 1. Samples manually prepared and loaded into the Vanquish autosampler

Sample	Peak area	Average	Standard deviation	RSD
1	78.7	78.5	0.2	0.23%
2	78.2			
3	78.5			
4	78.5			

Table 2. Samples automatically prepared and injected

Sample	Peak area	Average	Standard deviation	RSD
1	73.7	73.5	0.2	0.24%
2	73.2			
3	73.5			
4	73.5			

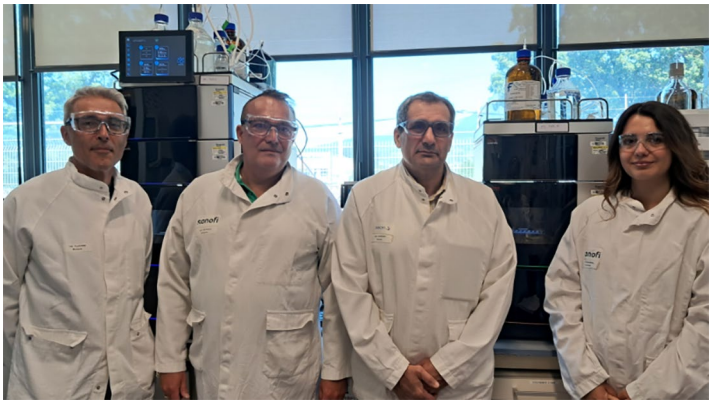
Conclusion

This proof of concept has been demonstrated with a comparative analysis between traditional manual and automated system showing negligible differences in calibration and peak area. It demonstrates the reliability of the automated system and its suitability for high-throughput environments and rapid decision making in drug manufacturing.

- **Enhanced efficiency and precision:** The integration of the Vanquish UHPLC system and Chromeleon CDS facilitates the rapid and repeatable optimization of continuous flow chemistry processes, enhancing efficiency and ensuring high-quality analytical outcomes.
- **Automation:** The use of triggers, eWorkflow, script commands, and Intelligent Run Control in the Chromeleon software automates complex tasks and dynamically adjusts parameters, optimizing workflow efficiency and reducing manual intervention.
- **Improved lab integration:** The seamless integration and control of various components, including the pump and valves, streamline data sharing and enhance laboratory interoperability, making the system adaptable to changing needs.
- **Productivity:** The fully automated system allows 24/7 operation without the need for constant human monitoring.

Acknowledgment

We would like to extend our heartfelt gratitude to the dedicated team at Sanofi for their exceptional work.



Left to right: Richard Flacher, Grégoire Mathieu, Jérôme Cezerac, Salomé Soulier

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