PHARMA

PAT-Driven Real-Time Reaction Monitoring by Integrating synTQ with Bruker's Fourier 80 Benchtop NMR

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Innovation with Integrity

In modern pharmaceutical development and manufacturing, the ability to monitor reactions in real time and respond dynamically to changes in process conditions through Process Analytical Technology (PAT) is increasingly seen as both a scientific necessity and a regulatory imperative. The integration of real-time analytical techniques with process control systems is a key enabler for the implementation of PAT and Quality by Design (QbD) frameworks in pharmaceutical manufacturing. This application note describes the coupling of Bruker's Fourier 80 benchtop Nuclear Magnetic Resonance (NMR) spectrometer with a PAT software platform to achieve continuous, on-line and in-line reaction monitoring and automated control. This study highlights the potential of benchtop NMR as a practical, information-rich PAT tool that can help enhance process understanding, control and automation in pharmaceutical development and production environments.

Introduction

The digitalization and automation of the pharmaceutical industry as it enters the Pharma 4.0 era is driven by the principles of Quality by Design (QbD). According to these, product quality is considered throughout the entire process by monitoring critical quality attributes (CQAs) during all stages of manufacturing rather than at the end only. Process analytical technology (PAT) enables the adoption of a QbD approach through real-time process understanding, monitoring and control. As a result, pharmaceutical manufacturers can ensure consistent product quality. Regulatory bodies encourage pharmaceutical manufacturers to integrate PAT into their processes to improve overall quality control and regulatory compliance in a data-driven manner.

With on-line and in-line analytical instruments, manufacturers can leverage a highly responsive and accurate system to adjust processing conditions on-the-fly to meet quality targets with high efficiency, as downtime associated with off-line laboratory analysis is effectively eliminated. While high-field Nuclear Magnetic Resonance (NMR) spectrometers can deliver extremely accurate quality data, they are typically difficult to incorporate as on-line and in-line PAT instruments. In fact, their size, costs, need for cryogenic liquids, and the level of expertise needed to effectively operate them make such machines difficult to incorporate on the shop floor.

Leveraging its world-leading expertise as analytical instrument manufacturer, Bruker addressed these challenges by delivering an innovative solution: the Fourier 80 benchtop NMR system.[1] While this type of more cost-effective instruments may offer a lower resolution than high field NMR spectrometers, they are well suited to support advanced process monitoring because of their compact footprint, cryogen-free configuration, and easy to use setup. In addition, the Fourier 80 can be easily integrated within PAT frameworks in manufacturing facilities as an on-line and in-line instrument. In particular, it can be coupled with Bruker's InsightMR flow cell[2] and Optimal Industrial Technologies' synTQ market-leading PAT orchestration and knowledge management platform. This setup, known as Fourier PAT[3], offers an out-the-box solution to kickstart PAT-based operations. More precisely, it provides a unified approach to hardware and analytical data control through a single software platform. This provides an intelligent PAT tool that can support self-regulation, process optimization, big data analysis, and seamless integration into modern, digitized manufacturing systems.

By showcasing how a Fourier PAT setup consisting of a fully integrated Fourier 80 NMR and flow system based on synTQ can support an ethyl acetate hydrolysis reaction, this application note demonstrates how pharmaceutical manufacturers can benefit from the in-depth process understanding and monitoring that the system can enable.

Methodologies

To assess the capabilities of the integrated Fourier PAT approach and the capabilities of the Fourier 80 benchtop NMR, the acid-catalyzed hydrolysis of ethyl acetate was selected as a model reaction. This well-understood process involves the conversion of ethyl acetate and water into acetic acid and ethanol under acid conditions. From a mechanistic standpoint, the reaction offers a clean transformation with well-resolved NMR peaks for both reactant and product, making it ideal for real-time analysis.

Experiments were carried out at the Dynamic Reaction Monitoring (DReaM) facility at the University of Bath, Bath, United Kingdom[4], using Bruker's Fourier 80 NMR equipped with an InsightMR flow tube (**Figure 1a**). The set up included a piston pump and a recirculating heat exchanger to maintain the temperature of the transfer lines. synTQ was configured to control NMR spectra acquisition via IconNMR, Bruker's dedicated tool for automation NMR studies.

In addition, synTQ was set up to simultaneously monitor and adjust the pump speed and sample flow rates and reaction temperatures. The NMR and synTQ were connected through an instrument adapter, which allows users to select basic parameters, such as the experiment required, solvent used, and number of scans (**Figures 1b and 1c**). Once set, the experiments could be triggered directly from synTQ, which prompts NMR acquisition via IconNMR on a continuous or timed interval loop.

[1] Fourier 80 Benchtop NMR System: https://www.bruker.com/en/products-and-solutions/mr/nmr/fourier80.html

[2] InsightMR Reaction Monitoring: https://www.bruker.com/en/products-and-solutions/mr/nmr-pharma-solutions/InsightMR.html

[3] Fourier PAT: https://www.bruker.com/en/products-and-solutions/process-analytical-technology/fourier-pat.html

[4] Dynamic Reaction Monitoring Facility: https://www.bath.ac.uk/research-facilities/dynamic-reaction-monitoring-facility/

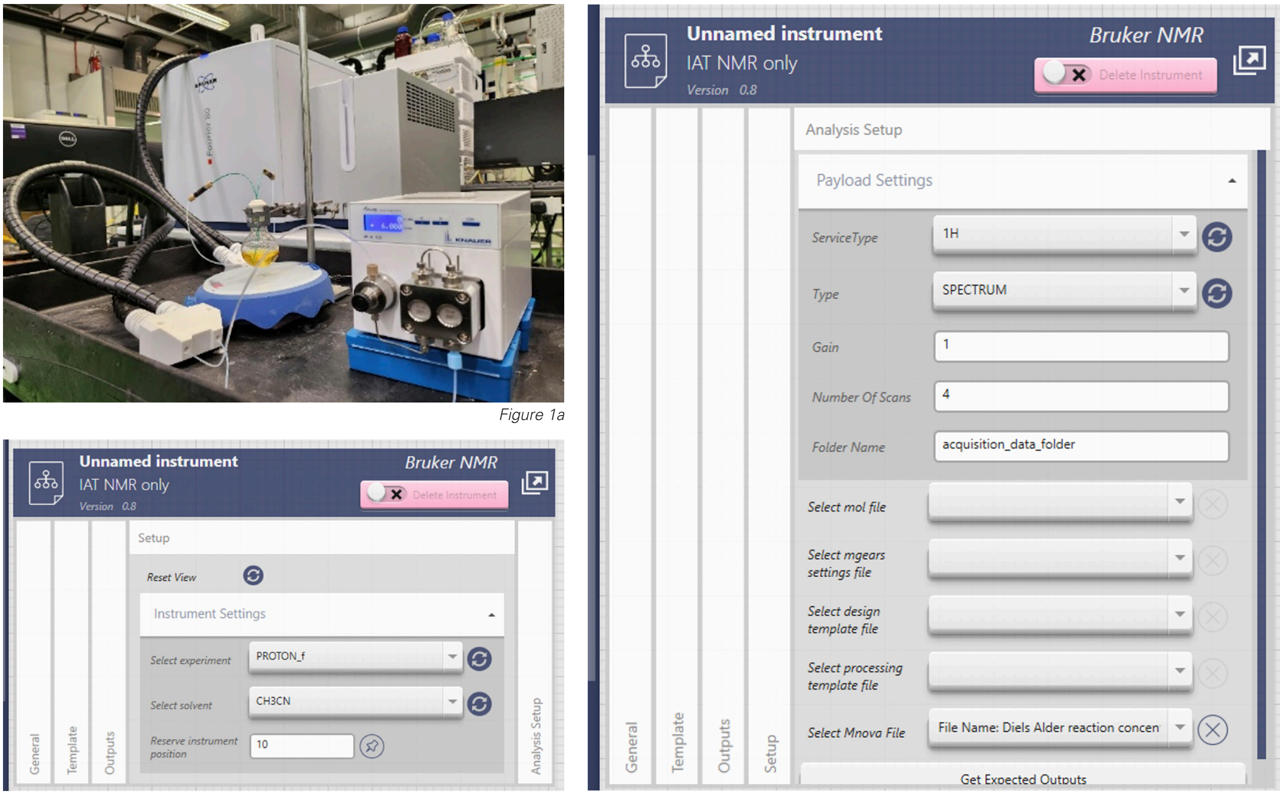

Figure 1a

Figure 1b

Figure 1c

Figure 1: (a) Typical set up used for reaction monitoring; (b) synTQ input window for selecting basic NMR instrument settings; (c) synTQ input window for selecting experimental parameters.

Flow and temperature control was enabled via separate synTQ adapters (**Figure 2**). Through these, users could control process parameters in real time from one single piece of software.

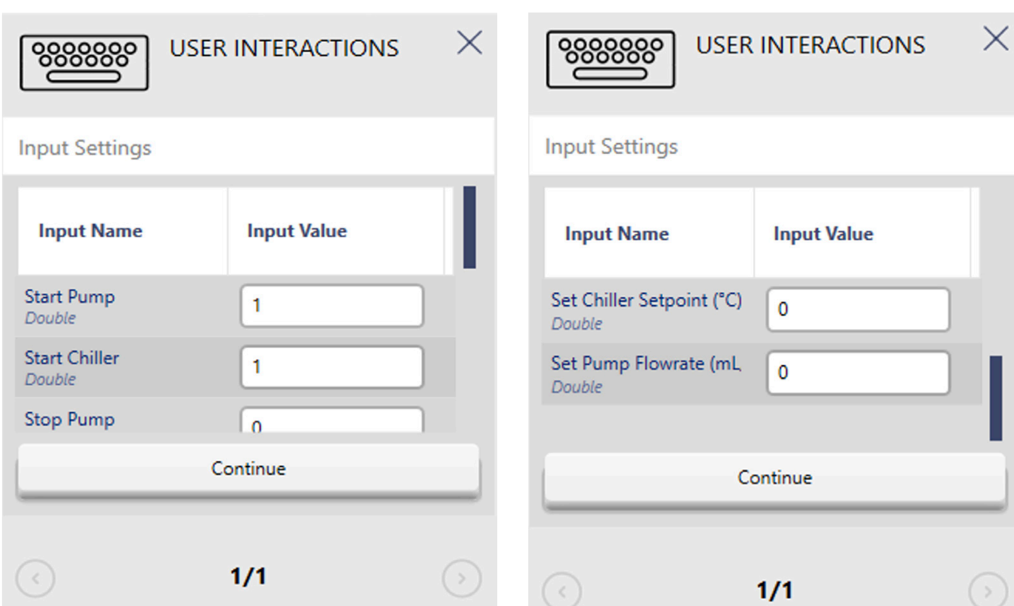

Figure 2: synTQ input windows for pump and heat exchanger control.

Results

To prepare for real-time reaction monitoring with the Fourier PAT environment, it is necessary to have prior knowledge of the characteristic chemical shifts of the starting materials, intermediates, and products. This is typically achieved by performing an initial test reaction. In this case, this was monitored externally using InsightMR software[5], Bruker's dedicated tool for reaction monitoring NMR studies. The acquired data, processed with Mnova, supported the generation of a stack plot of spectra over time, from which key signals could be identified and integrated (**Figure 3**). As a result, key resonances corresponding to the starting material (ethyl acetate), the product (acetic acid) and by-products (ethanol) were identified. This Mnova file is imported to synTQ and used as model for NMR orchestrations. These assigned signals in the model file served as references for use within synTQ for real-time recognition of spectral trends and process control applications.

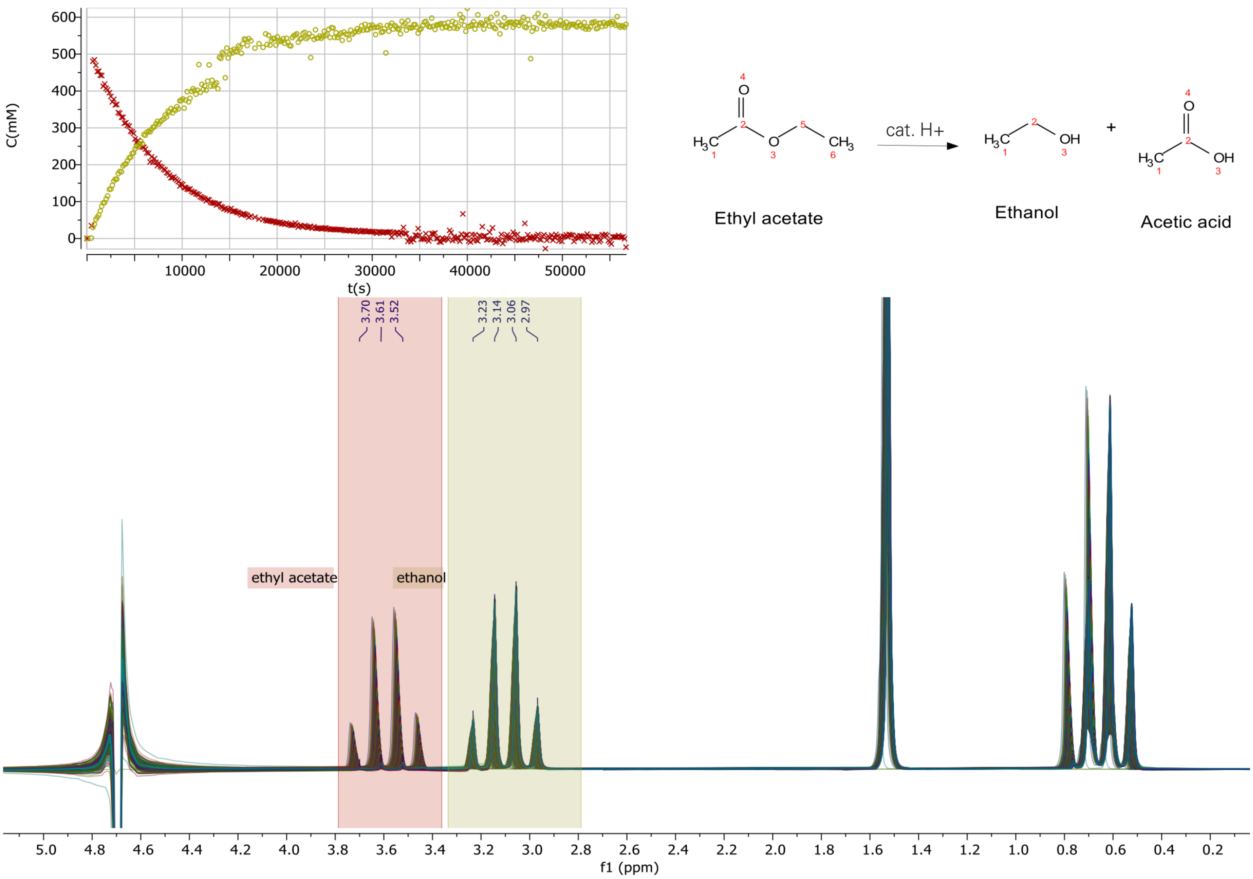

Figure 3: Mnova file used as model for synTQ NMR orchestration. K_WETDC_f was the pulse program used for NMR acquisitions with water peak suppression at 4.7 ppm (ns= 8, d1 = 5 s, l30 =1).

These integration values served as the foundation for real-time monitoring within synTQ. Once this model was established, the relevant Mnova file, containing the integral areas for the peaks of interest and if required, the associated concentrations, could be provided as input (**Figure 1c**) to synTQ. The PAT knowledge management platform could then visualize both spectral data and corresponding integrals directly in the synTQ interface, making it possible for operators to monitor reaction progress with a high degree of clarity and confidence. **Figure 4** shows data obtained from monitoring the hydrolysis reaction. The graph indicates a clear, progressive decline in the ethyl acetate signal and a corresponding rise in the acetic acid signal, confirming the expected stoichiometry and reaction progression. This experiment provided a compelling demonstration of how the Fourier 80 benchtop NMR can support highly accurate, granular information to support QbD systems.

[5] InsightMR: https://www.bruker.com/en/products-and-solutions/mr/nmr-software/insight-mr.html

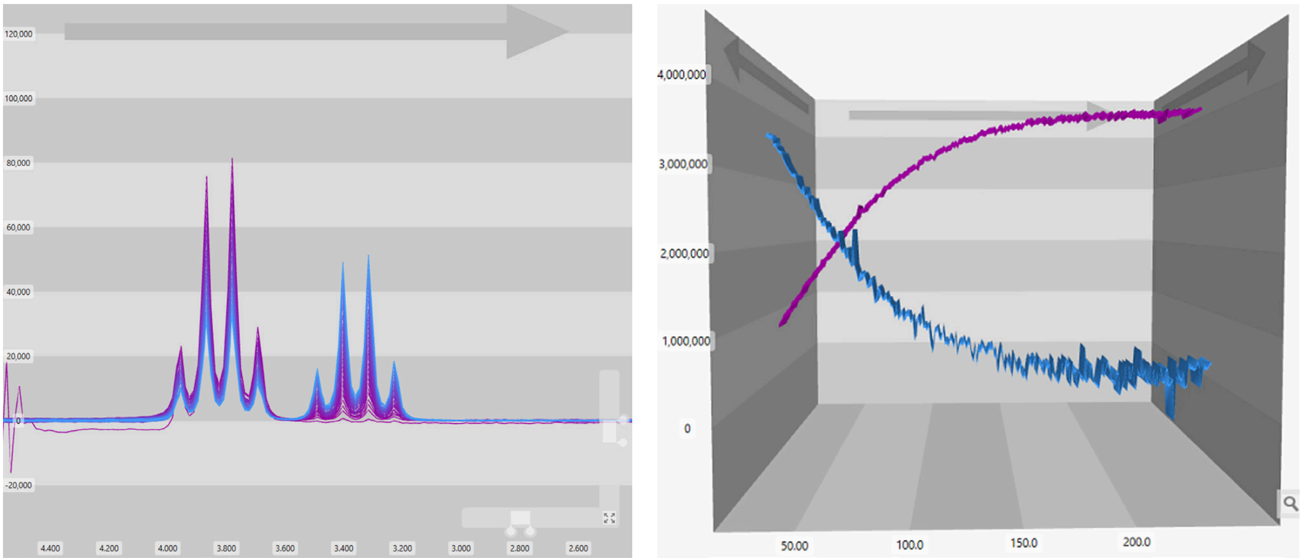

Figure 4: (left) NMR overlaid spectra of ethyl acetate and acetic acid visualized on synTQ; (right) Graph showing peak integrals as a function of time for reactant (blue) and product (purple) of the hydrolysis reaction.

A particular advantage of integrating process control and real-time reaction analysis in the same piece of software, namely synTQ, is the possibility of configuring conditions for autonomous self-regulation based on the NMR data obtained. In the ethyl acetate hydrolysis study, this is demonstrated by synTQ automatically stopping the pump once the reaction had reached completion. This was ascertained by the system when the product integral reached a pre-defined threshold in terms of integral value or concentration (**Figure 5**), which was indicative of complete conversion. Also in this case, the capabilities of the Fourier 80 NMR were adequate to support effective closed-loop feedback control. This type of process orchestration, driven by direct chemical observation rather than estimated parameters, represents a major advance in intelligent process management.

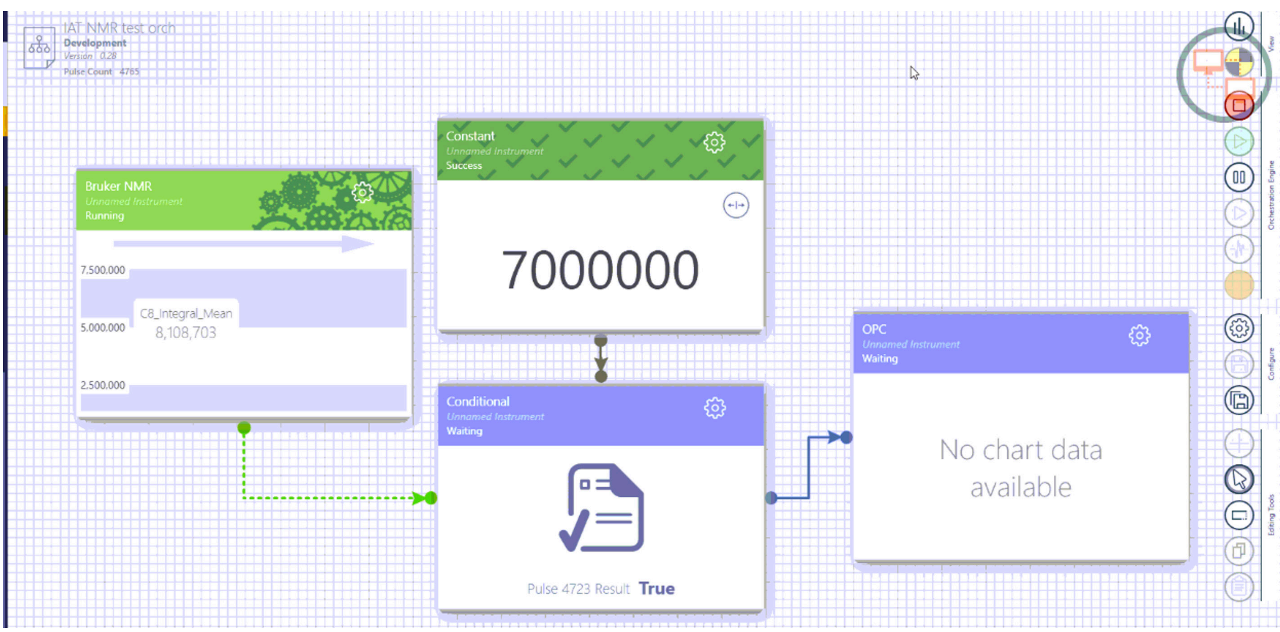

Figure 5: Example of synTQ conditional instrument orchestration. In this case, the software is designed to stop the pump once the NMR signal intensity of interest reaches 7000000.

Conclusions

Bruker's Fourier PAT setup leverages the power of the compact Fourier 80 benchtop NMR spectrometer, which is seamlessly integrated with the synTQ PAT knowledge management platform to drive intelligent process analysis and automation. This system allows pharmaceutical manufacturers to implement real-time monitoring, self-regulating, adaptive control, and increased process understanding without the complexity or cost of traditional high-field NMR systems. While this application note demonstrates how such a system can be applied to a simple model reaction, this approach is readily extensible to more complex reactions. Key advantages of the Fourier 80 NMR within the Fourier PAT setup include:

- Benchtop NMR with industrial robustness: The Fourier 80 delivers high-resolution spectra through a compact, cryogen-free design, making it ideal for installations on processing lines or in pilot plants.
- Seamless integration with automated workflows: Through synTQ, the Fourier 80 can trigger data acquisitions based on process events and provide real-time spectral feedback that supports automated, data-driven control and process parameter adjustments, such as pump flow rate or temperature adjustments.
- Real-time spectral insights: Both raw and processed spectral data are displayed and interpreted in real time, delivering immediate insights on CQAs while facilitating continuous process verification.
- Closed-loop control and optimization: By linking NMR output with actuators, such as pumps and heaters, the Fourier PAT setup supports adaptive control strategies that respond dynamically to chemical changes taking place during production processes.
- Customization and scalability: The system can be adapted to support different chemical processes, thanks to flexible software adaptors, and can be scaled to support applications ranging from laboratory to production environments.
- Enabler for the digital transformation: The data generated by the Fourier 80 can be fed to digital twins, supervisory control systems and advanced data analytics platforms, supporting a seamless integration into Industry 4.0 ecosystems.

This unified approach makes Bruker's Fourier 80 benchtop NMR a key tool to support PAT-driven manufacturing by making value-adding NMR analysis both accessible and practical across pharmaceutical research and development as well as manufacturing settings.

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