

IMPLEMENTATION OF A UNIFIED UPLC PLATFORM FOR THE ANALYSIS OF IN-PROCESS SAMPLES ACROSS MULTIPLE PROCESS STEPS

Waters

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OVERVIEW

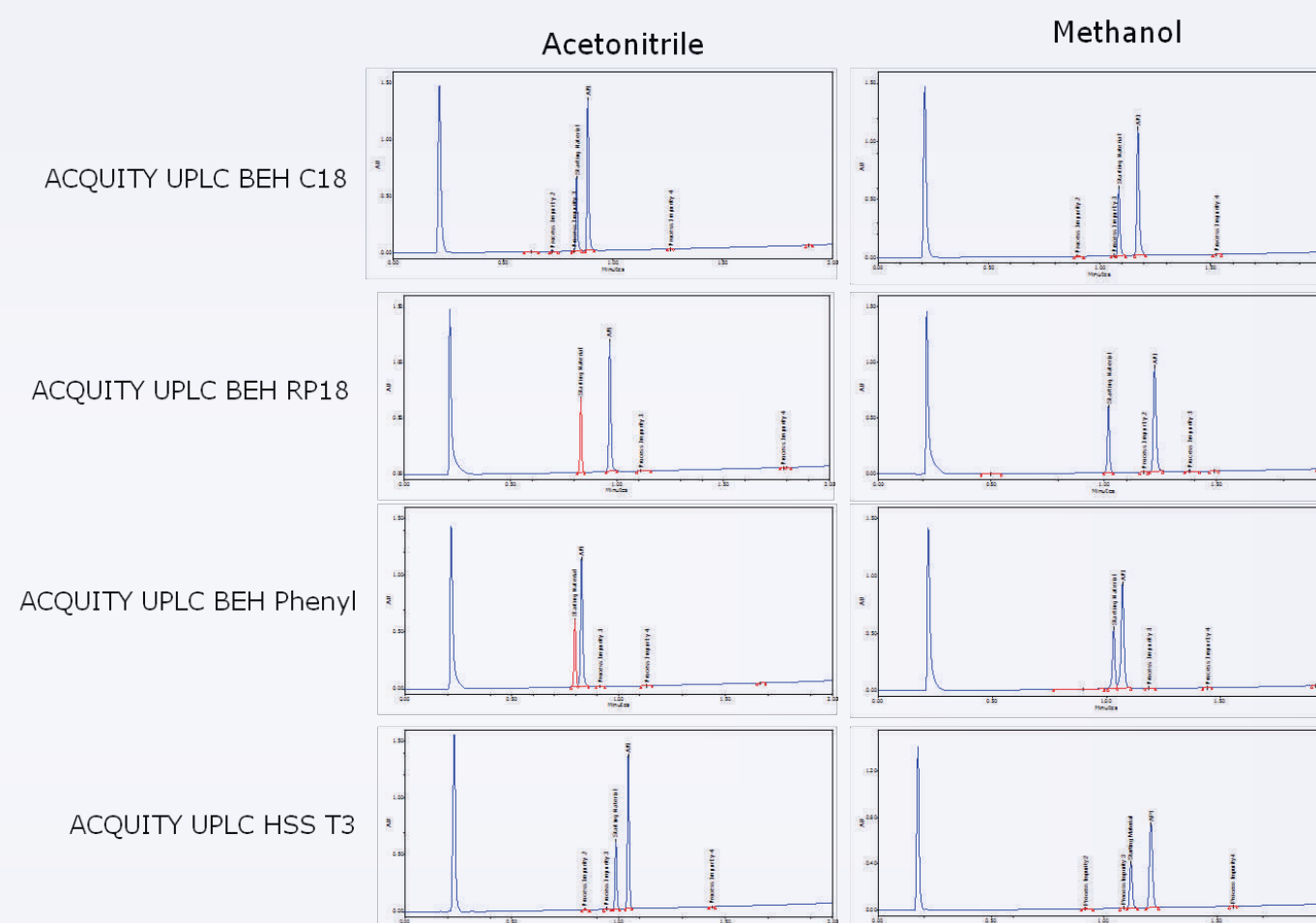
Throughout the manufacturing process of a pharmaceutical drug substance there are multiple steps where the introduction of atline or online monitoring is highly advantageous. These analysis points can include both upstream and downstream process steps. High performance liquid chromatography (HPLC) is the most commonly used off-line technique in the quality control (QC) laboratory for ensuring product quality. However LC is not routinely deployed on the manufacturing floor due to its long run times, hardware complexity, and need for sample preparation. However with ability to perform near real-time analysis with UPLC, the use of LC for process monitoring on the production floor is possible. The unified platform of a PATROL UPLC Process Analyzer to perform both atline and online analysis for the manufacture of an active pharmaceutical ingredient (API) is demonstrated. Additionally, with the same UPLC platform used in R&D, manufacturing for process monitoring and through to the QC laboratories, a direct link to historical data is available.

R&D Laboratories



Throughout the R&D process UPLC is an integral tool for determining critical information about the API. If UPLC technology is also used for process monitoring when the API is moved into manufacturing then these same UPLC methods can be used and the R&D data can be accessed as a historical reference.

BRIDGING THE TECHNOLOGY FROM R&D THROUGH MANUFACTURING

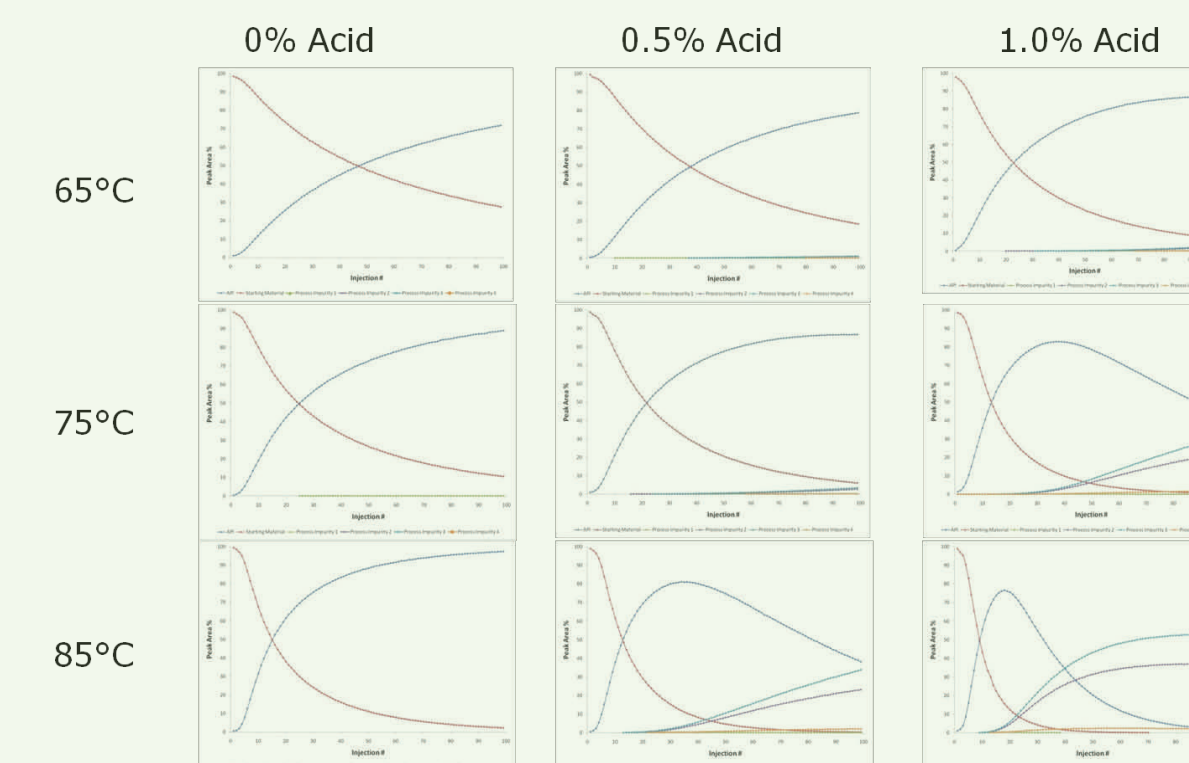
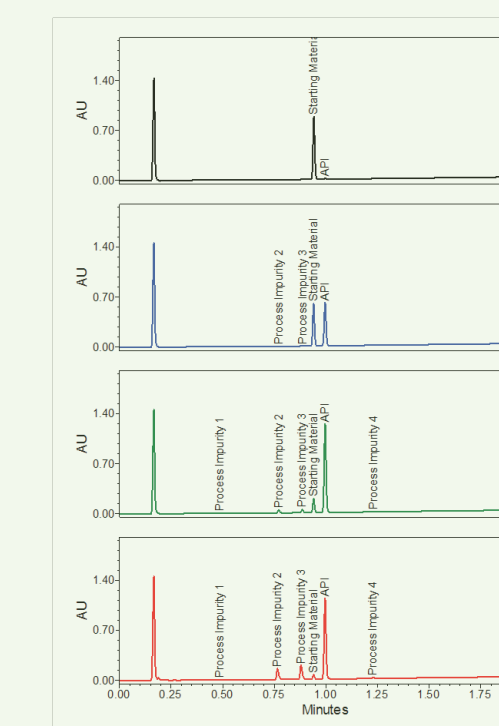


Methods developed during R&D can be used directly for online or atline process monitoring by UPLC or they can be redeveloped/optimized depending on the needs of a particular process step. The four column capacity of the ACQUITY UPLC Column Manager and the ability to select between different solvents combined with a method development software package such as SMATRIX provides a platform for a robust, automated method development strategy.

Process Method Development



Online monitoring by UPLC adds critical information to reaction optimization. The Process Sample Manager (PSM) can be used as a bench-top analyzer for process method development.



As critical reaction parameters are varied, the effect on the reaction maps can be investigated. This data in conjunction with chemometrics can be used to define the optimal conditions for the reaction. This will ensure the highest yield of API while minimizing the formation of undesired process impurities.

QC Laboratories

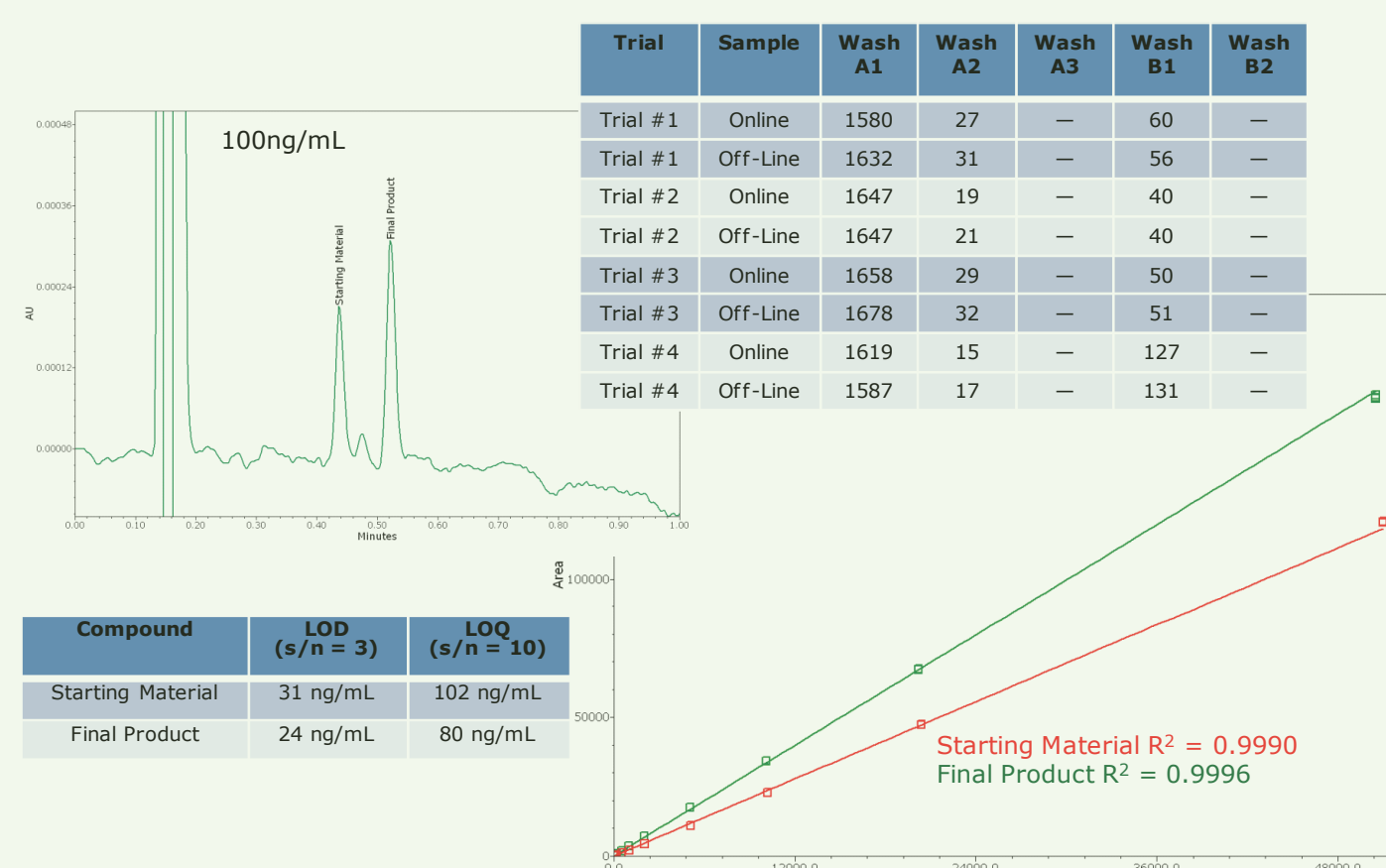


For final release testing, samples are sent to an off-line QC laboratory for testing. The same UPLC analytical methods that have been used throughout the entire development and manufacturing process are used and results can be compared to both historical and process data.

Manufacturing



The flexible platform of the PATROL UPLC Process analyzer allows it to be used for multiple process streams, with multiple applications, for both on-line and at-line applications. The simple to use interface and rugged, industrialized design enable easy introduction into a manufacturing environment.

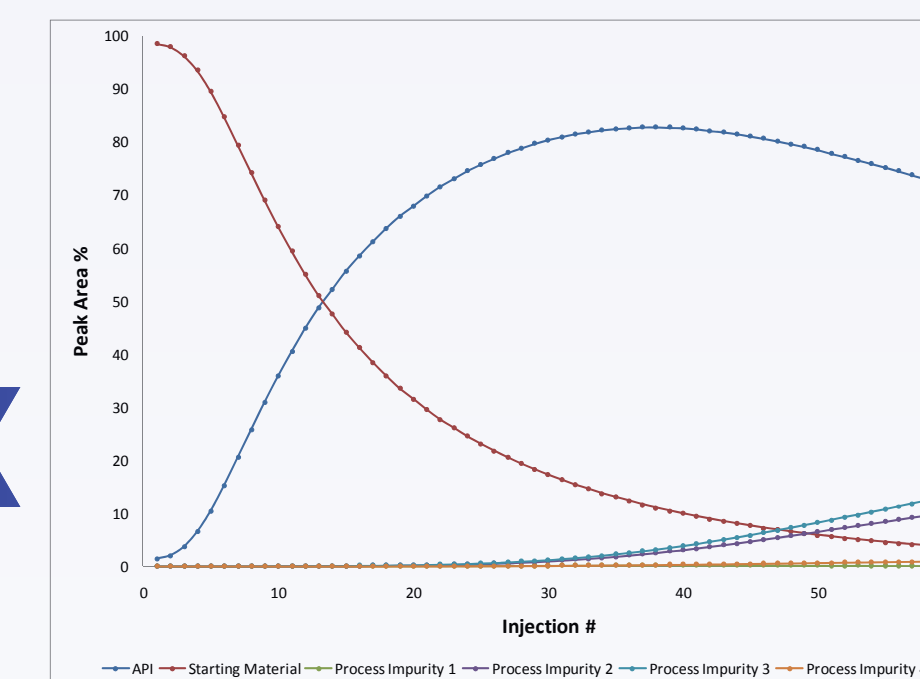


Compound	LOD (s/n = 3)	LOQ (s/n = 10)
Starting Material	31 ng/mL	102 ng/mL
Final Product	24 ng/mL	80 ng/mL

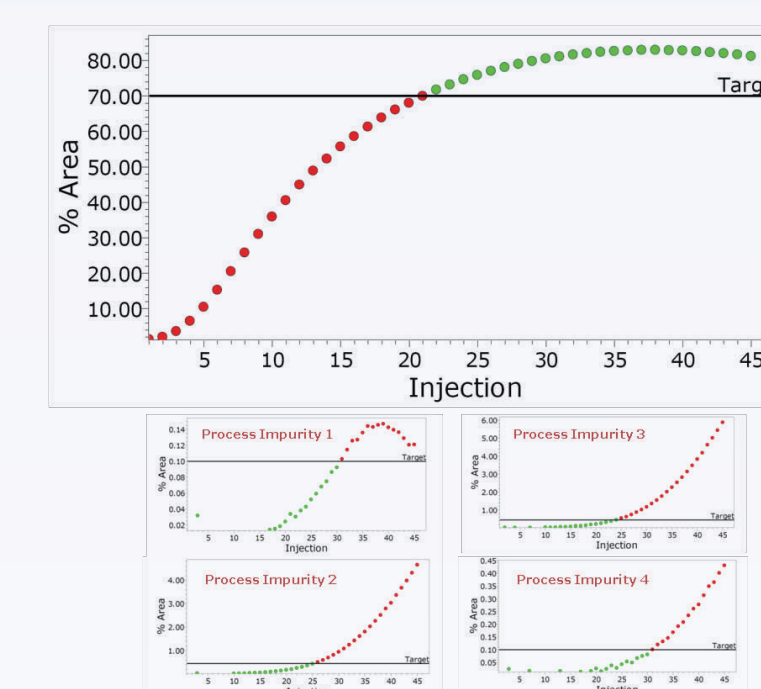
Starting Material R² = 0.9990
Final Product R² = 0.9996

The same system that is used for reaction monitoring can also be used for online monitoring of wash solvents and support cleaning validation. The benefits of online monitoring for cleaning validation include speed of analysis, reduced solvent consumption, and decreased manufacturing idle times. The same results achieved in an off-line QC laboratory for the analysis of wash solvents and swabs are achieved with the online monitoring of wash solvent with the PATROL UPLC Process Analyzer.

Pilot Plant



In the pilot plant, reaction progression is monitored on-line. The maps collected batch-to-batch can be used to create libraries. Deviations in the expected reaction maps can be compared against these libraries as well as data collected during process method development. Any unexpected peaks or results can also be referenced against the historical R&D data.



Based upon the process development data, limits can be set for the target API potency and thresholds for the formation of process impurities. These limits can be defined within the Empower Software to send results that will signal forward processing or flags and notifications when a deviation occurs.



For deployment to a pilot plant or manufacturing environment, a PAT sensor must be robust and reliable. The same proven fluidics (solvent delivery, inject valve, detector, and column) used in the ACQUITY UPLC System are used in the PATROL UPLC Process Analyzer.