THE WATERS ACQUITY UPLC SYSTEM
Migrating to UPLC Increases Throughput and Reduces Costs

Client: A state-of-the-art DMPK laboratory

BUSINESSsolution

BACKGROUND

The characterization and quantitation of drug metabolites in toxicological species is an essential part of the drug development process. As part of the regulatory submission, drug metabolism and pharmacokinetics (DMPK) laboratories are required to quantitatively profile drug metabolites during the administration of a candidate pharmaceutical compound to ensure that a sufficient safety window is demonstrated for each of the *in vivo* metabolites observed in humans.

This activity is normally achieved by the administration of a radio-labeled isotope of the compound under evaluation to the animal or human being tested. The biological fluids collected are then measured to determine how the compound is metabolized and eliminated in the body over a period of time, normally performed by liquid scintillation counting techniques. HPLC paired with a radiochemical detector yields information about the structural and quantitative differences in the metabolites produced across species and gender.

CHALLENGE

During a metabolism study, a large number of samples must be profiled to effectively compare inter-gender variation and the effects of dosing levels and repeat administration. Countering the need for high throughput is the need to ensure a high-resolution chromatographic separation that clearly resolves and detects all of the metabolites.

Where this throughput compromise is made, analytical run times of 40 to 60 minutes per sample are not uncommon.

In radio-labeled HPLC analysis, there are two approaches for analyte detection. One approach uses in-line detection using a radiochemical detector, during which the LC eluent is mixed with scintillation fluid and the resulting mixture enters the scintillation counter detection cell to measure radioactivity. With the second approach, LC fractions are collected, evaporate to dryness and mixed with a dry scintillant compound; radioactivity is measured using a microplate scintillation counter.

While the second option requires time-consuming evaporation steps to dryness—typically six to eight hours—it produces significantly more sensitive results. The true challenge is balancing analysis time needed to maintain sufficient chromatographic resolution against the demands of a high-throughput laboratory environment.

THE SOLUTION

In a state-of-the-art DMPK laboratory, a Waters® ACQUITY Ultra Performance LC™ (UPLC™) System and radiochemical detector (30 µL cell) configuration were chosen to solve the resolution/throughput challenge.

The first in-line approach employed an eluent flow rate of 0.5 mL/min, and was mixed with scintillation fluid at a ratio of 5:1, 2.5 mL/min. With this UPLC configuration, the analytical run time was reduced from 40 minutes to just 10 minutes, and the overall analysis was accomplished in only 12 minutes, compared against 50 minutes with HPLC.

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In all instances, the chromatographic resolution was improved or maintained in one quarter of the time. In a fraction collection mode, the typical well fraction volume was reduced from 600 µL for HPLC to just 15 µL for UPLC.

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The decrease in well fraction volume then reduced the average sample evaporation time to just one hour. And while the volume of scintillation fluid remained the same for both methods, the overall analysis time was reduced by approximately seven hours with UPLC.

BUSINESS BENEFIT

The DMPK laboratory saw significant gains in cost and throughput. For a typical HPLC run, the system would consume 200 mL of scintillant costing approximately $2.00, whereas UPLC used just 30 mL of scintillation fluid at $0.30—a 6.6-fold reduction in expenditures.

Moreover, 40 samples with UPLC could be analyzed in an eight-hour workday vs. just 10 HPLC samples—a four-fold throughput gain. Extending this productivity gain over a year's time, approximately 7,500 more UPLC samples were analyzed, a savings of 425 liters of scintillation fluid at a cost savings of $4,250.

The implementation resulted in an estimated cost reduction to $1.36 per sample for UPLC, from $5.20 per sample for HPLC, over a five-year instrument life.

Factoring in an additional radiochemical detector cost of $40,000, the implementation of UPLC in the large pharmaceutical DMPK lab resulted in an estimated cost reduction to $1.36 per sample for UPLC, from $5.20 per sample for HPLC, over a five-year instrument life.

WATERS ACQUITY ULTRA PERFORMANCE LC SYSTEM

The Waters ACQUITY UPLC System synergistically combines unique instrumentation, column chemistries, detectors, software for data acquisition and processing and support services, creating a singular solution with superior sensitivity, resolution, efficiency and sample throughput.

When coupled with Waters Micromass® MS Technologies, UPLC provides a level of separation, quantification and characterization previously unattainable with traditional HPLC methods.

UPLC today is being employed by companies that rely heavily on HPLC—bringing their laboratories measurable improvements in analytical sensitivity, resolution and speed. Ultimately, these firms are looking for meaningful ways to increase laboratory productivity, decrease operational costs, facilitate product development and increase revenue generation.

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