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Pharmaceutical QC Realizes Significant Cost Savings Through Reduced Holding Times and Consumable Costs

Organization: Chromicent GmbH
Technology: ACQUITY UltraPerformance Convergence Chromatography (UPC^2)

BACKGROUND

Chromicent GmbH, a pharmaceutical services company founded in 2013 by CEOs Alexander Schmidt and Mijo Stanic, provides method development, transfer, validation, and consulting services. Specialists in Quality-by-Design (QbD)[1, 2] and expert in troubleshooting, the company helps clients improve analytical workflows and methodologies using a wide range of analytical technologies. Chromicent offers consulting services and a wide range of theoretical and practical training courses relating to chromatography, QbD, and risk assessment, and their expertise in FDA, EP, and ICH regulatory guidelines is invaluable to their industrial customers.

With a passion for new technologies, Chromicent's business model is based on demonstrating the benefits of new approaches and innovation to their clients to help improve productivity and quality. When Waters® introduced ACQUITY® UltraPerformance Convergence Chromatography™ (UPC^2®) in 2012, Chromicent could see the potential benefits of this new technology for their customers and were amongst the first to implement UPC^2 in their laboratory.

chromicent Pharmaceutical Services

Development, Validation and Optimisation of Chromatographic Methods Employing Quality by Design

High separation efficiency with convergence chromatography

Of the chromatographic tools available today, the two most commonly utilized are gas chromatography and liquid chromatography (LC). Due to significant advancements in the performance of systems designed to manage supercritical fluids, convergence chromatography is a viable chromatographic approach for both complex and routine separation challenges. In convergence chromatography, separation is achieved by manipulating the density and composition of a supercritical fluid-based mobile phase. Because of the very high diffusivity of the mobile phase, high separation efficiency can be achieved. Additionally, the diversity of stationary phase and mobile phase (co-solvent) options give the chromatographer access to the largest selectivity space available to any separation technique. "Analytical chemists are always looking for more efficient techniques to overcome analytical challenges and meet today's regulatory and scientific requirements," says Mr. Schmidt.

With the ability to accurately and precisely deliver co-solvents at concentrations of less than 5%, convergence chromatography technology such as Waters ACQUITY UPC^2 system are greatly superior to the previous generation of repurposed HPLC/supercritical fluid chromatography (SFC) systems. The result is a robust chromatographic system with

excellent reproducibility. The use of supercritical fluids as a mobile phase in chromatography presents unique advantages compared with traditional HPLC as the low viscosity and high diffusivity allow faster and more efficient separations.[3]

When asked to develop or redevelop methods using HPLC or UPLC, the Chromicent team preferentially leverage UPC^2. This delivers a variety of advantages to their clients:

- Orthogonal information: two different separations approaches can provide more information about their samples
- More confidence in their data and reduced risk that impurities are coeluting with the API
- Future proofing: the client can register both methods at once, providing the option to use either LC and/or UPC^2 Technology in quality testing in the future
- Significantly reduced holding time: shorter UPC^2 run times compared with traditional HPLC methods
- Lower consumable costs through the use of a CO_2 mobile phase

"When we offer the customers the choice of two methods – a UPLC method and one that leverages the latest technology, UPC^2, we tell them, 'You should bring both into your application so that you are ready to implement the new technology when your product is approved by the authorities'," says Mr. Schmidt. "It makes sense to implement both for the same price and have the flexibility to move to the newer technology when the time is right."

Partnering as a strategy for continuous improvement of analytical methodologies

ICH Q10 advocates the use of new technologies in order to provide greater understanding and/or confidence when ensuring product quality. Chromicent has been successful in demonstrating this concept and has built strong relationships within the pharmaceutical industry supporting customers who are looking to continually improve their processes. Chromicent helps by providing guidance and support to improve analytical methodologies, and comprehensive training to ensure the methods can be successfully implemented.

Chromicent supports clients by running QC checks on methods developed using UPC^2 where the client is not yet ready to purchase their own system. In some cases, companies are looking to modernize their methods and realize cost savings but they need to have a critical mass of methods before they can justify the purchase of a UPC^2 System. Chromicent helps these clients by carrying out the analyses in their GMP registered facility until the clients invest in their own instrumentation.

UPC^2 facilitates faster product release

Schmidt and Stanic are widely renowned for their knowledge and experience in method redevelopment. For this reason, they were recently approached by a leading generics producer and asked to redevelop the existing European Pharmacopeia (EP) method for carbamazepine. The runtime of the EP method for carbamazepine is 110 minutes and it originally took days for this producer to carry out the release testing of a single batch. The situation worsened when a variety of products were produced using the same facility.

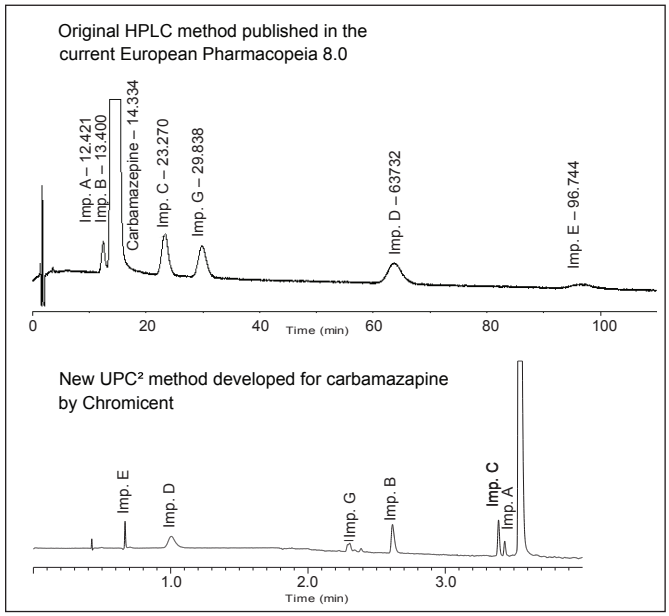

Figure 1. Chromicent used a systematic QbD method development approach to redevelop the original EP HPLC method for carbamazepine. The result is a robust UPC^2 method with a significantly shorter run time of less than 4 minutes.

The Chromicent team redeveloped the existing EP method for carbamazepine using ACQUITY UPC^2. They demonstrated that batch release test times could be significantly shortened. This, and the savings realized in consumable costs, reduced the client's overall costs by almost 60 percent when running the new method on one UPC^2 System versus the EP method on eight HPLC systems (calculation includes analytical system investment/depreciation and maintenance and estimates holding time savings.) The consumables costs associated with the new UPC^2 method were 96 percent lower than with the existing HPLC method.

"The run time of HPLC is the bottleneck," says Mr. Schmidt. He notes that investing in and maintaining eight HPLCs costs nearly

70 percent more than a single UPC^2 and still cannot match UPC^2's ability to accelerate holding time or lower consumable costs. "We show customers that by using this technology, they can save a great deal of money."

Faster troubleshooting of out-of-specification results

Often, EP and USP monographs are based on methods containing phosphate or similar buffers that are incompatible with mass spectrometry. However, when an out-of-specification (OOS) result occurs, e.g. appearance of an unexpected impurity, a quick look at the molecular mass of the compound can help to understand why the OOS has arisen. When approached by clients and asked to help identify unexpected impurities, Chromicent redevelops these methods on UPC^2, which is fully compatible with modern mass detection techniques.

When analyzing a drug product being developed as a treatment for Parkinson's Disease, one of Chromicant's clients found impurities that they were unable to identify. In this case, however, a high concentration of ion pair reagents and buffers in the eluent meant they could not use mass spectrometry (MS) to elucidate the unknown components. By transferring the method to a UPC^2-MS system, Chromicent was able to quickly identify the impurities, which resulted from interaction between the API and two excipients. By changing one of the excipients the problem could be fixed very easily and meant no delay in the registration process for this formulation.

Analysis of chiral compounds

Schmidt and Stanic also recommend UPC^2 for the development of methods for chiral impurities: "For the development of chiral methods, UPC^2 would be our first choice because we don't need to use toxic organic solvents. Workplace safety is a priority for us," Mr. Schmidt says.

In his *Bioanalysis*[3] article on the measurement of enantiomers, Mr. Schmidt comments that, "supercritical fluid chromatography allows fast and efficient separation of enantiomers." He adds "the combination of SFC-MS/MS allows for highly selective detection with very low limits of detection (LODs)."

Cleaner, faster, more efficient methods

To some, the adoption of an innovative technology like UPC^2 is seen as too big a risk, or too great a hurdle. However, Chromicent has been instrumental in supporting forward-looking companies to realize the significant benefits offered by modernizing their approach. Some of the realized benefits include lower solvent usage leading to reduced consumables costs, faster product release, an almost unlimited selectivity range, and compatibility with modern detection techniques such as mass spectrometry. For Chromicent, their promotion of a combined HPLC/UPLC and UPC^2 method development approach alone has, in a very short time, led to an estimated 5–10% growth in their business. Their clients want to be prepared for the future and have embraced the use of cleaner methods for more efficient product release.

References

1. *In silico* robustness testing of a compendial HPLC purity method by using of a multidimensional design space build by chromatography modeling – case study pramipexole. Alexander H Schmidt, Mijo Stanic and Imre Molnár. *Journal of Pharmaceutical and Biomedical Analysis* 91 (2014) 97-107
2. A QbD with Design-of-Experiments approach for development of a state-of-the-art UPLC purity method for carbamazepine. Alexander H Schmidt and Carsten Wess, *Journal of Liquid Chromatography & Related Technologies* 37 (2014) 2653-2666
3. What is the potential of measuring the enantiomeric ratio of drugs using supercritical fluid chromatography–MS? Maria Kristina Parr and Alexander H Schmidt, *Bioanalysis* 6 (2014) 3267-3270.

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Waters Corporation
34 Maple Street
Milford, MA 01757 U.S.A.
T: 1 508 478 2000
F: 1 508 872 1990
www.waters.com