Understanding the Role of Quality by Design in Chromatographic Method Development

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Introduction

Quality by Design (QbD) has become popular within the pharmaceutical industry and the FDA has cited a risk-based approach to drug development as a desirable state for the near future.[1] In this state, more complete information and transparency relating to risk assessment will be made available for new drug aplications speeding the approval process, and preventing late-stage failures.[1]

At the heart of QbD lies several principles, all leading toward the goal of building in quality from the earliest stages of drug development including knowledge retention, elimination of errors, and increased experimental scope. To be successful, QbD must be applied at every stage in the development and manufacturing process; however, one can consider processes within drug development on an individual basis to apply QbD principles.

One such process is the development of chromatographic methods for impurities and degradant studies. Ensuring both robustness and optimization from an efficiency standpoint is time-consuming and difficult. Generally, method development is carried out using a trial-and-error approach, and requires a large amount of manual data interpretation. However, QbD principles can be directly applied to this process resulting in better, more robust separations.

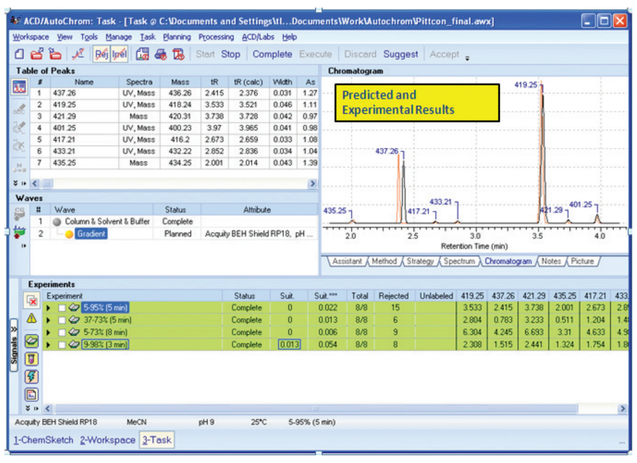

Figure 1: Prediction of retention times and simulation of other parameters such as temperature, gradient, and buffer concentrations allows the software to focus on the experiments that are most likely to yield better results before any injections are carried out. The size of the design space is effectively increased because more variations can be considered with less time and fewer injections.

Increasing the Size of the Experimental Design Space

The variety of parameters involved in chromatographic separation means that the combinations and permutations of possible parameters for investigation quickly become unfeasible to consider by manual experimentation. To cover a large-enough experimental space, the matrix of possible column types, temperatures, gradients, and buffer concentrations would result in thousands of experiments, requiring far more time and resources than are typically available to chromatographers in an industrial R&D lab. In order to work within limitations, the chromatographer has to choose a certain subset of parameters, and begins varying one at a time. The result is that localized optima are established before moving on to the next parameter. Often, the true optimum will be missed using this approach. The result of the trial-and-error approach commonly used today is a compromise between the best use of available resources and experimental rigor.

Advanced Chemistry Development Inc.,(ACD/Labs) offers method-development software that increases the feasibility of more thorough, systematic studies through intelligent selection of starting points, simulation of experimental results, recycling of previous experiments and project management, which includes automatic peak tracking and information overview, and instrument control for some of the industry's most popular chromatographic systems.

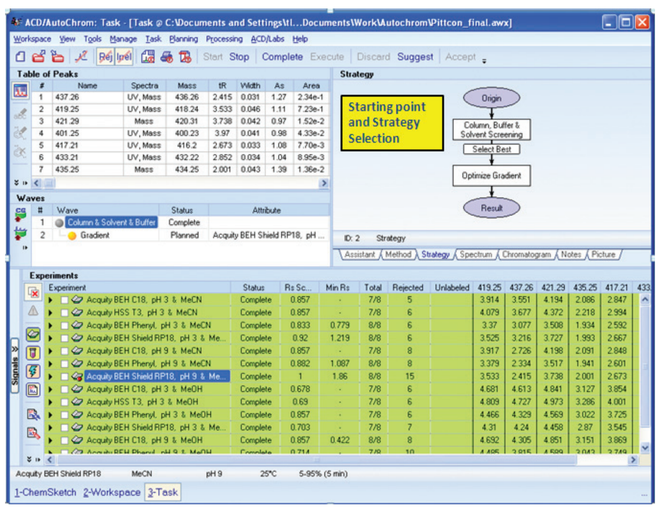

Figure 2: Choosing an appropriate starting point helps to reduce the amount of hands-on work required to optimize methods. Simulation and database searching to leverage prior method development are two methods that help determine a better point.

Starting Point Selection

By intelligently choosing a good starting point, combinations of parameters that are clearly inappropriate are eliminated from the scope of experimentation, in favor of areas that are most likely to produce results.[2] But how is a good starting point selected? Chromatographers use their experience and expertise, while software is capable of different approaches: (1)Comparing the chemical structures of compounds to be separated against a database of successful methods used for compounds with similar structural features[3]; and (2) Using predictive algorithms to model chromatograms and predict retention times.[3]

In the first approach, software such as ACD/ChromGenius is used to identify existing methods from a knowledgebase, where compounds similar in structure to the compound of interest were separated. Optimization for the new compound then proceeds, and any experimental obtained is added back to the database to be applied to future development.

The second approach uses software algorithms present in ACD/LC Simulator to predict physicochemical properties of the compound of interest, leading to an estimate of retention times under particular system conditions. Such an approach is appropriate when there is a lack of experimental data upon which to build a knowledgebase, or when the compound of interest belongs to a novel chemical class not represented in the knowledgebase.

Minimize the Potential for Error

With an appropriate starting point, the matrix of possible conditions is greatly reduced, however, a great deal of experimentation may still be needed to optimize the method for the current project. The potential for human error increases as the amount of manual data interpretation increases. Automated peak tracking, and automation of instrument control, help eliminate this potential and the time required for such interpretation.

ACD/AutoChrom Method Development Suite (MDS) uses full scan LC/MS data to track peaks between runs, analyzes results, and makes recommendations for the best next step. When configured with Agilent ChemStation or Waters Empower 2 systems, ACD/AutoChrom MDS also configures the instrument with the appropriate parameters and triggers injections. Upon completion of the runs, data is swept back to ACD/AutoChrom MDS for the next iterative step.

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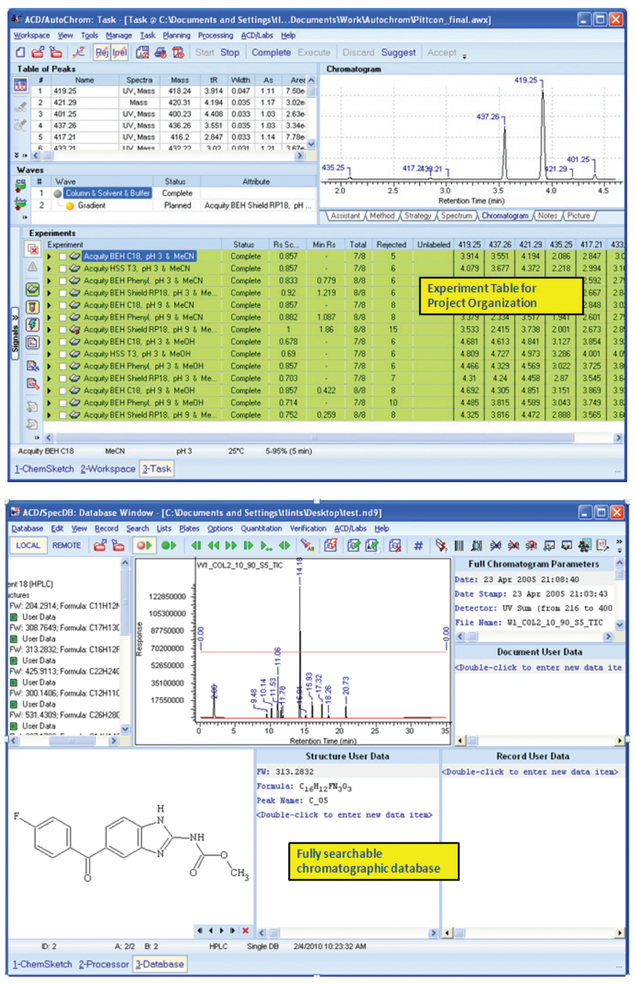

Figures 3 and 4: Effective project management with concise reporting, links to related data, and fully searchable databases of structures, chromatograms and method parameters simplifies reporting access to information for audits, reporting, and collaboration.

Knowledge Retention

An important aspect of QbD is maintaining complete knowledge of the process and having the ability to retrieve and share this information in the future. Manually collecting the data produced in a stability study is untenable when one considers the vast amount of data that is generated. However, building an applications database using ACD/ChromGenius or ACD/AutoChrom MDS makes collecting, organizing, and storing this information in an electronic database infinitely more manageable[4], and provides means of securing, reporting, and accessing the data for audit by colleagues or regulators.

A particular benefit of knowledge retention for impurity studies is the ability to retain chemical structure information and query it again later. Impurities that reappear can be quickly identified by searching the accumulated project data, eliminating the task of characterizing the impurity again.

Conclusion

QbD principles are directly applicable to LC method development in several ways: expansion of the experimental design space, eliminating the potential for error, and retention of project information. ACD/Labs chromatographic method development tools make this possible by guiding the process of choosing a better starting point, using predictive power to guide optimization, and allowing chromatographers to utilize the wealth of chemical knowledge already accumulated, applying it to current situations. Quality is built into the development of the method itself, resulting in better, more robust separations into the stability study process by producing well-developed, traceable, error-free results, and finally into the drug product by bringing novel products to market faster, and more cost effectively.

References

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