An Informatics Based Approach to Developing a Stability Indicating Method

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Introduction

Significant time and effort is spent on chromatographic method development during drug development. The aim of much of this work is to develop a validated analytical procedure that will measure the API in Drug Substance or Drug Product, separate from impurities, excipients, or degradation products (a stability indicating method).

Development of a stability indicating method is aided by an understanding of the process scheme and efficient communication between departments—from process chemistry to analytical R&D—often located in different geographies. Each group typically uses different systems to capture information, leading to Microsoft Excel and PowerPoint being the common means of communication. While easily accessible, these documents are a poor substitute for systems purpose built to handle complex scientific data, leaving results open to interpretation.

Here we discuss two software systems:
ACD/AutoChrom—method development software that enables a systematic and exhaustive approach towards method development with as much or as little expert intervention as desired.
Luminata™—an informatics system that captures structural, analytical, and process related data in a structured and searchable manner to facilitate inter and intra departmental communications

Using such systems allows Quality by Design (QbD) principles to be extended to the drug development process, leading to a safe, effective and well qualified product. Furthermore, it brings information critical to efficient development of stability indicating methods to the chromatographer's fingertips.

Developing a stability indicating method

ACD/AutoChrom provides:
•The capability to build strategies, following quality by design (QbD) principles, to help achieve robust methods
•Instrument control
•Automated peak tracking between runs to track the variation in compound elution
•A single interface to store method data, structures, and analyzed chromatograms to facilitate future method development efforts.

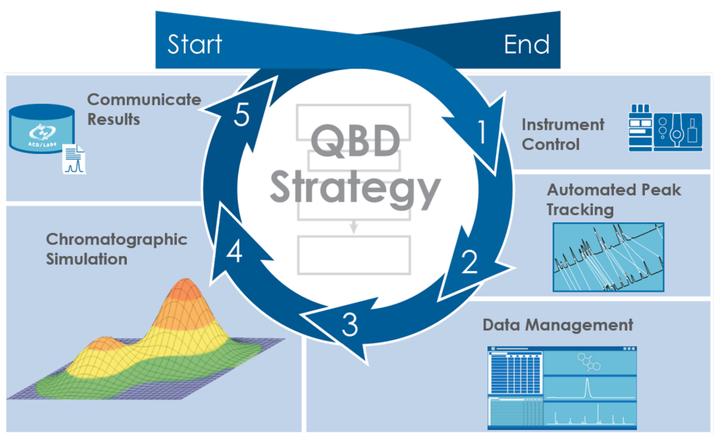


Figure 1 ACD/AutoChrom helps in the development of robust stability indicating methods following QbD principles.

A limited number of separations can be used to determine the affect of adjusting additional parameters. Communication of results to the system helps the software suggest the best screening and optimization runs to ultimately identify optimal separation conditions.

Managing process data in a purpose-built scientific system

Luminata facilitates the capture and visualization of structural and analytical data associated with a process (including associated impurities, degradants, and results of stability studies). Unification of this information helps the chromatographer access all process information as necessary.

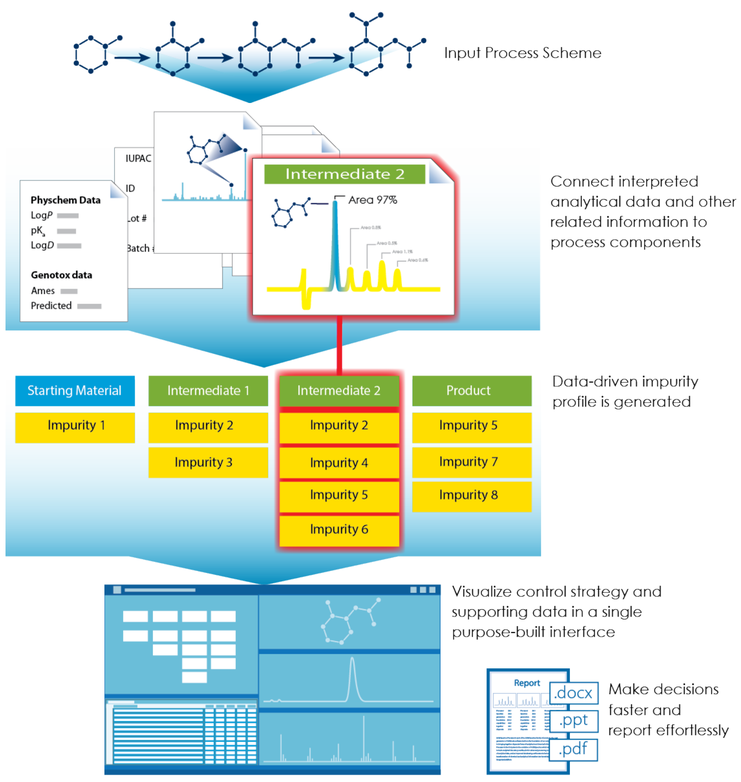


Figure 2 Impurity management software, Luminata, helps unify process knowledge and establish effective impurity control strategies.

Process schemes and structure data

The process scheme includes solvents, reagents, reaction conditions, and other structural entities—impurities and degradants, etc.—for easy review, analysis, and reporting. Compounds are color-coded to indicate starting material (blue), intermediate or API (green), or impurity (yellow). The process map may be customized to help visualize the information of interest to different users—to view impurity fate and purge.

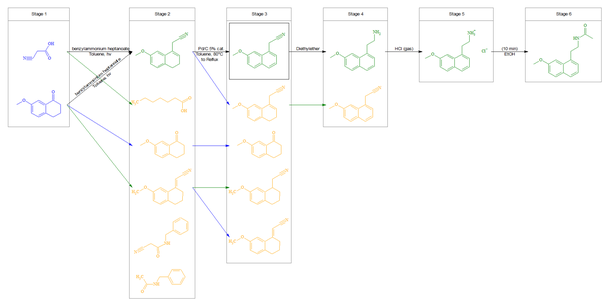


Figure 3 A synthetic route for Agomelatine, as visualized in Luminata, with process impurities observed at each stage.

Chromatographic, spectroscopic, quantitative, and process data

As entities are added to the process scheme and impurity map in Luminata, they are automatically added to the database where reference data can also be associated. Corresponding analytical data for a batch can be added by attaching LC-MS data to individual compounds/components; adding a new entity; or pulling data in with a *.txt, *.sdf, or *.csv file.

As analytical and/or process data is imported into the software, the Control Chart is automatically updated with quantitative information, such as peak areas from chromatograms. This information, conveniently collected in a single interface and extracted directly form the analytical data, ensures that errors from manual transcription are avoided and reduces the burden of data transfer by the scientist.

Details of the hardware used and method employed to separate samples is stored with the chromatogram for comprehensive, centralized knowledge management. Reasons for adapting a method may be included as notes for easy tracking and seamless knowledge transfer.

The Control Chart can be filtered to monitor impurity fate and purge, or to review differences between batches. Color coding of molecular entities follows throughout the software, indicating starting material, intermediate or API, or an impurity.

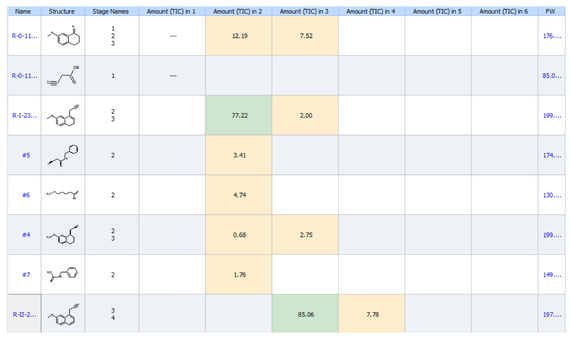


Figure 4 The Control Chart summarizes all entities, with quantities, in a given process batch.

Data in the Luminata knowledgebase is intelligently linked to allow the scientist to drill down from a compound to associated meta data such as supplier and physicochemical property information.

Reference and Batch Data

Reference analytical data can be viewed in the same interface alongside batch data. Spectra (NMR, MS, DSC, IR, UV, and more) can be overlaid for easy comparison, and visualized with chromatographic data.

Figure 5 View reference spectra and chromatograms with batch data for easy comparison in Luminata.

Forced Degradation and Stability Studies

The entities identified and characterized in forced degradation and stability studies can be added to the process scheme along with impurities and intermediates. The reaction scheme can be filtered to show only this data if desired. ICH guidelines were used to identify common types of degradation studies (acid, base, peroxide, heat, and UV) and stability studies (temperature, relative humidity, and time) that are made available in Luminata to facilitate data input and visualization.

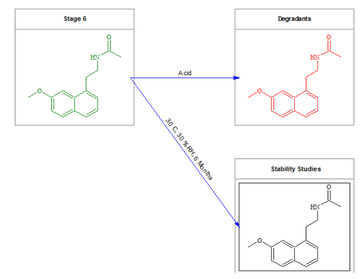


Figure 6 View degradants and results of stability studies within the process scheme and impurity map in Luminata.

Create composite chromatograms to aid stability indicating method development

Should new impurities be identified in forced degradation or stability studies, resulting chromatograms and method information can be imported into AutoChrom to facilitate further improvement of the stability indicating method, or imported at a later stage to store and track peaks.

Experiment	Gradient	Stop Time	Status	Suit.	Suit.***	Total	Rejected	#(TAC)
5-95% (5 min)	5-95% (5 min)	5.25	Complete	0	0.401	7/7	16	15
Blank	-	-	-	-	-	0/0		1
Control	-	-	-	0	0.403	4/4	4	2
Acidic	-	-	-	0	0.401	4/4	4	5
Basic	-	-	-	-	-	1/7	5	3
H2O2	-	-	-	-	-	6/7	5	4

Figure 7 Results from forced degradation studies using ACD/AutoChrom.

Composite chromatograms can be created from datasets to ensure that all desired components are separated. Should peak overlap occur, chromatographic simulation can be used to adjust parameters and generate optimal conditions for critical pair separation.

Figure 8 An example composite chromatogram in ACD/AutoChrom that brings together datasets, e.g., forced degradation including acid, base and peroxide studies.

Summary Reports

Reporting, for internal and external purposes, is made easier by Luminata with export of Batch Summary Tables directly to Microsoft Word and the capability to create customized reports that include process stages, affiliated data, meta data, and any notes that may have been included. AutoChrom, similarly, provides capabilities that allow for reporting of comprehensive method data and results.

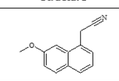
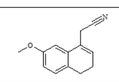
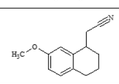
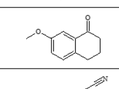
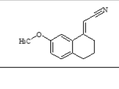
Name	Structure	All Batches	24011	24013	FW
(7-methoxynaphthalen-1-yl)acetonitrile		85.06-85.06	85.06	85.06	197.2325
(7-methoxy-3,4-dihydronaphthalen-1-yl)acetonitrile		2.00-2.00	2.00	2.00	199.2484
(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetonitrile		2.66-2.66	2.66	2.66	201.2643
7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one		7.52-7.52	7.52	7.52	176.2118
(2*E*)-(7-methoxy-3,4-dihydronaphthalen-1(2*H*)-ylidene)acetonitrile		2.75-2.75	2.75	2.75	199.2484

Figure 9 The Batch Summary table in Luminata (which associates entities with area % per batch) can be exported to Microsoft Word for easy reporting.

Conclusion

Specially designed software systems that allow for data transfer can assist scientists in their daily work. ACD/AutoChrom can be used to aid in the development of stability indicating methods and this information can be fed into the Luminata interface for easy visualization of process impurities and to track all associated analytical data in one place. Information from different contributing groups can be easily accessed in a single, chemically intelligent, searchable environment. Forced degradation studies can be enhanced with the ability to generate composite chromatograms and further develop a stability indicating method through the use of chromatographic simulation.

Acknowledgements

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