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Analytical Solutions for High Throughput ADME Studies

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Abstract

High throughput ADME (absorption, distribution, metabolism, and elimination) plays a critical role in identifying viable drug candidates in the early stages of drug discovery. *In vitro* ADME studies usually consist of a suite of assays including metabolism, stability, toxicity, and membrane permeability.

The ability to rapidly screen large quantities of compounds for ADME and physicochemical characteristics improves efficiency and aids in critical decision making by accelerating the conversion of hits to qualified drug candidates. The desire to produce high quality *in vitro* ADME data earlier in the drug discovery process has led to an acknowledged need for rapid analytical methodology.

Liquid chromatography and tandem quadrupole mass spectrometry (LC-MS/MS) techniques are widely used for *in vitro* ADME studies due to their sensitivity and selectivity as well as the ability to automate the workflow.

This study describes analytical methodology that facilitates high throughput collection of analytical data: automated targeted MS method optimization, sample acquisition, data processing and reporting allowing for faster interpretation of results and greater efficiency. Ultra-Performance Liquid Chromatography (UPLC) with electrospray detection (ESI) and a Xevo™ TQ-S micro Tandem Quadrupole Mass Spectrometer (MS) was used along with the CTC PAL3 RSI autosampler. The CTC PAL3 RSI System is a highly flexible X-, Y-, Z-robotic system offering extensive functionality. A microsomal stability assay was used to demonstrate how QuanOptimize fully

automates critical parts of the ADME workflow.

The methodology demonstrated excellent injection precision with less than 2% RSD (n=6) for all time course microsomal incubation measurements (T0, T15, T30, T45, T60, T90) for three test compounds.

Benefits

- Robust mass spectrometer capable of capturing high data rates to fully characterize the narrow peaks generated by fast chromatography, as well as comprehensive sensitivity requirements
- QuanOptimize fully automates optimization, method generation, acquisition, and data processing for increased workflow efficiency and decreased user intervention
- Highly reproducible injector with modifiable sample capacity and tray options for increased flexibility and functionality
- Customisable wash sequences for minimum carryover reducing the need to perform offline system flushing, thus maximising system uptime
- Customisable analysis speed with inject ahead function to accelerate inject-to-inject cycle times

Introduction

High throughput ADME (absorption, distribution, metabolism, and elimination) plays a critical role in identifying viable drug candidates in the early stages of drug discovery.[1] *In vitro* ADME studies usually consist of a suite of assays including metabolism, stability, toxicity, and membrane permeability.[2]

The ability to rapidly screen large numbers of compounds for ADME and physicochemical characteristics improves efficiency and aids in critical decision making by accelerating the conversion of identified hits to qualified lead development candidates.[1] The desire to produce high quality *in vitro* ADME data earlier in the drug discovery process has led to an acknowledged need for rapid analytical methodology.[3]

Fast liquid chromatography, utilizing high flowrates combined with tandem mass spectrometry (LC-MS/MS) are widely used for ADME studies due to the high quality of the data, speed, sensitivity, and selectivity as well as the ability to automate the technology.[3] Fast chromatography requires high mass spectrometry data speeds to accurately define the eluting peaks. Front end automation of the sample preparation combined with high-throughput analysis can greatly aid in reducing rate limiting points in ADME analysis.[4]

Before samples can be analyzed by LC-MS/MS, the MS/MS information needs to be derived for each prospective drug candidate, and methods need to be developed, which can be time consuming steps in the analytical workflow. In addition, timely delivery of ADME results is essential to facilitate the progression of lead candidates. High throughput analytical techniques generate a high volume of data which needs to be managed to prevent data backlogs.[5] Software automation and management of various parts of the workflow including, compound optimization, LC-MS/MS method development, data acquisition and data processing, increases efficiency.

This study describes the use of QuanOptimize™ software which is designed to fully automate high throughput collection of LC-MS/MS data, MS method optimization, acquisition, data processing and reporting allowing for faster interpretation and reporting of results.[6,7] Ultra-Performance Liquid Chromatography (UPLC™) with electrospray detection (ESI) and a Xevo™ TQ-S micro Tandem Quadrupole Mass Spectrometer was used along with the CTC PAL3 RSI autosampler. The CTC PAL3 RSI System is a highly flexible X-, Y-, Z-robotic system offering extensive functionality with its open bed autosampler allowing for rapid sample access and processing.[8]

Microsomal stability assays are routinely used for the prediction of intrinsic clearance, an important pharmacokinetic parameter that influences in vivo half-life.[9] In this study, a microsomal stability assay was performed using several positive control compounds to measure the disappearance of the parent drug, and to demonstrate how QuanOptimize fully automates critical parts of the ADME workflow including several time-consuming method development steps.

Experimental

Sample Preparation

Standards and reagents

The authentic standards of several drugs were purchased from Sigma Aldrich (St. Louis, MO). Optima LC/MS grade solvents and formic acid were purchased from Thermo Fisher Scientific (Waltham, MA). The authentic drug standards were weighed into glass scintillation vials using an analytical balance, where necessary, the weight of the salts was factored into the calculation. Initial dissolution of the solid compounds used 10% dimethyl sulfoxide following by 90% methanol to give 1 µM stock concentrations. The drug solutions were then further diluted to a concentration of 100 µM in acetonitrile in preparation for use in the microsomal stability assay.

For the optimization step, the drug standards were prepared at 1 µM in a 2 mL 96-deep well plate.

Microsomal Stability Study

Potassium phosphate monobasic, potassium phosphate dibasic and NADPH were purchased from Sigma Aldrich.The stock solutions for the study were prepared as follows:

1) 0.1 M potassium phosphate buffer (pH 7.4)
Potassium phosphate monobasic (P5655, 0.51 g) was measured into a weighing boat and transferred to a 200 mL reagent bottle. Potassium phosphate dibasic (P3786; 2.81 g) was measured into a second weighing boat and transferred to the reagent bottle. Deionized water (200 mL) was added, and the solution was sonicated for 5 minutes. The pH was adjusted to 7.4 to create the final solution.

2) NADPH (N8129) 20 mM in buffer
NADPH (20 mM) was prepared by weighing 56.8 mg into a glass scintillation vial followed by the addition of 4 mL 0.1 M potassium phosphate pH 7.4 buffer. Solutions were prepared on the day of the analysis and covered with foil to protect from the light.

3) Standards for incubation
Pharmaceutical standards were prepared at 100 µM in acetonitrile (2 µL)

The following procedure was applied to 96-well plate for the microsomal stability study:

1) Several tubes of male, Sprague Dawley pooled, rat liver microsomes (RLM) (0.5 mL, 20 mg/mL, BioIVT, Westbury, NY) stored at -80 °C, were thawed out slowly on ice prior to the experiment (approx. duration 60 minutes). The vials were combined and gently shaken to produce a homogenous solution.

2) The total volume of the incubation mixture for all time points was 200 µL with a final protein concentration of 2.0 mg/mL.

3) The T0 time points, representing no reaction were prepared by the addition of 20 µL of microsomes, 178 µL of buffer, and 2 µL of drug. NADPH was not added to the T0 time point.

4) The T15-T90 time points for each drug were prepared by the addition of 20 µL of microsomes, 178 µL of buffer, and 2 µL of drug.

5) A drug blank was prepared using 20 µL of microsomes, 160 µL of buffer and 20 µL of NADPH solution.

6) Prior to addition of the test compounds the incubation mixture was placed in a water bath at 37 °C for 5

minutes to equilibrate.

7) The T0 time points were removed to a waiting quenching plate containing 600 µL of cold ACN.

8) A cap mat was placed securely on the incubation plate which was incubated in a water bath at 37 °C.

9) The solutions at each time point T15, T30, T45, T60, and T90 were successively removed to the quenching plate containing 600 µL of cold acetonitrile. The quenching plate was shaken to stop the reaction.

10) After reaction completion, the plates were centrifuged for 10 minutes at 4000 rpm. The resulting supernatant was moved to a clean plate and either injected directly or diluted 1:10 with 75:25 acetonitrile/water in preparation for analysis by LC-MS/MS.

The analytical system consisted of a binary pump (BSM) capable of pressures up to 18k psi. The column manager allowed the selection of two column positions in addition to a bypass channel which was reserved for compound optimization (Table 1). Column position 1 was used for the acquisition of the microsomal stability samples. A prototype chemistry free column designed to act as a combination mixer and restrictor was used to provide sufficient minimum back pressure to the pump, as well chromatographic peak broadening to aid in the optimization process. An alternative way to induce peak broadening and backpressure is to use the appropriate combination of PEEK tubing lengths and/or inside diameters.

Table 1. LC conditions

LC and Column Manager conditions	
UPLC pump:	ACQUITY UPLC BSM
Column:	CORTECS T3 Column, 120Å, 1.6 µm, 2.1 × 30 mm
Flow rate:	1.0 mL/min
Mobile phase A:	0.1% formic acid in water
Mobile phase B:	0.1% formic acid in acetonitrile
Column Manager positions:	Optimization (bypass channel); acquisition (Column 1)
Column temp:	55 °C

The CTC PAL3 RSI autosampler equipped with an LCMS-P Tool and 100 µL Smart Syringe was used to deliver the samples to the high-pressure valve (VICI) (Figure 1). The autosampler included the fast wash station module which allows customizable washing speeds and sequences from two solvent reservoirs aiding to minimize carryover (Table 2).

Two Tray Holder modules capable of accommodating 6 x 96-well plates and a refrigerated Peltier stack, with equal sample capacity, set to 4 °C were used (Figure 1A and 1B).

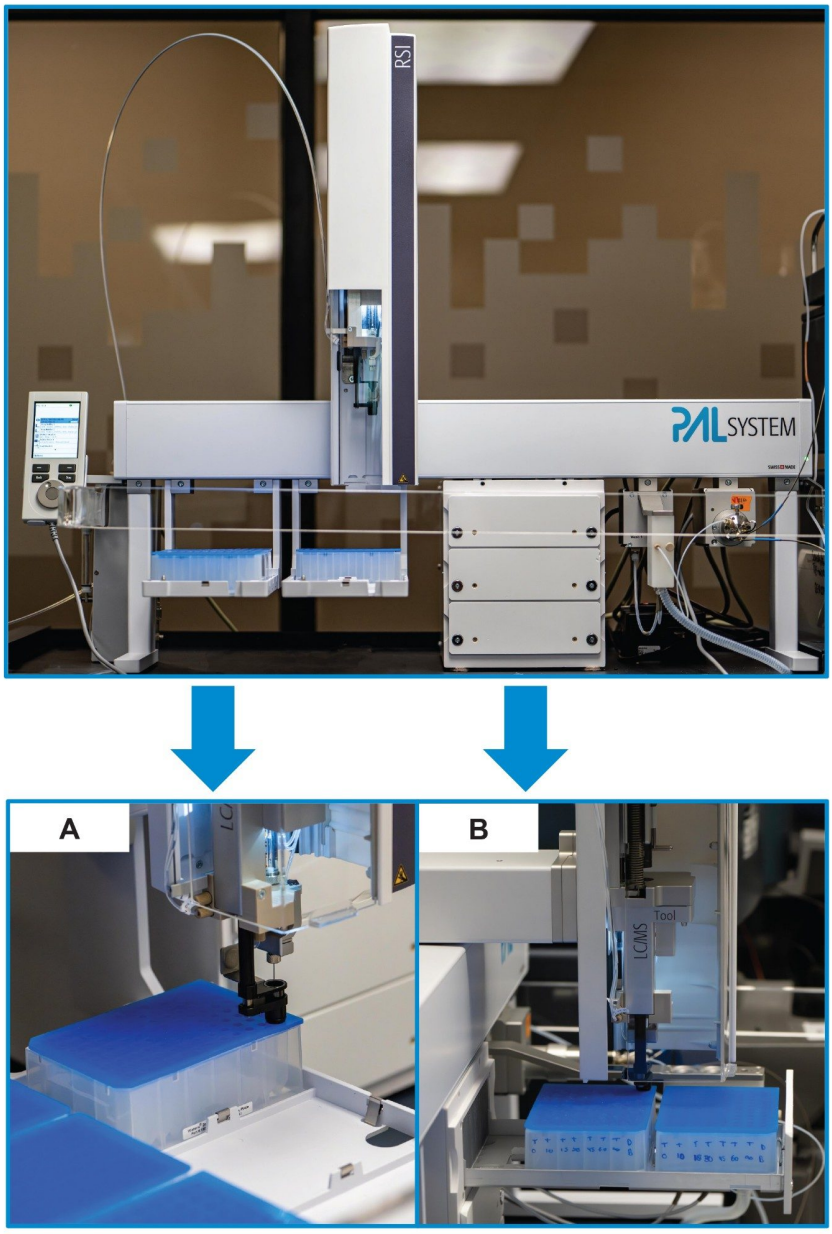


Figure 1. The CTC PAL3 RSI System (top) and the Tray Holders (A) and Peltier Cooler Stack module (B).

Table 2. Autosampler Conditions

Inspector conditions	
Autosampler:	CTC PAL3 RSI
LC/MS tool:	LCMS-P-100 tool w/100 µL Smart Syringe
Plates:	96-well sample collection plate, 2 mL square well
Cap mats:	Cap-mat square plugs, silicone/PTFE treated pre-slit
Injector volume:	1 µL loop w/10x overfill
Script version:	Open architecture V1.1
Wash solvent 1:	70:30 Acetonitrile/Water
Wash solvent 2:	25:25:25:25 Water:Methanol:Acetonitrile:IPA

A generic gradient was used along with a stationary phase designed to maximise the retention of polar analytes under reversed phase conditions (Table 3). The T3 particle provides conventional C_{18} characteristics for polar and non-polar analytes when using mobile phases with low percentages of organic solvents (up to 100% aqueous).

Table 3. Gradient program

Time (min)	Flow rate (mL/min)	%A	%B	Curve
0.00	1.0	95	5	Initial
0.05	1.0	95	5	6
0.25	1.0	60	40	3
0.40	1.0	45	55	6
0.55	1.0	1	99	1
0.70	1.0	95	5	11

The Xevo TQ-S micro Tandem Quadrupole Mass Spectrometer was used to acquire the MS data (Table 4) with generic source parameters. The compound optimisation, MRM method generation, data acquisition, quantification method generation, data processing and report generation were fully automated using the QuanOptimize application within MassLynx Software.

Table 4. MS Conditions

MS conditions	
Ionization mode:	ESI positive
Capillary voltage (kV):	1.0 kV (1:10 dilution of 1 µM samples) 3.5 kV (optimization and 1 µM samples)
Cone voltage (V):	QuanOptimize Various
Collision energy (eV):	QuanOptimize Various
Source temp. (°C):	600
Desolvation temp. (°C):	150
Desolvation gas flow (L/hr):	1000
Cone gas flow (L/hr):	100

QuanOptimize Automated Method Development and Acquisition

QuanOptimize Application Manager within the MassLynx Software streamlined and simplified the individual steps required to complete the ADME workflow, with minimum user intervention. The software is applicable to any lab requiring high throughput quantitative measurements. The fully automated workflow is shown in Figure 2. The parameters for each step are defined in the QuanOptimize method editor. The software is highly adaptable to individual laboratory requirements with the ability to perform each step together or separately.

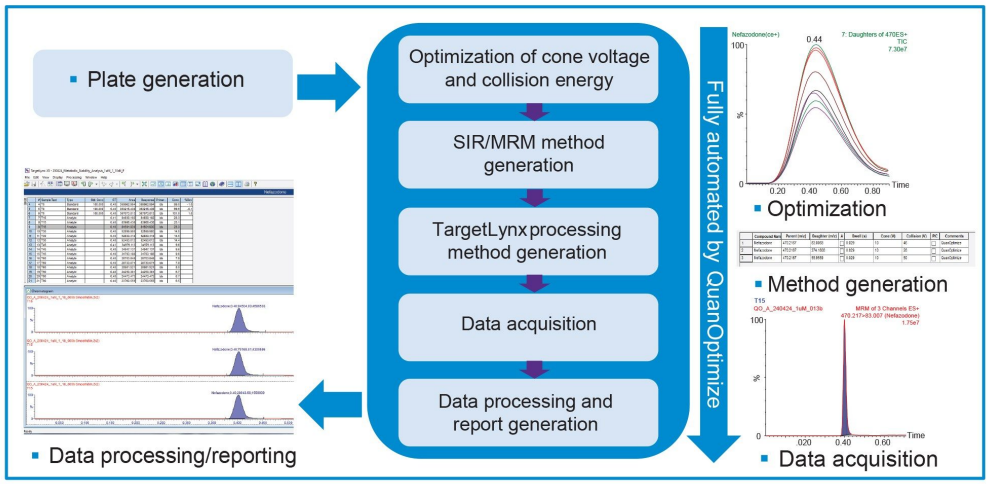
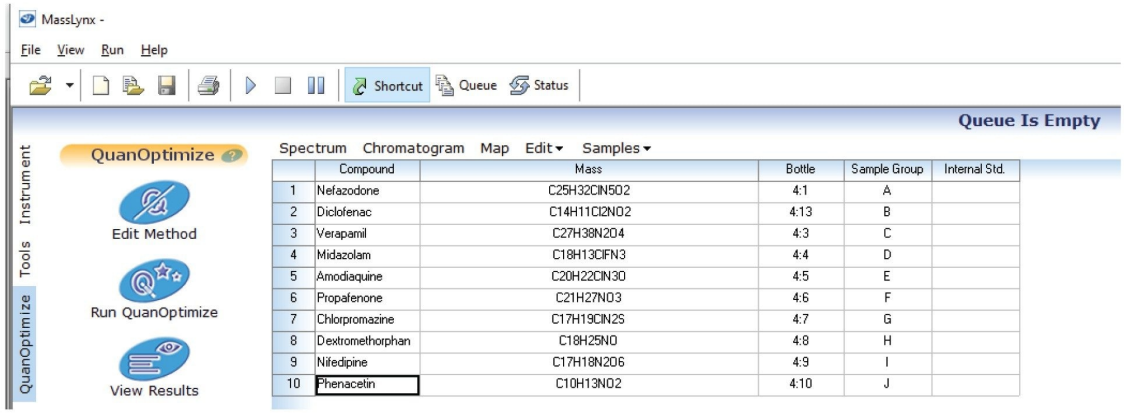


Figure 2. The fully automated QuanOptimize workflow.

The compound optimization was performed by injecting 1 µM concentrations of the test compounds using a loop injection, through the bypass channel, one of the flow paths available in the column manager. QuanOptimize uses a pre-formatted sample list, the Compound List, where information pertaining to the samples including name, mass or elemental composition, sample location, and a Sample Group (used to organize compounds that are grouped together for analysis) is entered (Figure 3).



	Compound	Mass	Bottle	Sample Group	Internal Std.
1	Nefazodone	C25H32ClN5O2	4:1	A	
2	Diclofenac	C14H11Cl2NO2	4:13	B	
3	Verapamil	C27H38N2O4	4:3	C	
4	Midazolam	C18H13ClFN3	4:4	D	
5	Amodiaquine	C20H22ClN3O	4:5	E	
6	Propafenone	C21H27NO3	4:6	F	
7	Chlorpromazine	C17H19ClN2S	4:7	G	
8	Dextromethorphan	C18H25NO	4:8	H	
9	Nifedipine	C17H18N2O6	4:9	I	
10	Phenacetin	C10H13NO2	4:10	J	

Figure 3. The QuanOptimize Compound List format used for optimization.

Based on the information in the Compound List, and the settings in the QuanOptimize method editor, (Figure 4) the cone voltage and collision energy are optimized using multiple MS functions at the optimum ionization polarity determined for the specific compound.

The QuanOptimize method editor is the location where the parameters for all processes relating to the automation of the analytical workflow are coordinated. Generic LC methods, MS tune files and settings upon which the auto-generated MS methods will be based, are browsed into the method editor.

Successful compound optimization is important to ensure optimum sensitivity and specificity. Multiple MS functions are used in the optimization step based on the ranges of cone voltage and collision energy (CE) specified in the method editor. The MS functions used to optimize the cone voltage and collision energy will be acquired simultaneously as shown in the superimposed chromatograms from the CE loop injection optimization in Figure 4 where a range of 10 eV-50 eV was specified in the method.

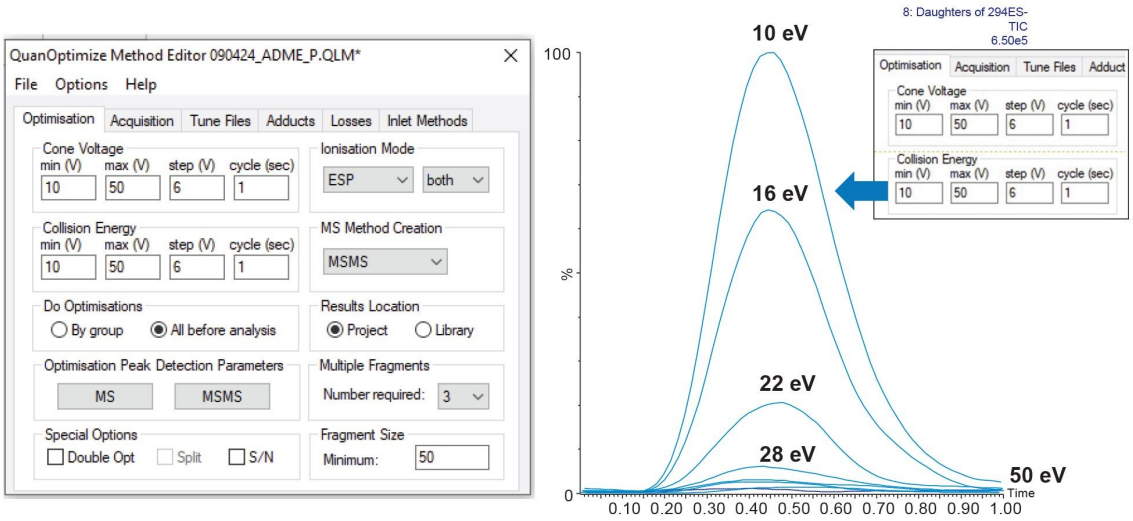


Figure 4. The QuanOptimize method editor where all settings pertaining to the optimization and acquisition, are coordinated (left). Superimposed chromatograms showing the CE optimization (right).

An example optimization report for multiple compounds and a QuanOptimize generated MS method for nefazodone are displayed in Figure 5.

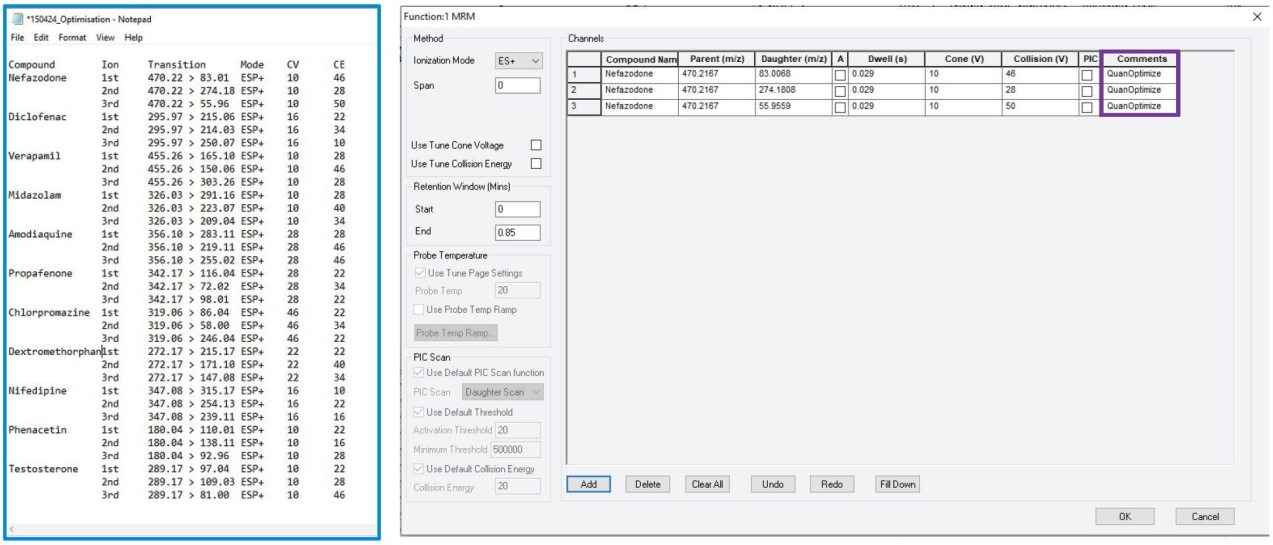
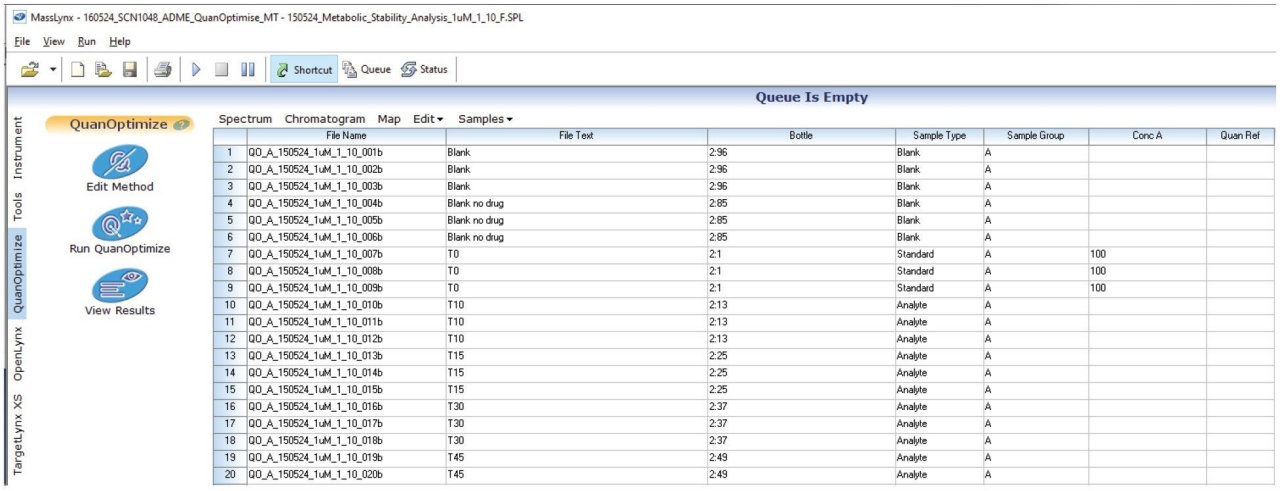


Figure 5. Example QuanOptimize Optimization results report (left) and auto-generated MS method for nefazodone (right).

A second pre-made sample list, the Analysis List, is used to acquire the analytical data. This sample list is where the file names, sample definitions, concentrations, and the locations of the samples are identified. MS methods and LC methods do not need to be specified as these are managed by QuanOptimize (Figure 6).



	File Name	File Text	Bottle	Sample Type	Sample Group	Conc A	Quan Ref
1	QO_A_150524_1uM_1_10_001b	Blank	2:96	Blank	A		
2	QO_A_150524_1uM_1_10_002b	Blank	2:96	Blank	A		
3	QO_A_150524_1uM_1_10_003b	Blank	2:96	Blank	A		
4	QO_A_150524_1uM_1_10_004b	Blank no drug	2:85	Blank	A		
5	QO_A_150524_1uM_1_10_005b	Blank no drug	2:85	Blank	A		
6	QO_A_150524_1uM_1_10_006b	Blank no drug	2:85	Blank	A		
7	QO_A_150524_1uM_1_10_007b	T0	2:1	Standard	A	100	
8	QO_A_150524_1uM_1_10_008b	T0	2:1	Standard	A	100	
9	QO_A_150524_1uM_1_10_009b	T0	2:1	Standard	A	100	
10	QO_A_150524_1uM_1_10_010b	T10	2:13	Analyte	A		
11	QO_A_150524_1uM_1_10_011b	T10	2:13	Analyte	A		
12	QO_A_150524_1uM_1_10_012b	T10	2:13	Analyte	A		
13	QO_A_150524_1uM_1_10_013b	T15	2:25	Analyte	A		
14	QO_A_150524_1uM_1_10_014b	T15	2:25	Analyte	A		
15	QO_A_150524_1uM_1_10_015b	T15	2:25	Analyte	A		
16	QO_A_150524_1uM_1_10_016b	T30	2:37	Analyte	A		
17	QO_A_150524_1uM_1_10_017b	T30	2:37	Analyte	A		
18	QO_A_150524_1uM_1_10_018b	T30	2:37	Analyte	A		
19	QO_A_150524_1uM_1_10_019b	T45	2:49	Analyte	A		
20	QO_A_150524_1uM_1_10_020b	T45	2:49	Analyte	A		

Figure 6. The QuanOptimize Analysis List.

All steps in the workflow are initiated through the QuanOptimize Wizard. The steps can be executed independently or together based on laboratory needs (Figure 7).

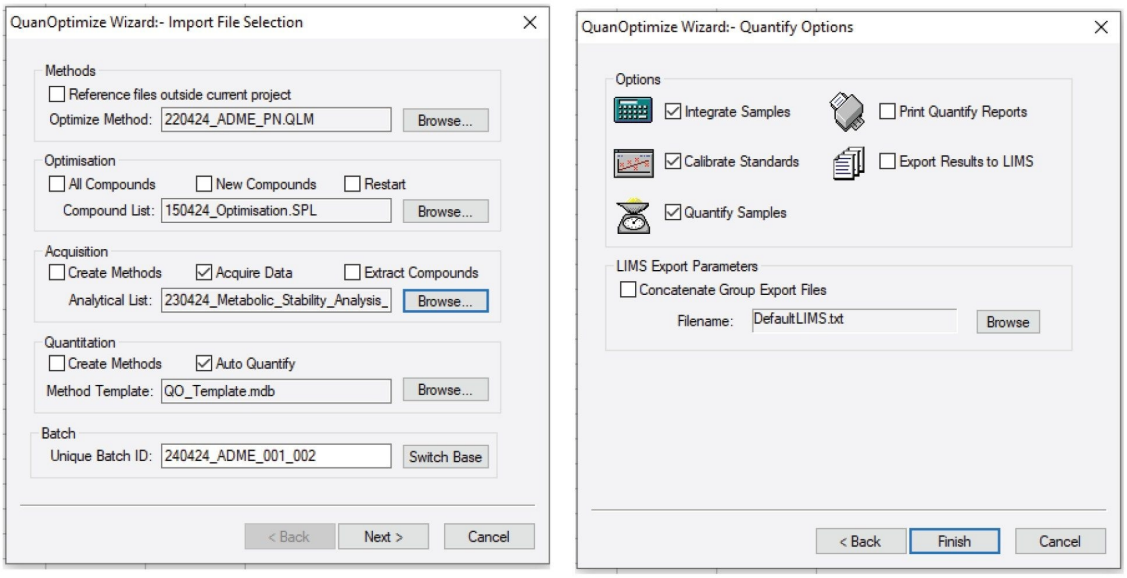


Figure 7. The QuanOptimize Wizard and Quantify options. Steps can be executed together or separately.

Results and Discussion

Automation of the Microsomal Stability Workflow using QuanOptimize

Following the automation of the method development process, QuanOptimize was used to manage the data acquisition as well as processing method generation and reporting for a microsomal stability study. Figure 8 shows the TargetLynx report for the RLM microsomal stability results of nefazodone which were analyzed in triplicate. The measurement of the change in peak area response was used to calculate the percentage parent remaining relative to T0 which was defined as a standard and assigned a value of 100%. The time points T15-T90 were quantified relative to T0.

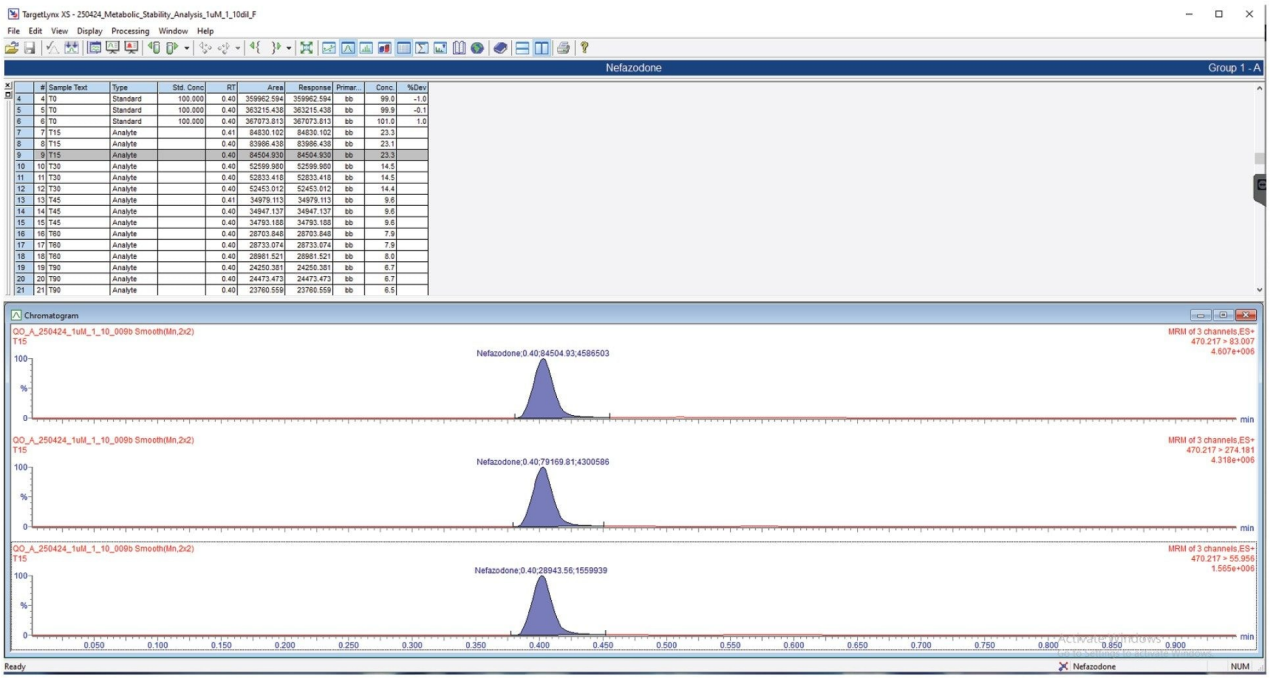


Figure 8. Auto-generated TargetLynx quantitation report showing a table of microsomal stability profile data for nefazodone incubated at 1 µM with RLM over the range T0-T90 (n=3).

The percentage remaining drug (n=3) were plotted against time to assess the microsomal stability profile of nefazodone (Figure 9).

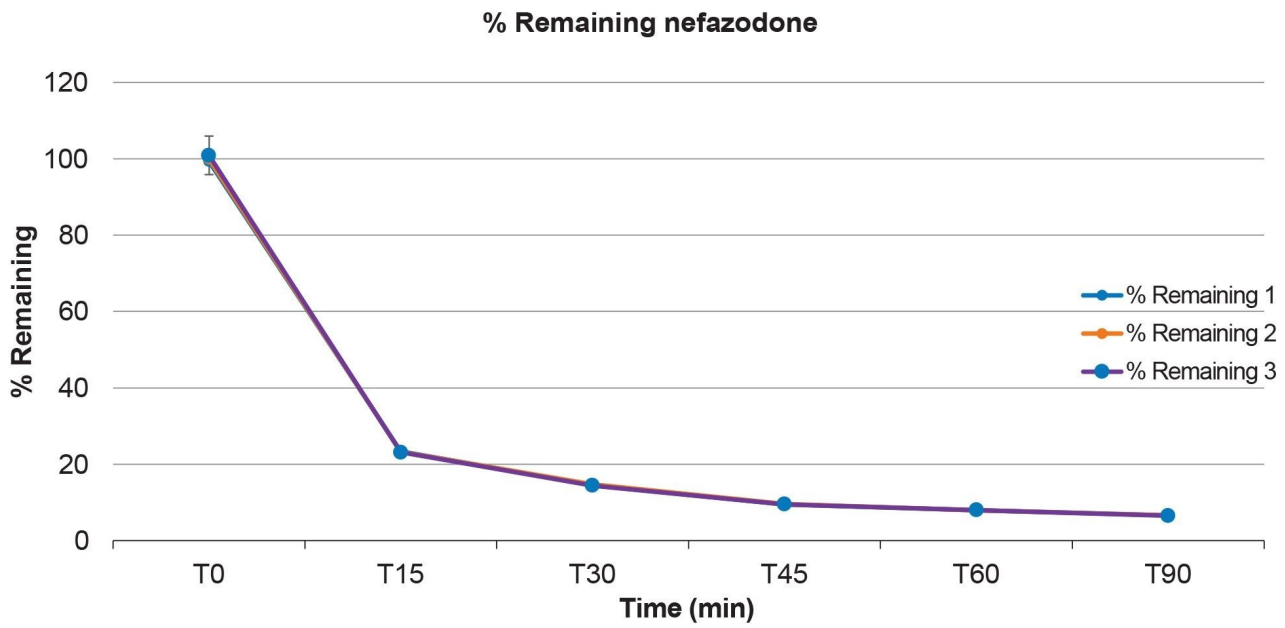


Figure 9. Microsomal stability profile of nefazodone (percentage remaining versus time) over the range T0-T90 minutes (n=3) (incubated at 1 µM using RLM, 1:10 dilution, 1 µL loop with 10x overfill).

The % RSD was used to assess the reproducibility of the analytical system. The time course points for the nefazodone samples (1:10 dilution, 1 µM incubations) were injected six times. The data is represented as a table as well as graphically in a bar chart (Figure 10). The RSDs were <1.5% for each of the injections at any time point in the time course, demonstrating this to be a highly reproducible analytical system. The reproducibility study was repeated for two additional compounds, the RSD for each test compound for any time point were <2% (n=6) (data not shown).

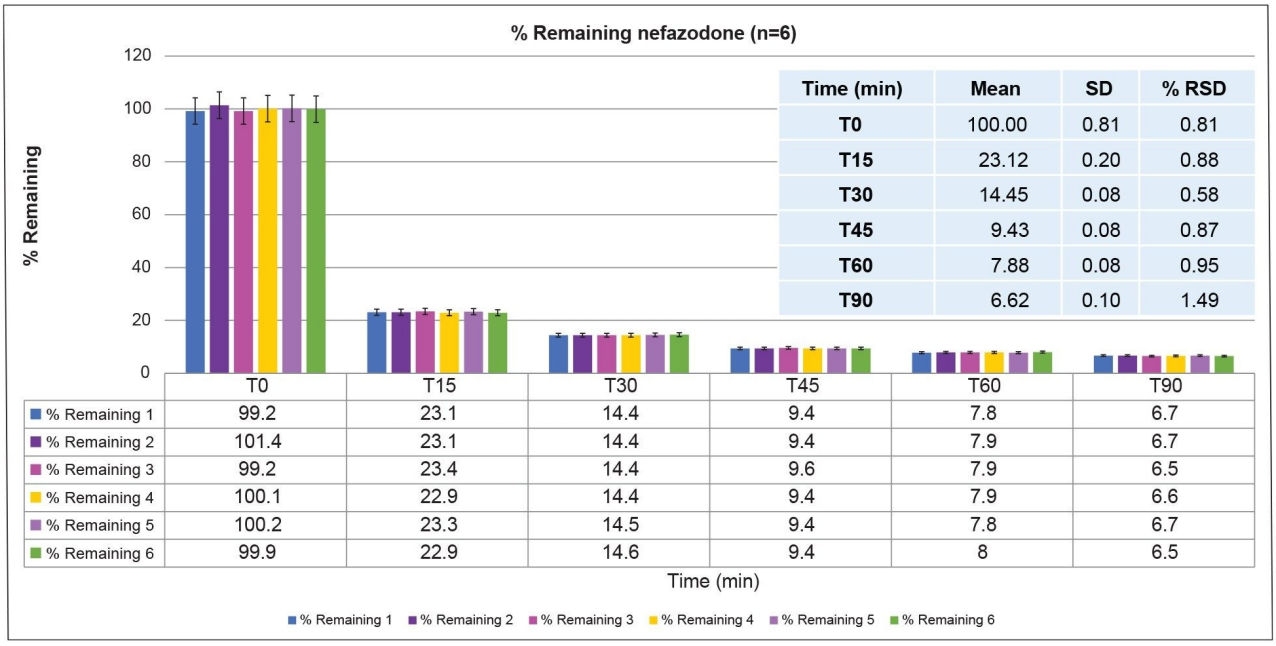


Figure 10. Bar chart and associated data represented in tabular and graphical format showing the replicate injections (n=6) of nefazodone time course over the range T0-T90 minutes (incubated at 1 µM using RLM, 1:10 dilution, 1 µL loop with 10x overfill).

Microsomal Stability Profiles of Positive Controls

The auto-generation of MS methods, used with a generic LC gradient allowed initial evaluation of the chromatography (Figure 11) to ensure good peak shape and retention for each analyte. The stationary phase of the CORTECS T3 1.6 µm, 2.1 x 30 mm solid-core particle column is designed to improve retention of polar analytes (Table 1). Decreasing the particle size and using solid-core particle technology improves the chromatographic resolution due to the increase in column efficiency which can be important for the separation of matrix components and metabolites subject to insource fragmentation back to the parent molecule. The efficiency gains are enhanced when using low dispersion chromatographic systems.[2] The use of high flow rates and short column lengths can greatly decrease the analytical run times while still ensuring good retention and peak shape. Good chromatographic peak shape will help avoid manual integration during data analysis.

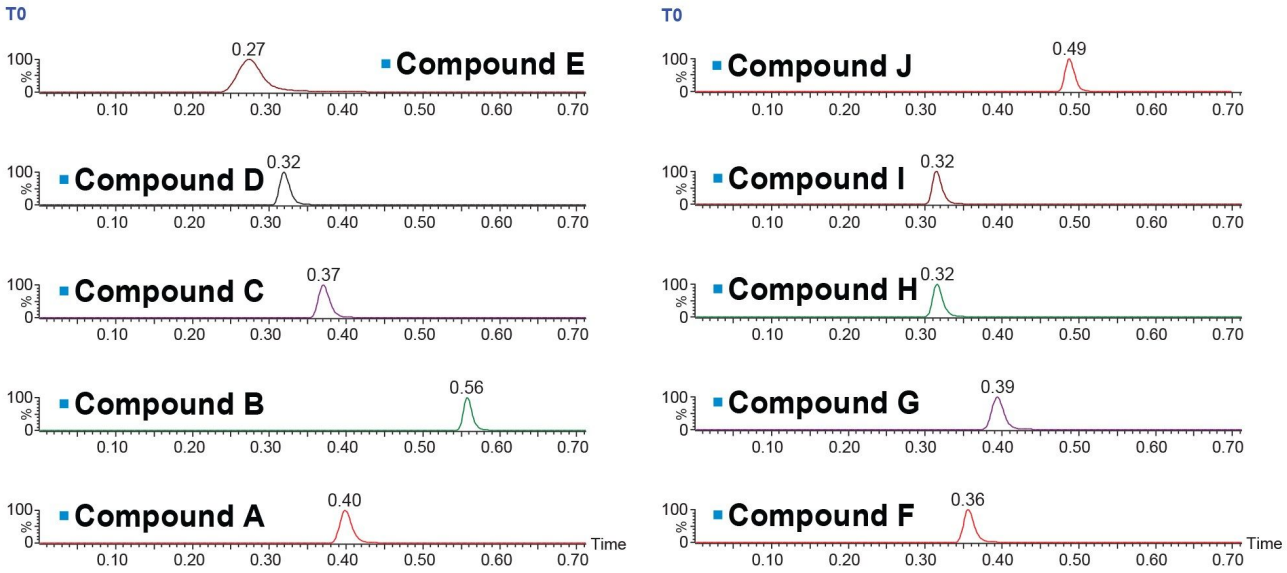


Figure 11. Chromatograms resulting from the analysis of positive control compounds at 1 µM in acetonitrile, 1 µL loop with 10x overfill.

Time course RLM incubations (T0, T15, T30, and T45) were performed using structurally diverse positive control compounds at 1 µM concentration. The samples were injected in triplicate and the average for each time point was used to plot the microsomal stability profiles from T0-T45 (Figure 12).

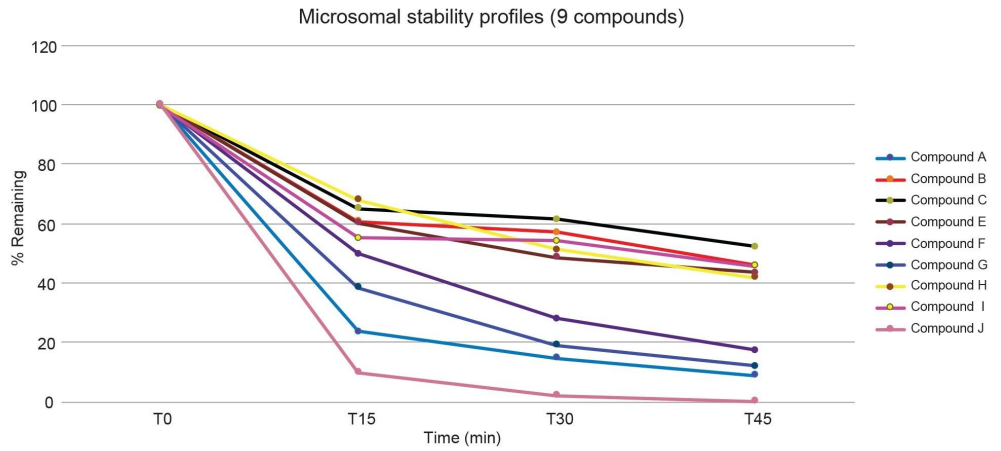


Figure 12. Microsomal stability profiles of nine positive control compounds (percentage remaining versus time) over the range T0-T45 minutes (incubated at 1 µM using RLM, 1 µL loop with 10x overfill).

Single point software management of the entire analytical workflow using QuanOptimize allowed the data to be generated and interpreted with minimal user intervention.

Conclusion

Microsomal stability experiments using RLM incubations were used to demonstrate the ease of use and efficiency gains of the QuanOptimize workflow for ADME studies. The need for pre-analysis or tuning of new compounds can be eliminated by managing the optimization through the method editor, ensuring rapid turnaround of results to project teams. The software streamlines and simplifies the individual steps required to complete the ADME workflow with minimum user intervention. The workflow is highly adaptable to individual laboratory requirements with the ability to perform each step together of separately.

The CTC PAL3 RSI System was used as the injector together with a Waters UPLC pump, a multipath column manager and a robust mass spectrometer capable of delivering comprehensive sensitivity requirements and high data quality. This analytical system facilitates, high-throughput chromatography, highly customizable injection sequences including inject ahead functionality which eliminates the sample loading delays thus accelerating

analysis times. The fast wash module can perform customizable wash sequences and speeds for minimum carryover.

This analytical methodology and software is suitable for labs needing to rapidly analyze high numbers of samples from ADME and other *in vitro* assays to increase analytical efficiency and reduce the method development and data processing burden.

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