C190-E278E

SHIMADZU
Excellence in Science

Solution for Method Development and Analytical Quality by Design

LabSolutions MD

Improve the Efficiency of Analytical Condition Screening with Experimental Design

Analytical condition settings can be efficiently screened in fewer attempts using an experimental process design to collect data.

Screening Phase

Optimization Phase

Use Design Space to Visualize the Robustness of Analysis Methods

The software can graph factor-response relationships and suggest the most robust analytical conditions. It even supports chromatogram simulation.

Validation Phase

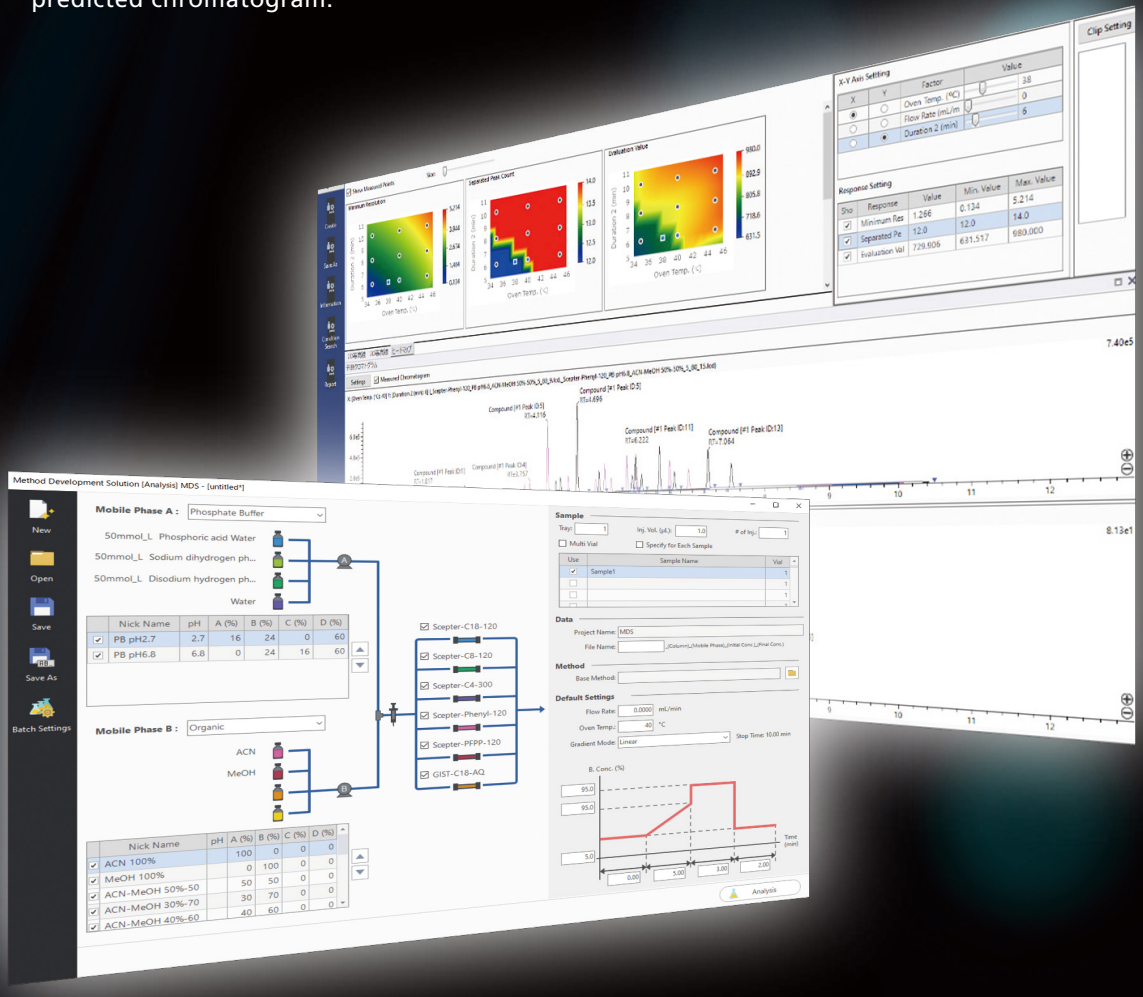
Centrally Manage All Experiment Results in a Database

The software outputs a report that summarizes the experimental design, design space, chromatograms, and other relevant information. It also manages the information in a database to ensure data integrity.

AQbD

Improving Efficiency of the Entire Method Development Workflow

LabSolutions™ MD improves method development efficiency by taking an Analytical Quality by Design (AQbD) approach.
This software efficiently develops reliable analysis methods by configuring mobile phases, columns, and other parameters using an analysis function that automatically generates analysis schedules with the experimental design method and a data analysis function that plots a design space and predicted chromatogram.



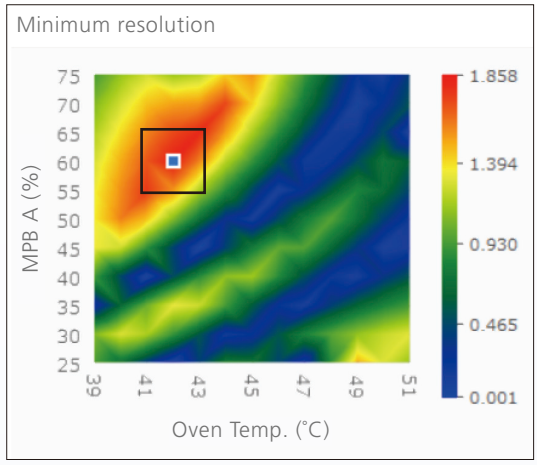
LabSolutions MD Features

for Each Phase of Analysis Method Development using the AQbD Approach

All steps involved in the screening, optimization, and validation phases of the method development workflow can be completed using LabSolutions MD. These include analyzing samples using experimental design, building a design space using the analytical results, and evaluating robustness after deciding the optimal analytical conditions.

			Response	
Column Nick Name	MPA pH	MPB A (%)	Evaluation Value	Minimum Resolution
Scepter-Phenyl-120	6.8	50	546.000	3.224
Scepter-C8-120	6.8	0	469.894	0.093
GIST-C18-AQ	2.7	0	465.124	1.075
GIST-C18-AQ	6.8	50	443.580	1.826
Scepter-C8-120	6.8	50	436.241	0.026
Scepter-Phenyl-120	2.7	50	419.659	1.743
Scepter-C18	2.7	0	419.338	1.518

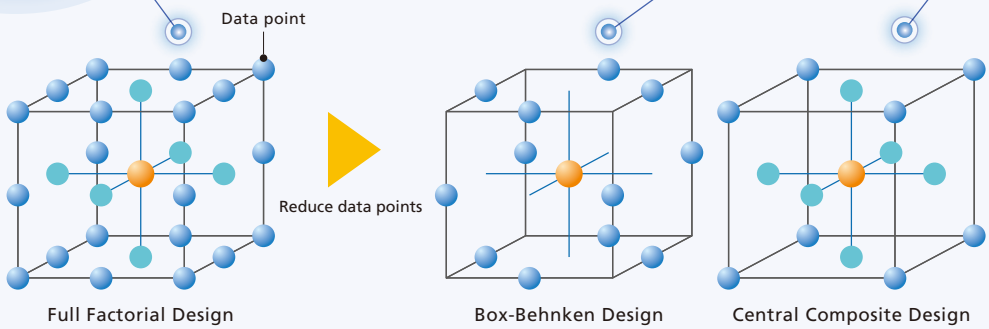
Quickly Screen for Optimal Analytical Conditions by Ranking Chromatograms ▶ p.9



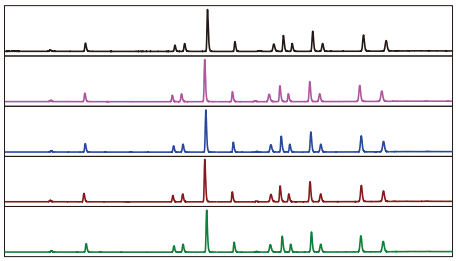
Visualize the Most Robust Analytical Conditions Using the Design Space ▶ p.11

ANALYTICAL INTELLIGENCE

Screening Phase



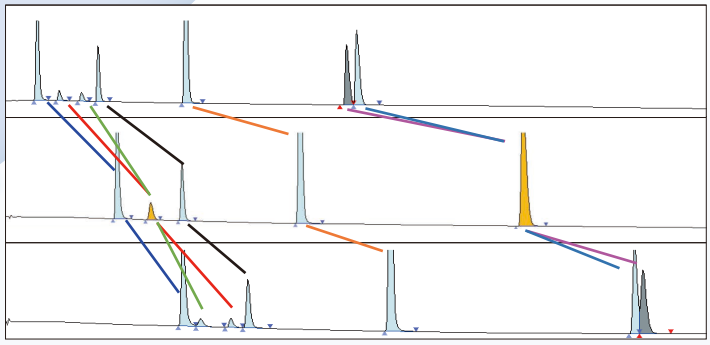
Reduce Data Points Using Experimental Design ▶ p.10



Confirming Robustness ▶ p.13

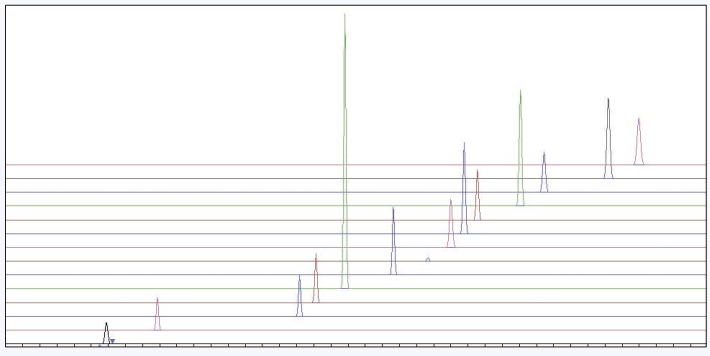
Validation Phase

Optimization Phase



Automatically Identify Compounds by Peak Tracking ▶ p.10

ANALYTICAL INTELLIGENCE



Chromatogram Simulation ▶ p.11

ANALYTICAL INTELLIGENCE

ANALYTICAL INTELLIGENCE

Automated support functions utilizing digital technology, such as M2M, IoT, and Artificial Intelligence (AI), that enable higher productivity and maximum reliability. Allows a system to monitor and diagnose itself, handle any issues during data acquisition without user input, and automatically behave as if it were operated by an expert. Supports the acquisition of high quality, reproducible data regardless of an operator's skill level for both routine and demanding applications.

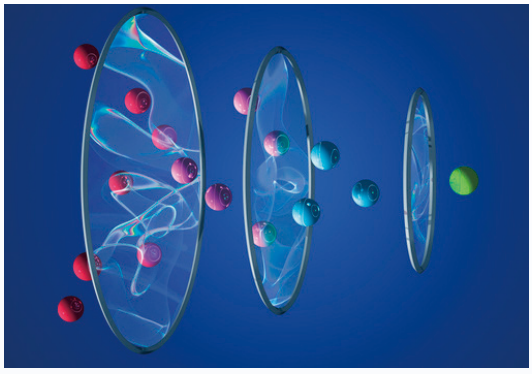
Workflow of AQbD Approach for Method Development

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) suggests the AQbD approach for method development. It is recommended to acquire data by conducting efficient experiments, such as with the use of experimental design, verifying the parameters that have a large effect on analytical results, and then building a design space to understand the effective domain of the parameters with respect to the analysis results. This risk-based approach ensures the development of robust, low-risk methods without relying on user experience.

Screening Phase

Initial Screening

▶p.8

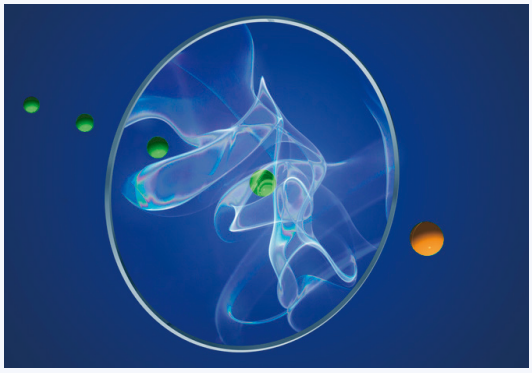


Initial screening is based on parameters that have a major effect on peak retention time and separation, such as the pH of aqueous mobile phases, the mixture ratio of organic mobile phases, and the type of column.

Optimization Phase

Optimization

▶p.10



With the analytical conditions determined by initial screening results as a starting point, optimal setting levels are verified for other parameters, such as pump gradient and column oven temperature conditions.

Validation Phase

Robustness Evaluation

▶p.13

Validation verifies that small variations in the optimized analytical condition settings affect measurement values only within an allowable range.

The following pages describe the various functions of LabSolutions MD software based on an example of using the workflow indicated on the left page to screen analytical conditions for simultaneous analysis of small-molecule drugs. For details, click the icon below and refer to the Technical Report entitled "Efficient method development Based on Analytical Quality by Design with LabSolutions MD Software (C190-E284)".

Application

Analytical Conditions for Simultaneous Analysis

Analytes
(12 small-molecule drugs)

1: Probenecid
2: (S)-(+)-Naproxen
3: Acetylsalicylic acid
4: Diclofenac sodium
5: Papaverine hydrochloride
6: Dibucaine hydrochloride
7: Amitriptyline hydrochloride
8: Indometacin
9: Antipyrine
10: Lidocaine
11: Quinidine
12: Metoclopramide

Mobile phase:
Pump A: A: 20 mmol/L (Sodium) phosphate buffer (pH 2.7)
B: 20 mmol/L (Sodium) phosphate buffer (pH 6.8)
→ 2 aqueous types

Pump B: A: Acetonitrile
B: Acetonitrile / Methanol = 1 : 1
C: Methanol
→ 3 organic types

Column: 1: Shim-pack Scepter™ C18-120 (100 mm × 3.0 mm I.D., 1.9 µm)
2: Shim-pack Scepter C8-120 (100 mm × 3.0 mm I.D., 1.9 µm)
3: Shim-pack Scepter C4-300 (100 mm × 3.0 mm I.D., 1.9 µm)
4: Shim-pack Scepter Phenyl-120 (100 mm × 3.0 mm I.D., 1.9 µm)
5: Shim-pack Scepter PFPP-120 (100 mm × 3.0 mm I.D., 1.9 µm)
6: Shim-pack™ GIST C18 AQ HQ (100 mm × 3.0 mm I.D., 2.0 µm)
→ 6 column types

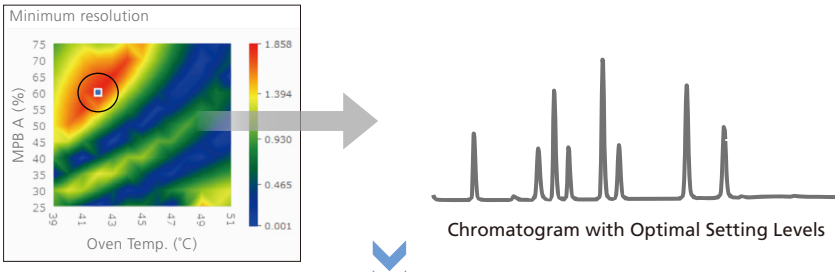
Analytical condition: Time program : B.Conc. 5%(0 min)→80%(8.01-11 min)→5%(11.01-15 min)
Flow rate : 0.7 mL/min
Inj.vol. : 1.0 µL
Temperature : 40 °C
Detection : Max plot 220- 400 nm (SPD-M40)
→ Basic conditions

STEP 1 Initial Screening ▸p.8

Using full factorial design, select the optimal combination of mobile phase (from 2 aqueous types and 3 organic types) and column (6 types).

STEP 2 Optimization ▸p.10

Create a design space in terms of three parameters: organic mobile phase mixture ratio, pump gradient conditions, and column oven temperature. Then specify analytical conditions by determining the optimal level of each.



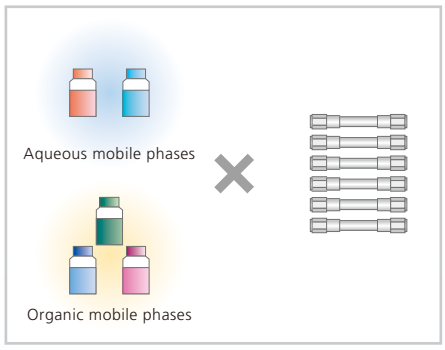
Chromatogram with Optimal Setting Levels

STEP 3 Robustness Evaluation ▸p.13

Using iterative experimental design, evaluate robustness with respect to variations in the organic mobile phase mixture ratio and column oven temperature levels.

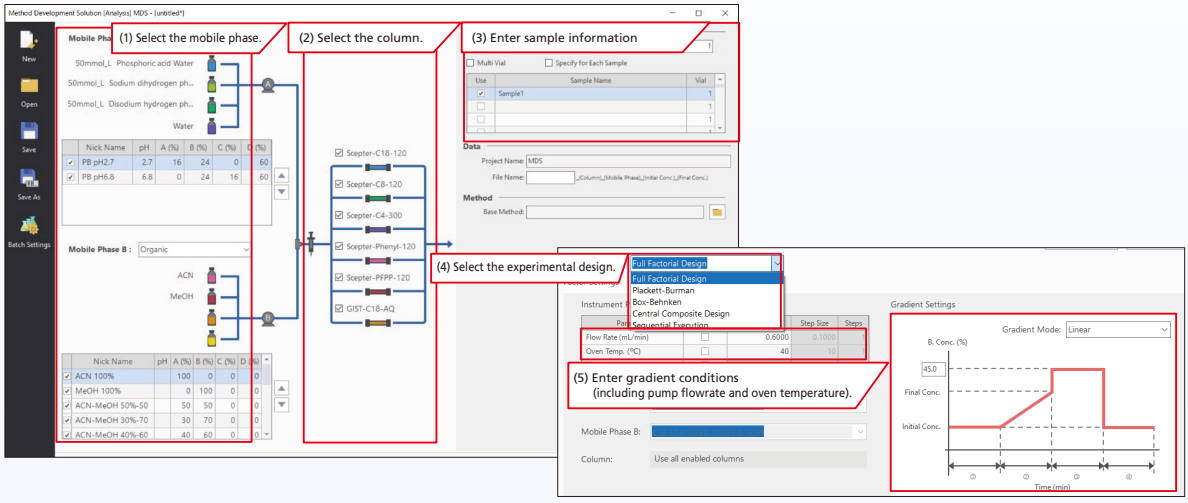
Initial Screening

Use the two types of aqueous mobile phases, three types of organic mobile phases, and six types of columns to acquire a total of 36 data points (full factorial design) for screening mobile phase and column conditions.



Easily Create Analysis Schedules with Experimental Design

The process of creating the vast number of method files and analysis schedules required for screening can be completed quickly by simply following steps (1) to (5) below. The mobile phase and column can be selected with a single click and a comprehensive schedule reflecting column equilibration and blank analysis is generated automatically. In addition to improved operational efficiency, this process can reduce human errors. The experimental design can also be selected with a single click.

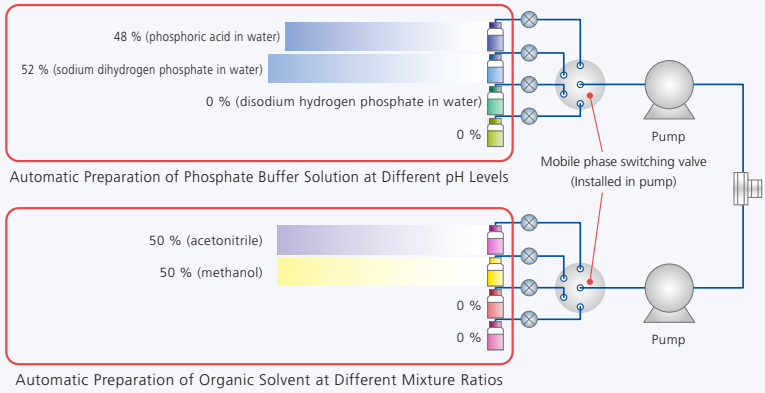


Click the icon on the right for an example of automated pH screening of mobile phase.

Application

Automation of Mobile Phase Preparation with Mobile Phase Blending Function

The mobile phase blending function can improve the efficiency of mobile phase preparation by automatically preparing mobile phases based on factors such as the user-specified pH level or the mixture ratio of organic mobile phase, with only a few types of mobile phases prepared in advance. This not only greatly reduces the burden of manual preparation but also prevents human errors in blending.



Automatic Mobile Phase Preparation with Mobile Phase Blending Function

Quickly Determine Optimal Conditions

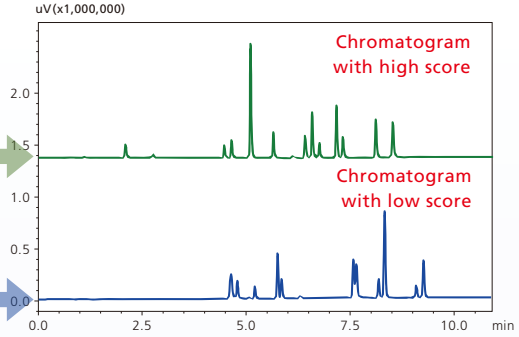
Because screening generates as many chromatograms as the number of conditions considered, they must be evaluated to determine which is optimal. If all the chromatograms had to be scrutinized by an operator, it would be very tedious. LabSolutions MD can quickly and easily determine optimal analytical conditions using equation (1) below to quantitatively evaluate the separation status resulting from each set of analytical conditions.

$E = P \times (R_1 + R_2 + \ldots R_{P-1})$ ... (Eq. 1)

The evaluation value (E) is calculated as the number of peaks detected (P) multiplied by the sum of the separation level (R) for all peaks.

			Response	
Column Nick Name	MPA pH	MPB A (%)	Evaluation Value	Minimum Resolution
Scepter-Phenyl-120	6.8	50	546.000	3.224
Scepter-C8-120	6.8	0	469.894	0.093
GIST-C18-AQ	2.7	0	465.124	1.075
GIST-C18-AQ	6.8	50	443.580	1.826
Scepter-C8-120	6.8	50	436.241	0.026
Scepter-Phenyl-120	2.7	50	419.659	1.743
Scepter-C18	2.7	0	419.338	1.518
Scepter-C18	6.8	50	396.000	4.326
Scepter-C4-300	2.7	0	394.239	0.402
Scepter-C18	6.8	100	384.553	2.046

Ranking Based on Each Condition and Evaluation Value

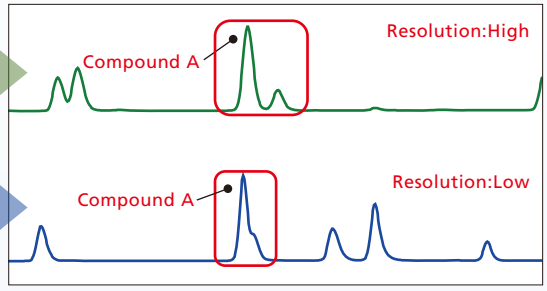


Comparison of Chromatograms with High and Low Evaluation Value

Target Peak Resolution can be used to evaluate the resolution on a specific peak while Evaluation Value considers all the peaks detected.

			Response
Column Nick Name	MPA pH	MPB A (%)	Target Peak Resolution
GIST-C18-AQ	2.7	50	1.461
Scepter-C18	6.8	0	1.224
Scepter-C4-300	2.7	0	1.016
Scepter-Phenyl-120	2.7	0	0.966
Scepter-C18	6.8	50	0.729
Scepter-C18	6.8	100	0.647
Scepter-PFPP-120	2.7	50	0.561

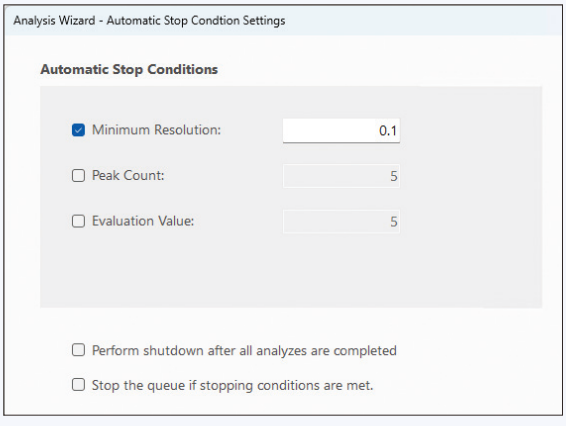
Ranking the Resolution of a Specific Peak Based on Target Peak Resolution



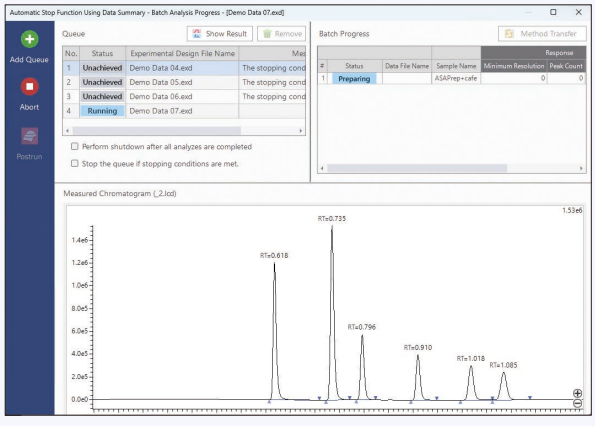
Comparison of Resolution for Specific Compound A

Complete Screening More Efficiently with the Automatic Stop and Schedule Functions

In screening for analysis method development, the various combinations of mobile phases and columns are comprehensively examined, which takes time. With LabSolutions MD, an automatic stop function for screening is built in, so the search can be ended if conditions are found that match the configured standards. Furthermore, with the multiple registration function for screening, different screening conditions can be automatically searched for in sequence.



Criteria Setting for Stopping the Screening Automatically

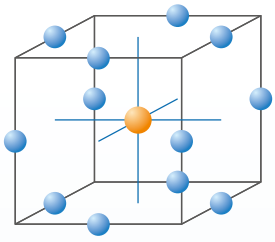


Progress Confirmation Window for Batch Analysis

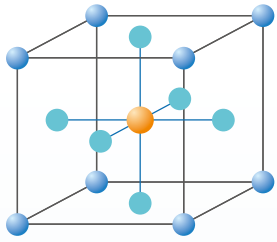
Reduce the Number of Data Points Using Experimental Design

Box-Behnken design and central composite design can shorten analysis times because they require fewer data points than full factorial design. For example, if determining the three optimal levels for the organic mobile phase mixture ratio, pump gradient conditions, and column oven temperature, full factorial design requires 27 data points (3 × 3 × 3) for optimization whereas Box-Behnken design requires 13 points and central composite design requires 15 points.

Box-Behnken Design



Central Composite Design

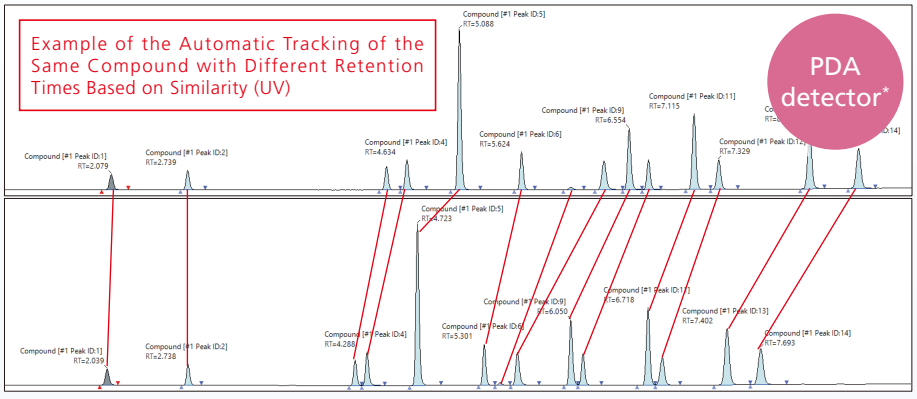


	Required Experiment Data Points
Full Factorial Design	27 points
Box-Behnken Design	13 points (52 % reduction of analysis time)
Central Composite Design	15 points (44 % reduction of analysis time)

Comparison of Data Points Required for Each Experimental Design Method (Given 3 Levels of 3 Parameters)

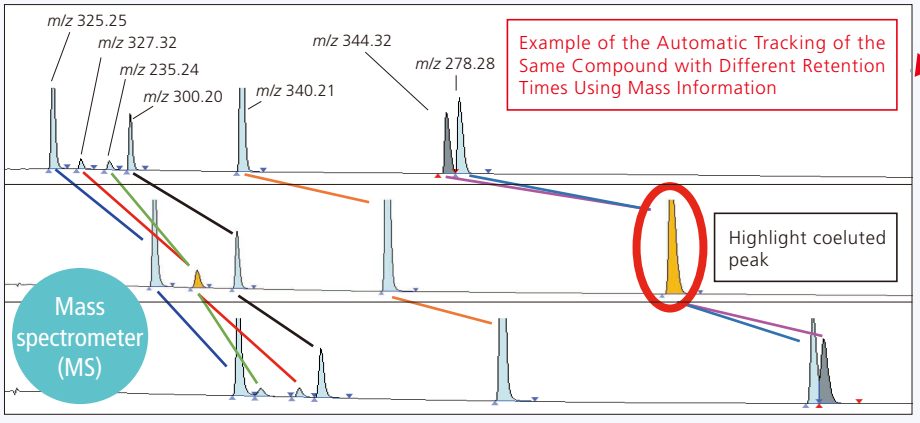
Automatic Identification of Compounds by Peak Tracking (i-PeakTracer™)

ANALYTICAL INTELLIGENCE



*photodiode array detector

When an analytical condition is changed, the retention time of each compound can also change. It's a time-consuming process to manually identify each compound in the acquired data. i-PeakTracer can automatically identify target compounds by peak tracking through all the data.



Parameters Available with i-PeakTracer

Parameter
Peak Number ±
Area (μV•sec) ±
Height (μV) ±
Area% ±
Height% ±
Ret. Time (min) ±
Similarity (UV)
Similarity (MS)
Base Peak m/z ±
Molecular Weight ±

i-PeakTracer automatically sets the parameters for peak tracking to make it effortless for anyone to track peaks through all the data.

By using mass information, the software can perform highly reliable peak tracking even for compounds with similar UV spectra. Further, peaks suspected of coeluting are highlighted in orange.

NEW For oligonucleotides, peptides, and other medium-sized molecular compounds, peak tracking can be performed using molecular weights estimated by deconvolution.

Click the icon on the right for an example of efficient method development using a single quadrupole mass spectrometer.

Application

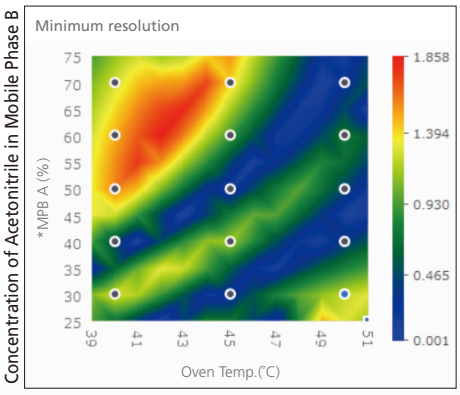
Click the icon for an example of optimal method development (peak tracking based on molecular weights) for oligonucleotides.

Application

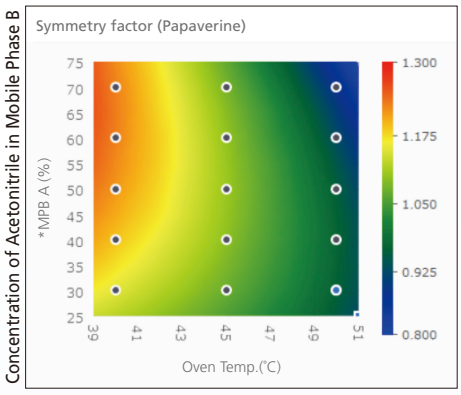
Visualize the Most Appropriate Analytical Conditions by Design Space

ANALYTICAL INTELLIGENCE

Using the configured conditions for the initial screening, the organic mobile phase mixing ratio, column oven temperature, and final concentration of the gradient were optimized.
The optimized results are displayed using the LabSolutions MD design space drawing function, so the degree of separation, symmetry coefficient, and number of theoretical plates were evaluated.

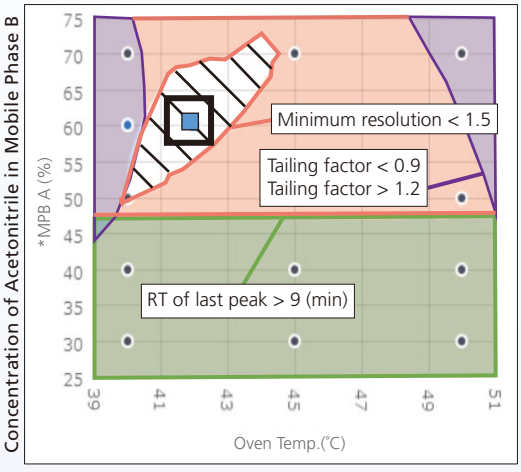


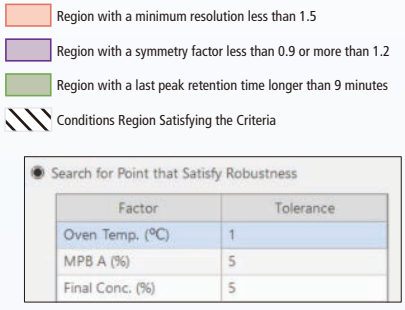
Design Space of Minimum Resolution
(Gradient Final Concentration: At 75 %)
* MPB A : acetonitrile
The black dots in the figure are points where the analysis was implemented.



Design Space of Symmetry Factor (Papaverine)
(Gradient Final Concentration: At 75 %)
* MPB A : acetonitrile
The black dots in the figure are points where the analysis was implemented.

With design space, different conditions are configured for the vertical axis and horizontal axis, and the results can be visualized with color, enabling the optimal conditions range to be grasped at a glance.





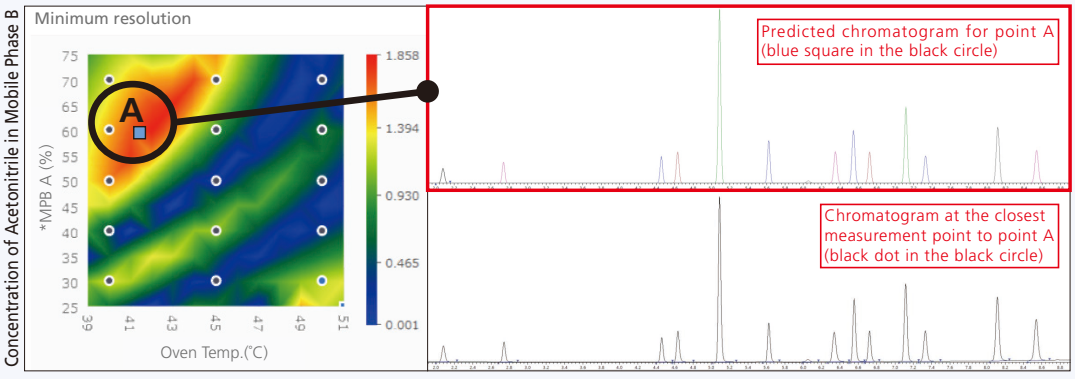
If permitted values for variations in the parameters (factors) are entered, the software will propose robust analytical conditions (the black rectangle in the figure at left) that satisfy the permitted range.

Multiple elements can be investigated simultaneously by overlaying design spaces. As an example, the figure at left shows overlapping design spaces when the minimum degree of separation, the tailing factor, and the analysis time are the criteria.

Prediction of Chromatograms for Any Set of Analytical Conditions

ANALYTICAL INTELLIGENCE

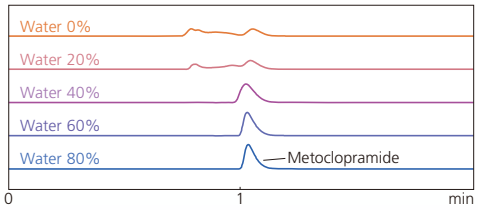
Click on the analytical conditions at any point A (the blue square in the black circle). The software can then display a visual prediction of the changes to the chromatogram when the analytical conditions are changed.
This function allows quickly observing how the separation will change without running an analysis.



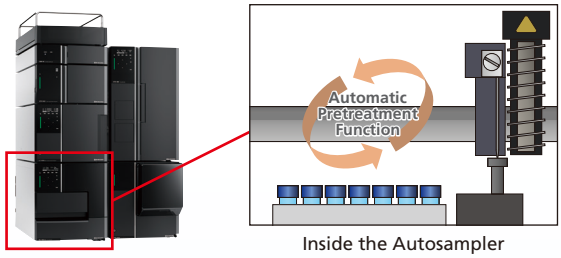
The black dots in the figure are points where the analysis was implemented.

NEW Support for Method Development from the Analysis Sample Adjustment Stage

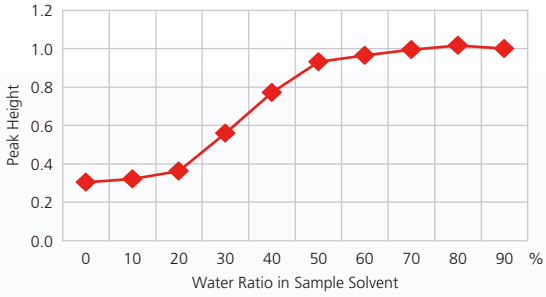
In LC method development, it is important to consider the composition of the sample solvent in order to obtain appropriately shaped peaks. If the sample solvent has a stronger elution capacity than the mobile phase, the concentration of the solute at the column inlet will be insufficient, which is known to broaden the peaks. Using LabSolutions MD, analysis can be performed while automatically changing the sample solvent composition. As a result, the impact of the sample solvent composition on the peak shape can be checked without the need for manual adjustment, substantially reducing the effort involved in determining the optimal sample solvent composition.



Change in the Chromatogram when the Proportion of Water in the Sample Solvent Differs



Inside the Autosampler



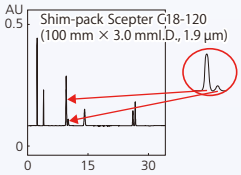
Items Optimized by the Automatic Pretreatment Function

- Investigation of the organic solvent ratio for the sample solvent
- Investigation of the dilution ratio for the analysis target
- Investigation of co-injected solvents

Application

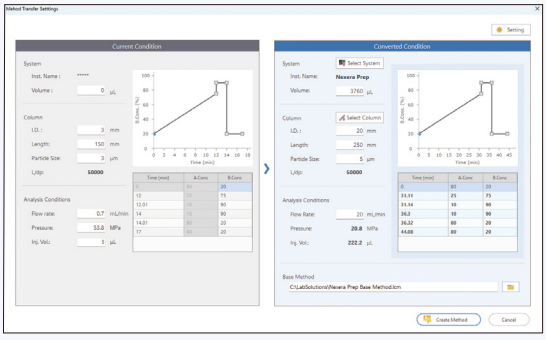
NEW Support for Method Transfer from a System for Analysis Method Development to a General-Purpose System

Analytical methods are sometimes transferred to general-purpose instruments after development with dedicated instruments. This procedure is called method transfer. The method must be adjusted in consideration of the columns used and the change in instrument. LabSolutions MD has a method conversion function for transferring from the system used for method development to the actual operating instrument. Further, the function can investigate the conditions using a system and columns suited to high-speed analysis, and convert the results to a method for a general-purpose instrument.

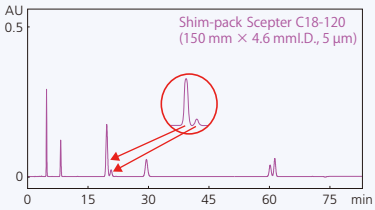


Analysis method development via high-speed conditions

Method transfer



Setting Window for Method Transfer



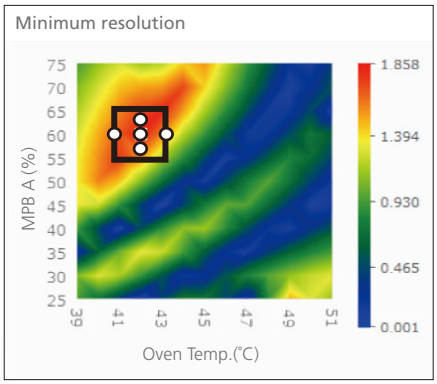
Confirmation of separation with a general-purpose instrument

Application

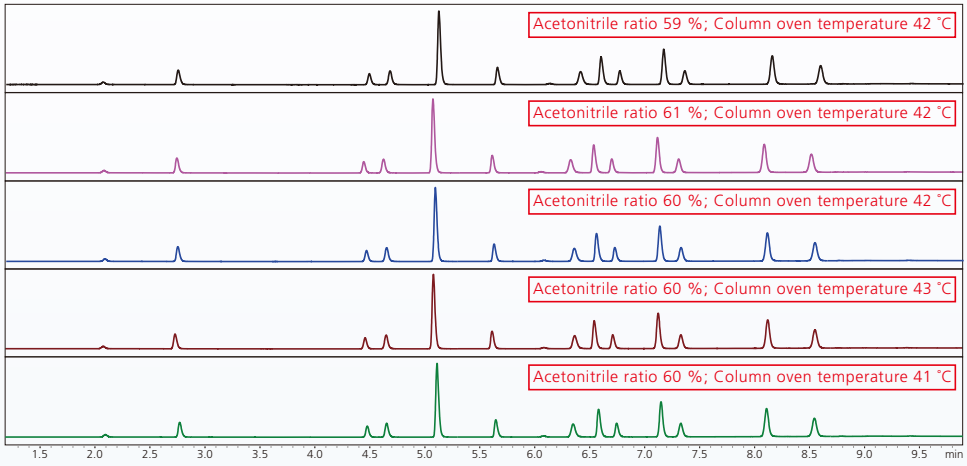
Robustness Evaluation

Evaluating Robustness Using Sequential Experimental Design

LabSolutions MD can create a sequential experimental design to perform robustness evaluation, which is an important process for understanding how variations in parameters will affect results and for ensuring the reliability of methods. LabSolutions MD creates a sequential experimental design automatically by changing the parameters of an optimized method in a small range to evaluate the robustness. In this example, the mixture ratio of organic mobile phase was changed by 1 % (59, 60, 61 %) and oven temperature by 1 °C (41, 42, 43 °C) (white circles in the right figure) to verify the effect on separation.



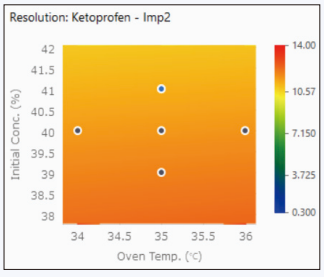
Shown below are the chromatograms obtained for robustness evaluation. Varying the parameters had little effect on separation, showing robustness of the optimized method constructed by design space.



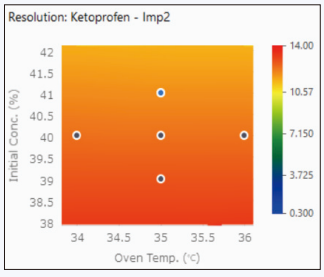
Chromatograms of Robustness Evaluation at Each Data Point

Robustness Evaluation Across Different Column Lots

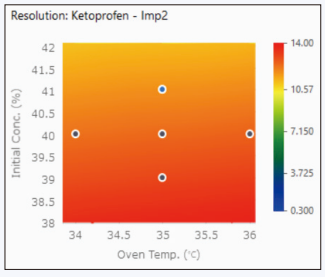
Applying design spaces to different lots of columns improves the efficiency of robustness evaluation. The figures below show the design spaces of resolution with columns from three different lots for the analysis of ketoprofen and its impurities. In all of the design spaces, it is evident that the regions with high resolution (orange and red) are distributed over the entire area, confirming that the optimized conditions are highly robust regardless of the column lot.
For details, refer to Application News "Efficient Method Development on Pharmaceutical Impurities Based on Analytical Quality by Design (01-00335-EN)".



Column Lot 1



Column Lot 2



Column Lot 3

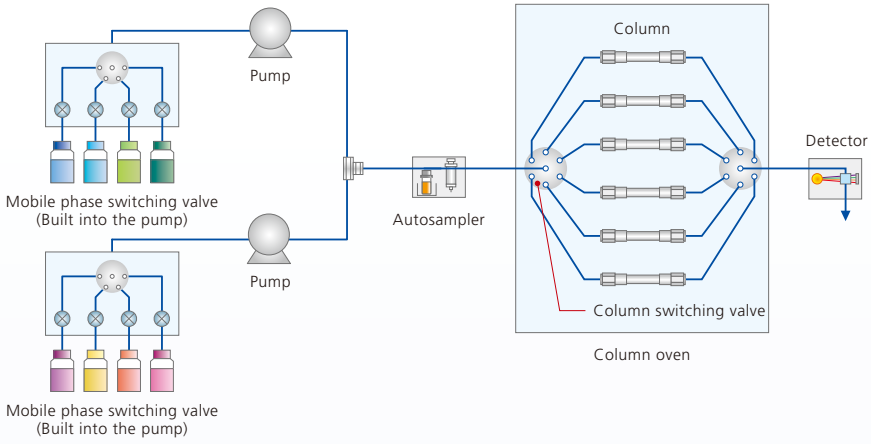
Application

Automated Column and Mobile Phase Switching

In addition to automatically switching between multiple mobile phases and columns, mobile phase blending functionality can save labor by automating mobile phase preparation. LabSolutions MD is compatible with Nexera series and i-Series systems.

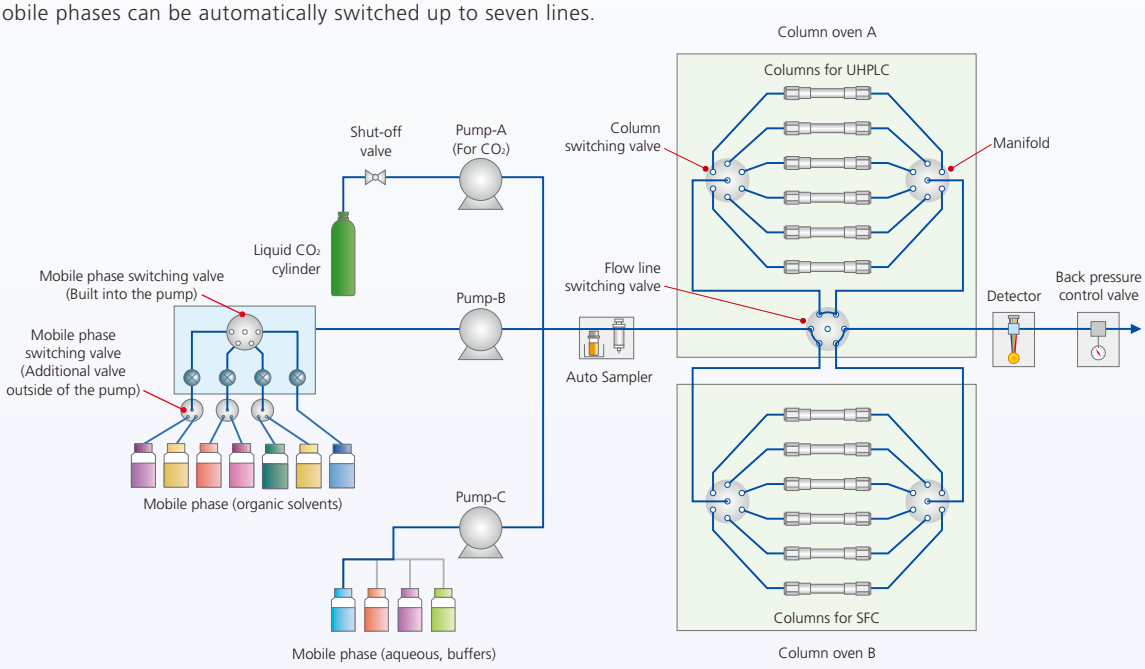
Nexera™ Series

These ultra-high-performance liquid chromatographs have a maximum pressure capacity of 130 MPa and support up to 192 combinations of 8 types of mobile phases and 12 types of columns (4 × 4 × 12).



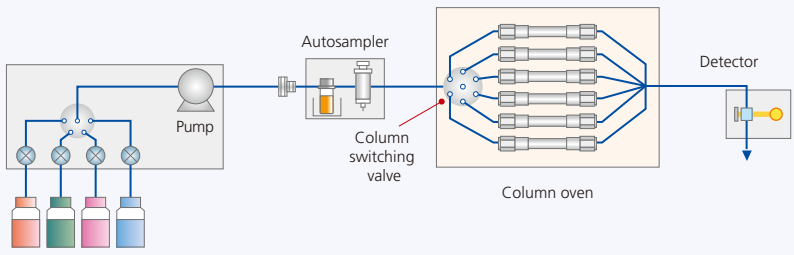
Nexera UC
UHPLC / SFC Switching System

By switching LC and SFC in a single system, the optimum conditions can be determined efficiently. In SFC analysis, mobile phases can be automatically switched up to seven lines.



i-Series

This is an integrated LC system with a maximum pressure resistance of 70 MPa.



Combine with a Mass Spectrometer for Even More Productivity

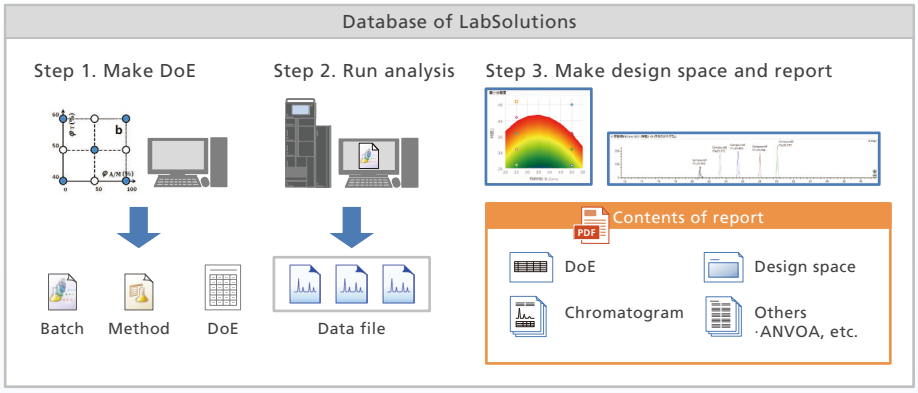
Single Quadrupole
Mass Spectrometer

Triple Quadrupole
Mass Spectrometer

With LabSolutions MD, peak tracking is possible using scan data from single quadrupole and triple quadrupole mass spectrometers.
By taking advantage of the excellent selectivity of mass spectrometers, analysis method development for chromatograms with many eluted peaks can be carried out more efficiently.

Ensure Data Integrity by Database Management

LabSolutions MD ensures data integrity by managing all the data in a single database of LabSolutions. This database also enables seamless operation, from creating an analysis schedule and running the analysis to data processing using design space, and eliminates time-consuming file importing or exporting steps.



Column Kits for Reverse-Phase Analysis Method Development

C18 (ODS) columns have different resolution properties. A variety of C18 columns are included in the Shimadzu Shim-pack series of LC columns. Shimadzu has bundled columns with different resolution characteristics into kits to make selecting candidate columns easier. These column kits are intended for reversed-phase analysis method development applications. In combination with LabSolutions MD, they enable more efficient column selection.

Kit types	HPLC	UHPLC	HPLC (LC-MS)	UHPLC (LC-MS)
① L1 Kit for HPLC C18 only	◎			
② L1Kit for HPLC / UHPLC (LC-MS) C18 only	◎	◎	◎	◎
③ Maximum Selectivity RP Kit for HPLC / UHPLC Type A	◎	◎	○	○
④ Maximum Selectivity RP Kit for HPLC / UHPLC Type B	◎	◎	○	○
⑤ Maximum Selectivity RP Kit for HPLC / UHPLC (LC-MS)	○	○	◎	◎

*These column kits do not guarantee the appropriate separation for customer analyses.

◎: Most suitable
○: Compatible

Brochure

List of LabSolutions MD Applications

- Efficient Method Development on Pharmaceutical Impurities Using Single Quadrupole Mass Spectrometer
- Efficient Method Development through Design Space Evaluation on Different Brands of Columns
- Efficient Method Development by Automated pH Screening with LabSolutions MD
- Efficient Method Development Based on Analytical Quality by Design with LabSolutions MD Software
- Efficient Method Development of Oligonucleotides by Reversed-Phase Ion-Pair Chromatography
- Efficient Method Development on Pharmaceutical Impurities Based on Analytical Quality by Design
- Efficient Method Development of Monoclonal Antibody Size Variants by Size Exclusion Chromatography

LabSolutions MD Package Contents

License of Method Development Solution

CD for installation (Instruction manual, Technical explanation)

"LabSolutions MD ~Automated Gradient Optimization Based on AI Algorithm~"

Brochure

Shimadzu Corporation
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