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Technical Report

Improving Efficiency in the Preparation of Test Reports for Chemistry, Manufacturing, and Control (CMC) Using Multi Data Report

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Abstract:

In order to demonstrate the quality of pharmaceutical products, pharmaceutical manufacturers must perform process studies into the active pharmaceutical ingredients (API) and studies into the pharmaceutical preparation process, and quality assessment for both of these as part of their chemistry, manufacturing, and control (CMC) activities. HPLC is used widely in such investigations for reaction tracing and impurity identification in API process studies, uniformity testing, and dissolution testing in pharmaceutical preparation development studies, and for analytical method validation in assay development for quality assessment studies.
The results of these studies must be tabulated according to the objectives and summarized in reports. It is often the case that these results are copied into Excel or similar software before a report is created. This article describes three examples of how the LabSolutions Multi Data Report feature is used in pharmaceutical development studies.
(1) API process studies: Outputting scouting results for chiral compounds
(2) Pharmaceutical preparation development studies: Outputting trend plots for dissolution testing
(3) Quality assessment studies: Outputting results from analytical method validation

Keywords: LabSolutions DB/CS, Multi Data Report, analytical method validation, method scouting, dissolution testing

1. Introduction

LabSolutions offers a Multi Data Report function that can combine multiple types of analytical data and create an Excel-like report. Using this function provides substantial efficiency improvements during the preparation of test reports for CMC.

Although Excel has long been used to create these reports, this method requires the manual copying of analytical data, which is both labor-intensive and can introduce errors. Excel document change control is also often left to the individual operator, which introduces the risk of multiple templates existing simultaneously, and the possibility of tampering with formulas or results.

The Multi Data Report function uses report templates that allow formulas similar to Excel to be included, so report formats previously used in Excel can be used in the Multi Data Report function. Report templates are managed securely in the LabSolutions database, and the change history for report templates can be saved as an audit trail.

When reports are created using the Multi Data Report function, they are populated with analytical results in a seamless process that saves on labor and prevents the introduction of transcription errors when Excel is used, thus enabling substantial improvements in data reliability and work efficiency to be achieved.

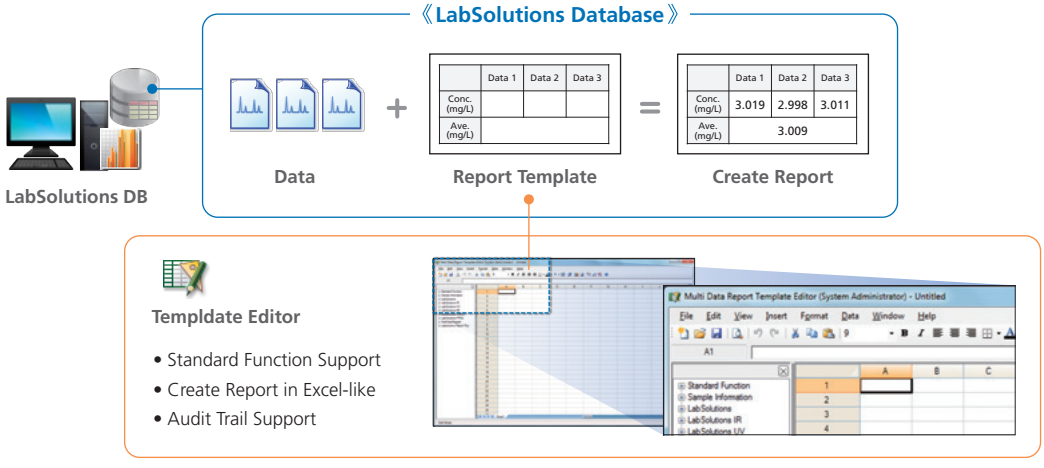


Fig. 1 Outline of the Multi Data Report Function

1 Analytical & Measuring Instruments Division

2. Usage-Case Examples

2-1. API Process Studies: Outputting Scouting Results for Chiral Compounds

In the API research area, chiral columns are being studied for quick and efficient resolution of optical isomers. Finding the appropriate column and mobile phase conditions for a given analysis from the wide variety of chiral columns available is a time-consuming and labor-intensive process, so there is a demand for more efficient means of developing separation conditions for chiral compounds.

Shimadzu offers a "Method Scouting System," which by combining solvent switching valves and column switching valves, is capable of automatically and continuously acquiring comprehensive data from up to 192 column and mobile phase combinations. However, determining optimum resolution conditions from the large volumes of data obtained during method scouting is time-consuming work that has its own set of issues, such as different operators generating different results from the same dataset.

The Multi Data Report function described in this article facilitates quantitative analysis of the large volumes of data acquired during method scouting.

Fig. 2 shows data obtained from methylclothiazide screening and Fig. 3 compares different resolution conditions. Data are displayed as graphs ranked in the order of degree of resolution, so the user can quickly determine the most appropriate column and resolution conditions for a given chiral compound.

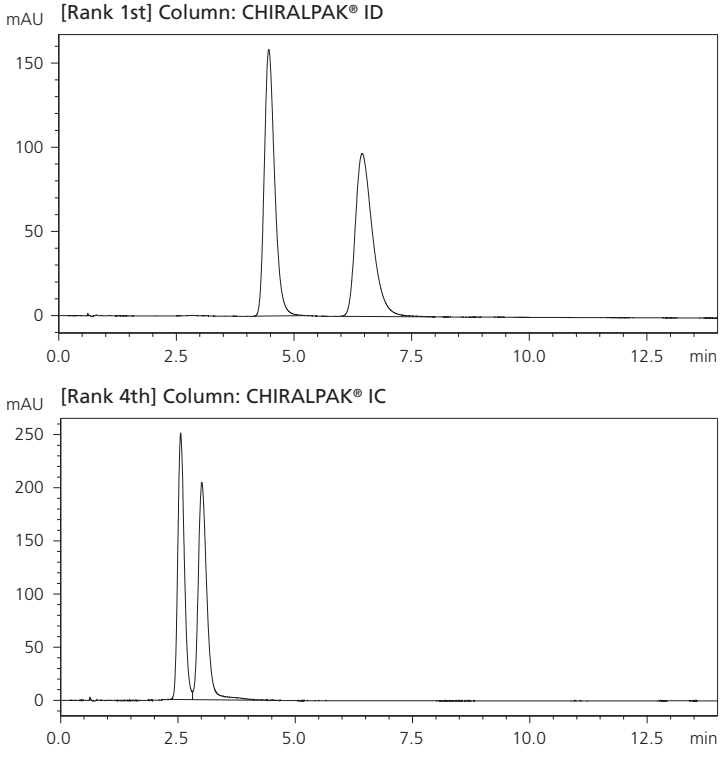
In addition to the degree of resolution, other parameters obtained during analysis such as the symmetry factor, number of peaks detected, and number of theoretical plates can be used freely to create evaluations according to the application.

This method removes operator influence from column scouting, and through the use of qualitative data also improves the reliability of scouting results.

Scouting Report Summary

Rank	Data File	Evaluation Value	Peak Count	Separated Peak Count	Resolution	Resolution Factor	Tailing Factor1	Tailing Factor2	k'1	k'2	Area%1	Area%2
1	Methylclothiazide_ID_n-Hex_EtOH_3_analysis_B20%_14min_035.lcd	7.569	2	2	3.785	1.523	1.310	1.463	5.665	8.626	49.777	50.223
2	Methylclothiazide_IF_MC_EtOH_6_analysis_B2%_4min_078.lcd	6.173	2	2	3.086	1.858	1.127	1.094	1.390	2.583	52.748	47.252
3	Methylclothiazide_IB_MC_EtOH_6_analysis_B2%_4min_070.lcd	4.912	2	2	2.456	2.248	0.715	1.094	0.443	0.995	45.633	54.367
4	Methylclothiazide_IC_n-Hex_EtOH_3_analysis_B20%_14min_033.lcd	3.155	2	2	1.577	1.238	1.264	1.300	2.821	3.493	47.960	52.040
5	Methylclothiazide_IF_n-Hex_EtOH_4_analysis_B100%_18min_052.lcd	3.030	2	1	1.515	2.759	1.465	-	0.102	0.282	48.153	51.847
6	Methylclothiazide_IF_MTBE_EtOH_8_analysis_B2%_4min_104.lcd	2.602	2	0	1.301	1.327	-	-	1.361	1.806	48.306	51.694
7	Methylclothiazide_IF_n-Hex_IPA_2_analysis_B40%_14min_026.lcd	2.433	2	1	1.217	1.807	1.854	-	1.436	2.595	48.504	51.496
8	Methylclothiazide_IA_n-Hex_EtOH_3_analysis_B20%_14min_029.lcd	2.326	2	0	1.163	1.156	-	-	4.943	5.714	48.006	51.994
9	Methylclothiazide_IC_n-Hex_IPA_2_analysis_B40%_14min_020.lcd	2.295	2	0	1.147	1.296	-	-	1.962	2.543	48.356	51.644
10	Methylclothiazide_IA_MTBE_EtOH_8_analysis_B2%_4min_094.lcd	2.202	2	0	1.101	1.209	-	-	2.128	2.573	46.618	53.382

Fig. 2 Screening Results Summary



Analytical conditions

- Mobile phase : Hexane/Ethanol=8/2 (v/v)
- Flowrate : 3 mL/min
- Analysis time : 14 min
- Column temperature : 40 °C
- Injection volume : 10 µL

Fig. 3 Comparison of Resolution Conditions

2-2. Pharmaceutical Preparation Development Studies: Outputting Trend Plots for Dissolution Testing

Dissolution testing is widely used in the field of pharmaceutical development for development and quality control activities, and also in the field of generic drugs for bioequivalence testing. With an increasing number of working hours being accounted for by the growing numbers of test samples, there is demand for a means of reducing the time spent in determining results from dissolution testing.

In pharmaceutical preparation development, the dissolution of pharmaceutical preparations is checked by creating a report in the form of a time-series plot of dissolution rate at short sampling intervals. Since dissolution rates must be calculated using formulas in the Pharmacopoeia, reports are commonly created using Excel and so validation and the control of templates used in this work often presents problems.

The Multi Data Report function described in this article can be used alongside the dedicated dissolution testing software "DT Solution," which reduces the work involved in creating complex reports and in file management.

"DT Solution" offers the ability to not only create an analysis sequence starting with the System Suitability Test (SST), but it also makes it possible to include information needed to calculate the dissolution rate, such as sample interval and measured component weight, within the data. The Multi Data Report function then uses this information to calculate the dissolution rate.

Fig. 5 is a report with a plot showing the trend in dissolution rate. This method offers the ability to automate operations, from analysis to report. In addition, Multi Data Reports also make it possible to automatically calculate the dissolution rate from the measured weight and display this information graphically as a trend plot.

Report templates can be stored securely in the LabSolutions database, and report template change histories can be saved as an audit trail, freeing the operator from administrative tasks.

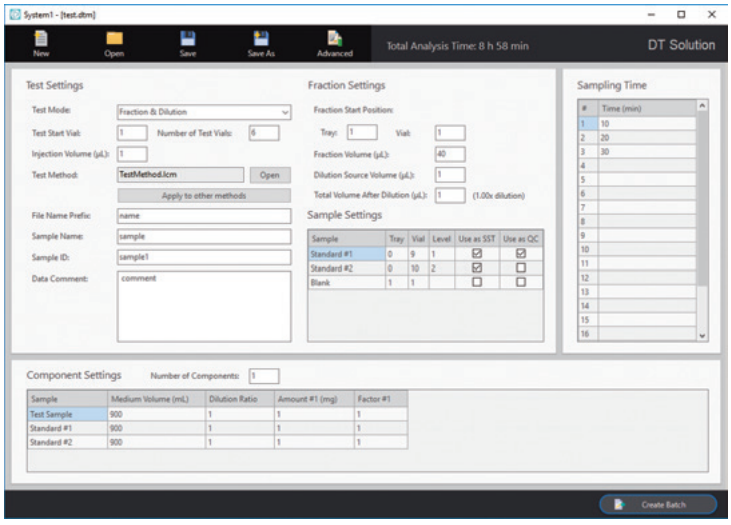


Fig. 4 DT Solution

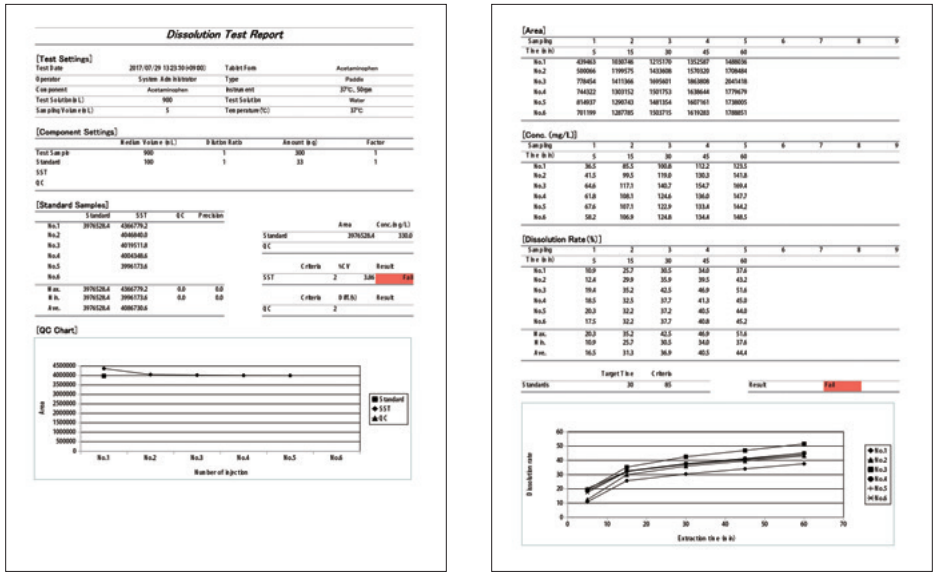


Fig. 5 Trend Graph Report

2-3. Quality Assessment Studies: Outputting Results from Analytical Method Validation

Analytical method validation is an important task specified in ICH guidelines that is used to demonstrate the validity of an assay method. Analytical method validation involves verifying the accuracy, precision, specificity, detection limits, quantifications limits, linearity, and range of an analytical method. As with dissolution testing, Excel is often used during analytical method validation since results must be calculated with formulas. Component area data and concentration data obtained from chromatograms must be transcribed by hand into Excel — a time-consuming task that comes with the risk of error.

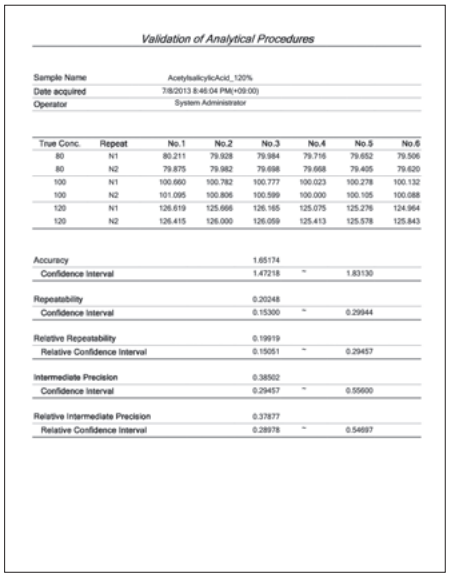
This article describes an example in which the Multi Data Report function is used to accurately incorporate all analytical method validation parameters in full, offering a huge improvement in validation work efficiency.

Fig. 6 shows a report on accuracy and precision. Accuracy represents deviation of mean (measured) concentration from the theoretical value, and precision represents relative standard deviation from (measured) concentration. Precision is expressed in terms of intra-assay precision (repeatability) and within-laboratory reproducibility (intermediate precision).

Fig. 7 shows a report on detection limits. A detection limit is calculated based on standard deviation (σ), which is the error distribution of measured values, and the slope (S) of the standard curve for concentration near the limit of detection.

$$LOD = 3.3\sigma/S$$

There are two methods of calculating standard deviation (σ). The standard deviation can be calculated as the residual error of a regression curve, or as the standard deviation of measured values at concentration zero as estimated from a regression curve. This article shows results calculated using both methods.



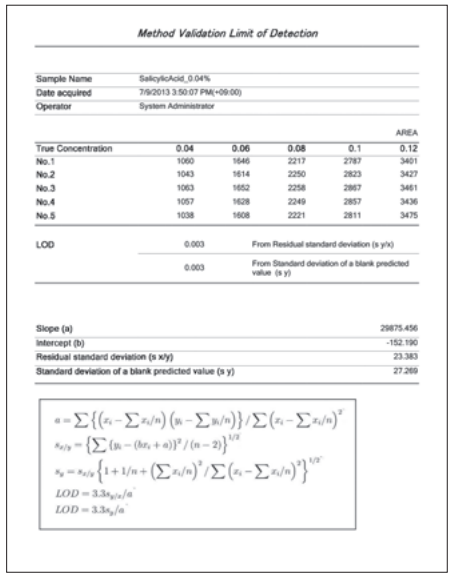
Validation of Analytical Procedures

Sample Name	AcetylsalicylicAcid_120%
Date acquired	7/8/2013 8:46:04 PM(+09:00)
Operator	System Administrator

True Conc.	Repeat	No.1	No.2	No.3	No.4	No.5	No.6
80	N1	80.211	79.928	79.984	79.716	79.652	79.506
80	N2	79.875	79.982	79.698	79.668	79.405	79.620
100	N1	100.660	100.782	100.777	100.023	100.278	100.132
100	N2	101.095	100.806	100.599	100.000	100.105	100.088
120	N1	126.619	125.666	126.165	125.075	125.276	124.964
120	N2	126.415	126.000	126.059	125.413	125.578	125.843

Accuracy		1.65174	
Confidence Interval	1.47218	~	1.83130
Repeatability		0.20248	
Confidence Interval	0.15300	~	0.29944
Relative Repeatability		0.19919	
Relative Confidence Interval	0.15051	~	0.29457
Intermediate Precision		0.38502	
Confidence Interval	0.29457	~	0.55600
Relative Intermediate Precision		0.37877	
Relative Confidence Interval	0.28978	~	0.54697

Fig. 6 Accuracy and Precision Report



Method Validation Limit of Detection

Sample Name	SalicylicAcid_0.04%
Date acquired	7/9/2013 3:50:07 PM(+09:00)
Operator	System Administrator

					AREA
True Concentration	0.04	0.06	0.08	0.1	0.12
No.1	1060	1646	2217	2787	3401
No.2	1043	1614	2250	2823	3427
No.3	1063	1652	2258	2867	3461
No.4	1057	1628	2249	2857	3436
No.5	1038	1608	2221	2811	3475

LOD	0.003	From Residual standard deviation (s y/x)
	0.003	From Standard deviation of a blank predicted value (s y)

Slope (a)	29875.456
Intercept (b)	-152.190
Residual standard deviation (s x/y)	23.383
Standard deviation of a blank predicted value (s y)	27.269

$$a = \sum\left\{\left(x_i - \sum x_i/n\right)\left(y_i - \sum y_i/n\right)\right\} / \sum\left(x_i - \sum x_i/n\right)^2$$
$$s_{x/y} = \left\{\sum\left(y_i - (bx_i + a)\right)^2 / (n-2)\right\}^{1/2}$$
$$s_y = s_{x/y}\left\{1 + 1/n + \left(\sum x_i/n\right)^2 / \sum\left(x_i - \sum x_i/n\right)^2\right\}^{1/2}$$
$$LOD = 3.3s_{y/x}/a$$
$$LOD = 3.3s_y/a$$

Fig. 7 Detection Limit Report

3. Conclusion

This article has described how the Multi Data Report function can be used to achieve substantial efficiency improvements during the creation of test reports for CMC by outputting trend plots for chiral compound scouting and dissolution testing, and by saving time during analytical method validation.

In addition, the use of the Multi Data Report function introduced in this article, combined with the LabSolutions database, encourages the adoption of paperless procedures and the computerization of documentation control of reports during pharmaceutical development. It also allows quality test data to be used and managed over the long term while helping pharmaceutical lifecycle management (the strategy of maximizing total sales of pharmaceutical products by considering the pharmaceutical product lifecycle).

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