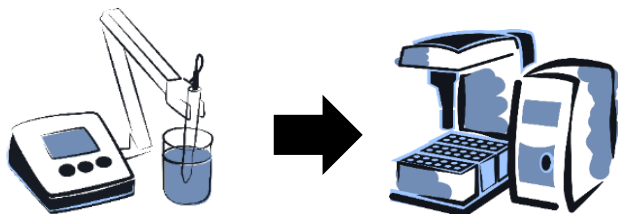


Conductivity Bridge Study: From Benchtop Meter and Probe to Automated Sievers* M9

APPLICATION NOTE

Objective

The objective of this study is to facilitate method transfer for measuring Stage 1 conductivity of USP <645> compliant water samples from a current state with a benchtop meter and probe to a future state with a Sievers M9 Total Organic Carbon (TOC) Analyzer with Conductivity by demonstrating analytical performance equivalency.



Scope

Conductivity for compendia water testing is a measurement of the degree to which an aqueous sample conducts ion-facilitated current across a known voltage, calculated as the ratio of the current density to the resultant electric field. Conductivity can be measured either with an offline benchtop meter and probe or with an inline conductivity cell sensor. Water molecules naturally dissociate into intrinsic ions as a function of temperature and pH; as a result, they have very predictable conductivity. The presence of extraneous ions also affects the conductivity of an aqueous solution and may have a significant effect on the water's chemical purity and suitability for use in pharmaceutical manufacturing.

Consequently, global harmonized pharmacopeias have prescriptive monographs for measuring conductivity in water for pharmaceutical production as an indication of its purity and suitability. Specific

requirements are stated in USP <645> for the instrument meter measuring conductivity along with three identified stages with different acceptance criteria to accommodate online and offline testing. Stage 1 testing, while the most restrictive for acceptance criteria, is the easiest to implement. Stage 2 and 3 testing require a laboratory technician to perform offline, time consuming benchtop testing. The most desirable stage to implement for pharmaceutical manufacturers is Stage 1 either offline or online. According to USP <645>, if measuring offline, the measurement must be performed in a suitable container.

For measuring offline conductivity, a suitable container is constructed of a material that does not contribute ions when in contact with the sample. Traditional borosilicate glass vials will leach sodium and other ions when in contact with an aqueous sample and therefore are not suitable for measuring compendia water samples. Sievers Dual Use Conductivity and TOC (DUCT) vials, caps, and septa have demonstrated that, even with a sample hold time of five days, there is not a significant TOC or conductivity contribution from the DUCT vial into the sample.

The current state for many pharmaceutical manufacturers measuring conductivity of compendia water samples is offline Stage 1 or Stage 2 testing with a benchtop meter and probe. The current state for measuring conductivity has several undesirable, but unavoidable attributes, including data integrity vulnerabilities, limited sample integrity, exposure to atmosphere, and inefficient deployment of resources. The desired future state for measuring conductivity of compendia water samples is automated, Stage 1 conductivity testing in an electronic, secured database that is fully compliant with 21 CFR Part 11 as well as the latest data integrity guidance. The Sievers M9 TOC Analyzer with Conductivity enables users to reach the future state.

The following procedure is a road map for how to perform a bridge study between the current state of offline Stage 1 conductivity testing with a benchtop meter and probe to the desired future state of automated, Stage 1 conductivity testing with the Sievers M9 TOC Analyzer with Conductivity.

Materials

Sievers M9 Portable TOC Analyzer with Conductivity option (SN# 0043)

Mettler Toledo SevenCompact Meter with an InLab 741 ISM Conductivity Probe

One case of Sievers DUCT Vials (HMI 77500-01)

Two sets of Sievers 100 $\mu\text{S}/\text{cm}$ KCl Conductivity Calibration Standard (STD 74470-01), if applicable

One 500 mL bottle Ricca 100 $\mu\text{S}/\text{cm}$ KCl Standard, at 25°C (CAT# 5887-16)

10 mL and 1000 μL pipettes and pipette tips

Analytical Procedure

1. Ensure proper calibration of the M9 with the 100 $\mu\text{S}/\text{cm}$ standard set (STD 74470-01). Calibration is performed by using the System Protocol “Sample Conductivity Calibration” either within DataPro2 (see below) or directly from the M9 touchscreen.



2. Ensure proper calibration of the Mettler Toledo SevenCompact Meter and InLab 741 ISM conductivity probe with the 100 $\mu\text{S}/\text{cm}$ standard set (STD 74470-01). Be sure to select the proper conductivity calibration value.

For the Mettler Toledo SevenCompact Meter, the navigation to select the proper calibration standard is: Menu/Calibration, Settings/

Calibration Standard/Customized Standard. Enter 100 $\mu\text{S}/\text{cm}$ at 25°C.

3. In order to minimize atmospheric contamination of CO_2 from fluid transfer or from secondary containers, all standards should be prepared directly in a DUCT vial. Using the 100 $\mu\text{S}/\text{cm}$ KCl stock solution, prepare one set of 100, 75, 50, 25, 12.5, 10, 5, 2.5, 1.25, and 1 $\mu\text{S}/\text{cm}$ concentrations in 30 mL DUCT vials using good sampling technique. It is best practice to prepare the standards in order from highest concentration to lowest. This will allow for the shortest possible time between preparation and analysis of the sensitive low-level standards. See **Table 1** for corresponding volumes to be used.
4. Due to the sensitive nature of the low-level standards, immediately run the lowest conductivity standard first and the highest last with the method conditions shown in **Figure 1**. The M9 reports raw conductivity, temperature, and temperature compensated conductivity. USP <645> specifies that all Stage 1 conductivity testing is non-temperature compensated for unknown water samples. When performing calibration, verification, or comparison studies, pure standards of known compounds are used. For example, the aforementioned calibration standard is 100 $\mu\text{S}/\text{cm}$ KCl at 25 °C. To properly compare a measurement to this value, the conductivity measurement must be compensated back to the reference temperature of 25 °C. Similarly, as these pure, known standards are measured on the two conductivity measurement platforms, temperature compensation is required to ensure proper comparisons.

Table 1. Preparation volumes for diluting 100 $\mu\text{S/cm}$ KCl standard into DUCT vials.

Expected Conductivity ($\mu\text{S/cm}$)	KCl Sol. Vol. (mL)	UPW Vol. (mL)	Total DUCT Vol. (mL)
100	30.000	0.000	30
75	22.500	7.500	30
50	15.000	15.000	30
25	7.500	22.500	30
12.5	3.750	26.250	30
10	3.000	27.000	30
5	1.500	28.500	30
2.5	0.750	29.250	30
1.25	0.375	29.625	30
1.00	0.300	29.700	30

Figure 1. Sievers M9 TOC Analyzer with Conductivity method conditions for measuring conductivity samples.

- Using the 100 $\mu\text{S/cm}$ KCl stock solution, prepare an additional set of 100, 75, 50, 25, 12.5, 10, 5, 2.5, 1.25, and 1.00 $\mu\text{S/cm}$ concentrations in DUCT vials using good sampling technique to measure on the meter and probe. Again, due to the sensitive nature of the low-level standards, on the meter and probe, measure the lowest conductivity standard first and the highest last using the conditions in **Figure 1**. Be sure to fully immerse

the probe into the DUCT vial. Liquid will be displaced and spill over, so it is advisable to place each vial in a secondary container to catch the overflow when measuring with the meter and probe.

- For the Mettler Toledo SevenCompact Meter, ensure 25 °C is selected as the reference temperature and that measurements will be temperature compensated. It is important that the accurate compensation curve and reference temperature are selected on both the meter and M9. At low levels, KCl has a non-linear temperature correction curve. For this reason, we recommend choosing a non-linear compensation curve on the meter. When taking a measurement, place the probe into the sample and press the "Read" button. The measurement will stabilize, and the meter will prompt to either "Save" or "Exit." For all samples, the data are recorded on the meter and later exported for analysis.

Results and Discussion

Figure 2 shows the data from the Mettler Toledo Meter with InLab 741 ISM Conductivity Probe's measured response versus expected response. A linear trend line is fitted to the response values to provide the R^2 value as well as the slope for method comparison. The data shown in **Figure 2** demonstrate that the linearity of the Mettler Toledo Meter with InLab 741 ISM Conductivity Probe is suited for measuring Stage 1 conductivity for compendia water samples.

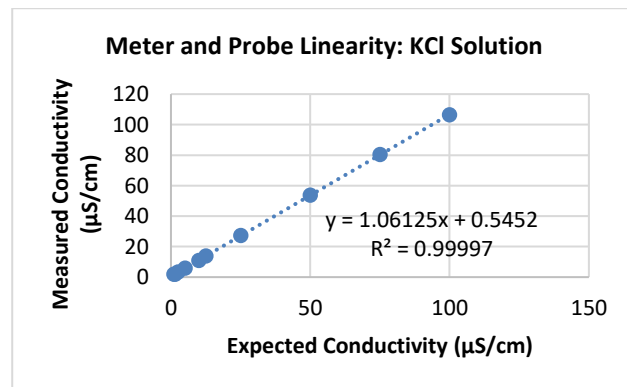


Figure 2. Mettler Toledo SevenCompact Meter with InLab Conductivity Probe measured versus expected conductivity response data.

Figure 3 shows the data from the Sievers M9 TOC Analyzer with Conductivity's measured response

versus expected response. A linear trend line is also fitted to the response values to provide the R^2 value as well as the slope for method comparison. The data shown in **Figure 3** demonstrate that the linearity of the Sievers M9 TOC Analyzer with Conductivity is also well suited for measuring Stage 1 conductivity for compendia water samples.

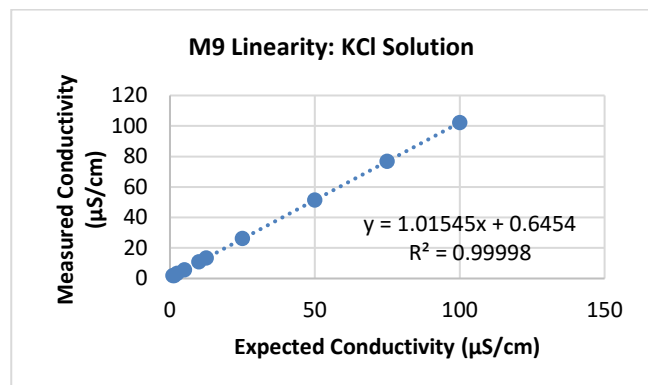


Figure 3. Sievers M9 TOC Analyzer with Conductivity measured versus expected conductivity response data.

Table 2 contains the compiled linearity method comparison metrics between the Mettler Toledo Meter with InLab 741 ISM Conductivity Probe and the Sievers M9 TOC Analyzer with Conductivity.

The data collected from the two different method responses show a slight improvement for both R^2 and slope response for the Sievers M9 over the Mettler Toledo Meter with InLab 741 ISM Conductivity Probe.

The data from this bridge study confirm both method equivalency and method superiority for the Sievers M9 TOC Analyzer with Conductivity.

Table 2: Compiled slope and R^2 values from linear fit trend lines for the conductivity measurements taken on both the Mettler Toledo Meter and Probe as well as the Sievers M9 TOC Analyzer with Conductivity.

	Meter and Probe	M9	Ideal
Slope	1.06125	1.01545	1.00000
R^2	0.99997	0.99998	1.00000

In part, the differences observed between the two methods can be attributed to effective isolation of the sample from the atmosphere. While both sets of standards are prepared in DUCT vials for analysis, the meter and probe standards require removal of the caps to allow the probe in during measurement. When the caps are removed from the vial, atmospheric CO_2 will contaminate the sample.

In addition to improved linearity, slope response, and sample handling, the Sievers M9 also offers additional benefits over a traditional benchtop meter and probe for measuring conductivity. The data collected from a meter and probe are often stored locally on the meter in a .txt or .csv format. These are unsecured data formats that are vulnerable to data integrity scrutiny from auditing agencies. The Sievers M9 utilizes secured data formats that are not vulnerable to data integrity scrutiny. Additionally, the transfer of these data files from the meter to a PC is often only accomplished with a USB storage device which is vulnerable to data integrity scrutiny from auditing agencies, whereas the M9 data can be exported automatically via ethernet to a LIMS system, SCADA system, or other data management platform.

Lastly, a benchtop meter and probe require a technician's dedicated time and attention to prepare and run the samples. Stage 2 conductivity testing can take up to 30 minutes per sample due to temperature, agitation, and measurement stabilization requirements. The use of an autosampler with the Sievers M9 TOC Analyzer with Conductivity allows for automated sample analysis and data collection. These factors, in combination with superior analytical results make the process of method transfer from a benchtop meter and probe to a Sievers M9 TOC Analyzer with Conductivity highly valuable to pharmaceutical manufacturers (**Table 3**).

Table 3. Conductivity Method Comparison highlighting differences between the current state of a benchtop meter and probe to a future state with a Sievers M9 TOC Analyzer with Conductivity.

	Current State (Meter and Probe)	Future State (M9 with Conductivity)	Comments
Application Suitability	✓	✓	Both methods are suitable for measuring conductivity of compendia water.
Sample Integrity	✗	✓	Sievers DUCT vials effectively isolate the sample from atmospheric contamination.
Data Integrity	✗	✓	Sievers M9 uses encrypted file formats for all database entries without the need for USB transfer.
Automation	✗	✓	Sievers DataPro2 Software enables automation of instrument verification and sample data collection.

Conclusion

Analytical method transfer can be a complex process, especially going from a traditional benchtop process to an automated one. This bridge study successfully demonstrates how to transfer a method for measuring conductivity with a benchtop meter and probe to a Sievers M9 TOC Analyzer with Conductivity. This is achieved by demonstrating equivalent analytical performance for measuring USP <645> Stage 1 conductivity compliant water samples. Additionally, this bridge study demonstrates the relative ease by which the method transfer can be accomplished. Lastly, as highlighted in **Table 3**, the added value of data integrity, sample integrity, and automation benefits when using a Sievers M9 over a benchtop meter and probe makes the method transfer process very attractive to pharmaceutical manufacturers seeking lean processes.