online TOC comparison: sensors and analyzers

overview

Pharmaceutical manufacturers rely on total organic carbon (TOC) measurements to meet compendial requirements for release of water and equipment for production. Accurate and consistent TOC analysis is critical to meet the acceptance criteria limits for USP regulations. Regulatory compliance may be achieved with a limit test. In this study, five TOC technologies were evaluated for performance and capability to be validated for pharmaceutical applications. Validated instruments that satisfy instrument qualification, method validation, and data integrity requirements are essential to reliable manufacturing processes.

technology comparison

TOC sensors

TOC sensor technologies measure conductivity pre- and post-oxidation and derive the TOC result from the assumption that all measured conductivity post-oxidation arises from organic carbon conversion to CO_2. The conductivity is measured without any discrimination against interfering ions, which can lead to over- and under-reporting. Additionally, there is no differentiation between CO_2 from inorganic carbon (IC) and organic carbon as required by USP <643>[1]. Sensors can effectively pass the limit test, but because methods cannot be validated[2] during performance qualification for specificity and robustness, actual analytical performance for organic compounds is widely variable. Proper method validation is imperative in CGMP manufacturing settings, especially considering pharmaceutical grade water touches many facets of the manufacturing process.

TOC analyzers

The Sievers* 500 RL and M500 are carbon *analyzers,* wherein a gas permeable membrane separates CO_2 from interfering compounds to allow for accurate measurement of carbon. This technology accurately and precisely measures both the IC as required by USP <643> and the TOC, allowing for successful performance qualification and effective analysis for specificity and robustness compounds.

experimental summary

Online TOC sensors and analyzers have similar performance specifications in regards to range, accuracy, and precision. The performance for a broad range of common organic compounds was determined. The organics evaluated in this study are listed in **Table 1**. These include cleaning agents, difficult-to-oxidize compounds, and volatile compounds to represent common organics found in pharmaceutical water and processes.

Table 1. Organic compounds tested

Potassium Hydrogen Phthalate (KHP)
Sucrose
Sodium Dodecylbenzenesulfonate (SDBS)
1,4-Benzoquinone
Urea
Nicotinamide
Acetic Acid
Isopropanol
Trimethylamine
CIP 200
Minncare

[1] USP <643>

[2] ICH Q2(R1)

The five instruments used in this study were set up on the same ultrapure water (UPW) source for the analyses. Each organic compound was introduced at 500 ppb TOC to all the instruments in parallel through a pump. UPW was used to rinse each instrument before and after each analysis to ensure a clean sample path.

results

Figure 1 demonstrates the TOC results using the five instruments for each compound at 500 ppb. All the instrument platforms perform well for sucrose and 1,4 benzoquinone (USP <643> system suitability compounds). However, the sensors struggle to accurately measure other compounds.

There are no urea results on the Anatel PAT700 due to its inability to analyze the compound.

The Sievers 500 RL and M500 demonstrate consistent recovery for all compounds. The Mettler Toledo 5000TOCi and 6000TOCi and the Anatel PAT700 display over- and under-recovery for many of the compounds. This is due to the fact that direct conductivity sensors do not distinguish CO_2 from organic carbon and other conductive species present in the oxidized sample. Therefore, ionic species in cleaning agents, such as CIP 200 and Minncare, or halogens, such as chloroform, result in much higher results than actual values.

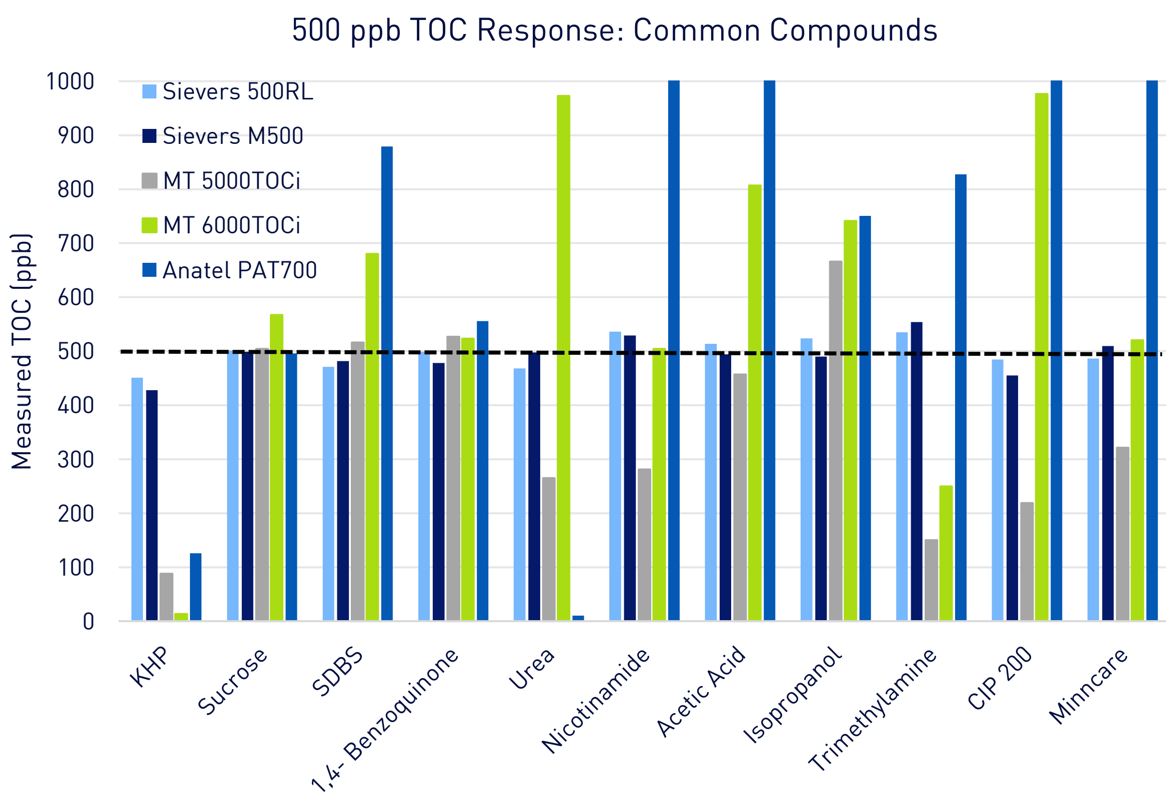

Figure 1. Organic compound results for 500 ppb TOC analysis

summary

The Sievers 500 RL and M500 TOC Analyzers offer precise, accurate, quantitative, and robust carbon analysis able to pass performance qualification and validation, providing the user an accurate assessment of the state of the water system. With validated and accurate results, data can be used to make important decisions, release water and equipment, troubleshoot, and optimize water monitoring and cleaning processes.

Under-reported values translate into risk of disinfection byproducts and other harmful compounds present in the water system contaminating final product. On the other hand, over reporting TOC can cause unnecessary and time-consuming out-of-specification (OOS) investigations where no definitive root cause is identified.

With sensor technology, not only is there a risk to product safety due to false reporting, but sensors can also pose compliance and efficiency concerns.

The data from this study demonstrate actual instrument performance for compounds commonly encountered in water systems. Sievers membrane technology consistently delivers accurate and precise carbon analysis for these compounds, while sensor technologies vary widely in accuracy. When deploying TOC technology, it is important to consider both upstream and downstream risks on the process from false reporting.