Application Notes

THORNTON
Leading Pure Water Analytics

5000TOC Total Organic Compound Sensor

Importance of TOC measurement for Pharmaceutical Water System

Application Notes
AN0115:Total Organic Compound Sensor

Water is the most widely used excipient in Pharmaceutical Manufacturing and accurate measurement of water quality is critical to the Pharmaceutical Industry. Purified Water and WFI systems are a significant part of the regulatory quality inspections for the Pharmaceutical industry. The two principal monitored attributes for Pharmaceutical waters are TOC and Conductivity. TOC is a measure of the aggregate carbon impurities, while conductivity is a measure of the ionic, conductive impurities in the water. Microbiology Requirements for Water systems are the most widely audited and monitored attribute of PW, HPW and WFI in the Pharmaceutical industry.

The water treatment industry continues to develop and improve purification technologies and while the systems can consistently produce Purified Water, Highly Purified Water and WFI, the testing and documentation requirements have become more stringent. Pharmaceutical-grade water systems must meet strict water quality requirements. This highly regulated industry mandates the monitoring of Total Organic Carbon levels for PW (Purified Water), WFI (Water for Injection) and HPW (Highly Purified Water). The instruments used in this application must also undergo periodic testing to verify the ability to accurately

measure TOC. Testing requirements are spelled out in the USP Chapter <643> and EP 2.2.44 guidelines. For TOC, the EP and USP methods are considered fully harmonized. A Pharmaceutical company must follow the pharmacopoeia of the country where they wish to market and sell their products. TOC Instrumentation Requirements for USP <643> TOC and EP 2.2.44

- Limit of Detection of 0.050 mg carbon/L (50 ppb)
- Calibrate according to Manufacturer's recom mendations
- Must meet System Suitability testing periodically
- Measurement must discriminate inorganic carbon

METTLER TOLEDO

The Japanese Pharmacopoeia (JP) still relies heavily on wet chemistry for control of pharmaceutical waters, but a major revision is planned. JP 15, developed in cooperation with the USP's Pharmaceutical Water Expert Committee, is expected to come into force in 2005 or 2006, replacing most of the wet chemical methods with tests equivalent to those of the USP for conductivity and TOC.

In USP 27, which was effective from January 2004, there were no immediate major changes planned in general chapters 645 (conductivity) and 643 (TOC). There is, however, a major revision of the "Method of Manufacture Requirements" for WFI. Previously, WFI could be made by distillation or reverse osmosis (RO), now the USP requires merely "distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and microorganisms". This change will open the door to all validatable manufacturing methods for WFI, while retaining distillation as the "gold standard". Europe will continue to allow distillation only; in Japan, distillation or RO plus ultra-filtration is required.

Measurement of TOC in PW, WFI and HPW systems

Microbial contamination can result in the loss of millions of dollars in pharmaceutical products being destroyed and is the most widely audited requirement in the industry, so Pharmaceutical companies constantly monitor their Water systems. While a direct correlation between organics in the water system and microbial contamination is difficult, organic levels are a significant indicator of the 'health' of the water system. Organics provide a food source for any bacteria that may exist in the distribution system, storage tanks, and the process technology or treatment modules. Accurate, fast and convenient measurement of the organic level in a PW, WFI or HPW system can save millions of dollars in lost product, Pharmaceutical manufacturing downtime and regulatory investigations. The new 5000TOC sensor and 550TOC analyzer provide the performance needed to meet these requirements, while offering the added benefits such as continuous online measurement in a low-maintenance, industrial package with proven Multi-Parameter technology. The 5000TOC sensor can operate at elevated temperatures to 90°C, useful where hot water sanitizing is required and interfaces directly with the 770MAX instrument which provides additional measurement parameter capability.

The TOC testing requirement has been established by the different Pharmacopoeia organizations and currently most Pharmaceutical Companies will monitor the water at the distribution return loop before storage. This testing methodology meets the established requirement for TOC testing; it does so at the risk of testing after the water has been used in final product production. In the past Pharmaceutical companies had not installed additional testing because of instrument cost. The 5000TOC sensor and 770MAX multi-parameter instrument package make multiple testing points not only economical but outstanding investments for risk reduction.

Organic Sources in Water Systems

The major source of organics is make-up water. Surface waters have higher levels of naturally occurring organics than ground waters. But ground water sources are being depleted in many areas. As a result, there is greater reliance on surface water, reclaimed water and even municipal wastewater as the raw source for high purity make-up water for the water/steam cycle. A further complication is that surface water sources typically have significant seasonal variations in concentration and types of organics. A treatment system that produces water with low organics during one season may be seriously challenged in another season. Even greater changes in source water composition impact a treatment system if it must alternate between surface water high in organics during wet seasons and ground water high in minerals in dry periods. There are a number of unit operations that can reduce organ-

ics in make-up water including improved flocculation, membrane processes, final oxidation, and others. Treatment must be tailored for the specific water composition and site conditions.

The second most important source of organics is from ion exchange resins in the treatment system. They are, after all, beads made of organic polymers. Resin fines from physical breakdown can find their way into process if they are not removed via properly sized filtration. Chemical breakdown of resins can produce trace contaminants: sulfonic acids from cation resins and amines from anion resins. In addition, traces of processing solvents may also be released. These contaminants may include inorganic constituents in their structure such as chloride and sulfates. Additional sources of organic contamination are directly in the process and distribution system, including pump lubricants, pump seals, polishing resins, and system dead legs.

Detection

Conductivity is the common and economical measurement for detection of ionic contaminants—usually minerals. Conductivity will detect organic acids and bases but is insensitive to the majority of organic contaminants. For this reason, total organic carbon (TOC) analyzers oxidize organics to a completely oxidized, ionic form as carbonic acid in order to detect them by conductivity. The delta in conductivity before and after oxidation gives a measure of the difference in conductivity readings and a TOC measurement is provided.

On-Line TOC by UV Oxidation/Conductivity

- CxHyOz ? CO2 + H2O ? H2CO3 ? H+ + HCO3-
- Hg lamp emits 185 nm and 254 nm UV light
- Light, chemicals, surfaces, and time move the reaction forward
- Accurate conversion of temperature and conductivity is required

Monitoring TOC in the make-up water treatment system after the last deionization stage is an important checkpoint for organics to prevent them from entering the polishing and production process. Additional measurements upstream and downstream can help diagnose where the organics are breaking through, e.g. whether it is a membrane failure or ion exchange resin deterioration or pump failure.

The Thornton 5000TOC Sensor with 770MAX Multiparameter Instrument provides an ideal and economical analytical package. The 770MAX can accept 3 other analytical sensors in addition to TOC, including conductivity, pH, ORP or dissolved oxygen, plus pressure, tank level or two flow sensors. The 770MAX can also interface with two 5000TOC sensors, leaving two additional smart channels for conductivity, pH or DO measurement and two pulsed flow channels are also available. See Thornton data sheets ML0067 for more information on the 770MAX Instrument and ML0103 for more information on the 5000TOC Sensor.

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