

Water management in the manufacturing process of Pharmaceutical products with TOC-5000A

Water is a raw material in the manufacturing process of pharmaceutical products and is also used for cleaning. The water used in these operations is laid down in the GMP (Good Manufacturing Practices: Clauses 2.5 and 3.7 of article 5 of ordinance No. 4, Ministry of Health and Welfare). Appropriate water is selected and monitored in accordance with the applications in the ordinance and this is accompanied by tests and inspections that are required.

An important monitoring item among water controls for pharmaceutical manufacturing water is organic impurities that may have a relationship to fluctuations in microorganisms and pyrogens. Usually a potassium permanganate consumption test is used for organic matter tests, but in recent years the use of TOC (Total Organic Carbon) - with its superb accuracy, high sensitivity, speed and ease of use - is becoming popular. Shimadzu's worldwide bestseller TOC analyzer TOC-5000A is also widely used for applications such as water monitoring and residual matter evaluation of cleaning validation in pharmaceutical manufacturing.

This Application News edition features reports on the ability of the Shimadzu TOC-5000A to accommodate the requirements of GMP. JP (Japanese Pharmacopoeia) and USP (United States Pharmacopoeia) as well as comparisons with competitor TOC analyzers and an actual example of continuous monitoring of water used in pharmaceutical manufacturing using the online TOC-5000A WM.



The ability of the Shimadzu TOC-5000A to meet domestic and overseas legislation

Suitability for USP and EP TOC testing methods

The organic impurities measuring method employed by United States Pharmacopoeia (USP) and European Pharmacopoeia (EP) has changed from the potassium permanganate consumption testing method to the TOC testing method, and WFI (water for injections) and PW (purified water) can only have up to TOC 0.5mg/L. The TOC testing methods for USP and EP are laid down as follows under the condition that a TOC analyzer is used.

- TOC analyzer must be able to measure TOC 0.05mgC/L.
- The recovery rate of P-benzoquinone of 0.5mgC/L shall be 85 to 115% in comparison with the measurement of sucrose 0.5mgC/L as the criterion (system suitability test).

Suitability for GMP water quality monitoring

Water quality monitoring is required for water validation in GMP manufacturing. If TOC is used for this application, organic impurities can be quickly and easily monitored with high sensitivity and superb accuracy. Furthermore, as shown in the following example, online monitoring is also possible. As TOC is already used under the general testing method in accordance with the 12th revision for JP, TOC should be used for GMP manufacturing. In the general testing method, the following three items are stipulated as conditions for TOC analyzers.

- TOC analyzer must be able to measure TOC 0.05mgC/L.
- Can be calibrated using the potassium biphthalate standard solution.
- Recovery rate for sodium dodecylbenzenesulfonate with TOC concentration 0.5mg must be 90% or more.

Water source monitoring

The JP explanation document states that the use of a TOC analyzer that can measure water sources (tap water, river water, ground water, etc.) is desirable in certain situations for the monitoring of the manufacturing process for WFI. This TOC monitoring of water sources is recommended as water source quality affects the quality of the water to be used in an end product.

Comparisons with competitor TOC analyzers

The Shimadzu TOC-5000A fulfills all the TOC analyzer conditions laid down in the above USP, EP and JP. Note, however, that certain analyzers depending on their measuring system do not fulfill these conditions, so due care and consideration should be given to the targeted use of such equipment.

For example, as TOC analyzers employing ultraviolet

oxidizing/conductivity detector systems are unable to measure ionized organic matter such as organic acid, amino acid and amino due to reasons related to the measuring principle, they cannot measure the potassium biphthalate (standard fluid for calibration) and sodium dodecylbenzenesulfonate (system conformity testing fluid) that are conditions for TOC analyzers used in accordance with the JP general testing method.

An actual example of continuous monitoring of water used in Pharmaceutical manufacturing using the online TOC-5000A WM

The TOC-5000A WM - based on the highly rated TOC-5000A that is widely used around the world - has been developed to continuously monitor the TOC of water used in the manufacture of pharmaceutical products including WFI, PW and rinse water. The following is an example of the Shimadzu online TOC analyzer TOC-5000A WM in actual use.

Purpose

Monitoring of water used in pharmaceutical manufacturing

Measuring conditions

Measuring range: 0 to 500ppb C

Measuring method:

TOC (NPOC) measuring

TOC measuring after removal of IC (inorganic carbon) from water sample by acidifying and sparging.

Results

Measuring results are shown in the figure on the right.

Three measurements were taken in one hour, and the average value is shown in the MEAN column (The measuring period can be altered. Minimum measuring period is approximately 5 minutes).

Benefits

- The device can be used for water quality monitoring in water validation for GMP pharmaceutical manufacturing.
- Constant monitoring of manufacturing water is possible to see if it is suitable or not for JP and USP.

Practical uses

Validation of manufacturing water

- Monitoring of water manufacturing systems (validation)
- Monitoring of organic impurities in manufactured pure water
- Monitoring of deterioration in functional materials (ion-exchange resin, activated carbon, etc.)
- Monitoring of degeneration and pinholes in ultra filtering modules (enables timely module replacement and equipment maintenance)
- Water source monitoring: Avoidance measures can be taken when there are abnormalities
- Water quality evaluation when restarting a line after a long layoff.

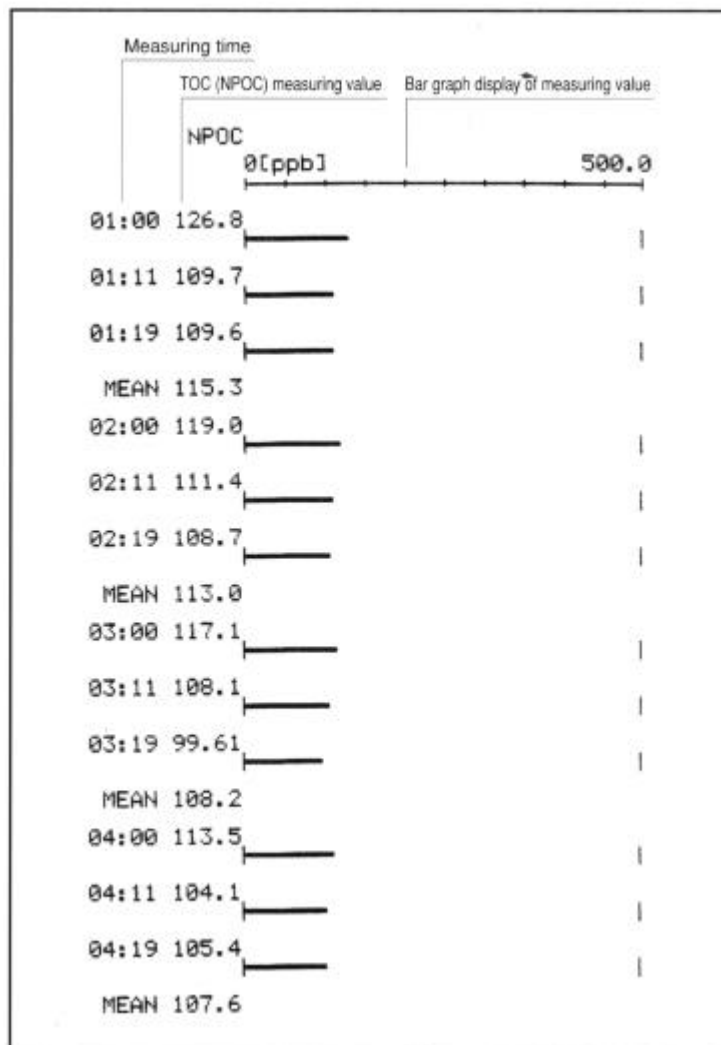


Fig. 1 Measuring results

Cleaning validation

In the case of pharmaceutical manufacturing equipment, this provides scientific validation that residue of previously manufactured products or cleaning agent and externally mixed-in matter is at the tolerated limit or below.

- Rinse water sampling
- Final rinse water is taken as a sample and TOC measured
- Swab sampling (Swab: A specific area of the equipment surface is swabbed with swab material. Recommended by the Ministry of Health and Welfare, Japan and FDA.)
- Swab/water extraction/TOC measuring method
Organic residual matter extracted using water after swab, and TOC measured.
- Swab/direct fired carbon measuring method
Measuring method developed by Shimadzu
Direct measuring of organic residual matter of each swab Material after swabbing by the solid sample TOC measuring system TOC-5000A.

Features of the Shimadzu TOC-5000A WM

The TOC-5000A WM (type I, II and III) - based on the highly rated TOC-5000A that is widely used around the world - has been developed to continuously monitor the TOC of water used in the manufacture of pharmaceutical products including WFI, PW and cleaning water.

1. A high detection rate is always achieved whatever the organic components contained in the cleaning water as this analyzer uses the "680 Combustion - NDIR" method that has a highly rated track record in many fields.
2. There is no need for special consideration of discharged fluid disposal as the TOC analyzer does not discharge large volumes of oxidizing agent and acid during measuring.
3. The analyzer has an automatic span calibration function.
4. Even Samples with greatly varying concentrations can be measured as measuring conditions are automatically changed and measuring re- performed when 4 `scale over" occurs.
5. Measuring can be externally controlled (option).



TOC-5000A WM