TOC Analyzers Play an Essential Role in Pharmaceutical Industry

Effective Means of Water-quality Monitoring and Cleaning Validation

Fig. 1 The TOC-VCSH laboratory TOC analyzer employing the combustion catalytic oxidation method

TOC (Total Organic Carbon) measurement is a technique that determines the total amount of organic substances in water or solid samples. TOC analyzers are important to the pharmaceutical industry, where they are primarily used for two purposes:

1) quality monitoring of pharmaceutical water, and
2) cleaning validation for pharmaceutical production equipment.

Shimadzu TOC analyzers are highly valued for their superior sensitivity, accuracy, and detection of organic substances

Quality Monitoring for Pharmaceutical Water

The US Pharmacopoeia (USP) and European Pharmacopoeia (EP) require TOC monitoring of water used at all stages of pharmaceutical manufacturing, including water for injection. The Japanese Pharmacopoeia (JP) also demands TOC monitoring of water for injection that is produced by ultrafiltration. These measures aim to prevent the deleterious effects of unintentional inclusion of organic contaminants in pharmaceutical products.

The TOC analyzers used for this purpose must meet a variety of strict conditions in terms of sensitivity, accuracy, and the ability to detect organic substances that do not readily decompose. The detection rate – one of the essential conditions – is evaluated through the system suitability test. Shimadzu, as a pioneer of the 680 °C combustion catalytic oxidation method (highly regarded for its sensitivity, accuracy, and detection rate), offers TOC analyzers that are fully responsive to the demands of pharmacopoeias around the world.

Fig. 1 shows the Shimadzu TOC-VCSH laboratory type TOC analyzer that employs the combustion catalytic oxidation method. Fig. 2 shows an example of the USP system suitability test on a TOC-VCSH analyzer. This test requires that the measured value for a solution of 1,4-benzoquinone, whose TOC concentration has been adjusted to 500 mg/L, lies within ±15% of the measured value for a sucrose solution with the same TOC concentration. The 1,4-benzoquinone solution is used as the system suitability solution for representing samples containing hard-to-decompose organic matter, while the sucrose solution is the standard for representing samples containing easily decomposed organic matter. Fig. 2 shows that the TOC-VCSH achieved a near 100% recovery rate for 1,4-benzoquinone, in full compliance with the requirements of the system suitability test.

In addition to combustion catalytic oxidation TOC analyzers, Shimadzu offers the TOC-VW wet-oxidation TOC analyzer, which also satisfies the demands of major Pharmacopoeias around the world.

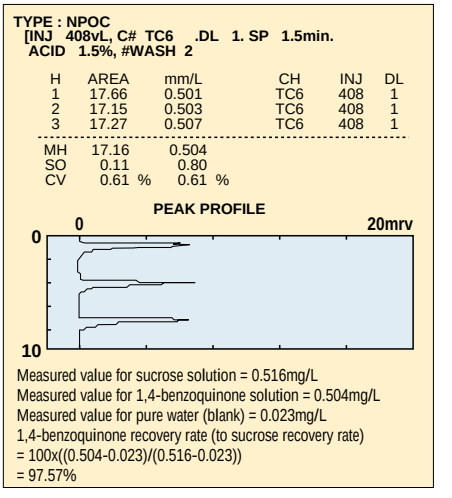

Fig. 2 USP system suitability test on a TOC-VCSH analyzer

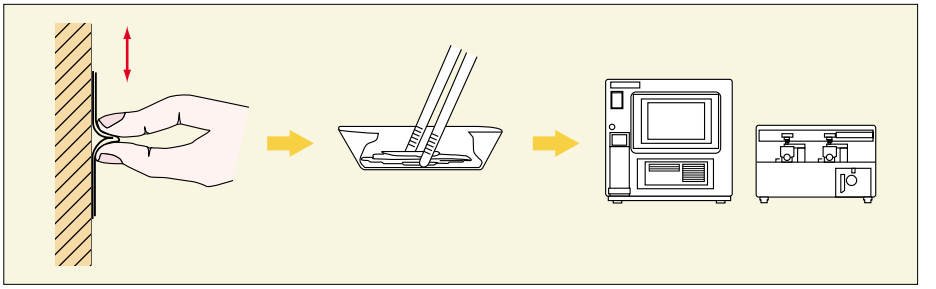

Fig. 3 Procedures of the 'swab/direct combustion TOC analysis' method. The surface of the pharmaceutical production equipment is wiped with a swab material and swabbed substances are analyzed.

Cleaning Validation for Pharmaceutical Production Equipment

A field where operation efficiency and a wide measurement range make a difference

To receive approval for pharmaceutical manufacture, pharmaceutical manufacturing plants must comply with the GMP (Good Manufacturing Practice) stipulated by governmental organizations such as the US Food and Drug Administration (FDA) and the Japanese Ministry of Health, Labour, and Welfare and with other relevant guidelines. The latest GMP prioritizes cleaning validation as a prerequisite for pharmaceutical manufacture.

Cleaning validation is a part of comprehensive processes for verifying the performance of equipment used in pharmaceutical manufacturing, which focuses on the validity of the process of cleaning the equipment. In practice, cleaning validation scientifically verifies that residues of previously processed products and detergent, as well as foreign matter from the environment in the production equipment, do not exceed certain predetermined limits.

There are two major sampling methods for cleaning validation: the rinse water sampling method, in which the residues in the final rinse solution from the cleaning process are measured, and the swabbing method, in which a certain area of the production equipment surface is wiped with a swab material and the residues on it are analyzed.

Traditionally, HPLC has been used to detect organic impurities contained in the sample. However, with the increased concern over residual detergents and contamination from unforeseen foreign matter, TOC analysis has become an important option due to its ability to detect any type of organic substance.

Special mention must be made of the swab/direct combustion TOC analysis method, originally developed by Shimadzu and now widely used. The conventional swabbing method involved dissolving the organic matter on the swab material and then identifying the target components using HPLC. This was a time-consuming and labor-intensive procedure.

Fig. 3 shows the procedure for Shimadzu's swab/direct combustion TOC analysis method.

In this method, the surface of the equipment is wiped with an inflammable swab material and the swab material is directly analyzed in the solid-sample TOC analyzer. This method is highly efficient compared to the conventional method, and allows for the detection of all organic contaminants, including those that are insoluble in water or solvents. These advantages make the swab/direct combustion method a preferable choice for cleaning validation.

The major benefits of TOC analysis in the pharmaceutical industry can be summarized as follows:

1) Measurement of the total amount of organic substances, regardless of their type (that is, it can detect not only expected components but also substances that cannot be predefined as analysis targets, such as detergents and accidentally generated contaminants)

2) Simple principle and construction for easy operation

3) Rapid measurements for efficiency and the analysis of a large number of samples

4) High sensitivity and easy modification for on-line use

With the growing appreciation of these advantages, TOC analysis is becoming an ever more important tool for Pharmacopoeias in major countries. Consequently, further diversified applications will be found for the TOC analyzer in the pharmaceutical industry.