



## 2. Pharmaceutical industry

Pharmaceutics is an ancient science that has supported people with remedies to help alleviate pain and heal illnesses. After medication, certain substances are expected to unfold their beneficial effects – while side effects from interfering substances and contaminations are undesirable. This is why it is important to use the purest possible substances and purified equipment and materials in the production of drugs.

To meet this standard, legislators have published Pharmacopoeias. These include methods and rules for the manufacture, storage, quality and testing of drugs. For drug manufacturers, complying with the rules and methods of the Pharmacopoeia is mandatory.

TOC determination is also described in the Pharmacopoeia (for instance the

European Pharmacopoeia = EP). The sum parameter serves as a measure of contamination by organic compounds. Not only the method itself is described, but also a test to verify the suitability of a TOC analyzer for the analysis.

In addition to ultrapure water required for the manufacture of drugs, water for injections – water that is directly injected into the bloodstream of the human or animal body – is also tested for its TOC content. The Pharmacopoeia actually specifies a maximum TOC limit value for such specific waters.

Many drugs are manufactured in batch mode operation. Prior to the production of the next batch, materials and working equipment must be extensively cleaned. In order to verify that the equipment is free from the 'previous'

drug batch, the TOC parameter is used for the evaluation of the cleaning process. The TOC not only mirrors the presence of drugs, but also reveals other contaminants such as those from cleaning agents.

With its TOC analyzers, Shimadzu offers systems that are suitable for many different TOC analysis issues in the pharmaceutical industry. In addition to the lowest detection sensitivity, the robust analyzers offer the highest precision and accuracy. Just like the analyzers themselves, the operation and evaluation software complies with all requirements of the FDA and the Pharmacopoeia.

Further information can be found in the individual application notes (for instance 'TOC determination in ultrapure water, cleaning validation or in accor-

dance with EP 2.2.44'). In addition to pharmaceutical applications, there are also application notes and information on 'Environmental analysis', 'Chemical industry', 'TOC special applications', 'TOC in daily practice' and 'TOC process analysis.'

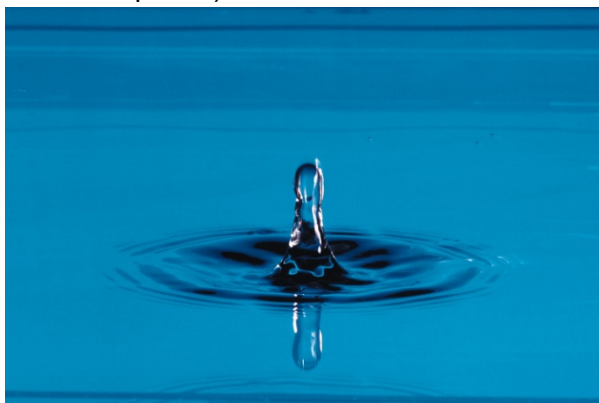
## Application News

**No.** SCA-130-201

Sum parameter – Total Organic Carbon

### TOC determination in ultrapure water – Comparison of the various oxidation techniques

Ultrapure water is one of the most widely used excipients in the production of pharmaceuticals. It is also used for cleaning purposes. Different application areas require different grades of ultrapure water quality. These grades are defined in the European Pharmacopoeia, which distinguishes between 'Purified Water', 'Highly Purified Water' and 'Water for Injection' ('The United States Pharmacopoeia, however, does not use the same classification as the European Pharmacopoeia').



**Water for injection** is used for the preparation of injection solutions and is produced by distillation. The TOC content may not exceed 0.5 mg/L (water for injection in bulk).

**Water Highly Purified** is a sterile ultrapure water for the manufacture of pharmaceuticals that do not require a 'Water for Injection' standard. It is also often used for the final rinse during cleaning and is usually produced by reversed osmosis. The TOC content may not exceed 0.5 mg/L.

**Water Purified** is used in the manufacture of pharmaceuticals that do not require any other standard. The organic content is determined either via the TOC value (0.5 mg/L) or via the permanganate test (purified water in bulk).

#### ■ TOC determination in ultrapure water

Two oxidation techniques are now commonly used in TOC analysis:

1. Catalytic combustion, where carbon compounds are converted into CO<sub>2</sub> using a catalyst under high temperatures with subsequent detection of the resulting CO<sub>2</sub> using an NDIR detector.
2. Wet chemical oxidation, which uses a combination of UV irradiation and persulfate for oxidation. Both methods can be applied for the determination of ultrapure water.



#### ■ TOC-L<sub>CPH</sub>: Oxidation via catalytic combustion

The TOC-L<sub>CPH</sub> uses the proven catalytic oxidation at 680 °C.

The integrated ISP sample preparation unit (an 8-position switching valve with syringe and sparging gas connection) considerably reduces the users' workload, as the instrument carries out dilution, acidification and sparging fully automatically.

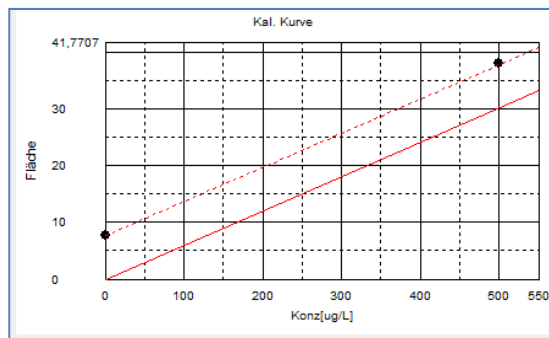


Fig. NPOC- Calibration (Blank and 500µg/L)

When using the high sensitivity catalyst, the detection limit is approximately 4µg/L. In addition, the combustion technique can be used in combination with the TNM-L module, whereby a single injection is sufficient for simultaneous determination of the total bound nitrogen. Simultaneous TOC/TN<sub>b</sub> determination is highly suitable for cleaning validation, as this enables differential determination between cleaning agent and product.

#### ■ TOC-V<sub>WP/WS</sub>: Wet chemical oxidation

The key technique of the TOC-V<sub>WP/WS</sub> analyzer is the powerful oxidation via the combination of sodium persulfate and UV oxidation at 80 °C. The TOC-V<sub>WP/WS</sub> features an automatic reagent preparation function that eliminates possible contamination of the persulfate solution. This ensures that the TOC value truly originates from the sample – and not from the reagent solution used. The large injection volume (up to 20.4 mL) in combination with the highly sensitive NDIR detector, leads to an extremely low

detection limit (0.5µg/L) and excellent reproducibility in the lower ppb range. The TOC-V<sub>WP/WS</sub> is therefore highly suitable for TOC determination in the ultra-trace range.

#### TOC-V WP Sample measurement

Method: NPOC (3% Acid, 3 min sparge)

Persulfatsol.: 1,5mL

Injection vol.: 20,4 mL

Result: 2,44 ± 0,42 µg/L TOC (NPOC)

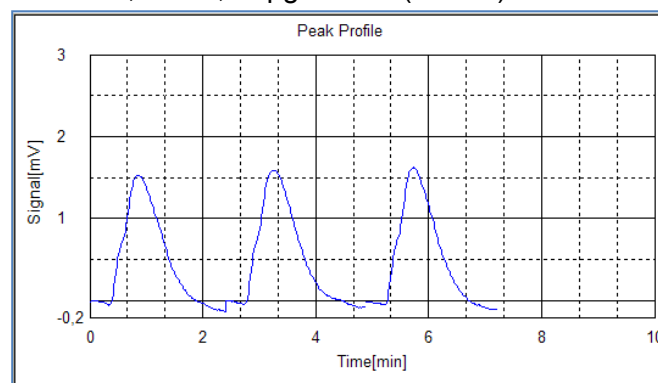


Abb. Peak graphik of TOC-V<sub>WP</sub> measurement

#### ■ Conclusions

Both types of instruments with their different oxidation methods can be used for TOC determination according to the European Pharmacopoeia. The advantage of the combustion method is its high oxidation potential, particularly for samples containing particulate matter. Moreover, simultaneous TOC/TN<sub>b</sub> measurements can be carried out, leading to a higher information content of the analysis. The advantage of wet-chemical oxidation is its high injection volume, which leads to higher sensitivity and therefore enables high precision measurements in the lower ppb range.

#### ■ Recommended analyzer / Configuration

TOC-L<sub>CPH</sub> with high sensitivity catalyst  
ASI-L (40ml), External Sparge-Kit.

TOC-V<sub>WP</sub> with ASI-V (40ml)

## Application News

**No.** SCA-130-202

Sum parameter – Total Organic Carbon

### TOC determination in cleaning validation – final rinse

The highest purity and most careful handling of substances and active ingredients is an important requirement in the manufacture of pharmaceuticals. An effective removal of production residues in pharmaceutical plants is an essential precondition. A well-cleaned pharmaceutical production system prevents contamination and, consequently, the adulteration of the produced drug. This is particularly important in the production of active ingredients in batch processes, as the system is used for different products and contamination of the next product must be prevented.



#### ■ Cleaning methods: Clean in Place

CIP cleaning (clean in place) is performed automatically and without disassembly of the production system. The production system must, therefore, have a CIP design. This includes the use of rinsing heads, no dead volumes, collection tank and recycling possibilities for the detergents.

Because time and temperature, as well as the use of cleaning agents and solvents are optimized, CIP cleaning is highly effective. Moreover, automatic cleaning allows a standardized and, therefore, an easily validated procedure.

#### ■ Sampling and analysis

In case of CIP cleaning, the rinsing liquid of the final rinse solution is sampled and analyzed. This is a very simple, easily automatable and fast method. When water is used as a solvent, TOC analysis is suitable for subsequent analysis.

#### ■ TOC-Analysis

TOC analysis is applied for the determination of the total organic carbon content as a sum parameter. The carbon content of the sample is oxidized to CO<sub>2</sub> and detected by an NDIR detector. Analysis of final rinse samples is, therefore, fast and simple (analysis time: approx. 4 min). The determined TOC value reflects any contamination by starting materials, products, byproducts or cleaning agents, as long as they contain carbon.

#### ■ Shimadzu TOC Series

With its TOC-L series, Shimadzu offers a highly suitable tool for cleaning validation. The modular design simplifies the analysis – no matter whether one wants to measure final rinse samples or swab samples.



The TOC-L<sub>CPH</sub> employs the proven catalytic oxidation at 680 °C. The integrated sample preparation (ISP) module greatly reduces the users' workload, as the instrument automatically carries out the dilution, acidification and degassing steps.

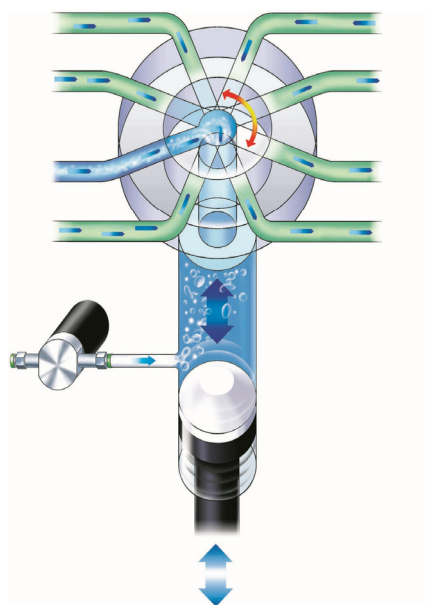


Fig. ISP-Module of TOC-L series

The possibility for simultaneous determination of the TNb (total nitrogen) using the TNM-L module enables, if necessary, a differentiation between cleaning agent and product. This may be of great importance, particularly for biopharmaceutical products.

For users who prefer wet-chemical oxidation for the determination of TOC, the TOC-V<sub>WP</sub> analyzer with its various options, is available. The key technique of the TOC-V<sub>WP</sub> analyzer is the powerful oxidation via the combination of sodium persulfate and UV oxidation at 80°C.

#### Practical Example:

##### ■ Instrument / Measurement parameter

Unit: TOC-L<sub>CPH</sub>  
Catalyst: High sensitivity catalyst  
Meas.-typ: NPOC  
Cal-Curve: 2-Punkt Calibration Curve  
0-3 mgC/L (KHP)  
Injection vol.: 500 µL

##### ■ Results

Compound	TOC-Result	Recovery
Blank	0,030mg/L	
Tranexamic acid	2,14mg/L	105 %
Anhydrous caffeine	2,19mg/L	108 %
Isopropylantipyrine	2,20mg/L	109 %
Nifedipine	2,17mg/L	107 %
Gentashin ointment	0,117mg/L	4,35 %
Rinderon ointment	0,333mg/L	15,2 %

From the results, it can be concluded that the final rinse method only shows good recoveries for water-soluble compounds.

(Further information is available in the application note Japan TOC O41)

## Application News

**No.** SCA-130-203

Sum parameter – Total Organic Carbon

### TOC –Determination in cleaning validation - swab method

Cleaning validation substantiates the effectiveness of a cleaning process and ensures that no residues remain on the surfaces of the production equipment. For the detection of contaminations, validated analytical methods must be used that are sensitive enough to determine the defined acceptable residue level. In general, residue limits of 10 ppm or 1/1000 of the usual therapeutic dose of an active substance are used as acceptance criteria.



#### ■ Cleaning methods: Clean out of Place

For COP cleaning, the entire production system must be disassembled and the components must be cleaned individually. This procedure is very time consuming and labor intensive. Due to the individual cleaning, this procedure cannot be standardized. Advantages are, however, the low investment costs of the system and the possibility of visual inspection.

#### ■ Sampling and analysis

In COP cleaning, the wiping method (swab) is used for sampling of visible residues. These include coatings, crusts, material deposited in corners and edges, and especially poorly soluble substances. The swab can be extracted in a solvent and the extracted solution is subsequently analyzed. If water is used for extraction, TOC analysis is suitable for subsequent analysis. Alternatively, the swab can also be measured directly (using a carbon-free swab) using a TOC solid-sample module.

#### ■ Measuring system for the swab test

The modular design of Shimadzu's TOC-L series now enables the additional determination of the swabs using the same instrument. For this purpose, a solid-sample module (SSM-5000A) was connected to the main instrument, either a TOC-L series combustion system or the wet-chemical model of the TOC-V series.



For TC determination, the swab is placed in a ceramic boat and transferred into the oven, which is heated to 900 °C.

There, all carbon compounds are oxidized to CO<sub>2</sub>. To ensure complete oxidation, there is an additional catalyst in the combustion tube. The resulting CO<sub>2</sub> is then transported to the detector in the main instrument. The NDIR detector of the TOC-L series contains a tandem cell that consists of a long cell (200 mm) and a short cell (1 mm). By default, the long cell is used for water analysis and the short cell for solid-sample analysis. To attain a higher sensitivity for the analysis of solids, the solid-sample module can also be connected to the long, and thus the more sensitive, measuring cell. This can be realized using an upstream switching valve. This way, the system can now readily be used for cleaning validation without any loss in flexibility of switching between water and solid-sample analysis.

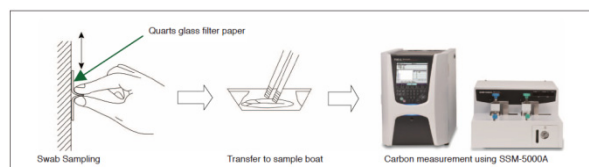
#### ■ Preparation

As the TOC analysis involves a sum parameter, it is important to ensure that the measured carbon really originates from the sampled surface. Some preparation is, therefore, important.

First, the swabs used must be carbon-free. This is why fiber optics swabs are used, which are annealed at 600 °C and are stored under dry conditions using an inert gas. The same pretreatment is required for the ceramic boat. All tools used, such as tweezers and glass containers must be free from carbon.

#### ■ Swab test

For the wiping test, two pretreated swabs are sampled, the lower swab is moistened with water and the defined surface is wiped according to the prescribed procedure. The used swab is now folded, placed in the clean ceramic boat and transferred to the TOC measuring system.



Depending on the expected concentration or defined limit value, the system configuration and calibration curve is selected. The calculated amount of carbon is now correlates directly to the area of the wiped surface.

#### Practical example:

##### ■ Instrument/ Measurement parameter

Unit: TOC-LCPH + SSM-5000A  
(shortcut of IC-flow line)

Detector cell: Short Cell

Carrier gas: 400 mL/min oxygen (SSM)

Meas.-typ: TC

Cal-Curve: 1-Point Calibration curve with 30µL of 1%C Glucose solution

Swab: Advantec QR-100 quartz glass Filter paper (45 mm)  
Prepared at 600°C, 15min

#### ■ Result

Compound	TOC-Result	Recovery
Blank	0,00	
Tranexamic acid	202 µgC	101 %
Anhydrous caffeine	201 µgC	100 %
Isopropylantipyrine	210 µgC	105 %
Nifedipine	212 µgC	106 %
Gentashin ointment	200 µgC	100 %
Rinderon ointment	209 µgC	104 %

(Further information is available in the application note Japan TOC O41)

## Application News

**No. SCA-130-204**

Sum parameter – Total Organic Carbon

TOC-Determination according to  
EP 2.2.44

Since the USP (United States Pharmacopoeia) regulations for the determination of Aqua Purificata and Aqua ad injectabilia has been implemented into the European Pharmacopoeia (EP), TOC analysis has become increasingly established in quality control. Users who test the TOC content in pharmaceutical water must regularly test their TOC system using a system suitability test according to the method described in the EP 2.2.44 guidelines.



### ■ European Pharmacopoeia

The EP 2.2.44 guidelines do not prescribe any particular oxidation technique for TOC determination. The TOC systems, however, must be able to differentiate between inorganic and organic carbon. This can be carried out either via removal of the inorganic carbon (NPOC method), or via a separate determination (difference method). The limit of detection for TOC should be at least 0.05 mg /L. The applicability of the method must be determined via a system suitability test.

### ■ System suitability test

For the system suitability test, a standard sucrose solution with a carbon content of 0.5 mg/L is prepared. A control solution of 1,4-benzoquinone with the same carbon content was subsequently prepared. The blank water (ultra-pure water) used for this purpose may not exceed a TOC content of 0.1 mg/L. For the system suitability test, all solutions including the blank water are subsequently measured and the resulting signals are recorded.

Blank water:  $r_w$

Standard solution (sucrose):  $r_s$

Control solution (benzoquinone):  $r_{ss}$

The peak area of the blank water is subtracted from the peak areas of both standard solutions. The recovery of the benzoquinone standard is then calculated with respect to the sucrose standard.

$$\text{Recovery in \%: } \frac{r_{ss} - r_w}{r_s - r_w} \times 100$$

Results between 85 - 115% are acceptable. The ultrapure water sample corresponds to the guidelines when its response signal ( $r_u$ ) does not exceed  $r_s - r_w$ .



■ TOC-Control L software

The TOC-Control L software simplifies the implementation of the system suitability tests using integrated templates for the creation of calibration curves and the measurement of the control sample.

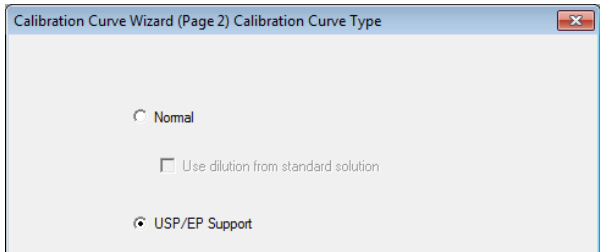


Fig. Calibration curve wizard

The following figure shows an example of an EP calibration curve (2 points, blank and 500 µg/L).

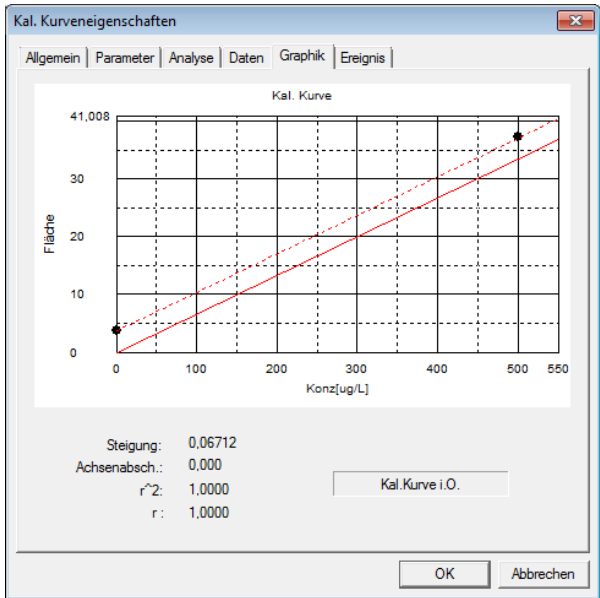


Fig. Calibration Curve

The determination of benzoquinone is set in the sample / method properties wizard.

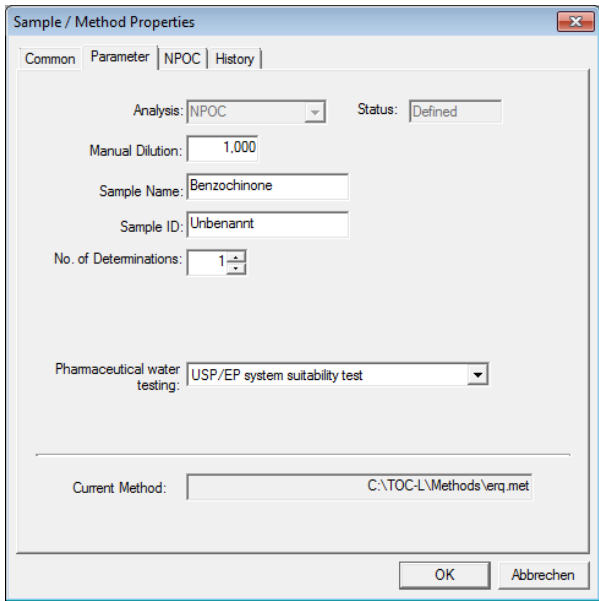


Fig. Benzoquinone-Determination

After measuring the benzoquinone sample, the software automatically calculates the recovery according to EP 2.2.44, whereby the peak area values for the blank sample and the sucrose sample are obtained from the calibration curve. The result is listed under the column 'Notes' in the sample table (Figure below).

Washing / Untitled NPOC:0,000mg/L						
	Typ	Analyse	Probenname	Original	Ergebnis	Notizen
15	Unbekannt	NPOC	Washing		NPOC:0,000mg/L	
16	Unbekannt	NPOC	Washing		NPOC:0,000mg/L	
17	Standard	NPOC	Untitled	npoc_sucrose_500ppb.2012_02_03_13_37_01.cal		
18	Unbekannt	NPOC	Benzoquinon	npoc_sucrose_500ppb.cal	NPOC:592,7ug/L	107.5% : USP/EP system suitability test: Pass
19	Unbekannt	NPOC	Washing		NPOC:0,000mg/L	

Fig. Result of system suitability test in sample table