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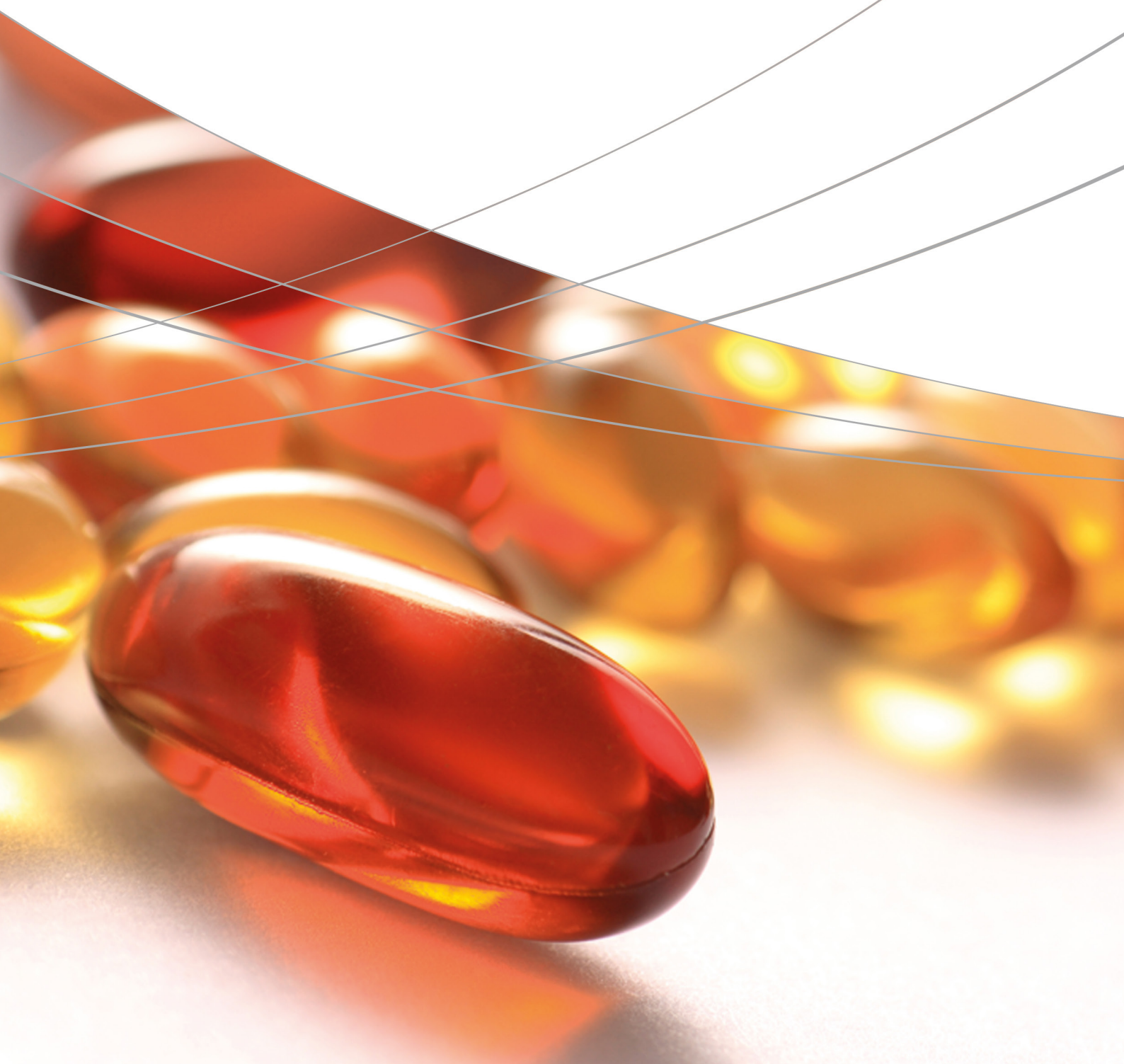
2. Pharmaceutical industry



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 accordance 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.'

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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.

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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_2 using a catalyst under high temperatures with subsequent detection of the resulting CO_2 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_{CPH}: Oxidation via catalytic combustion

The TOC-L $_{CPH}$ 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.

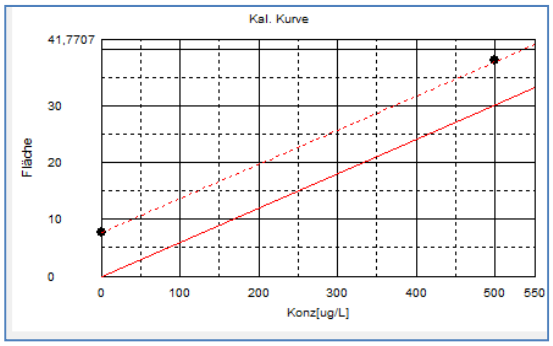

Fig. NPOC- Calibration (Blank and 500µg/L)

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_b determination is highly suitable for cleaning validation, as this enables differential determination between cleaning agent and product.

■ TOC-$V_{WP/WS}$: Wet chemical oxidation

The key technique of the TOC-$V_{WP/WS}$ analyzer is the powerful oxidation via the combination of sodium persulfate and UV oxidation at 80 °C. The TOC-$V_{WP/WS}$ 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-$V_{WP/WS}$ 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)

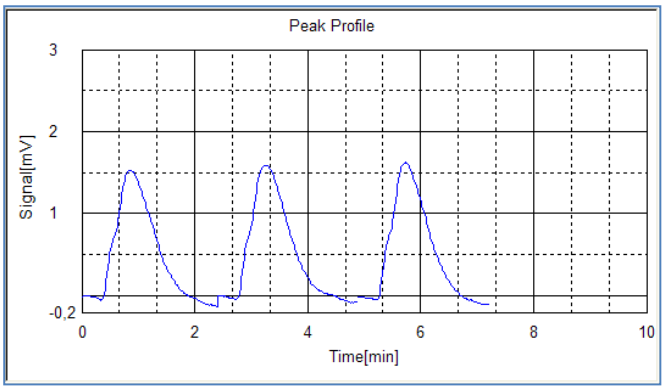

Abb. Peak graphik of TOC-V_{WP} measurement

■ 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/TNb 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 $_{CPH}$ with high sensitivity catalyst
ASI-L (40ml), External Sparge-Kit.

TOC-V_{WP} with ASI-V (40ml)

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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_2 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_{CPH} 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.

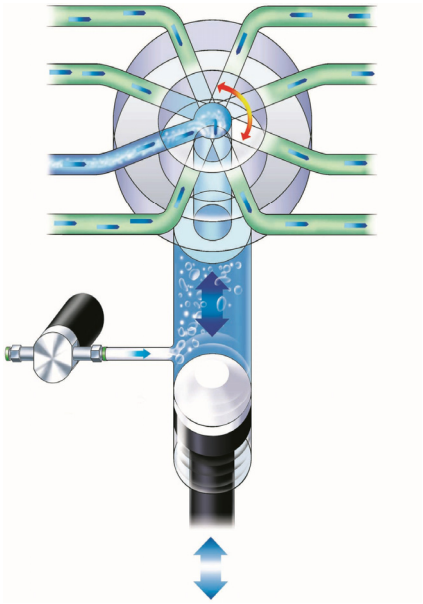

Fig. ISP-Module of TOC-L series

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_{WP} analyzer with its various options, is available. The key technique of the TOC-V_{WP} 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_{CPH}
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)

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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.

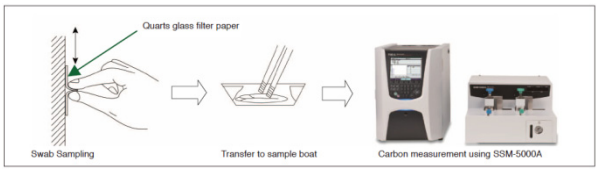
There, all carbon compounds are oxidized to CO_2. To ensure complete oxidation, there is an additional catalyst in the combustion tube. The resulting CO_2 is then transported to the detector in the main instrument. The NDIR detector of the TOC-L series contains a tandem cell that consists of a long cell (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 wiht 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)

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Application News

Sum parameter – Total Organic Carbon

TOC-Determination according to EP 2.2.44

No. SCA-130-204

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 Pharmacopeia

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.

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.

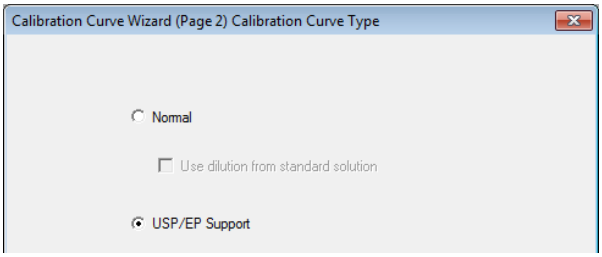

Fig. Calibration curve wizard

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

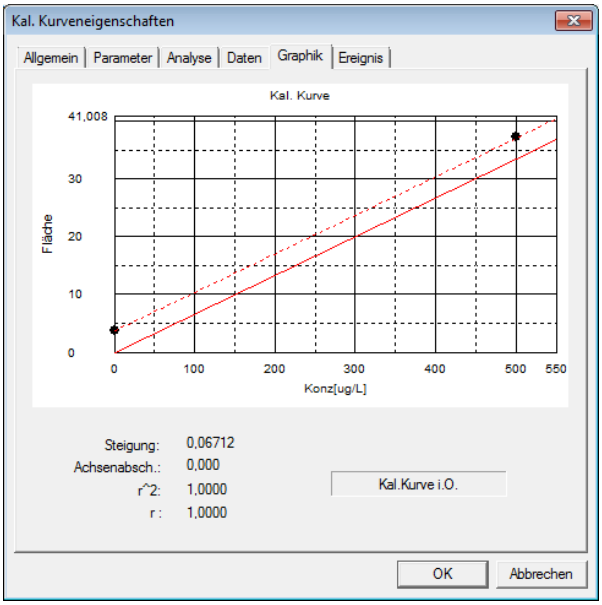

Fig. Calibration Curve

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

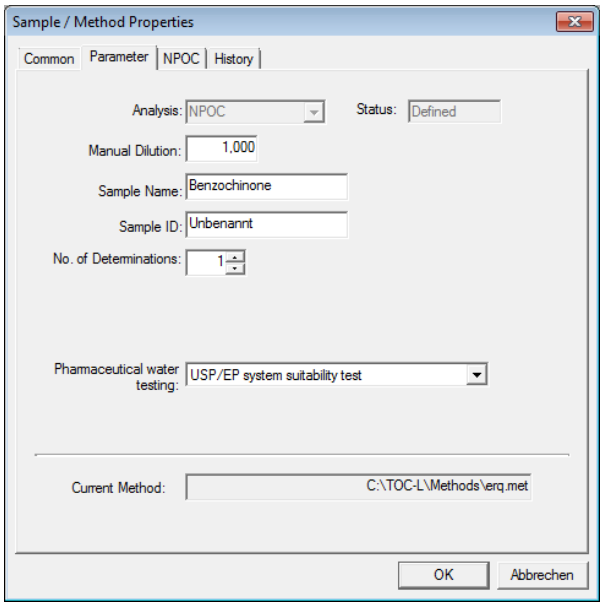

Fig. Benzochinone-Determination

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	Benzochinon	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

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Application News

No. SCA-130-205

Sum parameter – Total Organic Carbon

TOC determination in ultra pure water with wet chemical oxidation

The quality of ultra pure water is of crucial significance in a large number of application areas such as monitoring of water quality in water treatment plants, and in industries such as chip manufacture or pharmaceutical production. Determination of Total Organic Carbon (TOC) is playing an increasingly important role in quality control.

The TOC value indicates whether ultra pure water still contains any organic contaminants. TOC determination is fast and accurate and is defined in the European Pharmacopoeia (EP) as a control parameter for WFI-water (water for injection).

■ TOC determination in ultra pure water

Two oxidation techniques are now commonly used in TOC analysis: catalytic combustion and wet-chemical oxidation. In catalytic combustion, carbon compounds are converted to CO_2 using high temperatures and a catalyst, with subsequent detection of the resulting CO_2 using an NDIR detector. Wet-chemical oxidation uses a combination of UV irradiation and persulfate oxidation. Both methods are suitable for TOC determination in ultrapure water.

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

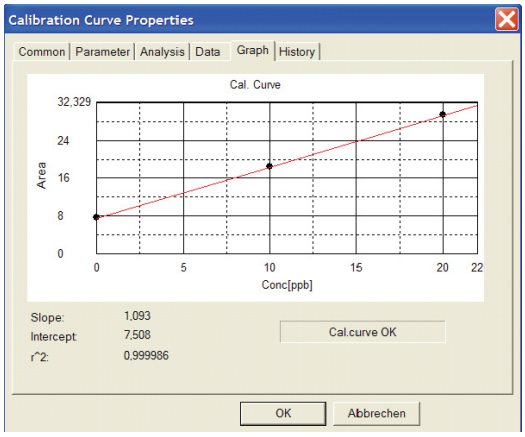
■ TOC-V WP with wet chemical oxidation

The fundamental technique of the TOC-V WP/WS analyser is powerful oxidation via the combination of sodium persulphate and UV oxidation at 80 °C. These features guarantee that all dissolved carbon species will be detected. An automatic reagent preparation function eliminates possible contamination of the reagent solution and minimizes the blank value of the instrument. These features, together with the high injection volume (up to 20.4 mL) and the highly sensitive NDIR detector, result in extremely low detection limits and excellent reproducibilities in the low ppb-range.

This is why the TOC-$V_{WP/WS}$ is especially suitable for TOC determination in the ultra-trace range.

■ Calibration:

Method:	NPOC
Acidification:	3%
Sparge time:	3 minutes
Oxidizer:	1,5%
Injection volume:	20,4 ml



Data according to DIN 32645

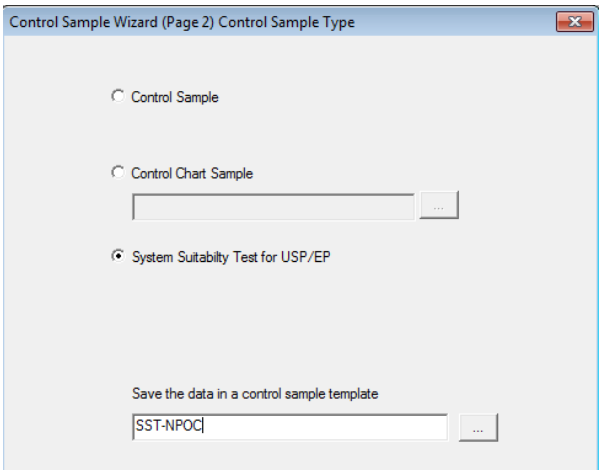
Limit of detection: 0,3µg/l TOC (NPOC)
Limit of quantification: 2,2µg/l TOC (NPOC)

■ TOC-Control V Software

In the pharmaceutical industry TOC systems are used in a regulated laboratory environment and therefore these systems are subject to various regulations that particularly apply to instrument software.
The TOC-Control V software running the TOC-V series provides full support for complying with the regulations, while still remaining extremely user-friendly.
Already during software installation, the operating criteria of the software are decided. The selected parameters cannot be deactivated later.

The software use is enabled via user access rights. It offers user accounts on four different levels, each protected through own passwords. The administrator can individually change access rights for each user. The software allows changing of login during ongoing operation. This is especially important for laboratories working under multiple shift operation
All software operations are stored automatically in the audit trail. This happens entirely in the background. Only when existing parameters are changed is a user comment required. Data storage takes place in an MSDE database.

The TOC-Control V 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.
The system suitability test is defined in a special control sample template. Subsequent to the measurement of the control sample (benzoquinone), the recovery is calculated automatically, compared with the predetermined limits (85 – 115 %) and documented.



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Application News

Sum parameter – Total Organic Carbon

TOC – Determination according to USP 643 (USP 36-NF 31)

No. SCA-130-206

In 1996, the US Pharmacopeia has introduced the TOC parameter for the determination of impurities in purified water and water for injections. For other waters used in the pharmaceutical industry, the wet-chemical potassium permanganate test continued to be used. Meanwhile however, TOC determination has proven to be so effective that it now replaces the wet-chemical test.

In the current version of the UPS <643> (USP 36-NF 31) a distinction is made between 'bulk water' and 'sterile water'. The chapter 'Bulk Water' includes purified waters that are to be used right away as purified water, water for injection, water for hemodialysis and as condensate of pure steam. The following known conditions apply to TOC determinations:

Limit of detection:	< 0.05 mg/L C
Blank water, r_w:	max. 0.1 mg/L C
Standard (sucrose), r_s:	0.5 mg/L C
SST (benzoquinone), r_{ss}:	0.5 mg/L C
Permitted response:	85 – 115%
Limit response (waters) r_u:	< (r_s-r_w)

The chapter 'Sterile Water' is new. It includes sterile purified water, sterile water for injections, sterile water for irrigation and sterile water for inhalation. Sterile water can be stored in various packaging configurations. In comparison to bulk water, however, other conditions for TOC determination apply:

Limit of detection:	< 0.05 mg/L C
Blank water, r_w:	max. 0.1 mg/L C
Standard (sucrose), r_s:	8 mg/L C
SST (benzoquinone), r_{ss}:	8 mg/L C
Permitted response:	85 – 115%
Limit response (waters) r_u:	< (r_s-r_w)

■ Impact of the new determination

The present requirements of the UPS <643> (bulk water) are consistent with the requirements of the European Pharmacopeia (limit of detection, concentration of the standard solution (sucrose) and system suitability solution (benzoquinone and response). Validation of the TOC system for both determinations is therefore sufficient.

In accordance with the new USP <643>, the implementation of a system suitability test using higher concentrations is required.

For users of Shimadzu's TOC systems, this just means the creation of an additional calibration curve (sucrose, 8 mg/L, see figure 1) and control sample (benzoquinone, 8 mg/L, see figure 2) as well as extension of the current validation process with these data.

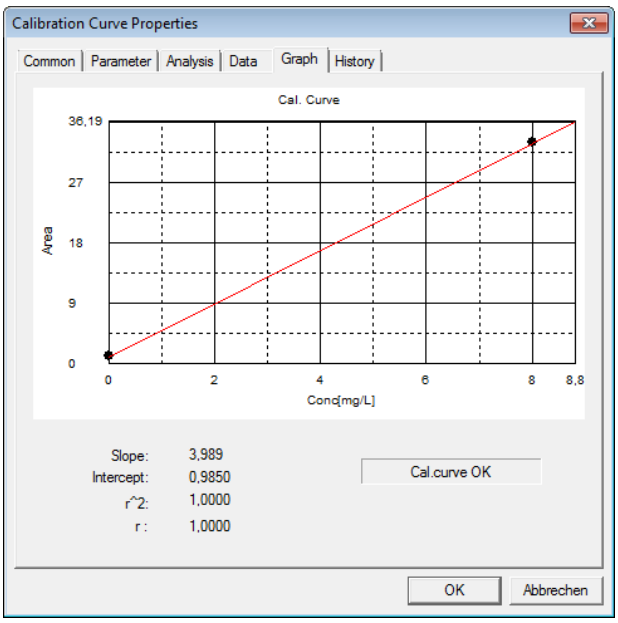


Figure.1 : Calibration Curve, Sucrose 8mg/L

Additional modifications of the TOC system are not necessary.

■ Shimadzu TOC-System

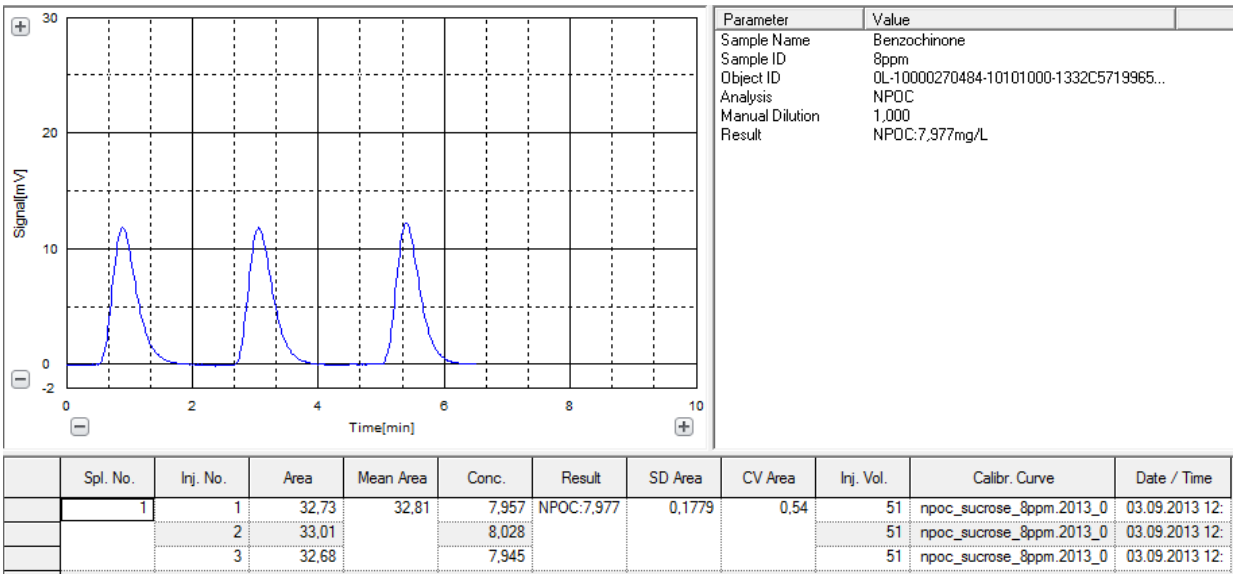
Shimadzu offers two systems that are ideally suitable for TOC determination in ultrapure water. The TOC-VWP/WS uses wet-chemical oxidation, whereas the TOC-LCPH uses catalytic combustion at 680 °C. With their wide measuring range of 0.5 µg/L up to 30,000 mg/L, the instruments support any application – from ultrapure water (for instance in cleaning validation) to highly polluted waters (such as wastewaters). Shimadzu TOC-Systems.

Both types of instrument with their different oxidation methods can be used for TOC determination in accordance with the new United States Pharmacopeia (USP <643>) and the European Pharmacopeia (EP 2.2.44). The advantage of the combustion method is its high oxidation potential, especially for samples containing particulate matter. Moreover, simultaneous TOC/TN_b measurements can be carried out, leading to a higher information content of the analysis. The advantage of wet-chemical oxidation is its very high injection volume, which leads to higher sensitivity and therefore enables high precision measurements in the lower ppb range.

■ Recommended Analyser / Configuration

TOC-L $_{CPH}$ with high sensitive catalyst
ASI-L (40ml), external sparge kit

TOC-V_{WP}
ASI-V (40ml), external sparge kit



	Spl. No.	Inj. No.	Area	Mean Area	Conc.	Result	SD Area	CV Area	Inj. Vol.	Calibr. Curve	Date / Time
	1	1	32,73	32,81	7,957	NPOC:7,977	0,1779	0,54	51	npoc_sucrose_8ppm.2013_0	03.09.2013 12:
		2	33,01		8,028				51	npoc_sucrose_8ppm.2013_0	03.09.2013 12:
		3	32,68		7,945				51	npoc_sucrose_8ppm.2013_0	03.09.2013 12:

Figure. 2: SST, Benzochinone 8mg/L

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Application News

No. SCA-130-207

Sum parameter – Total Organic Carbon

TOC – Determination according to USP 661.1 Testing of Plastic Packaging Systems and their Materials of Construction

Plastic packaging systems for pharmaceutical products must be suitable for their intended use. The US Pharmacopeia revised the related chapter. It is published in USP 39-NF34, which will be valid from May 2016.

Besides to the change of the title “Plastic Packaging Systems and their materials of Construction”, two new chapters are established.

This application note is related to the first chapter 661.1.

■ 661.1 Plastic Materials of Construction

The purpose of this chapter is to provide test methods and standards for plastic materials (e.g polyethylene, polyolefins, polypropylene) of construction used in packaging systems for therapeutic products. The characterization is done by identity, biocompatibility (biological reactivity), General physicochemical properties and Additives and extractable metals.

The TOC parameter as an indicator for extractable material is part of the physiochemical properties that must be determined.

For the TOC determination a purified water extraction is prepared. For example 25g plastic material is placed in a glass flask, 500ml purified water added and boil under reflux condition for 5h. After cooling, the solution is pass through a sintered-glass filter. The parameter of the sample weight, purified water volume and heating temperature and time depends of the used plastic sample.
The TOC of the ultra-pure water is subtracted for the measured value of the extraction solution. The resultant TOC value must not exceed 5mg/l.

■ TOC determination in pharmaceutical application

The TOC determination is performed according to the USP<643>. This regulation describes the TOC determination for pure water, purified water and water for injection. It does 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.
However, material extracts may have TOC values that are higher than those of purified water because of extracted organic substances.
Thus the TOC analyses performed should have a limit of detection of 0,2mg/L and should have a demonstrated linear dynamic range from 0,2 – 20mg/L.

■ Shimadzu TOC-System

Shimadzu offers two systems that are ideally suitable for TOC determination in ultrapure water. The TOC-VWP/WS uses wet-chemical oxidation, whereas the TOC-LCPH uses catalytic combustion at 680 °C.
Both types of instrument with their different oxidation methods can be used for TOC determination in accordance with the United States Pharmacopeia (USP <643>) and the European Pharmacopeia (EP 2.2.44).

■ Linear dynamic range from 0,2 – 20mg/L

To prove the required dynamic range, a calibration with TOC-L CPH (with high sensitivity catalyst) was carried out in a range of 1,0 mg/L – 20mg/L.

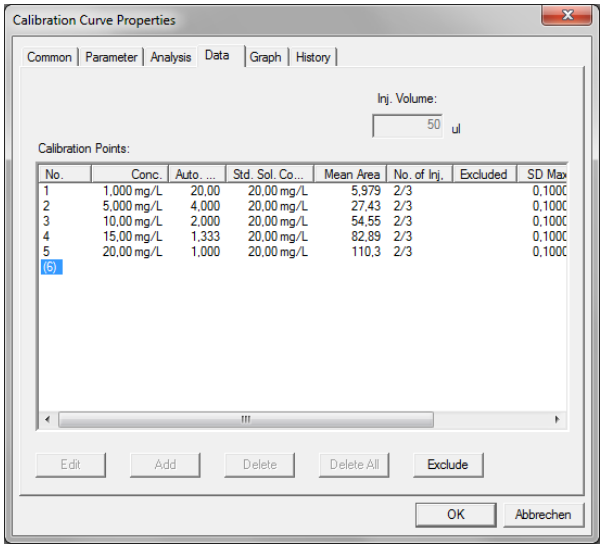

Figure.1 : Calibration Curve 20mg/L, results

For the dilutions, the automatic dilution function of the TOC-L system was applied.

The injection volume is determined, based on the highest calibration standard. For 20mg/L the default injection volume is 50µl.

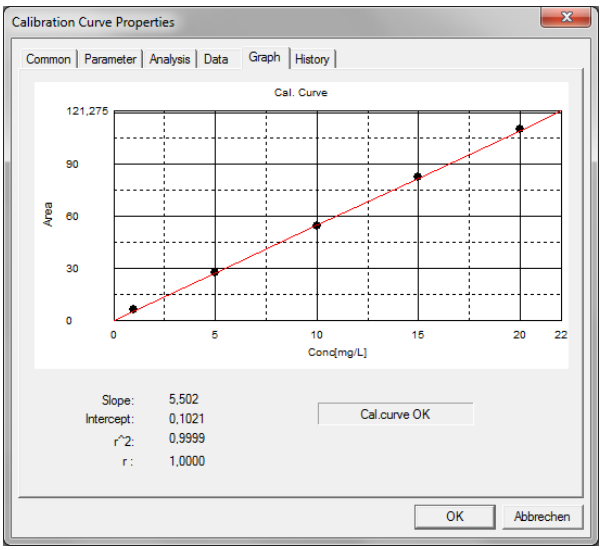

Figure.2 : Calibration Curve 20mg/L, graphic

The calculation of the limit of detection limit according to DIN 32645:

Characteristics

Slope a:	5,503
Intercept b:	0,091
Correlation coefficient r:	0,9999
Result uncertainty:	33,3%
Probability of error (a):	5,00%
Number of injections:	2

Limit of detection: 0,2mg/L

These results show that the TOC-CPH with high sensitivity catalyst covers the required linear dynamic range from 0,2 – 20mg/L. This means both applications, purified water and this extraction solution can be measured with a single TOC-L CPH instrument.

■ Recommended Analyzer / Configuration

TOC-L $_{CPH}$ with high sensitive catalyst
ASI-L (40ml), external sparge kit

■ **Source**: www.usp.org

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Application News

No. SCA-130-208

Sum parameter – Total Organic Carbon

TOC – Determination according to USP 661.2 Testing of Plastic Packaging Systems and their Materials of Construction

In the pharmaceutical industry plastic packaging is used in various forms – for example for intravenous bags, bottles, cartridges or pre-filled syringes. The packaging must be tested for suitability for these uses. It is published in USP 39-NF34, which will be valid from May 2016.

Besides to the change of the title “Plastic Packaging Systems and their materials of Construction”, two new chapters are established.

This application note is related to the second chapter 661.2.

■ 661.2 Plastic packaging system

This chapter deals with the required testing of the final packaging system since packaging often consists of than one plastic material. Characterization takes place by identifying and determining the biocompatibility, general physicochemical properties and Additives.

The TOC Parameter as an indicator for extractable organic material is part of the physio-chemical characteristics that must be determined.

For testing the packaging system, it is filled with ultra-pure water, sealed and heated in an autoclave. The temperature and dwell time depend in the plastic used. In order to determine the blank value, ultra-pure water is poured into a glass flask and heated to the same temperature. The TOC of both solutions is determined. The difference between the two measured TOC values should not exceed 8mg/L.

■ TOC determination in pharmaceutical application

The TOC determination is performed according to the USP<643>. This regulation describes the TOC determination for pure water, purified water and water for injection. It does not prescribe any particular oxidation technique for TOC determination.

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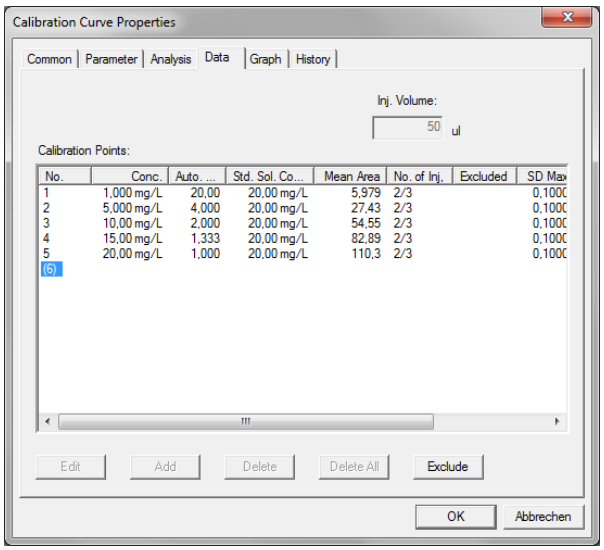

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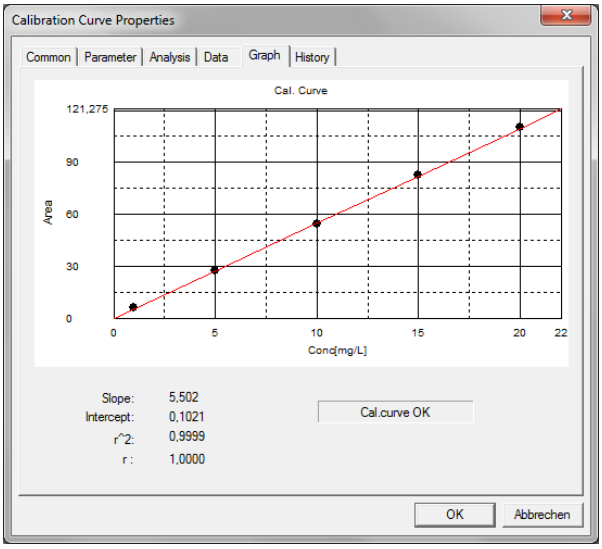

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■ Recommended Analyzer / Configuration

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ASI-L (40ml), external sparge kit

■ **Source**: www.usp.org

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