Challenge

After revision of USP TOC monographs, a wider concentration range has to be covered by the TOC method applied and an SST test at 8 ppm must be passed

Solution

Adapted calibration strategy to cover a TOC working range up to 20 ppm and successful application of the state-of-the art SST test sequence in the multiWin pro device software

TOC System Suitability Test According to USP <643>

Introduction

The USP <643>[1] represents the general method for TOC testing in pharmaceutical applications and provides guidance on how to qualify the analytical technique for use as well as guidance on how to interpret instrument results for use as a limit test.

The TOC monograph <643> of the US pharmacopoeia describes two different TOC testing approaches addressing different pure water qualities. These are "Bulk Water" (e.g., Purified Water [PF], Water for Injection [WFI], Water for Hemodialysis, and condensate of Pure Steam) and "Sterile Water" (e.g., Sterile Water for Injection [SWFI], Sterile Purified Water [SPW], Sterile Water for Irrigation, and Sterile Water for Inhalation).

For bulk water quality, the testing procedure and limit values are established as follows:

Parameter	Values
LOD for the applied TOC analyzer	0.05 mg/L (ppm)
Max. preparation water TOC blank	0.1 mg/L
TOC limit for sample testing	0.5 mg/L
SST concentration level	0.5 mg/L

For the sterile water quality, the testing procedure was modified and limit values according to different container volumes were established as follows:

Parameter	Container Volume [mL]	Limit 1 [mg/L TOC]*)	Limit 2 [mg/L TOC]*)
LOD for the applied TOC analyzer	-	0.1	0.1
Max. reagent water TOC blank	-	0.5	0.5
	≤5	32.00	48.00
	>5 and ≤100	24.00	36.00
	>100	8.00	12.00

*) Concentration levels checked by a sucrose QC standard only
**) Concentration levels utilized to determine the system suitability requirements (with system suitability solution USP 1,4-benzoquinone RS in reagent water and standard solution USP sucrose RS in reagent water) for the container volume being tested.

This application note demonstrates that the multi N/C x300 analyzers allow straightforward and reliable TOC testing for sterile water at higher TOC levels according to USP <643>.

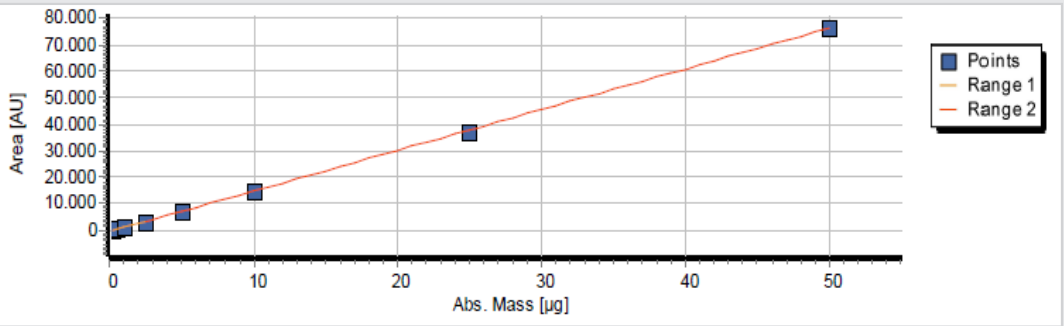
Materials and Methods

Samples and reagents

Samples were taken from tap water and water from a filtration plant, where different filters were applied to clean up raw water. The samples had been stored in the refrigerator at 4 °C. System suitability test solutions of 12, 36, and 48 mg/L mg/L sucrose and p-benzoquinone, respectively, were prepared from 1000 mg/L stock solutions by dilution with ultrapure water and subsequently run with the SST sequence integrated in the software before the samples were measured.
After several rinse steps the samples were filled into 40 mL sampler vials, sealed with aluminum foil, and placed into the AS vario sample rack. Using the autosampler, the samples were acidified with 1 M H_2SO_4 (multi N/C 4300 UV) and 2 M Cl (multi N/C 3300 and multi N/C 3300 HS), respectively, and subsequently purged with the carrier gas according to the method settings for complete TIC removal prior to NPOC measurement.
During the oxidation process in the high-power, long-life UV reactor or in the Pt catalyst filled combustion tube, respectively all carbon compounds are quantitatively converted to CO_2. The wide-range Focus Radiation NDIR Detector was used for quantitative determination of CO_2 content in the measurement gas

Calibration

The analyzers were calibrated for NPOC in the range from 0.2 to 50 mg/L with standard solutions prepared from a 1,000 mg/L sucrose stock solution. A multipoint calibration type was used. The calibration curve and its characteristics are shown in Figure 1.



Ranges

#	k0	k1	k2	DF	R²	Limit of Detection	Limit of Quantification	Range borders
0	-213,28	1402,10	-	-	0,99974	0,05 mg/L	0,23 mg/L	0,200 µg to 2,500 µg
1	-737,69	1540,02	-	-	0,99991	0,42 mg/L	1,67 mg/L	2,500 µg to 50,000 µg

Figure 1: NPOC calibration curve and characteristics

Instrumentation

The method settings listed in Table 1 were used to determine the TOC content:

Table 1: Method settings

Parameter	multi N/C 4300 UV	multi N/C 3300 HS, multi N/C3300
Measurement parameters	NPOC	NPOC
Digestion	UV radiation assisted by $Na_2S_2O_8$	high temperature oxidation using Pt catalyst at 800 °C
Number of single repetitions	min. 3, max. 4	min. 3, max. 4
NPOC purge time	360 sec	360 sec
Rinse with sample before injection	3 times	3 times
Injektion volume	5 mL	2 mL (multi N/C 3300 HS), 1 mL (multi N/C 3300)

Results and Discussion

After system calibration, two tap water and two sterile water samples were measured as described above. Results are displayed in table 2.

Table 2: Results

Sample ID	NPOC Average [mg/L]	NPOC RSD [%]
Tab Water 1	0.856	1.1
Tab Water 2	1.231	0.8
Sterile Water 1	4.638	0.5
Sterile Water 2	9.893	0.7

System suitability test for bulk water (Figure 2 and 3) as well as for sterile water at 12 ppm (Figure 4 and 5) and 36 ppm (Figure 6 and 7) were run and test reports together with peak graphs for p-benzoquinone are shown here.

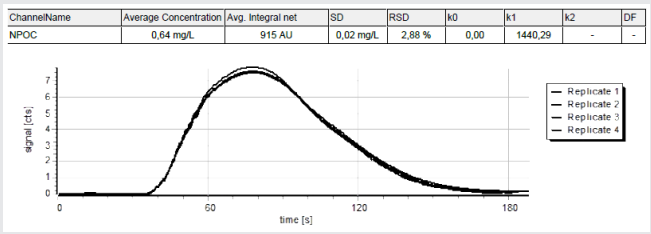


Figure 2: TOC peak graph for p-benzoquinone SST solution at 500 ppb

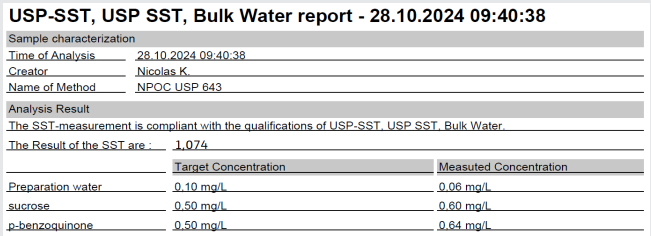


Figure 3: Device software SST report for bulk water at 500 ppb

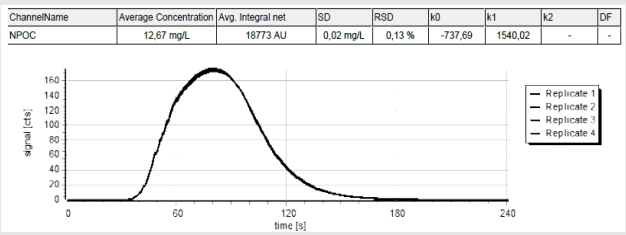


Figure 4: TOC peak graph for p-benzoquinone SST solution at 12 ppm

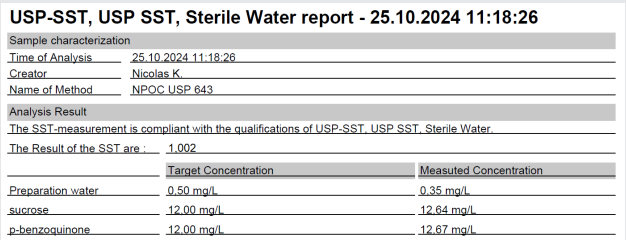


Figure 5: Device software SST for sterile water at 12 ppm

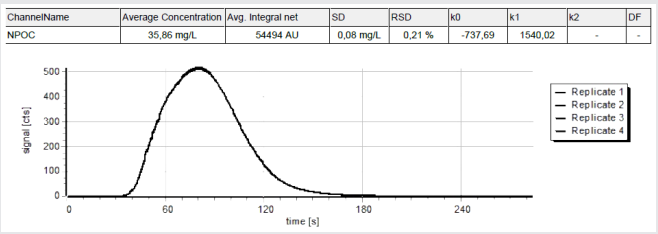


Figure 6: TOC peak graph for p-benzoquinone SST solution at 36 ppm

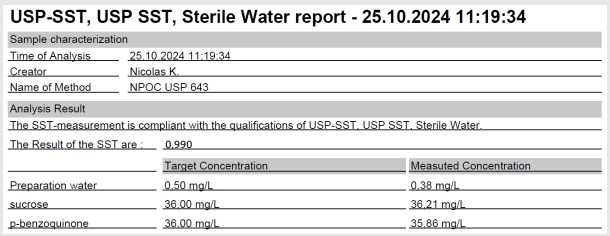


Figure 7: Device software SST report for sterile water at 36 ppm

Summary

With the implementation of container volume dependent TOC limit values for sterile water the USP TOC monograph has clearly broadened the pharma application range for TOC analyzers. With SST levels at 12, 36 or even 48 mg/L TOC different calibration strategies and method settings are required in order to cover the working range properly.

This application note clearly demonstrates that the multi N/C x300 analyzers with their high-oxidation power and sophisticated design provide the required performance characteristics for the new challenges in pharmaceutical TOC testing beyond the 500 ppb limit.

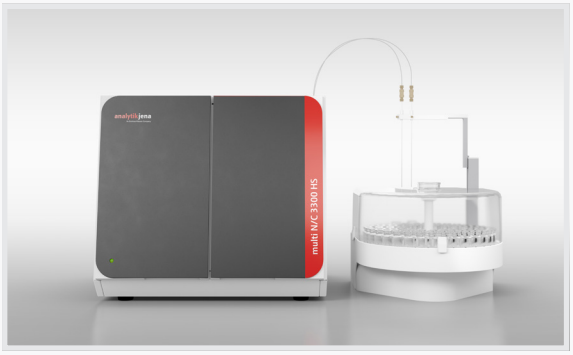


Figure 8: multi N/C 3300 HS with AS vario

References

[1] USP <643> TOTAL ORGANIC CARBON, USPNF 2021 Issue 3, 1-Sep-2021

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