Challenge

Detection of total organic carbon down to 0.05 mg/l and minimum recovery of 90 % of the test substance sodium dodecyl benzene sulfonate (SDBS) at a 500 ppb level according to JP XVII, section 2.59 TOC.

Solution

Full compliance to the Japanese performance test with excellent recoveries for SDBS and lowest detection limits using the analyzers of the multi NC pharma series.

TOC Performance Test as per Japanese Pharmacopoeia

Introduction

A System Suitability Test (SST) or Performance Test has to be performed at regular intervals to check the suitability of a TOC analyzer for the use in pharmaceutical applications. This test solely serves to check the digestion capacity of the analyzer, i.e. the CO_2 yield in complete oxidation of the analytes. By definition, the SST must be performed using two standard substances: one readily oxidizing compound is used as the reference, while the other poorly oxidizing compound is used as the test substance. The calibration of the device should be performed with the reference substance.

In contrary to the European and US pharmaceutical regulations (Pharm. Eur., USP) which prescribe sucrose and p-benzoquinone as reference and test substances, the Japanese Pharmacopoeia 17, General Tests section 2.59, prescribes potassium hydrogen phthalate as reference substance (standard solution) and sodium dodecyl benzene sulfonate as test substance (test solution).

The analyzer should be capable of generating not less than 0.450 mg/l of total organic carbon when measuring a solution containing 0.806 mg/l of sodium dodecyl benzene sulfonate (nominal TOC concentration of 0.500 mg/l) as sample. In case, the required recovery rate of minimum 90 % is not achieved it may be necessary to replace the catalyst (high-temperature combustion systems) or check the oxidation reagent or exchange the UV lamp (UV/wet chemical digestion systems).

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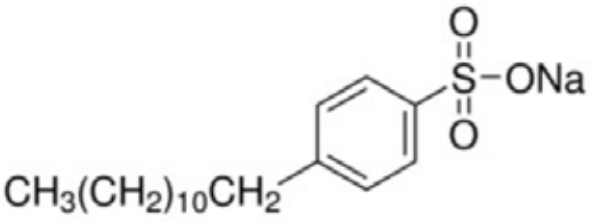
According to the Japanese TOC monograph a TOC analyzer applied for pharmaceutical water testing must provide a sufficient sensitivity to measure the amount of TOC down to 0.050 mg/l. It is also stated, that the reagent purity of water used to prepare standard solutions or reagents (for oxidation or TIC decomposition) should contain not more than 0.250 mg/l TOC. This application note clearly demonstrates that the instruments of the multi N/C pharma series meet all performance requirements according to Japanese Pharmacopoeia.

Materials and Methods

Samples and Reagents

Potassium hydrogen phthalate standard and SDBS test solution respectively, were prepared from 100 mg/l stock solutions by dilution with high quality ultrapure water from the ultrapure water plant in the lab (TOC blank <50 ppb). A certified sodium dodecyl benzene sulfonate as pharmaceutical secondary standard from Sigma-Aldrich with a TOC content of 49.7 % was used to prepare the stock solution. The potassium hydrogen phthalate from Merck was of analysis grade.



For sample acidification 2 M H_2SO_4 (multi N/C pharma UV) and 2 M HCl (multi N/C pharma HT, 3100 pharma) were used. Freshly prepared and acidified preparation water, reference standard and test solution were filled into 40 ml sampler vials after several rinse steps, sealed-off with aluminum septa, and placed into the AS vario auto sampler rack.

Calibration

The multi N/C pharma analyzers were calibrated in NPOC mode with a one-point calibration using potassium hydrogen phthalate solution at a concentration of 0.600 mg/l. To eliminate the influence of carbon in the water used for the preparation of the standard solution, the TOC blank value was measured and automatically subtracted from standard reading by multiWin software. Both solutions were acidified with the same volume and type of acid and purged to eliminate the inorganic carbon present in trace level. The calibration curve and its characteristics are presented in Figure 1.

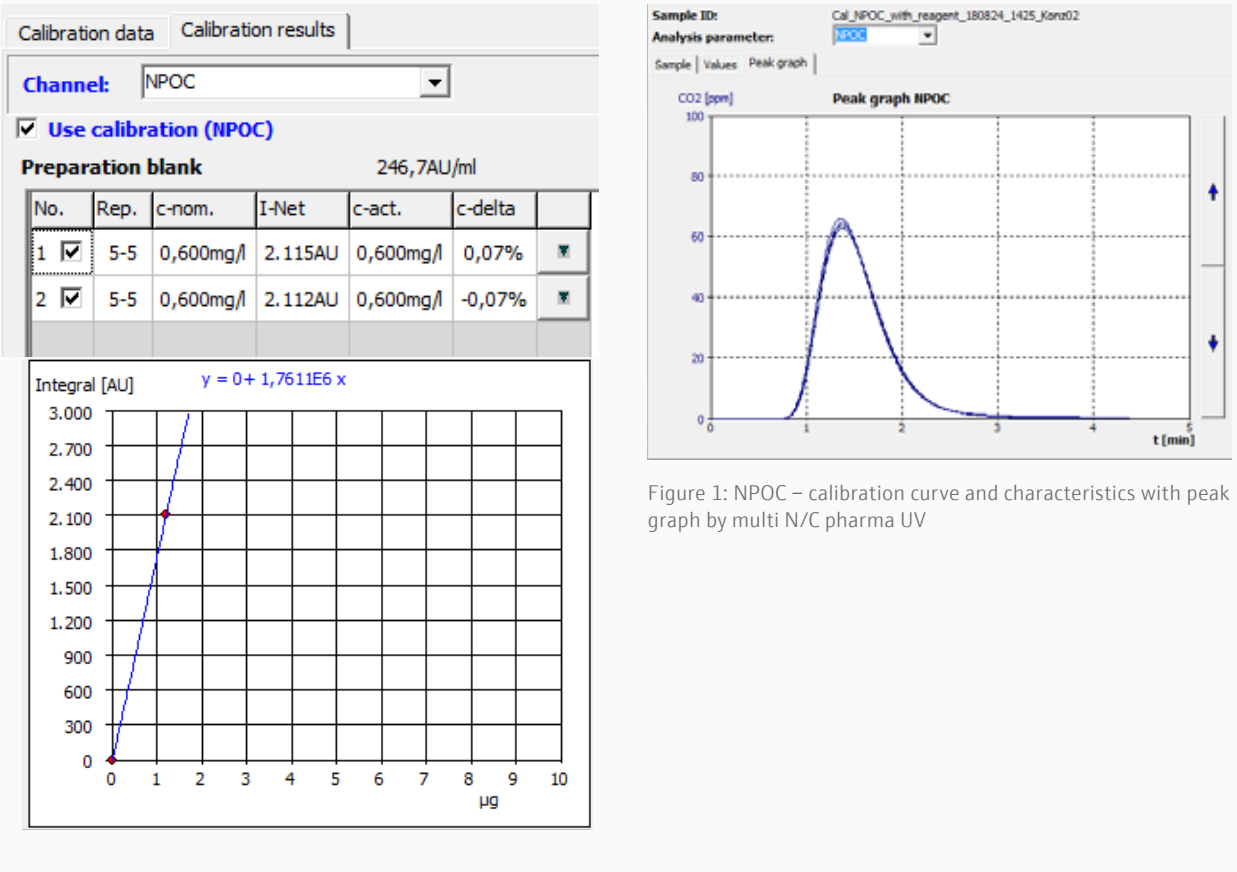


Figure 1: NPOC – calibration curve and characteristics with peak graph by multi N/C pharma UV

Instrumentation

The analysis was performed on the multi N/C pharma UV, the multi N/C pharma HT and the multi N/C 3100 pharma. For complete TIC removal prior to NPOC measurement the solutions were automatically purged with carrier gas according the method settings. During the oxidation process in the high-power, long-life UV reactor or in the Pt catalyst filled combustion tube, respectively all organic carbon compounds were 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.
The following method settings were used to determine the TOC content:

Table 1: Method settings

	multi N/C pharma UV	multi N/C pharma HT, multi N/C 3100 pharma
Parameter	NPOC (direct TOC measurement)	NPOC (direct TOC measurement)
Digestion	UV radiation assisted by $Na_2S_2O_8$ (160 g/l)	high-temperature oxidation using Pt catalyst at 800 °C
Number of repetitions	min. 3, max. 4	min. 3, max. 4
NPOC purge time	300 sec	300 s
2nd purge time	60 sec	60 sec
sample rinses before injection	3 times	3 times
Injection volume	5 ml	2 ml (pharma HT), 1 ml (3100 pharma)

Results and Discussion

Three sodium dodecyl benzene sulfonate solutions with a nominal organic carbon concentration of 0.500 mg/l were prepared and acidified as described earlier. By measurement with sample type AQA standard, the subtraction of the preparation water blank was done automatically by multiWin software. The following TOC measurement results were obtained by multi N/C pharma UV (Table 2). The peak graph of sodium dodecyl benzene sulfonate solution is presented in Figure 2.

Table 2: Measurement results

Sample ID	NPOC Average [µg/l]	RSD [%]	% Recovery
1	494.9	1.24	99.0
2	515.2	0.74	103.0
3	485.8	0.34	97.2
Mean Value	**498.6**	**-**	**99.7**

For the performance test according to JP XVII, section 2.59, the analyzer has to ensure a recovery rate of 90.0 % (450 µg/l TOC in a solution of 806 µg/l SDBS). Due to the high oxidation power, the FR-NDIR detector and the sophisticated design, the multi N/C pharma analyzers from Analytik Jena achieve a recovery rate of 99.7 %.

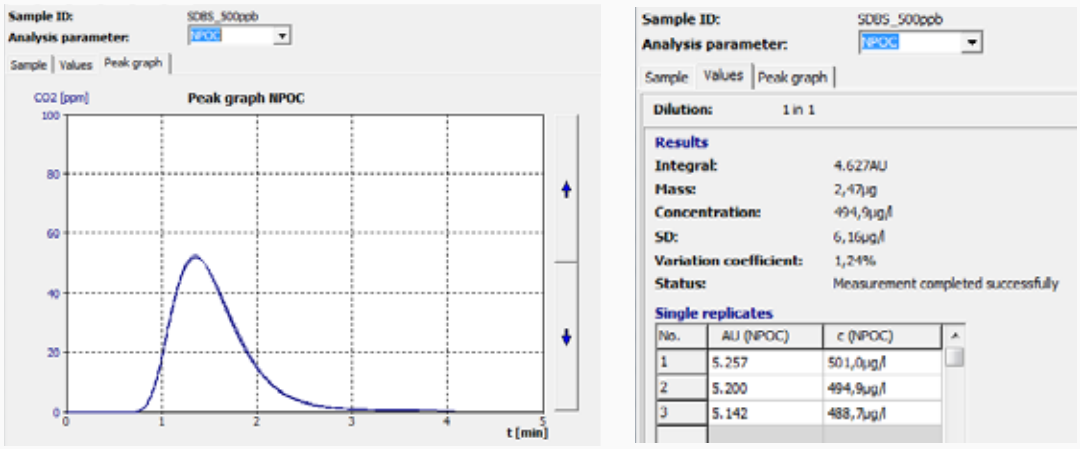


Figure 2: NPOC – Peak graph and result of sodium dodecyl benzene sulfonate solution.

TOC measurement below 0.050 mg/l

The Japanese pharmacopoeia states, that the analyzer should be capable of measuring the amount of organic carbon down to 0.050 mg/l. For this purpose ultrapure water blank measurements, as well as TOC AQA standard measurements were carried out at a concentration of 0.050 mg/l of potassium hydrogen phthalate solution. Excellent results were obtained as shown in Table 3. The multi N/C pharma analyzers from Analytik Jena exceed the TOC measurement criteria value of down to 0.050 mg/l stipulated in the Japanese Pharmacopoeia. The result and peak graph is shown in Figure 3a and 3b.

Table 3: Measurement results

Sample ID	NPOC Average [µg/l]	RSD [%]	% Recovery
blank 1	15.08	0.76	-
50 ppb KHP AQA - 1	47.24	2.25	94.5
50 ppb KHP AQA - 2	53.14	0.67	106.3
50 ppb KHP AQA - 3	50.01	1.45	100.0
Mean value	**50.13**	**-**	**100.3**

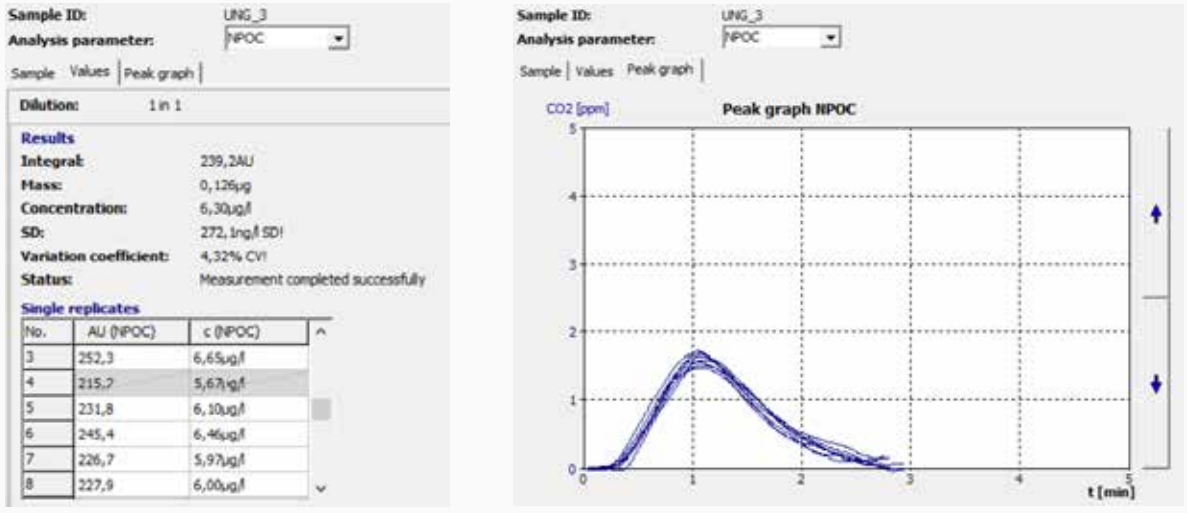


Figure 3a: NPOC – Result and peak graph of a blank measurement (injection volume 20 ml).

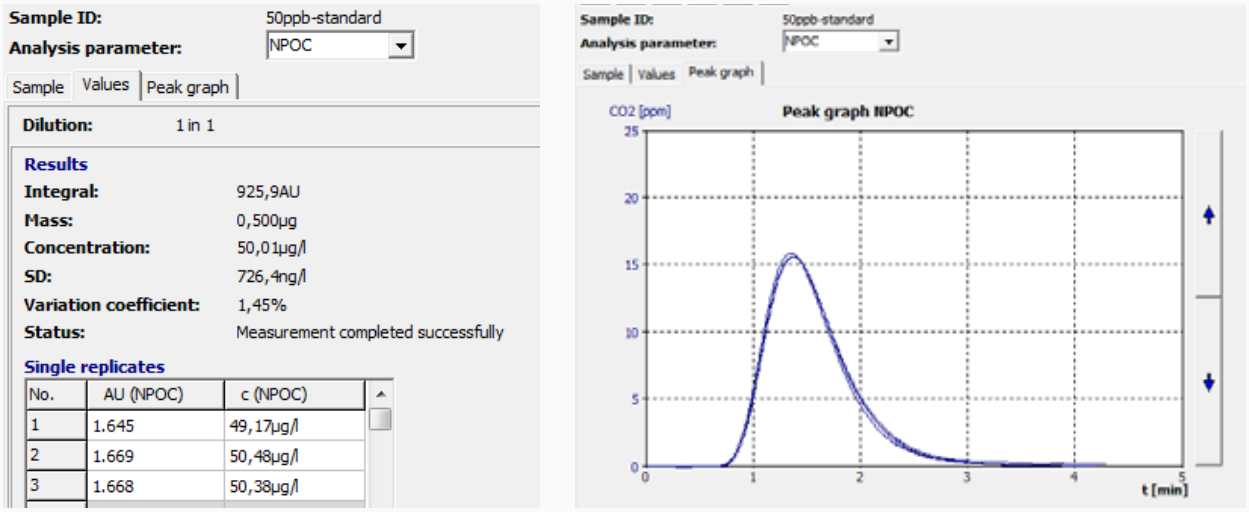


Figure 3b: NPOC – Result and peak graph of a 0.050 mg/l TOC standard solution measurement (example: multi N/C pharma UV).

From the ultrapure water blank measurement, the detection limit for the method can be calculated by the blank value method, which is the 3-fold standard deviation:

Detection limit = 3 x 0.272 µg/l = **0.82 µg/l**

Conclusion

The results show that the analyzers of the multi N/C series clearly exceed the requirements of JP XVII, section 2.59 in terms of recovery rates and trace TOC measurement competence. This also demonstrates the sample digestion capacity of the multi N/C pharma UV, whose oxidation capability is extraordinarily high due to the high-performance reactor with two wavelengths. The specially designed quartz glass reactor encloses the UV radiation source directly without interfering air film and uses UV light of 254 nm and additionally a very "hard" radiation of 185 nm of high energy. Thus, the high-power reactor ensures complete oxidation even of difficult-to-oxidize compounds like sodium dodecyl benzene sulfonate and p-benzoquinone.
The catalytic combustion based TOC analyzers multi N/C pharma HT and multi N/C 3100 pharma provide equivalent recovery rates for the poorly oxidizing test substances. In addition, they allow simultaneous TN determination for more product specific cleaning validation approaches for protein or enzyme based products in biopharmaceutical production.

Due to the high oxidation power, the FR-NDIR detection and the sophisticated design the multi N/C pharma analyzers from Analytik Jena provide more than the required performance characteristics to make your lab fit for the challenges in pharmaceutical TOC testing.

References

JP XVII 2.59 Test for Total Organic Carbon

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