Application Note · multi N/C 3300, 3300 HS and multi N/C 4300 UV

Challenge
TOC detection 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 acc. to JP and KP.

Solution
Full compliance to the Japanese and Korean performance test with excellent recoveries for SDBS and lowest detection limits using the analyzers of the multi NC x300 series.

TOC Performance Test as per Japanese and Korean 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 U.S. pharmaceutical regulations (EP and USP) which prescribe sucrose and p-benzoquinone as reference and test substances, the Japanese Pharmacopoeia method, 2.59 "Test for Total Organic Carbon" and the Korean Pharmacopoeia method, appendix 5, „Total Organic Carbon" (both to be found in the General Tests sections), 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).
According to the Japanese or Korean 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 not contain more than 0.250 mg/L TOC. This application note clearly demonstrates that the instruments of the multi N/C x300 series used in this study meet all performance requirements according to Japanese and Korean Pharmacopoeia.

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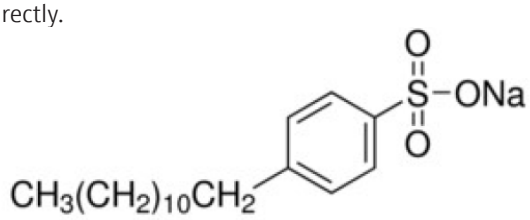
Materials and Methods

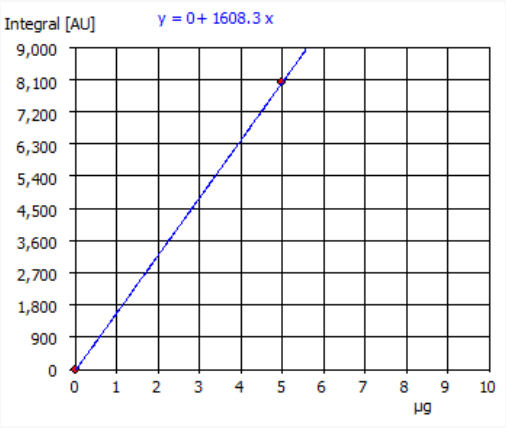
Samples and reagents

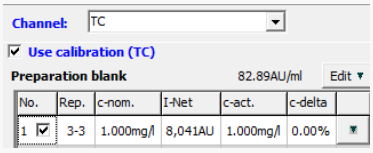
Potassium hydrogen phthalate standard and sodium hydrogen carbonate standard were prepared from 1000 mg/L stock solution by dilution with high quality ultrapure water from the ultrapure water plant in the lab (TOC blank <50 µg/L). The SDBS test solution was prepared from 100 mg/L stock solution as well. Sodium dodecyl benzene sulfonate from Kanto Chemical with a TOC content of 99.2 % was used to prepare the stock solution. The stock solution of potassium hydrogen phthalate for water analysis was from Fujifilm Wako Pure Chemical and inorganic carbon. from sodium hydrogen carbonate standard was from ERA. Freshly prepared water, reference standard and test solution were prepared with 250 mL volumetric flask and measured directly.



Calibration

The multi N/C x300 analyzers used in this study were calibrated in TOC differential mode with a one-point calibration using potassium hydrogen phthalate solution and sodium hydrogen carbonate solution. The concentration of TOC and TIC was 0.5 mg/L respectively. The calibration curve and its characteristics are presented in Figure 1 and 2.





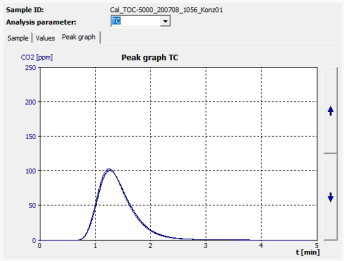
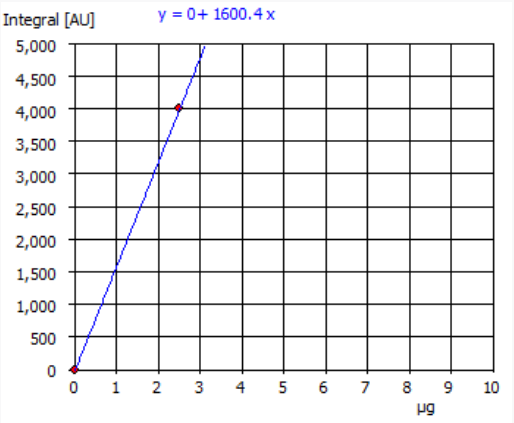
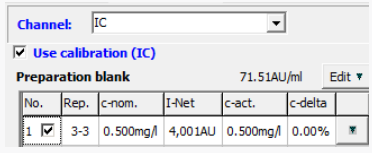


Figure 1: TC calibration curve and characteristics with peak graph by multi N/C 4300 UV





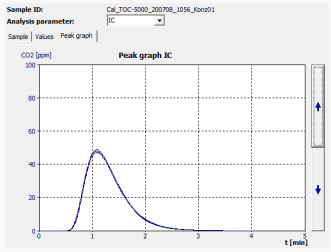


Figure 2: IC calibration curve and characteristics with peak graph by multi N/C 4300 UV

Instrumentation

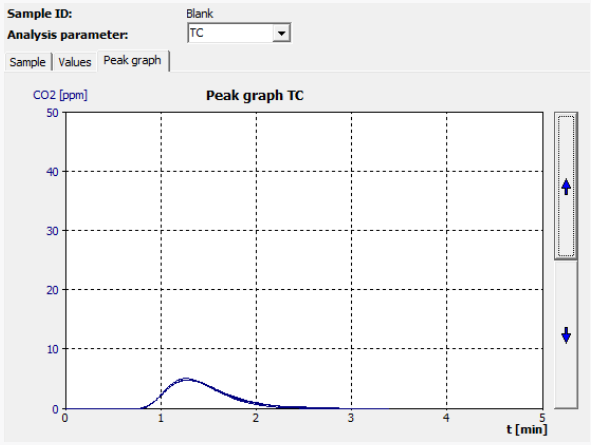
The analysis was performed on the multi N/C 4300 UV, the multi N/C 3300 HS and the multi N/C 3300. During the oxidation process in the high-power, long-life UV reactor or in the Pt catalyst-filled combustion tube, respectively all organic carbon compounds were quantitatively converted to CO_2. The wide-range Focus Radiation NDIR-Detector was used for quantitative determination of CO_2 content in the measurement gas.

Table 1: Method settings

	multi N/C 4300 UV	multi N/C 3300 HS, multi N/C 3300
Parameter	TOC differential mode (TOC=TC-TIC)	TOC differencial mode (TOC=TC-TIC)
Digestion	UV radiation without oxidation agent	High-temperature oxidation using Pt catalyst at
Number of repetitions	3 times	3 times
Sample rinses before injection	3 times	3 times
Injection volume	5 mL	2 mL (multi N/C 3300 HS), 1 mL (multi N/C

Results and Discussion

Sodium dodecyl benzene sulfonate solutions with a nominal organic carbon concentration of 0.500 mg/L were prepared as described earlier. The peak graph of sodium dodecyl benzene sulfonate solution is presented in Figures 3a to 3b. The following TOC measurement results were obtained by multi N/C 4300 UV (see also table 2).



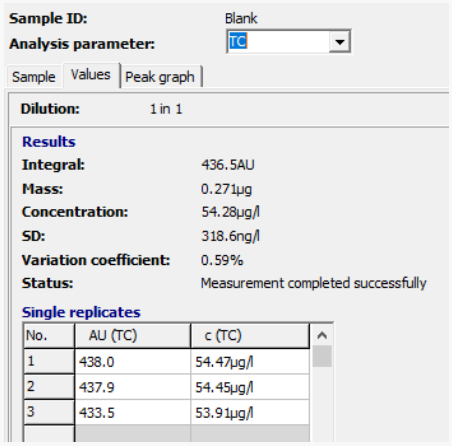
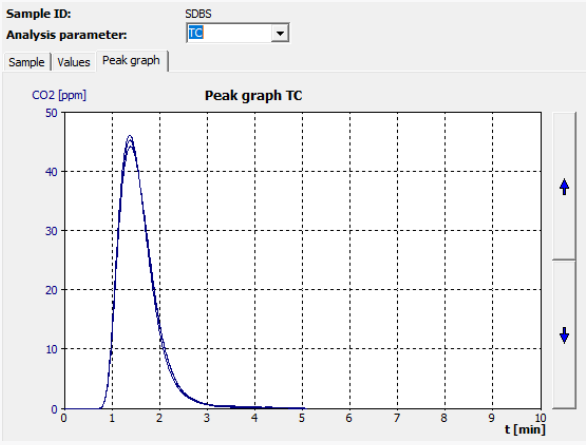


Figure 3a: TC - Peak graph and result of preparation water blank.



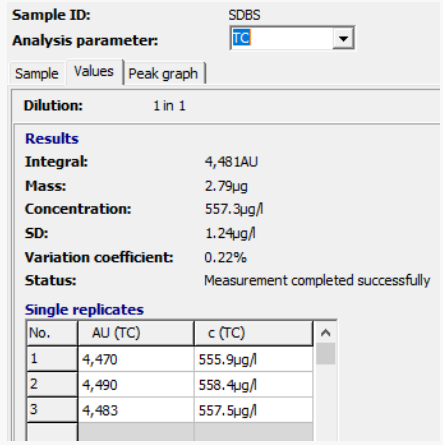
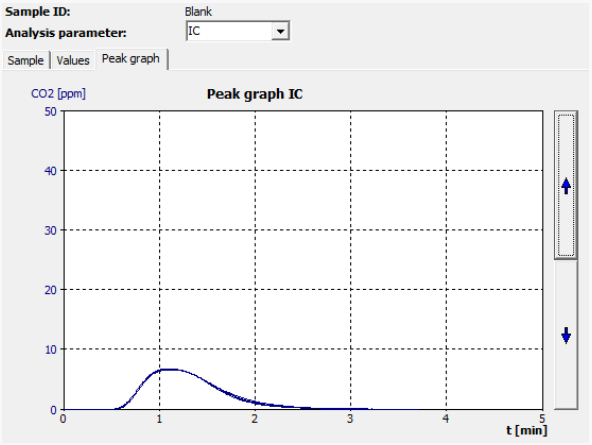


Figure3b: TC - Peak graph and result of Sodium dodecyl benzene sulfonate solution.



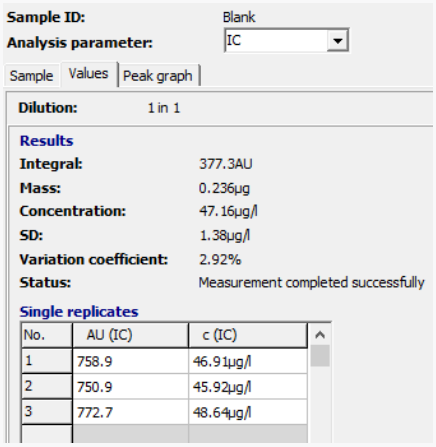
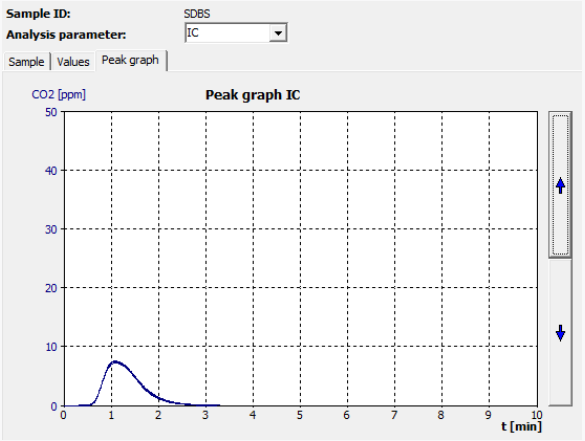


Figure 3c: IC - Peak graph and result of preparation water blank



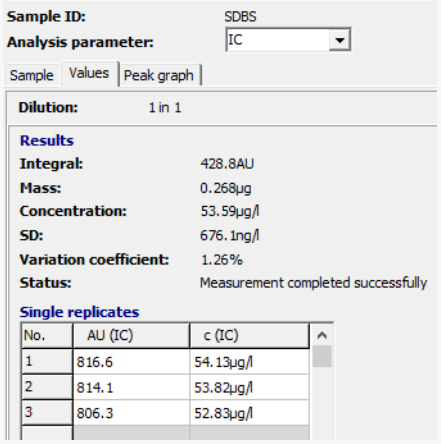


Figure 3d: IC - Peak graph and result of Sodium dodecyl benzene sulfonate solution.

Table 2: Measurement results

Sample ID	TC Average [µg/L]	RSD [%]	TIC Average [µg/L]	RSD [%]	TOC Average [µg/L]	Recovery TOC [%]
① **Blank**	54.3	0.59	47.2	2.92	7.12	
② **SDBS**	557.3	0.22	53.6	1.26	503.7	
② - ①					**496.6**	**99.3**

For the performance test according to JP method 2.59 and KP TOC monograph, 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 Focus Radiation NDIR-Detector and the sophisticated design, the multi N/C x300 analyzers from Analytik Jena achieve a recovery rate of 99.3% even without use of any oxidation reagent and therefore avoiding the influence of TOC blank level is such reagent onto the final result.

TOC measurement below 0.050 mg/L

The JP and KP monographs state 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 QC 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 analyzers of the multi N/C x300 series from Analytik Jena exceed the TOC measurement criteria value of down to 0.050 mg/L stipulated in the Japanese and Korean Pharmacopoeia. The result and peak graph are shown in Figure 4a and 4b.

Table 3: Measurement results

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

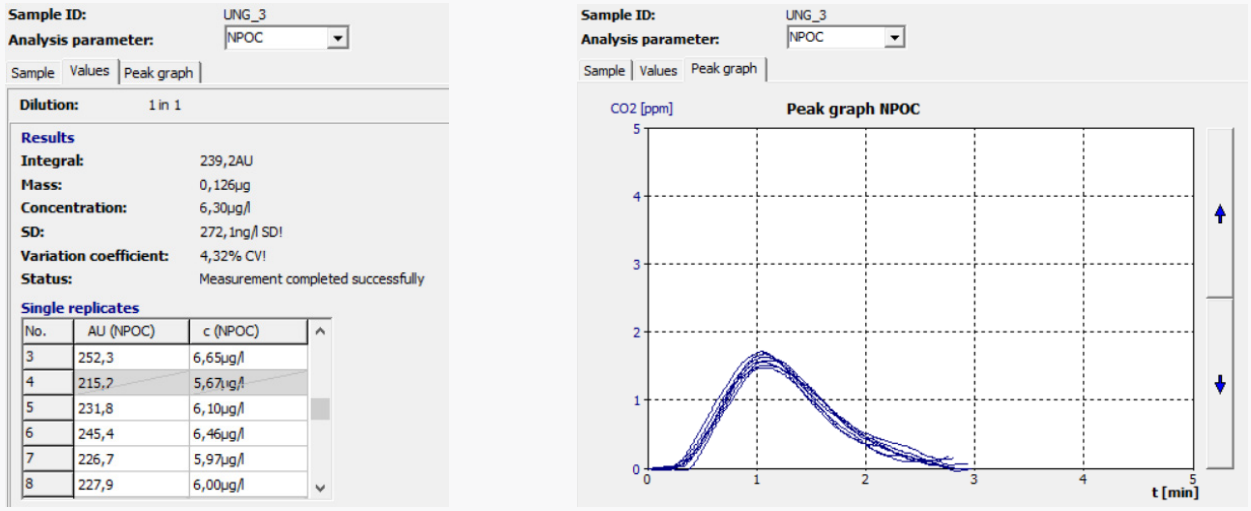


Figure 4a: NPOC – Result and peak graph of a blank measurement (injection volume 20 mL).

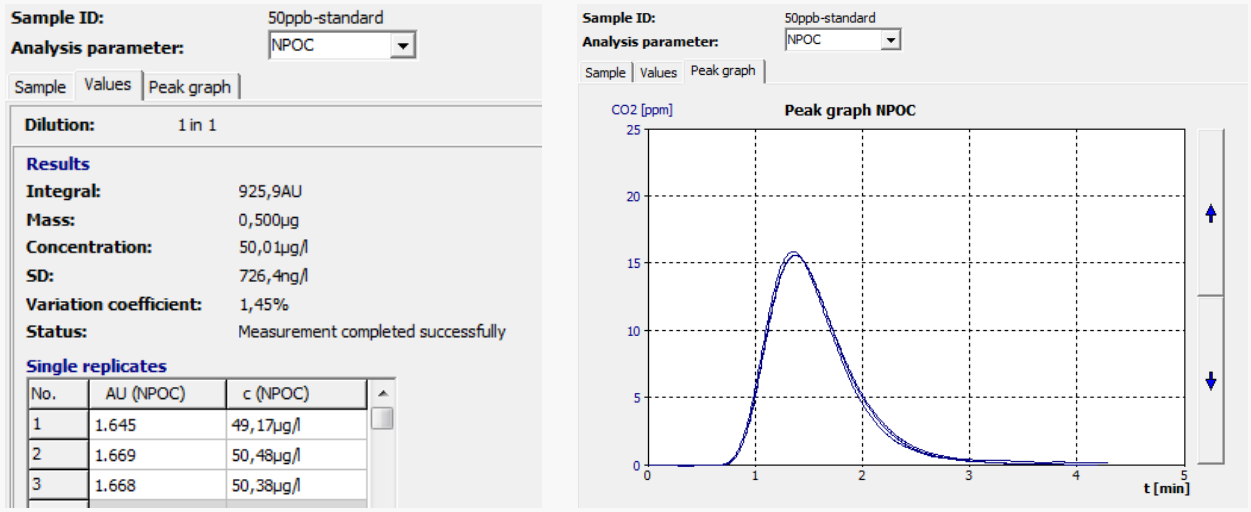


Figure 4b: NPOC – Result and peak graph of a 0.050 mg/L TOC QC standard solution measurement (example: multi N/C 4300 UV).

From the ultrapure water blank measurement by multi N/C 4300 UV, the detection limit for the validated TOC method can be calculated according to the blank value method, which is the 3-fold standard deviation:

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

Summary

The results show that the analyzers of the multi N/C x300 series clearly exceed the requirements of JP and KP monographs in terms of recovery rates and trace TOC measurement competence. This also demonstrates the sample digestion capacity of the multi N/C 4300 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 3300 HS and multi N/C 3300 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 industry.

Due to the high oxidation power, the Focus Radiation NDIR detection and the sophisticated design the analyzers of the multi N/C x300 series from Analytik Jena provide more than the required performance characteristics to make your lab fit for the challenges in pharmaceutical TOC testing.

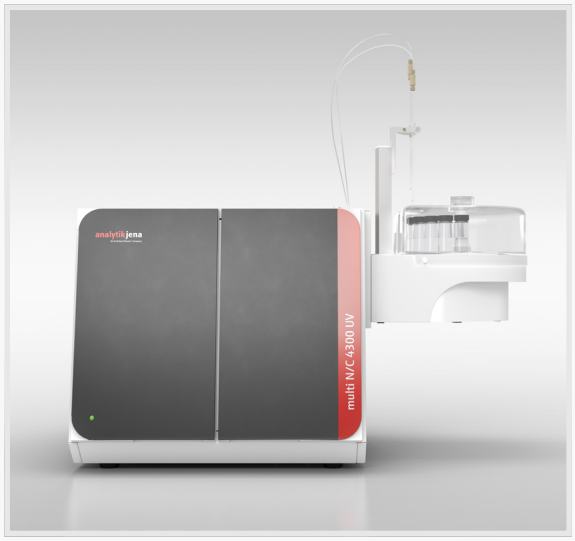


Figure 2: multi N/C 4300 UV with AS21 autosampler

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