Challenge

TOC samples derived from cleaning validation are characterized by changing concentration levels, demanding a TOC analyzer without memory or carry-over effects

Solution

Successful demonstration of a measurement sequence of samples with trace level and higher TOC concentrations and calibration strategy to cover a wide linear TOC working range

GMP Compliant TOC Cleaning Validation in Pharmaceutical Industry

Introduction

To minimize or prevent cross contamination from product to product in pharmaceutical production equipment, manufacturers are obliged to establish defined cleaning processes in accordance with the pharmaceutical operating regulations. According to the ICH Q7[1] GMP guideline, the effectiveness of these cleaning procedures is to be demonstrated regularly by the use of analytical measuring techniques. This means that after successful cleaning a check must be carried out for residues of active pharmaceutical ingredients (API), additives, detergents, and their decomposition and reaction products, using a representative and validated sampling and analysis method.

Both, substance-specific targeted analysis techniques (HPLC, GC, etc.), as well as non-specific non targeted analysis techniques like the sum parameters total organic carbon (TOC) or total nitrogen (TN) are used. Further indicators are visual inspection, conductivity, pH and surface tension. Since each of the possible contaminants listed above typically represents organic compounds and can be addressed by total organic carbon, TOC has been chosen and pushed by the FDA to become the number one non-substance specific screening parameter in cleaning validation.

Additionally TOC determination is a mandatory parameter in WFI (water for injection) and AP (aqua purificata – purified water for pharmaceutical use) quality control and a well described pharmacopoeia method with ultralow detection limits below 50 ppb according to Pharm. Eur. 2.2.44[2] and USP <643>[3] monographs.
Cleaning validation limits and acceptance criteria are calculated according to different approaches listed in the PDA technical report no. 29[4] and 49[5], e.g., based on drug active dose or toxicity to establish acceptable residue levels (ARL).
Two strategies – the post-final rinse and the swab test – are followed during cleaning validation to prove the cleanliness of production equipment. The particular advantage of the post final rinse or swab extracts procedure is that both sampling approaches can be established more easily, are less

error-influenced and the resulting TOC samples can be processed by a standard TOC analyzer using typical method settings and quality assurance checks.

Materials and Methods

Samples and reagents

Two customer-provided rinse samples and two samples from swab surface sampling were prepared and analyzed according to USP resp. Pharm. Eur. guidelines for total organic carbon measurements.

Sample preparation and measurement

In the post-final rinse the production equipment is rinsed once more after the final rinse of the cleaning procedure to transfer any potential organic surface contamination into this rinse water and to make it available for TOC measurement.

With the swab test (Figure 1a, 1b), on the other hand, previously defined risk locations, such as recesses, welding seams and obstacles, are purposefully sampled by using e.g., cotton or polymer fiber swabs. The swab material is moistened and rinsed with ultrapure water before and during the sampling. The sampling area, usually limited using a template (normally approx. 100 cm^2) is wiped in layers cross-wise. The swab is then eluted/extracted with ultrapure water, by aid of shaking or sonication, topped up to a fixed volume of for example 40 mL and subsequently measured for TOC content.

A special procedure is the swab sampling for completely water-insoluble contaminants using inorganic fiber swabs (e.g., quartz fleece) to wipe the equipment surfaces for mechanical sampling. Subsequent direct swab combustion by catalytic high-temperature oxidation is applied for determination of the TOC load on the swab material. However, in this procedure various factors must be taken into account, such as the availability of swab materials with a consistently low TOC blank value, loss of fiber material during sampling or even surface abrasion by the wiping process.

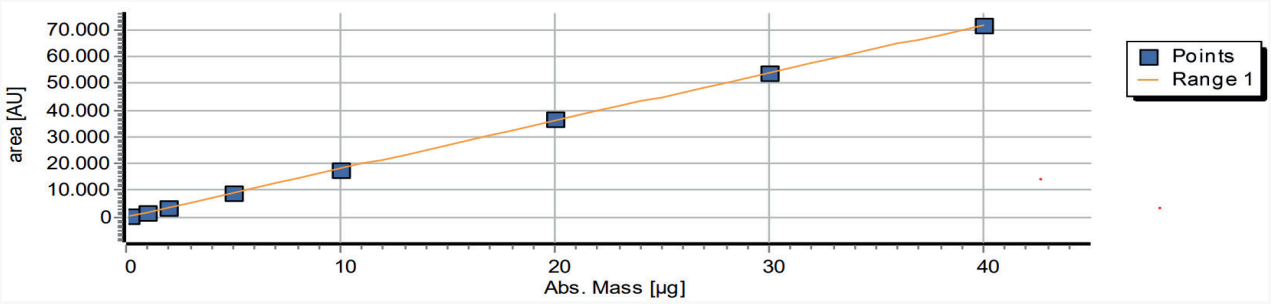
The rinse samples were collected during the post-final rinse process with pure water. The swab samples were provided readily extracted with pure water in 40 mL vials.

Sample vials were directly placed onto the autosampler without transferring the sample into other vials. Automatic acidification was performed to a pH <2 and as part of NPOC sample preparation the TIC was purged from the acidified samples automatically by a carrier gas stream. Further method parameters are referenced in the instrumentation section below. The formed CO_2 gas was transferred by a carrier gas stream into the Focus Radiation NDIR detector for quantification.

Figure 1a–b: Swab sampling on a test specimen, cross-wise in lanes

Calibration

The analyzers of the multi N/C x300 series were calibrated for NPOC in the range from 0.1 to 20 mg/L with standard solutions prepared from a sucrose stock solution containing 100 mg/L C. A multi-point calibration type was used. The calibration curve and its characteristics are presented in Figure 2. An outstanding linearity could be demonstrated throughout the whole calibration range from 0.1 to 20 mg/L for all three used analyzer models of the multi N/C x300 series.



#	k0	k1	k2	DF	R^2	Limit of Detection	Limit of Quantification	Range borders
0	56,65	1797,68	-	-	0,99995	0,08 mg/L	0,30 mg/L	0,200 µg to 40,000 µg

Figure 2a-b: TOC peak graph for extracted swab sample 1 (example of multi N/C 3300 HS)

Instrumentation

TOC measurements were performed on all pharma TOC analyzers: the multi N/C 4300 UV, the multi N/C 3300 HS and the multi N/C 3300. Following method settings were used to determine the TOC content:

Table 1: Method settings

	multi N/C 4300 UV	multi N/C 3300 HS, multi N/C 3300
Parameter	NPOC (direct TOC measurement)	NPOC (direct TOC measurement)
Digestion	UV radiation assisted by $Na_2S_2O_8$	high-temperature oxidation using Pt catalyst at 800 °C
Number of repetitions	min. 3, max. 4	min. 3, max. 4
NPOC purge time	300 s	300 s
Rinse with sample before injection	3 times	3 times
Injection volume	5 mL	2 mL (multi N/C 3300 HS), 1 mL (multi N/C 3300)

Results and Discussion

Four cleaning validation samples were measured alongside with different QC check standards and pure water samples in one sequence after system calibration as described above. Results for the multi N/C 3300 are summarized in Table 2.

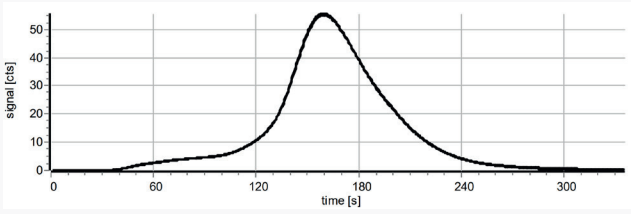


Figure 3: TOC peak graph for extracted swab sample 1

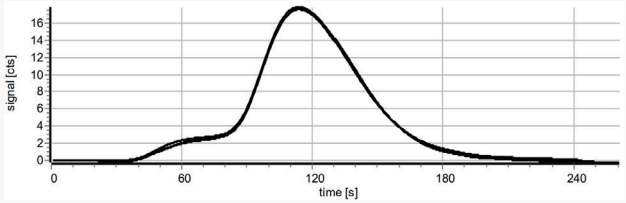


Figure 4: TOC peak graph for QC sample 1

Table 2: Results

Sample ID	NPOC Average [mg/L]	RSD [%]
Post final rinse sample 1	0.327	1.9
Post final rinse sample 2	0.943	1.3
QC sample 1 (0.5 mg/L NPOC)	0.509	1.6
QC sample 2 (20 mg/L NPOC)	20.11	0.6
Pure water sample	0.058	3.7
Swab extract sample 1	1.742	0.9
Swab extract sample 2	15.79	0.5
QC sample 1 (0.5 mg/L NPOC)	0.504	1.7
QC sample 2 (20 mg/L NPOC)	20.22	0.7
Pure water sample	0.065	3.3

Conclusion

The results clearly demonstrate that the discussed TOC analyzers of the multi N/C x300 series provide very good performance characteristics for the measurement of cleaning validation samples. Very low TOC concentrations can be determined besides higher loaded samples with high precision and accuracy. The instruments do not show carry-over effects in case of higher polluted samples which might occur in a sample sequence. With their high oxidation power, the FR-NDIR detector and a sophisticated design, the instruments allow reliable TOC determination in a wide linear measuring range.

With the multi N/C 3300 HS and multi N/C 4300 UV you are well prepared for the challenges of cleaning validation and pharmaceutical TOC testing.

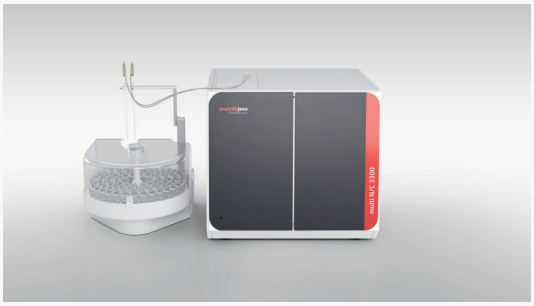


Figure 5: multi N/C 3300 with AS vario

References

[1] ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients - Guidance for Industry, Revision 1, U.S. Department of Health and Human Services Food and Drug Administration, September 2016

[2] EP 2.2.44. TOTAL ORGANIC CARBON IN WATER FOR PHARMACEUTICAL USE

[3] USP <643> TOTAL ORGANIC CARBON

[4] Points to Consider for Cleaning Validation, Technical Report No. 29, Revised 2012, Parenteral Drug Association, Inc. (PDA)

[5] Points to Consider for Biotechnology Cleaning Validation, Technical Report No. 49, 2010, Parenteral Drug Association, Inc. (PDA)

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