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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.

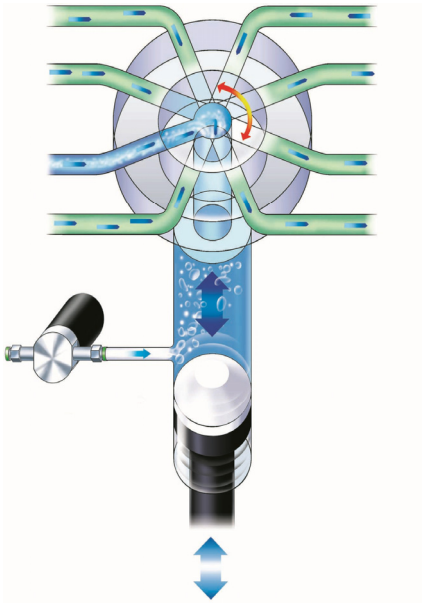

Fig. ISP-Module of TOC-L series

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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