

Implementing Total Organic Carbon Analysis for Cleaning Validation

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Total organic carbon (TOC) analysis is a fast and effective analytical technique for cleaning validation. Understanding the various types of TOC technologies is essential for choosing the best solution.

Total organic carbon (TOC) analysis is a fast and effective analytical technique for cleaning validation in pharmaceutical manufacturing. This nonspecific method can be used to test for residues of previously manufactured products, cleaning detergents, chemicals, solvents, by-products, degradants, and microbial contaminants. However, many factors must be considered before implementing a TOC cleaning validation program, including detergent selection, establishing TOC acceptance criteria, and choosing from the variety of TOC technologies available.

Background

21 *CFR* 211.67 states, "Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements" (1). Medicines are intended to promote good health; however, when residual compounds remain in the manufacturing process, the potential for side effects from toxic levels of contaminants increases. A good validation of the cleaning process documents at what points the cleaning procedure will fail when parameters are reduced to the worst-case scenario. Typical laboratory testing includes the development and implementation of analytical methods that test for residues of previously manufactured products, cleaning detergents, chemicals, solvents, by-products, degradants, and microbial contaminants (from wet environments after the cleaning process).

Detergent selection

Detergent selection is a critical step in the development a cleaning validation. FDA's 1993 guide "Inspection of Validation of Cleaning Procedure" states, "As with product residues, it is important and it is expected that the manufacturer evaluate the efficiency of the cleaning process for the removal of residues. However, unlike product residues, it is expected that no, or for ultra sensitive analytical test methods very low, detergent levels remain after cleaning. Detergents are not part of the manufacturing process and are only added to facilitate cleaning during the cleaning process. Thus, they should be easily removable. Otherwise, a different detergent should be selected" (2).

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The chemistry of the detergents must be investigated before the detergents are used to clean various surfaces. Some surfaces are intolerant to solutions or compounds with certain pH levels. Cleaning methods (clean-in-place, clean-out-of-place, manual cleaning, immersion, etc.) may influence which detergent properties are desirable. Because most cleaning solutions contain water, the purity of the water used must be determined. In addition, the effluent produced from the cleaning process must be investigated to ensure that the facility is within the bounds of the regulations of local municipalities.

Sampling techniques

A cleaning validation method may include various sampling techniques to ensure effectiveness of the cleaning process (see Table I). FDA's 1993 guideline states, "There are two general types of sampling that have been found acceptable. The most desirable is the direct method of sampling the surface of the equipment. Another method is the use of rinse solutions." Sampling the

Table I: Common sampling techniques used in cleaning validation.

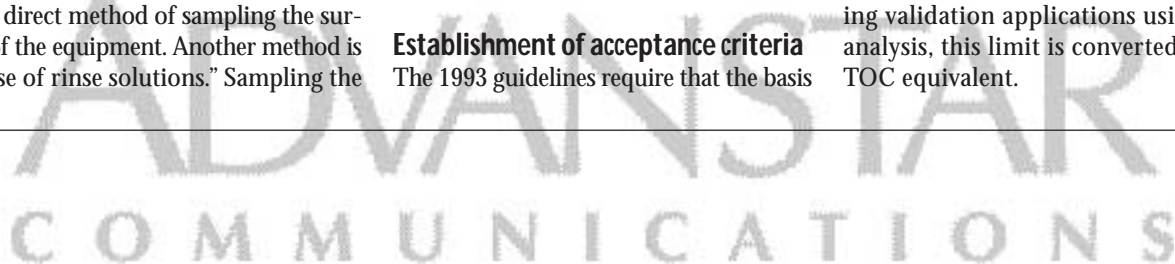
Technique	Description
Visual inspection	Qualitative, subjective
Rinse water sampling and analysis	Quantitative
Swabs for surface sampling and analysis	Quantitative, removes adherents, defined sample area
Swabs for surface sampling from coupons	Quantitative, similar surface to equipment

rinse water is most useful in analyzing a large surface area or inaccessible areas, whereas the use of swabs (a direct method) can remove contaminants that may adhere to surfaces even following rinsing. The swab technique typically involves moistening a polyester swab with purified water (acidified with phosphoric acid, if necessary) to wipe a measured area in a systematic manner. Cleaning validation kits that are specifically designed for TOC swabbing purposes are commercially available for this purpose.

Establishment of acceptance criteria

The 1993 guidelines require that the basis

of any acceptance limits be "scientifically justifiable." Acceptance criteria is typically set at 1/1000 reduction of the lowest therapeutic dose of the previous drug product (the active ingredient in most cases) or of the LD50 toxic dose of the cleaning solutions. If the calculated limit is >10 ppm carryover of the residual contaminants, then the acceptance criteria is set at a more rigorous 10 ppm (depending on medical opinion and/or other safety considerations). For cleaning validation applications using TOC analysis, this limit is converted into its TOC equivalent.



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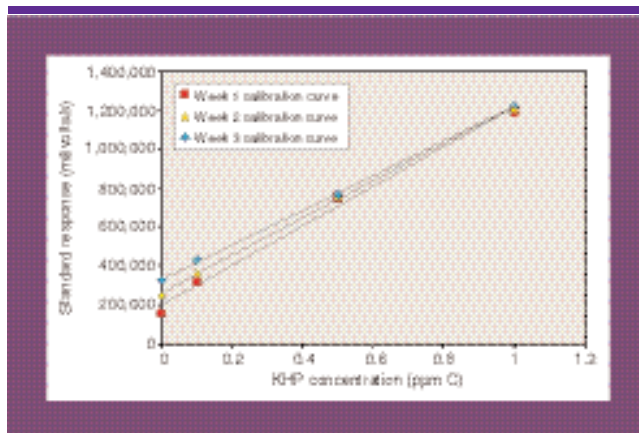


Figure 1: Combustion TOC analysis shifting blank.

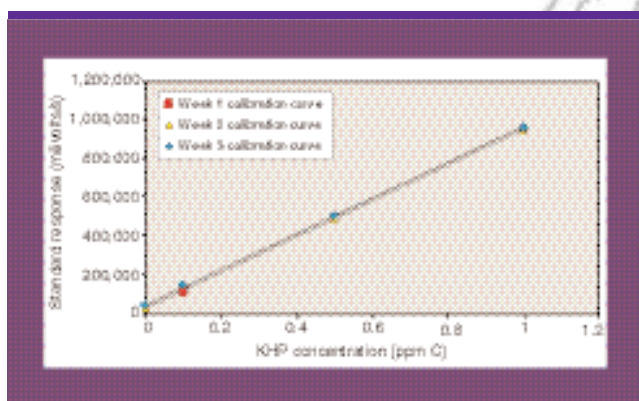


Figure 2: UV-persulfate TOC analysis consistent blank.

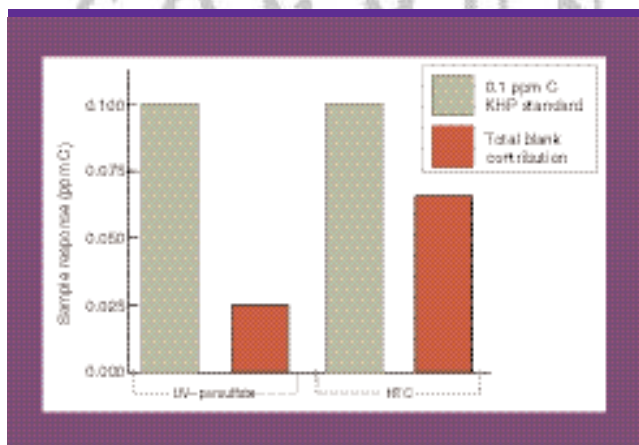


Figure 3: Combustion vs. UV-persulfate blank proportion for a 0.1-ppm carbon KHP standard.

Analytical methods

A variety of analytical methods are available for use in cleaning validation, including high-performance liquid chromatography (HPLC), conductivity, ion chromatography, pH, TOC, and even visual analysis. Each technique has advantages and disadvantages. For water-soluble matrices however, almost any residual compound can be detected if the following nonspecific analytical (screening) tests are used for a cleaning validation: TOC (for carbon/organics characteristics), pH (for

acid/base characteristics), and conductivity (for ionic characteristics). This combination of methods can identify contaminants from various sources including process waters, active ingredients, excipients, and cleaning agents. To use these techniques, the entire residue detected is assumed to be the worst compound (active ingredient) and then is compared to the established acceptance criteria. If the results are above the acceptance criteria, then additional cleaning processes are required.

Jenkins et al. found strong support for the use of TOC analysis in cleaning validation, stating, "TOC has low-level detection, rapid analysis time, is low cost compared to other methods, and can detect all carbon-based residuals" (3). They compared TOC, HPLC, thin-layer chromatography, spectrophotometric (UV), enzyme-linked immunosorbent assay, electrophoresis, pH, conductivity, and visual analysis, and found that TOC analysis performed as well or better than HPLC and spectrophotometric methods. In another study, Strege et al. found that TOC analysis was preferred to total protein analysis. They used TOC for their cleaning validation on equipment that was used with water-soluble drugs, excipients, and cleaning agents (4).

TOC methodology capabilities

Once the target analyte or worst-case compound with acceptance criterion is determined, the appropriate oxidation and detection scheme for TOC analysis is identified. Cleaning validation applications must achieve accurate low-level TOC detection (ranging from <50 ppbC to 5 ppmC or more) while ensuring proper analyte recovery. The most common TOC oxidation technologies include UV, UV-persulfate, and high-temperature combustion (HTC), whereas detection methods include nondispersive infrared (NDIR) and conductivity detection.

Oxidation technologies. For TOC analysis of ultra-pure water and cleaning validation, three techniques are commonly used: UV oxidation, which uses UV radiation to oxidize the organics present in the sample; UV-persulfate oxidation, which combines UV radiation and a persulfate reagent to substantially boosts oxidation efficiency; and HTC oxidation, which oxidizes the sample by heating it to 680–1000 °C.

UV oxidation is ideal for TOC analysis of purified water and water for injection (WFI) but typically is not strong enough for the carbon-containing matrices found in most cleaning validation applications. By contrast, the UV-persulfate oxidation technique is powerful enough for almost all cleaning validation needs yet still performs well for ultra low-level TOC waters. The HTC technique, although strong enough for complete oxidation of the sample, is not ideal for low-level TOC analysis because of the elevated and highly variable TOC background present in this method compared to typical sample response (see Figures 1 and 2).

The key to achieving accurate low-level TOC results is maximizing sample carbon response while minimizing background carbon response. As a result of its superior sample-to-noise response, the UV-persulfate technology achieves higher precision and lower limits of detection, and also achieves good accuracy throughout the range of analysis, yet requires significantly less effort and maintenance than the HTC technique (see Table II).

TOC detection schemes

The choice of a TOC detection scheme is just as important as the selection of an oxidation method. The two basic technologies are conductivity and NDIR. Conductivity detectors function by measuring the conductivity of the sample before and after it is oxidized and attributing the difference to the TOC in the sample. Conductivity detection is suitable for purified water and water-for-injection applications, but the method has several drawbacks in the cleaning validation application. Conductivity measurements >50 ppb TOC of the sample vary with the carbon-containing species present and can lead to significant error

(5). Ascertaining all chemical constituents of an analyte is nearly impossible, and as a result, deriving a formula to compensate for conductivity and temperature errors becomes difficult, because conductivity and temperature depend on chemical and TOC concentrations (6).

The use of hydrophobic gas-permeation membranes with conductivity detection allows for a more-selective passage of the dissolved CO₂ gas to the "zero" water for subsequent conductivity analysis and improves the accuracy of TOC analysis. However, the use of the membranes in the sample pathway can cause additional concerns for many particulate-laden cleaning validation applications, including clogging, micro leaks, flow problems, dead spots, microbial growth (blockage), and potential chemical reactions within the membrane itself. In addition, in comparison to other detection schemes, membrane-conductivity detection requires a substantial amount of time and rinsing to return to normal operation after the application of the high levels of TOC that are required for testing.

Table II: Comparison of typical low-level TOC results for potassium hydrogen phthalate (KHP) standards using HTC and UV/persulfate oxidation technologies.*

Sample ID (n = 4 replicates)	HTC (Apollo 9000 HS)		UV/persulfate (Phoenix 8000)	
	TOC result**	Standard deviation	TOC result	Standard deviation
1.00 ppm C	1.000	0.035	1.000	0.002
0.50 ppm C	0.506	0.010	0.496	0.004
0.25 ppm C	0.251	0.014	0.248	0.003
0.10 ppm C	0.098	0.009	0.100	0.002
0.05 ppm C	0.043	0.016	0.048	0.001
Reagent water	0.012	0.013	0.007	0.001

* All KHP standard results display a corrected value (the response of reagent water used to prepare the standard was subtracted from the actual result).

**All results and standard deviations are expressed as ppm of carbon (C).

NDIR detection offers a more practical, interference-free method for detecting CO₂ in TOC analysis (7). NDIRs measure the CO₂ generated by oxidation of the organic carbon in the gas phase and are therefore immune to the interference effects of other compounds of the test solution. Time to recover from a high TOC sample is not required in most instances, which permits faster TOC analysis and higher productivity. Typical run times for duplicate TOC analysis can be as little as 10 min, more than twice as fast as conductivity-based analyzers. This time savings can translate into faster cleaning validation of the manufacturing process and increased productivity.

Conclusion

TOC analysis is a quick and accurate screening technique. Understanding the differences in various types of TOC technology and choosing the best solution are the keys to achieving the benefits of this technique. The UV-persulfate oxidation technique with NDIR detection provides low sensitivity and high productivity and also filters out problematic interferences.

References

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