Application Note

Validating the TOC Method for Cleaning Validation Applications in the Pharmaceutical Industry

Pharmaceutical drug manufacturers looking for gains in quality and efficiency have led to a growing interest to use Sievers* Total Organic Carbon (TOC) Analyzers for cleaning validation. Most pharmaceutical or biotech facilities currently own a TOC analyzer for compendial USP water testing requirements to release purified water or water for injection for use in cleaning or production. Consequently, most facilities already have a means of determining TOC for cleaning validation.

TOC is a FDA-accepted[1] method that evaluates all the carbon-contributing compounds for a given sample, providing confidence that all equipment can be cleaned below the established cleaning criteria. TOC analysis allows development of one method that will detect the carbon concentration contributed by compounds, analytes or residues through direct (swab) or indirect (rinsate) sampling methods. Potential target residues include active pharmaceutical ingredients (APIs), product excipients, proteins, protein byproducts and cleaning agents or components.

In 1996, the ICH (International Conference on Harmonization), with the assistance of the FDA (CDER & CBER[2]), created the guidance document *Q2B; Validation of Analytical Procedures*. The intent of the document was to provide a direction for pharmaceutical companies to consider specific characteristics during the validation of analytical methods for cleaning validation applications. This Application Note echoes the Q2B guidance document by providing various examples pertaining to the following parameters as they relate to TOC method validation:

- Detection and quantitation limits
- Determination of accuracy and precision of the analyte
- Linearity and percent recovery verification
- Robustness of the analytical method[3]

Detection and Quantitation Limits

The limit of detection (LOD) is used to evaluate when a signal is a result of instrument noise or a response of the compound. The LOD is considered the lowest detectable amount of analyte in the sample, but not necessarily quantified with adequate statistical certainty.

The limit of quantitation (LOQ) is the value established to provide guidance on meaningful versus non-meaningful data. A response from the instrument below the LOQ indicates the presence of organics but does not quantify the actual concentration. Readings from the analyzer above the established LOQ are considered quantifiable, or meaningful data.

To determine concentration of background TOC and derive LOD and LOQ for a cleaning validation protocol, it is necessary to prepare low-TOC water blanks or swab blanks (if applicable) that account for the carbon contribution of the water and the vial used in the experiment. Once the standard deviation has been determined from these samples, it is customary to multiply the standard deviation by 3 and 10 to obtain LOD and LOQ, respectively.[4]

Determination of Accuracy and Precision of the Analyte

It is important to distinguish between accuracy and precision during TOC analytical method validation. Accuracy relates to how close the measurement of the analyte is to the true value. Typically, accuracy is derived from the percent difference (i.e. +7%) of a measured TOC concentration standard versus the expected concentration of a TOC standard during instrument validation.

Precision is measured as the standard deviation, or RSD (coefficient of variation). Precision relates to the closeness with which multiple analyses of a given sample agree with each other.

During TOC method validation, accuracy and precision can be determined by analyzing samples prepared (spiked) with a known concentration of the target residue, and evaluating the percent difference and RSD. The ICH documents recommend that accuracy and precision be assessed using a minimum of nine determinations over a minimum of three concentration levels covering the specified range for the instrument.[5]

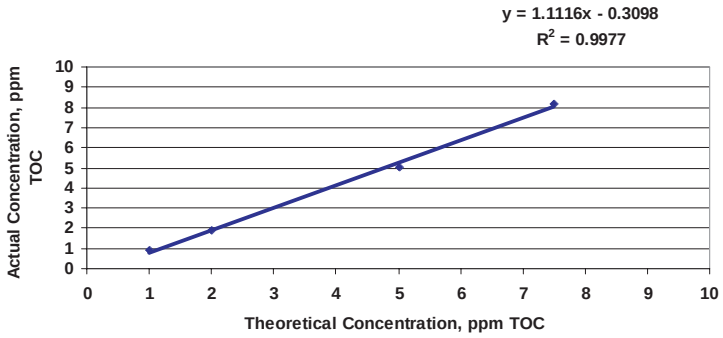

Figure 1. Linearity, BSA*

*Data obtained using Sievers 900 Laboratory TOC Analyzer

Linearity and Percent Recovery Verification

Typically, linearity tests verify that the instrument response has a linear relationship with the concentration of the analyte of interest. Figure 1 demonstrates the linear relationship of Bovine Serum Albumin (BSA) over a TOC concentration range from 1.00 ppm to 7.50 ppm, where vials containing low-TOC water were spiked with known concentrations of BSA. This example demonstrates the linear relationship between the theoretical concentration (x-axis) plotted against the observed concentration (y-axis), y = (m)x + b. The response of the analyzer should produce a correlation coefficient (R^2) greater than 0.97 for the compound of interest.

Table 1
Percent Recoveries Obtained from Coupon Surface (Analyst 1)*

Theoretical (ppm), C	Observed (ppm), C	Percent Recovery %	RSD (Precision) %
5.33	5.44	102.2	1.2
1.07	1.073	100.3	2.1
0.32	0.32	100.0	0.3

** Results courtesy of Steris Corporation with the use of a Sievers TOC Analyzer*[6]

Table 2
Percent Recoveries Obtained from Coupon Surface (Analyst 2)*

Theoretical (ppm), C	Observed (ppm), C	Percent Recovery %	RSD (Precision) %
5.05	5.11	101.3	2.0
1.03	1.070	105.8	2.1
0.29	0.32	104.9	1.9

** Results courtesy of Steris Corporation with the use of a Sievers TOC Analyzer*[6]

To determine suitability of the TOC method for analysis of the target residue, it is necessary to determine the level of recovery achievable by the analytical method. The following example demonstrates the direct sampling method technique by preparing a solution of known TOC concentration using CIP-100, and placing a known amount of the sample on a stainless steel coupon. As with the BSA example, three incrementally increasing concentrations of CIP-100 cleaning solution were spiked on the coupon, the coupon was swabbed and the swab was then placed in a known amount of low-TOC water. Table 1 provides results of the percent recoveries obtained from the surface of the coupon.

Robustness of the Analytical Method

Just as important as the actual recovery is the reproducibility or robustness of the TOC analytical method being used to determine the percent recovery of the compound of interest. Robustness is used during cleaning validation method development as a measurement of the method's capacity to remain unaffected by small but deliberate variations in the method parameters, or sample to sample variability. It also provides an indication of reliability during normal usage (e.g., sampling method from analyst to analyst). While a high recovery is desirable, it is equally, if not more important, that the recovery is reproducible in a consistent fashion and should be tested at length during method development studies. Tables 1 and 2 provide information on the CIP-100 swab recovery analysis performed by two different analysts testing the sample-to-sample variability.

Final Points to Consider

Test procedures for assessment of the quality levels of pharmaceutical products are subject to various requirements. Specific to cleaning validation, the current Good Manufacturing Practice regulations [21 CFR 211.194(a)] require that test methods, which are used for assessing compliance of pharmaceutical products with established specifications, must meet proper standards of accuracy and reliability.[7]

Also consider that validation of an analytical method is the process that establishes, by laboratory studies, that performance characteristics of the (TOC) method described in this application note meet certain requirements for the intended analytical applications such as compendial water release and cleaning validation.

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References

1. FDA Web Site: www.fda.gov/cder/guidance/cGMPs/equipment.htm.
2. CDER (Center for Drug Evaluation and Research) and CBER (Center for Biologics Evaluation and Research).
3. Guidance for industry *Q2B: Validation of Analytical Procedures.* Methodology. November 1996. ICH, FDA, CDER, CBER.
4. Taylor, John K. *Quality Assurance of Chemical Measurements.* Lewis Publishers imprint of CRC Press; 1987.
5. USP <1225> *Validation of Compendial Methods.*
6. *The Swab Recovery Determination of CIP-100 in Solutions by TOC Analysis Using a Sievers TOC Analyzer,* Steris Corporation Analytical Method; 1993.
7. 21 CFR 211.194(a) *Laboratory Records.*

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