Water Technologies & Solutions
application note

validating the TOC method for cleaning validation applications in the pharmaceutical industry

Pharmaceutical drug manufacturers can increase quality and efficiency using Total Organic Carbon (TOC) analysis for cleaning validation. As an accepted method for evaluating the carbon content of a given sample, TOC can provide confidence that equipment is cleaned below the established cleaning criteria. TOC analysis allows for development of a single method (after proper instrument qualification[1]) that can 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. As most pharmaceutical facilities currently use TOC for compendia USP water testing, they already have a means of determining TOC for cleaning validation.

The Q2B Validation of Analytical Procedures guidance document released by ICH [2] provides recommendations on how to consider various validation characteristics for analytical procedures. This provides a direction for pharmaceutical companies to consider during the validation of analytical methods for cleaning validation. This application note echoes the Q2B guidance by providing examples pertaining to the following parameters as they relate to TOC method validation:

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

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 study. Once the standard deviation is determined from these samples, it is customary to multiply the standard deviation by 3 and 10 to obtain LOD and LOQ, respectively.[3]

determination of accuracy and precision

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 of a measured TOC concentration versus the expected concentration of a TOC standard during instrument validation.

Precision is measured as the relative 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 known concentrations of target residues 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.[4]

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 and analyzed with a Sievers* Lab TOC Analyzer. The response of the analyzer should produce a correlation coefficient (R^2) greater than 0.97 for the compound of interest. **Figure 1** demonstrates the linearity of the Sievers Analyzer within this range (R^2 = 0.9977).

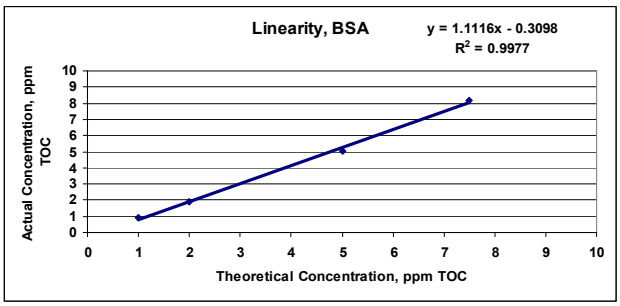

Figure 1. Data obtained using Sievers Lab TOC Analyzer

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. In the following example using direct sampling methods, a solution of known TOC concentration is prepared with CIP-100, and a known volume of the sample is placed on a stainless-steel coupon. As with the BSA example, three incrementally increasing concentrations of CIP-100 cleaning solution are spiked on the coupon, followed by swabbing and placing the swab in a known amount of low-TOC water. **Table 1** provides the percent recoveries obtained from the surface of the coupon[5].

Table 1. Percent recoveries from swab samples (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

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[5].

Table 2. Percent recoveries from swab samples (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

final points to consider

Test procedures for assessing pharmaceutical product quality 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.[6]

When validation TOC methods, it must be established by laboratory studies that performance characteristics meet certain requirements for the intended analytical applications such as compendial water release and cleaning validation. This application note provides examples using Sievers TOC Analyzers of how various parameters, including linearity, percent recovery, and precision, relate to TOC method validation for cleaning validation.

References

1. USP <1058> Analytical Instrument Qualification.
2. Guidance for Industry. Q2B Validation of Analytical Procedures: Methodology. November 1996. ICH, FDA, CDER, CBER.
3. Taylor, John K. Quality Assurance of Chemical Measurements. Lewis Publishers imprint of CRC Press; 1987.
4. USP <1225> Validation of Compendial Methods.
5. The Swab Recovery Determination of CIP-100 in Solutions by TOC Analysis Using a Sievers TOC Analyzer, Steris Corporation Analytical Method; 1993.
6. 21 CFR 211.194(a) Laboratory Records.