TOC for cleaning validation: swab recoveries of worst-case compounds (feasibility testing)

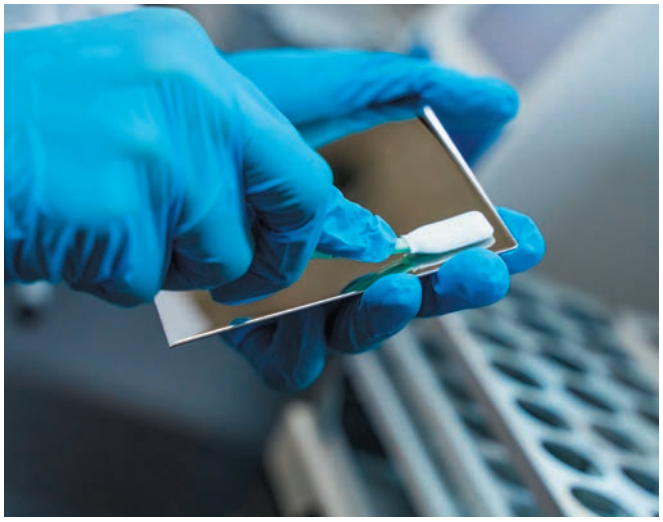
THE PARENTERAL Drug Association Technical Report No. 49 serves as a resource to help guide the development and evaluation of a cleaning validation programme. The report highlights that a cleaning validation programme should include elements of design, equipment qualification and continued verification, with key points to consider based on an understanding of the cleaning process itself. This includes understanding critical performance parameters (CPPs) such as temperature, time, cleaning agent concentration and analytical methods such as TOC analysis.

Although degradation is a key mechanism of a cleaning process, it affects various elements of cleaning validation. For example, after a cleaning process, the active pharmaceutical ingredient (API), protein, excipient or cleaning agent should not be present on cleaning surfaces. However, at times the CPPs may not be monitored or controlled properly, leading to residual compounds remaining on surfaces. In this case, a feasibility test using TOC swab recovery should be performed. As a nonspecific analytical method, TOC analysis provides information about residual APIs, detergents, degradants or other excipients that may be present. A specific analytical method for potential degradants is not usually an appropriate analytical technique to determine whether the cleaning process is effective.

The purpose of the feasibility test highlighted in this application note is to demonstrate the recovery capability of the TOC method under worst-case conditions (using low solubility compounds) or in the situation of a cleaning process design failure.

Materials for the feasibility study

- Stainless-steel coupons, washed with an alkaline cleaning agent, rinsed with low TOC water and allowed to dry
- Volumetric flasks, washed with an alkaline cleaning agent, rinsed with low TOC water and allowed to dry



- Low TOC swabs (part number HMI 90600)
- Low TOC vials, preferably Sievers certified pre-acidified (part number HMI 90090-01 or HMI 90690-01) or filled pre-acidified vials (part number HMI 90691-01)
- Volumetric pipettes
- Sievers TOC Analyzer.

Solubility determination procedure for the feasibility study

To minimise organic contamination, powder-free gloves were worn for the entire study. The solubility of each compound tested was determined empirically by adding the compounds to low TOC water. The mixtures were shaken, stirred and sonicated to help solubilise the compounds prior to analysis. After visual inspection of the flasks, the carbon concentrations of the stock solutions were calculated as shown below:

$$\frac{Mass\ of\ compound\ (in\ mg)}{Volume\ (in\ L)} \times \%\ C = ppm\ C$$

Percent carbon is derived from the empirical formula for the compound.

$$\%\ Carbon = \frac{Milligrams\ C}{Molecular\ weight}$$

For example, percent carbon for compound $C_{20}H_{22}N_4O_{12}S$ is:

$$\%\ Carbon = \frac{12 \times 20}{510.3} = 47\%\ Carbon$$

The stock solutions of the compounds can be found in **Table 1**. TOC stock solutions for compounds A and B were analysed directly from low-TOC vials and for the stock solutions of compounds C through F, a 10-fold dilution was made. The stock solutions were then used as 'spikes' on the clean coupons. Prior to the TOC analysis, each vial was acidified with phosphoric acid with a small aliquot to prevent any compounds sticking to the glass and affecting the results of the TOC recovery. If using pre-acidified vials, skip this step.

Note: to further increase efficiency and reduce chances of errors during swab testing, SUEZ now offers filled pre-acidified vials. These come with low TOC water and acid already added.

For this study, the following solutions were prepared:

- 1 vial of reagent water
- 1 vial of swab background (blank)
- 1 vial of coupon background (blank)
- 1 vial of each of the spike solutions (direct solubility controls – six total)
- 1 vial of each of the swab recovery solutions (direct sampling technique – six total).

Table 1

Results of swab recovery vials (feasibility study)

Reagent water (blank) 40ppb C					
Swab background (blank) 244ppb C					
Compound	**Compound class**	**Stock solutions Solubility in water (ppm C)**	**Control (ppm C)**	**Swab recovery (ppm C)**	**Percent recovery**
A	Steroid	17	0.557	0.773	99%
B	b-Lactam	25	0.821	0.976	94%
C	Sulfonamide	280	1.62	1.79	98%
D	Sulfonamide – HCl	150	1.03	1.20	97%
E	Pyrimidine	51	0.875	0.927	83%
F	Excipient	50	1.05	1.26	100%

TOC recovery study

The following descriptions highlight best practices for this type of recovery study and all vials were labelled appropriately:

Reagent water: a volumetric pipette was used to fill 15 pre-cleaned low-TOC vials with 40ml of low TOC water. After filling, each vial was immediately capped until further use.

Swab background: the swab blank was prepared by breaking off the tips of two swabs into the respective vial. Two swabs were further used for this study.

Coupon background: the coupon blank was prepared by swabbing a dry, but clean, stainless-steel coupon. The first swab used was wetted by low-TOC water from a clean glass beaker. The second swab was dry and was used to swab the coupon in an opposing pattern of the first swab.

Both swab tips were placed in the vial by breaking off the tips from the swab handle. Please note that these results should be very similar to the swab background results.

$$\%\ recovery = \frac{(TOC\ swab\ recovery\ solution - TOC\ background\ swab\ solution)}{(TOC\ spike\ solution - TOC\ reagent\ water)} \times 100$$

Example calculation (Compound A)

$$\%\ recovery = \frac{(0.773 - 0.244)}{(0.577 - 0.040)} \times 100\% = 99\%$$

Spike solutions (controls): the spike solutions were prepared by spiking an aliquot of stock solutions (aliquots ranged from 0.1–1.0ml) into low-TOC vials containing reagent water. For each compound, the selected aliquot made a final spike solution concentration of approximately 1ppm C, or the typical 'default' limit for TOC and cleaning validation.

Swab recovery solutions: to prepare the swab recovery solutions, the same aliquot of stock solution used to prepare the controls was placed onto a stainless-steel coupon. The solution was distributed evenly over a 10x10cm coupon surface area and the coupon was allowed to dry. Two swabs (one pre-moistened with low-TOC water) were used in succession to swab the surface of the coupon. The swab tips were then broken off into their respective vials. All vials were shaken vigorously before analysis.

TOC analysis: all vials were analysed using a Sievers TOC Analyzer with membrane conductometric technology, appropriately qualified per USP <1058> guidelines and validated for unique cleaning agents or surrogate compounds that are most common in the pharmaceutical or biopharmaceutical industries. The acid and oxidiser flow rates were optimised based on the concentrations of the compounds. The acid flow rates ranged from 0.2–1.0µl/min and the oxidiser flow rates ranged from 0.75–1.5µl/min. Four replicates were analysed from each vial. The first replicate of each vial was disregarded and the last three replicates were averaged.

These data were used to calculate percent recoveries based on the following equations. Results of the recovery tests are shown in **Table 1**.

Conclusion

The compounds tested were recovered successfully from stainless-steel coupons using swabbing techniques and TOC analysis. This study demonstrates the feasibility of using TOC analysis for cleaning validation applications.

Although compounds A through F are described in the Merck Index as "substantially insoluble" or "practically insoluble" in water, we have empirically determined that solubility at ambient temperature is in the parts per million (ppm) range and the compounds are indeed sufficiently soluble to be recovered using TOC analysis. This represents worst-case scenarios when designing a cleaning programme, especially in a situation where cleaning performance parameters are not met or not controlled.

For further information, visit:

www.sieversinstruments.com

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