

⟨643⟩ TOTAL ORGANIC CARBON

Total organic carbon (TOC) is an indirect measure of organic molecules present in pharmaceutical waters measured as carbon. Organic molecules are introduced into the water from the source water, from purification and distribution system materials, from biofilm growing in the system, and from the packaging of sterile and nonsterile waters. TOC can also be used as a process control attribute to monitor the performance of unit operations comprising the purification and distribution system. A TOC measurement is not a replacement test for endotoxin or microbiological control. Although there can be a qualitative relationship between a food source (TOC) and microbiological activity, there is no direct numerical correlation.

A number of acceptable methods exist for analyzing TOC. This chapter does not endorse, limit, or prevent any technologies from being used, but this chapter provides guidance on how to qualify these analytical technologies for use as well as guidance on how to interpret instrument results for use as a limit test.

Apparatuses commonly used to determine TOC in water for pharmaceutical use have in common the objective of oxidizing the organic molecules in the water to produce carbon dioxide followed by the measurement of the amount of carbon dioxide produced. Then the amount of CO₂ produced is determined and used to calculate the organic carbon concentration in the water.

All technologies must discriminate between the inorganic carbon, which may be present in the water from sources such as dissolved CO₂ and bicarbonate, and the CO₂ generated from the oxidation of organic molecules in the sample. The discrimination may be accomplished either by determining the inorganic carbon and subtracting it from the total carbon (total carbon is the sum of organic carbon and inorganic carbon), or by purging inorganic carbon from the sample before oxidation. Although purging may entrain organic molecules, such purgeable organic carbon is present in negligible quantities in water for pharmaceutical use.

BULK WATER

The following sections apply to tests for bulk *Purified Water*, *Water for Injection*, *Water for Hemodialysis*, and the condensate of *Pure Steam*.

Apparatus Requirements: This test method is performed either as an on-line test or as an off-line laboratory test using a calibrated instrument. The suitability of the apparatus must be periodically demonstrated as described below. In addition, it must have a manufacturer's specified limit of detection of 0.05 mg/L (0.05 ppm) or lower of carbon.

When testing water for quality control purposes, ensure that the instrument and its data are under appropriate control and that the sampling approaches and locations of both on-line and off-line measurements are representative of the quality of the water used. The nature of the water production, distribution, and use should be considered when selecting either on-line or off-line measurement.

USP Reference Standards ⟨11⟩: USP 1,4-Benzoquinone RS. USP Sucrose RS.

Reagent Water: Use water having a TOC level of not more than 0.10 mg/L. [NOTE—A conductivity requirement may be necessary in order to ensure method reliability.]

Container Preparation: Organic contamination of containers results in higher TOC values. Therefore, use labware and containers that have been scrupulously cleaned of organic residues. Any method that is effective in removing organic matter can be used (see *Cleaning Glass Apparatus* ⟨1051⟩). Use *Reagent Water* for the final rinse.

Standard Solution: Unless otherwise directed in the individual monograph, dissolve in the *Reagent Water* an accurately weighed quantity of USP Sucrose RS to obtain a solution having a concentration of 1.19 mg/L of sucrose (0.50 mg/L of carbon).

System Suitability Solution: Dissolve in *Reagent Water* an accurately weighed quantity of USP 1,4-Benzoquinone RS to obtain a solution having a concentration of 0.75 mg/L (0.50 mg/L of carbon).

Reagent Water Control: Use a suitable quantity of *Reagent Water* obtained at the same time as that used in the preparation of the *Standard Solution* and the *System Suitability Solution*.

Water Sample: Obtain an on-line or off-line sample that suitably reflects the quality of water used.

Other Control Solutions: Prepare appropriate reagent blank solutions or other specified solutions needed for establishing the apparatus baseline or for calibration adjustments following the manufacturer's instructions, and run the appropriate blanks to zero the instrument, if necessary.

System Suitability: Test the *Reagent Water Control* in the apparatus, and record the response, r_w . Repeat the test using the *Standard Solution*, and record the response, r_s . Calculate the corrected *Standard Solution* response, which is also the limit response, by subtracting the *Reagent Water Control* response from the response of the *Standard Solution*. The theoretical limit of 0.50 mg/L of carbon is equal to the corrected *Standard Solution* response, $r_s - r_w$. Test the *System Suitability Solution* in the apparatus, and record the response, r_{ss} . Calculate the corrected *System Suitability Solution* response by subtracting the *Reagent Water Control* response from the response of the *System Suitability Solution*, $r_{ss} - r_w$. Calculate the percent response efficiency for the *System Suitability Solution*:

$$\% \text{ response efficiency} = 100[(r_{ss} - r_w)/(r_s - r_w)]$$

where r_{SS} is the instrument response to the *System Suitability Solution*; r_W is the instrument response to the *Reagent Water Control*; and r_S is the instrument response to the *Standard Solution*. The system is suitable if the percent response efficiency is not less than 85% and not more than 115%.

Procedure: Perform the test on the *Water Sample*, and record the response, r_U . The *Water Sample* meets the requirements if r_U is not more than the limit response, $r_S - r_W$. This method can be performed using on-line or off-line instrumentation that meets the *Apparatus Requirements*.

STERILE WATER

The following sections apply to tests for *Sterile Water for Injection*, *Sterile Purified Water*, *Sterile Water for Irrigation*, and *Sterile Water for Inhalation*.

Follow the requirements in *Bulk Water*, with the following exceptions.

Apparatus Requirements: In addition to the *Apparatus Requirements* in *Bulk Water*, the apparatus must have a manufacturer's specified limit of detection of 0.10 mg/L (0.10 ppm) or lower of carbon.

Reagent Water: Use water having a TOC level of not more than 0.50 mg/L. [NOTE—A conductivity requirement may be necessary in order to ensure method reliability.]

Standard Solution: Unless otherwise directed in the individual monograph, dissolve in the *Reagent Water* an accurately weighed quantity of USP Sucrose RS to obtain a solution having a concentration of 19.0 mg/L of sucrose (8.0 mg/L of carbon).

System Suitability Solution: Dissolve in *Reagent Water* an accurately weighed quantity of USP 1,4-Benzoquinone RS to obtain a solution having a concentration of 12.0 mg/L (8.0 mg/L of carbon).

Water Sample: Obtain a sample that suitably reflects the quality of water used. Before opening, vigorously agitate the package to homogenize the water sample. Several packages may be required in order to collect sufficient water for analysis.

System Suitability: Test the *Reagent Water Control* in the apparatus, and record the response, r_W . Repeat the test using the *Standard Solution*, and record the response, r_S . Calculate the corrected *Standard Solution* response, which is also the limit response, by subtracting the *Reagent Water Control* response from the response of the *Standard Solution*. The theoretical limit of 8.0 mg/L of carbon is equal to the corrected *Standard Solution* response, $r_S - r_W$. Test the *System Suitability Solution* in the apparatus, and record the response, r_{SS} . Calculate the corrected *System Suitability Solution* response by subtracting the *Reagent Water Control* response from the response of the *System Suitability Solution*, $r_{SS} - r_W$. Calculate the percent response efficiency for the *System Suitability Solution*:

$$\% \text{ response efficiency} = 100[(r_{SS} - r_W)/(r_S - r_W)]$$

where r_{SS} is the instrument response to the *System Suitability Solution*; r_W is the instrument response to the *Reagent Water Control*; and r_S is the instrument response to the *Standard Solution*. The system is suitable if the percent response efficiency is not less than 85% and not more than 115%.

Procedure: Perform the test on the *Water Sample*, and record the response, r_U . The *Water Sample* meets the requirements if r_U is not more than the limit response, $r_S - r_W$, determined in the *System Suitability* requirements in *Sterile Water*.