2.4.30 Total Organic Carbon in Water

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Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

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Change **to**: ## 2.4.30. Total Organic Carbon in Water

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 also can 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 as well as 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 carbon dioxide 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 carbon dioxide and bicarbonate, and the carbon dioxide 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 (the sum of organic carbon and inorganic carbon), or by purging inorganic carbon from the sample before oxidation. Although purging may entrain volatile organic molecules, such purgeable organic carbon is present in negligible quantities in water for pharmaceutical use.

Procedures

1. Bulk Water

The following sections apply to tests for bulk *purified water* and *water for injections.*

Instrumentation 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 instrument must be periodically demonstrated as described below. In addition, it must have a manufacturer's specified limit of detection of 0.05 mg per litre (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 water purification process, distribution, and use should be considered when selecting either on-line or off-line measurement.

Reagent water. Use water with a TOC level of not more than 0.10 mg per litre. (*NOTE — A conductivity requirement may be necessary to ensure method reliability*).

Container preparation. Organic contamination of labware and sample containers results in higher TOC values. Therefore, use labware and containers that have been carefully cleaned of organic residues. Any method that is effective in removing organic matter can be used. Use reagent water for the final rinse.

System suitability solution. Dissolve an accurately weighed quantity of *1,4-benzoquinone IPRS* in reagent water to obtain a solution having a concentration of 0.75 mg per litre (0.50 mg per litre of carbon).

Reference solution. Unless otherwise directed in the individual monograph, dissolve an accurately weighed quantity of *sucrose IPRS* in the reagent water to obtain a solution having a concentration of 1.19 mg per litre of sucrose (0.50 mg per litre of carbon).

Reagent water control. Use a suitable quantity of reagent water obtained at the same time as those used in the preparations of the reference 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.

Limit response. Measure the TOC of the reagent water control in the instrument, and record the response (r_w). Also measure the TOC of the reference solution in the instrument, and record the response (r_S). Calculate the corrected reference solution response, which is also the limit response (r_L), for the contribution from the reagent water, by subtracting the reagent water control response from the reference solution response:

$$r_L = r_S - r_W$$

r_S = instrument response to the reference solution
r_W = instrument response to the reagent water control

The limit response (r_L) of 0.50 mg per litre of carbon will be equal to this corrected reference solution response.

System suitability. Measure the TOC of the system suitability solution in the instrument, and record the response (r_{SS}).

Calculate the corrected system suitability solution response (r_C) by subtracting the reagent water control response from the system suitability solution response:

$$r_C = r_{SS} - r_W$$

r_{SS} = instrument response to the system suitability solution
r_W = instrument response to the reagent water control

Calculate the percent response efficiency (r_E):

$$r_E = 100 \times (r_C / r_L)$$

r_C = corrected instrument response to the system suitability solution
r_L = corrected instrument response to the reference solution (also known as the limit response)

The TOC measuring system is suitable if the percent response efficiency (r_E) is not less than 85 per cent and not more than 115 per cent. The suitability of the instrument must be periodically demonstrated.

Procedure. Measure the TOC of the water sample and record the response (r_U). The water sample meets the requirements if r_U is not more than r_L. This method can be performed using on-line or off-line instrumentation that meets the instrumentation requirements.

2. Sterile Water

The following sections apply to tests for *sterile water for injections* and *sterile water for inhalation*. The sterile waters are derived from *purified water* or *water for injections*, and therefore have been determined to be compliant with the Bulk Water requirements before being stored and sterilized in the container.

Follow the requirements for container preparation and other control solutions as described under Bulk Water. Prepare the reference solution and the system suitability solution that correspond to the limit response for the volume of the container being tested as specified in Table 1 and as described in steps 2 and 4 in procedure.

Table 1 – TOC limit based on container volume

Nominal Container Volume (ml)	Limit 1 (L1) (mg per litre of carbon)	Limit 2 (L2)* (mg per litre of carbon)
≤ 5	32.00	48.00
> 5 and ≤ 100	24.00	36.00
> 100	8.00	12.00

*Limit 2 concentrations are utilized to determine the system suitability requirements for the container volume being tested.

Instrument requirements. The suitability of the instrument must be periodically demonstrated as described below. In addition, it must have a manufacturer's specified limit of detection of 0.10 mg per litre (0.10 ppm) or lower of carbon.

Reagent water. Use water with a TOC level of not more than 0.50 mg per litre. (*NOTE — A conductivity requirement may be necessary to ensure method reliability*).

System suitability solution. Dissolve an accurately weighed quantity of *1,4-benzoquinone IPRS* in reagent water to obtain a solution with a concentration that corresponds to the container volume being tested, as specified in Table 2:

Table 2 – System suitability solution based on container volume

Nominal Container Volume (ml)	1,4-Benzoquinone (mg per litre)	Equivalent Carbon Concentration (mg per litre of carbon)
≤ 5	72.00	48.00
> 5 and ≤ 100	54.00	36.00
> 100	18.00	12.00

Reference solution. Unless otherwise directed in the individual monograph, dissolve an accurately weighed quantity of *sucrose IPRS* in the reagent water to obtain a solution with a concentration that corresponds to the reference solution, measured for the container volume being tested, as specified in Table 3:

Table 3 – Reference solution based on container volume

	Limit 1 (L1)		Limit 2 (L2)	
Nominal Container Volume (ml)	Sucrose Concentration (mg per litre)	Equivalent Carbon Concentration (mg per litre of carbon)	Sucrose Concentration (mg per litre)	Equivalent Carbon Concentration (mg per litre of carbon)
≤ 5	76.00	32.00	114.00	48.00
> 5 and ≤ 100	57.00	24.00	85.50	36.00
> 100	19.00	8.00	28.50	12.00

Reagent water control. Use a suitable quantity of reagent water obtained at the same time as those used in the preparations of the reference solution and the system suitability solution.

Water sample. Obtain water samples that suitably reflect the quality of the sterile water batch being tested. (*NOTE—See Container preparation under Bulk Water*) Before opening the water packages to remove water samples for analysis, vigorously agitate the packages to homogenize any TOC residues that may be present in packages. For small packages, several packages may be required in order to collect a sufficient water volume for analysis. Otherwise test water samples individually.

Limit response. Measure the TOC of the reagent water control and record the response (r_W). Also measure the TOC of the reference solution prepared at concentrations corresponding to the appropriate Limit 1, and, if required for step 4 in procedure, Limit 2 values from Table 1 for the container volume being tested. The values in this table are the TOC limits based on container volume. Finally, record the instrument response to each of the reference solutions for Limit 1 (r_{S1}) and, if required, Limit 2 (r_{S2}) from Table 1.

Calculate the corrected instrument response to the reference solutions prepared at the Limit 1 (r_{L1}) or Limit 2 (r_{L2}) concentrations, as appropriate, by subtracting the reagent water control response (r_W) from the Limit 1 reference solution response (r_{S1}) and, if required, the Limit 2 reference solution response (r_{S2}):

$$r_{L1} = r_{S1} - r_W$$

and if required:

$$r_{L2} = r_{S2} - r_W$$

r_{S1} = instrument response to the Limit 1 reference solution

r_{S2} = instrument response to the Limit 2 reference solution
r_W = instrument response to the reagent water control

System suitability. Prepare the reference solution at the TOC concentrations corresponding to the Limit 2 in Table 3 for the container volume being tested. Prepare the system suitability solution according to Table 2 for the container volume being tested. Measure the TOC of the reagent water control in the instrument, and record the response (r_W). Measure the TOC of the reference solution, and record the response (r_S). Calculate the corrected reference solution response ($r_S - r_W$), by subtracting the reagent water control response (r_W) from the reference solution response (r_S). Measure the TOC of the system suitability solution in the instrument, and record the response (r_{SS}). Calculate the corrected system suitability solution response ($r_{SS} - r_W$) by subtracting the reagent water control response (r_W) from the system suitability solution response (r_{SS}).

Calculate the per cent response efficiency (r_E):

$$r_E = 100 \times [(r_{SS} - r_W)/(r_S - r_W)]$$

r_{SS} = instrument response to the system suitability solution
r_w = instrument response to the reagent water control
r_s = instrument response to the reference solution

The system is suitable if the per cent response efficiency is not less than 85 per cent and not more than 115 per cent. The suitability of the instrument must be periodically demonstrated.

Procedure

1. Measure the TOC of the water sample and record the response (r_U).
2. Compare the r_U to the corrected instrument response (r_{L1}) for Limit 1 [see limit response] for the appropriate nominal container volume.
3. If r_U is not more than r_{L1}, then the water sample meets the requirements and the test is completed.
4. If r_U is more than r_{L1}, then compare r_U from step 1 to r_{L2} for the appropriate nominal container volume.
5. If r_U is more than r_{L2}, then the water sample does not meet the requirements and the test is completed.
6. If r_U is more than r_{L1} but not more than r_{L2}, then use suitable analytical procedures appropriate for the intended use to identify and quantify each individual organic impurity exceeding a concentration of 0.20 mg per litre of carbon.
7. If there are no individual impurities that exceed 0.20 mg per litre of carbon, then the water sample meets requirements and the test is completed.
8. If there are individual impurities that exceed 0.20 mg per litre of carbon, then evaluate them for safety at the concentrations found in this testing.
9. If the evaluation of the organic impurities is deemed safe, then the water sample meets the requirements and the test is completed.
10. If the evaluation of the organic impurities is deemed to impact patient safety, then the water sample does not meet the requirements and the test is completed.