# Total Organic Carbon Analysis for Purified Water and Water for Injection

## Application Note


## Abstract

In pharmaceuticals, water, specifically Purified Water (PW) and Water for Intravenous Injection (WFI), is vital for drug preparation. Producing and ensuring the cleanliness of this water entails very strict quality control and precise analytical testing methods. The United States Pharmacopeia (USP) and Japanese Pharmacopeia (JP) have promoted Total Organic Carbon (TOC) analysis as the procedure to verify PW and WFI are free of TOCs and therefore able to be used for pharmaceutical purposes. A TOC system is considered suitable, under the USP, if it can recover 90% of a 0.5mgC/L system suitability standard, 1,4-benzoquinone. The JP requirement uses a dodecylbenzenesulfonic acid standard with a 90% recovery criterion.

This application note will present data following these strict criteria. In addition, this study will verify the suitability of Teledyne Tekmar's TOC Analyzer (Figure 1) for analysis of TOC at 0.05 mgC/mL, as opposed to the current standard of 0.5 mgC/L.


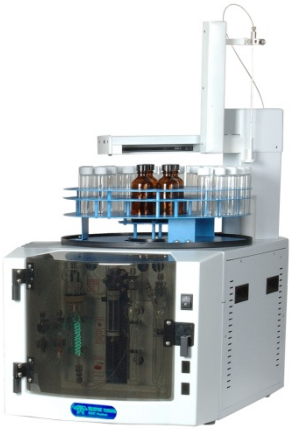

Figure 1. Teledyne Tekmar's Fusion TOC Analyzer

## Introduction

In pharmaceuticals, water, specifically Purified Water (PW) and Water for Intravenous Injection (WFI) is vital for the preparation of intravenous drugs. Since these medications are normally introduced directly into the bloodstream, the reagents used to make them need to be as clean as possible. The United Stated Pharmacopeia (USP) and Japanese Pharmacopeia (JP) lay out strict regulations that mandate that PW and WFI are free of Total Organic Carbon (TOC) to be used for pharmaceutical applications. These methods also demand extremely sensitive instruments to detect TOC at the levels they require.

The JP test method for TOC specifies, "The instrument should be capable of measuring the amount of organic carbon down to 0.050 mgC/L."[1] Also, the system should be capable of generating not less than 0.450 mgC/L when using a 0.806 mg/L solution of dodecylbenzenesulfonic acid as a sample. This solution has a carbon concentration of 0.500 mgC/L and the JP method specifies that the instrument must be capable of oxidizing 90% (0.450 mgC/L) of this solution as a measured sample.




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This application note will show the capability of the Teledyne Tekmar Fusion TOC analyzer of meeting these two requirements set forth in Japanese Pharmacopeia test method for total organic carbon.

## Experimental-Instrument Conditions

For this study, analysis was performed on the Teledyne Tekmar Fusion, a UV/Persulfate TOC Analyzer using the default Japanese Pharmacopeia method (Table 1).

| General Parameter | Value | Advanced Parameter | Value |
|---|---|---|---|
| Sample Volume | 9.0 mL | Needle Rinse Volume | 5.0 mL |
| Dilution | 1:1 | Vial Prime Volume | 2.0 mL |
| Acid Volume | 0.1 mL | IC Sample Prime Volume | 2.0 mL |
| Reagent Volume | 0.6 mL | IC Sparge Rinse Volume | 5.0 mL |
| UV Reactor Pre-rinse | Off | Baseline Stabilize Time | 1.60 min |
| UV Reactor Pre-rinse Volume | 0.0mL | Detector Pressure Flow | 300.0 mL/min |
| Number of UV Reactor Pre-rinse | 1 | Syringe Speed Waste | 10 |
| IC Sparge Time | 0.50 min | Syringe Speed Acid | 7 |
| Detector Sweep Flow | 500.0 mL/min | Syringe Speed Reagent | 7 |
| Pre-Sparge Time | 0.0 min | Syringe Speed DI Water | 7 |
| System Flow | 500.0 mL/min | NDIR Pressurization | 50 psig |
| | | Syringe Speed Sample Dispense | 7 |
| | | Syringe Speed Sample Aspirate | 4 |
| | | Syringe Speed UV Dispense | 7 |
| | | Syringe Speed UV Aspirate | 5 |
| | | Syringe Speed IC Dispense | 5 |
| | | Syringe Speed IC Aspirate | 5 |
| | | NDIR Pressure Stabilize | 1.75 min |
| | | Sample Mixing | Off |
| | | Sample Mixing Cycles | 1 |
| | | Sample Mixing Volume | 10.0 |
| | | Low Level Filter NDIR | Off |

*Table 1: Fusion Japanese Pharmacopeia Method Parameters*

## Sample Preparation

KHP (Potassium Hydrogen Phthalate) and dodecylbenzenesulfonic acid were used as sources of TOC. A stock solution of KHP was prepared at 1000 mgC/L in a 1 L volumetric flask. From this KHP stock solution, serial dilutions were made to prepare 0.500 mgC/L and 5.00 mgC/L working solutions. A 50 mgC/L stock solution of dodecylbenzenesulfonic acid was prepared by dissolving 80.6 mg/L of dodecylbenzenesulfonic acid into deionized water. A 0.500 mgC/L working solution was prepared by diluting this stock.

## Results

### A. Recovery of Dodecylbenzenesulfonic Acid

The Japanese Pharmacopeia mandates that the system "should be capable of generating not less than 0.450 mg/L of carbon when using the dodecylbenzenesulfonic acid as the sample."[1] The Fusion TOC analyzer was calibrated using a 5.00 mgC/L KHP stock solution utilizing the auto-dilution feature. The regression factor ($r^2$) for the curve was determined to be 0.9995 over a calibration range of 0.050-2.50 mgC/L. Figure 2 illustrates the calibration curve developed for this study. A sample of dodecylbenzenesulfonic acid with a carbon concentration of 0.500 mgC/L was analyzed as a sample. The results from this analysis can be seen in Table 2.



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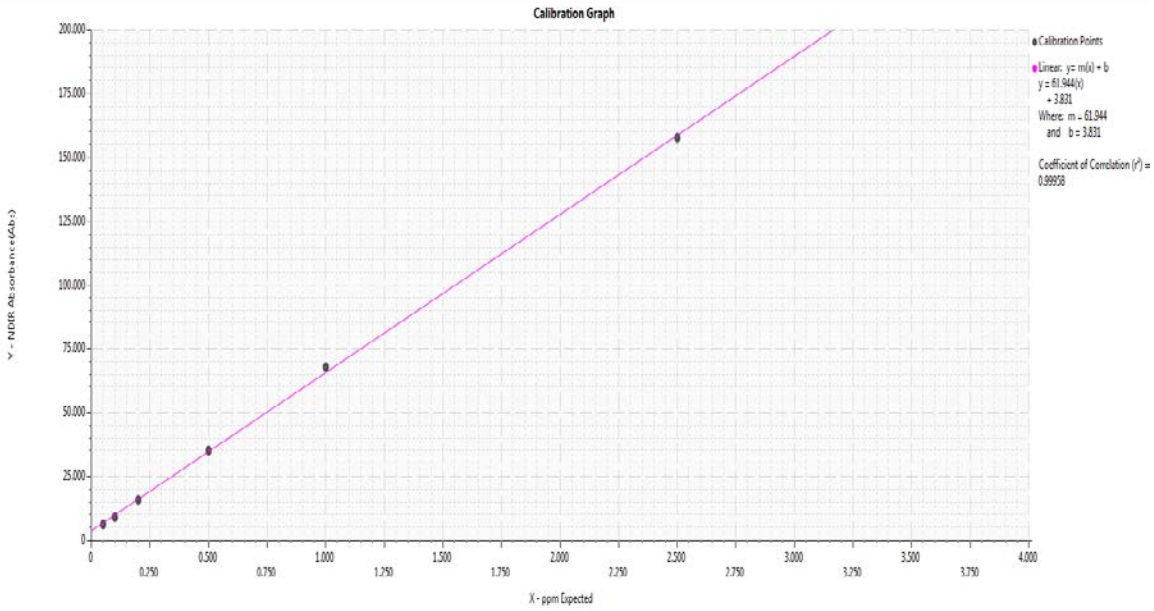


*Figure 1: TOC Calibration curve for the Dodecylbenzenesulfonic Recovery Test*

| Sample Name | Concentration (mgC/L ) | Std. Dev. (mgC/L) | %RSD |
|---|---|---|---|
| dodecylbenzenesulfonic acid with a carbon concentration of 0.500mg/L* | 0.503mg/L | 0.009 | 1.85 |
| dodecylbenzenesulfonic acid with a carbon concentration of 0.500mg/L* | 0.504mg/L | 0.012 | 2.50 |

*Table 2: TOC data for 0.500 mgC/L dodecylbenzenesulfonic acid. *n=2*

The analysis preformed on dodecylbenzenesulfonic acid with a carbon concentration of 0.500mgC/L had a recovery of 100.6%. This satisfies the 90% recovery criteria that is set forth in the total organic carbon test method for the Japanese Pharmacopeia.

## B. TOC Detection Below 0.050mg/L

The Japanese Pharmacopeia also indicates “The instrument should be capable of measuring the amount of organic carbon down to 0.050 mgC/L.”[1] For this analysis, the Fusion was calibrated using a stock KHP solution of 0.500 mg/L of carbon utilizing the auto-dilution feature. The regression factor ($r^2$) for the calibration curve (Figure 3) was determined to be 0.9995 over a range of 0 to 0.500mgC/L. A set of check standards were analyzed at 0.050 and 0.125 mgC/L to simulate the low level that is required by the JP TOC Method. The results for these check standards are found in Table 3.



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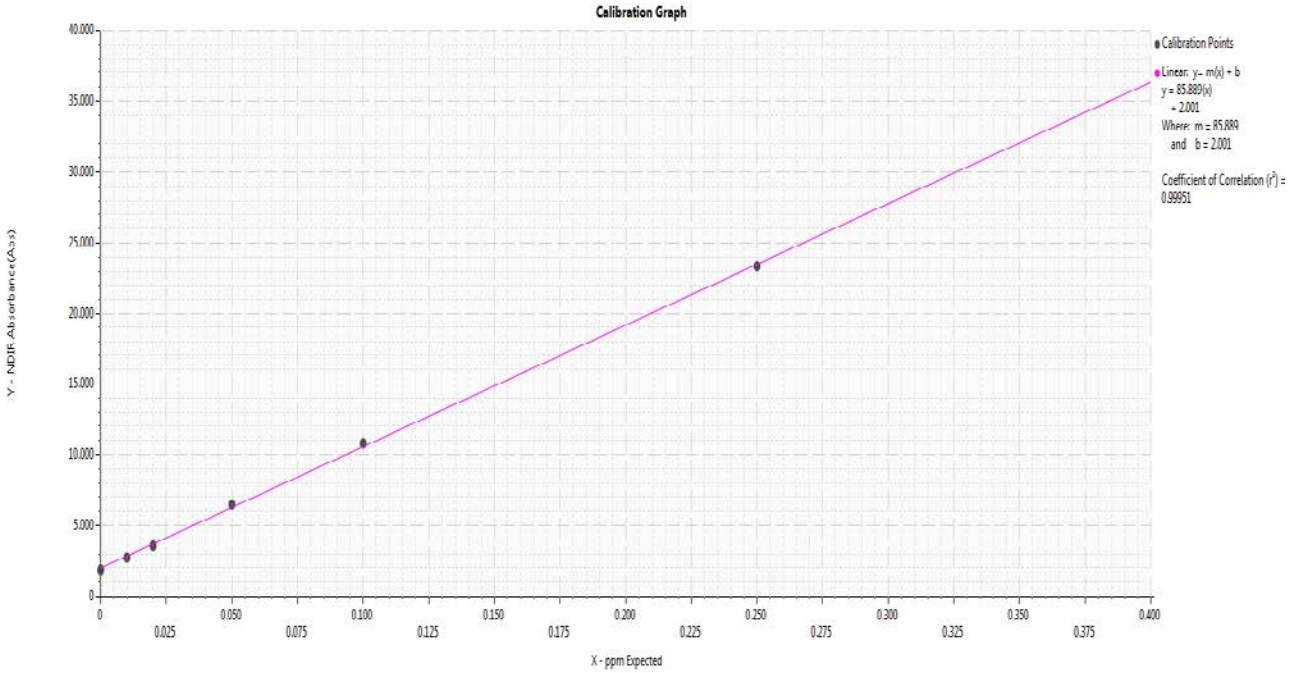


*Figure 3: Calibration curve for the low level TOC analysis*

| Sample Name | Concentration (mgC/L ) | Std. Dev. (mgC/L) | %RSD |
|---|---|---|---|
| Check Sample 0.050mg/L of Carbon | 0.0503mg/L | 0.0007 | 1.35 |
| Check Sample 0.050mg/L of Carbon | 0.0515mg/L | 0.0023 | 4.39 |
| Check Sample 0.125mg/L of Carbon | 0.1248mg/L | 0.0018 | 1.43 |
| Check Sample 0.125mg/L of Carbon | 0.1276mg/L | 0.0025 | 1.99 |

*Table 3: Data for the low level TOC analysis*

The results of this low level analysis meet the method criteria of accurately measuring the amount of organic carbon down to 0.050 mgC/L. Even at such a low level, the samples show excellent reproducibility as evident by the low %RSDs (1.35 to 4.39%). Since these samples were ran as a check standards, the Fusion software automatically subtracts the blank contribution of carbon that is present in the system and deionized water. The data listed in Table 3 satisfies the criteria set forth in the total organic carbon test method for the Japanese Pharmacopeia.



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## Conclusions

When dealing with pharmaceuticals, specifically Purified Water (PW) and Water for Intravenous Injection (WFI) the implications on human health require very strict regulation. One of the methods of determining the cleanliness of these reagents is total organic carbon testing. Both the USP and JP lay out detailed guidelines that must be followed, with the main difference being the system suitability test material. For the JP method, the TOC instrument must be capable of recovering 90% of a 0.500 mg/L carbon sample of dodecylbenzenesulfonic acid. The Fusion met and exceeded these criteria, recovering 100.6% of the 0.500 mgC/L sample of dodecylbenzenesulfonic acid. The second part of the JP TOC system suitability states that the system must be able to measure a carbon sample down to 0.050mgC/L. Data presented using the Fusion also met this criteria, with accurate and reproducible results, even at low levels. This study demonstrates the suitability of Teledyne Tekmar's Fusion TOC Analyzer for this analysis by meeting and surpassing all method performance criteria.

## References


1. Japanese Pharmacopeia General Test/ Test for Total Organic Carbon pg.93-95
2. U.S. Pharmacopeia General Chapter <643> Total Organic Carbon. www.usp.org




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