European Pharmacopeia (EP) 2.2.44 using the Teledyne Tekmar Fusion UV/Persulfate TOC Analyzer

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Abstract

European Pharmacopeia (EP) Method 2.2.44 "Total Organic Carbon in Water for Pharmaceutical Use" provides method and technique guidelines to the Pharmaceutical industry. These guidelines help to qualify the TOC analysis system through a System Suitability Test that compares the recovery of a Standard Solution (r_s) of 0.500 ppmC sucrose (a relatively easy compound to oxidize) to a System Suitability Solution (r_{ss}) of 0.500 ppmC 1,4-benzoquinone (a difficult to oxidize compound). The response of Reagent Water (r_w) must be less than 100 ppbC and is subtracted from each of these solutions' responses to yield a corrected response. The corrected responses are then compared and must be within 15% of each other to confirm the system will thoroughly oxidize organic carbon compounds with differing affinities for oxidation. The Response Efficiency must meet the 85% - 115% requirement using the equation in Figure 1.

Figure 1 Formula Used to Calculate the Response Efficiency per EP 2.2.44

$$\text{Response Efficiency} = \frac{r_{SS}-r_W}{r_S-r_W} \times 100$$

Introduction

The Fusion UV/Persulfate TOC analyzer is Teledyne Tekmar's most sensitive and accurate Total Organic Carbon (TOC) analyzer. Its ability to achieve quantitative low ppb levels makes it ideal for clean pharmaceutical sample matrices such as purified water (PW), water-for-injection (WFI) and cleaning validation (CV). The Fusion was purposely designed to achieve the 100 - 500 ppb range needed to calculate the Response Efficiency specified in EP 2.2.44. Additionally, the Fusion TOC TekLink software includes numerous features for 21 CFR 11 compliance including electronic signatures, auto-archiving and of authority checks. The software streamlines analytical workflow with features such as auto-calibration and built in System Suitability Check Standards that are tailored to pharmaceutical applications.

Sample Preparation

A 5.000 ppmC Calibration Stock Standard was made from potassium hydrogen phthalate (KHP) according to the procedure in the *Fusion User Manual*. The Fusion's auto-calibration feature was then used to automatically dilute the stock standard to create a calibration curve consisting of 0.100, 0.250, 0.500, 1.000 and 2.500 ppmC calibration standards; greatly reducing standard preparation time, and eliminating human error.

System Suitability Standards of 0.500 ppmC sucrose, 0.500 ppmC 1,4-benzoquinone were prepared according to EP 2.2.44 guidelines. All samples and standards were run in triplicate to demonstrate the instrument's precision.

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Experimental Instrument Conditions

The TOC TekLink software's default TOC Pharmaceutical Method was modified for method optimization. All calibration and system suitability standards were analyzed using the Fusion method parameters shown in Table I and Table II.

Table I EP 2.2.44 Fusion General Method Parameters

Parameter	Value
Sample Volume	9.0 mL
Dilution	1:1*
Acid Volume	0.5 mL
Reagent Volume	0.6 mL
UV Reactor Prerinse	On
UV Reactor Prerinse Volume	10.0
Number of UV Reactor Prerinses	1
IC Sparge Time	0.50 mins
Detector Sweep Flow	500 mL/min
Presparge Time	0.20 mins
System Flow	500 mL/min
* This parameter can range from 1:1 to 1:200. A 1:1 dilution ratio is 1 part sample and 0 parts DI water (not 50% sample/50% DI water).	

Table II EP 2.2.44 Fusion Advanced Method Parameters

Advanced Parameter	Value
Needle Rinse Volume	5.0 mL
Vial Prime Volume	2.0 mL
IC Sample Prime Volume	2.0 mL
IC Sparge Rinse Volume	5.0 mL
Baseline Stabilization Time	0.50 min
Detector Pressure Flow	300 mL/min
Syringe Speed Waste	10
Syringe Speed Acid	7
Syringe Speed Reagent	7
Syringe Speed DI Water	7
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	7
Syringe Speed IC Aspirate	5
NDIR Pressure Stabilize	1.75 min
Sample Mixing	Off
Low Level Filter NDIR	Off

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Results

Calibration Results

The 5-point, 0.100 - 2.500 ppmC calibration curve exhibited a generally accepted laboratory standard linearity greater than 0.999, at .99983. The %RSDs were all less than 4%.

Figure 2 Calibration Results

Calibrations

Name: TOC Pharmaceutical Water (TOC)

Version:	v16	Calibration curve formula:	TOC: y = 61.553x + 3.832
Ver Creation:	2020/03/20 08:18	r^2 value:	TOC: r^2 = 0.99983
Comment:			
Operator:	Joy (Joy)		
Basic Analysis Type	TOC		

Basic Analysis Type: TOC

Sample ID	Y Raw Value	X Expected	Message	End Time
0.100 ppm	10.9800	0.1000		2020/03/19 14:40
0.250 ppm	19.1137	0.2500		2020/03/19 15:04
0.500 ppm	33.3997	0.5000		2020/03/19 15:28
1.000 ppm	65.5693	1.0000		2020/03/19 15:52
2.500 ppm	157.8540	2.5000		2020/03/19 16:16

Sample Type: Calibration Standard: EP 2.2.44 (Creating calibration TOC Pharmaceutical Water v15 r1)

Pos	BAT	Concentration (ppm)	STD Conc	Dil	Sample ID	Result (Abs)	Std. Dev. (Abs)	RSD
A	TOC	0.1000	5 ppmC	1:50	[TOC] EP 2.2.44 [0.100 ppm]	10.9800	0.3961	3.61%
A	TOC	0.2500	5 ppmC	1:20	[TOC] EP 2.2.44 [0.250 ppm]	19.1137	0.3378	1.77%
A	TOC	0.5000	5 ppmC	1:10	[TOC] EP 2.2.44 [0.500 ppm]	33.3997	0.4056	1.21%
A	TOC	1.0000	5 ppmC	1:5	[TOC] EP 2.2.44 [1.000 ppm]	65.5693	0.3849	0.59%
A	TOC	2.5000	5 ppmC	1:2	[TOC] EP 2.2.44 [2.500 ppm]	157.8540	3.7627	2.38%

System Suitability Results

0.500 ppmC Sucrose and 1,4-benzoquinone System Suitability Standards were prepared according to EP 2.2.44 guidelines. To pass EP 2.2.44, the reagent water must be less than 0.100 ppmC and the sucrose and 1,4-benzoquinone standards must have a response efficiency within 85 - 115% of each other, using the equation shown in Figure 1. The response efficiency confirms how closely a difficult to oxidize compound and easy to oxidize compound respond in the system. Ideally, response efficiency between the two should be as close as possible. As shown in Figure 3, the Fusion TOC TekLink software report calculates Response Efficiency and identifies passing and failed standards to remove the possibility of human error and expedite workflow.

Figure 3 TOC TekLink Report Showing System Suitability Results and Automated software Calculations

Sample Type: System Suitability — From Schedule Version 2

Pos	System Suitability Sample Type	Sample ID	Result	Std. Dev.	RSD	Start Time
D	Reagent Water	[ReagentWater] USP 643 / EP 2.2.44 [Reagent Water]	0.0403 ppm (PASS)	0.0011 ppm	2.65%	2020/03/20 10:08
B	Standard Solution	[StandardSolution] USP 643 / EP 2.2.44 [Sucrose (500 ppb)]	0.5660 ppm	0.0120 ppm	2.11%	2020/03/20 10:32
C	Suitability Solution	[SuitabilitySolution] USP 643 / EP 2.2.44 [1,4-Benzoquinone (500 ppb)]	0.5429 ppm	0.0098 ppm	1.81%	2020/03/20 10:56

Response Efficiency: 95.61%
(Acceptance Criteria 85% to 115%)

Limit Response (Ru): 525.7 ppb

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To demonstrate that the Fusion TOC TekLink software calculated the Response Efficiency correctly according to EP 2.2.44, a manual calculation was performed:

$$\text{Response Efficiency} = \frac{r_{SS}-r_W}{r_S-r_W} \times 100$$

$$\text{Response Efficiency} = \frac{(0.5429-0.0403)}{(0.5669-0.0403)} \times 100$$

Response Efficiency = 95.605%

The result for 1,4 Benzoquinone less reagent water (r_{ss}- r_w) is 0.5026, which is 100.52% accurate.

The result for Sucrose less reagent water (r_s- r_w) is 0.5266, which is 105.32% accurate.

Conclusion

The Teledyne Tekmar Fusion UV/Persulfate TOC analyzer successfully performed the System Suitability Test according to EP 2.2.44. The difficult to oxidize, 1,4- benzoquinone and easy to oxidize, sucrose, had a Response Efficiency of 95.61%, falling easily within the 85% - 115% mandatory requirement. The Fusion TOC TekLink software System Suitability function correctly calculated the EP 2.2.44 Response Efficiency. The software's auto-calibration and System Suitability Check Standard features resulted in a highly-efficient analytical process. Lastly, the software's 21 CFR 11 compliance tools enforced user-account management and audit trails to support required pharmaceutical regulations.

References

1. European Pharmacopoeia 5.0. Chapter 2 Methods of Analysis. 2.2.44. Total Organic Carbon in Water for Pharmaceutical Use. Pg. 68.

See how the Teledyne Tekmar Fusion UV/Persulfate Analyzer can help you comply with pharmaceutical or environmental standards! Contact a sales representative at 1.800.874.2004 or visit http://www.teledynetekmar.com/contact/sales-contacts. See genuine customer reviews of the Fusion UV/Persulfate TOC analyzer at http://www.selectscience.net.

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