TELEDYNE TEKMAR
Everywhereyoulook™

Pharmaceuticals

Applications for TOC and VOC Analysis

Today's pharmaceutical laboratories are tasked with providing a wide array of analytical analyses for every stage of the production process, from ensuring the cleanliness of process equipment and raw ingredients to quality control analysis of finished products. With ever increasing demands for higher production at lower costs, laboratories need equipment that they can rely on to perform reliably and with low maintenance costs.

Teledyne Tekmar is an industry leader in analytical instrumentation manufacturing. We provide TOC and VOC solutions for laboratories of all sizes and budgets. We offer a full suite of 21 CFR 11 compliance tools, and application notes geared toward United States Pharmacopoeia, European Pharmacopoeia and Japanese Pharmacopoeia methods for TOC and VOC methodologies. For all of your TOC and VOC needs, look no further than Teledyne Tekmar.

Total Organic Carbon

The Pharmaceutical Industry's Need for Total Organic Carbon Analysis

Clean-in-place or **cleaning validation** procedures verify that equipment used to manufacture pharmaceuticals is clean prior to making the next batch. Total Organic Carbon (TOC) is a great "catch all" for major manufacturing contaminates because cross-contamination from previous batches, cleaning agents, foreign materials (paint, hair, building materials), and bacteria all contain carbon.

Purified Water (PW) and **Water for Intravenous Injection (WFI)**, is vital for drug preparation. The water for these applications must be in the ppb or even sub-ppb carbon range. Producing and ensuring the cleanliness of this water entails very strict quality control and precise analytical testing methods.

The United States Pharmacopeia (USP) European Pharmacopeia (EP) and Japanese Pharmacopeia (JP) have promoted TOC analysis as the procedure to verify that Cleaning Validation, PW and WFI meet the high standards of the pharmaceutical industry.

TOC Technique Selection

Membrane Conductivity

The Conductivity method measures the conductivity of the sample before and after oxidation. The sample, once oxidized, forms dissolved carbon dioxide (CO_2) which acts as a weak acid and changes the conductivity of the sample. The difference in conductivity is then correlated to a concentration of TOC. In newer designs, membranes were added to improve the accuracy of the conductivity measurement. A hydrophobic gas permeation membrane allows for greater discrimination for dissolved CO_2 over other chemical compounds.

Chemical Oxidation

UV Persulfate (UVP) systems transfer a sample aliquot to a UV reactor where oxidation is achieved through the combination of a chemical oxidizer, usually sodium persulfate, and UV light. The oxidized carbon in the sample is converted to carbon dioxide (CO_2) gas. This gas is swept through a detector that uses a traditional Non-Dispersive Infrared (NDIR) detector.

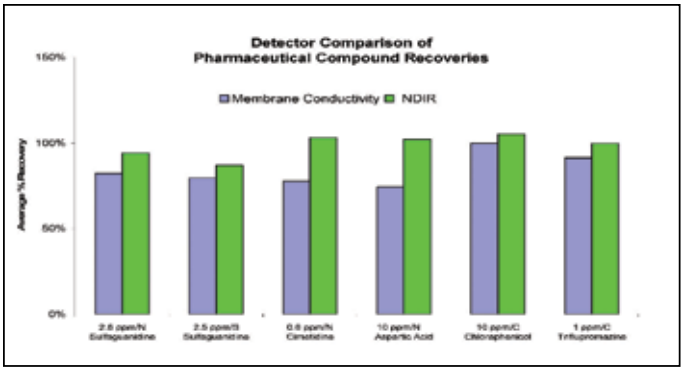
Combustion Oxidation

Catalytic Combustion systems utilize a catalyst to assist in the combustion of organic carbon to CO_2. The catalyst tube is enclosed in a furnace, which heats to 680 °C -1000 °C. The combination of temperature, an oxygen rich environment from the carrier gas (generally Ultra Zero Air or Oxygen), and catalyst is used to oxidize the carbon in the sample to CO_2. The CO_2 is then swept to the NDIR detector.

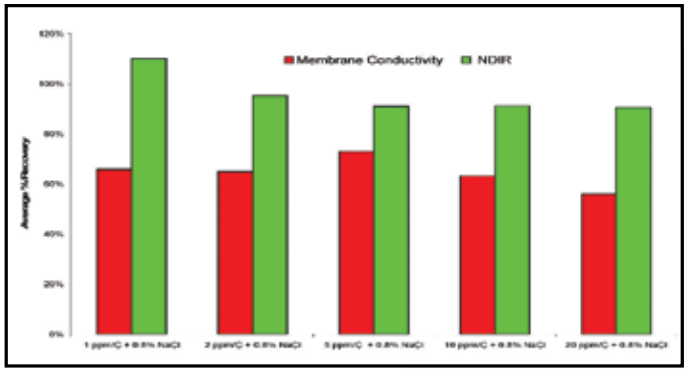
NDIR

NDIR detectors measure the amount of Infrared (IR) energy absorbed by a sample to determine the presence and concentration of CO_2. An IR beam transmits through the sample chamber as the sample gas containing CO_2 fills the chamber. Pressurized front and rear cells connected by a mass flow sensor are located within the detector. An optical filter allows only light of a predetermined wavelength to reach the detector cells from the IR source. When IR energy passes through CO_2 gas, it creates a unique absorption spectrum making CO_2 distinguishable from other gases. To align the IR light through the sample chamber and to increase optical efficiency, a parabolic reflector assembly surrounds the light source, which typically has a gold lining.

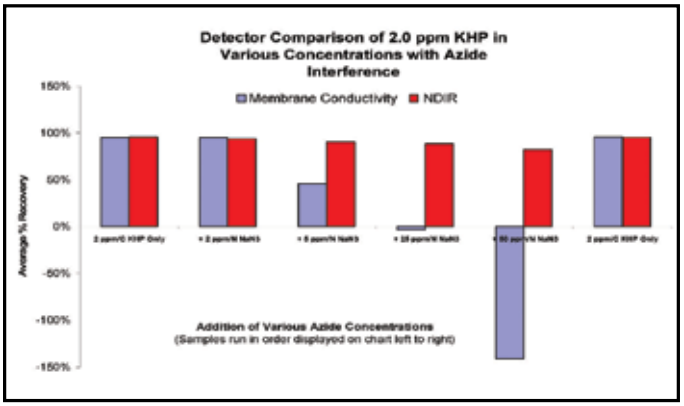
Studies have shown that NDIR has the best recoveries.



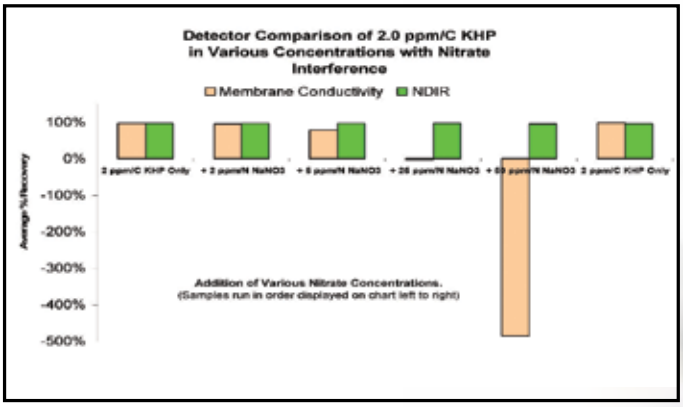
A Detector Comparison of Pharmaceutical Compounds



A Detector Comparison of Carbon Recoveries in 0.8% Salinity Samples



A Detector Comparison of TOC Analysis with Increasing Amounts of Azide interferences



A Detector Comparison with Various Nitrate Interference

Table I: QC Analytical Results OCPs in Water		
Technique	**Benefits**	**Limits**
Membrane Conductivity	• Great sensitivity • Provide online processing • Long–standing calibration • Well-documented method • Easily adapted to online techniques	• Membranes can clog and cleaning process takes hours • Amines can pass through the membrane and give false high results • Ionic Contaminations can cause false low results • Limited analytical range, cannot analyze > 50 ppmC • Cannot handle salts, acids, or particulates
Chemical Oxidation/NDIR (UV/Persulfate)	• Great sensitivity, sub ppb level • Easy and quick sample pathway cleaning process • Accurate analytical results • Few interferences • Well-documented method • Large analytical range	• High level carbon samples > 4000 ppm • Cannot run particulates > 0.3 mm in diameter • Cannot run salinity > 1% • UV lamps can fade overtime • More sample volume is needed for analysis • Recommend nitrogen as a carrier gas, which is more costly than air
Combustion Oxidation/NDIR	• Robust and can handle a variety of sample matrices: salts, particulates, oils, etc. • Can handle large amounts of carbon • Solids matrix option • Large analytical range • Well-documented method	• Not sensitive enough for WFI and PW • High background carbon • Prone to leaks due to the heating and cooling of the furnace • Difficult to achieve quantifiable results < ~200 ppb • Catalyst maintenance

Our Understanding

The pharmaceutical industry must manufacture safe and effective medications. The industry is under strict guidelines to deliver what they promise on the label so accuracy and sensitivity are of the utmost importance.

Accuracy: The medications need to contain active ingredient(s) and nothing further. There must be no contamination from cleaning agents, dirty water, bacteria or other medications.

Sensitivity: The level of contamination must be as low as possible so the sensitivity of chemical instrumentation is essential to determining trace level contamination.

Budget Friendly Operation: Pharmaceutical companies are under pressure to pay back research costs associated with bringing a product to FDA approval and commercialization. This pay back can take decades in some cases. It is important that they find cost saving measures in other places. Reagents can be made in-house to save on operational costs.

Our Solution: The Fusion

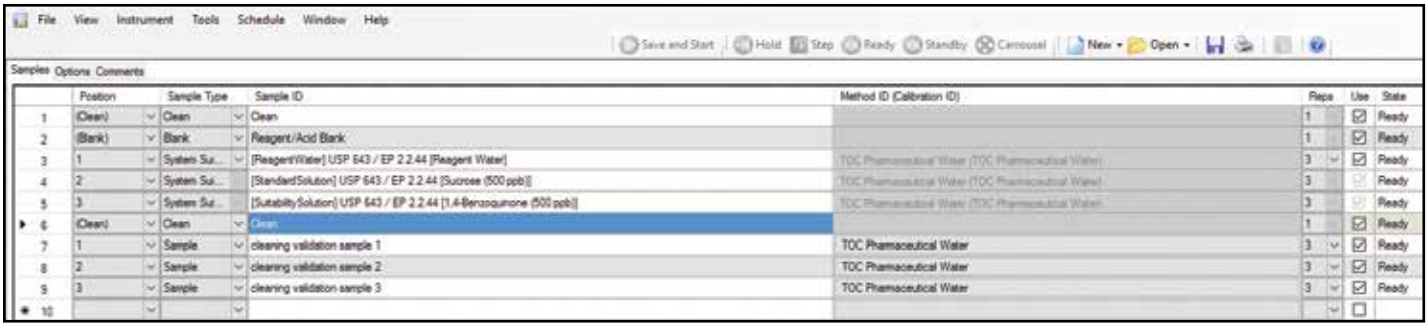
The Teledyne Tekmar Fusion UV/Persulfate Analyzer was designed with the pharmaceutical industry in mind to provide an ideal solution for clean-in-place, water-for-injection, and ultra-pure water applications. With its extremely low detection limit of 0.2 ppbC and its ability to handle high levels of carbon, acid, particulates, and salt, it is a very versatile analyzer for pharmaceutical sample matrices.

The Fusion uses safe, proven and well-documented UV/Persulfate oxidation of carbonaceous material to CO_2 followed by NDIR detection of the CO_2 product to produce superior and consistent results. UV/Persulfate contributes very little background carbon, lower than TOC combustion systems, making it the better choice for drinking water and ultra-pure water applications. The Fusion, also, does not suffer from an affinity to interferences like membrane conductivity systems. Membrane conductivity is very sensitive to interferences like salt, acid, azide, halogenated organics and other compounds. The Fusion is the ideal TOC analyzer for accurate, versatile, and sensitive pharmaceutical applications.

Fusion Features

- **Mass Flow Controller (MFC)** – The patented MFC regulates either flow or pressure depending on the mode of operation. It allows for higher flows for clean up between samples and allows the user to optimize the sparge flow for each sample to ensure the optional Inorganic Carbon removal, and to ease troubleshooting. Because of the MFC, the instrument automatically validates the system integrity by recording the pressure each time a sample is run. The MFC also performs automated leak checks.
- **Intellidilution** – This feature automatically dilutes and reruns samples whose measured concentration falls above the calibration range.
- **Autocalibration** – Using a single stock solution, the system will automatically dilute final volumes based on the user's linear calibration points, thus eliminating the need for multiple manual preparations of the calibration points. This feature eliminates the likelihood of human error and minimizes labor time.
- **Static Pressure Concentration (SPC)** – After the sample oxidizes, it is swept into the detector and pressurized with carrier gas to ensure that the entire sample is present. The Non-Dispersive Infrared (NDIR) detector then measures the concentration of CO_2. This patented sensing technology enables the Fusion to reach new levels of detection required by todays demanding pharmaceutical requirements.

Fusion UV/Persulfate Analyzer



	Position	Sample Type	Sample ID	Method ID (Calibration ID)	Reps	Use	State
1	(Clean)	Clean	Clean		1	☑	Ready
2	(Blank)	Blank	Reagent/Acid Blank		1	☑	Ready
3	1	System Sui...	[ReagentWater] USP 643 / EP 2.2.44 [Reagent Water]	TOC Pharmaceutical Water (TOC Pharmaceutical Water)	3	☑	Ready
4	2	System Sui...	[StandardSolution] USP 643 / EP 2.2.44 [Sucrose (500 ppb)]	TOC Pharmaceutical Water (TOC Pharmaceutical Water)	3	☐	Ready
5	3	System Sui...	[SuitabilitySolution] USP 643 / EP 2.2.44 [1,4-Benzoquinone (500 ppb)]	TOC Pharmaceutical Water (TOC Pharmaceutical Water)	3	☐	Ready
6	(Clean)	Clean	Clean		1	☑	Ready
7	1	Sample	cleaning validation sample 1	TOC Pharmaceutical Water	3	☑	Ready
8	2	Sample	cleaning validation sample 2	TOC Pharmaceutical Water	3	☑	Ready
9	3	Sample	cleaning validation sample 3	TOC Pharmaceutical Water	3	☑	Ready
10						☐	

Fusion Software

- Pre-programmed pharmaceutical methods (TOC, TC, TC-IC, IC)
- Software tools for 21 CFR 11 compliance
- Ability to import and export to LIMS
- Self-diagnostic and troubleshooting capabilities including leak check
- Pre-programmed system suitable standards (sucrose and 1,4 benzoquinone)

Pharmaceutical Methods

- High Purity Water: ASTM D4779 and
- Cleaning Validation: USP <643> / EP 2.2.44 / JP 16 2.59

The Pharmaceutical Industry's Need for VOC Analysis

Organic solvents, such as hexanes, methanol, and others are vital to the production of many pharmaceutical drugs. Many of these solvents are toxic at high concentrations, and can have negative health impacts if found in sufficient concentration in finished drug products. As a result, pharmaceutical manufacturers closely monitor the solvent concentration through many stages of the manufacturing process, not just in the final product.

Numerous characteristics of drug compounds and solvents can impact headspace analysis, including but not limited to:
- matrix interferences
- polarity of the solvents
- solubility of the solvents in water

As a result, standard methods have been set forth by United States Pharmacopeia, USP <467>.

Volatile Organic Compounds

High Performance Solution

The HT3 Static and Dynamic Headspace System incorporates several features that make it ideal for residual solvent applications. First and foremost, is the 10-position platen, which allows samples to be heated in advance of their analysis. The result is faster analyses, without the need to wait on long sample equilibration times. Another beneficial feature is the 60-position carousel that allows for adequate sample volume in busy manufacturing environments. Last but not least, the HT3 offers a full suite of 21 CFR 11 compliance tools including user access restrictions, and complete sample history logging, allowing labs to meet demanding compliance requirements.

Additional features that make the HT3 a versatile and indispensable tool in any lab include:

Optional Dynamic Trapping Feature
The optional dynamic trapping feature allows for increased sensitivity by using the same trapping technology as Tekmar's line of purge and trap systems, while still retaining all of the benefits of headspace analysis. By sweeping the headspace above the sample, and depositing VOCs onto the trap, the dynamic HT3 increases sensitivity without bubbling through the sample, thus leaving any contamination in the vial (like traditional static headspace).

High Temperature Gas Pathway Capability
Samples can be heated to 300 °C due to the high temperature pathway feature. This allows for the analysis of off-gassing in plastics and packaging, and/or the analysis of other high boiling-point compounds.

Mass Flow Controller (MFC, patented)
The MFC allows for both accurate pressure measurements in the static mode, and accurate flow rates in dynamic mode. The MFC is calibrated for both helium and nitrogen, so no matter the purge gas, flow rates will always be controlled accurately.

HT3 Static & Dynamic Headspace System

HT3 Advantages

- Increased sensitivity from 50 to 100 times with the Dynamic Headspace option (compound dependent) for those times when low end sensitivity is needed, or for compounds with high solubility in the sample matrix.
- Removable sample path allows for troubleshooting and maintenance to be done on the bench top, greatly simplifying the process.
- High temperature capability to 300 °C expands range of applications beyond that of other static headspace analyzers.
- Inert sample pathway including transfer line, sample needle and loop provide superior analytical results by eliminating adsorption and reducing carryover
- Automated Leak Check and Benchmark for quick troubleshooting
- Automated method development using Method Optimization Mode (M.O.M.) allows for a range of method parameters to be tested without the timely process of creating each method independently.

Cost Effective Solution

Static headspace is one of the most popular volatile organic compound (VOC) techniques due to its versatility for analyzing VOCs in a complex variety of matrices. This is due to the elimination of tedious sample preparation steps and prevents contamination problems that are common to other sample introduction techniques. The Versa is an excellent static headspace system for budget-conscious pharmaceutical labs, and/or for any laboratory environment in which 20 positions is adequate for the sampling volume handled.

The Versa has several features that make it ideal for USP <467> including:

Pressure Measurements and Adjustments for Reproducible Results
The Versa employs pressure transducers that allow for fast, sensitive and accurate feedback on system pressure, allowing for consistent sample volumes and reproducible results.

21 CFR 11 Compliant Software
Pharmaceutical labs will appreciate the 21 CFR 11 compliance package available for the Versa TekLink that allows for user access restrictions, full system history logging and pressure data capture and storage.

TekLink Software Method Optimization Mode (M.O.M.)
Multiple method parameters can be tested without manually creating multiple methods. This unique software feature allows for unattended method development. This is achieved by allowing the user to access selective method variables and the ability to program changes in values and replicates for the method. The built-in autosampler is then automatically programmed within the schedule and each individual change is executed and recorded as a new method as well as in the sample history log for easy chromatographic comparison.

Versa Advantages

- Small on size yet big on value (only 12" wide)
- 20-position autosampler/single position platen oven for static sampling analysis of 22 mL vials
- Sample heating to 200 °C throughout pathway
- Inert sample pathway including transfer line, sample needle, and loop provide superior analytical results by eliminating adsorption and reducing carryover
- Automatic Leak Check and Benchmark test for quick troubleshooting

Versa Automated Headspace Vial Sampler

More From Teledyne Tekmar

24/7 Online Ordering

Spare parts and consumables are available to order 24/7 with our user-friendly website.
https://store.teledynetekmar.com

Validation Services

We offer an Installation Qualification, Operation Qualification and Performance Qualification by our highly skilled service engineers.

Customer Service

Our Technical Support Department is the leader in the market pertaining to response time and capability to resolve your instrument problems in a prompt and courteous manner.

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