Confirm Water System Sanitization with Reliable Ozone Measurement

Ozone is being increasingly used in the sanitization of pharma water systems. The new pureO₃™ sensor provides fast, dependable measurements plus the lower operating cost benefits of Intelligent Sensor Management.

A natural and powerful oxidizer
Dissolved ozone, a naturally occurring form of oxygen, is one of the most aggressive oxidizers used to manage and control biological contamination in pharmaceutical and life science water systems.

Ozone is an effective oxidant that quickly destroys biofilm and aqueous microbial contamination with low, easy-to-control dosages and minimal contact time.

The molecule’s very short half-life is typically accelerated with exposure to UV light (at 254 nm wavelength) leaving no residual chemicals or traces of ozone after sanitization, and meeting the “no added substances” regulation.

Control of biological contamination is mandatory
Microbiological monitoring and control is required for regulated waters globally. Purified Water and Water for Injection system operators diffuse ozone gas into their water loops at the precise quantities needed to sanitize the system to protect against contamination. Once sanitization is complete, the remaining ozone gas is destroyed using UV light. Monitoring and control are required to limit the total ozone gas levels needed for sanitization (100 – 150 ppb) and also to confirm that all ozone gas is removed from the water system after sanitization and prior to release. Ozone monitoring and analysis manages this process exactly and provides an audit trail to ensure compliance with global regulations.
Stable and repeatable ozone determination

For determining ozone oxidation levels to confirm complete sanitization, METTLER TOLEDO Thornton’s new, robust pureO3 sensor with ISM offers a fast responding measurement that is stable and repeatable. The same pureO3 sensor also measures trace levels of dissolved O3 to confirm that all ozone is destroyed after sanitization and prior to water distribution and use.

Lower operating costs

ISM technology allows pre-calibration of sensors for fast, error-free, Plug and Measure startup. In addition, ISM offers advanced sensor diagnostics that enable longer measurement point uptime and more efficient maintenance which can be scheduled in advance. ISM’s features decrease operational costs and simplify sensor handling while allowing operators to make more informed decisions about process conditions.

When coupled with an innovative transmitter from METTLER TOLEDO such as the multi-parameter, multi-channel M800, the pureO3 measurement solution provides convenient, state-of-the-art dissolved ozone monitoring and control to enhance plant performance and safeguard regulatory compliance.

Resilient, economical solution

Dissolved ozone is an attractive option for sanitizing pharmaceutical and life science water systems because it is easily infused and controlled while reaching all parts of a water system. Ozone eliminates potentially dangerous handling of chemical oxidants or the expense that heat or steam sanitization alternatives require. And it is easy to remove, leaving no residual compounds prior to use. The METTLER TOLEDO pureO3 sensor with ISM provides a durable and cost-effective solution to monitor and control dissolved ozone sanitization effectively and efficiently.

www.mt.com/pureO3

pureO3 Ozone Sensor

- High accuracy at very low ppb ozone concentrations
- Reinforced silicone membrane for exceptional durability and repeatability
- Fast response: 60 seconds for 90%
- Plug and Measure startup
- Advanced predictive diagnostics
Convenience at a Touch
Next Generation M300 Transmitter

The enhanced M300 multi-parameter transmitter offers excellent measurement performance and ergonomic design. A combination of greater flexibility, improved usability, and attractive pricing make it highly suited to end-users and water system fabricators alike.

Designed for today and tomorrow
The popular M300 transmitter series has been updated with new features to provide greater ease-of-use and improved performance in water and Clean in Place processes.

The one- / two-channel M300 accepts analog probes as well as digital Intelligent Sensor Management (ISM®) sensors, making it a logical investment in a plant’s future. Multi-parameter ability means one M300 can be used for many process analytical applications and reduces replacement stock.

Intuitive operation simplifies use
The M300 provides very user-friendly operation in 10 selectable languages with a 4”, high-contrast black and white touch-screen, easy-to-read display of important measurement information, and logical menu structure.

Reduce configuration time
Using the unique M300 Transmitter Configuration Tool, transmitter configurations can be uploaded to the M300 via a PC or USB stick. For consistent functionality throughout a system, a configuration can be downloaded from an M300 to a USB stick or PC for upload on another unit. Pre-calibrated sensors and Plug and Measure feature ensure fast, error-free measurement point startup.

Monitor sensor "health"
ISM sensor diagnostics allow operators to see the “health” of sensors so that calibration or replacement can be scheduled before processes are affected.

The next generation of M300 multi-parameter transmitters creates a measurement solution perfectly suited for water and CIP applications.

> www.mt.com/M300

M300 Transmitter
- One- or two-channel, multi-parameter transmitter series
- Measures pH/ORP, dissolved oxygen, conductivity/resistivity, and dissolved ozone
- Available in a water resistant ½ DIN enclosure for wall and outdoor installations and ¼ DIN for panel mounting
DO Sensor Tolerates Organic Solvents and Reduces Catalyst Costs

When using an oxygen-sensitive catalyst, the process vessel must be free of oxygen both in the headspace and in the liquid medium. But when organic solvents are being used, ensuring media are oxygen free is not easy. For an API manufacturer an intelligent dissolved oxygen sensor proves tough and reliable, and saves catalyst.

Protect expensive catalyst
Using an oxygen-sensitive catalyst in a solvent requires that the dissolved oxygen content of the medium must be as low as possible to protect the integrity of expensive catalyst. Creating an oxygen-free environment requires purging the reactor vessel headspace with nitrogen, for example, for a certain period.

Frequently, the time required for making the inert atmosphere is based on industry experience and historical recommendations. A major chem-pharma company who was using such a time-based technique, suspected that they were sometimes consuming nitrogen gas in excess and on other occasions that insufficient time was given for total air purging. The latter case was leading to loss of catalyst due to residual oxygen in the medium, and facility managers asked METTLER TOLEDO if we could help.

Solvent-tolerant sensor
The company was using tetrahydrofuran (THF) as the solvent, which meant a standard DO sensor would not have been suitable as sensor membranes and O-rings can degrade in the presence of THF. In addition, the solubility factor used in calculations that all dissolved oxygen measurements are based on, is for water. For non-aqueous solutions, the solubility factor can be very different, so the readings from the transmitter have to be converted using known literature values for the particular solvent.

With these cautions in mind, we presented the company with a system comprising the InPro®6850i DO sensor and M700 transmitter.

The amperometric InPro 6850i sensor was the ideal choice for this application. It provides fast, accurate data in a range from 6 ppb to saturation, has a PTFE-
coated membrane, and is available with Kalrez® O-rings. Both materials resist solvent degradation.

Tremendous savings
After a significant period of testing to ensure the sensor would tolerate the process conditions, the METTLER TOLEDO system was put into full operation. The real-time data from the sensor gives engineers much greater insight as to what was happening during the purging process. They are now able to determine with accuracy when nitrogen purging is sufficient and when the catalyst should be introduced. These improvements have resulted in tremendous savings on catalyst expenditure.

No guesswork on when to calibrate
As the system incorporates Intelligent Sensor Management (ISM®), the engineers also appreciate the benefits of the technology’s predictive diagnostic tools that inform them when calibration or maintenance will be required. These diagnostics are particularly beneficial when working with non-aqueous solutions as solvent influence on sensor membrane lifetime can be unpredictable.

The chem-pharma company is pleased to have found a reliable solution to measuring the presence of oxygen in non-aqueous solvents, and is planning on installing further METTLER TOLEDO systems for other catalytic reaction vessels at their production site.

Kalrez is a registered trademark of DuPont Performance Elastomers LLC.
Corrosive gases create challenging conditions

One of the world’s leading pharmaceutical companies operates a chem-pharma facility in China where APIs are produced in great quantities. In preparation of an intermediate product, a large oxidation reactor is used to treat organic raw materials. Conditions in the reactor have to be carefully controlled in order to ensure high yield and prevent a runaway reaction that could result in an explosion. To maximize safety, oxygen must be maintained at a level below the Limiting Oxygen Concentration.

During the process, sodium bromide and sodium hypochlorite are injected into the reactor. This results in the generation of hydrogen bromide and chlorine gas. For plant engineers these highly corrosive gases and other conditions in the reactor present serious challenges in obtaining oxygen measurements.

Standard technologies do not perform well

Two commonly-used oxygen measurement technologies had been tried on the reactor, both with limited success and at a high running cost. An electrochemical fuel cell analyzer required regular replacement of the costly fuel cell. Further, the required sample extraction and conditioning equipment suffered from frequent breakdowns due to corrosion, during which times the process could not be run. A paramagnetic analyzer was also tried but the conditioning equipment not only failed regularly, the system did not efficiently remove dust, moisture and corrosive gases in the sample, resulting in recurrent maintenance and regular replacement of the sensitive oxygen measurement cell. This also led to lost production time.

A laser-sharp approach to O₂ measurement

Engineers at the facility desperately required a more reliable solution. A search for a better technology led them to METTLER TOLEDO’s GPro® 500 Tunable Diode Laser (TDL) oxygen analyzer. The main advantage of TDL analyzers is that they operate in situ, directly in the gas stream; therefore, sample extraction and conditioning is not required. They are also largely immune to interference from moisture, dust and background gases, and exhibit very low drift.

TDL analyzers measure gases using a spectroscopic technique: A laser beam that is tuned to a specific, very narrow frequency range passes through the sample gas to a receiver. Analysis of the incoming light’s spectrum determines the quantity of the target gas in the sample.

No alignment issues

With the GPro 500, METTLER TOLEDO has combined TDL technology with our expertise in analytical instrument design to create a gas spectrometer that combines...
the convenience of an in-line sensor with the level of measurement confidence of a top-line analyzer.

Other TDL solutions are of a cross-stack design, meaning that the light-receiving unit must be positioned directly opposite the laser source. This causes installation difficulties, particularly on large reactor vessels, and can require regular, troublesome realignment.

The compact GPro 500 incorporates a probe with a corner cube at the end. This reflects the laser beam back to the receiver in the sensor head; therefore, alignment is never an issue. And because the laser beam travels twice through the gas stream, the optical path length is doubled, resulting in more accurate \( \text{O}_2 \) measurement.

“Flawless” performance

After consulting with their local METTLER TOLEDO representatives, the production facility installed a GPro 500 in their oxidation reactor. The engineers were immediately impressed with the high performance and reliability of the unit and in the six months since installation, operation has been “flawless”.

They are particularly pleased with the durability of the GPro 500. Because it has no moving parts, servicing amounts only to annual verification and periodic cleaning of the optics. Further, the GPro 500’s probe is constructed from corrosion-resistant metal. Should it need replaced it is a simple matter of removing it from the sensor head that houses the laser and electronics, and fitting a new one.

The GPro 500 is the ideal choice for oxygen monitoring when maintaining safety is critical.

▶ www.mt.com/GPro500
Innovative Techniques to Synthesize Breakthrough Molecules

Due to the increase in molecule complexity, shorter timelines and high scale-up confidence required by industry, new techniques are necessary to develop better chemistry. EasyMax synthesis workstations provide a simple and repeatable way to control reaction parameters 24 hours a day.

Many chemists and engineers are constrained at the bench when exploring a wide range of experimental conditions. Due to inherent shortcomings associated with traditional equipment, the ability to discover new synthetic pathways in a timely manner is highly limited. The main challenges are:

1. Reaction temperature, a critical parameter, cannot be truly investigated with traditional synthesis equipment.
2. Expanding experimental evaluations to other critical process parameters, such as dosing rate, stirring and pH.
3. The requirement to record key process and performance data electronically and synchronize it with other analytical measurements for historical or regulatory purposes.

Traditional equipment to support chemical synthesis, such as heating mantles, ice baths and cryostats combined with standalone dosing funnels and stirrer motors have limited temperature range, poor control capabilities, are manually intensive and do not easily (automatically/electronically) capture and report real-time data as the synthesis proceeds. Today,
researchers are applying and enabling effective technology solutions to expand the research and development of innovative molecules. Synthesis workstation technologies open new possibilities for the control, optimization and reporting of critical process conditions.

Tailored reaction temperature
Traditionally, synthesis design space has been limited to three operating temperatures below room temperature: 0 °C, –10 °C and –78 °C. In reality, many reactions operate in a more desirable manner when they are run at temperatures other than these historic conditions. With EasyMax synthesis workstations, chemists have control and can explore innovative reaction conditions by simply operating at the temperatures best suited for their chemistry.

Expanded experimental evaluations
Screening a range of process parameters (e.g. pH, dosing, etc.) during an experiment ensures that results are more reproducible, enables comparison between experiments with less repetition and scale up has a higher probability of success. EasyMax synthesis workstations provide 24-hour unattended safe and repeatable control of dosing, temperature and mixing parameters.

Automatic data management
With a synthesis workstation, all experimental data gets captured and automatically shared. Fellow researchers can overlay batch results in a shared software platform for powerful data analysis and reporting.

Simple and repeatable parameter control
Due to the increase in molecule complexity, shorter timelines and the high scale up confidence required by industry, new techniques are necessary to develop better chemistry. EasyMax synthesis workstations provide a simple and repeatable way to control reaction parameters 24 hours a day ensuring that the chemist can remain focused on improving chemistry.

Text: Francis Van Der Eycken, AutoChem Innovation Head

White paper: Techniques to Synthesize Breakthrough Molecules
Read how four leading pharmaceutical companies implement new synthesis techniques and the impact on the chemical synthesis lab performance.

Download the white paper now
www.mt.com/Synthesis-Techniques
Real-Time Bioburden Analyzer
Continuous, On-line, Accurate

Time-consuming and error-prone culture-based lab measurements used to be the only way you could measure microbial levels in Purified Waters. Now, accuracy and speed are achievable on-line. The 7000RMS™ offers exact, continuous and real-time determination of microbial contamination.

Determining bioburden in Purified Water and Water for Injection by growing cultures in a lab is time consuming, retrospective and regularly generates false-positive results.

METTLER TOLEDO Thornton’s 7000RMS is a new on-line analyzer for real-time measurement of bioburden in pharmaceutical water systems. It uses laser-induced fluorescence to instantly and continuously measure microbial levels and also determines contamination from inert particles that can come from diaphragms, filters, etc.

The 7000RMS analyzer can provide continuous and accurate data on bioburden contamination throughout a water system. Assurance of in-specification microbial levels and real-time identification of excursions leads to improved product quality, greater process understanding, risk reduction, and lower operating costs.

► www.mt.com/7000RMS

Your benefits

- **Instant bacterial and particle counts**: Real-time display of microbial and inert particle contamination. Allows timely and effective investigation of any microbial event.

- **Easy operation**: Touchscreen user interface. Alarms can be set for alert, action and specification limits. No sample preparation or reagents required.

- **Wide measurement range**: Dependable measurements from 1 cell/100mL to 2000/ml. Counts particles from as small as 0.52 microns.
Get the white paper on real-time microbial monitoring:
▶ www.mt.com/7000RMS-wp
Get in-line with METTLER TOLEDO

Sensors That Learn
Give You the Most Reliable Diagnostics

To maximize product quality and yield, you need to know if your sensors are performing correctly. That is why we have always made diagnostics the main focus of Intelligent Sensor Management (ISM®). And with our new version of ISM we offer a world’s first – sensors that actually learn from your processes to give you unequalled diagnostics performance.

Find out more and get the free brochure

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