Pharmaceutical & Biotechnology

Perspectives in Liquid Process Analytics

25 News

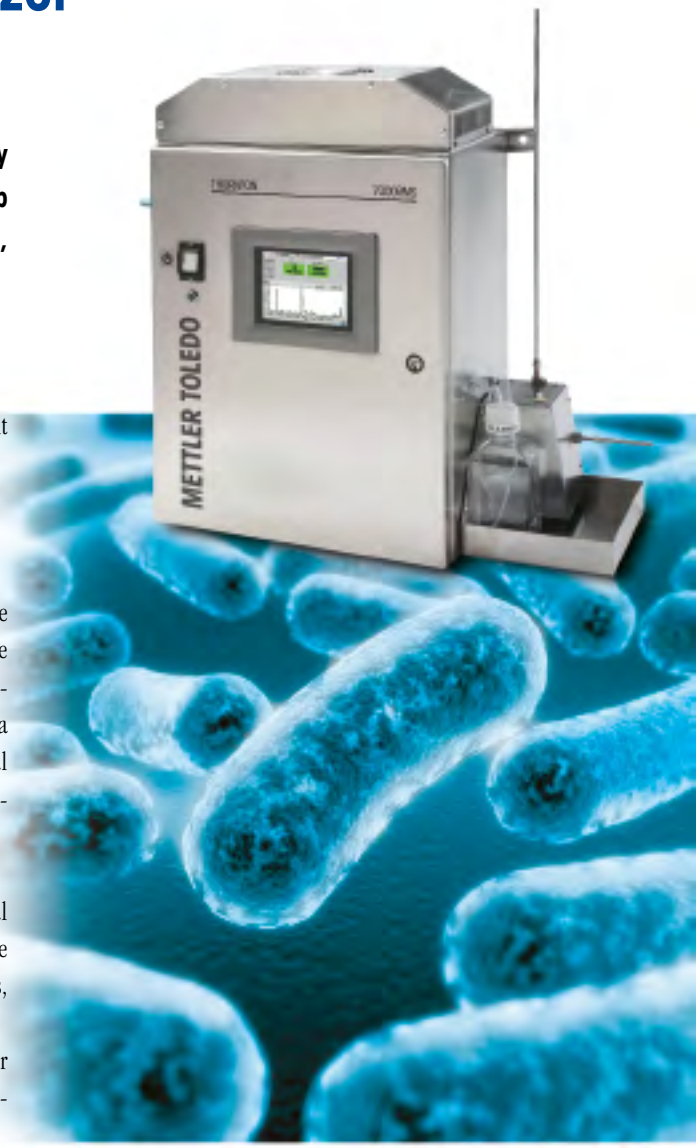
INGOLD
Leading Process Analytics

THORNTON
Leading Pure Water Analytics

New! Real-Time Bioburden Analyzer

Continuous, On-line, Accurate

Measuring microbial levels in Purified Waters has almost exclusively depended on time-consuming and error-prone culture-based lab measurements. Now, the 7000RMS™ offers accurate, continuous, on-line determination of microbial contamination.



Lab measurements are slow and costly

The real-time monitoring of the conductivity and Total Organic Carbon level of Purified Water and Water for Injection is well-established and widely used. But for another vital pharmaceutical waters measurement, microbial counts, it is the traditional lab measurement of cell culture growth in an agar media that dominates. This method is not only time-consuming and retrospective, it regularly results in the costly investigation of false-positive results.

Further, due to the high number of points-of-use (POU) in an average production facility, a single POU may only be tested a few times in a month. This can make the identification and remediation of microbial issues a significant challenge.

Industry requirement for on-line analyzers

The pharmaceutical industry therefore requires real-time monitoring to provide instant notification of microbial excursions. In 2013, in recognition of this, a group of seven leading pharmaceutical companies formed the Online Water Bioburden Analyzer (OWBA) workgroup.

The OWBA believes that pharmaceutical companies can benefit from an on-line microbial analyzer in a number of ways, including:

1. Lower costs through a reduction in labor due to less sampling, and reduced conventional testing and materials.

METTLER TOLEDO

2. Fewer investigations of, and improved responsiveness to, microbial excursions.
3. Greater process understanding and product safety through real-time monitoring.

Spectroscopic measurement technique

Laser-induced fluorescence (LIF) is a bioburden measurement technique that can meet industry needs. All microorganisms contain metabolites which are used to regulate organism growth and development. These metabolites fluoresce when exposed to light of certain wavelengths. LIF is a highly sensitive technique that exploits this phenomenon to detect microbes.

Accurate, real-time bioburden data

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

The accuracy of the analyzer's measurements results in a significant reduction in false-positive results. And unlike other microbial analyzers, the 7000RMS does not use any dyes or reagents and has no moving parts. It is therefore very easy to operate and maintain.

The analyzer's touchscreen interface displays the readings for microbes and inert particles. Alarms can be set for alert, action and specification limits. The 7000RMS offers SCADA connectivity with ModBus TCP, multiple analog outputs and is Wi-Fi capable.

Improved product quality at a lower cost

The advanced LIF technology employed in 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**

7000RMS bioburden analyzer

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Greater Production Efficiency
with In Situ CO_2 Measurement

Carbon dioxide is a critical parameter influencing growth conditions in many bioprocesses. For a US biopharma research company, the data from in situ dissolved CO_2 monitoring has increased productivity.

Understanding cell growth is vital

A US, research-based biopharmaceutical company discovers, develops and commercializes innovative medicines. During process development they require full understanding of how process parameters affect overall cell growth. To achieve this, they needed to install a dissolved CO_2 measurement system that would connect to the FOUNDATION fieldbus™ DeltaV platform they use.

We supplied a solution comprising our InPro 5000 i sensor and M400 FF transmitter.

Intelligent CO_2 monitoring

InPro 5000 i is a fully sterilizable-in-place and autoclavable, in-line CO_2 sensor. It features a class N5 surface and EHEDG certification for compliance with hygienic requirements. The sensor's membrane provides an excellent barrier against volatile organic acids, ensuring errorless measurement. The sensor's Intelligent Sensor Management (ISM®) features include predictive diagnostics and electronic documentation of sensor calibration and maintenance.

The M400 FF transmitter is a multiparameter, single-channel unit for dissolved carbon dioxide, pH / ORP, amperometric and optical oxygen, and conductivity sensors. Due to its implemented FOUNDATION fieldbus interface communication capability, remote monitoring of sensor diagnostics is easily achieved, enabling more efficient maintenance of measurement systems.

Rapid ROI

The accurate, real-time measurements from the sensor, plus the system's ISM features, have allowed technicians at the company to associate CO_2 data with the other process control measurements.

Now, CO_2 levels can be directly monitored and correlated to sparge rates and DO levels. After only a few months of implementation, improved production efficiency and the valuable collected data have already provided a return on system investment.

- ▶ **www.mt.com/InPro5000**
- ▶ **www.mt.com/M400-2wire**

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.

Breakthrough innovation

Since its launch in 2006, ISM technology has gone on to help hundreds of companies across the world increase process reliability, reduce maintenance costs and simplify sensor handling. One of the central features of ISM is its diagnostic algorithms that predict when sensor maintenance, cleaning or replacement will be required.

With our new, advanced algorithms we provide a breakthrough innovation – sensors that actually learn from and adapt to processes. This gives you exceptionally reliable diagnostics that are specific for every single process.

No more guesswork

ISM sensor diagnostics do not give you raw data that has to be interpreted: they provide easy-to-read tools that tell operators what needs to be done and when, to keep sensors and your processes running reliably.

Sensor diagnostics mean you can confidently plan maintenance for when it is actually needed – neither late which can damage production, nor early when it is not required.

Keep your processes in the lead

There is a huge variation in processes found across manufacturing, so the latest ISM sensors actually adapt to the conditions they operate in. As a consequence, ISM diagnostics represent each and every process more accurately than ever before. This enables you to further optimize maintenance and calibration procedures to get the most out of your resources.

Diagnostics speed saves time

Exchanging sensors can lead to risk exposure as a measurement point is taken off-line, so a fast ramp-up and getting back to reliable operation is key. To always ensure your sensors are up and running quickly, the new algorithms provide accurate diagnostics in only 24 hours.

They not only learn – they teach

In some applications the process conditions mean that it can take some time for algorithms to stabilize and give you precise diagnostics data.

We have solved this by giving ISM sensors the ability to learn from other sensors that have already been used in an application. For example, when a pH probe is removed from a process and is connected to our 21 CFR part 11-ready iSense™ software, information on the conditions of that particular process can be stored as an application profile. This profile can then be transferred into a different pH sensor.

"I can transfer the knowledge of one sensor to another with just a click."

When this second sensor is installed in the same process, because it carries the knowledge of its predecessor, it does not need time to acclimatize. And if conditions in the process alter, the sensor diagnostics adjust themselves appropriately.

Sensor maintenance exactly when it is needed

Now diagnostics are accurate as soon as a sensor is installed and you can be sure you are conducting maintenance when it is necessary. Which means that you can be certain your sensors are always performing at their best.

Beyond Plug and Measure

With the application profile database on iSense and the ability to calibrate ISM sensors away from the process, you can build a stock of ready-to-go application specific sensors. Now you can replace a sensor at the measurement point in seconds, without having to adjust the transmitter.

For today's processes and tomorrow's

The new advanced diagnostics and other ISM developments, such as a mobile app that provides a quick sensor check on the go, mean that ISM will remain the leading technology in analytical measurement.

▶ **www.mt.com/sensors-that-learn**

Request a free demo:
▶ **www.mt.com/ISM-onsite**

More Batches and Higher Yield
in Italian Fermentation Plant

The advantages offered by digital sensor technology are convincing more and more pharmaceutical companies to switch from analog systems to Intelligent Sensor Management (ISM®) technology. One such company is Patheon Capua. Now they are benefiting from greater productivity and reduced batch failure.

Global science company

Patheon is a North American multinational pharmaceutical company. It has annual net sales of around USD 2 billion and employs approximately 6,000 people worldwide. Patheon's Capua facility outside Naples, Italy is a Contract Manufacturing Organization dedicated to the production of pharmaceutical API and pharma and food enzymes. With over 20 reactors, the facility is one of Italy's largest fermentation plants.

Over the last few years, pH and oxygen measurement points installed on the reactors were changed from standard analog sensor systems to METTLER TOLEDO's digital Intelligent Sensor Management (ISM) technology. This task was overseen by Sergio Andreutti, Reliability Engineer at Patheon in Capua. Pharmaceutical & Biotechnology News spoke to him about the move to ISM.

Mr Andreutti, what issues were you having with the analog sensors you were using?

Firstly, we had to keep a dedicated log book for each sensor to record calibration data, etc. That was very inconvenient and carried too much risk of information being entered or read incorrectly. We also had to calibrate pH sensors twice: in the workshop after maintenance and again after connection in the field. Obviously this meant we were spending a lot of time on calibration. And thirdly, we had no real idea as to when a pH sensor would no longer measure reliably or when an oxygen sensor's membrane would need exchanged.

What first attracted Patheon to Intelligent Sensor Management?

When we discovered that we could record and trace the history of sensors, such as the number of CIP or SIP cycles they'd been exposed to and calibration history, we became interested in ISM.

In 2011 we were planning to change our control system for fermentation operations. We took the opportunity to move from analog sensors to state-of-the-art technology, and so we decided to implement ISM.

According to your experiences, what are the most important benefits that ISM technology has brought to your plant's processes?

Mainly two. Firstly, traceability. With ISM's iSense™ software we can trace all the information about sensor use, maintenance we've performed on sensors, and also can follow-up all the aspects of a sensor's performance over its life. This is very important when we have to analyze some process failure, or the performance of a sensor, and to study how to assess the maintenance activities on a sensor.

And with ISM's diagnostics we can plan well in advance when to maintain or replace a sensor.

The other important benefit is that this technology allows us to reduce maintenance activities due to the fact that we do not need to calibrate sensors two times. Now we just calibrate in the workshop and connect the sensor to the transmitter in the field. This has allowed us to reduce the

Mr. Sergio Andreutti, Reliability Engineer at Patheon's Capua facility.

turnaround around time between fermentation runs. Thanks to that we have increased fermenter availability in order to raise batch numbers and to add new campaigns over the year.

What cost savings has ISM delivered?

Of course spending less time calibrating sensors has reduced costs but the main savings have been achieved through increasing plant reliability and reducing the number of failed or low yield batches due to sensor failure.

Are you planning to expand the use of ISM in your processes?

Our fermentation processes are now fully-covered with ISM technology. There are downstream processes where we can implement ISM and we're now looking at how to do that.

▸ **www.mt.com/ISM-pharma**

Find out how much you can save with ISM
▸ **www.mt.com/ISM-pharma-calc**

Morphological Changes in Drug Compounds
Under the Microscope

Heated crystalline pharmaceutical compounds undergo morphological changes that can be observed under a microscope. Changes in melting points and ranges or crystallization can be visualized using hot-stage microscopy. This is important for research and QC purposes in order to influence drug stability or effectiveness.

Hot-stage microscopy (HSM) is the combination of microscopy and thermal analysis. It enables the study and physical characterization of materials as a function of temperature and time. The yielded insights are of special use in pharmaceutical companies to either formulate more stable and effective drugs or to test the pharmaceutical compounds according to industry QC standards.

HS 1 control unit
HS82 & HS84 microscope
Hot Stage Controller

Polymorphic changes

Polymorphism is when a substance exists in several different crystal structures that also look different. This affects physicochemical properties, stability and performance. HSM is an ideal tool for identifying different polymorphs through the visualization of diverse crystal appearances and by determining their unique melting points.

Suberic acid exhibits crystallization and several solid-solid transitions as soon as it is heated from the glassy state. Figure 1 shows the sample at 40 °C where it exists in form V. If the substance is heated slowly to 135 °C, it undergoes a transition to form I (Figure 2). Under polarized light, it is easily possible to differentiate between the various forms.

Isothermal crystallization studies

The crystallization behavior can also be studied as a function of cooling rate and temperature. Chlorpropamide, a drug used to treat diabetes mellitus, crystallizes readily from the melt. The sample can be cooled at a constant rate or held isothermally. Crystals of different morphology form depending on the cooling profile. Figure 3 shows different crystalline forms of chlorpropamide that were obtained through isothermal crystallization at 100, 90 and 80 °C.

Both the size and the number of crystals are influenced by temperature. At high temperatures, nucleation rate is low and crystal growth rate high forming a small number of large crystals (left). The lower the temperature, the higher the nucleation rate becomes and the lower the crystal growth rate. This can be seen from the increasing number of small crystals at lower temperatures (Figure 3: Middle and left).

Solvate studies

A solvate of a crystalline solid is an inclusion compound containing both the molecular solid and one or more types of solvent entrapped in isolated sites, layers or channels within the crystal structure. A special form is the hydrate where the included solvent is water.

There are two ways to investigate solvates / hydrate using hot stage microscopy. In a dry preparation (Figure 4) the sample is placed between a microscope slide and a cover glass and then heated. Occurring desolvation (where the solvent is expelled from a solid) is often associ-

Figure 1

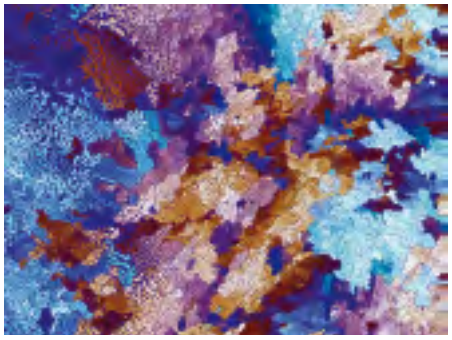

Figure 2

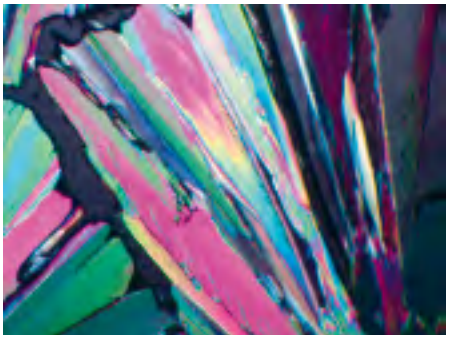

Figure 3a

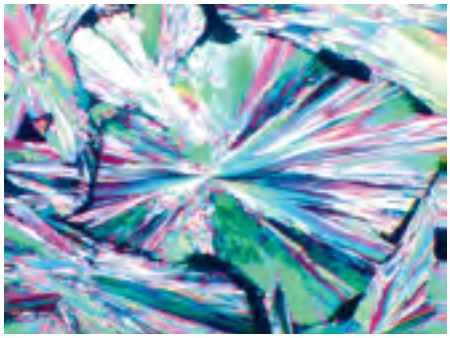

Figure 3b

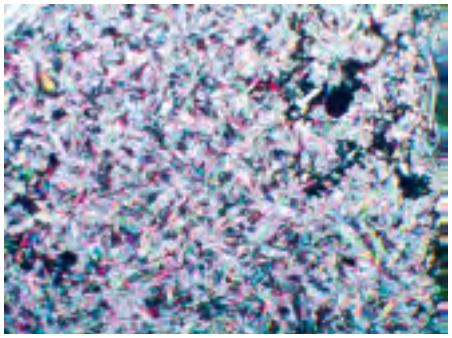

Figure 3c

Figure 4a

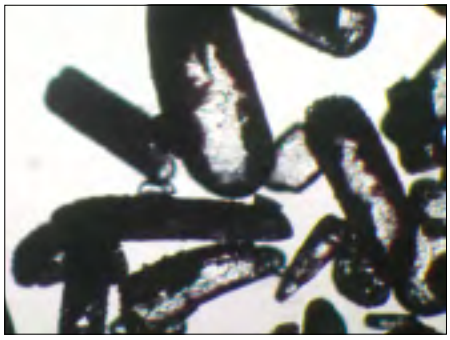

Figure 4b

Figure 4c

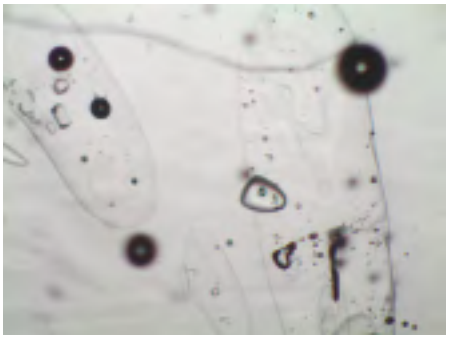

Figure 5

ated with internal changes in crystal structure and makes them look darker due to the decreased light transmittance of the new structure.

In a wet preparation, (Figure 5) the sample is placed in immersion oil and heated. Gas evolution can be observed as bubbles at the interface solid/oil when the crystals desolvate.

Hot stage: The suitable method

Hot stage microscopy delivers valuable information about the thermal behavior of pharmaceutical samples by visually observing the sample appearance as a function of temperature and time. METTLER TOLEDO's HS82 and HS84 speed up this process and are very easy to operate.

Text: Matthias Wagner
Thermal Analysis Product Manager

► **www.mt.com/ta-hotstages**

Easy Traceability
Keep Track of Your Sensors

The multi-channel, multi-parameter M800 transmitter platform covers all major measurement parameters in one instrument. Logbook and user management features provide excellent sensor traceability and operating security.

You need a record of the performance of your sensors, you have to ensure operating security, and you want to monitor a number of process measurements from one point. Now, this is all possible with one transmitter. The M800 combines a wealth of valuable features to make your life with our sensors even simpler.

Touchscreen technology and the intuitive user interface provide incomparable ease of use. And for the first time, you are able to use both Ingold and Thornton sensors on the same platform.

Find out what the M800 can do for you – go to:
▶ **www.mt.com/M800**

Your benefits

Logbook and user management
Two levels of user-selectable security restrict access to sensitive menus or functions. For additional security, the internal logbook records the last 250 transmitter operations and alarms.

Multi-parameter and multi-channel
The M800's multi-parameter abilities give you greater flexibility, less complexity, and less training and inventory. Two- and four-channel models provide multiple measurements from a single unit.

Intelligent diagnostics
With its unique iMonitor predictive diagnostics functionality, based on METTLER TOLEDO's ISM technology, the M800 tells you not only what is wrong with a sensor but how to fix it – before an issue arises.

ISM®

M800 multi-parameter,
multi-channel transmitter

Get in-line with METTLER TOLEDO

Ask an Expert
Jim Knows Best

Industry expert Jim Cannon can help you with your questions regarding pharmaceutical waters regulations, applications, and calibration.

▶ **www.mt.com/jim-knows-best**

Cost Savings Calculator
for pH and DO Systems

Find out how much time and money you can save by switching to Intelligent Sensor Management (ISM®) pH and dissolved oxygen measurement systems.

▶ **www.mt.com/ISM-pharma-calc**

Compliance by Design
in Pharmaceutical Water Systems

This guide is designed to provide a valuable and convenient information resource to aid in the design of pharma water systems that are compliant with the requirements of global pharmacopeias.

▶ **www.mt.com/pro-water-compliance**

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