Reliability Straight out the Box
High Performance pH and DO Monitoring

A US biotech company was looking for new pH and DO measurement systems. Its expectations of performance and durability were very high. After a 12-month trial of many products, METTLER TOLEDO’s “intelligent” solutions secured the deal.

Recombinant proteins
Chinese hamster ovary (CHO) cells are favored for use in fermentation processes because of their rapid growth, high protein production, and resistance to most human pathogenic viruses.

In the process development lab of a leading US manufacturer of heart medications, technicians produce recombinant proteins using CHO cells in 5 L glass vessels. A pH and a dissolved oxygen (DO) sensor are installed in each vessel to monitor conditions over the 11 day batch fermentation. Process pH is particularly critical and must be maintained at 7.4 ± 0.2 over the complete run.

Lab technicians were disappointed with the pH electrodes they were using, and were experiencing a 15% failure rate due to out-of-box failures and sensor drift during runs. The DO sensors they employed functioned well but were difficult to strip and rebuild during maintenance.

Year-long trial
The biotech company decided to initiate a year-long trial of sensors from a number of manufacturers, including METTLER TOLEDO. Expectations from the company’s technicians were high: they wanted no out-of-box failures, sensors durable of withstanding more than 20 autoclaving cycles, and pH sensor drift of less than 0.2 pH units during runs. In addition, they required systems that would allow them to monitor pH and DO on their PLC via Foundation fieldbus/DeltaV.
METTLER TOLEDO confidently put forward our InPro 3253i pH electrode, InPro 6850i DO sensor, and M700 Fieldbus-enabled transmitter. The InPro 3253i is a pre-pressurized, liquid electrolyte, low-maintenance pH and temperature sensor with sterilization-resistant glass, designed for biotech applications.

Built of FDA compliant materials, the autoclavable and sterilizable InPro 6850i DO sensor has a detection limit of 6 ppb. Its 3-electrode measurement principle delivers high measurement accuracy and stability, and its Quick Disconnect system allows the sensor’s membrane body to be replaced in seconds.

The M700 is a multi-parameter transmitter based on a modular concept. This allows integration of up to three modules – two for measurement parameters and one for communications – in a single unit.

**On-board intelligence**

The complete measurement solution of pH electrode, DO sensor, and transmitter offers a significant benefit our competitors’ systems do not: Intelligent Sensor Management (ISM). ISM simplifies the handling and maintenance of measurement systems through a number of advanced features, three of which were of particular interest to our potential customer: predictive diagnostics, sensor pre-calibration, and automatic sensor data capture.

Predictive diagnostics tools constantly monitor the “health” of ISM sensors and display the results on the connected transmitter or a PC running our iSense Asset Suite software. Discarding a pH electrode or servicing a DO sensor after a predetermined number of autoclave cycles is no longer required, as the diagnostics inform the user whether the sensor can be safely used for the next batch, or what maintenance is required to restore the sensor.

**Pre-calibration for installation convenience**

Using iSense software, ISM sensors (connected to the computer with a USB cable) can be accurately calibrated, and stored until they are required. With the Plug and Measure feature, a pre-calibrated pH electrode is quickly and simply exchanged at the reactor. Pre-calibrated DO sensors require only a one-point process calibration once installed in the reactor.

ISM sensors include a microprocessor in the sensor head that carries individual sensor data including serial number, calibration history, and maximum exposed temperature. When any ISM sensor is connected to a PC running iSense, this data is automatically uploaded to the software’s database and a PDF can be generated for validation purposes.
Impressive results
Results of the testing showed that the InPro 3253 i pH electrodes surpassed expectations. Drift was minimal (< ± 0.1 pH units), the sensors survived more than 20 autoclaving cycles, and there were no out-of-box failures. The InPro 6850 i DO sensors also performed exceptionally well and proved simple and fast to maintain.

Operators found the M700 easy to operate, and with the installation of a Foundation fieldbus module, supplied the required communication to the PLC. In addition, the M700 is capable of displaying mmHg units, which facilitates technicians when performing the one-point post-sterilization step that uses blood gas analyzer-determined values. This eliminates the historical requirement for manual calculations from mmHg/Torr to % SAT when performing a post-sterilization data entry step.

Success for METTLER TOLEDO
At the end of the trial the customer selected the METTLER TOLEDO solutions, not just because of the sensor performance but also because of the handling and maintenance benefits that ISM provides. Our customer has converted all their pH and DO measurement points (> 100) to ISM systems and is implementing CO₂ monitoring also using METTLER TOLEDO sensors.

Find out how ISM could help you at:  
► www.mt.com/ISM
Increased Production Uptime
Thanks to High-performance DO System

Dissolved oxygen in parenteral solutions can oxidize the products, rendering them unusable. For a Spanish producer, METTLER TOLEDO systems not only reliably monitor DO down to trace levels, they have also led to greater productivity.

Parenteral solutions producer
Our customer is a Spain-based, multinational pharmaceutical and chemical company. It is a major supplier of intravenous immunoglobulin, albumin, and Factor VIII as well as other products and various services to hospitals, pharmacies, and healthcare professionals across the globe.

At their production plant in Spain, the company produces parenteral nutrition solutions which it supplies in flexible polypropylene bags. In order to increase production capacity and reduce costs, the company commissioned their own engineering division to design and implement a fully-automatic dispensing line to be added to the production area which was also designed by their engineering division.

Importance of inert atmosphere
Parenteral nutrition solutions typically contain a significant percentage of amino acids and vitamins. During production and dispensing, exposure to oxygen and UV light must be kept to a minimum to prevent product oxidation. For this reason, nitrogen-inerted stirred vessels are employed in the production area. Measuring dissolved oxygen (DO) in the process fluid allows production technicians to monitor and control inerting efficiency. After production, the parenteral solution, which has a very low DO content, is transferred to the most critical element in the production chain, the dispenser.

Rapid product detection prevents product loss
The engineering division designed and built the dispensing unit with the aim of achieving better quality and safety levels than those possible with equipment available on the market. The stainless-steel dispenser has a production capacity of up to 3,000 units/hour using bags from 50 to 1000 ml. In order to minimize the possibility of contamination, purified water flows through the dispenser between production runs. To prevent product loss during filling, sensors that can rapidly measure trace levels of oxygen are required to quickly identify when pure product has reached the filling tubes.

Highly-robust DO sensors
In respect of DO monitoring in these processes, the company requirements were for fast responding, extremely reliable sensors that would tolerate CIP cycles. METTLER TOLEDO provided the solutions.

For use with the production reactors, the InPro 6800 DO sensor and M400 transmitter were selected. The InPro 6800 is CIP, steam sterilization, and autoclaving tolerant, and features a hygienically polished surface finish and rugged PTFE-coated membrane. Its detection limit of 6 ppb ensures failure of the inerting system is quickly identified.
Flexible transmitter
The M400 single-channel, multi-parameter transmitter features a mixed-mode input for the connection of conventional analog or METTLER TOLEDO’s digital Intelligent Sensor Management (ISM) probes.

ISM significantly simplifies sensor handling and maintenance, and increases process safety. It achieves this via a range of features including Plug and Measure for fast measurement point start up, and predictive diagnostics that tell the user when sensor maintenance will be required.

Intelligent solution monitors sensor “health”
The ISM-equipped InPro 6970i sensor with the M400 transmitter was chosen for trace-level DO monitoring at the dispenser filling line. Here, ISM’s predictive diagnostics tools provide technicians with real-time information on sensor “health”, allowing the probes to be maintained at peak operating efficiency, and minimizing the possibility of production downtime due to sensor failure.

The InPro 6970i is one of METTLER TOLEDO’s growing range of optical oxygen sensors. Optical measurement technology offers fast response and very low drift, making the InPro 6970i highly suitable for this particular application.

Increased production
Our customer is very satisfied with the performance and durability of the DO sensors. But in particular, they are pleased with the benefits ISM gives them. Plug and Measure combined with predictive diagnostics has led to higher than anticipated production uptime, helping them meet demand for their parenteral solutions.

Find out more about our DO sensors at: ▶ www.mt.com/DO
Disintegration and Dissolution Testing Assures Drug Product Quality

Dissolution testing is carried out in order to monitor the performance of oral dosage forms. However, routine testing is often not adequate enough to fully understand disintegration and dissolution mechanisms. Innovative testing methods provide a better understanding of how tablet disintegration and dissolution are affected by changes in the tablets during storage.

Changes in dissolution performance, which are of significant interest in product quality control, may often occur due to the storage of material at elevated temperatures and humidity. Common methods of measuring dissolution endpoints, using UV or HPLC monitoring, provide incomplete information about the tablet dissolution process. Focused Beam Reflectance Measurement (FBRM®) can be utilized for in situ monitoring of particulates suspended in the dissolution medium throughout the dissolution test. FBRM® provides complementary information about tablet and granule disintegration and dissolution.

Dr. Carrie Coutant, of Eli Lilly and Company, discusses the use of FBRM® in situ particle monitoring for a more thorough analysis of dissolution performance. In this case study, a drug product is known to undergo conversion to a less soluble form during storage at high humidity. FBRM® and fiber optic UV detection were applied in order to improve dissolution mechanism understanding for the original (unstressed) tablets and the converted (poorly soluble) tablets.

Innovative Test Methods

Testing was performed using industry standard USP dissolution apparatus II (paddles) with UV and FBRM® process analytical technologies for in situ monitoring of both the solution phase and the particles in suspension. Method development experiments were first performed to determine suitable probe position, medium volume, sample concentration, and mixing rate. The effect of the probe on the dissolution profile, as measured by UV, was also evaluated and found to be insignificant under test conditions.

Dissolution testing with fiber optic UV and FBRM® monitoring was performed on active and placebo tablet materials at a variety of media pH. Samples of final blend, uncoated tablets and coated tablets were evaluated to help identify the rate-limiting step in the dissolution of unstressed tablets. Active tablets stressed at different moisture levels to induce a range of conversion levels were also tested.
Result: A Better Understanding of Tablet Dissolution

Monitoring the disintegration and dissolution profiles with FBRM® identified an inverse relationship between the amount of drug in solution and the number of large particles that remained undissolved. Solubility of the active ingredient, which is affected by both medium pH and crystal form, impacted the rate of granule disintegration and dissolution of the API. Tests with placebo materials did not detect a significant difference based on storage conditions.

Tablets containing higher quantities of the less soluble form were found to have a different pharmacokinetic performance compared to tablets with higher quantities of the more soluble form. FBRM® was successfully used for in situ monitoring of tablet dissolution, leading to an improved understanding of product performance. Tracking tablet dissolution helped the characterization of how form conversion impacted dissolution rates and drug availability.

www.mt.com/formulations
Purified Water

Less Lab Testing and More System Uptime at French Medical Device Company

For a producer of medical biopolymers, quality from the purified water loop must be very high, and out-of-spec conditions responded to immediately. Switching to METTLER TOLEDO Thornton on-line measurement solutions has significantly reduced lab testing and increased availability of the water system.

Experts in biopolymer production
SYMATESE, located in Chaponost, France specializes in the extraction, purification, and transformation of implantable organic polymers (such as collagen types I and IV, calcium alginate, hyaluronic acid gels, etc.), and the manufacture of implantable medical devices.

Real-time monitoring of purified water loop
The procedure of transforming SYMATESE biopolymers requires the highest water quality and quick reaction to any potential non-conformity. It is therefore necessary to monitor certain physicochemical parameters such as total organic carbon (TOC) and ozone ($O_3$).

In order to reduce the number of laboratory tests, eliminate potential sampling errors, and increase the speed of response, the Methods and Industrialization Manager at SYMATESE decided to implement on-line measurements in the purified water loop. This on-line instrumentation also enables simultaneous testing of the water quality in real time. TOC is therefore measured in the purified water return loop and ozone is monitored continuously in the process stream. Ozone levels are measured daily before UV (for effective ozonization), continuously following UV treatment (to verify that it has been removed), and during sanitization (to check that this process has been completed satisfactorily).

Stable, reproducible, and reliable measurements
SYMATESE found daily sample testing to monitor TOC and the associated waiting period difficult to manage. Furthermore, taking multiple samples increased the risk of false positives resulting from possible contamination when taking the samples, particularly from airborne contamination and sampling technique. The representatives in France for METTLER TOLEDO Thornton solved this problem by switching SYMATESE to on-line measurement.

The Methods and Industrialization Manager at SYMATESE wanted stable, reproducible, precise and reliable measurements, with accurate, easy to maintain, and reliable equipment that conform to European EP standards, as well as United States USP <643> (for TOC) and <645> (for conductivity), which are required for this type of processing. It was important for him to have real-time access to the TOC and $O_3$ values, and he also demanded simple installation and configuration that required little user training, as well as minimal maintenance of sensors.
On-line solution meets the challenge
In order to meet all of these requirements, METTLER TOLEDO Thornton proposed the following solution:
- Thornton 5000TOC sensor and 770MAX transmitter
- Dissolved ozone sensors for M300 transmitter

SYMATESE also established continuous monitoring of the values in order to maintain a record. The measurements are transmitted to a PLC that provides the ability to record and maintain a record of the system’s performance and keep the documented performance for regulatory review.

Advantages of the METTLER TOLEDO Thornton solution
METTLER TOLEDO Thornton instruments meet the customer’s requirements with these benefits:

- Thornton 5000TOC sensor and 770MAX transmitter
  - Complete tracking and tracing of the process: continuous measurement and real-time response
  - Easy operation, maintenance, and calibration
  - Simple and direct installation at the appropriate measurement points

- Dissolved ozone sensor
  - Cost savings: reduced maintenance of measuring points
  - Increased reliability of measurements: precise results, high level of performance
  - Time savings: reduced installation time and maintenance

- M300 transmitter
  - Simple operation thanks to its advanced design and user-friendly software, allowing quick handling without the need for prior training
  - Optimized process control
  - Quick installation and ability to keep a record of the system configuration

Reduced costs, greater availability
The solution provided by METTLER TOLEDO Thornton has allowed SYMATESE to obtain immediate and reliable measurements. Thanks to on-line measurements, the company has reduced the costs of laboratory testing. Furthermore, the installed ozone system has resulted in a reduction in the amount of time the loop is immobilized during sanitization.

SYMATESE is very satisfied with our solution and plans to use more equipment from the METTLER TOLEDO range in its future projects.

Discover more of the benefits of continuous on-line measurements at:
➤ www.mt.com/Thornton
Easy Handling, Exceptional Performance
A New Benchmark in DO Sensors

The InPro 6860 i combines the advantages of optical measurement with exceptional installation flexibility and the benefits of METTLER TOLEDO’s Intelligent Sensor Management (ISM) technology. The result is a DO probe that offers unequalled performance in biopharma applications.

Low drift, fast response, and less maintenance make optical sensors highly suited to monitoring batch fermentations. The new InPro 6860 i DO sensor adds to this by incorporating the easy handling and predictive diagnostics benefits of METTLER TOLEDO’s ISM platform. This combination of technologies makes the InPro 6860 i the ideal choice for all DO measurement applications across the biopharma industry.

Find out more at: www.mt.com/InPro6860i

Your benefits

Compatible with digital and analog installations
Digital and analog outputs from the sensor ensure compatibility with bench-top bioreactors.

High measurement stability
Automatic Stability Control compensates for any measurement drift.

Pre-batch diagnostics
Intelligent diagnostics provide confidence in sensor condition before a batch.
InPro 6860 i optical dissolved oxygen sensor

ISM
Get in-line with METTLER TOLEDO

Easy Sensor Calibration
with Free Maintenance Software

Intelligent Sensor Management (ISM) is helping to improve productivity in process industry companies the world over.

iSense Asset Suite, the partnering software for ISM sensors, allows easy sensor calibration in a convenient location away from the process, sensor diagnostics for increased process uptime, traceability over a sensor's lifetime, and much more.

A free version of iSense, iSenseLight, has all the main features of the full software. No license is required and there is no need for registration.

With iSenseLight, ISM sensors and transmitter, and an iLink USB cable you immediately get all these benefits:

- Fast and easy sensor calibration in a convenient location
- Predictive maintenance diagnostics
- Configuration of optical oxygen sensors
- Printable calibration reports

www.mt.com/iSenseLight

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