Pharmaceutical

Perspectives in Liquid Process Analytics

12 News

INGOLD

Leading Process Analytics

Production Monitoring and On-line Control of Injectable Solutions

Accurate oxygen measurement during inertization is critical to prevent oxidation of the product solution. METTLER TOLEDO oxygen sensors with ISM technology ensure precise and reliable measurement with advanced diagnostics capabilities.

Injectable solution production

Generally, the production of injectable solutions is done by dissolving active substances. A particular attention has to be placed on the non-alteration of the active substance and / or the reagents. When alteration takes place, product non-conformance and its negative consequences on yield and manufacturing efficiency are the result.

Inertization is key to reduce oxidation

If the products are sensitive to oxidation then the properties of active substances, reagents or of injectable solutions can be altered when dissolved, stored or transferred to distribution lines. To avoid any risk, any contact with oxygen should be eliminated. This is actually done by inertization, where the air in the process lines is replaced by an inert gas. The effectiveness of inertization is best improved by measuring the residual gas phase oxygen present in the system. By regulating the incorporation of inert gas, any risk of oxidation can be eliminated without excessive use of gas.

Threshold control with on-line oxygen measurement

A gas phase oxygen sensor connected to a transmitter is placed directly into the tank. A critical oxygen threshold is established with off-line samples. If the oxygen level exceeds the set threshold then the inertization phase starts and additional inert gas has to be applied. Once the critical threshold is reached, the inertization

METTLER TOLEDO

phase can be stopped either automatically or manually.

On-line oxygen measurement optimizes the quantity of gas used and avoids production breaks for control purposes; this is done to achieve costs reduction and prevention of risks of product alteration during production.

Production of injectable solutions is pH sensitive

Preventing any alteration of the active substance and / or of the reagents by using on-line measurements is indispensable for controlling the process of preparation of injectable solutions. It is also important to ensure the quality of the reagents or active substances.

Therefore, on-line pH measurement plays a crucial role in quality assurance and control of the processes. The on-line measurements save response time when compared to laboratory testing. Quick reaction due to on-line measurement reduces the errors, and increases the reliability of the process and of the products coming out of production. Moreover, production costs are lowered by reducing waiting time due to sampling when performing measurements on samples in the laboratory.

Inertization Process

During production and transfer to the distribution lines nitrogen is added for inerting the installation to prevent oxidation of the solution. The inerting phase lasts between 20 and 30 minutes and the dissolved oxygen critical value is around 0.5 ppm. Throughout production, the slightly acidic pH value of the solution is monitored at the preparation tank.

METTLER TOLEDO solution for pH measurement

The solution recommended by METTLER TOLEDO for monitoring pH at the preparation tanks comprises:

- a M400 pH transmitter,
- an InPro 2000 i ISM pH electrode, and
- an InTrac 776 e retractable housing.

The M400 transmitter is a state-of-the-art transmitter offering superior performance, advanced sensor and transmitter diagnostics. It provides an efficient control and regulation of the process. The M400 includes 2 current outputs for simultaneous measurement of pH and temperature, a PID controller and continuous electrode diagnostics (SensoCheck™).

The InPro 2000 i liquid electrolyte electrode provides excellent measurement precision as well as long life. It has an integrated temperature sensor, enabling auto-

Multi-parameter transmitter M400.

Retractable housing InTrac 776 e.

pH electrode InPro 2000 i.

pH measuring loop.

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matic temperature compensation during sampling and measurement. It is resistant to sterilization temperatures of up to 140 °C (284 °F) which makes it an ideal electrode for frequent CIP / SIP (Clean-in-Place / Sterilization-in-Place).

The process adaptation is done via a sanitary INGOLD stainless steel port that enables increased reliability through its design.

The InTrac 776 e retractable housing combines security with cost reduction in the operation of the measurement loop. With its built-in flushing and cleaning chamber, all maintenance operations can be performed wihout process interruption.

This INGOLD complete measurement loop makes it possible to take advantage of pH measurement directly at the heart of the preparation tank while affording maximum flexibility for maintenance and sampling of the sensor without interruption of the process.

METTLER TOLEDO solution for oxygen measurement

METTLER TOLEDO offers a scalable, highly reliable solution for the measurement of dissolved oxygen, consisting of:

- a M400 transmitter,
- an InPro 6850 i ISM sensor, and
- an InTrac 777 e retractable housing.

The M400 Type 2 O_2 transmitter includes all of the principal features in addition to functions specific to oxygen measurement such as pressure correction or Dynamic Lifetime Indicator (DLI) of the ISM sensor.

The InPro 6850 i sensor ensures very accurate continuous measurements under the most stringent conditions that necessitate high sensitivity and sanitary compliance with safety norms. This sensor's detection limit is 0.006 ppm. Its maintenance takes only a couple of minutes thanks to the easy-to-replace membrane module and the Quick-Disconnect sensitive element. Its IP 68 connector ensures perfect seal and very high handling reliability. Its sanitary design complies perfectly to the EHEDG and the FDA recommendations relative to surface finish. Finally, it is autoclavable and sterilizable.

Note: EHEDG means "European Hygienic Engineering & Design Group".

Important customer benefits of these solutions

- Reliable on-line instrumentation meets the requirements of quality and safety associated with the production of batches of injectable solutions.
- The transmitter, by means of a 4 – 20 mA output, controls the input of nitrogen and thus the inertization phase.
- On-line monitoring of gas-phase oxygen during the inertization phase makes real-time information possible but also indicates implementation of any addition or stoppage of inert gas.
- The functions and design of METTLER TOLEDO pH or oxygen measuring products allow accurate measurements, predictive actions and ultimately the reduction of very costly downtimes which means a considerable advantage for the user.

Multi-parameter transmitter M400.

Retractable housing InTrac 777 e.

Oxygen sensor InPro 6850 i.

Oxygen measuring loop.

www.mt.com/pro-pH

www.mt.com/DO

New Optical Oxygen Sensor
for High Accuracy and Reliability

The new optical sensor InPro 6880 i for reliable dissolved oxygen measurements in fermentation processes offers high accuracy combined with outstanding reproducibility and particularly low maintenance.

Improved process stability and reduced maintenance

The InPro 6880 i optical sensor with integrated electronics is based on a chemo-optical measurement principle. It uses light to accurately determine the dissolved oxygen during fermentation. Marker molecules immobilized in an oxygen-sensitive layer are excited by green light and emit red light through a chemo-optical fluorescence process. The optical sensor does not need electrolyte or require polarization extending its operational availability and eliminating inadvertent handling errors. This also reduces the risk of batch contamination and production delays. To tap the full potential of the InPro 6880 i it is recommended to complete the measuring loop with the new M400 transmitter.

ISM technology provides enhanced sensor diagnostics

The InPro 6880 i uses ISM technology (Intelligent Sensor Management) which further increases process reliability and allows for an optimized maintenance planning. Additional status information is analyzed on-line providing the user with real-time warnings of end-of-life of the marker optical cap.

Process safety and batch-to-batch consistency

This innovative technology was combined with long-standing excellence of INGOLD in controlling bioreactor applications to produce the most advanced measurement system. The result was a new standard for enhanced performance and ease of use.

The InPro 6880 i provides:

- extremely reproducible results with
- outstanding accuracy, leading to
- high measurement consistency and
- faster process development.

Benefits to the customer

The InPro 6880 i sensors offer significant advantages which provide the perfect answer to mission-critical issues such as process reliability and batch-to-batch consistency:

- high operational availability combined with
- excellent measurement quality, and
- minimum and easy-to-perform maintenance.

ISM

Oxygen sensor InPro 6880 i.

Multi-parameter transmitter M400.

www.mt.com/inpro6880i

M400 – the Versatile Transmitter
for Advanced Process Measurements

The new flexible M400 transmitter is designed for demanding applications and features ISM® technology with a new unique Dynamic Lifetime Indicator. It covers pH/ORP, oxygen and conductivity measurements, and accepts analog as well as ISM sensors.

M400 – the multi-parameter transmitter for more flexibility

Keep your inventory complexity low with the versatile M400:

- Each model can be used for several input parameters
- 3 types are available to suit your process needs
- The M400 can input either any analog or innovative ISM sensor. You decide which sensor type is best suited for each application

Real-time status information with ISM® technology

ISM makes it much easier to operate process analytical systems from initial installation to maintenance right through to sensor replacement. ISM is available for all key analytical measurement parameters. Real-time status information from the ISM sensor allows true predictive maintenance:

- The Dynamic Lifetime Indicator (DLI) tells you when the sensor needs to be replaced
- Only calibrate when necessary: The Adaptive Calibration Timer (ACT) monitors the time to next calibration
- Traceability support thanks to built-in "Clean-in-Place"/"Sterilization-in-Place" counter and calibration history

Plug and Measure™ feature minimizes maintenance costs

Plug and Measure allows the user to start measuring within seconds:

- Minimized risk of installation troubles thanks to simplified commissioning
- Up-to-date calibration data are stored in ISM sensors and sent directly to the transmitter

High reliability even in advanced process applications

The M400 transmitter is the choice for advanced applications in the pharmaceutical industry due to its high reliability and advanced ISM capabilities. It can input either any analog or innovative ISM sensor.

In addition, the unique iSense Asset Suite for pH and DO (to be released in Q4/2008) offers a reliable control calibration in a QA Lab and ensures a fully traceable documentation for each sensor over its lifetime.

www.mt.com/m400

The multi-parameter transmitter M400 is compatible with ISM® electrodes and sensors.

iSense is a very user-friendly and unique software. Just connect your sensor via a USB port to your computer.

Titration of Injectable Production
Controlled With pH Measuring System

The neutralization process during the production of pharmaceutical injectables can be successfully controlled with the pH electrode InPro 3253 i preventing an overshooting of the target pH value which would result in batch rejection.

Production of pharmaceutical injectables

In the process pharmaceutical formulation, active pharmaceutical ingredients and excipients are combined, which will be used to make medical products. In the manufacturing process for pharmaceutical injectables, pre-weighed solids and Water For Injection (WFI) are mixed in a portable tank. The resulting solution is usually quite acidic and must be neutralized by addition of a caustic solution (commonly NaOH). The final pH value of an injectable solution is very important because any unwanted reactions in the patient's body after injection have to be avoided. In a titration process the pH value can be brought up. This neutralization process seems to be a very simple application. As the practice shows, however, the technique is a very tricky one!

Possible problem in titration process

Why is the titration process such a critical one? Whereas the addition of caustic is needed to raise the pH values as required, excessive caustics can damage or destroy a whole batch. In cases when too much caustic is applied, it is not allowed to make a new correction by adding acids again. A high concentration of caustic due to a too fast addition must be avoided. Poor mixing will result in wrong measurements of the pH value due to time delay and noise. The pH value measured at the end control should be the same as the one measured in the portable mixing tank. The titration process takes place under clean room conditions in a portable stainless-steel tank, mostly with top entry port for the installation of the pH electrode. With the pH measuring system a peristaltic pump is controlled for proper dosage of the caustic.

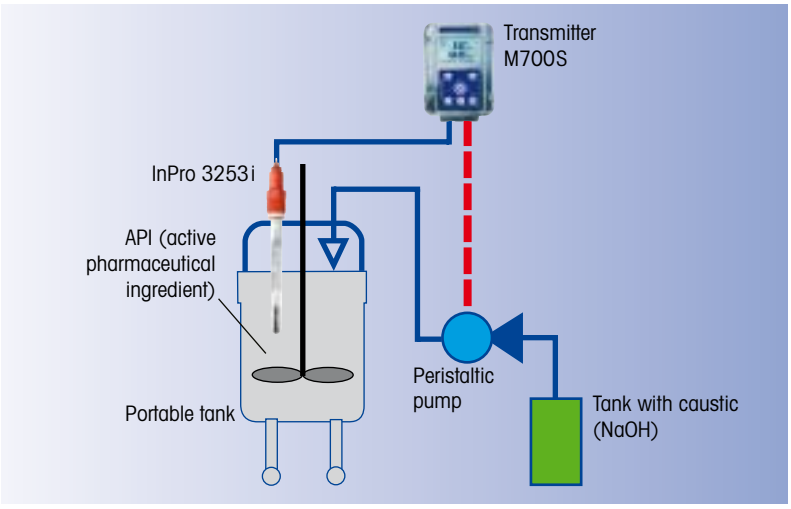
METTLER TOLEDO solution

Beyond a good mixing system and a proper setting of the pH controller a fast responding pH measurement system is essential. As titration is the final production step before filling into vials or infusion bags, the highest compliance level of FDA/USP regulations must be applied. Traceability and documentation of all operation steps regarding pH adjustment should be recorded. METTLER TOLEDO offers its unique ISM system to handle these requests. (ISM® stands for Intelligent Sensor Management).

The pH measuring system consists of:
- pH electrode InPro 3253 i (with ISM technology)
- pH transmitter M700 S

iSense™ ISM Asset Suite

With the iSense™ Asset Suite the performance of each ISM sensor is maximized. Pre-calibration of the pH electrodes can be easily done with iSense installed on a PC in the lab. The pre-calibrated sensor can be connected to the transmitter and is ready for use, as all calibration data are stored in the head of the pH ISM electrode. There is no need for calibration work with buffer solutions inside the clean room!



Direct benefit to the customer

- The accurate pH electrode InPro 3253 i prevents an overshooting of the target pH value and prevents the whole batch from being rejected.
- The fast response of the measuring system together with a perfect controller setting optimizes cycle time by avoiding a too slow caustic dosage.
- The high process security not only improves the reliability but also helps to optimize the process which in turn reduces expenses and maintenance!

Multi-parameter transmitter M700 S.

High quality of WFI guaranteed with THORNTON measuring solution

WFI, as used in the presented article, has to follow highest demands as stated in the different international Pharmacopeias. Mettler-Toledo Thornton is an international leader in the quality of WFI by measuring TOC and conductivity. For more details please contact your local METTLER TOLEDO representative.

Key features of the pH electrode InPro 3253 i

- Reliable and highly accurate
- Pre-pressurized liquid electrolyte prevents process ingress into reference
- "Plug and Measure" functionality
- Advanced sensor diagnostics
- Sensor wear / adaptive calibration timer to be integrated into your PLC via fieldbuses
- CIP / SIP counter

Key features of the multi-parameter transmitter M700 S

- Measures two parameters with temperature
- Supervisor password protection (21 CFR part 11 option)
- Intelligent Sensor Management (ISM) allows "Plug and Measure" and advanced diagnostics. It simplifies the installation, handling and maintenance of measurement equipment.

iSense™ Asset Suite

- Easy and fast calibration
- Traceable documentation of sensor history
- Predictive sensor diagnostics

ISM

pH electrode InPro 3253 i.

www.mt.com/pro-pH

Process Analytics Product Catalog
New Edition 08/09 Available

Get an overview of the latest INGOLD and THORNTON products available for your process application with the new product catalog 08/09.

The catalog offers comprehensive overview on product features and specifications, benefits and recommended application areas, order details and much more for process analytics measurement solutions.

The product catalog covers complete measuring solutions for the parameters:

- pH
- Dissolved oxygen and O_2 in gases
- Ozone
- Dissolved CO_2
- Conductivity
- Turbidity
- TOC
- Flow

The featured product range includes:

- Electrodes / sensors
- Housings
- Process connections
- Transmitters / analyzers
- Cleaning and Calibration systems
- Cables
- Accessories

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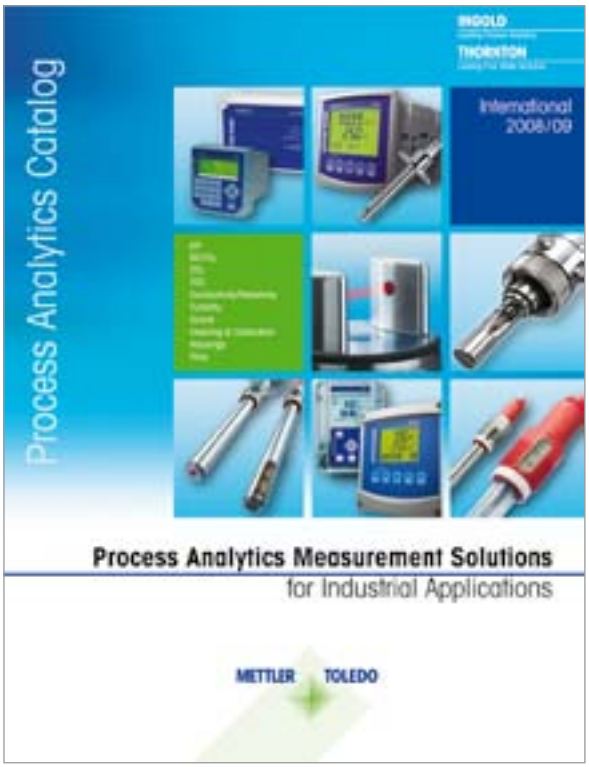

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