



New high-end pH electrode improves accuracy at Werthenstein Chemie

In the biotechnology and pharmaceutical industries, an increasing demand for extremely precise measurement of the pH value has been seen over the past few years. The pH in fermentation is especially critical in that. It directly affects the yield of the process. Werthenstein Chemie, a pharmaceutical company with development facilities in Switzerland, was enthusiastic about the performance of the InPro 3253.



Werthenstein Chemie AG is a subsidiary company of Schering-Plough Corp. At their site in Switzerland, approximately 100 scientists, engineers as well as technical and administrative employees work in close cooperation with the mother company in order to develop new drugs.

The company focuses on the development of new processes and the pilot production of pharmaceutical agents for pre-clinical testing and clinical studies. Active agents are either derived by chemical synthesis or are so-called biopharmaceutical agents, which are generated in a fermentation process.

Accurate pH measurement is crucial in fermentation processes

In fermentation processes, microorganisms (human or animal cells, viruses)

generate the active pharmaceutical agents. Proper process conditions such as temperature and gas partial pressures in the fermenter are crucial to the yield. An optimum pH value is especially critical because the maximization of yield lies in a small range between pH 7.0 and 7.8. Therefore very accurate pH measurement means higher yield and in the end more money for the operator. So far, Werthenstein Chemie AG has been using a competitive electrode. In a new scale-up fermentation process for a biopharmaceutical agent, problems suddenly arose: A redundant in-line pH measurement with two identical competitive electrodes showed a significant pH drop in the process, while threefold measurement in the laboratory displayed constant pH. The fermentation was repeated several times, but the phenomenon



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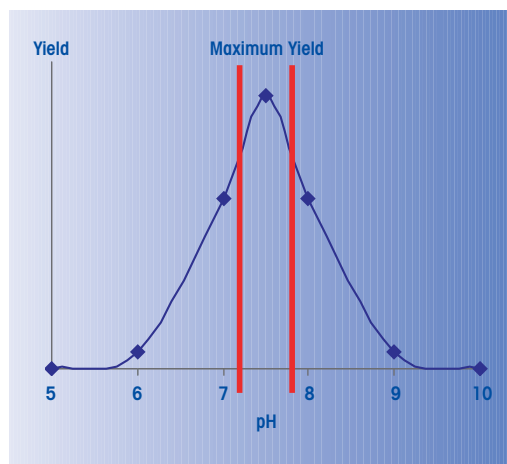
always occurred at the same run time of the process, just after 105 hrs! Whenever the inline measurement misleadingly displayed a pH drop in the system, the control loop automatically added sodium hydroxide to the process in order to adjust the pH. Consequently, the optimum pH range for maximization of yield was exceeded. For several weeks, the entire biotech fermentation group tried to find the reason for this issue – without success.

Then Mrs. Nicole Heller, the supervisor of the group called in Mr. Beat Schultheiss, Sales Manager at METTLER TOLEDO Switzerland. He suggested the replacement of the competitive product with the new

METTLER TOLEDO InPro 3253 with pre-pressurized liquid electrolyte. “Nobody knew what exactly happened in the process after those 105 hrs”, Beat told us. “Since many stability problems of the pH measurement are related to the reference system, and the competitor product was not pre-pressurized, I was pretty sure to overcome the problem with the new pre-pressurized InPro 3253”.

InPro 3253: Advantages of an electrode designed for pH measur- ement under sterile conditions

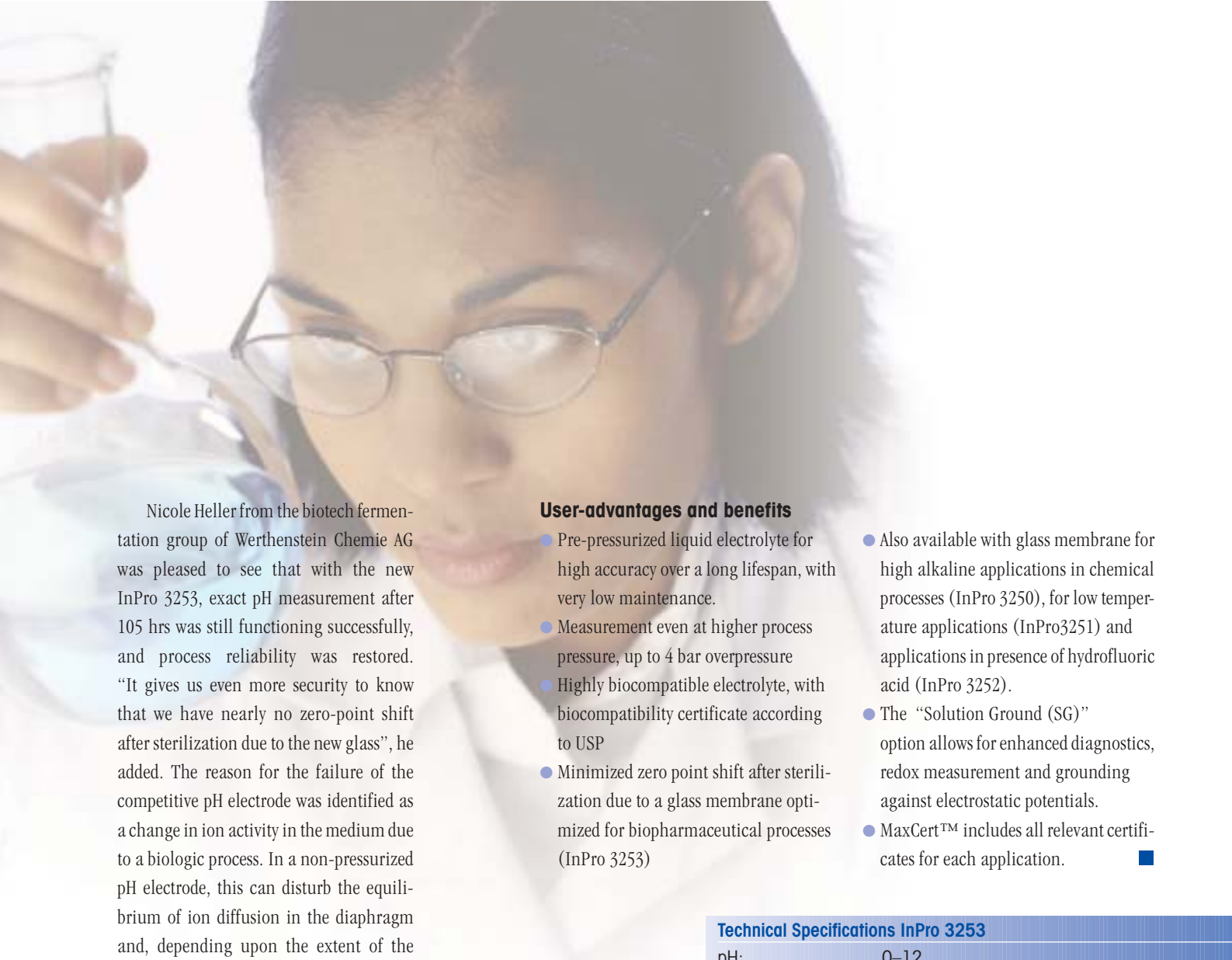
The InPro 3253 belongs to the new InPro 3250 series which is an upgrade of the successful InPro 3200 series. It pre-



In a fermentation process the maximum yield is achieved in a small range around the optimum pH value.

serves the important benefits of the InPro 3200, like highest accuracy and long lifetime and also has a pre-pressurized reference system. Since the reference electrolyte of the entire InPro 3250 series is no longer a gel but a liquid, it was possible to utilize a diaphragm with smaller pores. This causes the InPro 3250 series to meet higher pressure specifications, up to an overpressure of 4 bar (58 psi).

The InPro 3250 series also offers an extended range of pH membrane glasses. In the case of our Swiss customer, the InPro 3253 was chosen. Its glass membrane consists of a “biopharma” glass, which was developed in order to minimize zero-point shift of the electrode after sterilization.



Nicole Heller from the biotech fermentation group of Werthenstein Chemie AG was pleased to see that with the new InPro 3253, exact pH measurement after 105 hrs was still functioning successfully, and process reliability was restored. “It gives us even more security to know that we have nearly no zero-point shift after sterilization due to the new glass”, he added. The reason for the failure of the competitive pH electrode was identified as a change in ion activity in the medium due to a biologic process. In a non-pressurized pH electrode, this can disturb the equilibrium of ion diffusion in the diaphragm and, depending upon the extent of the activity change, substantially influence the pH signal.

A pre-pressurized reference system eliminates this effect by guaranteeing a constant ion diffusion driven by the overpressure inside the electrode.

“...we have nearly no zero-point shift after sterilization...”

Also the head of the biotechnology plant, Mr. Markus Tanner, is convinced:

“In the future, we will only utilize InPro 3253 in this process, and we will check where else in our facility we can use it. The MaxCert package with its biocompatibility certificate even allows a simple change in validated processes”.

User-advantages and benefits

- Pre-pressurized liquid electrolyte for high accuracy over a long lifespan, with very low maintenance.
- Measurement even at higher process pressure, up to 4 bar overpressure
- Highly biocompatible electrolyte, with biocompatibility certificate according to USP
- Minimized zero point shift after sterilization due to a glass membrane optimized for biopharmaceutical processes (InPro 3253)
- Also available with glass membrane for high alkaline applications in chemical processes (InPro 3250), for low temperature applications (InPro3251) and applications in presence of hydrofluoric acid (InPro 3252).
- The “Solution Ground (SG)” option allows for enhanced diagnostics, redox measurement and grounding against electrostatic potentials.
- MaxCert™ includes all relevant certificates for each application. ■

Technical Specifications InPro 3253

pH:	0–12
Temperature:	0–100 °C / 212 °F for operation up to 140 °C / 284 °F for sterilization
Pressure:	0–4 bar / 0–61 psi (overpressure)
Reference:	pre-pressurized liquid electrolyte
MaxCert™	Eex and FM certification PED certification EHEDG certification Biocompatibility certification
Connector:	VarioPin(VP) IP68



The InPro 3253, the new gold standard pH electrode from METTLER TOLEDO for applications under sterile conditions where accuracy and reliability are crucial.

Online monitoring and control of injectable solution production at Sanofi-Synthelabo

The online monitoring and control of physicochemical parameters such as pH, conductivity or dissolved oxygen is a key task in the pharmaceutical industry, enabling real-time process control and quality monitoring throughout the production chain. One example is the production of injectable solutions.

Overview of injectable solution production

Injectable solutions are produced by dissolving active ingredients and/or reagents in ultrapure water (known as water for injection or WFI).

Several critical factors must be monitored during manufacture:

- the quality of the solvent water
- the production phase
- the stability of the active ingredient and/or reagents

The water for injection is prepared by distillation or equivalent (or superior) methods for elimination of inorganic and microbiological impurities.

Inerting phase

The properties of the active ingredient, reagents or injectable solution may deteriorate during their dissolution, storage or transfer to the distribution lines. Products sensitive to oxidation are susceptible, so contact with the air or oxygen dissolved in the water must be avoided to eliminate any risk. This is achieved by inerting, a process in which the air in the tanks and pipelines is replaced by an inert gas. Dinitrogen (N₂) is commonly used for this purpose. In practice, the tanks or pipelines are usually "swept" before initial filling. An inert gas blanket effectively offsets subsequent withdrawals and top-ups. Measurement of dissolved oxygen is essential during this phase and allows the levels of oxygen present in both the WFI and injectable solution to be monitored. Regulating the

supply of inert gas avoids any risk of oxidation and ensures optimal gas usage, i.e. no excess.

Oxygen measurement

A dissolved oxygen sensor linked to a transmitter is placed directly in the preparation and/or storage tank. A critical oxygen threshold is determined in advance by sample measurements in the laboratory and then set at the transmitter. If the threshold is exceeded either an alarm is triggered to alert production staff or the inert gas supply is switched on. If the level falls below the threshold, the inerting phase can be stopped either automatically or manually after a triggered alert. Online measurement thus optimizes the volume of gas used and avoids production downtimes for control purposes. Production costs are reduced and risks of product deterioration avoided throughout the production process.

Production of injectable solutions

Monitoring WFI quality and avoiding any deterioration of the active ingredient and/or reagents through online measurement is an essential means of control in injectable solution production. Verification of the properties of the dissolved reagents or active ingredients and the finished products is also important. Online measurement of pH thus plays a key role in quality assurance and process control.

Summary:

Online measurement saves time compared to manual sampling for occasional laboratory controls. A faster reaction time can reduce the risks and increase the safety of the process and the resulting products. Online measurement can also help lower manufacturing costs by reducing production downtimes for maintenance or sampling and measurement.

SANOFI-SYNTHELABO, Quetigny (France)

Injectable solution production at the SANOFI-SYNTHELABO plant at Quetigny in eastern France employs METTLER TOLEDO online measurement systems. Production in 2004 will be 70 million ampoules. Effective production control, improving equipment reliability and quality levels are standard production site requirements for this world-renowned pharmaceutical group. Online measurement in the production of injectables facilitates automation of the cleaning and sterilization-in-place systems as far as the distribution chains. Measurements taken in the preparation tanks include pH and, more recently, dissolved oxygen.

Production sequence

Preparation tanks larger than 1m³ are part-filled with WFI prior to addition of the active ingredients. When the reagents have been dissolved, WFI is added to complete initial filling. Inerting takes place during manufacture and transfer to automated distribution lines. The system is inerted

with nitrogen to avoid oxidation of the solution by dissolved oxygen. The inert phase usually lasts 20 or 30 minutes. The critical limit for dissolved oxygen is 0.5 ppm. Throughout the production process, the pH value of the solution in the preparation tank is monitored and should be between 4.0 and 6.0.

METTLER TOLEDO solution for pH measurement

METTLER TOLEDO recommends the following solutions for pH monitoring:

- 2100e transmitter
- InPro 2000 electrode, protective sleeve
- InTrac 776e retractable housing

The outstanding performance and accurate diagnostics of the 2100e transmitter provides all the data needed for effective process control. They are fitted with two current outputs, a PID and diagnostics continuous controller (SensoCheck®). The combination InPro 2000 pH electrode offers precise measurement and a long service life. The system includes a temperature sensor for automatic compensation during calibration and measurement. The electrode is resistant to sterilization temperatures up

to 140 °C, making it ideal for frequent CIP/SIP. The 776e retractable housing combines safety with reduced operating costs, by allowing regular cleaning and calibration of the electrodes. This complete INGOLD range allows direct pH measurement in the preparation tank while offering maximum flexibility for maintenance or calibration of the sensor without interrupting the process.

METTLER TOLEDO solution for DO measurement

METTLER TOLEDO offers an upgradeable technical solution for measurement of dissolved oxygen:

- 4100e transmitter
- InPro 6800 sensor, protective sleeve
- InTrac 777e retractable housing

The 4100e transmitter has additional functions for specific measurement of dissolved oxygen, as pressure correction. The InPro 6800 sensor is designed for continuous high-precision measurement under the strictest conditions requiring high sensitivity. Its detection limit is 0.006ppm. The sensor needs very low-maintenance thanks to the Quick-Disconnect system for the membrane body and

sensing element. The VP IP68 connector ensures complete watertightness and its surface finish is fully EHEDG*- and FDA-compliant. The sensor is autoclavable and sterilizable.

System benefits and tests

Online measurement can satisfy the reliability and safety needs of injectable solution production. SANOFI-SYNTHELABO successfully deploys the METTLER TOLEDO solutions for the measurement of pH and dissolved oxygen. The transmitter allows control of nitrogen supply and thus the inerting phase via a 4-20mA output. Online measurement of dissolved oxygen provides real-time data on effective implementation of the inerting phase and any adjustments (turning inert gas up or off) required to produce an injectable solution that meets quality standards. In terms of functionality and design, the METTLER TOLEDO products for measuring pH or dissolved oxygen are ideal tools for SANOFI-SYNTHELABO in its efforts to automate the production of injectable solutions ■

*EHEDG :
European Hygienic Engineering & Design Group



Turbidity measurement, indispensable for monitoring of crystallization processes

Intermediate and end products in the pharmaceuticals industry are frequently harvested from a clear solution by means of batch crystallization.

To initiate a crystallization process, weak acid is pumped into the crystallizer in order to adjust the pH value, or the solution may be cooled, until the first crystals begin to form. At this “cloud point”, dosing of acid must be interrupted or the temperature program changed in order to prevent spontaneous, uncontrolled crystallization. In many cases, seed crystals are additionally fed into the solution to achieve a defined crystal structure.

Process

If the process of crystallization is being monitored by a process operator and his decision to intervene in the process is based solely on what he perceives visually through the sight glass, then this can lead to substantial variations in product quality from batch to batch. Insufficient process control results in slow settling behavior of the finer crystals in the process vessel, as well as poor filterability. The first mentioned fact leads to loss of yield, since the fractions containing the smaller crystals

mostly go to waste and, in the second instance, production time is extended, resulting in lower productivity.

A reliable and reproducible recognition of the cloud point can be achieved by the installation of a turbidity sensor in the crystallizer. The associated transmitter, programmed in accordance with the process sequence, allows automation of the acid and seed crystal dosing or, alternatively, of the temperature program. This achieves a uniform crystal size distribution, resulting also in shorter filtration and washing cycle times. The fraction bearing the smallest crystals is minimized, thereby increasing yield by 5...10 %. A positive side-effect is the reduction in consumption of wash-solution after the filtration phase.

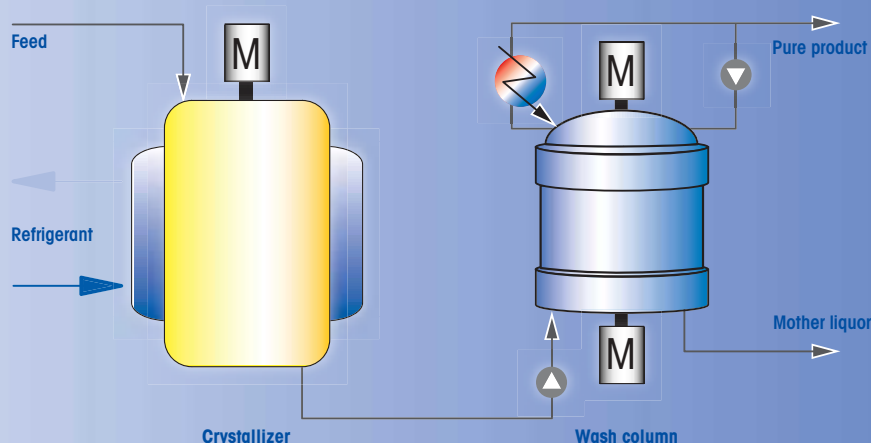
METTLER TOLEDO solution, the turbidity sensor InPro 8200

The turbidity sensors of the InPro 8000 series are available in different materials and lengths to meet various requirements. For instance, the sensor shaft can be made of stainless steel or Hastelloy, depending on the aggressiveness of the reaction solution. The use of a scratch-proof sapphire window on the InPro 8200 sensor permits their use over an extended period – even in the presence of abrasive crystals. The signal transmission between sensor and transmitter using optic fiber technology allows the sensor to be installed in Ex-classified zones.



Turbidity transmitter Trb 8300 and housing InFit 761

A measuring system is completed by a turbidity transmitter Trb 8300 and an optional static InFit 761 housing or an InTrac 779e retractable housing. ■



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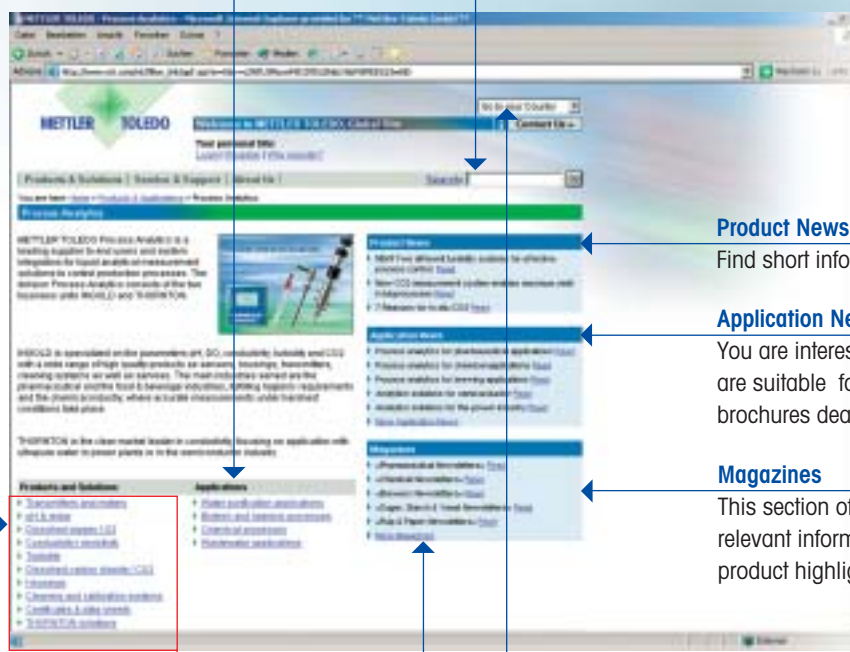
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