

## Backscattered light measurement optimizes crystallization of penicillin

**Increase of yield and productivity in a penicillin crystallization process has been successfully achieved by reproducible detection of the nucleation point. The detection was possible by introducing METTLER TOLEDO's turbidity system to control the crystallization process.**

Harbin Pharmaceutical Co. Ltd. is one of the biggest Chinese pharmaceutical enterprises and the second largest producer of penicillin in China. With more than 8,000 employees, a sales volume of 5 billion US\$ was achieved in 2002. Process analytical systems for inline measurement of pH, dissolved oxygen, conductivity and turbidity play a major role in increasing productivity and complying with high quality assurance standards.

### The penicillin process

Penicillin kills infectious diseases caused by bacteria. Different forms of penicillin are widely used as liquid, tablets or injection for effective antibiotic treatments. Industrial production of penicillin usually begins with the aerobic fermentation of *P. chrysogenum* in batch

fermenters. The broth is then filtered to remove the cells which are washed to remove any entrapped penicillin. The filtered broth is acidified and put into contact with butyl alcohol which results in the selective transfer of the penicillin into the organic phase. Depending on product specifications, carbon adsorption to remove pigments and other impurities may be the next separation step. Finally an excess of potassium or sodium acetate is added in a mixing tank to induce crystallization. A centrifuge or drum filtration unit then collects the crystals which are washed and dried to produce the final product.

A controlled crystallization of the penicillin derivate is crucial for batch to batch consistency and efficient downstream isolation processes. Reproducible

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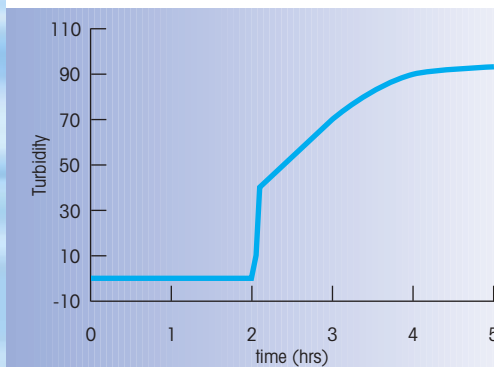


Fig. 1 Turbidity signal during crystallization of penicillin.



Fig. 2 The desired crystal shape as a result of controlled crystallization conditions.

detection of the nucleation point is used for appropriate temperature and stirrer control as well as control of the vacuum.

Fig. 1 shows the turbidity signal during the crystallization process. The point of turbidity increase is a good indicator of the nucleation point and this can be used to control the process in order to produce uniform crystals with good filterability. The desired crystal form can be seen in Fig. 2 – long needle-shaped crystals with good filterability. In comparison, Fig. 3 shows crystals resulting from non-reproducible crystallization conditions.

### METTLER TOLEDO'S Trb 8300 / InPro 8200 turbidity system for detection of nucleation point

The Trb 8300/InPro 8200 turbidity is based on the backscattered light technology for detection of undissolved particles in liquids. The light of a Near-Infrared-LED placed in the Trb 8300 transmitter is transmitted via fiber optic cable to the sensor tip. The InPro 8200 sensor is designed for direct installation in the process vessel. An optical sapphire window protects the fiber optic cable from abrasive crystals. The light is beamed from the sensor tip into the process media. As soon as undissolved crystals appear in the solution, light is scattered back from these crystals and transmitted to a photocurrentdetector in the transmitter via a second fiber optic cable. The use of a fiber optic cable enables a sensor design with a

uniform, unbroken surface structure. Consequently freedom from fouling and the ability to clean thoroughly in-place is guaranteed. Furthermore, passive fiber optic signal transmission allows sensor installation in hazardous areas (Ex-proof).

The measuring system is completed by a suitable housing – for example a static InFit 761 housing.

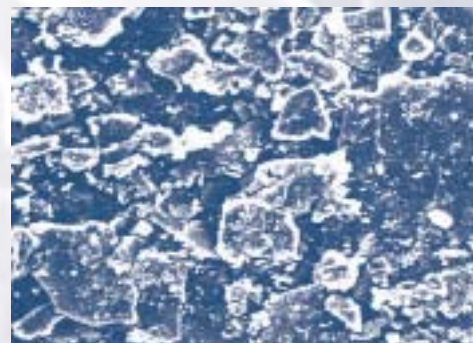


Fig. 3 Heterogeneous crystal structure with poor filterability.

### Short payback period

The installation of several turbidity systems at Harbin Pharmaceutical resulted in a short payback period due to a penicillin yield increase of 5% and a 10% decrease in the consumption of butyl alcohol.

A big achievement when compared to the visual sight glass detection of the nucleation point which was state-of-the-art before installing the turbidimeters! ■

# Successful inline CO<sub>2</sub> in various bioprocesses at the Blaise Pascal University, France

**For many fermentation processes, CO<sub>2</sub> is a critical parameter in influencing optimal growth conditions. Several tests were made with the new METTLER TOLEDO CO<sub>2</sub> measuring system, focusing on linearity, the measuring range, and mass transfer coefficient for the modeling of bioprocesses. The parameters measured were pH, DO, cell density, and pCO<sub>2</sub> all of which strongly influence productivity and metabolic rates.**

The “Laboratoire de Génie Chimique et Biochimique” at the Blaise Pascal University in Clermont-Ferrand is particularly well known for its research in the fields of biotechnology, food and chemical processes. The laboratories are equipped with several bioreactors and related equipment for the analysis of metabolisms, the determination of mass and energy equilibrium and the development of new culture strategies.

The new CO<sub>2</sub> system was tested under different conditions including an aerobic bacteria cultivation and an anaerobic bacteria fermentation with CO<sub>2</sub> partial pressure of up to 1500 mbar (21.75 psi).

The first test runs confirmed the specified measuring range from 10 to 1000 mbar (0.145 to 14.5 psi) CO<sub>2</sub> partial pressure. The system even responds at partial pressures down to as low as 0.1 mbar (0.0145 psi) even if this is outside the linear range.

The CO<sub>2</sub> values measured with the new METTLER TOLEDO system were compared to an absolute infrared analyser (0-10%) in the exhaust gas. pH and dissolved oxygen were also controlled by METTLER TOLEDO sensors. Gas balance on oxygen was performed with a paramagnetic differential analyser.

## Results

The InPro 5000 CO<sub>2</sub> sensor is very suitable for use in bioprocesses, provided assuming the proper calibration procedures are respected of course. The first step is a conventional pH calibration (removing the membrane) followed by a process calibration with a gas containing CO<sub>2</sub> after sterilisation. The correlation with infrared gas analysis showed to be excellent. Only an in-situ sensor measures exactly the same partial pressures as “seen” by the cells. There is no interference observed in media at pH 6 and pH 7. The sensor seems suitable also for work in photobioreactors in which CO<sub>2</sub> is the main substrate as long as the pH value of the broth remains below pH 9. The linearity is very good in the specified range. Comparative tests (Fig. 2)





Test bioreactor.

were made to measure  $K_L a_{CO_2}$  and  $K_L a_{O_2}$  values ( $K_L a$ =volumetric mass transfer coefficient).

For industrial-scale bioreactors, oxygen transfer and carbon dioxide evolution rate are key design elements for scale up. Why should the performance of a culture be so different at 10,000 litres than at 10 litres? Why does performance change with scale? The answer lies in the difficulty of being able to maintain consistency in large systems which are subject to particular changes in surface to volume ratios, and changes in the cultures themselves due to the increased duration of the culture process.

Online  $CO_2$  measurement is a tool for evaluating fermentation performance as well as the physiological state of the culture. Under steady-state mass transfer conditions, OTR (oxygen transfer rates) and CTR (carbon dioxide transfer rate) are a good approach to analysing the physiologically important parameters of OUR (oxygen intake rate) and CER (carbon dioxide evolution rate). In this way it is possible to estimate the respiratory quotient RQ, an important metabolic indicator. In-situ  $CO_2$  measurement has proven to be a valuable tool in process monitoring.

The solubility of  $CO_2$  is quite a complex phenomenon, classically influ-

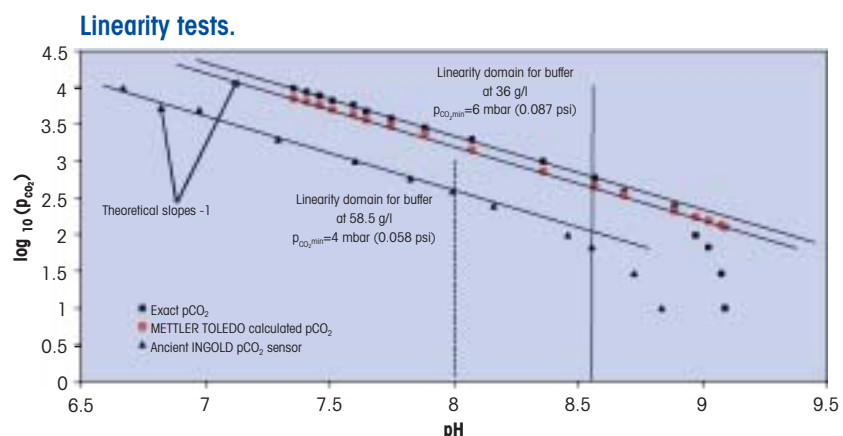


Fig.1 Confirmation of measuring ranges of METTLER TOLEDO  $CO_2$  systems.

## Comparison of mass transfer coefficients.



Fig.2 The volumetric mass transfer coefficient of CO<sub>2</sub> is much lower than the coefficient of O<sub>2</sub>.

enced by temperature and medium composition, but also highly influenced by the pH value. The on-line monitoring of dissolved oxygen and pH is already standard in bioreactors but, by using the new in-situ CO<sub>2</sub> system, valuable additional information can be obtained from the process. The new CO<sub>2</sub> measuring system allows the implementation of an improved CO<sub>2</sub> strategy to optimise yield and product quality.

### About the CO<sub>2</sub> system

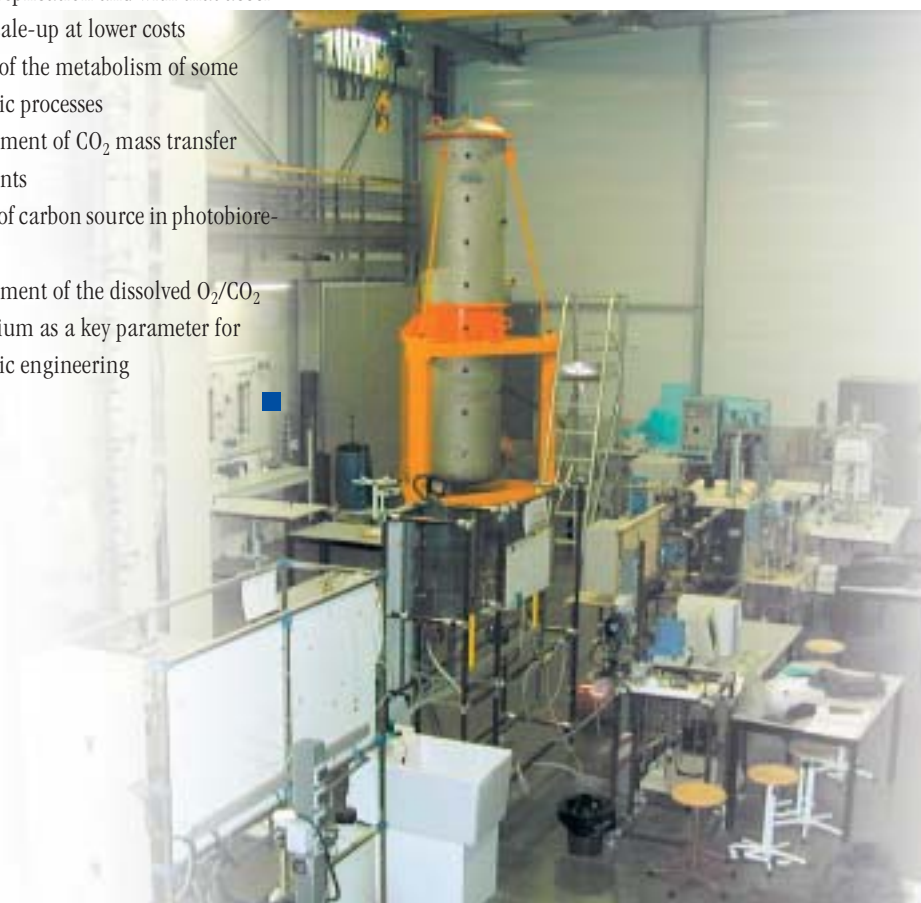
The new CO<sub>2</sub> systems consisting of the CO<sub>2</sub> sensor InPro 5000 and the CO<sub>2</sub> transmitter 5100 e are designed for in-situ measurements in bioreactors.

### What is new?

- Robust industry-proven technology ensures lower system and maintenance costs and less complexity than today's indirect measurement systems
- Compliant with hygienic regulations (EHEDG)
- All materials used are compliant with FDA 21 CFR 117.2600
- The transmitter offers the same advanced user-interface, unique sample calibration routine and diagnostics as other METTLER TOLEDO analytical parameters (pH, DO, conductivity, turbidity)

### Key reasons for in-situ CO<sub>2</sub> control in biological processes

- Only an in-situ sensor measures exactly the same partial pressure as “seen” by the cells
- Higher CO<sub>2</sub> concentrations can be toxic to mammalian cells
- Direct CO<sub>2</sub> measurement allows process replication and with that accelerates scale-up at lower costs
- Control of the metabolism of some anaerobic processes
- Measurement of CO<sub>2</sub> mass transfer coefficients
- Control of carbon source in photobioreactors
- Measurement of the dissolved O<sub>2</sub>/CO<sub>2</sub> equilibrium as a key parameter for metabolic engineering



# New "Premium Line" Transmitter M 700

With the M 700 transmitter, METTLER TOLEDO, a leading supplier for process analytics measurement solutions, offers now a unique system configurable to your individual application.



## The M 700 concept

The new M 700 transmitter line is based on a completely new concept. So far, conventional in-line measuring systems for analytical parameters consisted of a transmitter and the corresponding sensor.

Being highly modular the M 700 is different, giving up the simultaneous measurement of up to three parameters. The basic unit is designed to accept modules for pH, conductivity and dissolved oxygen. A special high-resolution module for dissolved oxygen is offered to enable measurements to be taken at ppb level. Additional modules for PID control, output and limit contacts, as well as a PROFIBUS® communication module complete the M 700 concept. This remarkably versatile transmitter line guarantees a high standard of measurement together with optimal safety in the management of your process.

## High versatility

The instruments offer a range of powerful features through a menu-driven set-up program supported by graphical pictograms. The large and clear backlit LC display shows 2 process parameters. The side display can be configured to show process temperature, sensor-related data, differential measurement and much other important information. Special attention has been paid to the many maintenance functions and sensor diagnostic tools implemented in the basic unit of the M 700. A variety of options, such as an extended logbook, a two-channel measuring recorder, a service scope function, FDA 21 CFR Part 11 compliance and others, are available to optimize the functionality of the M 700 according to customer needs. All data and configurations are stored on a SmartMedia™ card. This storage medium is used worldwide as standard and allows easy data processing in peripheral computer systems.

The M 700 system comes in two designs. As well as a coated stainless steel enclosure for chemical process applications a robust hygienic stainless-steel enclosure is perfectly suited for biotechnology and pharmaceutical applications. Both enclosures are available for use with a standard power supply. ■

## Compliance

- Hygienic design
- FDA 21 CFR Part 11 compliance support



M 700 S  
Stainless  
steel polished



pH



DO



OUT (output)

- Parameter sets
- Extended logbook



SmartMedia™ card

# System Integration made easy

Analytical measuring systems from METTLER TOLEDO are particularly easy to link to modern process control systems and allow substantial cost savings for installation, configuration and maintenance. The communication protocols HART®, FOUNDATION Fieldbus and PROFIBUS® are fully supported by a variety of transmitters from METTLER TOLEDO.

METTLER TOLEDO offers measuring systems with standardized interfaces for HART®, PROFIBUS® and Fieldbus Foundation. This enables full exploitation of the advantages of digital communication for ease of instrument parameterization and maintenance. Process and instrument data are recorded via the interfaces, using software in accordance with Guidelines 21 CFR Part 11.

## HART® integration

METTLER TOLEDO transmitters use registered device description (DD) technology for the hand-held instrument HART® Communicator 275. Various instruments are also suited to the Management Software included in process control systems, e.g. AMS™ Suite from Emerson.

METTLER TOLEDO transmitters available for HART® are:

- pH 2100e and pH 2220
- O<sub>2</sub> 4100e and O<sub>2</sub> 4220
- Cond 7100e and Cond 7220
- Cond Ind 7100e and Cond Ind 7220

## PROFIBUS® PA integration

PROFIBUS® PA (Process Automation) is a standardized, open digital communication system for all fields of application in process automation. PROFIBUS PA (EN 50 170 P4) is a further development of PROFIBUS DP and includes two special features for process automation, namely bus powering and communication of field units using 2-wire technology. The transmitter units listed are also suitable for use in hazardous areas.

METTLER TOLEDO instruments are fully integrated into PDM (Process Device Manager) from SIEMENS.

METTLER TOLEDO offers a choice of PROFIBUS® transmitters including:

- pH 2100 PA
- O<sub>2</sub> 4100 PA
- Cond 7100 PA
- Cond Ind 7100 PA
- M 700 for pH, O<sub>2</sub> and Cond

## FOUNDATION Fieldbus integration

FOUNDATION Fieldbus (FF) is also a vendor-neutral, standardized and open digital communication protocol for all application fields. From the home page of [fieldbus.org](http://fieldbus.org), all relative integration data sets for the new FF transmitters from METTLER TOLEDO, pH 2100e and O<sub>2</sub> 4100e, can be downloaded.

METTLER TOLEDO transmitters suited to FOUNDATION Fieldbus are:

- pH 2100e
- O<sub>2</sub> 4100e
- Cond 7100e
- Cond Ind 7100e

Emerson has also tied in METTLER TOLEDO transmitters to its AMS™ Suite software.

## Complete product offering

With HART®, PROFIBUS® and FOUNDATION Fieldbus, METTLER TOLEDO now has at its command, state-of-the-art digital fieldbus protocols able to be linked to the respective process control system without any difficulty. ■



pH 2100e transmitter.

▶ [www.mtpro.com/transmitters](http://www.mtpro.com/transmitters)

HART® is a registered trademark of HCF  
PROFIBUS® is a registered trademark of Profibus Int.  
AMS™ Suite is a trademark of Emerson

# Why choose METTLER TOLEDO as your service solution provider?

## Our focus is customer success

The METTLER TOLEDO organization has the largest, best-trained global service network in the industry. Our global presence and reputation for quality make us the logical choice not only to provide classical services but also for services that go far beyond those of other service providers. We understand that today customers are less interested in repair services but much more in value-added solutions that give them competitive advantages in the marketplace. That is what we strive to provide our customers. Providing the highest levels of service and customer satisfaction is very important to Mettler-Toledo Ingold and we understand that our customers expect not only the highest quality products, but also superior customer and technical support when they need it. The service that INGOLD provides goes far beyond the initial purchase. We pride ourselves in being available for our customers, whether it is to answer a technical question, provide details on system operation or to manage requests for service. When you purchase products from Mettler-Toledo Ingold you have the satisfaction of using excellent products in your process and having a world class service organization standing behind them. ■

## Our customers receive:

- Quicker repairs and calibration
- Reliable, professional, efficient service
- Fast response time when you need it
- Higher system "uptime"
- Innovative and leading edge support services that meet future needs
- Regulatory compliance
- Improved productivity and enhanced competitiveness



### NEW - dedicated lines:

Mettler-Toledo Ingold has expanded and improved its US & Canadian support services, beginning with separate toll-free hotlines for Customer Service/Order Entry and Technical Services/Repair. To serve our customers better, calls will be immediately directed into the support center of choice, where skilled representatives will be prepared to quickly process your request.

#### Customer Service/Order Entry Hotline 1-800-352-8763

- Knowledgeable order entry representatives
- Quality products - stocked locally

#### NEW! Technical Services/Repair Hotline 1-888-687-7687

- Expertly trained service and repair technicians
- Comprehensive understanding of markets and applications

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