



In-line process control cuts process time by 40% at Mibelle Cosmetics

Mibelle AG Cosmetics in Switzerland introduced in-line analytical systems from METTLER TOLEDO, replacing traditionally performed off-line measurements. The adoption of automated non-glass pH measurement solutions has been a smooth transition which is already providing tangible benefits in terms of higher production efficiency and increased yield.

Cost pressure and more demanding regulations drive cosmetic producers

To meet consumers' growing awareness for well-being and desire for "pH-neutral" products, as well as comply with more stringent regulations, cosmetic producers strive for production process requirements more similar to those adopted by the pharmaceutical industry. Top players not only face intensified competition but also manufacturing cost pressure and tougher regulatory requirements. Contract manufacturers assigned by well known cosmetic players are accordingly influenced by the same trends. This article illustrates how a cosmetic producer took proactive action to meet these challenges.

Mibelle AG Cosmetics, Buchs, Switzerland

Mibelle does not only manufacture private label products for its parent company Migros, Switzerland's largest retailer with sales equivalent to around 17 billion US\$ (2004), but also for international retail chains like Body Shop. Mibelle specializes in "non-decorative cosmetics" such as hair, skin, sun and personal care products. Sales accounted for about 170 million US\$ in 2004, with 50% of the production exported. Mibelle is a dynamic growing company employing over 400 people, a figure that has doubled over the last five years. To face increasing customer demand, a plant extension is under construction in Buchs.



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Time consuming and inefficient off-line measurements

The production is focused on surfactant-based products such as shampoo, conditioners, shower gel, etc. and emulsion-based products like facial skin care products and body lotions. Presently, the production is set up of fifteen mixing tanks ranging from 500 l to 5000 l, including four 5000 l tanks dedicated to high-volume surfactant-based production.

In the manufacture of cosmetic products, pH measurement plays an important role in quality assurance and process monitoring. Neutralization of pH (ranging between 4 and 7) is usually done with either citric acid or caustic soda, depending on product and formulation. Until recently these measurements were performed off-line at Mibelle, procedures that were circumstantial and time consuming. "To determine the pH for our surfactant-based products, the sample taking, lab tests and adjustments of raw material supply could take up to 1 hour, assuming that more extensive adjustments were necessary. During the tests, the production had to be put on hold." Salvatore Bella, Bulk Production Supervisor in Buchs explains.

Off-line pH measurement the major bottleneck

Mibelle produces 800 different orders every year. To be able to produce more cost efficiently the company installed a new filling line, with a capacity of up to 200 bottles per minute, which is up to 25 tons per day. It became evident that the off-line measurements would be the major "bottleneck" making full utilization difficult. Reto Widmer, Bulk Production Manager, together with Mr. Bella and his team, began

New legislation/regulations likely to increase the need for in-line measurements

Regulations in the cosmetic industry are not (yet) as demanding as in the pharmaceutical industry. This is however a situation that is changing. Producers of cosmetic products are presently not obliged, but recommended to comply with the principles and guidelines of GMP. Larger companies currently already self-regulate and apply GMP, hygiene and safety standards. Contract manufacturers' present approach to regulations is often depending on their customer requirements. Cosmetic producers will likely adopt new in-line measurement solutions to anticipate more stringent legislations expected in the near future.



to discuss ways to optimize the production process. In-line measurements were considered; however, an imperative was the non-glass requirement. The use of glass electrodes for in-line measurements had for a long time not been an option, due to the risk of potential breakage. “Non-glass is mandatory in the cosmetic industry”, Mr. Widmer and Mr. Bella both claims. A search for suitable suppliers was initiated and a new door was opened when Mibelle was introduced to Mettler-Toledo INGOLD’s non-glass pH-sensor based on ISFET technology.

INGOLD automatic in-line solution for cosmetic manufacturer

METTLER TOLEDO provided a test installation demonstrating how Mibelle could reduce their processing time per batch with improved quality control standard, less labor and better consistency using an automated in-line analytical measurement solution. An InPro 3300 (ISFET) with automatic cleaning system – EasyClean 350e and an InTrac 777e retractable housing were installed in one of the four 5000 l tanks used for high-volume production of hair and skin care products.

Key customer benefits – 40% shorter process time and 50% higher yield

“One of the key advantages we have seen is that the processing time has been reduced by up to 1 hour per batch of 2 to 3 hours. If we earlier could produce 4 batches per day and 5000 l tank we can now produce 6, which is equivalent to around additional US\$ 8500 per day in semi-finished product value, depending on product and assignment. The new in-line system not only saves us time and cost, but also gives us a better batch-to-batch quality consistency due to continuous monitoring. Moreover, real time data enables immediate corrective actions, if needed. The goal of optimum utilization of the new filling line by producing a batch in one and a half hours has been reached”, Mr. Bella states.

Summary

- Time savings of up to 40% per batch
- Increased production efficiency through time savings resulted in:
 - 50% higher yield (6 batches instead of 4 per day and tank), equivalent to an increased value of around US\$ 8500 per day
 - fully utilized filling line capacity-minimized batch re-adjustments
- Better batch-to-batch quality consistency due to continuous monitoring
- Real time data allows immediate reaction
- Increased process reliability due to repeat accuracy
- Less labor and reduced human involvement leads to less human error

Outlook at Mibelle – Turbidity

After successful tests, Mibelle installed a complete solution consisting of InPro 3300, EasyClean 350e and InTrac 777e retractable housing in all of the four 5000 l tanks devoted to high-volume production of hair and skin care products. Mibelle has also expressed interest in testing an in-line turbidity system. At present, turbidity tests are performed optically comparing a batch sample with a reference sample. An in-line turbidity system ensuring that the batch is properly mixed and that all particles have been dissolved is an interesting option, according to Mr. Bella. “Such a system would not only reduce the processing time for stirring, but would also provide us with higher quality end products, increased product consistency and much more qualitative and reliable measurements”. ■



▶ www.mtpro.com/pH

▶ www.mtpro.com/cleaning

Cleaning system EC 350e and the InTrac 777e retractable housing.



In-situ CO₂ measurements to determine growth phase of *Saccharomyces*

Autumn Clapp, Virginia Bioinformatics Institute at Virginia Tech, USA

In conjunction with pH and dissolved oxygen, in-situ measurement of dissolved CO₂ is a critical parameter in evaluating the respiratory efficiency of microorganisms in cell culture. Virginia Bioinformatics Institute utilized the METTLER TOLEDO in-situ CO₂ measurement system to study *Saccharomyces cerevisiae* cells (yeast) in batch culture in order to accurately and reproducibly determine the growth phase of the culture as a function of CO₂.

The production of CO₂ by yeast in a batch culture can indicate the stage of growth for that culture. During the exponential phase, yeast cells grow by fermenting the available sugar and producing ethanol and CO₂ as by-products. The amount of CO₂ generated during the exponential growth phase can be directly correlated to optical density (OD₆₀₀) values which are generally used to determine the progression of the growth phase.

Experimental design

In the project developed by the Virginia Bioinformatics Institute, the response of *Saccharomyces cerevisiae* cells to oxidative stress induced by hydroperoxides was studied. Yeast cells were grown in a fermenter with controlled conditions of pH and dissolved oxygen to ensure that the response obtained was a response to oxida-

tive stress and not to other environmental conditions. Monitoring CO₂ production allows for a more accurate determination of the growth phase of the culture as opposed to just using OD measurements. This is important because the oxidant must be added at a specific point of the growth curve. Hence, the requirement of observing reproducible CO₂ curves during yeast growth.

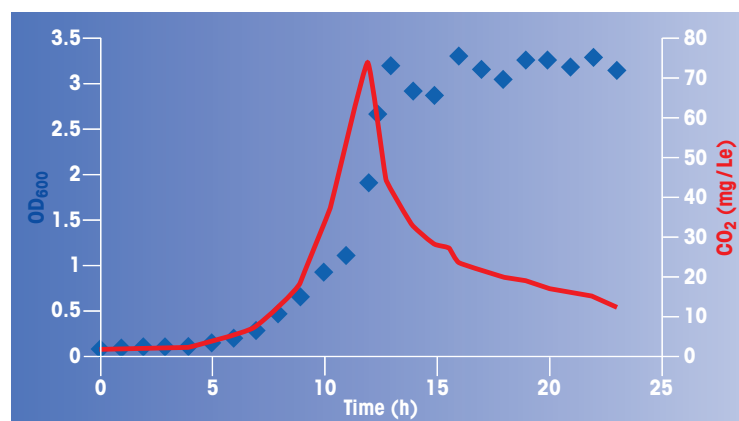
The first experiment was designed to test the reliability of the InPro 5000 CO₂ sensor, comparing its CO₂ measured values with the CO₂ results obtained via a GC-MS. A yeast culture was grown in a fermenter for 24 hours. Culture samples were collected from the fermenter for the determination of OD at 600nm and headspace samples were collected for CO₂ analysis by gas chromatography – mass spectrometry (GC-MS). Samples of 100µl drawn from

the fermenter headspace were injected at a split ratio of 10:1 into a GC-MS system. Mass spectra were recorded at 10 scans per second over a range of 30-100 m/z.

The second experiment was designed to test the reproducibility of the InPro 5000 CO₂ sensor. Two yeast cultures were grown in fermenters for 24 hours. Culture samples were collected for the determination of OD₆₀₀, and CO₂ measurements were recorded.

Results-Easier handling and less contamination risk

Autumn Clapp, the Fermentation Microbiologist for the Virginia Bioinformatics Institute at Virginia Tech in Blacksburg, VA stated, “the results obtained from the METTLER TOLEDO InPro 5000 CO₂ sensor were much easier to obtain than those from GC-MS. Using the InPro 5000,



Superimposition of graphs to show relationship between cell growth and CO₂ production.

cerevisiae

there is less chance of contamination to the culture as the sensor may be sterilized within the fermenter. In order to take samples from the fermenter for GC-MS analysis, a syringe must be introduced into the system which may introduce contamination. The InPro 5000 CO₂ sensor and 5100e transmitter interface also lends to easy readouts with no wait time as compared to GC-MS, and there is also no need for extensive data processing that is sometimes involved with GC-MS results”.

Benefits of the METTLER TOLEDO in-situ CO₂ system

The METTLER TOLEDO in-situ CO₂ system provides an accurate measure of CO₂ production that is comparable to a GC-MS, but the METTLER TOLEDO unit has several obvious advantages. The clearest advantage is that the InPro 5000 sensor is present inside the fermenter and

provides real-time measurement data that can be collected instantly, whereas an off-line system creates a lag time in the generation of results. The in-situ CO₂ system also is engineered with the highest possible hygienic design which virtually eliminates contamination where the off-line systems require user sampling that may compromise the fermentation.

Special thanks to: Autumn Clapp, A. M. Martins, Joel Shuman, and Vladimir Shulaev Virginia Bioinformatics Institute, Virginia Polytechnic Institute and State University Bioinformatics Phase II, Washington St., Blacksburg VA 24061-0477 USA

► www.mtpro.com/CO2



Distinctive benefits of CO ₂ sensor InPro 5000	
Easy to use	Modular design
Process calibration	Improved accuracy
Process safety	Hygienic design
MaxCert™ including	3.1B certificate EHEDG certificate End control certificates
Easy to maintain	Replaceable interior body



InPro 5000 CO₂ sensor.

Efficient pH control in a bioreactor

Many active pharmaceutical ingredients are produced today by microbial fermentation. In its simplest form, the bioprocess can be seen as just mixing micro-organisms with a nutrient broth and allowing the components to react. More advanced and sophisticated processes operating on larger scales need to control the entire system so that the bioprocess can proceed efficiently and be easily and exactly repeated with the same amount of raw materials and inoculum to produce precisely the same amount of product.

Acidification in bioprocesses

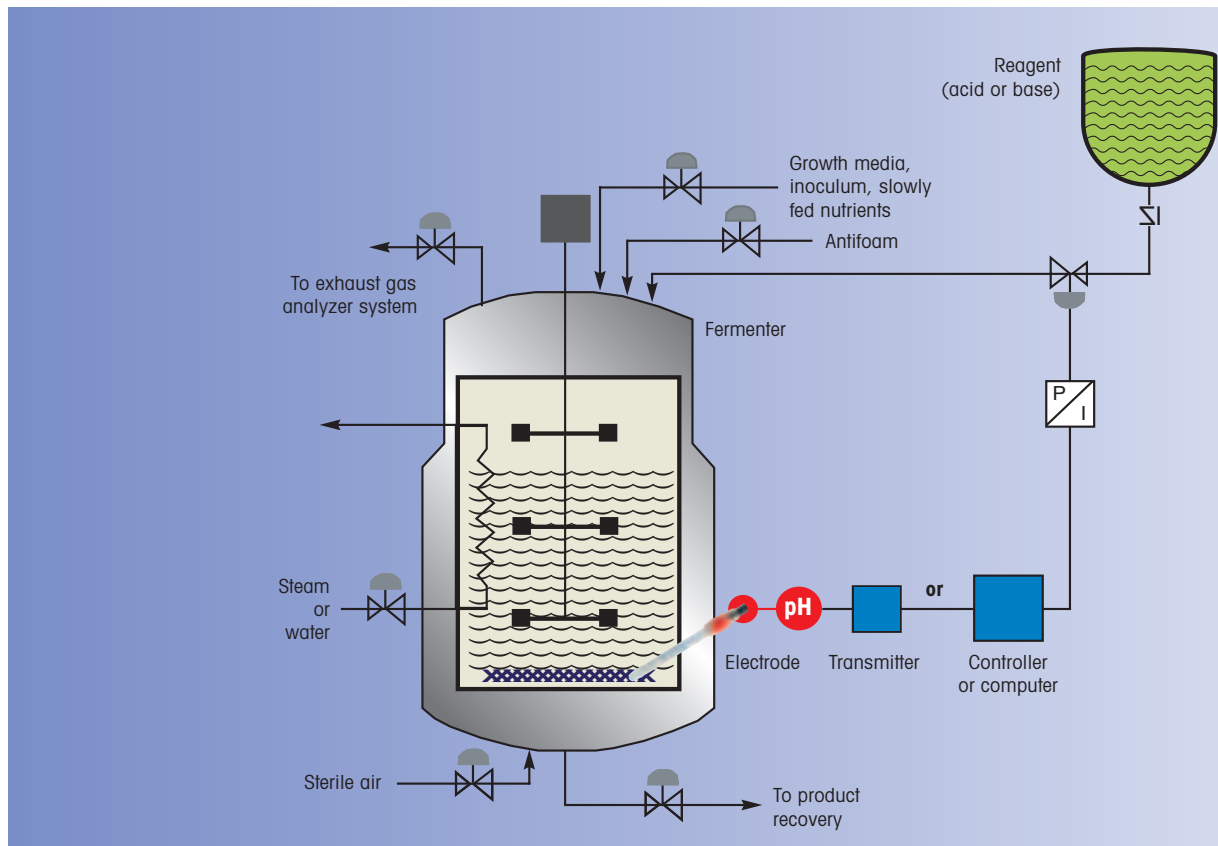
pH is one of the variables often controlled in bioprocesses operated in bioreactors because of enzymatic activity, and therefore, metabolism is very sensitive to pH changes. The acidification derives in most cases predominantly from the ammonia uptake when ammonium ions are provided as a nitrogen source. NH_3 is consumed and the proton left from the NH_4^+ causes a drop in pH.

The importance of precise pH control

Penicillin can be produced by fungal fermentation. The filamentous fungus *Penicillium chrysogenum* is used for bulk production by the pharmaceutical industry. In this process the pH of the broth must be closely monitored and controlled in both the growing phase and the production phase. Early in the growth phase, the pH of the broth is carefully maintained between pH 4.5 and 5.5, depending on the broth formulation. The range is set to ensure the most favourable condition for

growth. The metabolism of glucose and rapid consumption of ammonia during this phase adversely affect the medium by lowering the pH. If the medium is not correctly pH adjusted, growth will be inhibited and the fermentation will take a long time to reach the optimal range required for penicillin production. In the production phase, the organism starts to metabolize other sugars (lactose) and amino compounds because of the depletion of glucose. The liberation and accumulation of ammonia from the metabolism of amino compounds will cause the pH to rise

Fig. 1 pH control loop on standard fermenter.



slowly. The pH is allowed to rise to about 7 and is controlled at this point until the end of production. Depending on the culture and several other factors, it has been found that the optimum pH range for penicillin production lies between 6.8 and 7.8. The pH is carefully monitored and controlled in this range by the addition of sulfonic acid. Finally, at the end of the fermentation, the pH rises and production stops. Figure 1 depicts the pH control loop implemented on a standard bioreactor.

Certified METTLER TOLEDO solutions

The pH electrode of choice for fermentation is the InPro 3253. The biocompatible, pre-pressurized liquid reference electrolyte ensures constant performance and reproducibility. With a pressure specification of 4 bar (58 psi) this electrode can also be installed in large production bioreactors. The built-in temperature sensor allows for an easy calibration without manual temperature setting at the pH transmitter. The calibrated electrode will be sterilized together with the bioreactor. The InPro 3253 is designed for sterilization temperatures up to 140 °C (284 °F) and shows excellent performance even after many sterilization cycles. The electrode can be mounted into an InFit 761e housing, meeting the highest hygienic standards. pH is such an important parameter that often two pH electrodes are installed in one bioreactor. The M 700 transmitter can be equipped with two pH measurement

modules and fits perfectly for this double measurement with enhanced sensor diagnostics. The M 700 transmitter is compliant to FDA 21 CFR part 11 and allows a hierarchic access to device settings and functions. The electronic signature allows identification of individual users.

The combination of InPro 3253pH electrode with the M 700 transmitter and InFit 761e housing is a sophisticated pH measuring system for control of bioprocesses. Controlled growth conditions during fermentation will lead to higher yield and improved repeatability from batch to batch. ■

► www.mtpro.com/pH



InPro 3253 pH-electrode

- excellent performance after many sterilization cycles at temperatures up to 140 °C/284 °F
- for overpressures up to 4 bar/58 psi
- EEX proof provided with ATEX and FM certificates
- supplied with a biocompatibility certificate



InFit 761e – CIP housing

- fulfills highest hygienic standards
- designed with ideally positioned o-rings
- provides multiple insertion lengths
- all parts in contact with the medium meet the N5 and R16 requirements



M 700 transmitter

- stores extended data with SMARTMEDIA™ card
- two simultaneous pH electrode measurements
- compliant to FDA 21 CFR part 11
- On-line sensor diagram reduces downtime with unique sensor diagnostic tool

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