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Universities of Applied Sciences

Fachhochschulen – Hautes Ecoles Spécialisées

PAT at the Universities of Applied Sciences

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Abstract: An overview of activities in the field of Process Analytical Technologies (PAT) at the Universities of Applied Sciences in Switzerland is presented.

Keywords: Applied Research and Development · Life Sciences · PAT · Process Analytical Technologies

Introduction

Process Analytical Chemistry (PAC), a field that could be considered the predecessor of PAT, was developed over half a century ago by the petrochemical industry. Process analyzers, applying standard laboratory analytical techniques directly in the production area traditionally included tools such as the automatic titrator, the pH-meter or gas chromatography.[1] Since the beginning of the current century, significant development has been achieved in on-line instrumentation and we have today a wide range of analyzers, such as specific gas sensors or spectroscopic tools (FT-IR, NIR, Raman). The term Process Analytical Technology (PAT), coined in 2004 by the FDA, is used to describe the application of analytical chemistry to gain process understanding, control manufacturing processes and improve the consistency in product quality (Fig. 1). Aiming to increase productivity and quality, the FDA, and other regulatory bodies, encourage the pharmaceutical and chemical industries to systematically implement the PAT strategy in their processes.[2]

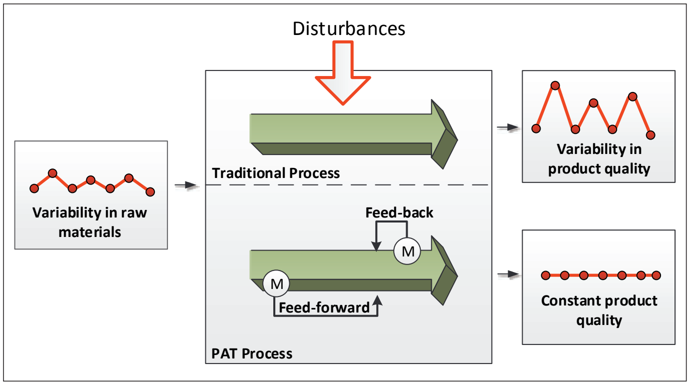

Fig. 1. Schematic illustrating the difference between a traditional process, where variations in raw materials and process disturbances induce the variability in product quality, and a PAT process, where on-line measurement and control ensure constant product properties.

Nowadays, PAT is widely applied throughout the chemical, physical and biological process fields, spanning batch to continuous production processes. The Universities of Applied Sciences in Switzerland are active in this area and some example projects are described below.

HES-SO – Haute école d'ingénierie et d'architecture de Fribourg

The Institute of Chemical Technology (ChemTech) at the School of Engineering and Architecture of Fribourg is active in the field of Process Analytical Technologies applied to chemical processes at various scales: from micro- and mesoreactors to lab-scale and pilot plant production vessels. The fields of application span chemical synthesis reactions, bioprocesses and polymer extrusion systems.

An applied research project, completed in 2013, addressed the issue of monitoring and controlling the quality of polylactic acid (PLA), a bio-sourced and biodegradable polymer produced by reactive extrusion. The aim of the study was to ensure constant and optimal properties of the polymer despite process disturbances and variations in the properties of the raw material – a criterion of great importance in the plastics industry. The average molar mass of the polymer was monitored on-line using an NIR spectrometer. Periodic off-line analysis provided reference measurements that served to validate and correct the spectrometer's calibration model and ensure its accurateness. Information delivered by the NIR was used by a feed-forward/feedback controller that, in turn adjusted the process parameters.

The PAT strategy is also useful for continuous processes. Microreactor technology is based on continuous flow chemistry through a tubular reactor with a typical diameter of less than 1 mm. Microreactors offer many advantages, such as rapid heat and mass transfer, which enhances the control of temperature, ratio of reactants and reaction time. Several PAT applications have been developed with this technology with a Modular Microreactor System (MMRS) of Ehrfeld Microtechnik BTS, as illustrated below:

Case 1: The photochemical decolorization of azo dye by UV/H_2O_2 advanced oxidation process (AOP) was optimized in a continuous photoreactor. On-line measurement by visible spectroscopy using an optical flow cell (Fig. 2a) was used to adjust the amount of oxidizing agent.

Case 2: A transesterification reaction of pentyl acetate with ethanol was followed in-line by ATR FTIR (Fig. 2b) and chemometrics. Temperature and retention time were adjusted to keep a constant yield.

HES-SO Valais-Wallis

The successful commercialization of the bioplastic poly(3-hydroxybutyrate) (PHB) is hindered mainly by the relatively high production cost. One practicable way of reducing the production

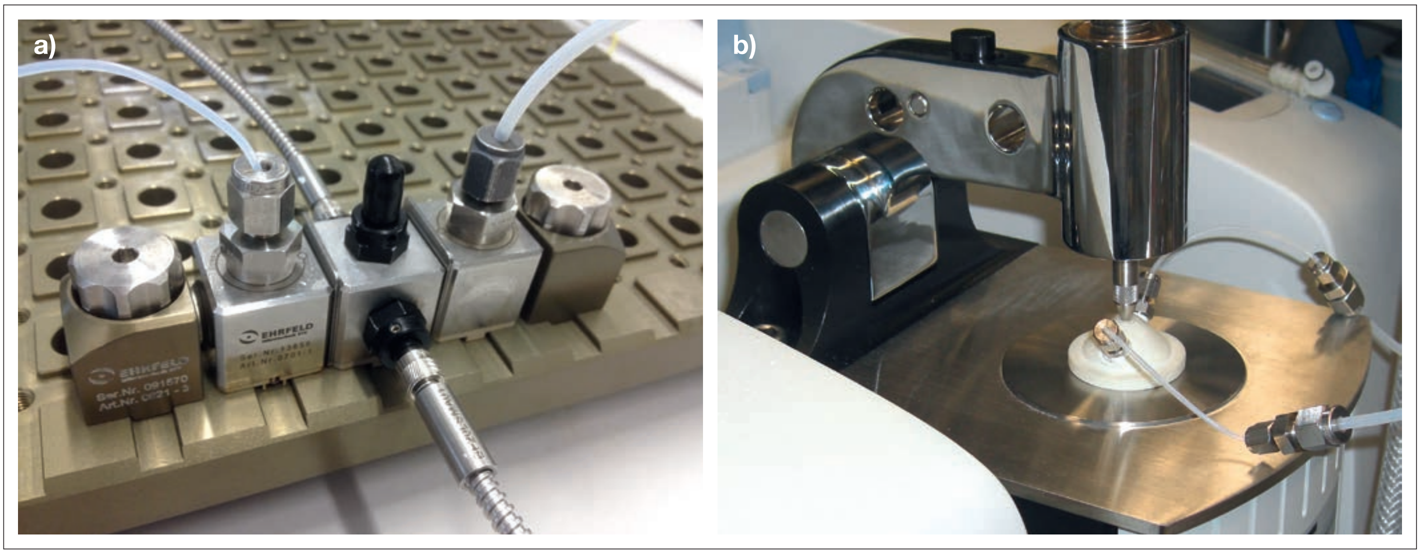

Fig. 2. a) Ehrfeld microreactor with optical flow-through cell. b) Perkin-Elmer Spectrum 100 FT-IR with ART module and flow-cell.

cost is to use waste sources as cheap substrates. Within the European project SYNPOL (*www.synpol.org*) we investigate the application of syngas (also known as synthesis gas) as a suitable source of energy and carbon.

A special fermentation platform placed in two fume hoods was established that allows the cultivation of *Rhodospirillum rubrum* (Fig. 3). Two independently controllable bioreactors of 3.6 and 13 L (Labfors 5, Infors AG, Bottmingen, Switzerland) equipped with CIP and SIP (cleaning and sterilization in place, respectively) can be supplied with particular gas mixtures containing H_2, CO, CO_2, and N_2 that can be adjusted individually by mass flow controllers. The bioprocess itself can be monitored by real-time analysis of the off gas by mass spectrometry (QIC20, Hiden Analytical LTD, Warrington, U.K.) equipped with a CO analyzer in ppm range and by the redox signal (Easyferm plus ORP Arc 325, Hamilton Bonaduz AG, Bonaduz, Switzerland) indicating the metabolic activity in the culture broth. A PHA staining protocol using BODIPY, originally established for *P. putida,* was adapted to *R. rubrum* and thus enables the quantification of PHB at a single cell level using flow cytometry. Consequently, the PHB accumulation but also the intracellular recycling of PHB under carbon starvation can be studied and correlated to the changes in the chemical environment. Recently, we have established a liquid handling system run by LabView in order to further automatize sampling, appropriate dilution to 10^6 cells mL^{-1} as well as optimized staining of the cells. Thus, we will be able to assess the cell physiological response to changes in the environment and based on these findings develop tailored control strategies for the cultivation of *R. rubrum* and PHB production under fed-batch and continuous cultivation.

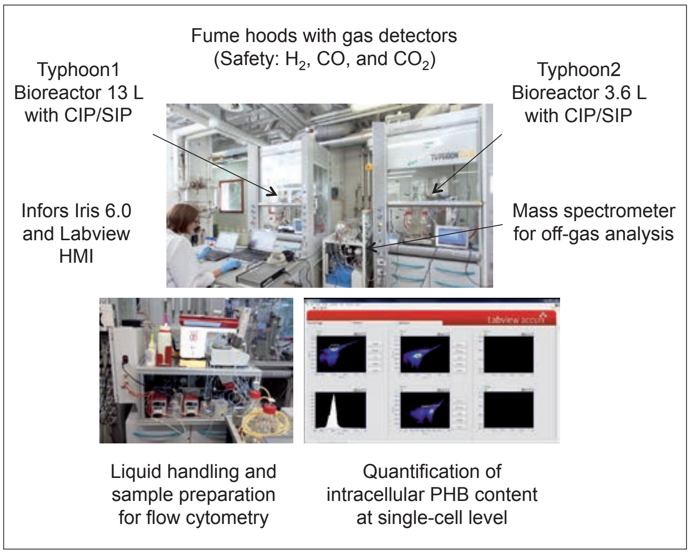

Fig. 3. The PAT platform for the syngas fermentation established at HES-SO Valais-Wallis enables safe experimentation and development of bioprocesses for *Rhodospirillum rubrum* to produce poly(3-hydroxybutyrate).

FHNW Muttenz

Beside the main requirements of PAT for continuous process analytics and parameter control of sophisticated processes, there is a need for a specific measurement and control device which can be used for the measurement of the target product along the process chain, too.

For binary liquid mixtures, optical measurement devices like refractometers can be used for the on-line detection of one of the two components with an accuracy of up to 1/1000 mass percent if calibration curves are available. However, in the presence of secondary components, this precision declines rapidly to an unacceptable range. As a result, a refractometer cannot be used as a PAT instrument.

The Chemical Engineering department at the School of Life Sciences, FHNW, developed a membrane-based de-alcoholization unit for beer.[3] By using nanofiltration membranes beer can be separated in two streams: one, the so-called retentate contains almost all beer components, including alcohol, whereas the color-free, clear permeate includes mainly water and some of the alcohol. In batch mode operation, up to 500 l of beer can be dealcoholized within 2–3 hours. By adding (oxygen-free) water to the retentate in order to achieve the initial beer volume, the alcohol content can be reduced to a very low limit (<0.1 vol.%).

Membrane processes in general and the de-alcoholization of beer by means of membranes in particular require skilled operators in order to supervise both the stability of the membrane and the endpoint of the batch process. At a certain effort and cost, the operator's experience can be programmed into a control-system consisting of several measurement and regulation devices to achieve a reliable automated process operation. Yet it could be shown that with the use of an on-line refractometer, placed on the permeate side, the alcohol concentration in beer could be detected with an accuracy of 0.02 vol.% due to the fact that the selected membrane does not shift the alcohol/water ratio either in the retentate or in the permeate. However, the measurement of the alcohol concentration in beer with the refractometer leads to an accuracy of only 0.2 vol.%. Hence, the refractometer signal can be used as a measurement of the actual alcohol concentration in the retentate (alcohol-free beer). Moreover, the sufficient high difference in refractive index of both the beer and the permeate allows the detection of membrane leakage. Whenever unfiltered beer passes to the permeate side unattended, the refractive index immediately increases (Fig. 4). This signal surge can be detected easily and allows a quick shut-down of the operation, reducing product losses.

Thus, the combination of membrane technology with innovative on-line measurement generates a robust measurement and regulation of a demanding process in a PAT fashion.

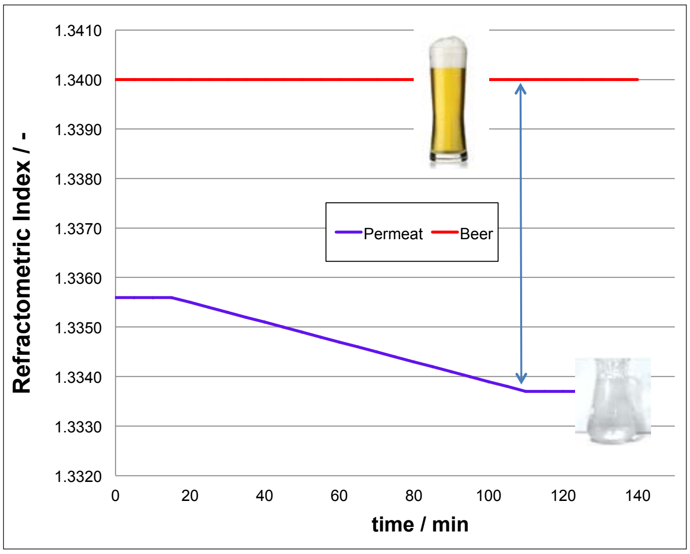

Fig. 4. Refractive index in beer and in the permeate during the membrane de-alcoholization process.

ZHAW Wädenswil

The Institute of Chemistry and Biological Chemistry is equipped with a broad range of Process Analytical Technologies (PAT) used for on-line measurement of all states of matter (gaseous, liquid, solid) to obtain relevant process information. Examples include chromatographic methods (on-line GC for the monitoring of transformer oils[4]), as well as mass spectrometry (on-line PTR-MS to control the roast degree of coffee[5a,b]), spectroscopic methods (at-line fluorescence spectroscopy for cleaning validation[6]) and flow cytometry (on-line flow cytometry for bioprocess monitoring[7]). Due to the generation of large amounts of real-time and generally multivariate data, chemometric data analysis is typically used.

Spectroscopic process analytical technology is particularly useful for gaining basic process understanding during process development. Therefore, the Center for Industrial Chemistry focuses on on-line spectroscopic methods covering the whole spectral range from ultraviolet and visible to near- and mid-infrared thus using absorption, reflection and scattering to analyze industrial processes. Defined work packages are often investigated by students in preliminary project phases.

Recently, in-line IR spectroscopy was used to monitor the development of an enzymatically catalyzed synthesis of a non-ionic surfactant. It was found that the transesterification reaction could be continuously analyzed in-line, even in presence of the dispersed heterogeneous catalyst. In contrast to the laborious, slow and low-frequency gas-chromatographic offline process analysis, process understanding was gained in a relatively short time. Applying multivariate regression methods to the acquired IR spectra, the synthesis of the surfactant was monitored over 48 hours and the declining reactant concentration was determined (Fig. 5).[8]

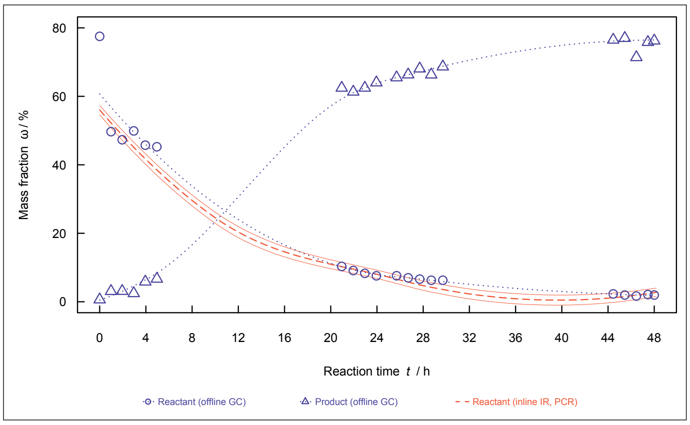

Fig. 5. Mass fraction of reactant and product: off-line gas-chromatrographic laboratory analysis (blue circles and triangles) and prediction model by means of principal component regression (PCR) based on in-line IR-spectra (red broken line with range of uncertainty).

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