Online Monitoring of TOC Contaminations in Clean-in-Place Processes for Optimized Process Control, Increased Process Efficiency and Quality

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A Process Analytical Technology (PAT) compliant unit (acronym PATOV) was designed for online monitoring of Clean-in-Place (CIP) processes used in the pharmaceutical and food industry. The PATOV unit tends to significantly optimize CIP processes by online monitoring Total Organic Carbon (TOC) equivalent contaminations in the CIP off-stream to increase the efficiency and the quality of the cleaning process. The data will be used for an online control of the process to ensure optimal cleaning in minimized time. This will certainly allow for extensive savings of energy, water, and cleaning agents. Commercially available TOC analyzers qualified for the purpose require several minutes to provide a reliable TOC result. By implementing a mid-IR laser absorption technology, more precise a sensor based on an External Cavity-Quantum Cascade Laser (EC-QCL), the necessary information can be gained within seconds. An experimental CIP pilot plant was installed to reproduce CIP procedures by cleaning a vessel of a typical size used in pharmaceutical production processes. A continuous sample flow is gathered from the CIP off-stream and fed into the PATOV unit which is placed close to the CIP pilot plant. The contamination of the CIP process water can be measured with a time resolution down to one second. The retention time of contaminations from the CIP pilot plant to the PATOV unit was minimized to <10 s by the design of an optimized sampling system. Currently, the TOC can be detected within the short timelines mentioned for single contaminants down to a concentration of e.g. 20 ppm for glycerol. Provided that the detection of lower concentrations and the calibration for other model contaminants, such as xanthan and proteins can be achieved, the PATOV unit has a high potential to improve the efficiency and the quality of CIP processes in the pharmaceutical and food industry.

1. Introduction

The cleaning of production equipment in pharmaceutical and food industry is a crucial part of the production process. While the invention and further development of automated CIP systems decades ago substantially increased the reliability and efficiency of the cleaning processes compared to manually cleaning by process operators, still a high potential for improvement of the cleaning processes remains. CIP equipments provide Water for Injection (WFI) along with cleaning agents at predetermined temperatures and pressures for realization of preconfigured cleaning cycles. To guarantee high level regulations demanded by the Food and Drug Administration (FDA) and other regulatory institutions (US FDA - CDER, 2005), the cleaning cycles usually last considerably longer than necessary. Typically, laboratory testing of a sample taken from the final rinse verifies if the requirements are fulfilled and the production process can resume. Apparently, this approach leads to waste of water, cleaning agents and energy and additional to long periods of process downtime.

Today, an established approach to verify cleaning processes is the quantification of the TOC in CIP off-stream samples. An overview on cleaning validation is e.g. given by Lakshmana (2010), savings strategies for cleaning fluids have been investigated e.g. by Dif et al. (2012). Analyzing a sample for TOC is typically based on entirely oxidizing the sample. Thus every contained carbon atom reacts to CO_2 which can be quantified using dispersive near-infrared techniques. While by now several online TOC analyzers are commercially available, as far as we know, up to now none of them is suitable for covering the whole cleaning process regarding a real time validation from very high ($>10^4$ ppm) down to very low TOC (<1 ppm) contaminations. Commercially available online TOC analyzers to be considered for this task typically provide results with a frequency of several minutes. Even if the actual measurement time might be shorter, cleaning procedures or sample preparation extend the time before the analyzer can measure the next sample.

To significantly optimize CIP processes by introducing an online, real time cleaning validation system a PAT compliant unit (acronym PATOV) was designed for online monitoring. The PATOV unit intends to ensure optimal cleaning, while simultaneously controlling cleaning time and cleaning agents used and to provide additional analytical information. The optimized process control has a high potential to significantly increase process efficiency and quality and therefore reduce cleaning costs and process downtime.

The PATOV unit is based on a mid-infrared (mid-IR) laser absorption technology. The application of mid-IR spectroscopy to monitor the cleaning process is a promising alternative to the use of commercially available TOC analyzers. The mid-IR spectral region includes electromagnetic radiation with wavelengths between ~3 μm and ~20 μm. In this spectral region the fundamental vibrational states of molecules can be found, i.e. that molecules irradiated with mid-IR light will show absorption of specific wavelengths. According to the Beer-Lambert law, the concentration of an analyte can be determined by the amount of the absorbed light. The Beer-Lambert law is defined as

$$A = -\log I / I_0 = \alpha \cdot c \cdot d \tag{1}$$

where I is the intensity spectrum of the sample [a.u.], I_0 the intensity spectrum of the background or solvent [a.u.], α the molar absorption coefficient [L mol^{-1} m^{-1}], c the sample concentration [mol L^{-1}] and d the interaction length (= optical pathlength in the sample) [m]. Mid-IR absorption spectroscopy is molecular specific, direct and reagent-free. It offers online capability and quasi-continuous measurements with time resolutions down to <1 s. It is therefore a promising technique for application to process monitoring in CIP environment.

2. Experimental CIP pilot plant

To optimize process equipment and for testing of the PATOV unit, a base case CIP system was configured and installed. The base case was defined with regard to real pharmaceutical CIP systems, though the design was limited to necessary procedures and equipment sufficient for the testing purpose. The pilot plant enables to reproduce CIP procedures by cleaning a vessel of a typical size used in pharmaceutical production processes. A picture of the experimental CIP pilot plant is shown in Figure 1. It consists of a water storage tank, a heat exchanger, pumps for cycling the water and the connecting pipes. The vessel is located in the center of the pilot plant. A spraying device installed in the lid of the vessel delivers the cleaning fluid to the walls.

Figure 1: Experimental CIP pilot plant.

Table 1: CIP steps

Step	Notation	Liquid	Temperature	Operation
1	1st rinse	WFI	ambient	once through
2	1st wash	WFI, NaOH, 2%	70 °C	recycle 15 - 60 min
3	2nd rinse	WFI	ambient	once through
4	2nd wash	WFI, HNO_3, 2%	ambient	once through
5	Final rinse	WFI	ambient	once through

To avoid build-up fluid in the vessel, a self-priming pump is mounted on the CIP system. It is used to pump the fluid out of the vessel, either back to the water storage tank for recirculation or directly to the drain. The experimental CIP pilot plant covers the major process challenges existing in real pharmaceutical CIP systems. The pilot plant is equipped with additional instruments and signals for experimental investigations. The gained supplemental data are used for optimization of the CIP system. Three sampling points are implemented to verify the optimal location for the PATOV unit, which have been identified by CFD simulations. To retrieve a gas free sample for the PATOV unit an additional separator unit was developed and installed. Finally, successive CIP steps (listed in Table 1) have been defined to represent the model process.

3. PATOV analytical unit

The PATOV unit with the implemented IR equipment is placed close to the CIP pilot plant. The PATOV unit consists of several components which are assembled in a custom built frame made out of aluminum profiles and aluminum boards with protective covers of acrylic glass (not shown). A scheme with the major parts and connections is shown in Figure 2.
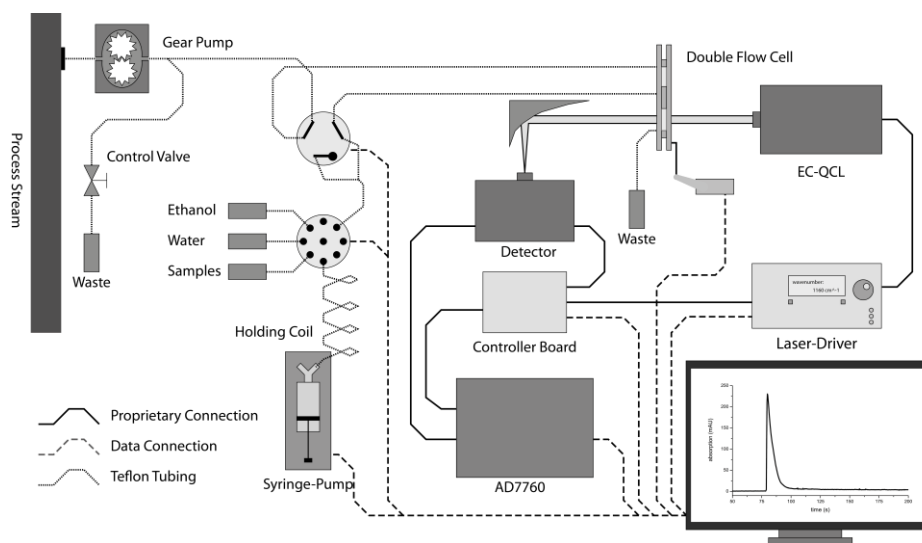

Figure 2: Scheme of the PATOV analytical unit

The core element of the PATOV unit is the mid-IR absorption set-up consisting of the mid-IR laser light source, a transmission flow cell where the sample is placed into the optical path, and a thermoelectrically cooled mercury cadmium telluride (MCT) infrared detector. A novel broadly tunable QCL (Daylight Solutions Inc., USA) is used as light source. Compared to standard Fourier Transform IR (FTIR) spectrometers, the light intensity is much higher (more than four magnitudes higher than for glow bars) and the emitted wavelength can be controlled electronically, resulting in a device without an interferometer. The wavelength is set by an internal rotating grating that enables the laser to emit from 1,030 to 1,230 cm^{-1}. Tuning over the whole emission range and moving back to the start point takes ~4 s. The maximum spectral emission power density is approximately 350 mW. The transmission flow cell consists of two CaF_2 windows that are separated by a 160 µm layer of Polytetrafluoroethylene (PTFE) and an aluminum construction, holding the parts together. Due to the high intensity of the QCL, the optical path length is increased compared to conventional FTIR spectroscopy. The increased path length reduces the vulnerability to clogging which is an important factor in practical field application. As the laser beam is

~3 mm in diameter, an off-axis parabolic mirror is used to focus the light onto the detector element (element size ~1x1 mm). Conventional detectors in mid-IR spectroscopy require liquid nitrogen cooling which makes them unsuitable for applications outside the lab. To circumvent that, a MCT-detector with an implemented Peltier cooling element is used. This cools the detector element down to -58 °C. Due to the MCT-technology, every single laser pulse (repetition rate: 100 kHz) can be resolved.

The interface between the PATOV unit and the CIP pilot plant is realized by a bypass system consisting of a gear pump, a T-connector and a control valve. The injection valve (6-port, VICI, Switzerland) offers the possibility to select between the process stream and the calibration channel with the cleaning agent or the calibration samples (Figure 2) to be directed to the transmission flow cell. Every analyte shows different extinction coefficients, depending on the used wavelength. In order to calculate the proper contaminant concentration those coefficients have to be determined. This is done by measuring samples with different concentrations of the analyte/contaminant and fitting an appropriate calibration curve. Hence, a calibration channel is used for injection of the background liquid (WFI) and for cleaning the transmission flow cell as well as for injection of off-line samples used for calibration of the prototype device.

The PATOV analytical unit offers two modes of operation – scan mode and single wavelength mode. In scan mode a full absorption spectrum of over 200 cm^{-1} (maximum tuning range of the currently used QCL) is recorded. The spectral information offers the possibility to not only measure the amount of contamination but to even discriminate between the type of contamination. The time resolution in scan mode is currently limited to 6 s (limited by the used QCL). In contrast to that the single wavelength mode increases the time resolution to values <1 s. However, it is only possible to measure at a single emission wavelength, i.e. there is no spectral information available.

4. Results

Two different CIP steps (see Table 1) have been investigated: rinses and recycles. In both configurations either a single contaminant or a mixture of two contaminants (glycerol, xanthan, soy peptone) has manually been placed into the reaction vessel. The results presented here are restricted to glycerol contaminations, ambient temperature and Water/WFI as cleaning fluid (no caustic). The CIP system was activated and the contaminated off-stream process water was measured on-line by the PATOV unit. In recycle mode the cleaning water was pumped in a closed cycle. In rinse mode the cleaning water was pumped once through to the drain. For reference measurements samples were manually taken at defined intervals. The TOC measurements were conducted afterwards off-line using a Shimadzu TOC-VCSH/CSN TOC Analyzer.

4.1 Calibration

Calibration was performed by measuring a number of predefined glycerol solutions with the PATOV analytical unit. Data were acquired in single wavelength mode and served as calibration for calculating the TOC level which corresponds to the measured absorption. To improve the calibration a second procedure was tested by using a vessel equipped with a stirrer. The water in the vessel was weighed and defined amounts of tracer substance were added in steps. A calibration curve was calculated by averaging ten data points, ten seconds after each spiking step. This procedure resulted in a higher linearity compared to the manual calibration procedure. The calibration data are given in Table 2.

Table 2: Calibration data

first calibration	second calibration
R^2 = 0.9993	R^2 = 0.99986
LOD_{TOC} ~ 90 ppm	LOD_{TOC} = 20.6 ppm

4.2 Laboratory experiments

Laboratory experiments were conducted using the experimental CIP pilot plant described in Section 2. An example of an on-line measurement performed in scan mode is shown in Figure 4(a). The reaction vessel was contaminated with approx. 1,000 g glycerol (operating conditions: flowrate: 2,000 kg/h, temperature ~20 °C, vessel volume 320 L, spray ball Sani Midget). The start of the cleaning process is indicated by the dashed arrow. The CIP system was used in recycle mode. Therefore, the contamination peaks reappear several times before further cycling has no impact anymore since the contamination is evenly distributed in the process water. The dotted arrow indicates a cleaning step of the flow cell. After the cleaning step, the glycerol contamination remains constant. Clearly the scan mode offers extensive spectral information of the contamination, yet the time resolution is significantly decreased compared to single wavelength mode.
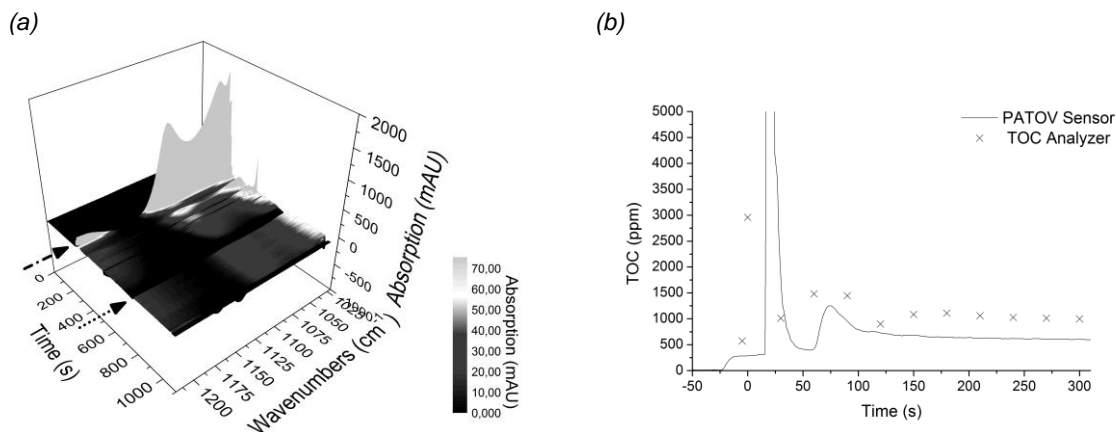
(a)   *(b)*

Figure 4: *Cleaning cycle with glycerol as contaminant measured in scan mode (a) and measured in single wavelength mode (b). Measurement results for TOC off-line samples are included by symbols*

In Figure 4(b) an example of a glycerol recycle performed in single wavelength mode is shown (operating conditions: contamination approx. 1,000 g glycerol, flowrate 2000 kg/h, temperature ~20 °C, vessel volume 320 L, spray ball Sani Midget). The absorption measured by the PATOV analytical unit was converted to a TOC equivalent using the calibration data given in Section 4.1 (first calibration). The TOC equivalent is shown as a function of time. Even though the cleaning effect depends on various parameters (e.g. flow rate, spray ball, contamination), all measured TOC curves exhibit basically similar progressions like the example shown in Figure 4(b). A first peak appears only a couple of seconds after starting the CIP process as the distance between the contaminated vessel and the sampling unit is very short. After the process water has passed one cycle a second peak is visible, which indicates that the cleaning is still productive. Finally the TOC approaches an asymptotic behavior indicating that further operation will not be worthwhile. The signal gained by the PATOV unit provides valuable on-line process information. Samples for TOC off-line measurements have been taken every 30 s during the cleaning cycle. The measurement results are included by symbols. Evidently, the results show large quantitative deviations, while qualitative agreement is obtained regarding the progression.

4.3 Field operational tests

Field operational tests were conducted at a Biopharmaceutical Contract Manufacturing company (project partner CMC Biologics A/S in Copenhagen, Denmark) using a simplified version of the experimental CIP pilot plant (see Section 2). The most important differences were the use of a slightly smaller vessel (Sartorius BBI Biostat D), single pass flow of cleaning liquids and that the separation unit was not included. Only rinse steps have been tested due to operational restrictions. The experiments were performed by initially filling the water storage tank with high purity water and heating the water up to approximately 20 °C. Afterwards the vessel was contaminated with 100 g pure glycerol using a syringe. The cleaning process was started by pumping the high purity water into the spray ball and cleaning subsequently the vessel. The gear pump, which transported the liquid from the bottom of the vessel to the PATOV unit, was started with a delay of approximately 3 s to make sure that the sample point is filled with water. The signal of the PATOV unit was recorded with a data rate of approximately 3 data points per second.

Some promising results have been obtained. One example is shown in Figure 5(a) (operating conditions: flowrate: 490 kg/h, temperature ~20 °C, vessel volume 150 L, spray ball small HAKE). The continuous lines represent the data of the PATOV unit and the symbols are the results off-line sample measurements. Again the off-line measurements show significant deviations, but a qualitative agreement regarding the progression. Certainly various errors have to be considered with the comparison, in particular differing sampling volumes and sampling positions. The PATOV unit works with a continuous pump flow and small dead volume. Each offline sample contained approximately 50 mL of cleaning liquid and it took 2 to 5 s to take each sample. Further examples are presented in Figure 5(b) (operating conditions: flowrate: 1,370 kg/h, temperature ~20 °C, vessel volume 150 L, spray ball big HAKE type X1-1). Data of the PATOV unit are shown for two experiments conducted for identical parameters (flow rate, spray ball, temperature, type and amount of contamination, etc.). The curves show a significant difference, which can be expected due to diverging cleaning effects from the different start contaminations at the vessel surface. In fact the line integral matches in the order of about 94 %.
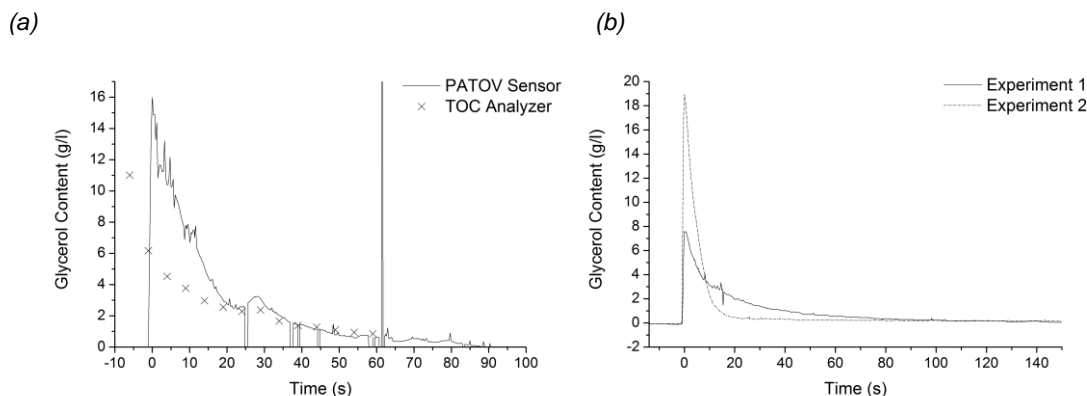
Figure 5: Rinse tests with glycerol as contaminant measured in single wavelength mode (a, b). The measurement results for TOC off-line samples are included by symbols (a).

5. Summary and conclusions

Based on mid-IR absorption the new developed PATOV unit offers quasi-continuous measurements with time resolutions down to one second. Bearing in mind that the time delay caused by the sampling system is in the order of 10 s, the PATOV unit enables online monitoring of CIP processes. The PATOV unit was successfully applied to experimental CIP process equipment. Calibration for glycerol was conducted with high linearity down to a detection limit of 20 ppm. First laboratory experiments and field operational tests show promising results. Valuable process information was gathered which could be used to significantly optimize the cleaning procedures resulting in increased process efficiency and quality. It has to be emphasized that the sampling position must be well chosen and short connection lines to the PATOV unit have to be established. Also, experimental data with regard to IR-QCL / TOC comparison have to be considered as preliminary. TOC measurement of off-line samples show large quantitative deviations - partly due to a difficult sampling situation at the plant site, therefore validation of the on-line data will be a very important target for future investigations. Extension of the analytical device for application to proteins is currently being processed by manufacturing a QCL light source for the protein spectral region. Improving the detection of lower concentrations and calibrating for other model contaminants and real-world contaminations will be objectives for further investigations. Future applications of the PATOV unit may also involve CIP of food processing plants.

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