Elimination of APIs by UV Oxidation in Wastewater from CIP-Rinsing at a Multiple API-Formulation Facility Using Advanced Oxidation Process

Martin Sörensen[1], Jürgen Weckenmann[1], Frank Zegehagen[1], Tara Miller-Reichling[1], Ulrich Schaffer[2], Uwe Waldeck[2], Elisabetta Marani[3], Mark Incledion[3]

[1]enviolet GmbH, Karlsruhe, [2]Catalent Germany Eberbach GmbH, Eberbach, [3]Catalent U.K. Swindon Zydis Ltd., Swindon, United Kingdom

Correspondence: Dr.-Ing. Martin Sörensen, Enviolet GmbH, Schenkenburgstr. 18, 76135 Karlsruhe, Germany; e-mail: MS@enviolet.com

ABSTRACT

In order to achieve an environmentally-friendly and cost-effective solution to treating wastewater from CIP-rinses in their facility for multiple API formulations, Catalent in Eberbach, Germany, commissioned an advanced UV oxidation plant to reliably and flexibly treat their highly variable wastewater so it could be released directly into the municipal wastewater system. A comparison of alternative methods led to the selection of UV oxidation and laboratory tests and feasibility studies pinpointed the best oxidation procedure for the degradation of harmful and toxic compounds in the industrial effluent to be UV oxidation (Advanced Oxidation Process, AOP). After the implementation phase, a careful analysis of the first 6 batches of treated wastewater during validation verified the laboratory results, consistently achieving at least a 99.999 % destruction of all APIs examined, a significant reduction in Chemical Oxygen Demand (COD) and an increase in biodegradability. Furthermore, considerable cost savings compared to the initial situation were attained.

ZUSAMMENFASSUNG

Abbau von pharmazeutischen Wirkstoffen im Abwasser eines Lohnherstellers für eine Vielzahl von Rezepturen mittels UV-Oxidation als Erweitertes Oxidationsverfahren

Bei Catalent, einem Lohnhersteller für Softgel-Kapseln, wurde eine umweltfreundliche und sehr kosteneffiziente UV-Oxidationsanlage zur Behandlung von Abwasser aus einer pharmazeutischen Formulierung installiert, sodass das Abwasser wirkstofffrei in die öffentliche Kanalisation abgegeben werden kann. Da Lohnhersteller eine Vielzahl von Produkten und in diesem Fall bis zu 177 Wirkstoffe verarbeiten, muss die Abwasseranlage sehr flexibel arbeiten. Zunächst wurden verschiedene Behandlungsmethoden verglichen. Anhand der Ergebnisse entschied man sich für die UV-Oxidation (Advanced Oxidation Process, AOP) als Methode der Wahl, um die hochpotenten Wirkstoffe in einer komplexen Matrix nachhaltig zu zerstören. Dieser Beitrag fasst auch die Ergebnisse der Validierungsphase zusammen. Des Weiteren wird gezeigt, dass sowohl die Wirkstoffe zu über 99,999 % bis unter die Nachweisgrenze als auch der Chemische Sauerstoffbedarf (CSB) deutlich abgebaut werden konnten und die Bioverfügbarkeit der toxischen Abwässer signifikant anstieg. Ein positiver Nebeneffekt ist die massive Kosteneinsparung durch die Behandlung.

1. Introduction

The pharmaceutical facility in Eberbach, Germany, is a large softgel development and manufacturing facility with a capacity of 12.8 billion capsules per year. The system handles highly potent hormonal and cytotoxic compounds from multiple formulations from 9 different production lines, comprising up to 177 different APIs, as well as their in-house Research and

Development department [1]. Since many active pharmacological ingredients can be harmful to humans and the aquatic environment, even at very low levels, proper technology has to be applied in order fulfill all current regulations and standards (e.g., biodegradability of at least 60 %).

Formerly, wastewater resulting from formulations was collected on site and then sent out-of-house for incineration. This procedure incurred costs of about 1,000 Euro/t wastewater, and with a daily discharge of up to 13 m³ the costs were considerable. An alternative on-site solution presented an enormous challenge due to the variation in the wastewater matrix, in which both the concentration of individual APIs and other constituents such as cytostatics, hormones, oils, emulsifiers and surfactants are constantly changing. This challenge was compounded by the fact that there are currently no EU guidelines regarding API concentrations in discharged wastewater. Local limits in Germany tend to be based on the predicted no-effect concentration (PNEC). This can be different for each API and a reliable approach must ensure compliance to possibly changing regulations.

2. Comparison of Treatment Methods

Before deciding to switch to UV oxidation technology, the user considered other options, the pros and cons as well as the investment and operating costs of which are summarized in Table 1.

Reverse osmosis (RO) is often applied in order to concentrate the wastewater, in turn decreasing the volume needing to be disposed of externally. However, in this case, the oily ingredients precluded any use of membrane technology due to the certainty of biofouling and limited throughflow. Even assuming technical feasibility, both investment and operating costs are higher than other methods considered and an external disposal of the concentrate would still be necessary. Since the unit would be contaminated with the highly potent APIs, service and maintenance was also seen as critical by the Health, Safety and Environment (HSE) department.

Although activated carbon (AC) is a relatively low-maintenance alternative with comparably low investment costs, the constitution of the wastewater already led to failure on a lab-scale, as fatty layers consistently coated the AC very quickly. Progressing to

Table 1

Technical and commercial aspects of processes compared by [2].

	Reverse Osmosis	External disposal	Activated carbon	Ozone	UV oxidation	Biological	Electrolysis
Dischargeable wastewater	Oil in the wastewater led to quick bio-fouling and highly limited throughflow.	no discharge	Activated carbon was not leading to a wastewater with sufficient API reduction in the effluent.	Ozone was not able to show a reduction of API below required limits.	100 % of treated wastewater can be discharged.	All biological available components are metabolized, but typically no APIs.	Anode and cathode can be used for oxidation and reduction processes. Typically, specially coated electrodes, especially the anode are used for water treatment.
Main consumables	electricity, chemicals for frequent cleaning of filters	only at external site; no consumables at manufacturing site	activated carbon, labor	liquid oxygen, electricity, activated carbon	H_2O_2, electricity	air, electricity	electricity
Disposal	Increasing amount of concentrate containing the majority of the compounds must be disposed of, e.g., incineration.	100 % will be stored and disposed of, e.g., incineration.	Activated carbon must be disposed of or recovered.	Ozone in reactor off-gases must be handled/destroyed.	nothing to be disposed of	API contaminated sludge to be disposed of by external provider	nothing to be disposed of

■ **Table 1 – Continued**

	Reverse Osmosis	External disposal	Activated carbon	Ozone	UV oxidation	Biological	Electrolysis
Reliability	• Membrane is sensitive to many substances (membrane fouling) and must be cleaned. • Degree of concentration may be limited by fouling.	• easy to be realized • not dependent upon water quality • simple to handle	• easy to be realized • simple change of filtration tanks	technically reliable but results not reliable	• highly reliable and good process control • Can be adjusted to a high variation of wastewater concentrations.	• API typically not bio-available • unsuitable for API destruction	APIs are oxidized poorly as no selectivity can be observed.
Maintenance	Frequent and complete chemical cleaning required: approx. 1/month (see membrane fouling).	minimum maintenance of tank farm	very low maintenance	low to medium maintenance	low to medium maintenance	low to medium maintenance	Medium + ATEX-controls
Risk	• membrane fouling • lab testing required	unknown external price development	• unknown frequency of filter change depending strongly on wastewater matrix • lab testing required	no sufficient performance with external disposal in worst case	• process to be developed • test runs required	Bacteria can be killed by toxic APIs or other additives.	low efficiency and formation of Hydrogen – ATEX rules have to be adhered to.
Investment in Euro for core components (not turn key-price)	150,000–200,000	40,000	approx. 50,000	150,000	150,000	120,000	180,000
Operating Costs in Euro/m^3	40–60 at > 90 % API separation	1,000	30–50 at 90 % API separation	30–35 at 80 % API destruction	15–20 at 99.999 % API destruction	5–8 at no API destruction	20–30 at 70 % API destruction
Feasibility ranking*	– –*	– –	–	–	++	– –	–
Dominant criterion	fouling problems due to matrix	extremely high OPEX	poor results	insufficient API destruction	wide range of successful applicability	no impact on API levels	small impact on API levels

* ++very applicable, +applicable, 0 applicable with difficulty, – limited applicability, – – not applicable/realizable

large scale implementation would have brought up serious issues with on-site AC handling and disposal.

In general, the use of ozone is a highly effective method for wastewater disinfection when it comes to destroying viruses and bacteria, but it is cost-prohibitive when there are high levels of suspended solids, biochemical oxygen demand (BOD), chemical oxygen demand (COD) or total organic carbon (TOC) [3]. Furthermore, the efficiency of treating wastewaters with up to 20,000 mg/L of organics is very low since the solubility of ozone under the specific wastewater conditions is only on the order of approximately 20 mg/L. At the same time, ozone does not show a selective reaction with APIs, which would require additional consumption of treatment additives and a longer reaction time. In this case, testing with ozonation failed early on in the laboratory phase, since the surfactants present in the wastewater led to severe foaming. Another disadvantage of ozone is the additional and significant costs for destruction of the ozone from the reactor off-gases, and the need for liquid oxygen. Use of air for ozone generation is no longer state of the art due to higher CAPEX for the generator and the formation of unwanted nitrogen-oxide by-products.

Contrary to a still widespread belief that UV light is only suitable for the disinfection of clear waters, UV oxidation can degrade a wide range of APIs, even when the wastewater matrix includes oily emulsifiers, suspended solids and even surfactants [4], all present at the presented site. The reliability of UV oxidation in the destruction of APIs and other contaminants has already been proven extensively [5]. Consumables for this method are limited to H_2O_2, a safe, stable and economical oxidizing agent, and electrical energy. Furthermore, the UV oxidation process can run fully automatically and creates no by-products or substances that need to be disposed of, and break-down-products are all small organic acids, being environmentally friendly [6].

As learned through experience at other pharmaceutical sites, the use of a biological wastewater treatment plant is unsuitable for the destruction of APIs. Not only are the bacteria unable to metabolize the APIs, but they can even be killed as a result of API toxicity, further reducing the general efficacy of the wastewater treatment. Any reduction in the concentrations of APIs was a result of the homogenization with wastewater not containing APIs.

Electrolysis is a process most applicable to metal refining and recovery. The water treatment applications present attractive marketing possibilities for inert anode manufacturers, even though the suitability of electrolysis in this field is questionable. Successful applications are rare. The selective elimination of dedicated chemicals like intermediates and API is low and worsens even further with increasing organic background, since the method is not selective. Negative side-effects include ATEX issues, caused by the formation of explosive hydrogen gas. This in turn is a result of the low efficiency, owing to the fact that a significant amount of water is electrolyzed to oxygen and hydrogen.

Ultimately, the wide range of applicability, the convincing laboratory results for the UV oxidation method proposed by the advanced UV-oxidation specialist as well as the predicted cumulative cost savings and reliability led to the selection of this method for further feasibility testing, simulation and finally implementation.

3. Results of Lab Simulation

In order to be able to discharge the wastewater into the municipal biological water treatment facility, three objectives had to be met:

- detoxification of the wastewater, meaning the removal of highly potent substances that can have a detrimental environmental effect
- increase of biodegradability of the organic compounds remaining in the effluent after treatment
- reduction of chemical oxygen demand (COD), which is a measure quantifying the amount of oxidizable pollutants in the water

Preliminary samples were sent for a laboratory investigation in order to prove the feasibility of advanced oxidation and to determine the optimal oxidation treatment procedure. This oxidation procedure must not only maximize the reduction of unwanted API compounds and increase the bioavailability of the degradation by-products, but must also keep the use of consumables (H_2O_2) and UV irradiation to a minimum. Figure 1 shows three samples, whose highly variable compositions are clearly visible. The sample on the right is very inhomogeneous with flocs of solids and the middle sample has an oily layer on the surface. Other samples also contained surfactants, causing the wastewater to foam very easily, or various dyes.

First, a series of micro-tests (0.1–0.5 mL) was performed under well-defined and standardized conditions to determine the wastewater treatment class. Depending on the treatment, or rather the degradation, samples can be allocated a treatment class (TC): TC1 denotes substances which can be easily oxidized, for example Methanol, whereas TC5 refers to substances which are very recalcitrant, such as lignin-sulfonates. Further tests are then performed on a somewhat larger scale, typically 500 mL per sample, to verify the results of the first classification and to further develop a reliable oxidation procedure. Finally, macro-testing was carried out (5–10 L) to simulate the industrial application. From this last step, enough treated wastewater was generated to supply return samples for independent testing.

During laboratory simulation dimensionless treatment time is used because actual treatment hours can only be determined after the testing of all APIs is completed and all design information for the commercial plant is known. Figure 2 shows a reduction of the in-process indicated concentration of Product A

Figure 1: Typical example of three different wastewater samples before treatment (Source: Enviolet GmbH).

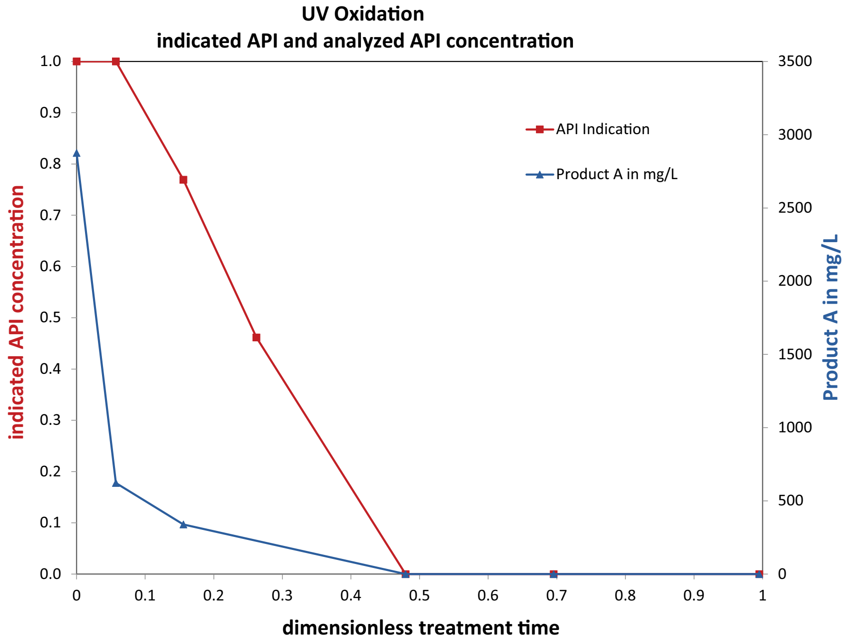

***Figure 2:** Laboratory comparison: API relative concentration (indicative measurements by the UV oxidation company) and independently measured values for Product A: below the detection limit after half of the treatment time.*

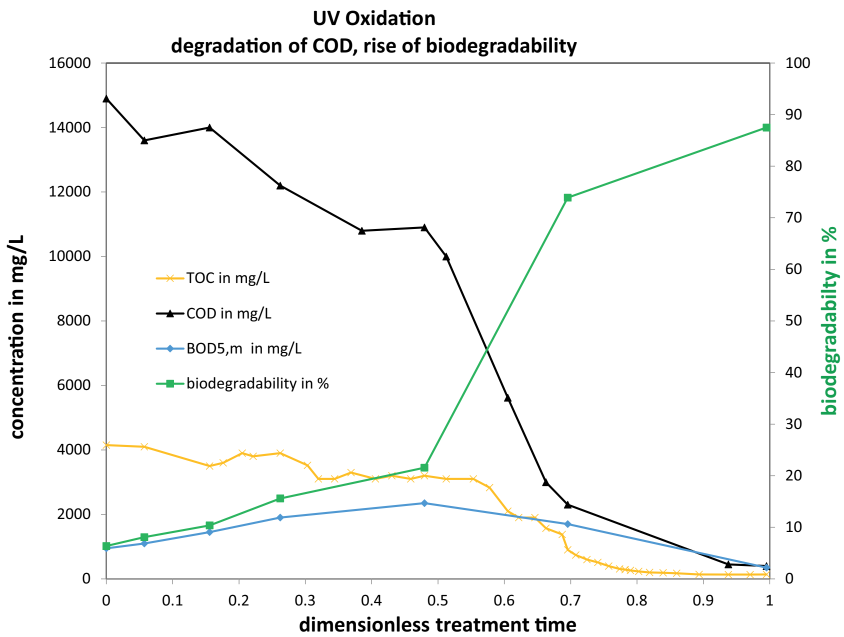

***Figure 3:** Sum parameters in an example treatment of Product A wastewater with various other APIs present in lower concentrations.*

(relative to the concentration of the starting sample) as well as the independently analyzed concentration in the treated samples. After half of the pure irradiation time, concentrations of Product A were below the limit of detection. At the same time, COD and TOC were reduced by approximately 50 %. The continued significant decrease in both COD and TOC after Product A had been eliminated (fig. 3) is a result of the carbon-containing degradation by-products, such as carboxylic acids (e.g., acetic acid), being further oxidized [7]. Since toxic or recalcitrant compounds are oxidized extensively at this stage and the remaining COD consists mainly of further biodegradable products, the biodegradability is continuously rising. This can be quantified by the observed $BOD_{5,m}$/COD ratio, also expressed as biodegradability ($BOD_{5,m}$/COD x 100 % = B/C ratio). Figure 3 shows that as the relative proportion of BOD in the COD becomes larger, the biodegradability increases. At the end of the irradiation time, nearly 90 % of all remaining carbons are of a biological nature and therefore biodegradable. $BOD_{5,m}$ values (Biological Oxygen Demand, five days incubation, modified method) were ascertained after the standard five-day incubation time, however with bacteria adapted to the UV supplier's laboratory scale biological treatment plant, which treats wastewater pre-treated by UV oxidation for feasibility testing.

It should be noted that even a 50 % biodegradability according to B/C ratio, without use of the Zahn-Wellens test, of the remaining organic carbons in an effluent is considered to be very good and fulfills the German regulations for release into the environment. A 50 % B/C ratio is comparable to > 90 % on a Zahn-Wellens test. A disadvantage of a standardized Zahn-Wellens test is the duration of 25 to 30 days per sample, from the start of the test until results are available. Quick validation required quick testing methods.

After the laboratory studies on representative samples proved that advanced UV oxidation was able to degrade all examined compounds to well below the predicted no effect concentration (PNEC) after a relatively short treatment time, no further tests or pilot

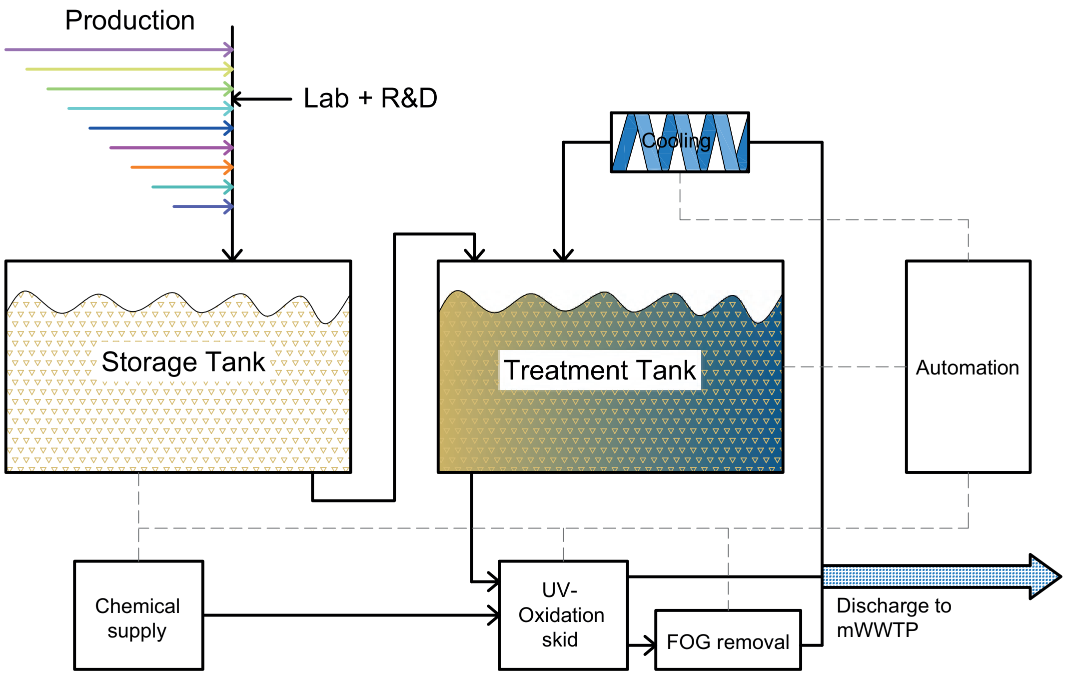

Figure 4: Schematic of advanced oxidation process for the removal of multiple APIs in pharmaceutical wastewater. Wastewater with APIs from multiple production lines is collected in the storage tank and subsequently treated with UV oxidation. The wastewater is cycled through the oxidation, FOG removal and cooling loop for a set period of time determined during the laboratory-scale tests. This period of time can be changed to handle future changes to the wastewater composition.

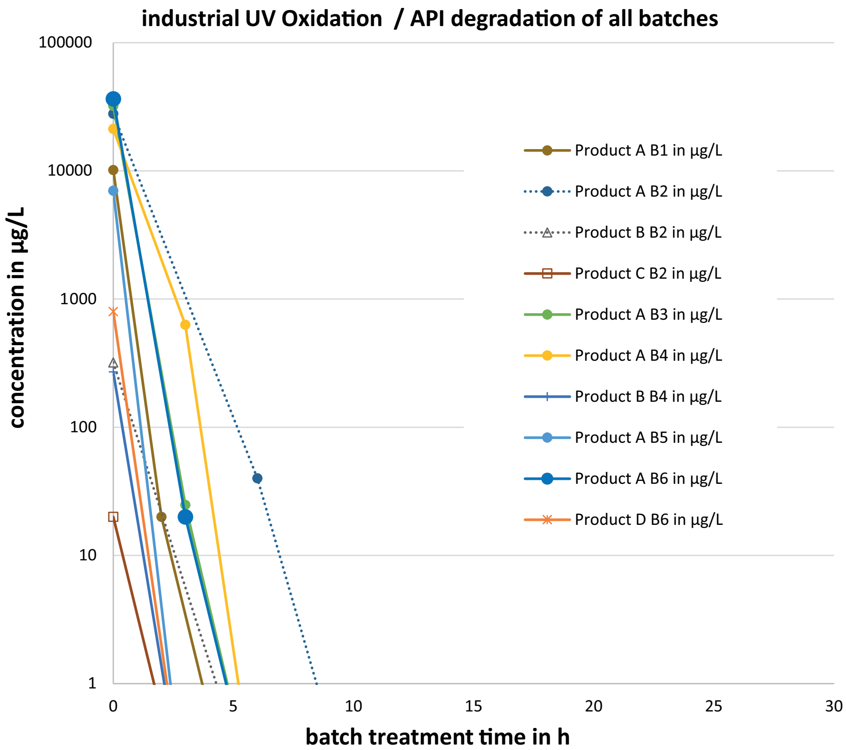

Figure 5: Degradation of various APIs for all batches. Batch-treatment time: Filling, treatment, neutralization and discharge.

installations were necessary. The oxidation process could immediately be transferred to an industrial scale, supported by results from similar applications.

4. Results and Discussion on Industrial Application and Process Description

The good test results for the UV oxidation of many different APIs and other contaminants allowed for batch treatment of the combined wastewaters from all production lines. This batch UV oxidation treatment is fully automated. The wastewater is collected in a storage tank, from where it is pumped by the process control system (PCS) into the batch treatment unit. Before being pumped in a loop through the UV reactors (see schematic in fig. 4), the combined wastewaters

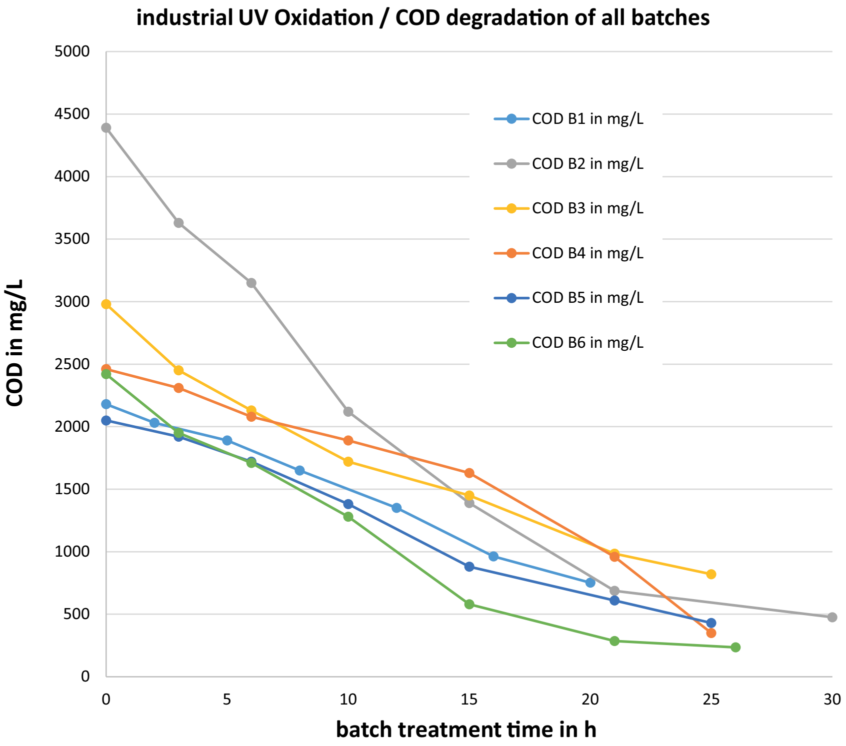

***Figure 6:** Results of the first six batches treated with the installed industrial plant at the pharmaceutical production site.*

***Figure 7:** One set of samples from different points during a batch treatment. Left is the untreated wastewater and right is the completed effluent.*

are dosed and thoroughly mixed with the oxidant. A homogeneous distribution of the oxidant is important in order to achieve the best possible oxidation rate. The process parameters, like temperature and pH, are continuously monitored and, if necessary, adjusted to the defined specification. The batch treatment duration was set based on the insights gained during the laboratory simulation. In this case, a conservative total processing time for a reliable reduction of COD by at least 60 % (the point at which is was proven that all APIs were eliminated below the limit from the wastewater) was set at 24 hours.

The first six batch treatments were followed and analyzed intensively. Figure 5 shows a rapid destruction of the investigated APIs in all batches, whereas fig. 4 illustrates the decline in COD in each batch. The variation between the batches is caused by the differing amounts and relative concentrations of the APIs in each batch. A larger output from one production line could cause an increased level of, e.g., Product D, which on a different day, or batch, might be present in much lower levels or even not at all. Although 177 different APIs are used at this site, only 10 were validated during the first six batch treatments, owing to the fact that only this specific subset was present in the collected wastewater treated during this time. Destruction of the remaining APIs will be validated over time as the wastewater matrix changes.

Figure 7 shows the progression of wastewater appearance during a typical batch treatment. The initial sample on the left has an inhomogeneous distribution of oily residue and solid flocs, whereas the final sample, on the right, is completely clear and suitable for discharge into the local water treatment facility.

One advantage to the batch treatment, shown in the photo (fig. 8) and schematic (fig. 4), is that the treatment time can simply be modified when needed, for example when much higher levels of API are present, or when wastewater from R&D, with very different specs from production wastewater, is added to the mix. Furthermore, a strong variation of the chemical matrix can easily be integrated into a modified treatment process. For this, simple analytical tests are performed prior to batch treatment using a specially developed standard operating procedure (SOP) supplied together with the treatment plant. This simplified daily operation is important in order to independently adapt the treatment and validate the process efficacy, without costly and time-consuming internal or external analytical services.

A further advantage to a batch treatment approach is that it fits neatly into the structures already in place in some pharmaceutical companies. In this case, and in the case of, e.g., Servier Laboratories, that recently implemented a similar solution [8], the wastewater was already being collected for external incineration. Where the collected wastewater was once pumped out for transportation and expensive disposal, it is now pumped through the UV oxidation loop and

***Figure 8:** UV oxidation plant at a softgel factory: On the right the storage and batch treatment tanks can be seen and the UV reactors and the electrical cabinet with the fully automated process control are at the rear. Chemical storage is on the left. The SOP makes the system adaptable to a changing wastewater matrix. The modular design also allows for relatively easy upscaling to handle, e.g., larger wastewater volumes.*

afterwards to the already existing biological treatment plant at that manufacturing site.

The average operating costs of the UV oxidation treatment with the installed plant at the softgel pharmaceutical company are between 10 and 15 Euro/m^3, including all consumables, electrical energy, spare parts and maintenance, which is a significant reduction to the original external disposal method.

5. Conclusion

The first six batch treatments in the industrial plant achieved more than the expected 99.999 % reduction of all targeted APIs. As predicted during the laboratory investigation and feasibility study into the proposed advanced oxidation plant, cost savings of almost 13,000 Euro per batch of wastewater were achieved, independent of the exact wastewater matrix or the concentrations of the individual APIs to be eliminated. Due to this flexibility, the facility will be able to handle any future changes to the effluent constituents caused by either increased production or new softgel production lines. Additionally, no special analytics are required once the system is operating in a validated mode.

The reduction of all APIs below the limit of detection also ensures that uncertainty regarding the development of binding EU guideline is eliminated and that the plant can run without modification regardless of where the limits may lie in the future.

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