Elimination of APIs in Pharmaceutical Wastewater by UV Oxidation

17 Years of Field Experience

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Abstract

In 2005 the first Active Pharmaceutical Ingredient (API) removal plant was built for a Contract Manufacturing Organization (CMO) producing female hormone Oral Solid Drugs (OSDs). Using UV oxidation for the elimination of APIs, the company, today a part of the Aenova Group, was a pioneer at that time, with the clear aim of an environmentally friendly production and no release of any APIs in the effluent [1].
In 2022, 17 years later, enviolet has realized about 200 UV oxidation plants for the elimination of APIs or intermediates for all types of pharmaceutical formulation applications, as well as at manufacturing sites for chemically active substances or their intermediates.
The challenges associated with this include dealing with the demand for extremely high elimination rates of active substances, handling strongly varying wastewaters, especially at CMOs or at CDMOs (Contract Development Manufacturing Organizations) and, last but not least, a very inhomogeneous matrix, containing for example solids or, in some cases, even oils and fats from creams that are produced.
The primary aim remains to treat the wastewater without producing any contaminated residuals while achieving the lowest possible costs for Capital Expenses (CAPEX) and Operational Expenses (OPEX) and the lowest possible environmental footprint, all within a very reliable and fully automatic operation.
Within this overview article some examples are shown for different applications, types of APIs, dimensions, and decision-making criteria.

Zusammenfassung

Abbau von pharmazeutischen Wirkstoffen im Abwasser mittels UV-Oxidation/17 Jahre Betriebserfahrung

Bereits 2005 wurde die erste UV-Oxidationsanlage zum Abbau von pharmazeutischen Wirkstoffen für einen Lohnhersteller von weiblichen Hormon-Präparaten in Betrieb genommen. Das Unternehmen (heute ein Teil der Aenova-Gruppe), das UV-Oxidation zur Elimination von Wirkstoffen einsetzt, war damals Pionier und mit dem klaren Ziel einer umweltschonenden Produktion und dem Ablassen von ausschließlich wirkstofffreiem Abwasser in die Kanalisation angetreten [1].
Im Jahr 2022, 17 Jahre später, hat enviolet rund 200 UV-Oxidationsanlagen zur Eliminierung von Wirkstoffen oder Zwischenprodukten für pharmazeutische Wirkstoffe im Bereich aller Formulierungsarten sowie an Produktionsstandorten der chemischen Wirkstoffe oder deren Zwischenprodukten realisiert.
Die Herausforderungen sind die Forderung nach extrem hohen Eliminationsraten der Wirkstoffe zum Erreichen der geringen Restkonzentrationen meist unterhalb der Predicted No-Effect Concentration (PNEC) sowie der Umgang mit stark schwankenden Abwasserzusammensetzungen (insbesondere bei Lohnherstellern oder bei Lohnentwicklern) und nicht zuletzt mit einer sehr inhomogenen Matrix, die auch Feststoffe oder teilweise sogar Öle und Fette enthalten kann, die beispielsweise bei der Herstellung von Cremes anfallen.
Das Hauptziel bleibt, das Abwasser so zu behandeln, ohne dass kontaminierte Rückstände oder Nebenprodukte anfallen, basierend auf einem Prozess mit niedrigsten Kosten für Investition und Betrieb, geringstmöglichem ökologischen Fußabdruck und einem sehr zuverlässigen und vollautomatischen Betrieb.
In diesem Übersichtsbeitrag werden einige Beispiele für verschiedene Anwendungen, Wirkstoffgruppen, Dimensionen und Entscheidungsgrundlagen gezeigt.

1. Introduction

The pharmaceutical and chemical industries manufacture and formulate medications based on pharmaceutically active substances. Even today, there are no clear legal regulations regarding the emission of these substances into the environment, but many manufacturers of these substances and user products have established their own targets for the reduction of these emissions into the environment, even before national governments have established or implemented corresponding regulations. In most cases, the self-imposed aims of the pharmaceutical manufacturers' treatment of factory wastewater are very challenging since they are based on the Predicted No-Effect Concentration (PNEC) in the environment. Once this treated wastewater is further diluted at the point of discharge into the receiving water body, the effective concentrations are on the order of 0.1 % of the PNEC. A leading American pharmaceutical company has carried out an investigation of its hormone formulation site in the Netherlands after a UV oxidation plant was put into operation. The results showed that the industrial wastewater from this female hormone formulation site contained fewer female hormones after the treatment with UV oxidation than the sanitary wastewater of the same factory [2]. This example illustrates how this industry sector is environmentally aware and working on sustainable solutions.

2. Short overview and comparison of treatment methods

2.1 Overview

UV oxidation is the combination of light emission in the range of 190 nm (vacuum ultraviolet) to about 400 nm (ultraviolet A) and chemicals such as for example hydrogen peroxide as an oxidant and acid or caustic soda for (final) pH-adjustment. The main objective of the oxidation is to destroy the Active Pharmaceutical Ingredients (APIs) to such an extent that not only the primary structure is destroyed, but also the remaining molecules are reduced to non-toxic organic matter, like small organic acids, or mineralized matter like carbon dioxide and salts. In many cases this effect can already be seen by the strong degradation of Total Organic Carbon (TOC), but data from toxicity measurements further underline the substantial change of characteristics of the ingredients [3].

2.2 Comparison of treatment methods

In the past, various methods have been used in different scenarios. A good overview of all technologies available was made by Lautenschläger in 2015 (table 1) to evaluate the possible solutions [4].

It is interesting to note that, in this rating, UV oxidation was considered to be the best technology for substantial API degradation. 20 years ago, UV oxidation was not taken seriously, as several companies failed to integrate the technology reliably and successfully into their treatment concept, exhibiting poor degradation rates (often less than 90 %) which is far away from the requirements today, by several orders of magnitude. Problems were posed by the wastewater matrix, including oily emulsifiers, suspended solids and even surfactants [5], all present in typical pharmaceutical wastewater, as well as by additional fouling problems, poorly designed UV-reactors and inefficient treatment processes. Today, all of these issues are solved, completely changing the appearance and meaning of the UV oxidation process. This has led to solutions that were formerly widely used being replaced in many cases, while new production facilities are equipped directly with this new state-of-the-art technology.

Reverse osmosis (RO) is often applied to concentrate the wastewater, in turn decreasing the volume needing to be disposed of externally by incineration at high costs. However, in this case, the oily ingredients precluded any use of membrane technology due to the certainty of bio-fouling and limited throughflow. Another critical aspect was the maintenance of a plant completely contaminated with APIs, which, in particular with OEB 4 and OEB 5 (Occupational Expose Band) substances, is always viewed critically 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 laboratory scale, caused by many factors, e.g., the wastewater matrix. Other issues include the handling of contaminated AC on site and the high cost of disposal.

Ozone treatment also falls within the classification of oxidative methods, but in projects in which the company had been involved, ozone or ozone/UV fell short of the required degradation of APIs by several orders of magnitude. More details can be found in the original publication [5].

Biological treatments are not able to eliminate APIs but are a perfect polishing step in cases where an effective oxidation is used as pre-treatment, meaning the remaining break-down products are exclusively small organic acids, which are ideal substrates for all types of biological wastewater treatment plants.

Electrolytic treatment 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 and selective elimination of dedicated chemicals like intermediates and APIs are low and worsen even further with increasing organic background, since the method is not selective. Negative side-effects include e.g. ATEX issues caused by the formation of hydrogen. 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.

The most important factor in the authors' view is that the UV oxidation now successfully treats many types of wastewaters which previously were

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Table 1

Technical and commercial aspects of processes compared by Lautenschläger.

	Reverse Osmosis	External disposal	Activated carbon	Ozone	UV oxidation	Biological	Electrolysis
Dischargeable wastewater	Oil in the wastewater led to quick biofouling and highly limited throughflow.	No discharge	Activated carbon did not lead to a 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, labour	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 (occasional lamp replacement)	API contaminated sludge to be disposed of by external provider	Nothing to be disposed of
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	API 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 + ATmosphères EXplosives (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 Euros for core components (not turnkey price)	150 000–200 000	40 000	Approx. 50 000	150 000	150 000	120 000	180 000
Operating Costs in Euros/m³	40–60 @ >90 % API separation	1 000	30–50 @ 90 % API separation	30-35 @ 80 % API destruction	15–20 @ 99,999 % API destruction	5–8 @ No API destruction	20–30 @ 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. Rating was based on the condition of the study [4].

Figure 1: Examples of different pharmaceutical Cleaning-in-Place (CIP) rinse wastewater samples (untreated) (source of all figures: the authors).

Table 2

Origins and properties of typical pharmaceutical wastewaters.

	API manufacturing	Formulation	
		OSD	Vials
Origin of wastewater	Chemical synthesis of API and intermediates	CIP-cleaning of equipment	Residuals and CIP-cleaning of equipment
Note	Wide range of chemical mixture, due to reactions made	API in low concentration Recipients Cleaning agents Water	API in low concentration Organic solvents, Water
Typical existing solution	Incineration, evaporation/incineration, RO/incineration, UV oxidation		
Aim of treatment	Detoxification, complete destruction of APIs, increase of bio-degradability and direct discharge at low costs		
Treatment proposed	UV oxidation, UV advanced oxidation processes (AOP) Often a special treatment, mostly with high flexibility for varying effluent compositions	UV oxidation, able to handle suspended solids	UV oxidation, able to handle some solvents
Following treatment	Often biological treatment	None	None
COD in mg/l of the CIP-rinse wastewater (range)	10 000–200 000	1 000–5 000	1 000–50 000
COD in mg/l (90th percentile)	As above	2 000–3 000	5 000–10 000 (with good solvent recovery)
TSS in g/l	Up to 250	2–4	2–4
Flow rate in m^3/h	5–1 000 m^3/d	5–500 m^3/d	5–200 m^3/d

sent for incineration, not only at high costs but also with a very negative environmental footprint. This factor helped many users of UV oxidation to reduce treatment cost while at the same time realizing a significant ecological improvement.

3. Examples of treated wastewaters for API destruction for different drug groups

As stated, the typical aims of pharmaceutical wastewater treatment, as shown for example in fig. 1, are the following:

- Elimination of the APIs below certain limits,
- A completely non-toxic wastewater,
- Strong reduction of the chemical oxygen demand,
- Fully bio-degradable wastewater for release to a biological wastewater treatment plant on site or of the municipality,
- In some cases, even a further treatment for gardening or grey-water reuse.

In most cases, the state of the art is a confirmation of treatment feasibility through simulation under real conditions. This is the procedure the authors recommend in order to eliminate risk and to present robust data to the local environmental protection agency before building a new treatment plant, even when using the same pre-treatment within an existing structure.

Figure 1 shows photos from different samples of CIP rinse wastewaters taken from the wastewater collection tank before disposal. The left 3 are from the same CMO on different days, while the other 5 samples include different pharmaceuticals from their API-contaminated wastewater. These particular samples were se-

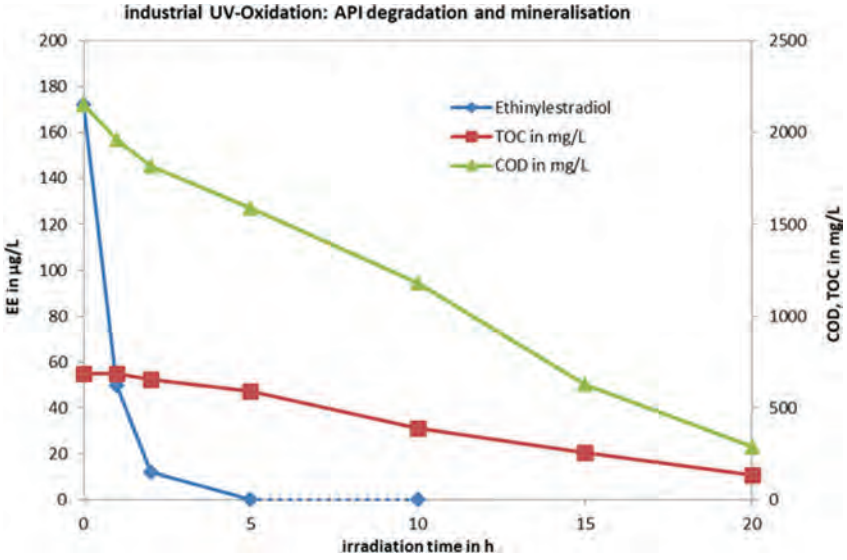

Figure 2: Degradation of Ethinylestradiol (dotted line=below limit of detection (LOD) of 1 ng/l), COD and TOC.

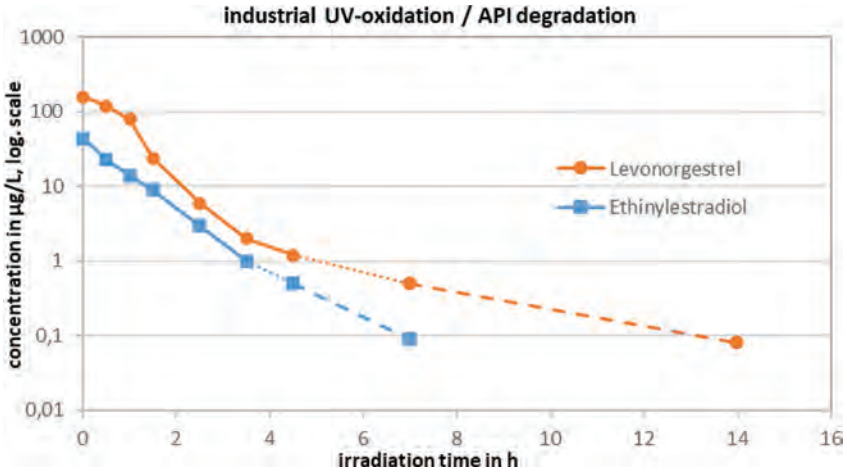

Figure 3: Degradation of 2 hormones (dotted line=below LOD of 1 µg/l, broken line: extrapolation).

lected in order to give an impression of the range of sample appearances. Table 2 summarizes typical wastewaters and their sources. Depending on the sources, the ingredients and concentrations can be very different, posing major challenges for the related treatment process. One common aim is the reduction of the API below the PNEC. Additional aims, such as a reduction of Chemical Oxygen Demand (COD) or TOC and a great improvement in biodegradability are also quite common.

The significant number of UV oxidation plants shows the importance of this technology as a solution to avoid expensive and environmentally critical methods of dealing with this type of wastewater, such as, for example, incineration.

■ 3.1 Degradation of hormones

The first treatment plant eliminating female hormones by UV oxidation with a proven a high elimination rate was in Munster, Germany [6].

The oxidation of APIs starts with the destruction of the initial structure and further oxidation results in several degradation pathways leading to the formation of smaller molecules, mainly carboxylic acids. The de-carboxylation within these breakdown products results in a decrease of TOC, as organic carbon dissolved in the wastewater leaves the molecular system of the wastewater body as carbon dioxide. The ratio of COD/TOC, typically around 3–4 in the untreated wastewater, always tends to decrease during the oxidation, while oxygen functional groups like -OH (hydroxyl), =O (aldehyde, ketone) and -CO_2H (carboxylic) continuously increase, which generally confirms these reaction pathways.

Additionally, APIs also undergo these degradation mechanisms leading to highly biodegradable products. Since, in this case, the PNEC of Ethinylestradiol is extremely low (0.01 ng/l), the treatment is extended, even after the LOD is reached (fig. 2). Over the past few decades, new analytic methods capable of detecting such low concentrations with reduced effort have been established. Figure 3 also shows that hormones initially present in higher concentrations, such as e.g., Levonorgestrel can also be reduced to very low concentrations.

In later projects, both lab tests and the first few treatment runs after the start-up of the industrial plant could be carried out with more sophisticated analytical monitoring. All 3 derivates of Estradiol (17a-Estradiol, 17a-Ethinylestradiol, and 17b-Estradiol) could be analysed to very low levels, in the range of 10 ng/l.

In fig. 4, Estradiol is the sum of all 3 Estradiol derivates. The lowest possible concentration of each hormone is defined by the LOD of each compound, which means that the signal of an Estradiol species cannot be differentiated from the matrix signal. As all 3 derivates have their own LODs, the "possible maximum concentration of Estradiol" cannot be above the sum of the 3 LODs.

It is obvious that the final concentrations depend on the LOD, which decreases with UV oxidation. The LODs in turn depend strongly on the matrix of the water, like undissolved excipients, surfactants, etc. As these are degraded, which indicates the degradation of the COD, the LODs decrease as well. The

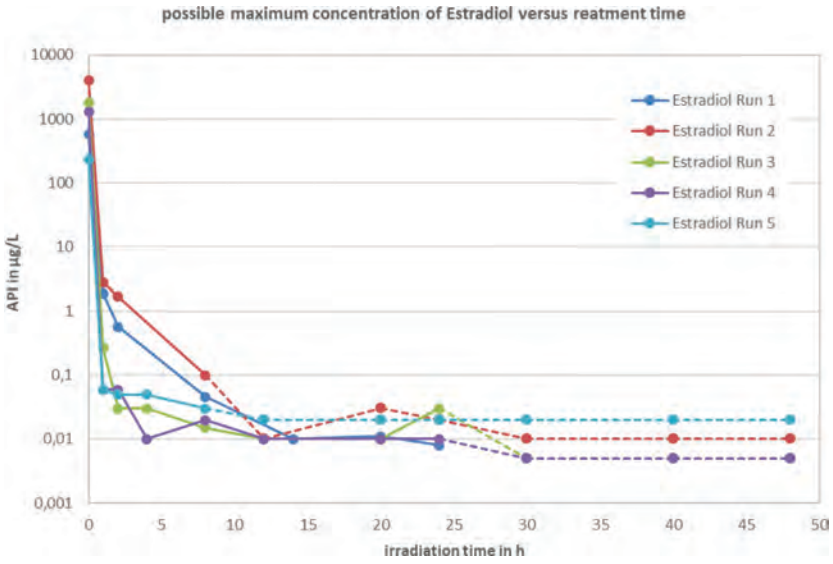

Figure 4: Degradation of Estradiol (=sum of 3 species, dotted line=below LOD).

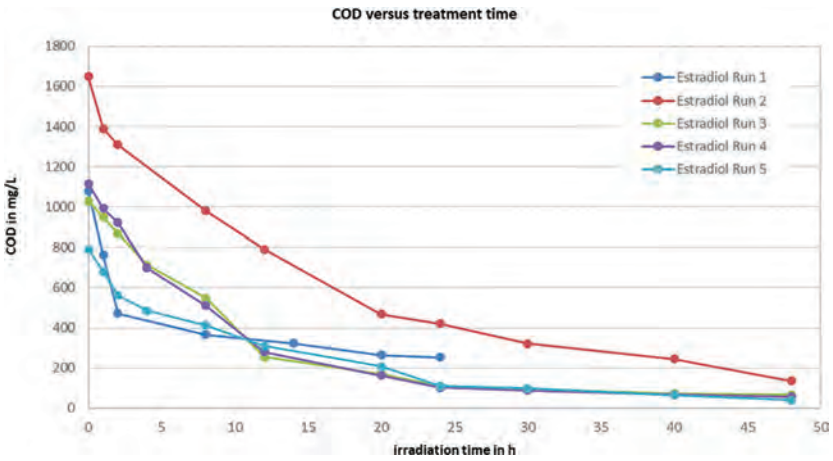

Figure 5: Degradation of COD of the Estradiol wastewater.

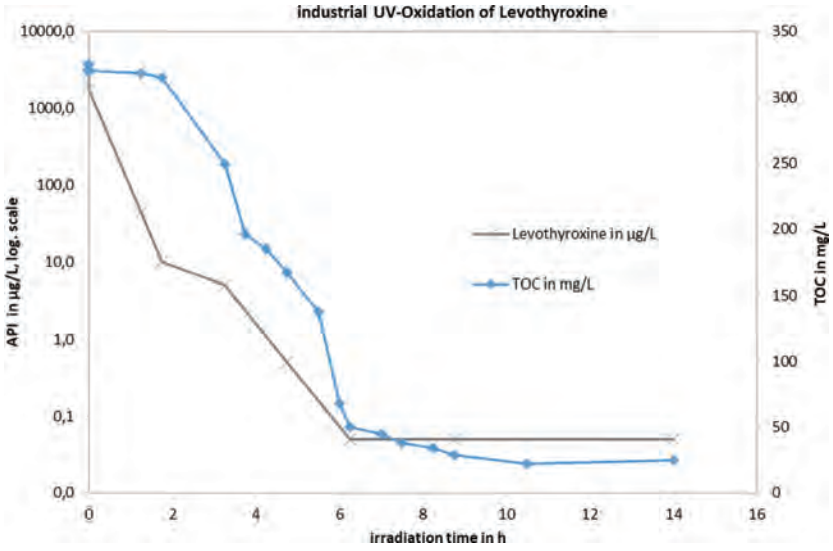

Figure 6: Degradation of Levothyroxine (dotted line=below LOD).

COD degradation of each batch treatment is displayed in fig. 5.

The authors expect the actual concentrations after the treatments to be much lower than the corresponding LODs. The specified goal is to reach the PNEC of <0.001 µg/l. However, it is very difficult to prove analytically that this aim has been reached. The Estradiol degradation data and curves do indicate a continuous degradation, aside from some outliers, until the concentration falls below the corresponding LOD.

Another UV installation at a pharmaceutical manufacturing site produces various high potency drugs. One of the APIs present is Levothyroxine, which should be degraded below 0.01 µg/l or below the detection limit. As described above, in this case the LOD again decreases with reduced amounts of other organic compounds in the water matrix, which means that the matrix limits the proof of degradation. In this case the TOC was analysed during the treatment (fig. 6), and it can be proposed that, with further oxidation of the organic matrix, the APIs are also further oxidized. The hypothesis is that the APIs are already below 0.1 ng/l in typical treatment systems, and new research work is being carried out to prove this effect with various new methods, for example with marked molecules.

Another important factor is toxicity tests. During start-up of the plant, samples at different treatment times were sent to a specialized lab to determine several eco-monitoring metrics. The value "G-Wert" is the dilution factor for reaching the standard conditions of a non-contaminated water sample like pure rainwater or tap water. The higher this value, the higher the toxicity, and a factor of 1 (undiluted) corresponds with the dilution factor in the Daphnia test, in which at least 90 % of the Daphnia retain their swimming ability. In the luminescent bacteria ("Leuchtbakterien") test, the light emission after 30 minutes of contact with the treated water is still at least 80 % of the original light emission, also corresponding

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Table 3

Analytical results, oxidation of Levothyroxine wastewater.

Sample Designation	Before UV oxidation	after 3 h UV oxidation	4.75 h	6.25 h	8.75 h	14.25 h	Limit
TOC in mg/l	321	250	167	50	29	25	-
COD in mg/l	1 140	793	516	180	85	59	-
DIN EN ISO 15088 „Fischei (G_{Ei}-Wert)“	4	n.a.	n.a.	2	1	1	2
DIN EN ISO 6341-L30 „Daphnia (G_D-Wert)“	14	n.a.	n.a.	1	1	1	8
DIN EN ISO 11348-1 2009-05 Leuchtbakterien (G_L-Wert)	384	8	n.a.	1	2	1	32

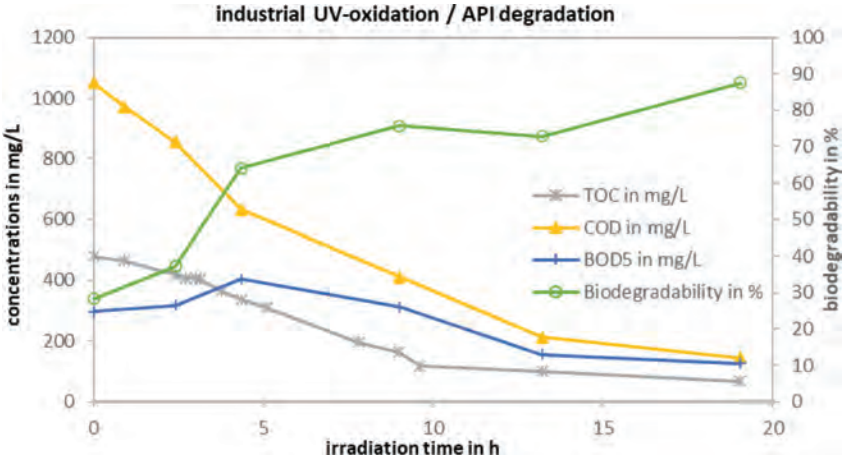

Figure 7: Oxidation of wastewater containing Capecitabine and Fluorouracil.

with a dilution factor of 1 in which no dilution is necessary. Similarly, in the fish egg (“Fischei”) test, this dilution level describes a scenario in which at least 90 % of the embryos show no developmental abnormalities after a defined exposure to the water.

After only half of the total treatment time, both the toxicity levels had reached a “G-Wert” of 1 and the API had been reduced below the detection limit (table 3). Note: The lowest possible value for the “G-Wert” dilution level is 1 and the value of the next possible level is 2. Intermediate values do not exist in the definition of the methods.

3.2 Degradation of oncologic APIs

3.2.1 Degradation of Capecitabine, Fluorouracil (and Imatinib)

Capecitabine and 5-Fluorouracil are cytostatic drugs that are widely used. They are on the World Health Organization's List of Essential Medicines. Fluorouracil was patented in 1956, whereby Capecitabine, which is a prodrug of 5-Fluorouracil, is the final active compound. Both show a high hazard potential because of poor degradability and high ecotoxicity [7].

For example, 5-fluorouracil can be degraded very well with UV oxidation, but even at low concentrations – as present in the environment – there is hardly any natural degradation [8].

The client treats their wastewater containing both substances to reach the desired low levels, below the LOD. As usual with UV oxidation, the biodegradability rises while the organic matter is oxidized, shown by the marked decrease in COD, Biochemical Oxygen Demand (BOD) and TOC (fig. 7). At the end of treatment, a high biodegradability is achieved when the remaining carbon compounds can be treated biologically or when the ratio of BOD to COD is high. In this case, the degradation of the aromatic structure can be detected via UV/VIS spectroscopy (fig 8). The relatively strong absorption in the range of around 300 nm and its decrease with continued oxidation shows that toxic compounds are degraded ever further. The curves for the batches P0–P9 vary due to different initial concentrations and the possible presence of additional compounds being degraded simultaneously.

Similar to the metabolic mechanisms, the degradation of Capecitabine by UV oxidation leads to the intermediate formation of 5-Fluorouracil, shown by an initial rise in 5-Fluorouracil concentration during the steepest decline in Capecitabine concentrations (fig. 9). The intermediate 5-Fluorouracil is then also degraded consistently below the LOD after a longer irradiation time.

Figure 10 and fig. 11 show the same general results are achieved during the treatment of Imatinib. The perfect match of the degradation of Imatinib (fig. 12) and the disappearance of the conjugated structures shows that with destruction of the Imatinib, structures initially remaining are oxidized further. This could also be found through previous research working on other molecules with complex structures [9].

3.3 Degradation of other APIs

Many other APIs like antibiotics, painkillers, anti-depressants, etc. also have

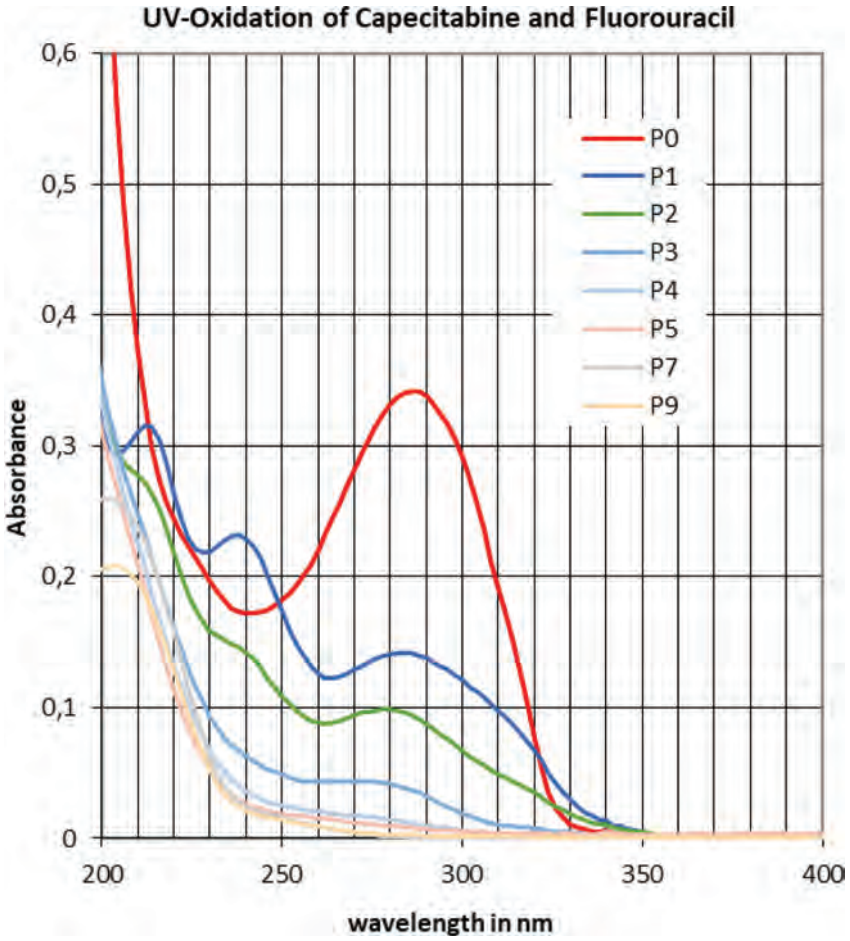

Figure 8: Degradation of aromatic structures.

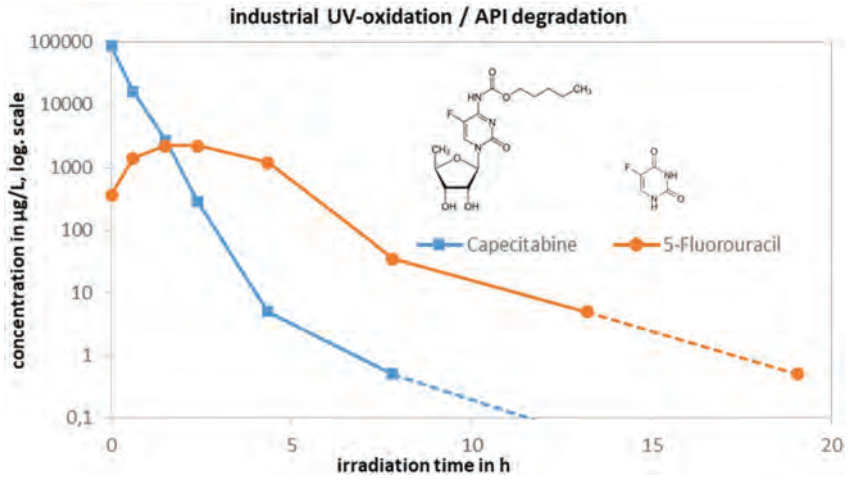

Figure 9: Oxidation of Capecitabine and 5-Fluorouracil (dotted line=below LOD).

to be eliminated to prevent their release into the environment by manufacturers or formulators.

Very obvious examples are plants for eliminating antibiotics, as wastewaters containing them are hard to treat with biological treatment plants, which are an omnipresent and very ecological treatment technology.

3.3.1 Morpholine Degradation [10]

The critical components in this wastewater are Morpholine (MOR) and N-Nitroso-Morpholine (NMOR). The legal limits of these compounds are 15 µg/l MOR and 100 ng/l N-MOR, respectively. It turned out that as soon MOR was oxidized below the legal limit NMOR concentrations were below the limit as well. MOR is used as a solvent in agro-chemistry and is a building block in the synthesis of numerous APIs [11]. In addition to MOR and NMOR there were fine beige particles of 2-(N-Morpholino) ethansulfonicacid (MES, as API) in this wastewater, which were also oxidized and dissolved during the UV oxidation process.

In this case, the degradation pathways could be reconstructed by balancing the main N-compounds leading to non-toxic intermediates and final products, shown in fig. 13 by the nitrogen balance.

During the first 3 months of operation at this industrial plant, the client monitored inlet and outlet concentrations. Despite variations and peaks in inlet concentrations, the improvement of the wastewater could not only be confirmed analytically but could also be perceived visually (fig. 14). The limits were consistently reached in the outlet (fig. 15).

3.3.2 Pantoprazole Degradation [12]

In 2004, the API Pantoprazole was found in detectable concentrations in the river Rhine. The analytic monitoring quite soon isolated the source as a manufacturing site for this substance. Several suppliers of wastewater treatment systems were contacted by the API manufacturer in order to develop a method for removing Pantoprazol from the wastewater. The special case requirements were to eliminate up to 7 g/l of the API in a concentrated production wastewater at economic costs, leaving only a fully bio-degradable wastewater for release. A lab-scale feasibility test (fig. 16) confirmed the suitability of UV oxidation for achieving this goal. In 2006, a UV oxidation treat-

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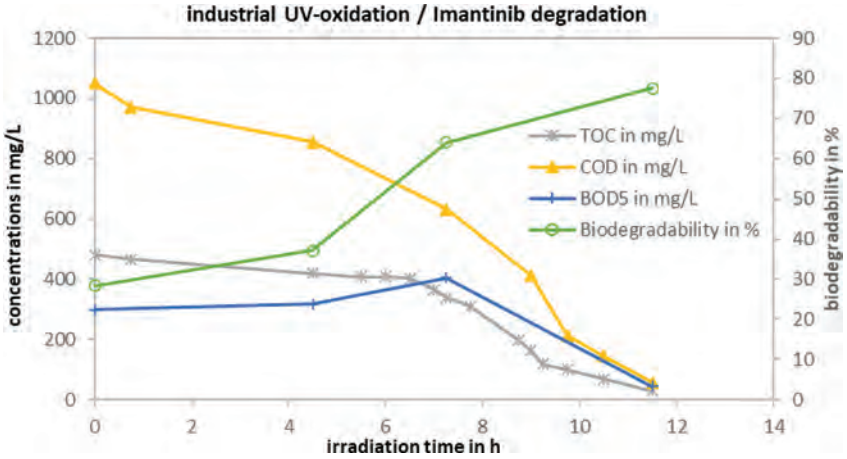

Figure 10: Oxidation of wastewater containing Imatinib.

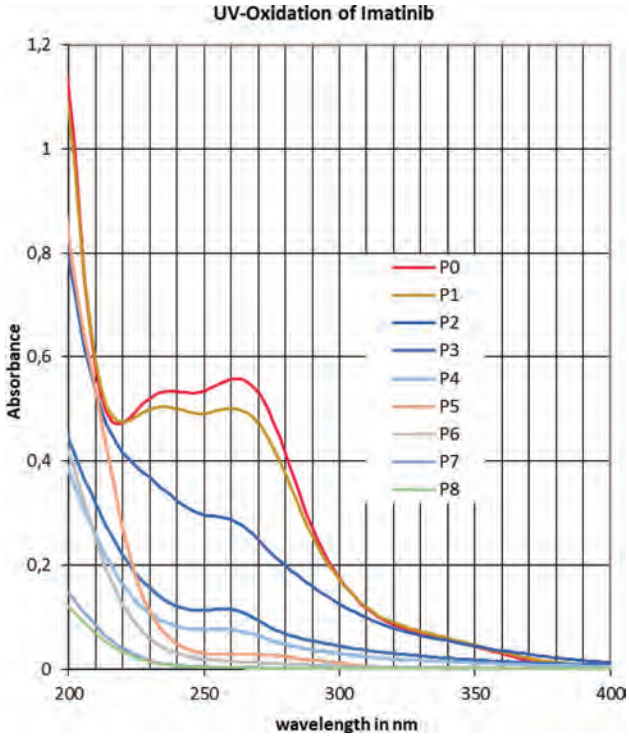

Figure 11: Degradation of aromatic structures during the oxidation of wastewater containing Imatinib.

ment plant started detoxifying the 36 m^3/d of mother liquor wastewater by extracting the API prior to mixing with other site wastewaters in the biological wastewater treatment station. The main objective of this pre-treatment was the elimination of the API below the limit of detection at its outlet. As a positive side-effect, the pre-treated mother liquor showed full bio-degradability, in turn significantly improving the performance of the on-site biological treatment. The special challenge for developing this application was handling polymerization of degradation products in the concentrated organic wastewater matrix. The specific reactor design and resulting flow conditions prevented build-ups or deposits on the UV-lamps. However, to avoid deposits within the treatment tanks, precautions had to be taken and were successfully implemented by appropriate treatment parameters.

In particular the direct photolysis of active substances enables a higher selectivity of the oxidation. This was shown already in earlier projects in which other contaminants (Erythromycin, Sulfamethoxazole, Penicillin-V-K and Trimethoprim) were destroyed in real wastewater with lab and industrial-scale plants [3]. X-ray contrast media have also been destroyed using this same wastewater treatment technology [12].

4. Examples of Industrial UV Oxidation Plants

The approximately 200 oxidation plants at pharmaceutical companies and intermediate producers are realized as batch-units or as continuous operation plants. The batch plants are typically used in cases with a smaller volume per day, in practice up to 30–50 m^3/d depending on individual circumstances. The advantage of a batch plant is the manageability for the operator. At higher volumes or loads continuously operating plants are required and, so far, the biggest plant in operation at a pharmaceutical site treats 30 m^3/h of API wastewater (about 700 m^3/d). However, several treatment plants with flows up to 120 m^3/h (3 000 m^3/d) will start up their operations in 2022. All these wastewaters are typical industrial wastewaters with significant organic loads, as well as APIs or pharmaceutical intermediates.

Batch treatment plants, like the one shown in fig. 17, typically have collection tanks to store the untreated wastewater prior to treatment, since the wastewater is processed batchwise. During the treatment no untreated wastewater can be added. After oxidation of the organic ingredients, the final step is typically a pH-adjustment before draining. In many cases, the discharge flows to an on-site biological treatment plant or to the municipal wastewater treatment station.

For higher volumes of wastewater, continuous treatment plants (fig. 18) are needed, as this does not require large storage infrastructure. The continuous treatment plants typically pro-

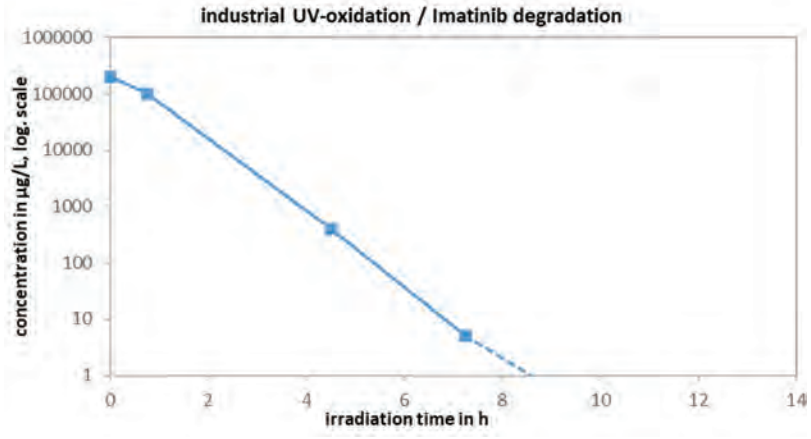

Figure 12: Oxidation of Imatinib (dotted line=below LOD).

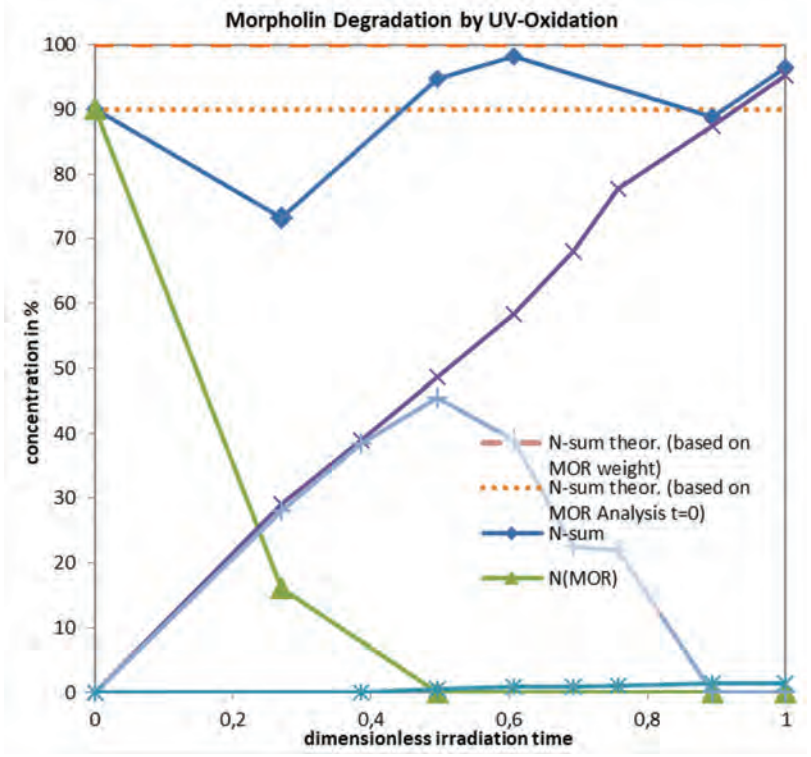

Figure 13: N-balance degradation in model wastewater spiked with MOR.

Figure 14: Samples during treatment by UV oxidation; from left to right: untreated wastewater to final treated wastewater.

cess the wastewater during several technically discrete treatment stages, with the same final results as a batch process. Also, discharge is typically quite constant, with low fluctuation. A well-designed continuously-operating plant can compensate for some peaks of flow and concentration in the untreated wastewater. Figure 19 shows the details of the UV-skid in a continuous treatment plant where the tank structure for treatment and chemical storage is placed in the floor level below the reactor unit shown in the photo.

5. Conclusion

For industrial use, important factors of any technology are high reliability and availability. In the case of UV plants, the prevention of fouling on the UV modules is a particular concern, which is, in practice, already solved. The wide range of applications and numerous large plants operating all over the world confirm this to be a reliable technology.

Another important factor to consider is the positive environmental effects, as in most cases the wastewaters were previously sent to direct or indirect incineration. This paradigm shift results in huge savings in resources, a reduction of carbon-dioxide emissions, as well significant costs savings. The low OPEX associated with these plants, in particular when compared to the previous approach of disposal and in many cases incineration, allows the initial CAPEX outlay to be amortized quickly.

The general result of this technology is always a full degradation of the API below their PNEC or even LOD and a non-toxic wastewater with a fully bio-degradable matrix, in most cases further polished by a biological treatment plant. In many cases the APIs are no longer detectable in the concentrated treated streams and even less so once the wastewater has been diluted multiple times by other streams, in the biological treatment plant and finally by the bodies of water in the communal collection or in the environment.

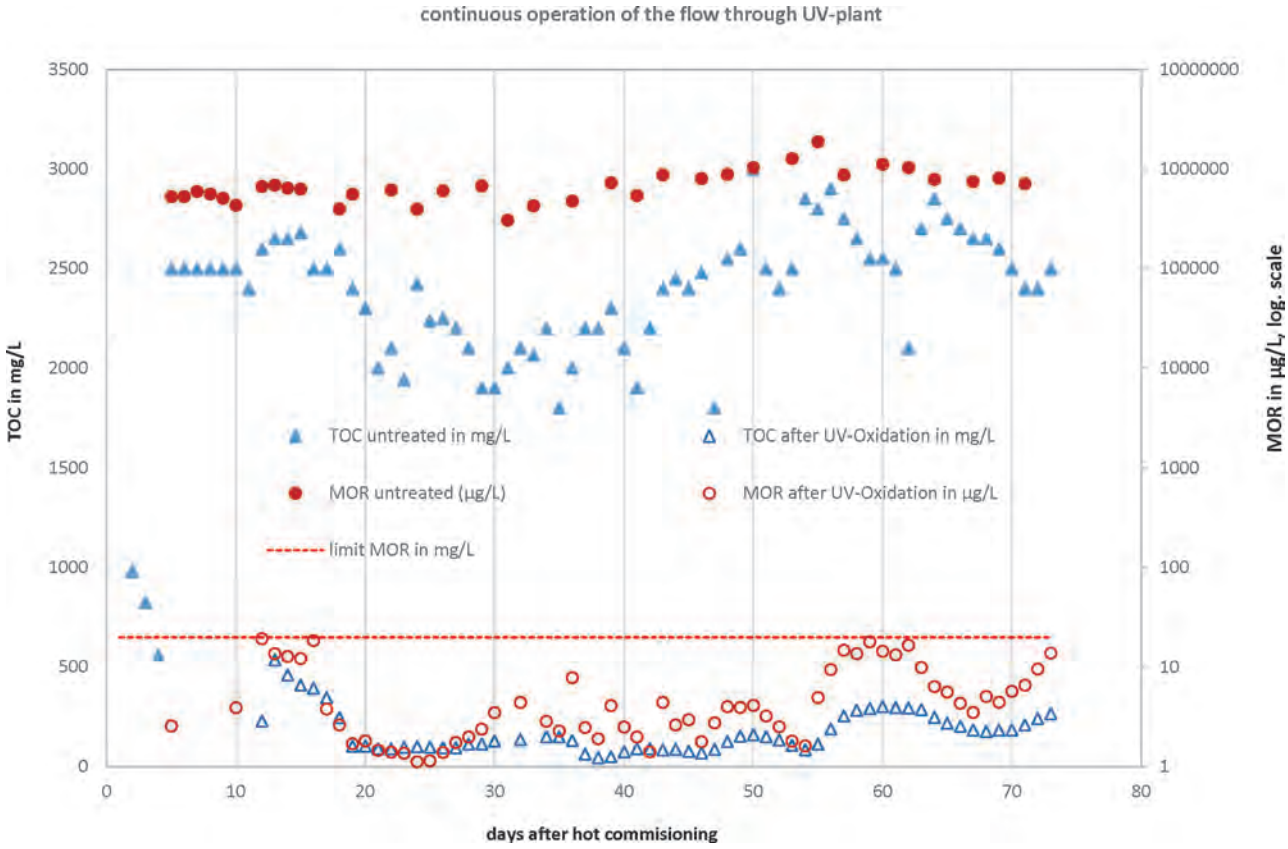

Figure 15: Treatment results of the industrial UV plant over a period of 74 days of operation after hot commissioning. It shows inlet concentrations of TOC and MOR as well as the outlet concentrations of the UV oxidation plant.

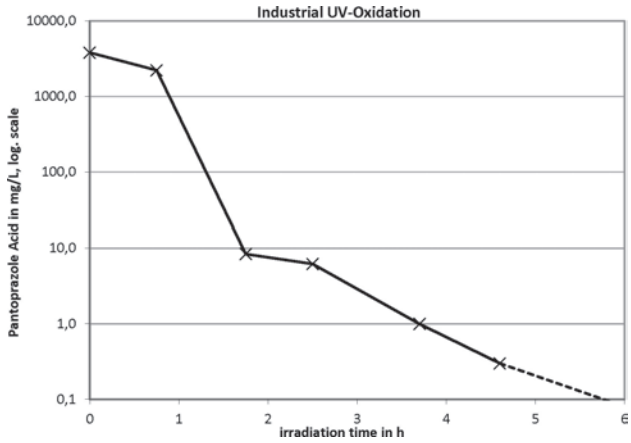

Figure 16: Degradation of Pantoprazole during lab-scale testing (dotted line=below LOD).

6. Acknowledgement

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Figure 17: Batch treatment plant for about 20 m³/d pharmaceutical wastewater containing APIs and bio-active material.

Figure 18: Continuous wastewater treatment plants at CMOs for CIP-rinse wastewater from API formulation with a max. of 200 m³/d, overview (left) and inside view (right) of the treatment container.

Figure 19: UV-skid of a continuous wastewater treatment plant placed at an API manufacturing site.

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