Elimination of Hormones in Pharmaceutical Waste Water

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To reduce discharging of endocrine substances into the aquatic environment, production and processing companies reduce the release of these substances by installing technical barriers. Haupt Pharma Münster produces hormone containing preparations such as contraceptives and was looking for a safe and environmentally friendly technology to avoid emitting of any APIs (pharmacologically active substances).
During the planning stage a conceptual design study compared four possible processes for waste water treatment: Reverse Osmosis, Activated Carbon, UV-Oxidation and disposal by a service provider.
After a comparison of technical and commercial criteria, which is reproduced in this article, the company decided to use UV-oxidation. The UV-oxidation process is described, as well the daily operating practice of the UV-plant.
The degradation of the hormones cyproterone acetate, letrozole, ethinylestradiol und levonorgestrel present in the waste water is shown. Either selective API degradation or a substantial mineralization of the organic matter can be achieved by the installed UV-plant in full automatic operation. The mineralization is documented by the degradation of TOC (Total Organic Carbon) and COD (Chemical Oxygen Demand).

Introduction

On Haupt Pharma's production site in Münster more than 160 employees work on high quality and on-time contract development and manufacturing. Dedicated areas are reserved for the production of oral high potency and low dose products (contraceptives, thyroid hormones, narcotics).

Handling of e.g. sex hormones as highly potent pharmacologically active substances requires increasingly complex facilities and machinery to protect the product, the workforce and the environment [1].

Therefore waste water had to be treated without releasing any pharmacologically active substances to the aquatic environment, as those substances are known to interfere in low concentrations. The new production line complies with all modern standards (e.g. latest FDA requirements) and has the minimum possible waste generation during regular production. The expected waste water quantity was 10 m^3/d coming from production, mostly generated by cleaning processes.

To find an appropriate technical solution to perform processing of waste water an independent consultant (D&B Pharmadesign, Halle/Westphalia) had been authorized to investigate established waste water technologies and compare them under technical and commercial aspects. The Company asked the consultant to compare methods within the range from complete external service to 100% in-house treatment.

Comparison of methods

The following methods have been taken into account for the evaluation:

- RO (Reverse Osmosis) for concentration and external disposal of the concentrates,
- Activated Carbon filtration with external recovery of the activated carbon,
- UV-Oxidation/AOP (advanced oxidation process) and
- Disposal of the untreated waste water by a service provider.

The technical aspects were stated by the consultant as given in Table 1. Compared were the fraction of water that can be discharged into the municipal sewage system after using the process and the part that has to be disposed of. Additionally reliability, maintenance effort and possible risks of each process were evaluated and compared.

The main disadvantage of reversed osmosis, activated carbon and external disposal is that there is still need of disposal of products after the treatment. Necessary transport, recycling or burning are part of the operating costs of these methods compared in Table 2. Most sustainable solution seemed to be the UV-oxidation, enabling the operator to discharge the complete waste water into the sewage system after UV-treatment. Precondition is that the

■ **Table 1**

Technical aspects of processes compared.

	Reverse Osmosis	Activated carbon	AOP	External Disposal
Waste water to be discharged	75 % of the treated waste water can be discharged because of reduction of the ingredients between 95–99 %	100 % of the treated waste water can be discharged	100 % of the treated waste water can be discharged	No discharge
Disposal	25 % concentrate containing the most part of the ingredients have to be disposed, e.g by burning	Activated carbon has to be disposed/ recovered	Nothing to be disposed of as most of ingredients will be mineralized	100 % will be stored and disposed of, e. g. by burning
Reliability	Membrane is sensitive to many substances (membrane fouling) and must be cleaned. Degree of concentration may be limited by precipitation, operation temperature is up to ca. 45 °C.	Easy to be realized, simple change of filtration tanks	High reliability and good process control. Can be adjusted to a high variation of waste water concentrations.	Easy to be realized, not depending on water quality and simple to handle
Maintenance	Frequent and complete chemical cleaning required ca. 1/month (see membrane fouling).	Very low maintenance	Low to middle maintenance effort. 1 lamp change per year, cleaning of system may be required.	Minimum, maintenance of tank farm
Risk	Membrane fouling, lab test required	Unknown frequency of filter change depending strongly on matrix, lab test required	Process to be developed, test runs required	Development of external costs

■ **Table 2**

Commercial aspects (database 2008) [2].

	Reverse Osmosis	Activated carbon	AOP	External Service
Investment in €	150 000–165 000	28 500–31 500	70 000–80 000	28 000–38 000
Operating costs in €/m³	40–60	20–30	5–8	150–300

■ **Table 3**

Concentrations in the simulated waste water [2].

Parameter	Concentration in the simulated waste water in mg/L
Cyproteron acetate	6,6
Letrozol	1,0
Ethinylestradiol	0,032
Levonorgestrel	0,16
Total Organic Carbon (TOC)	62
Chemical Oxygen Demand (COD)	163

■ **Table 4**

Ingredients of the waste water at Haupt Pharma Münster (10 m³/day).

Active Ingredients	Concentration in the formulation	Concentration in the wastewater
Steroids	1,0–30 %	2,0–56,0 mg/L
Aromatase inhibitor	1,0–30 %	2,2–56,9 mg/L
Oestrogens, Gestagens	0,5–20 %	0,2–18,1 mg/L
Excispients		
Lactose	10–40 %	
Microcrystalline Cellulose	10–40 %	
Kollidone/Povidone	2–3 %	
corn/potato starch	5–15 %	total 80–188 mg/L
Talcum	1–4 %	
Mg-Stearate	1–2 %	
Saccharide, refined sugar	30 %	

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active ingredients can be fully degraded by means of a thoroughly developed process and parameter set.

Based on these evaluation results and detailed costs UV-Oxidation as well as activated carbon treatment seemed to be most feasible and economic processes for the treatment of this specific process waste water.

Therefore the company decided that lab tests with both methods should be carried out. A defined simulated waste water was treated by a supplier of the activated carbon filtration and a supplier for UV-installations (Table 3 and 4). Both had to quote a commercial installation treating the waste water with specifications listed in Table 4.

Results of the laboratory simulation

The laboratory tests using UV-Oxidation showed the complete destruction of all compounds as shown in Fig. 1–3. Moreover the process led to the complete mineralization of all organic compounds which means that all organically bound carbon is oxidized to carbon dioxide.

The UV-Treatment was stopped when the detection limits for TOC and COD were reached (1 resp. 10 mg/L). On the basis of these data a commercial offer for an appropriate industrial UV plant for treating 10m^3/d was prepared.

Industrial application

Under commercial and technical aspects the company decided to treat the waste water with an Enviolet®-UV-oxidation plant (Fig. 4) as operating costs were the lowest possible. Moreover references showed this solution to be a strong and reliable tool for destruction of APIs or other contaminants [3, 4]. A. c. k.'s Oxidation reactors have shown their ability to treat even non-transparent solutions or water with high loads of particles [5].

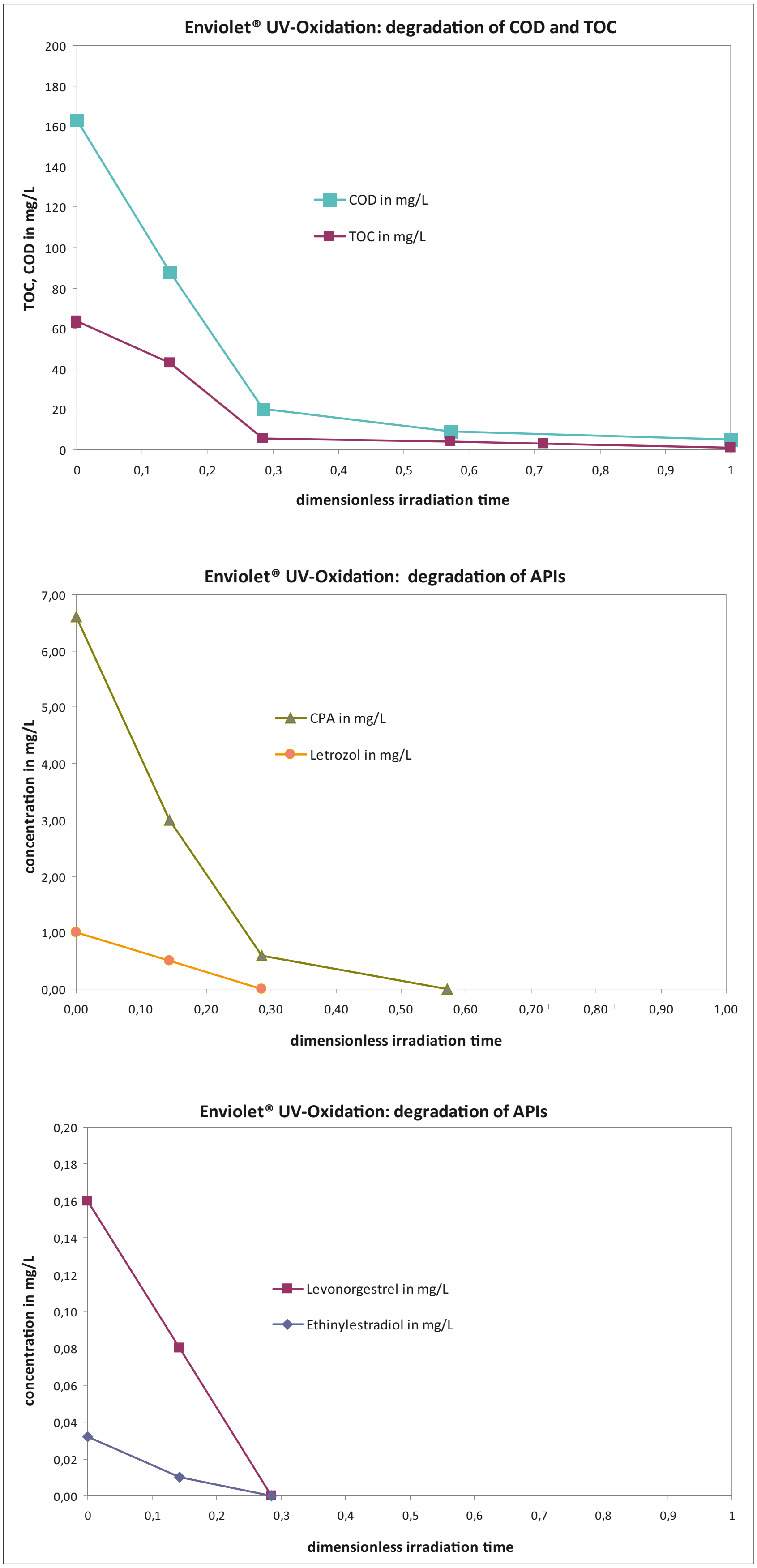

Fig. 1–3: Degradation of APIs, COD and TOC.

Fig. 4: Enviolet®-UV-Installation for 100 % destruction of APIs.

The installed UV-oxidation system is a batch treatment with a fully automatic process. The waste water is pumped by company into two parallel storage tanks of the UV-installation. From there the PCS (process control system) pumps the waste water into the batch-treatment unit where the process takes place. The solution is pumped from the 12 m^3 batch tank via a loop into the UV-reactors for oxidation; before entering the UV-reactors the oxidant is added and homogeneously mixed into the waste water to get the best degradation rate. During the process all parameters like temperature and pH-value are kept on specification.

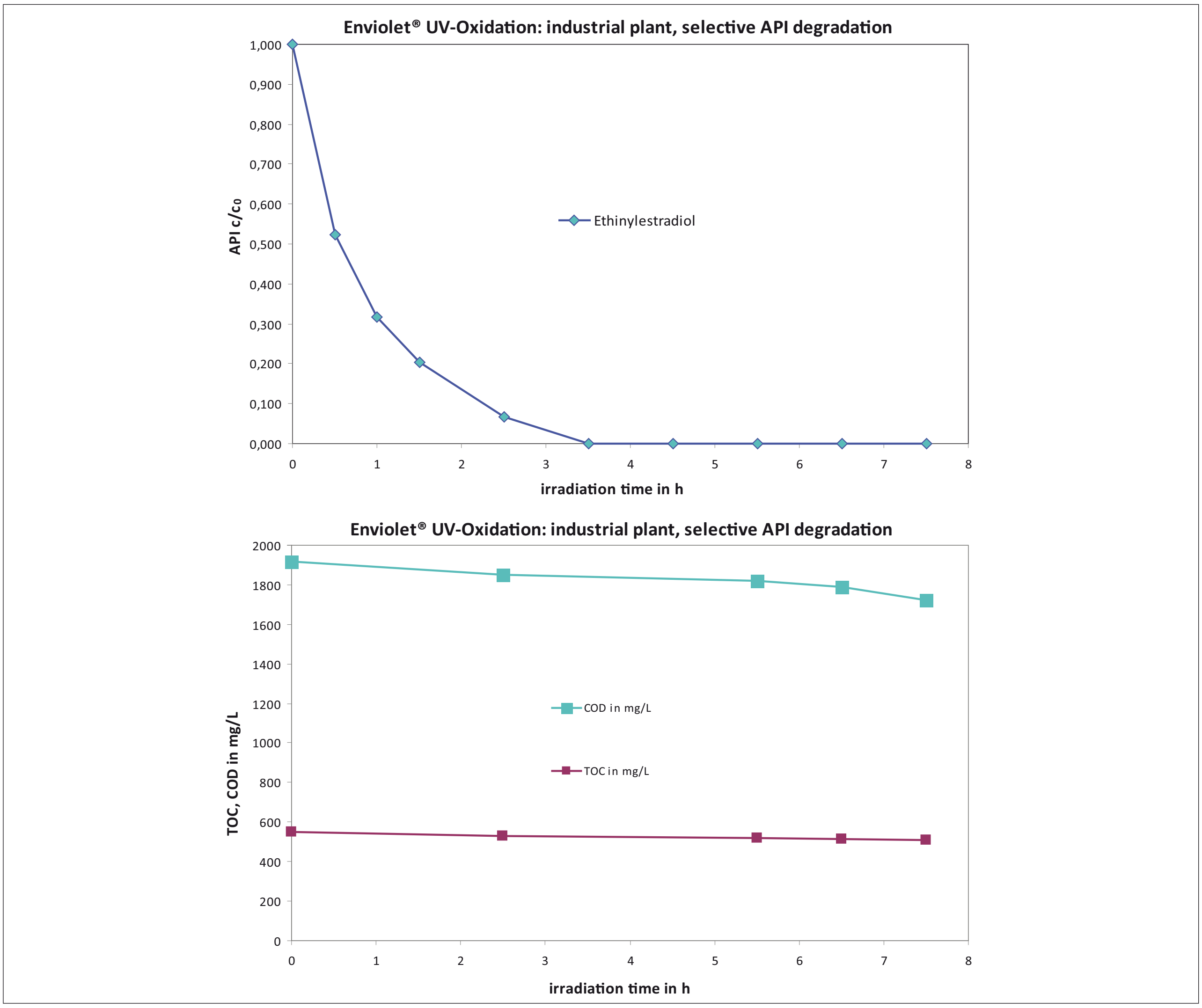

Fig. 5–6: Destruction of API, COD and TOC during UV-treatment of real waste water.

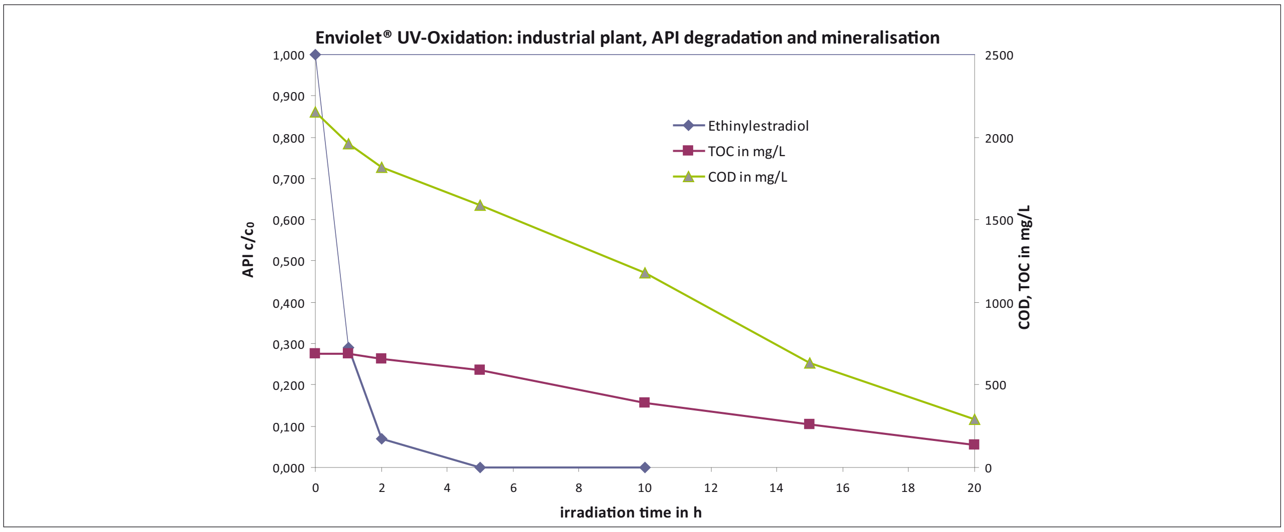

Fig. 7: Destruction of API, COD and TOC during UV-treatment of real waste water.

During the start-up phase of the industrial UV-plant treatments were accompanied with intensive sampling and analysis. At that time waste water was contaminated only with Ethinylestradiol, a sexual hormone.

In Fig. 5 it can be clearly seen, that after a short while of oxidation the sexual hormone is destroyed below the limit of detection with COD elimination less than 20 %. This means the APIs were degraded with high selectivity. Later, after the start-up phase, only one sample was taken and analysed after a completed UV-treatment. All analyses for different hormones (Table 3) showed concentrations below the detection limit. Hence there was no need for further analyses, not even for analyses of starting concentrations. Obviously all hormones even in possible higher initial concentrations were always destroyed completely using the same amount of consumables.

In case there was any API still found after a treatment, maybe because of unexpected much higher initial concentration, the treatment could easily be continued until limits are reached. This is another advantage of the UV-Oxidation installed as batch system. If there is waste water with different initial concentrations, the irradiation time can be adapted to the present concentration before treatment is started.

Striking is the much higher load of organic matter (COD, TOC) beside APIs and excipients in the real waste water in contrast to the simulated one (Table 3). COD values are in the range of 1 900 to 2 000 mg/L (Fig. 6) whereas the simulated water contained only 163 mg/L COD. This is because of cleaning solutions are part of the waste water as well containing phosphates and surfactants amongst others. Therefore in the real waste water a concentration of organics is measured that is more than 10 times higher than expected, however the concentration of the API is still in the specified range. Obviously this matrix doesn't inflict the API degradation significantly and there was no need for a raise of consumables. The operating costs for complete degradation remain the same.

Other technologies would require easily 10 times higher operating costs as determined before by the data of the simulated waste water. This is due to the very high selectivity of the described UV-Oxidation system.

Beside generation of hydroxyl radicals by UV-photolysis of H_2O_2 direct photolysis of the targets can be achieved as well. Both reactions lead to subsequent degradation reactions but especially the direct photolysis enables a higher selectivity of oxidation. This was shown already in former a.c.k. projects where other contaminants (Erythromycin, Sulfamethoxazol, Penicillin-V-K and Trimethoprim) were destroyed in real waste water with lab- and industrial-scaled plants [6].

Also to destruct possible by-products the oxidation is advanced up to 80 % COD reduction. At this degree of oxidation all organic compounds, even stable surfactants, are degraded mainly to carboxylic acids (Fig. 7).

To achieve 80 % COD degradation the process-parameters had to be adapted to this task. It was still possible to carry out one batch treatment in the given time frame.

An example for UV-oxidation of a complex mixture of toxic organic compounds in a real waste water (fine chemicals industry) containing phthalic acid derivates is illustrated in Fig. 8–9. This example is presented because detailed analyses of degradation products and bio availability exist. Concentrations of carboxylic acids are rising during the treatment by UV-Oxidation and after reaching a maximum their concentration is dropping as well. At this stage complete bio availability is already achieved. This was shown by meas-

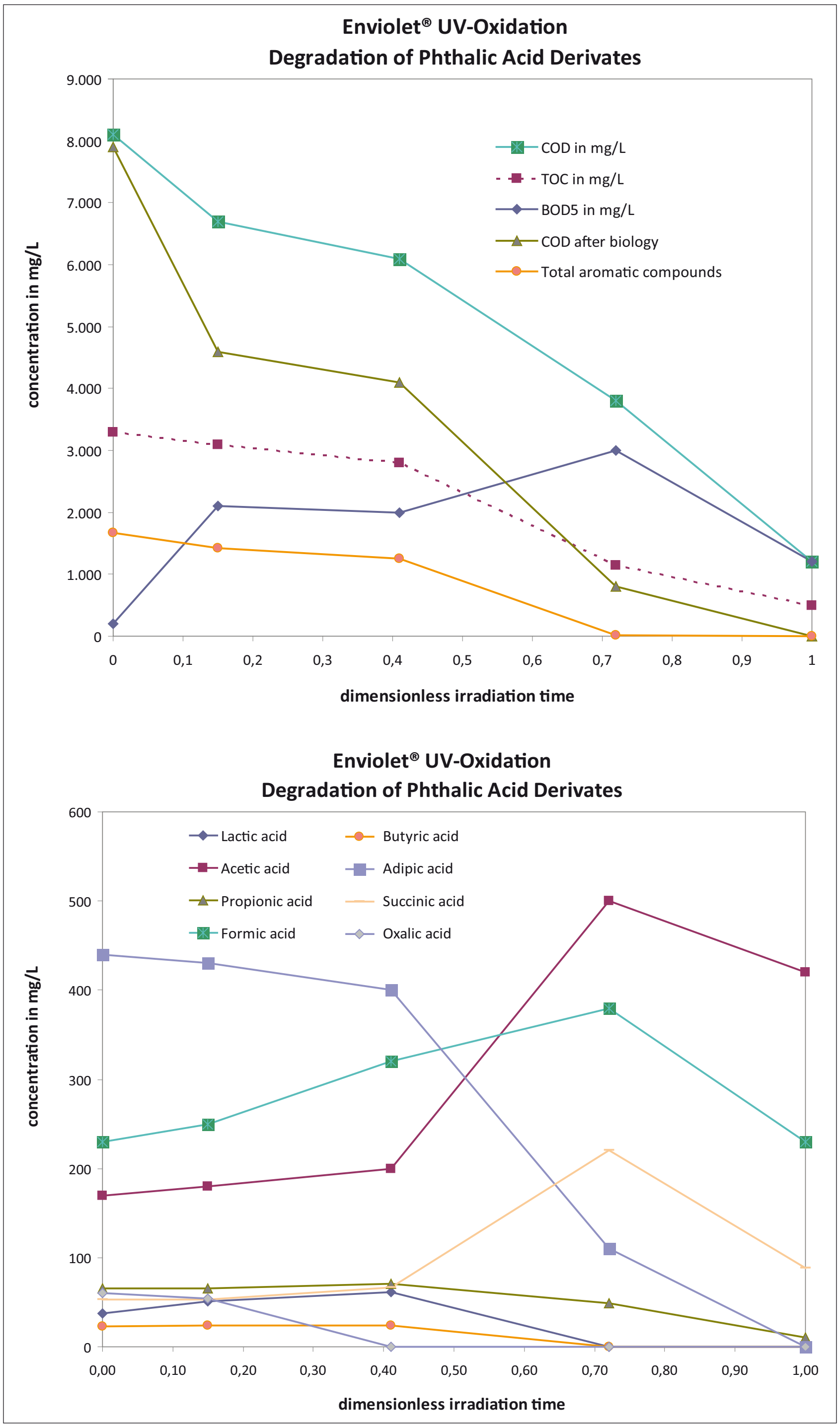

***Fig. 8–9:** Destruction of toxic compounds, COD and TOC during UV-treatment of real waste water. Generation of bio available degradation products.*

urement of BOD_5 (Biological Oxygen Demand after 5 days) and comparing it with the COD. An adapted activated sludge would lead to an even higher bio availability.

For all the above-mentioned reasons the company is convinced to have chosen the best method for waste water treatment when installing an UV-Oxidation. If there is more waste water in the future or much higher concentrations to be treated, the system can be easily upgraded by an additional UV-reactor without any more space requirements.

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