Monitoring of AOP degradation of selected pharmaceutical

Krpina, Ana

UNIVERSITY OF ZAGREB

FACULTY OF CHEMICAL ENGINEERING AND TECHNOLOGY

INTERNATIONAL GRADUATE STUDY

Ana Krpina

MONITORING OF AOP DEGRADATION OF SELECTED PHARMACEUTICAL

Master Thesis

Zagreb, July 2023

UNIVERSITY OF ZAGREB

FACULTY OF CHEMICAL ENGINEERING AND TECHNOLOGY

INTERNATIONAL GRADUATE STUDY

Ana Krpina

MONITORING OF AOP DEGRADATION OF SELECTED PHARMACEUTICAL

MASTER THESIS

Mentor: Prof. Šime Ukić

The examination committee: Prof. Šime Ukić

Assist. Prof. Matija Cvetnić

Sen. Lec. Lidija Furač, Ph.D.

Zagreb, July 2023

SUMMARY

Pharmaceuticals are extensively utilized globally and their persistent nature and potential adverse impacts on the environment and human health are well−documented. The ubiquitous usage of pharmaceuticals significantly contributes to water pollution which has become a major global issue. Advanced oxidation processes have emerged as a promising solution to address this problem. In our study, we focused on monitoring the degradation of a commonly used active pharmaceutical compound, pantoprazole, using UV/H_2O_2 and UV/$S_2O_8^{2-}$ advanced oxidation processes. We studied the influence of various water matrix factors, including pH, oxidant concentration, phosphate ion, sulfate ion, chloride ion, nitrite ion, nitrate ion, and humic acid, on the degradation rates of pantoprazole. To ensure efficient data collection while minimizing the experimental runs, we used the Taguchi design of experiment. The experimental results were analyzed using statistical software MiniTab. The analysis emphasized the notable influences of water matrix constituents on the degradation rates, which in most cases, were in agreement with previous scientific findings.

Key words: advanced oxidation processes, UV/H_2O_2, UV/$S_2O_8^{2-}$, pantoprazole

Table of Contents

1. INTRODUCTION

Water is essential for all forms of life and plays a crucial role in maintaining the health and functioning of ecosystems, human societies, and the global economy. Although it is considered to be a renewable resource, in recent decades it has become a major global concern due to the pollution mainly caused by human activities such as industry, agricultural practices, littering, and improper waste disposal. According to the UN World Water Development Report 2023, 2 billion people lack access to drinking water services that are safely managed. [1] The consequences are devastating, with an estimated 829,000 deaths per year attributed to unsafe drinking water, sanitation, and hygiene, with children under the age of five being the most vulnerable group, as the waterborne disease is the leading cause of mortality within this group. [2, 3]

Among many, active pharmaceutical ingredients (API) have emerged as a substantial category of water pollutants due to their widespread use and persistence in the aquatic environment. Contamination occurs throughout the lifecycle of pharmaceuticals, from manufacturing to consumption, and disposal. In the European Union, about 3,000 pharmaceutical substances are in frequent use, and the number is increasing every day. [4] Pharmaceutical residues have been detected globally in the surface water and groundwater, drinking water, sediments, wastewater and sewage sludge, and even animal tissue and edible plants. [5, 6]

Remediation of pharmaceutical pollution presents a major challenge due to pharmaceutical's low biodegradability and high hydrophilicity which often make their elimination from water systems using conventional wastewater treatment methods very difficult. [7] This is a major motivation behind the extensive ongoing research on the best approach for addressing this challenge. Currently, one of the most convenient solutions to this problem is advanced oxidation processes (AOPs). AOPs include different water treatment methods that are based on the oxidation of pollutants by highly reactive radical species, most commonly hydroxyl radicals. AOPs show high efficiency in the removal of persistent organic pollutants, including pharmaceuticals, without the formation of toxic by−products. [8]

The aim of this study is to analyze the kinetics of UV-C-based oxidation of the widely used pharmaceutical pantoprazole in different water matrices utilizing the two most commonly

used oxidants (hydrogen peroxide and persulfate). The synthetic water matrix is prepared to contain humic acid (HA) and five inorganic ions (nitrate, nitrite, chloride, phosphate, and sulfate). Degradation was monitored under both alkaline (pH = 10) and acidic (pH = 4) conditions. The experiment was conducted following the Taguchi experimental design, allowing us to analyze the effect of each of the eight factors (pH, oxidant, humic acid, nitrate, nitrite, chloride phosphate, and sulfate) on the degradation of pantoprazole. The results were processed and presented using the statistical software MiniTab.

2. REVIEW OF THE LITERATURE

2.1. Pharmaceutical industry

The modern pharmaceutical industry can trace its roots in the late 19th century with the merging of apothecary companies and dye and chemical companies that started out as research labs before discovering medical applications for their products. [9] Soon the objective became to identify and prepare synthetic drugs and to analyze their effects on pathological conditions. Significant growth in the industry was recorded with the introduction of research & development (R&D) into the industry, which was facilitated by different events such as the World Wars, collaborations between academics and pharmaceutical companies, and the increased funds by governments of developed countries into the industry. This era is referred to as the golden era of the pharmaceutical industry. [10] Since then, there is a constantly increasing trend in the use of pharmaceuticals all over the globe and it stands out as one of the greatest benefits of modern society.

Moving to the most recent time, the annual global use of pharmaceuticals in 2020 is estimated to be 4.500 trillion doses while the total global pharmaceutical revenue is valued at about 1.27 trillion U.S. dollars in 2020. [11] Despite fluctuations in the market caused by the pandemic of COVID−19, it is estimated that the pre−pandemic annual growth rate of approximately 6.5% will eventually continue so the revenue for 2026 will reach 1.8 trillion U.S. dollars. [12, 13] In terms of employment, in Europe alone, 835,590 people had been employed in the pharmaceutical industry between 1990 and 2021, out of which around 125,000 people were employed into R&D activities in major companies in the industry, as shown in Figures 1 and 2.

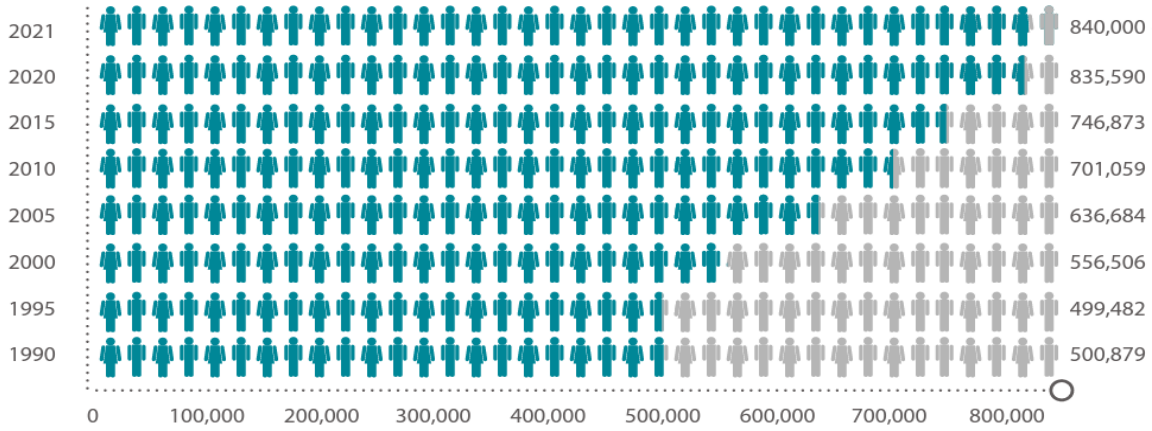


Figure 1. Employment in the pharmaceutical industry between 1990 and 2021. [14]

Data from Figure 1 includes Iceland (2017−2021), Croatia, Lithuania and Turkey (2010−2021), Bulgaria, Estonia and Hungary (2009−2021), Czech Republic (2008−2021), Cyprus (2007−2021), Latvia, Romania and Slovakia (2005−2021), and Malta, Poland and Slovenia (2004−2021).

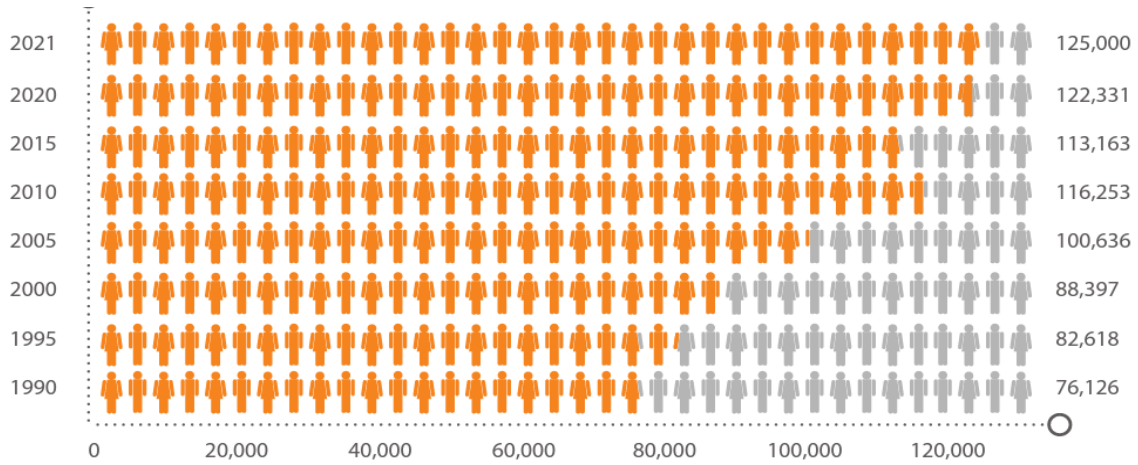


Figure 2. Employment in pharmaceutical R&D between 1990 and 2021. [14]

Data from Figure 2 includes Iceland (2017−2021), Greece and Lithuania (2013−2021), Bulgaria and Turkey (2012−2021), Poland (2010−2021), Czech Republic, Estonia, and Hungary (2009−2021), Romania (2005−2021) and Slovenia (2004−2021), in addition to major European countries like Germany and Switzerland. Other countries like Croatia, Cyprus, Latvia, Malta, Russia, Serbia, and Slovakia are not part of this number due to unavailable data.

The extent of the development of the pharmaceutical industry and the corresponding increase in the global distribution of pharmaceuticals have had a significant impact on the lives of individuals through successful treatments for a variety of pathological conditions, increased life expectancy, decreased infant mortality, improved prevention of diseases and improved quality of health. [15] With these individual benefits being intertwined, major impacts appear on the global or national scale. For example, some of the benefits this industry has on national economies include:

- reduction in public health expenditure,
- reduction of the burden on pension systems and medical care systems,
- improvement in health−related quality of life,
- total economic production value boost,
- maintenance of existing employment and new job opportunities creation, and

- increase in long−term economic growth and international competitiveness (via innovations, which is the outcome of a "well−aimed production of technological knowledge").

2.1.1. Pharmaceutical pollution

While pharmaceuticals play an important role in maintaining human and animal health, it is equally important to address the negative environmental impact of pharmaceutical residues entering freshwater systems. Pharmaceutical residues are unwanted yet present worldwide in freshwater sources like groundwater, surface water, and seawater. It has been reported that pharmaceuticals in the environment have been detected in 75 different countries and 771 substances have been found, sometimes at levels over the pollution thresholds. [16]

2.1.1.1. Sources

Pharmaceuticals and their metabolites find their way into the environment through production, consumption, and disposal. [17, 18] The major sources can be categorized into: households, health care facilities, pharmaceutical production, and application in veterinary medicine.

Households

The largest source of domestic or household emissions mainly originates from the excreted pharmaceuticals after consumption. About 30−90% of the pharmaceutical oral doses are generally excreted in their original form or as a metabolite. There is also a possibility that pharmaceuticals in the form of creams and ointments washed off skin may directly find their way into wastewater. [19] In addition, expired or used medicines contribute to a significant waste stream which if improperly disposed can contribute to household or domestic emissions. It is estimated that 3−50% of pharmaceuticals become waste. [20]

Health care facilities

Another major source from which pharmaceutical substances entry the municipal sewage networks are medical facilities like hospitals, healthcare services and long−term care

facilities. Although hospital effluents contain high concentrations of active pharmaceutical ingredients their contribution in total APIs load in municipal wastewater is only around 20%. [21] However, hospitals effluents as well often contain specialized pharmaceuticals (cytostatic drugs, some antibiotics and X−ray contrast agents) that are not used in households, but may pose greater threat to the environment and require special treatment to be successfully eliminated from the wastewaters. [18, 21, 22]

Pharmaceutical production

Indirect (e.g., leakage) and direct discharge (e.g., industrial wastes) of pharmaceutical production residues can pollute natural water sources. This source is generally considered a low−point source. The emissions from the manufacturing facilities in Europe and North America are generally considered low while in Asian countries may be higher as the research report that concentrations for single compounds in manufacturing effluents are reported to be in several milligrams per liter. [16, 17, 23]

Application in veterinary medicine

About 30−90% of the pharmaceutical consumed by animals is excreted through urine and feces as the original compound or a metabolite. However, in case of animals, there is an additional concern due to the use of feces as manure which also contributes to pollution of waterbodies through underground water. [18, 24] The European Federation of Animal health (FEDESA) approximates that 4,700 tons of veterinary pharmaceuticals were consumed in 1999 within the borders of European Union. [25] Despite the magnitude of this pollution source, there is still lack of scientific research with regarding to its contribution and effect on environmental pollution.

2.1.1.2. Pathways

The key entry pathways of pharmaceuticals into freshwater and terrestrial ecosystems are wastewater treatment plants (WWTPs) and landfilled municipal solid waste (MSW).

WWTPs are major pathway through which pharmaceutical compounds or their metabolites enter freshwater. This is because conventional WWTPs are unable to eliminate all pharmaceuticals. This supposedly treated wastewater is mostly discharged into the environment

or even directly used for purposes such as agriculture, thereby introducing APIs into waterbodies through groundwater, surface runoff, and other means. [26]

Landfilled MSW is another pathway by which pharmaceutical waste is introduced into the environment, especially water bodies. If the MSW is composed of a mixture of several wastes, there is a very high chance of it containing pharmaceutical active ingredients that can be carried into freshwater bodies in one way or another, especially when there is an incident of leaching and the leachate is not taken up and handled properly. Several studies have reported the presence of pharmaceutical residues and their metabolites in landfill leachate in different parts of the world such as, the United States, Shanghai, and Taiwan. [27−31] The sources and pathways of pharmaceutical wastes into the environment are summarized by Figure 3.

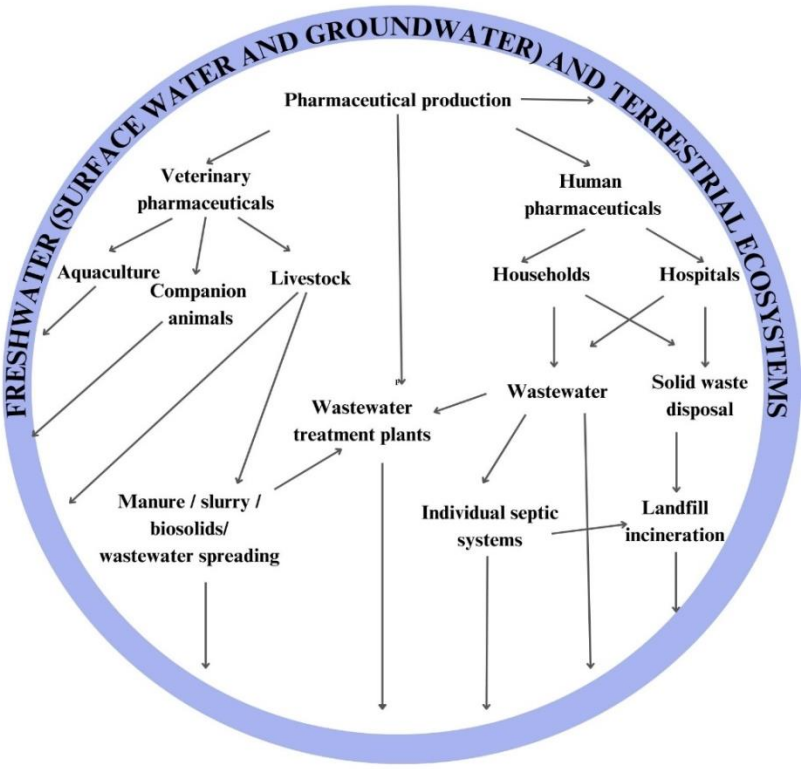


Figure 3. Main sources and pathways of entering of human pharmaceutical residues into the environment. [32]

2.1.1.3. Effects of pharmaceuticals on the environment

In recent years, much attention and research has been devoted to pharmaceutical waste in the environment and its effects. Caban [12] reported that there are no environmental toxicity data for 88% of pharmaceuticals. Even though most pharmaceuticals have not yet been studied

for their long−term toxicity, it has been proven that the occurrence of certain pharmaceuticals in the environment can result in undesired adverse effects on ecosystems, increase mortality in aquatic species, and changes to physiology, behavior or reproduction. [32] Of most concern for ecosytems are analgesics, hormones, antidepressants, anticancer and, antibiotics. For instance, ethinyloestradiol plays a role in the feminization of male fish in effluent−dominated rivers [33]; anticonvulsants like Carbamazepine are responsible for reproduction toxicity in invertebrates and development delay in fishes; analgesics like Ibuprofen cause organ damage in fish and hormonal disruption in frogs; while antibiotics have been discovered to cause reduced growth in organisms like environmental algae, bacteria, and aquatic plants. [34−37]

2.1.1.4. Policies and regulations

To reduce the environmental effect of pharmaceutical residues, several stakeholders at the national and continental levels are implementing policies and measures to address this critical problem of active pharmaceutical ingredients in the environment. These regulations are primarily concerned with the management and disposal of waste related with pharmaceuticals and personal care products, particularly environmentally persistent pharmaceutical pollutants.

In general, there is no universal approach or policy to regulate pharmaceutical waste pollution: different countries address this challenge with different regulations and policies. Some of the policy actions being implemented are discussed in further text.

Incineration of medical waste

This method is generally accepted as the most suitable method of disposing medical waste. It is based on incineration of pharmaceuticals at temperatures above 1200 °C with obligatory flue gas cleaning. This completely addresses the possibility of the pollution of freshwaters by pharmaceutical residues. Incineration is mostly applied in developed countries like the U.S., Canada, Germany, and Switzerland who account for most of the incineration of medical wastes. [38]

Promotion of green pharmaceuticals and circular economy

Green pharmaceuticals refer to new products that are more efficiently biodegraded at the same time maintaining their effective pharmaceutical qualities. There are advocations to

embrace green pharmaceuticals, and there is a growth in the production of these types of pharmaceuticals. A circular economy is an economic scheme aimed at promoting sustainable development, where the environment does not have to be subjected to further pollution and damages. In circular economy, a waste product of a given process is used as a raw material or feed to another production process. In other words, it is a zero−waste program. This economic scheme also applies to pharmaceutical products, where pharmaceutical wastes can be used as raw materials for another production process. [38]

Drug take−back programs

Drug take−back programs refer to a scheme whereby consumers are encouraged to return unused pharmaceutical products which is already in practice in Canada. The objective of the scheme is to reduce the chances of pharmaceutical constituents entering the environment. By collecting unused products, proper disposal measures can be implemented, reducing the potential environmental contamination. However, the exact contribution of this program is uncertain. [38]

Conduction of Environmental Risk Assessment on pharmaceutical products

One of the measures being implemented in the European Union aimed at addressing pharmaceutical pollution challenge from a supply perspective is the requirement of Environmental Risk Assessment from manufacturers of these products. Environmental Risk Assessment will determine the level of hazard that would be associated with this product, and as well make provisions on how to prevent the pollution of the environment by the pharmaceutical product. [38]

Wastewater treatment

Wastewater treatment covers the activities aimed at addressing the potential pollution of freshwaters through wastewater treatment. Conventional WWTPs were typically based on physicochemical processes (filtration, flocculation, coagulation, sedimentation, membrane filtration, chlorination, adsorption via activated carbon) and biological processes. While conventional WWTPs are efficient in removal of some pharmaceutical ingredients, it is documented that certain pharmaceuticals ingredients are partially or completely resistant to

these treatments. [26] This led to the necessity for development of more efficient techniques, namely advanced oxidation processes.

2.2. Advanced oxidation processes

Advanced oxidation processes (AOPs) are a group of water treatment methods characterized by the *in situ* generation of radical species with strong oxidative power in order to degrade or remove persistent organic and inorganic pollutants in water.

Table 1. Major mechanisms and types of advanced oxidation processes. [41]

AOP types	Oxidants	Other occurring mechanisms
O_3	OH•	Direct O_3 oxidation
O_3/H_2O_2	OH•	Direct O_3 oxidation
		H_2O_2 oxidation
O_3/UV	OH•	UV photolysis
UV/TiO_2	OH•	UV photolysis
UV/H_2O_2	OH•	UV photolysis
		H_2O_2 oxidation
Fenton reaction	OH•	Iron coagulation
		Iron sludge−induced adsorption
Photo−Fenton reaction	OH•	Iron coagulation
		Iron sludge−induced adsorption
		UV photolysis
Ultrasonic irradiation	OH•	Acoustic cavitation generates transient high temperatures (>5000 K) and pressures (>1000 atm), and produce H• and HO_2•, besides OH•
Heat/persulfate	SO_4^-•	Persulfate oxidation
UV/persulfate	SO_4^-•	Persulfate oxidation
		UV photolysis
Fe(II)/persulfate	SO_4^-•	Persulfate oxidation
		Iron sludge−induced adsorption
OH^-/persulfate	SO_4^-•/OH•	Persulfate oxidation

According to research data, these methods have been successfully used in the degradation of a wide range of persistent pollutants, often achieving complete mineralization. [39, 40] Unlike the traditional oxidants, such as chlorine and ozone that serve a dual purpose of decontamination and disinfection, AOPs are mainly used for the removal of organic pollutants and enhancement of wastewater biodegradability prior to biological water treatment. This is due to the fact that the radical species generated by AOPs have an extremely short half-life (on the order of microseconds) that is insufficient for disinfection purposes. [41] Nevertheless, AOPs are efficient and environmental-friendly methods to improve overall water quality, providing a comprehensive solution for removal of persistent pollutants including pharmaceuticals. AOPs are classified into various types depending on the type of radicals and mechanism of their generation, as summarized in Table 1. In addition, the most commonly used AOPs are discussed below, with UV-C-based oxidation explained in more detail since this method was used in the experimental part of the thesis.

2.2.1. Fenton−like processes

The Fenton process was discovered in 1894 and is the first AOP used to efficiently degrade pollutants. In the Fenton process, under acidic conditions (pH 3.0), Ferrous ions (Fe^{2+}) combine with hydrogen peroxide (H_2O_2) to generate hydroxyl radicals (HO•). During the photo−Fenton process, H_2O_2 oxidizes Fe^{2+} ions to produce Fe^{3+} and there is a generation of one equivalent (HO•). The generated Fe^{3+} serves as an electron acceptor during the photo−exposed reaction and leads to the production of one more radical whereas Fe^{2+} is reproduced in aqueous solutions [42−44] Fenton process preferably operates within a pH range of 2−4. Photo−assisted Fenton reaction, or simply photo−Fenton, is usually used instead of the conventional Fenton process to overcome the shortcomings of the Fenton process (dark−Fenton reaction). The photo−Fenton process in comparison to the dark Fenton reaction produces quicker mineralization and a higher reaction rate. [45]

2.2.2. Photo−catalysis

Photocatalysis is one of the most promising AOPs techniques for handling pharmaceutical wastewater because of its non−toxic nature, absence of mass transfer limitation, cost−effectiveness, chemically stable nature, and the possibility of carrying out the process at ambient temperature. [46−48] Photocatalysis can be categorized in different ways, such as by

the phase of the catalyst and substrate (homogeneous and heterogeneous catalysis) or by the pathway of oxidation (photogenerated catalysis and catalyzed photolysis).

In homogenous catalysis, the catalyst and the substrate both appear in the same phase while in heterogeneous, the process moves at the periphery of two phases, i.e., aqueous, or gaseous phase, and solid photo−catalyst phase. [49, 50] Various photo−catalysts which can be used for the treatment of persistent pollutants are iron(III) oxide (Fe_2O_3), zinc oxide (ZnO), tungsten trioxide (WO_3), titanium dioxide (TiO_2), zirconia (ZrO_2), and vanadium oxide (V_2O_5), among which titanium dioxide is the most common one. [51, 52]

Photo−induced catalysis involves a precursor molecule that, upon exposure to irradiation, absorbs photons and generates catalyst molecules that do not require further irradiation. The generated catalyst initiates a catalytic cycle, promoting the otherwise kinetically unfavorable conversion of a substrate into its photoproduct, while the catalyst molecule is fully regenerated. [52]

In contrast, catalyzed photolysis requires constant irradiation, as the catalytic specie has no catalytic activity in the absence of photons. In this process, the catalyst is an electronically excited semiconductor with electron−hole pair that oxidizes adsorbed water and oxygen molecules. These oxidation reactions result in the formation of radical species, primarily superoxide radical anions and hydroxyl radicals, which in turn oxidize pollutant molecules. Alternatively, pollutant molecules may be oxidized directly by the transfer of electrons at the h^+ side of the catalyst, which depends on the electron−donating properties of the substrate molecules. [52]

Various researchers have studied the degradation of pharmaceutical drugs using photocatalysis and observed the complete degradation. For instance, Safari et al. [53] studied the degradation of tetracycline antibiotic using TiO_2 photocatalysis with addition of H_2O_2 to enhance the reaction.

2.2.3. Ozone−based AOPs

Ozone is a potent oxidative agent that has been traditionally used for in situ water purification and disinfection. Although it can directly oxidize organic pollutants via electrophilic attack by molecular ozone (ozonation), this process may not effectively break down some persistent pollutants due to ozone's selectivity and low reaction rates. Therefore,

ozone based AOPs have been developed, combining ozone with other techniques to increase its decomposition and the production of hydroxyl radicals. Hydroxyl radicals are highly reactive and unselective making them significantly more effective at oxidizing pollutants than ozone. These AOPs include O_3/UV, O_3/H_2O_2, catalytic ozonation, photocatalytic ozonation, sonolytic ozonation, and O_3/Fenton processes. Studies have shown significant improvement in treatment efficiency and operational costs of these processes compared to traditional ozonization. [54]

2.2.4. Ultrasonication

Ultrasonication is an alternative AOP method often regarded as a green technology because it is chemical−free, easy to operate, and does not produce secondary pollutants. By applying ultrasound waves at specific frequencies, it induces physical and chemical degradation processes in liquid media. The ultrasound waves generate cycles of compression and expansion, leading to the formation and implosive breakdown of cavitation microbubbles. This process (combined with adiabatic heating of the bubble vapor phase) results in the creation of high temperature (approximately 4,200 K) and high pressure (975 bar) hotspots that cause water molecules to undergo thermal degradation, generating reactive H• and OH• radicals, as well as HO_2• in the presence of dissolved oxygen. These radical species then propagate a chain of radical reactions resulting in the oxidation of organic pollutants. Additionally, organic molecules that are in close proximity to the bubbles may as well undergo thermal decomposition leading to their degradation or even mineralization. [55] Ultrasound carries out acoustic cavitation at frequencies mainly above 20 kHz and up to 10,000 kHz, while large−scale applications predominantly proceed in the 20−40 kHz range. [56, 57] For example, the degradation of the pharmaceutical drug amoxicillin was studied by Matuoq et al. [58] It was observed that low−frequency sonication can efficiently degrade the compounds, making it an excellent pretreatment option prior to biological and other oxidation processes.

2.2.5. UV-C-based advanced oxidation

Organic pollutants in the natural environment mostly degrade as a result of hydrolysis and photolysis. Most of the pharmaceuticals intended for oral use are resistant to hydrolysis, so photolysis takes the main role in their abiotic transformation in the environment. However, the rate at which photolysis takes place in nature is much lower than the one that is taking place in AOPs with optimal degradation process conditions. [59]

Two main degradation pathways for UV-included AOPs are direct photolysis and radical indicated oxidation (indirect photolysis). Direct photolysis relies on the capability of pollutant molecules to absorb UV irradiation which directly leads to chemical transformation or degradation of the parent molecule. There are two main mechanisms of direct photolysis: 1) single-bond homolysis and 2) formation of superoxide radical and radical cations. [52]

Single-bond homolysis (Eqs. (1)–(3)) occurs when the target molecule is exposed to radiation with energy equal to or higher than the chemical bond dissociation energy. This process breaks the single R–X bond into two radical species. Formed radicals undergo further oxidation/reduction reactions. For example, the carbon−centered radicals (R•) react with molecular oxygen and form peroxyl radicals (R–O–O•) that finally degrade to the corresponding oxidation products. Single−bond homolysis is the main chemical pathway of direct photolysis. [52, 56]

$$R - X + h\nu \rightarrow X\bullet \quad (1)$$

$$R\bullet + \bullet O - O\bullet \rightarrow R - O - O\bullet \quad (2)$$

$$R - O - O\bullet \rightarrow \text{oxidation products} \quad (3)$$

Another mechanism of direct photolysis is shown by Eqs. (4)–(6). It includes electronic excitation of the parent molecule and electron transfer to the oxygen molecule. The formed radical cations are further transformed into the final products through recombination or hydrolysis. [52, 56] Overall, direct photolysis efficiency is limited by low UV absorption by the target molecule.

$$R - X + h\nu \rightarrow R - X\bullet \quad (4)$$

$$R - X\bullet + {}^3O_2 \rightarrow O_2^-\bullet + R - X^+\bullet \quad (5)$$

$$R - X\bullet + {}^3O_2 \rightarrow R - X + {}^1O_2 \quad (6)$$

On the contrary, indirect photolysis does not require the pollutant molecule to absorb UV-C radiation. Instead, the UV-C light is absorbed by other water constituents who generate highly reactive radical species that unselectively oxidize pollutant molecules resulting in complete mineralization. This makes indirect photolysis applicable for the degradation of wide range of pollutants. For example, direct photolysis of H_2O_2 generates two hydroxyl radicals (Eq. (7)) which further oxidize pollutant molecules (Eq. (8)). [8]

$$H_2O_2 \rightarrow 2HO\bullet \quad (7)$$

$$HO\bullet + R{-}H \rightarrow R\bullet + H_2O \quad (8)$$

Oxidants that are most frequently used in indirect photolysis are hydroxyl radicals (in the form of H_2O_2) and sulfate radicals (in the form of $Na_2S_2O_8$) as they are of the most powerful oxidation agents.

Table 2. Redox potentials of commonly used oxidants. [60]

Oxidant	Redox potential (V)
Fluorine [F_2]	3.0
Hydroxyl radical [HO•]	2.8
Sulfate radical [$SO_4^{-}\bullet$]	2.5−3.1
Ozone [O_3]	2.1
Persulfate [$S_2O_8^{2-}$]	2.1
Peroxymonosulfate [HSO_5^{-}]	1.8
Hydrogen peroxide [H_2O_2]	1.8
Permanganate [MnO_4^{-}]	1.7
Chlorine dioxide [ClO_2]	1.5
Chlorine [Cl_2]	1.4

Indirect photolysis includes radical species generation by direct photolysis and subsequent radical−induced oxidation of pollutants. These processes are dependent on three main factors: quantum yield, molar absorption, and radical reaction rate constant. [61] The molar absorption coefficient and the quantum yield define the probability of direct bond cleavage due to exposure to radiation while the radical rate constant describes the efficiency of indirect photolysis. [8]

The molar absorption coefficient is determined by the optical properties of the chemical compound and is described as the intensity of light the compound absorbs. It is proportional to the fraction of light absorbed by the compound.

Quantum yield, on the other hand, depends on the applied wavelength, pH, temperature, chemical compound concentration, solvent, and dissolved oxygen. It is a quantitative measure of the overall efficiency of a photochemical process. Quantum yield is unitless and usually ranges from zero to one. It is defined by the following ratio [8]:

$$\Phi(\lambda) = \frac{number\ of\ moles\ of\ reactant\ transformed\ or\ product\ formed}{number\ of\ moles\ of\ photons\ of\ \lambda\ absorbed} \quad (9)$$

When the given ratio is greater than one, it indicates photo−induced chain reactions, which may involve radical species or photo−generated catalysis. [52] Large molar absorption

coefficients and high quantum yields make photolysis a highly efficient method for the removal of micropollutants from contaminated water. [8]

In the next two paragraphs, the fundamentals of UV/H_2O_2 and UV/$S_2O_8^{2-}$ processes are discussed as they were used in the experimental part of the thesis.

2.2.5.1. UV-C/H_2O_2 process

The UV-C/H_2O_2 is the most extensively researched and commercially utilized UV AOP technique. It is a relatively simple method for producing hydroxyl radical which, with redox potential of 1.9–2.8 V, is the most reactive oxidizing agent used for water treatment purposes. [41]

The basis of this process is the direct photolysis of hydrogen peroxide to produce hydroxyl radicals that unselectively oxidize organic compounds (when in sufficient amounts) until the complete mineralization. The decomposition of hydrogen peroxide is initiated by its UV light absorption resulting in the production of two hydroxyl radicals per one photon absorbed (Eq. (10)). The formed hydroxyl radicals then engage in propagation and termination reactions and in reactions with organic compounds (Eqs. (15)–(17)). [41]

Initiation:

$$H_2O_2 + h\nu \rightarrow 2\ HO\bullet \quad (10)$$

Propagation:

$$HO\bullet + H_2O_2 \rightarrow HO_2\bullet + H_2O \quad (11)$$

$$HO_2\bullet + H_2O_2 \rightarrow HO\bullet + H_2O + O_2 \quad (12)$$

Termination:

$$HO_2\bullet + O_2\bullet^- \rightarrow H_2O_2 + O_2 \quad (13)$$

$$HO_2\bullet + HO_2\bullet \rightarrow H_2O_2 + O_2 + OH^- \quad (14)$$

Reactions of hydroxyl radicals with organic and inorganic compounds include hydrogen atom abstraction, radical addition to electron−rich sites (unsaturated bonds and aromatic rings), and electron transfer reactions. [52] The rate constants of hydroxyl radical reactions with organic compounds of environmental interest are relatively high and range from 10^6 to 10^{10} $M^{-1}s^{-1}$. [8, 52] These reactions generate carbon−centered radicals (R• or •R–OH) which, in the presence of oxygen, may transform into organic peroxyl radicals (ROO•).

All the formed radicals then trigger other chain reactions resulting in chemical degradation and even mineralization of organic compounds. [52]

Hydrogen atom abstraction:

$$HO\bullet + R–H \rightarrow R\bullet + H_2O \quad (15)$$

Electrophilic addition:

$$HO\bullet + R_2C=CR_2 \rightarrow \bullet CR_2–C(OH)R_2 \quad (16)$$

Electron transfer:

$$HO\bullet + M^{n+} \rightarrow M^{(n+1)+} + HO^-_{(aq)} \quad (17)$$

The high efficiency of hydrogen peroxide direct photolysis (Eq. (10)) relies on a high quantum yield of hydroxyl radical formation whereas, in pure water, with relatively high light intensity and low H_2O_2 concentrations, primary quantum yield equals 0.5 and overall quantum yield approaches unity. The limitation of this process is the fact that hydrogen peroxide is a weak UV radiation absorber with an extremely low molar absorption coefficient of 19.6 L mol^{-1} cm^{-1} at 254 nm. [52, 56] To compensate for the low molar absorption of H_2O_2 at 254 nm, high concentrations of hydrogen peroxide are required. However, at these high concentrations, hydrogen peroxide acts as a scavenger for the hydroxyl radicals (Eqs. (18)–20)) and ultimately reduces the overall effectiveness of hydroxyl radical formation. [8, 52, 56]

$$OH\bullet + H_2O_2 \rightarrow HO_2\bullet + H_2O \quad (18)$$

$$HO_2\bullet + H_2O_2 \rightarrow OH\bullet + H_2O + O_2 \quad (19)$$

$$HO_2\bullet + HO_2\bullet \rightarrow H_2O_2 + O_2 \quad (20)$$

For this reason, it is important to experimentally optimize hydrogen peroxide concentration specifically for each application. Adequate H_2O_2 dosage depends on several factors such as the water matrix, light source type and intensity, reactor design, pollutant reactivity towards hydroxyl radical, pollutant treatment level, and direct photolysis contribution to the overall treatment. [8]

2.2.5.2. UV/$S_2O_8^{2-}$ process

UV/persulfate (UV/$S_2O_8^{2-}$) advanced oxidation has grown in popularity over the last decade, as it is evident by the number of published publications quadrupling from 2012 to 2018. [60] This can be attributed to the advantages of persulfate over the traditional oxidants, some of which are: solid state and stability at room temperature (allows easy storage and transportation), longer half−life compared to HO• (30−40 μs compared to 20 μs, respectively) enabling sulfate radicals to achieve more stable mass transfer and greater contact with target molecules, and the ability of persulfate to be activated by longer wavelengths such as UV-A radiation. [60, 62, 63] The persulfate anion is found in the forms of salts with sodium, potassium, or ammonia cations, of which the compound with sodium is the most preferred because it shows the best solubility in water and produces the least toxic residual products. [64]

For the oxidation process, it is crucial to activate the persulfate anion, in the case of AOP, by applying energy in the form of UV radiation. This results in the formation of sulfate radicals according to the Eq. (21). [65]

$$S_2O_8^{2-} + h\nu \rightarrow 2\ SO_4^{-}\bullet \quad (21)$$

When sulfate radical is formed, it participates in propagation reactions (Eqs. (22) and (23)) that may produce other radical species, most notably HO•. [41, 64]

$$SO_4^{-}\bullet + H_2O \rightarrow HO\bullet + SO_4^{2-} + H^+ \quad (22)$$

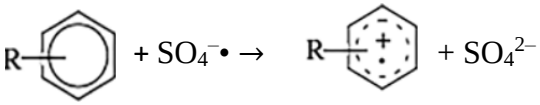
$$SO_4^{-}\bullet + OH^- \rightarrow HO\bullet + SO_4^{2-} \quad (23)$$

While reaction described by Eq. (22) is insignificant due to its slow kinetics, the one described by Eq. (23) takes a crucial role in alkaline conditions, making the hydroxyl radical the main radical available to oxidize organic matter. [64] Therefore, the term ”activated persulfate” in the literature includes the persulfate anion, but is also associated with the reaction intermediates such as sulfate radical and hydroxyl radical.

With organic compounds, sulfate radical can react in three main ways: by hydrogen abstraction (Eq. (24)), by single−electron oxidation (Eq. (25)), or by addition to an unsaturated bond (Eq. (26)).

$$RH + SO_4^{-}\bullet \rightarrow R\bullet + HSO_4^- \quad (24)$$

(25)



$$H_2C{=}CHR + SO_4^{-}\bullet \rightarrow {}^{-}OSO_2OCH_2{-}C\bullet HR \quad (26)$$

However, unlike hydroxyl radicals, sulfate radicals react significantly slower by hydrogen abstraction and addition, and more readily through electron transfer. [8] This is due to sulfate radical's selective electrophilic nature, making it more reactive towards certain compounds, such as aromatic molecules with electron−donating functional groups such as ammine (–NH_2), hydroxyl (–OH), and alkoxy group (–OR), and less reactive towards the compounds with electron−withdrawing groups such as nitro (–NO_2) or carbonyl group (C=O). However, in spite of numerous publications on the kinetics of sulfate radical reactions with organic compounds, the exact oxidation reaction mechanisms and pathways are mostly uncertain due to the complexity of radical chain reactions. [64]

The efficiency of the UV/$S_2O_8^{2-}$ process relies on a high quantum yield (ϕ = 0.7, for Eq. (21)) which is 40% higher compared to H_2O_2/HO• quantum yield at 254 nm irradiation, thus generating more radicals than the UV/H_2O_2 process. [65] On the other hand, sulfate radicals and hydrogen radicals have similar standard reduction potentials (2.5–3.1 V and 1.9–2.8 V, respectively) as well as the low molar absorption coefficient (14.0 L mol^{-1} cm^{-1} and 19 L mol^{-1} cm^{-1} at 254 nm, respectively). [63] The reaction rates of persulfate and sulfate radicals with common contaminants in soil and groundwater have been reported to be in the range 10^6–10^9 $M^{-1}s^{-1}$. [64] The main limitation of this process is that sulfate radicals easily and quickly react with chlorides, carbonates, and bicarbonates (Cl^-: $k = 2.48 \cdot 10^8$ $M^{-1}s^{-1}$, HCO_3^-: $k = (1.6–9.1) \cdot 10^6$ $M^{-1}s^{-1}$, CO_3^{2-}: $k = 6.1 \cdot 10^6$–$4.1 \cdot 10^8$ $M^{-1}s^{-1}$), which brings out the competitive kinetics of the components of the solution, resulting in a reduction in overall oxidation efficiency. [64] Additionally, the self−scavenging effect of sulfate radical might also occur when an excessive amount of persulfate is present (Eq. (27)). [63]

$$SO_4^{-}\bullet + SO_4^{-}\bullet \rightarrow S_2O_8^{2-} \quad (27)$$

2.2.5.3. Kinetics of UV-based oxidation

Photochemical reaction kinetics are primarily determined by the process light absorption conditions and the reaction quantum yield of the target pollutant. Therefore, any water matrix properties that influence two main reaction efficiency parameters (quantum yield and molar absorption coefficient), may impact the kinetics and pathway of the following radical reactions. These properties include water components, pH, ionic strength, dissolved oxygen concentration, and temperature. In UV-based oxidation processes (Table 3.) numerous

competitive radical reactions occur that affect the concentrations of reactants and overall kinetics. Despite their complexity, these reactions are typically described in the literature as second-order reactions, or pseudo-first-order. Pseudo-first-order rate constant can be considered because of the low concentration of pollutant and assumption that concentrations of highly reactive radicals are constant. [8, 56]

Table 3. Principal reactions in the UV/H_2O_2 and UV/$S_2O_8^{2-}$ processes. [66]

Reaction	k (M^{-1} s^{-1} or s^{-1})	Equation
$H_2O_2 + h\nu \rightarrow 2\ HO\bullet$		(28)
$S_2O_8^{2-} + h\nu \rightarrow 2\ SO_4^{-}\bullet$		(29)
$HO\bullet + H_2O_2 \rightarrow HO_2\bullet$	$2.7 \cdot 10^7$	(30)
$HO\bullet + HO\bullet \rightarrow H_2O_2$	$5.5 \cdot 10^9$	(31)
$HO\bullet + OH^- \rightarrow H_2O + O^-\bullet$	$1.3 \cdot 10^{10}$	(32)
$SO_4^-\bullet + S_2O_8^{2-} \rightarrow SO_4^{2-} + S_2O_8^-\bullet$	$6.6 \cdot 10^5$	(33)
$SO_4^-\bullet + SO_4^-\bullet \rightarrow S_2O_8^{2-}$	$3.1 \cdot 10^8$	(34)
$SO_4^-\bullet + OH^- \rightarrow HO\bullet + SO_4^{2-}$	$6.5 \cdot 10^7$	(35)
$SO_4^-\bullet + H_2O \rightarrow HO\bullet + SO_4^{2-}$	< 60	(36)
$HO\bullet + HCO_3^- \rightarrow CO_3^-\bullet + H_2O$	$8.5 \cdot 10^6$	(37)
$HO\bullet + CO_3^{2-} \rightarrow CO_3^{2-}\bullet + OH^-$	$3.9 \cdot 10^8$	(38)
$SO_4^-\bullet + HCO_3^- \rightarrow CO_3^{2-}\bullet + HSO_4^-$	$9.1 \cdot 10^6$	(39)
$SO_4^-\bullet + CO_3^{2-} \rightarrow SO_4^{2-} + CO_3^-\bullet$	$6.1 \cdot 10^6$	(40)
$HO\bullet + Cl^- \rightarrow HClO^-\bullet$	$4.3 \cdot 10^9$	(41)
$SO_4^-\bullet + Cl^- \rightarrow Cl\bullet + SO_4^{2-}$	$3.1 \cdot 10^8$	(42)
$Cl\bullet + H_2O \rightarrow H + HO\bullet + Cl^-$	$2.5 \cdot 10^5$	(43)
$HClO^-\bullet \rightarrow Cl^- + HO\bullet$	$6.0 \cdot 10^9$	(44)
$HClO^-\bullet + Cl^- \rightarrow Cl_2^-\bullet + OH^-$	$1.0 \cdot 10^5$	(45)
$Cl_2 + OH^- \rightarrow HClO^-\bullet + Cl^-$	$4.5 \cdot 10^6$	(46)
$HClO^-\bullet + H^+ \rightarrow H_2ClO\bullet$	$3.0 \cdot 10^{10}$	(47)
$H_2ClO\bullet \rightarrow Cl\bullet + H_2O$	$5.0 \cdot 10^4$	(48)
$H_2ClO\bullet + Cl^- \rightarrow Cl_2^-\bullet + OH^-$	$4.0 \cdot 10^6$	(49)
$Cl\bullet + Cl^- \rightarrow Cl_2^-\bullet$	$8.5 \cdot 10^9$	(50)
$SO_4^-\bullet + NO_3^- \rightarrow NO_3\bullet + SO_4^{2-}$	$5.0 \cdot 10^4$	(51)
$HO\bullet + SO_4^{2-}/HSO_4^- \rightarrow SO_4^-\bullet + OH^-/H_2O$	$3.5 \cdot 10^{10}$	(52)

Additionally, the kinetic model of UV-included AOPs proposed by Stefan [8] utilizes a pseudo−steady state approximation. This approach is built upon the previously mentioned premise that due to the high reactivity of radical species, they are consumed immediately after their formation, meaning the formation rate of each radical is equal to the consumption of that

radical. [8] Thus, the concentrations of radicals are considered negligible in time, *i.e.*, they reach pseudo−steady−state concentrations. For instance, the general expression of pseudo−steady state concentration for hydroxyl radical in the UV/H_2O_2 process can be described with equation (52) where the numerator describes the rate of formation of OH• due to direct photolysis, while the denominator represents hydroxyl reactions with all the water constituents, including the scavengers (S_i) and the pollutant.

$$[\mathrm{OH}]_{\mathrm{ss}}|_{\lambda} = \frac{\Phi_{\cdot\mathrm{OH}} f_{\mathrm{abs},\lambda}^{\mathrm{H_2O_2}} q_{p,\lambda}(1 - \mathrm{e}^{-A_\lambda})}{k_{\mathrm{OH,H_2O_2}}[\mathrm{H_2O_2}] + \sum_i k_{\mathrm{OH},S_i}[S_i]} \tag{53}$$

In this equation $q_{p,\lambda}$ represents photon flow entering the water, $f_{\mathrm{abs},\lambda}$ is a fraction of light absorbed by H_2O_2, and A_λ is absorbance of the solution. All the factors are defined for specific wavelength λ. The scavenging term $\Sigma_i k_{\mathrm{OH,Si}}[S_i]$ (often called OH• water background demand) is usually calculated from water quality parameters or determined experimentally. Finally, the rate of contaminant removal by both, direct photolysis and radical oxidation reactions at λ, under pseudo−steady−state approximation is described by equations:

$$[\mathrm{OH}]_{\mathrm{ss}}|_{\lambda} = \frac{\Phi_{\cdot\mathrm{OH}} f_{\mathrm{abs},\lambda}^{\mathrm{H_2O_2}} q_{p,\lambda}(1 - \mathrm{e}^{-\mathrm{A}_\lambda})}{k_{\mathrm{OH,H_2O_2}}[\mathrm{H_2O_2}] + \sum_i k_{\mathrm{OH},S_i}[S_i]} \tag{54}$$

$$-\left.\frac{\mathrm{d}C}{\mathrm{d}t}\right|_{\lambda} = \Phi_\lambda^C f_{\mathrm{abs},\lambda}^C q_{p,\lambda}(1 - \mathrm{e}^{-A_\lambda}) + k_{\mathrm{OH,C}} \frac{\Phi_{\cdot\mathrm{OH}} f_{\mathrm{abs},\lambda}^{\mathrm{H_2O_2}} q_{p,\lambda}(1 - \mathrm{e}^{-A_\lambda})}{k_{\mathrm{OH,H_2O_2}}[\mathrm{H_2O_2}] + \sum_i k_{\mathrm{OH},S_i}[S_i]}[C] \tag{55}$$

This model, with corrections in certain cases, has been successfully used in different studies to predict the kinetic model in different UV/AOP processes. [8]

2.2.5.4. Impact of water matrix

Water quality plays a crucial role in selecting an appropriate AOP and predicting its performance. To accurately assess AOP performance, it is essential to understand direct photolysis, radical generation, and the mechanisms of radical reactions involving target compounds, as well as key water matrix factors such as inorganic salts and organic compounds.

The effectiveness of AOP processes is strongly influenced by constituents present in the water matrix. These constituents can have different effects, either neutral, inhibiting, or promoting, depending on the specific process and the mechanism through which they interact with UV light and radical species. Organic species can act as inhibitors of the process by UV light absorption or radical scavenging effects. On the other hand, they can act as promoters by generating reactive oxygen species that enhance indirect photolysis. Inorganic species can as well have inhibiting or promoting effects. For instance, they can inhibit the degradation process

through radical scavenging effects or the formation of less active radicals. Conversely, they can act as promoters, such as nitrate ions that form reactive oxygen species or iron ions that act as an additional catalyst source. [67]

The available data on this subject is limited, and the specific roles and mechanisms of individual water components are still not fully understood. Further research is necessary to comprehensively investigate the diverse range of reactions that occur in complex wastewater and to promote the wider implementation of advanced oxidation technologies in urban wastewater treatment plants. [67] While the impact of chloride and carbonate anions is the most commonly studied, recent research suggests that a wider range of constituents should be investigated to better understand oxidation mechanisms in complex aquatic environments. [68]

With the aim to address this gap, the experimental part of the thesis examines the impact of nitrite, nitrate, phosphate, sulfate, chloride anions, and humic acid, as well as the influence of different pH values. The fifth chapter will discuss the impact of each water constituent on UV/AOP.

2.3. Design of Experiment

Design of Experiment (DoE) is a useful tool that relies on statistical methodology to predict product characteristics under varying conditions and optimize the performance and costs of the process.

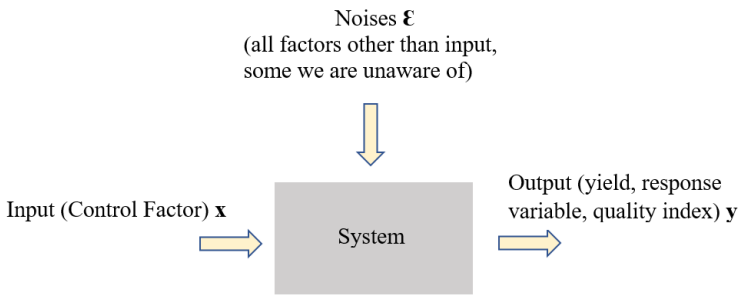


Figure 4. A general scheme of a basic design of experiment. [70]

DoE is widely used in diverse fields, including engineering, product development, the pharmaceutical industry, agriculture, social science, and others. It outperforms the traditional approach of changing "one variable at a time" with minimal experimental runs. [69]

Moreover, DoE identifies which variables (factors) have an effect on the response of the system and for which variables the system has the optimal response. The factors are controllable

parameters that vary at different levels and can be represented as continuous functions or discrete numerical values. Noise is the effect of random or uncontrollable input that causes the signal (response) to be less obvious. In order to avoid instability of the response, it is necessary to have a conscious approach toward the noises by estimating, minimizing, and keeping them constant. [70]

Depending on the type of variables, different experimental designs are applied, some of which are full factorial, fractional factorial, central composite, Box−Behnken, and Taguchi. Each approach requires a different number of experimental runs which depends on the number of factors being considered. Figure 5 shows the number of experimental runs *N* that each DOE technique requires depending on the number of input factors. [71]

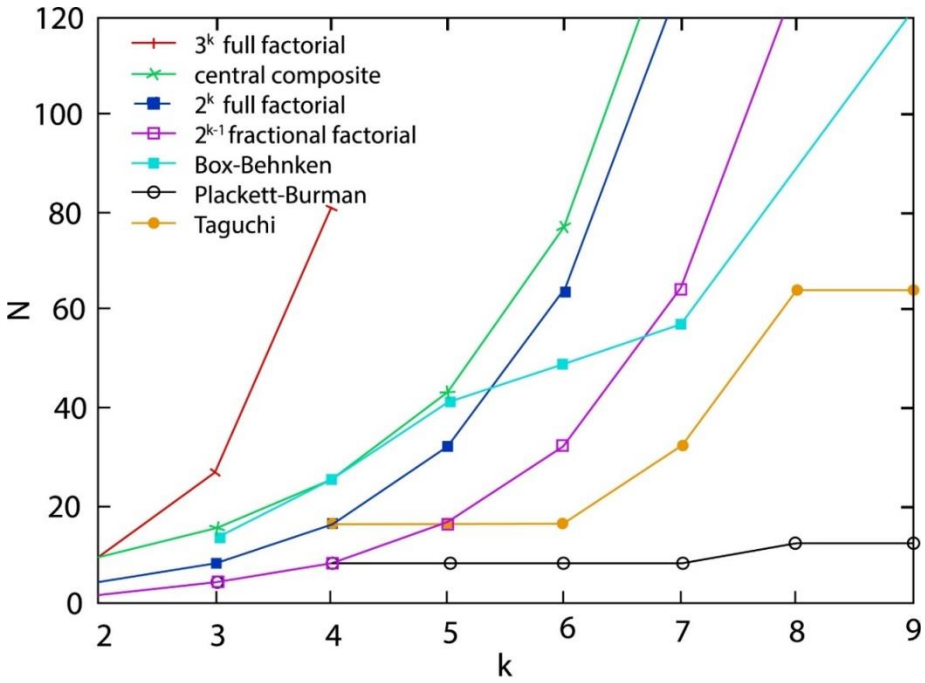


Figure 5. Number of experimental runs required by selected DoE techniques. [71]

Once the experiment is completed, the results are analyzed by statistical software such as Design Expert and MiniTab. The software delivers the analysis that can finally be used to draw contextual conclusions on the input factors−response relationship. [71]

2.3.1. Taguchi method

During the 1980s, Japanese engineer and statistician Genichi Taguchi developed a method for manufacturing high−quality products regardless of process parameter variations. It is based on a specific statistical approach resulting in a better understanding of the process, process robustness, and significant reduction of required time and costs to conduct a process.

Therefore, it has been widely applied in various fields including manufacturing, engineering, environmental studies, healthcare, service industries, and social sciences. In terms of chemical and environmental engineering, it is commonly used to increase the efficiency of wastewater treatment.

Table 4. Taguchi designs synoptic table. [71]

Number of variables	Number of levels			
	2	3	4	5
2,3	L4	L9	LP16	L25
4	L8	L9	LP16	L25
5	L8	L18	LP16	LP32
6	L8	L18	LP32	L25
7	L8	L18	LP32	L50
8	L12	L18	LP32	L59
9,10	L12	L27	LP32	L50
11	L12	L27	N./A.	L50
12	L16	L27	N./A.	L50
13	L16	L27	N./A.	N./A.
14,5	L16	L36	N./A.	N./A.
16−23	L32	L36	N./A.	N./A.
24−31	L32	N./A.	N./A.	N./A.

The objective of the method is to determine how each controllable factor impacts the response while minimizing the sensitivity of the response to noise. Taguchi relies on running only a portion of the total number of possible experiments using the orthogonal array (OA) approach. OA is a mathematical concept that represents a matrix of numbers where each column represents a specific factor and each row represents the levels of chosen factors of interest. Orthogonal arrays are designed in a way that ensures two types of balance among their columns. Firstly, the columns are balanced internally, meaning that each column has the same number of each factor level. Secondly, the columns are balanced externally so that any two columns combined form an equal number of possible combinations. Hence, in orthogonal array experiments, the number of experimental runs is reduced while keeping the pairwise balancing

property. [72] Table 4. summarizes recommended matrix arrays (number of possible designs) depending on the number of parameters and the number of levels. The abbreviation N./A. (not applicable) denotes that Taguchi design cannot be utilized in specific combinations of the number of variables and number of levels.

Once all the experimental runs are conducted, results are most commonly analyzed by a statistical approach known as analysis of variance (ANOVA). ANOVA is used to comprehend the contribution of each factor, as well as whether a higher or lower level produces the preferred result. Through this kind of analysis, the optimal process conditions are identified. [72]

2.4. Proton Pump Inhibitors

Proton−pump inhibitors (PPIs) are a class of drugs that cause significant and elongated suppression of stomach acid production. They reduce the secretion of gastric acid by inhibiting an enzyme in the parietal cells of the stomach that exchanges acid for potassium ions. In other words, they inhibit the activities of proton pumps. The first produced PPI was omeprazole in 1988, but over the last decades, many others like lansoprazole, pantoprazole, dexlansoprazole, esomeprazole, rabeprazole, and others were produced and widely prescribed. [73]

Today, PPIs have become one of the most widely prescribed medications worldwide. Their prescription is consistently on the rise, especially for long−term treatment since they are both effective and have a favorable safety record. Even though PPIs are well accepted, recently there has been a growing concern in connection to the use of these drugs, mainly due to the inappropriate prescription of these drugs, as Lenoir et al. [74] report that around 70% of the prescriptions for PPIs included in their study did not have a justified indication.

This often results in improper disposal of the drug remnants, which if not properly handled by environmental waste management authority, results in environmental pollution. This is in addition to the consumer's excretion of both active and inactive pharmaceutical ingredients through urine and feces. Kosma et al. [75] report that PPIs and their metabolites are only partially eliminated in WWTP resulting in their presence in surface waters, groundwater, and sediments.

2.4.1. Pantoprazole

Pantoprazole is an irreversible proton pump inhibitor, recognized as one of the top twenty selling drugs worldwide, under various trade names. Pantoprazole was approved for medicinal use in 1994. The structure shows that pantoprazole is in the form of a substituted benzimidazole sodium salt. It is a lipophilic weak base with low solubility at neutral pH, which increases with pH. [76]

Pantoprazole is primarily used to treat gastrointestinal disorders such as acid reflux, erosive esophagitis, *Helicobacter pylori* infection, and Zollinger−Ellison syndrome and is popular due to its longer activity compared to other PPIs. Furthermore, pantoprazole is as well often prescribed in combination therapy with antibiotics, profens, and others; to prevent issues associated with the digestive system. The implication of these factors explains a significantly high rate of pantoprazole consumption worldwide. [77]

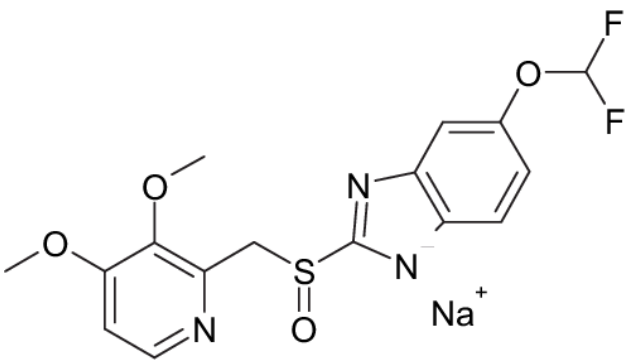


Figure 6. Chemical structure of pantoprazole sodium.

While pantoprazole is generally effective and well tolerated, it also poses certain challenges. Researchers have associated its long−term use with serious side effects such as: hypomagnesia, osteoporosis, bone fracture, and poor absorption of vitamin B12, iron salts, ketoconazole, and certain minerals. [78]

The consequences of pantoprazole residues in the environment have not been thoroughly investigated, despite its widespread production and consumption, which results in the release into the environment through different waste streams.

Pantoprazole air contamination may occur at production sites, although it is unlikely due to its low vapor pressure causing it to exist primarily in particulate form. This characteristic makes it easily removable through wet and dry deposition, resulting in the rare instances of air contamination. In soil, pantoprazole is immobile (log K_{oc}= 4.11), while due to pK_{a1} and pK_{a2}

values it mainly appears in protonated form making enhancing its likelihood to adsorb strongly to organic carbon and clay. [76]

On the other hand, water contamination is more probable due to its widespread human use. In aquatic environments, pantoprazole is not expected to volatilize but rather to adsorb onto suspended solids and sediment, driven by its K_{oc} value. Pantoprazole is reported to be non−biodegradable, and hydrolysis is not considered a significant environmental degradation pathway since PPS is missing functional groups that hydrolyze under environmental conditions. However, pantoprazole is susceptible to direct photolysis, with its maximum absorption occurring at 289 nm. [76]

Table 5. Characteristics of pantoprazole

Pantoprazole sodium	
Abbreviation	PPS, PAN
CAS number	138786−67−1
Chemical Formula	$C_{16}H_{14}F_2N_3NaO_4S$
Molecular weight (g/mol)	405.35
Solubility in water (mg/L), at 25 °C	48
pK_{a1}	3.9
pK_{a2}	8.19
log K_{ow}	2.22
log K_{oc}	4.11
Henry's Law Constant (atm m^3 mol^{-1}), at 25 °C	$5.84 \cdot 10^{-20}$
Half−life (h)	0.9−1.9
$k_{HO\bullet}$ M^{-1} s^{-1}	$1.0 \cdot 10^{14}$

Detection of pantoprazole residues in different water bodies worldwide further emphasizes the need for comprehensive research in this area. Research has shown that residues of this pharmaceutical mostly contaminate natural waters. [79−81] This is because around 70 to 95 % of the consumed pantoprazole used ends up being excreted into the urine and feces as metabolites that are inert or pharmaceutically active. [75] Della Rocca et al. [82] report that pantoprazole residues are found in domestic wastewaters in concentrations up to 18 μg L^{-1}.

Different methods have been applied towards addressing the challenges associated with the presence of pantoprazole residues in wastewater with different degrees of success. Some of

the methods include adsorption, peroxidation and photo−peroxidation, the Fenton process, and others. [82, 83] A lot of research is still ongoing with the aim of finding an efficient, eco−friendly, and economical method or integration of methods that are best suited for pantoprazole active residue.

3. Experimental

3.1. Materials

- Pharmaceutical:
  - Pantoprazole sodium, Xellia, Croatia
- Oxidants:
  - Hydrogen peroxide, 30%, Gram−mol, Croatia
  - Sodium persulfate, Sigma−Aldrich, USA
- pH adjustment:
  - Sulfuric acid (H_2SO_4), 0.05 M, Kemika, Croatia
  - Sodium hydroxide (NaOH), 0.02 M, Kemika, Croatia
- Water matrix:
  - Sodium nitrite ($NaNO_2$), Kemika, Croatia
  - Sodium nitrate ($NaNO_3$), Kemika, Croatia
  - Sodium chloride (NaCl), Gram−mol, Croatia
  - Sodium phosphate ($Na_3PO_4 \cdot 12H_2O$), Kemika, Croatia
  - Sodium sulfate (Na_2SO_4), Merck, Germany
  - Humic acid sodium salt (technical grade, H16752), Sigma−Aldrich, USA
- Other:
  - Ethanol 96%, Gram−mol, Croatia
- HPLC mobile phases:
  - Methanol (CH_3OH), HPLC grade, JT Baker, USA
  - Ammonium acetate ($C_2H_7NO_2$), 98%, Sigma−Aldrich, USA
  - Ultra−pure water, Millipore Direct−Q UV 3 system, Merck, Germany

3.2. Instruments

- HPLC (Series 20, Shimadzu, Japan) equipped with pump LC−20AD XR × 2 units, autosampler SIL−20AC XR, detector SPD−20AV, column oven CTO−20AC and LCMS−2020, Shimadzu, Japan
- Column: 3.5×150 mm, 4.6 µm Waters SunFire C18
- UV lamp Pen−Ray P/N 90−0012−01, 254 nm, UVP, Cambridge, UK
- Pen−Ray power supply PS−11, O.21 Amps, 230 V, UVP, Cambridge, UK
- pH meter, pH 50+ DHS XS instruments

- Milli−Q water maker TKA−GenPure
- Analytical balance Sartorius
- Magnetic stirrer MSH−300 BioSan

3.3. Development of HPLC method

The concentration of pantoprazole was determined with HPLC (Series 20) (Figure 7) and column Waters SunFire C18 4.6 µm, 3.5×150 mm. The developed method is a gradient method using 10 mM ammonium acetate solution as mobile phase A, and methanol (HPLC grade) as mobile phase B, as described in Table 6. The flow rate was 1mL/min with the injection volume of 10 µL. The detector used in analysis were UV (at 280 nm wavelength) coupled with MS.

Table 6. Gradient elution conditions.

Time / min	Mobile phase A / %	Mobile phase B / %
0	70	30
2.50	50	50
10.00	50	50
17.00	30	70
18.00	70	30
20.00	70	30

Figure 7. Shimadzu HPLC (Series 20).

3.4. Design of Experiment

To conduct the experiment, Taguchi design was followed, utilizing 8 factors with 2 levels each. Minitab version 20.2 was used to form the orthogonal array DoE matrix with total of 12 experiments for each process (Table 7.). The factors and their respective levels are specified in Table 8.

Table 7. Experimental layout using an L12 orthogonal array.

Exp. no.	pH	Oxidant	HA	NO_2^-	NO_3^-	Cl^-	PO_4^{3-}	SO_4^{2-}
1	1	2	1	2	2	1	2	2
2	2	1	1	2	2	2	1	2
3	1	2	2	1	2	2	1	2
4	2	2	1	2	1	2	1	1
5	2	2	1	1	2	1	2	1
6	1	1	1	1	1	2	2	2
7	2	2	2	1	1	1	1	2
8	2	1	2	1	2	2	2	1
9	1	1	1	1	1	1	1	1
10	1	2	2	2	1	2	2	1
11	2	1	2	2	1	1	2	2
12	1	1	2	2	2	1	1	1

Table 8. Factors and their levels.

Factor	Level 1 (low)	Level 2 (high)	Unit
pH	4	10	–
Oxidant	0.05	10	mM
HA	2	10	mg/L
NO_2^-	0.1	10	mg/L
NO_3^-	1	70	mg/L
Cl^-	10	250	mg/L
PO_4^{3-}	0.08	0.5	mg/L
SO_4^{2-}	20	600	mg/L

3.5. Preparation of aqueous solution of pantoprazole

Aqueous 0.1 mM solution of pantoprazole was prepared by dissolving 0.0432 g of pantoprazole Sodium crystalline powder in 1 L of Milli−Q water. The 1 L flask was covered with aluminum foil to block the light from reaching the solution. After one day of stirring with a magnetic stirrer, the aqueous solution was stored in the refrigerator at 4 °C.

3.6. Preparation of matrix solution

Five different inorganic salt solutions were utilized to form inorganic ions that were considered as factors in the Taguchi design. Table 9. contains concentrations and quantities of each factor. Solutions were prepared by dissolving respective quantities of salts in ultra-pure Milli-Q water and stored in plastic bottles at room temperature.

The quantity of factors used for making synthetic water matrix that are presented as minimum and maximum levels in the Taguchi design are shown in the Table 10.

Table 9. Factors' characteristics and used concentrations.

Factor	Molar mass (g/mol)	Concentration (ppm)	Quantity (for 1 L)
NO_2^- ($NaNO_2$)	69	1000	1 g
NO_3^- ($NaNO_3$)	84.99	10000	10 g
Cl^- (NaCl)	58.44	10000	10 g
PO_4^{3-} ($Na_3PO_4 \cdot 12H_2O$)	380.12	1000	1 g
SO_4^{2-} (Na_2SO_4)	142.04	100000	100 g
HA	–	400	–

Table 10. Quantities of factors for levels 1 and 2.

Factor	Level 1	Level 2
NO_2^-	8 µL	800 µL
NO_3^-	8 µL	560 µL
Cl^-	80 µL	2000 µL
PO_4^{3-}	6.4 µL	40 µL
SO_4^{2-}	16 µL	480 µL
HA	400 µL	2000 µL

3.7. Oxidants

In this study, two oxidants were used: hydrogen peroxide and sodium persulfate at concentrations of 0.05 mM and 10 mM respectively. The corresponding amounts of each oxidant at maximum and minimum level are presented in Table 11.

Table 11. Quantities of oxidants for levels 1 and 2.

Oxidant	Molar mass (g/mol)	Level 1	Level 2
H_2O_2	34.01	4.1 μL	82 μL
$Na_2S_2O_8$	238.01	0.0095 g	0.1904 g

3.8. UV-C based process

Figure 8 displays the experimental setup in which all experiments were conducted. The degradation process took place in a glass water−jacketed batch photoreactor with total volume V_T=0.1 L, while volume of synthetic water matrix solution added to the photoreactor is V_S=0.08 L. The photoreactor was equipped with a UV-C lamp that emits monochromatic light at 254 nm, providing an incident photon flux (P_0) is of $1.04 \cdot 10^{-6}$ E s^{-1}. The UV lamp had power supply of 48.3 W and operated at a frequency of 50−60 Hz. The experimental procedure began after preheating the UV-C lamp and placing it into a quartz cuvette that transmits UV-C light. The lamp was positioned in the center of the reactor with an irradiation path length (L) of 1 cm. To ensure effective mixing of the reaction solution, a magnetic stirrer was used at speed of 550 rpms. The temperature was maintained at t = 25.0 ± 0.2 °C.

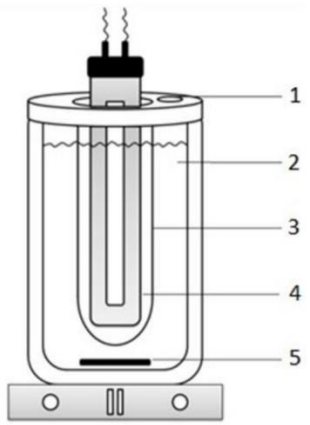


Figure 8. UV-C reactor: 1. inlet of the syringe for sampling, 2. sample solution, 3. quartz cuvette, 4. UV lamp, 5. magnetic stirrer.

In accordance with the Taguchi design, each UV-C degradation process involved 12 experimental runs. Each experiment lasted for 60 seconds, during which samples were collected at 10 second intervals. A total of 7 samples were taken from each experiment. Consequently, for the two UV-C based processes we obtained a combined total of 168 samples in HPLC vials. To stop the degradation process by quenching the radicals, we added 100 µL of methanol to each sample.

3.9. Calculations

The concentration of pantoprazole in the solution before and after the degradation process is represented by c_0 and c_t, respectively. To analyze the degradation kinetic data of both studied pharmaceuticals, we employed the pseudo-first-order kinetic model (Eq. (56)).

$$\ln (c_0/c_t) = -kt \tag{56}$$

4. Results

In this chapter, the experimental results are presented in the form of graphs and tables, providing a comprehensive overview of the obtained data on pantoprazole degradation under UV/H_2O_2 and UV/$S_2O_8^{2-}$ processes. These results will be further discussed and analyzed in the Discussion chapter, offering a deeper understanding of their implications and significance in the context of the research objectives.

Table 12. presents the Taguchi design matrix for the UV-C/H_2O_2 and UV-C/ $S_2O_8^{2-}$ processes, encompassing eight factors expressed in coded units (1: minimum level and 2: maximum level), and experimentally determined first-order degradation rates (*k*) for pantoprazole.

Table 12. Taguchi design matrix and experimentally determined first-order degradation rates (*k*) for pantoprazole in UV/H_2O_2 and UV/$S_2O_8^{2-}$ processes.

Experiment no.	Factors								First-order degradation rates, ($k \cdot 10^3$, s^{-1})	
	NO_2^-	NO_3^-	Cl^-	PO_4^{3-}	SO_4^{2-}	HA	pH	oxidant	UV/H_2O_2	UV/$S_2O_8^{2-}$
1	2	2	1	2	2	1	1	2	16	25.6
2	2	2	2	1	2	1	2	1	4.6	9.3
3	1	2	2	1	2	2	1	2	13.1	21.7
4	2	1	2	1	1	1	2	2	12.6	74.7
5	1	2	1	2	1	1	2	2	19.8	111.5
6	1	1	2	2	2	1	1	1	31	10.2
7	1	1	1	1	2	2	2	2	16.1	36.5
8	1	2	2	2	1	2	2	1	6.4	4.9
9	1	1	1	1	1	1	1	1	32.4	44.5
10	2	1	2	2	1	2	1	2	20.7	19.3
11	2	1	1	2	2	2	2	1	6.1	8.2
12	2	2	1	1	1	2	1	1	3.8	14.8

4.1. Influence of tested factors on degradation kinetics

Tables 13. and 14. present the average first-order degradation rate for each level of each factor. These response tables indicate which factor has the greatest influence on the degradation rate. The ranking and comparison of relative impact of the factors is based on Delta statistics. Delta is calculated by subtracting the lowest average from the highest average degradation rate value for each factor. Rank 1 and 6 are given to the factor with highest and lowest Delta value, respectively. By examining the average values in the response tables, we can identify which level of each factor yields the most favorable outcome.

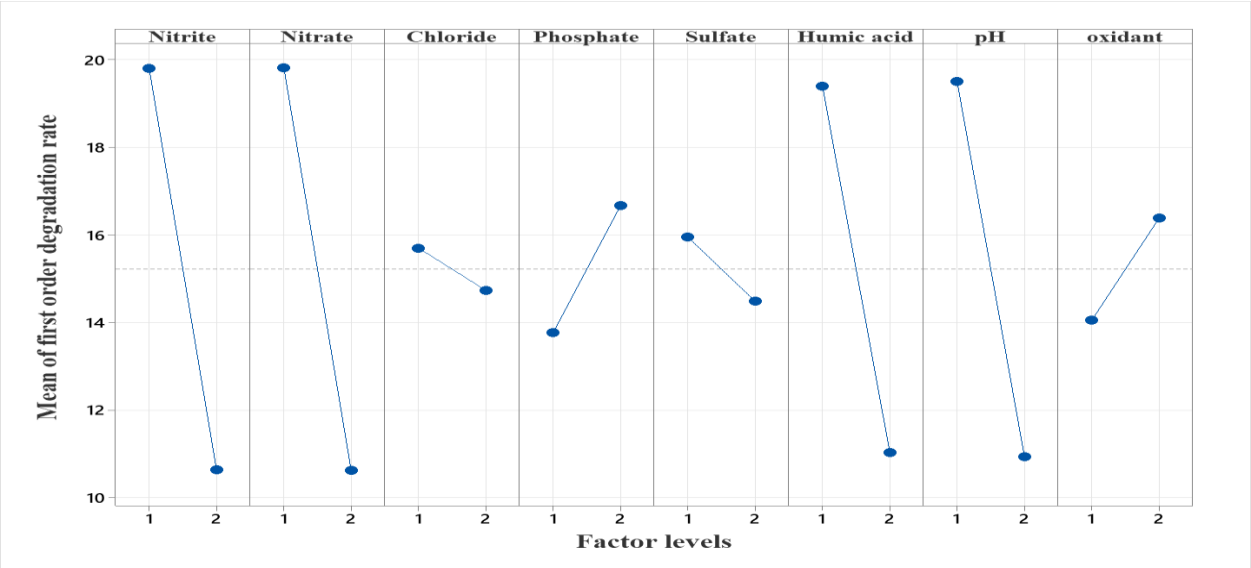


Figure 9. Main effects plot for first-order degradation rate of pantoprazole with UV/H_2O_2 process.

Table 13. Response table for means of first-order degradation rates of PPS by UV/H_2O_2 process.

Level	Nitrite	Nitrate	Chloride	Phosphate	Sulfate	Humic acid	pH	Oxidant
1	19.80	19.82	15.70	13.77	15.95	19.40	19.50	14.05
2	10.63	10.62	14.73	16.67	14.48	11.03	10.93	16.38
Delta	9.17	9.20	0.97	2.90	1.47	8.37	8.57	2.33
Rank	2	1	8	5	7	4	3	6

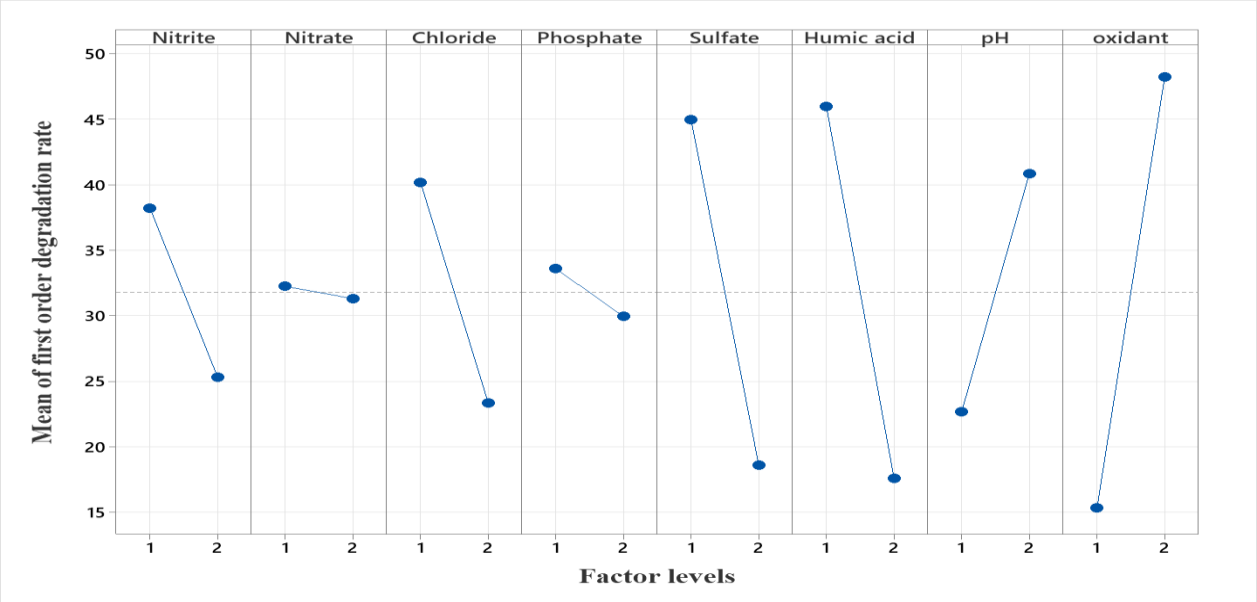


Figure 10. Main effects plot for first-order degradation rate of pantoprazole with UV/$S_2O_8^{2-}$ process.

Table 14. Response table for means of first-order degradation rates of PPS by UV/$S_2O_8^{2-}$ process.

Level	Nitrite	Nitrate	Chloride	Phosphate	Sulfate	Humic acid	pH	Oxidant
1	38.22	32.23	40.18	33.58	44.95	45.97	22.68	15.32
2	25.32	31.30	23.35	29.95	18.58	17.57	40.85	48.22
Delta	12.90	0.93	16.83	3.63	26.37	28.40	18.17	32.90
Rank	6	8	5	7	3	2	4	1

5. Discussion

This chapter provides a detailed analysis of the experimental results obtained from monitoring the degradation of pantoprazole under UV/H_2O_2 and UV/$S_2O_8^{2-}$ processes. This chapter aims to discuss the degradation kinetics of the processes as well as the influence of each water matrix parameter on the degradation rate.

5.1. Degradation kinetics

As the literature suggests that UV/H_2O_2 and UV/$S_2O_8^{2-}$ degradation processes conform to a pseudo-first-order kinetic model, we applied this model to our experimental results and observed a strong correlation between the degradation rate constants and the proposed pseudo-first-order kinetics under all tested conditions ($R^2 \geq 0.99$). [8]

The degradation rates in the conducted UV/H_2O_2 processes exhibit a notable variation depending on the different water matrices, ranging from $3.8 \cdot 10^{-3}$ s^{-1} to $32.4 \cdot 10^{-3}$ s^{-1}. In the UV/$S_2O_8^{2-}$ processes, the degradation rates span even wider range, extending from $4.9 \cdot 10^{-3}$ s^{-1} to $111.5 \cdot 10^{-3}$ s^{-1}. The significant variations observed in the degradation rates highlight the pronounced influence of water parameters and their levels on the degradation rates of this particular pharmaceutical compound. How each water parameter influences the degradation kinetics will be discussed in more detail in the following chapters.

To facilitate a comparative kinetic analysis of the two degradation processes, we utilized the average kinetic degradation rates presented in Table 15. It is evident that the UV/$S_2O_8^{2-}$ process overall exhibited a significantly higher degradation rate ($15.23 \cdot 10^{-3}$ s^{-1}) in comparison to the UV/H_2O_2 process ($31.77 \cdot 10^{-3}$ s^{-1}).

Table 15. Comparison of UV/H_2O_2 and UV/$S_2O_8^{2-}$ degradation rates.

Process	Average first-order degradation rates ($k \cdot 10^3$, s^{-1})	R^2
UV-C/H_2O_2	15.23	0.99
UV-C/$S_2O_8^{2-}$	31.77	0.99

The observed trend of higher degradation rates in the UV/$S_2O_8^{2-}$ process compared to UV/H_2O_2 is consistent with other research studies that have reported similar results for the degradation of various pharmaceutical compounds. For example, in a study conducted by Lui

et al. [84], the degradation of pharmaceutical atenolol was compared using UV/$S_2O_8^{2-}$ and UV/H_2O_2 under different conditions. The average first-order reaction rate constant was found to be 116.97 · 10^{-3} s^{-1} for UV/$S_2O_8^{2-}$ and 0.87 ·10^{-3} s^{-1} for UV/H_2O_2. Similarly, Zhang et al. [85] reported average first-order reaction rates of 14.3 · 10^{-3} s^{-1} and 4.7 · 10^{-3} s^{-1} for the degradation of amoxicillin for UV/$S_2O_8^{2-}$ and UV/H_2O_2, respectively. Additionally, Arman et al. [86] investigated the degradation of dexamethasone using these two processes and also observed higher efficiency in the UV/$S_2O_8^{2-}$ process, although they did not specify the first-order reaction rates. However, to the best of our knowledge, no research has been conducted on the monitoring of the degradation of pantoprazole or any other proton pump inhibitor using specifically UV/$S_2O_8^{2-}$ or UV/H_2O_2 processes.

All three mentioned studies explain that UV/$S_2O_8^{2-}$ process is more efficient due to three main reasons. First, the photolysis of persulfate yields a significantly higher amount of radicals than hydrogen peroxide photolysis does. This is due to the 40% higher quantum yield of persulfate than of hydrogen peroxide at 254 nm irradiation. Second, hydroxyl radicals tend to act as self-scavengers at significant rates, unlike sulfate radicals. Third, although the reactivity of sulfate radicals is generally lower than that of hydroxyl radicals, they exhibit a strong affinity to electron-rich contaminants, which results in higher selectivity towards numerous organic pollutants.

In our case, taking into account the structural formula of pantoprazole, it is plausible to assume that the presence of an aromatic ring and electron donating groups potentially contributed to the higher efficiency observed in the UV/$S_2O_8^{2-}$ process compared to UV/H_2O_2. This assumption is supported by Stefan [8] and Tsitonaki et al. [64] who emphasize the fact that sulfate radical's selectivity towards aromatic compounds with electron−donating groups, will significantly increase the rate of the reaction.

5.2. Influence of water matrix

Generally, the composition of water significantly influences UV/H_2O_2 and UV/$S_2O_8^{2-}$ processes through neutral, inhibitory, and enhancing effects. Inhibition arises from the strong UV absorption of water constituents or their ability to scavenge HO• and $SO_4^{\bullet-}$ radicals, while certain constituents enhance contaminant removal by generating highly reactive radicals. It is crucial to investigate the impact of both inorganic ions and organic compounds, since they are ubiquitous in water bodies and can dramatically change process performance.

In this study, we conducted experiments to investigate the effects of oxidant dosage, solution pH, humic acid, and five different inorganic salts (NO_2^- NO_3^-, Cl^-, PO_4^{3-}, and SO_4^{2-}). The effects were analyzed using main effects plots and response tables (Chapter 4. Results), which provide insight into the contribution of each factor in the UV/H_2O_2 and UV/$S_2O_8^{2-}$ degradation processes.

The summarized effects of the synthetic water matrix factors can be found in Table 16. The table shows that humic acid and all the inorganic anions have a negative impact on both processes, except in the case of phosphate which had a positive impact on the UV/H_2O_2 process. It is important to note that although water factors mainly exhibited inhibitory effects on the degradation of pantoprazole, some of the effects can be neglected due to their low contribution in certain cases

Table 16. Summary of the synergistic (+) and inhibitory (−) effects of water matrix factors on the degradation of pantoprazole under UV/H_2O_2 and UV/$S_2O_8^{2-}$ processes.

Process	NO_2^-	NO_3^-	Cl^-	PO_4^{3-}	SO_4^{2-}	HA	pH	Oxidant
UV/H_2O_2	−	−	−	+	−	−	−	+
UV/$S_2O_8^{2-}$	−	−	−	−	−	−	+	+

5.2.1. Effect of oxidant dosage

In this study, we examined the impact of two oxidants, hydrogen peroxide, and sodium persulfate, at two different levels of concentration. The concentrations used were 0.5 mM for level 1 and 10 mM for level 2. In both, UV/H_2O_2 and UV/$S_2O_8^{2-}$ degradation processes, higher concentrations of the oxidants resulted in greater degradation rates of pantoprazole. However, sulfate radicals present in the UV/$S_2O_8^{2-}$ process exhibited a strong enhancing effect on degradation rates, while hydroxyl radicals present in the UV/H_2O_2 process had a weaker impact on the degradation rates. This observation indicates that sodium persulfate demonstrates a higher redox potential compared to hydrogen peroxide in the degradation of pantoprazole under our experimental conditions, which has been discussed in more detail in chapter 5.1. Degradation kinetics.

5.2.2. Effect of nitrite

In line with expectations, our experimental findings revealed the inhibitory effect of nitrites on both degradation processes. These results align with the existing literature, which suggests that nitrites effectively function as scavengers for both sulfate and hydroxyl radicals. [8, 87]

The inhibitory effect was more pronounced in the UV/H_2O_2 process where nitrites had the greatest contribution of all tested factors. This can be attributed to the notably higher second-order rate constant for the reaction of nitrites with hydroxyl radicals ($1.0 \cdot 10^{10}$ M^{-1} s^{-1}) compared to the second-order rate constant of nitrites with sulfate radicals ($8.8 \cdot 10^{8}$ M^{-1} s^{-1}). Moreover, nitrites exhibit stronger radical inhibition compared to other inorganic anions due to their higher reaction rates with these radicals. [88]

In these reactions between nitrite and the two radicals, NO_2• radical is formed which has significantly weaker oxidative power (E = 0.93–1.03 V) compared to hydroxyl (E = 2.8 V) and sulfate (E = 2.5 V) radicals, causing the overall loss in efficiency of the degradation process. [8, 88]

$$NO_2^- + HO\bullet \rightarrow OH^- + NO_2\bullet \qquad k = 1.0 \cdot 10^{10}\ M^{-1}\ s^{-1} \qquad (57)$$

$$NO_2^- + SO_4^{-}\bullet \rightarrow SO_4^{2-} + NO_2\bullet \qquad k = 8.8 \cdot 10^{8}\ M^{-1}\ s^{-1} \qquad (58)$$

Previous studies have documented the inhibitory effects of nitrite ions on the degradation of pharmaceutical chloramphenicol in sulfate radical−based AOPs. [87] Interestingly, sodium nitrite has often been employed as a quenching agent in laboratory experiments to effectively terminate the reactions between sulfate radicals and organic pollutants. [87]

5.2.3. Effect of nitrate

Experimental results revealed the significant inhibitory impact of nitrate ions on the degradation of pantoprazole by the UV/H_2O_2 process and almost no impact by the UV/$S_2O_8^{2-}$ process. The different effects of nitrates in these two processes can be attributed to the photolysis of nitrates at a wavelength of 254 nm, resulting in the generation of hydroxyl radicals (Eqs. (59) and (60)). [89−91]

$$NO_3^- + h\nu \rightarrow NO_2\bullet + O^-\bullet \qquad \Phi = 0.09,\ \varepsilon_{254\ nm} = 3.16\ M^{-1}\ cm^{-1} \qquad (59)$$

$$O^-\bullet + H_2O \rightarrow HO\bullet + OH^- \qquad (60)$$

However, in the case of the UV/H_2O_2 process, this may have led to the excess amount of hydroxyl radical causing the self−scavenging effect (Eq. (61)) and, consequently, the degradation efficiency was reduced.

$$HO\bullet + HO\bullet \rightarrow H_2O_2 \qquad (61)$$

Stefan [8] suggests an alternative perspective on nitrate photolysis. In waters with high transmittance (98% at 254 nm) and a nitrate concentration ≥ 10−15 mg/L (in our experiment, a concentration of 70 mg/L was used), a significant amount of nitrite ions is formed through nitrate photolysis. [8] As mentioned in previous chapter, the nitrate formation even at low levels (μg/L) may result in a significant radical scavenging effect. This process can be described by the Eqs. (62) and (63). [91]

$$NO_3^- + h\nu \rightarrow NO_2^- + O\bullet \qquad \Phi = 0.06 \qquad (62)$$

$$NO_2^- + HO\bullet \rightarrow OH^- + NO_2\bullet \qquad k = 1.0 \cdot 10^{10}\ M^{-1}\ s^{-1} \qquad (63)$$

However, if these reactions were to occur, we would expect a negative impact on both the UV/$S_2O_8^{2-}$ and UV/H_2O_2 processes, which is not the case. Furthermore, nitrate does not function as a radical scavenger, nor as a strong UV radiation absorber, as indicated by their low second-order rate constants with these radicals ($k_{HO\bullet} = 5 \cdot 10^4\ M^{-1}\ s^{-1}$, $k_{SO4\bullet} = 2.1\ M^{-1}\ s^{-1}$) and molar absorption coefficient at 254 nm ($\varepsilon_{254\ nm} = 3.16\ M^{-1}\ cm^{-1}$). [65, 88] Therefore, the first offered explanation remains the most probable one.

5.2.4. Effect of chloride

Upon examining the influence of chloride on the degradation of pantoprazole, we observed that the presence of chloride exhibited a slight negative impact on UV/H_2O_2 degradation. However, the influence was more pronounced in the case of UV/$S_2O_8^{2-}$ degradation, where chlorides had a moderately negative effect.

Stefan [8] explains that the UV/$S_2O_8^{2-}$ process is more susceptible to the presence of chloride in the water matrix due to the pH-independent reaction of sulfate radicals with chloride

ions, while the reaction between hydroxyl radicals and chloride is relevant only in acidic conditions. Research of Zhang et al. [92] supported this, reporting a significant reduction in the degradation rate of organic pollutants in UV/$S_2O_8^{2-}$ in the presence of chloride, whereas the impact of chloride on UV/H_2O_2 was found to be negligible.

Chloride radical scavenges sulfate radicals yielding chlorine atom radical (Eq. (64)), which in our case, results in reduced overall oxidative power of the process. Furthermore, chlorine radical reacts with the chloride to form dichlorine radical (Eq. (65)), while the equilibrium constant of $K = 1.4 \cdot 10^5\ M^{-1}\ s^{-1}$ establishes between all species (Eq. (64) and (65)), implying that the dichlorine radical atom is the predominant chlorine radical in the water matrix containing chloride ions.

$$Cl^- + SO_4^{-}\bullet \rightarrow Cl\bullet + SO_4^{2-} \qquad k = 3.6 \cdot 10^8\ M^{-1}\ s^{-1} \qquad (64)$$

$$Cl\bullet + Cl^- \rightarrow Cl_2^{-}\bullet \qquad k = 7.8 \cdot 10^9\ M^{-1}\ s^{-1} \qquad (65)$$

While most researchers agree on the negligible effect of chloride in UV/H_2O_2 process, some report conflicting results regarding the influence of chloride on UV/$S_2O_8^{2-}$ process. For example, in contrast to Zhang et al. [92], Kwon et al. [66] reported a positive impact of chloride on the degradation rates of ibuprofen in the UV/$S_2O_8^{2-}$ process. They explain that Cl• and Cl_2^{-}• produced in reactions described by Eq. (64) and Eq. (65), may have positive or negative effects on the degradation of the target compound, depending on the selective reactivity of these radicals towards the compound.

5.2.5. Effect of phosphate

In our experiment, the presence of phosphates exhibited a moderately positive impact on the UV/H_2O_2 process, while showing a negligible negative impact on the UV/$S_2O_8^{2-}$ process.

To understand the possible mechanisms behind the effect of phosphate, it is important to note that the presence of phosphate ions in an aqueous solution strongly depends on the pH of the solution. Under our experimental conditions, which ranged from pH 4 to 10, hydrogen phosphate (HPO_4^{2-}) is the predominant form of phosphates. [93]

Hydrogen phosphate ions are reported to scavenge both sulfate and hydroxyl radicals producing hydrogen phosphate radicals by the following reactions [94, 95]:

$$SO_4^{\bullet-} + HPO_4^{2-} \rightarrow HPO_4^{\bullet-} + SO_4^{2-} \qquad k = 1.2 \cdot 10^6\ M^{-1}\ s^{-1} \qquad (66)$$

$$OH\bullet + HPO_4^{2-} \rightarrow HPO_4\bullet^- + OH^- \qquad k = 8 \cdot 10^5\ M^{-1}\ s^{-1} \tag{67}$$

In the UV/$S_2O_8^{2-}$ process, this resulted in a slightly negative effect, while in UV/H_2O_2 a moderately positive effect on the degradation of pantoprazole. This can be explained by the difference in reactivity and selectivity of these radicals towards organic pollutants.

Martire et al. [93] compared the reactivity and selectivity of $HPO_4\bullet^-$, $SO_4\bullet^-$, and HO• radicals towards different organic pollutants. Their findings indicate that in comparison to hydroxyl radicals, phosphate radicals are less reactive, however, they show significantly higher selectivity towards all pollutants included in the study. Moreover, they report that the overall reactivity trend follows the order of HO• > $SO_4\bullet^-$ > $HPO_4\bullet^-$, and selectivity $SO_4\bullet^-$ > $HPO_4\bullet^-$ > HO•.

Therefore, in the UV/H_2O_2 process, the positive effect of phosphate can be explained by the higher selectivity of hydrogen phosphate radicals towards organic pollutants. In fact, the high selectivity of sulfate radical is the main reason for higher degradation rates in UV/$S_2O_8^{2-}$ compared to the UV/H_2O_2 process, which highlights the importance of selectivity in these processes. Hence, in UV/$S_2O_8^{2-}$ process when $SO_4\bullet^-$ radicals are quenched, slightly less reactive hydrogen phosphate radicals are formed. Therefore, a minor inhibitory or negligible effect is expected, which aligns with the observations in our experiment.

Several studies have reported similar trends, for example, Ma et al. [94] report a negligible influence of HPO_4^{2-} on phenol degradation in UV/$S_2O_8^{2-}$ process, while Wang et al. [96] noticed enhancing influence on the degradation of sulfamethoxazole in the hydroxyl radical−based AOP process.

5.2.6. Effect of sulfate

Although it has been reported in the literature that sulfate ions do not scavenge sulfate radicals, we observed that the presence of sulfate ions significantly decreased the efficiency of the UV/$S_2O_8^{2-}$ process. This result aligns with the observations made by Wang et al. [95] who also noted a significant decrease in process efficiency due to the presence of sulfate ions. They proposed that this inhibitory effect arises from the negative impact of sulfate ions on the reduction potential of sulfate radicals based on the Nernst equation (Eq. (68)).

$$E\left(SO_4^{\bullet-}/SO_4^{2-}\right) = E^0\left(SO_4^{\bullet-}/SO_4^{2-}\right) + \left(\frac{RT}{zF}\right)\ln\left(\frac{SO_4^{\bullet-}}{SO_4^{2-}}\right) \tag{68}$$

$E(SO_4^{\bullet -}/SO_4^{2-})$ is the half-reaction reduction potential, $E^0(SO_4^{\bullet -}/SO_4^{2-})$ is the standard half−reaction reduction potential, R is the universal gas constant of 8.314 J K^{-1} mol^{-1}, T is the absolute temperature of 293.15 K, z = 1 is the number of electrons transferred in the half−reaction, and F is the Faraday constant of $9.63845 \cdot 10^4$ C mol^{-1}. From the equation, we can see that as sulfate ion concentration increases, the reduction potential of sulfate radical will decrease, which can explain the inhibitory impact we observed.

In the UV/H_2O_2 process, the presence of sulfate ions had a negligible impact on the degradation of pantoprazole. Wang et al. suggest that sulfate ions can react with hydroxyl radicals which results in forming sulfate radicals (Eq. 69). However, they did not provide a rate constant for this reaction. [95]

$$SO_4^{2-} + HO\bullet \rightarrow HO^- + SO_4^{\bullet -} \quad (69)$$

In fact, Duca et al. [97] suggest that this reaction does not occur, which aligns with our results. Furthermore, Kwon et al. [66] found similar results where sulfate ions had no significant effect on the removal of ibuprofen in the UV/H_2O_2 process. Further investigation is necessary to understand the precise mechanisms through which sulfate ions impact the UV/H_2O_2 process.

5.2.7. Effect of humic acid

The presence of humic acid in both the UV/$S_2O_8^{2-}$ and UV/H_2O_2 processes had a significant inhibitory effect.

Previous studies have reported both inhibitory and synergistic effects of humic acid on these processes, but in our case, the synergistic effect was not observed. This finding is consistent with the observations made by Kwon et al. [66], who also noted only the inhibitory effect and attributed it to two main reasons. First, humic acid exhibits high UV absorption at 254nm, which limits the fraction of light absorbed by hydrogen peroxide and perfulfate. As a result, the production of radical species is decreased. Additionally, the UV absorbance by humic acid can as well decrease the direct photolysis of the target pollutant.

Second, humic acid can scavenge radical species generated in the processes, reducing their availability for pollutant degradation. These scavenging effects contribute to the decreased reaction rates observed in both the UV/$S_2O_8^{2-}$ and UV/H_2O_2 processes. Westerhoff et al. [98] determined the rate constants between hydroxyl radical and humic acid to be in the range of $(2.2–6.7) \cdot 10^4$ L mg^{-1} s^{-1}, while Lutze et al [99] report lower reaction rate constants between

sulfate radicals and humic acid ((1.2−6.8) · 10^3 L mg^{-1} s^{-1}). In both cases, mass in mg relates mass of carbon.

In addition, Yuan et al. [100] investigated the influence of humic acid on the degradation rates of six different pharmaceuticals. They observed that with the addition of increasing amounts of humic acid, degradation rates decreased in all cases.

5.2.8. Effect of solution pH

In our experiment, we examined the effects of pH at two levels, 4 and 10, and observed different effects of increasing pH on the UV/H_2O_2 and UV/$S_2O_8^{2-}$ processes.

In the UV/H_2O_2 process, the degradation rate was negatively influenced at increased pH. This aligns with Zhang et al. [101] observations in the degradation of pharmaceutical azathioprine under UV/H_2O_2 process.

They attributed the negative impact of higher pH in UV/H_2O_2 process to the significant reduction in the oxidative power of hydroxyl radicals in the presence of higher concentrations of hydroxyl ions as pH increases, as predicted by the Nernst equation. The redox potential $E(HO•/H_2O)$ reduces from 2.56 to 2.21 V as pH increases from 4 to 10. [101]

$$E(HO•/H_2O) = E^0(HO•/H_2O) - 0.059 \cdot pH \quad (70)$$

In addition, alkaline conditions contribute to the formation of less reactive $O•^-$ radical ($E(O^-•, H_2O/2HO•)$ = 1.78 V) by the following reaction:

$$HO• + OH^- \rightarrow H_2O + O^-• \qquad k = 1.3 \cdot 10^9\ M^{-1}\ s^{-1} \quad (71)$$

Moreover, the $O^-•$ radical can act as a strong HO• scavenger which also contributes to the negative impact on the UV/H_2O_2 process. In contrast, UV/$S_2O_8^{2-}$ showed higher degradation rates in basic conditions.

In an aqueous solution, the sulfate radicals can participate in pH−dependent reactions to produce hydroxyl radicals following the reactions. This is particularly pronounced in alkaline conditions where the following reaction occurs:

$$SO_4^{-} + OH^- \rightarrow SO_4^{2-} + OH• \qquad k = 6.5 \cdot 10^7\ M^{-1}\ s^{-1} \quad (72)$$

Hence, the distribution of radical species changes in favor of hydroxyl radicals. However, considering the relative distribution of sulfate and hydroxyl radicals in water as a

function of pH determined we assume that at pH = 10 sulfate radicals are still the predominant radical specie with relative distribution of radicals being 80:20 in favor of sulfate radicals. [100]

According to Stefan [8] the water pH influences the efficiency of pollutant removal with UV/$S_2O_8^{2-}$ process through the combination of the following parameters:

- rate of production of radical species
- relative distribution of radical species in water
- whether the target pollutant is protonated or deprotonated (affects their reactivity towards radicals)
- radical scavenging capacity of the matrix at certain pH.

To gain a deeper understanding of the mechanism behind the UV/$S_2O_8^{2-}$ degradation of pantoprazole, further research regarding the mentioned parameter is necessary.

6. Conclusion

The degradation of pantoprazole, a pharmaceutical compound, was successfully achieved in both the UV/H_2O_2 and UV/$S_2O_8^{2-}$ processes. The degradation kinetics in both processes followed a pseudo-first-order pattern. Notably, the UV/$S_2O_8^{2-}$ process displayed higher degradation rates (with an average degradation rate of $31.77 \cdot 10^{-3}$ s^{-1}) compared to the UV/H_2O_2 process ($15.23 \cdot 10^{-3}$ s^{-1}), demonstrating its higher efficiency under the tested conditions. These findings align with previous literature on the degradation of pharmaceuticals using UV/$S_2O_8^{2-}$ and UV/H_2O_2 processes.

The utilization of the Taguchi design of the experiment allowed for the assessment of eight different factors at two levels while minimizing the number of experimental runs to only 12. This approach provided significant data regarding the impact of each factor on the degradation rates. Inorganic salt ions (including nitrite, nitrate, chloride, phosphate, and sulfate) were found to generally inhibit both processes, except for phosphate in the UV/H_2O_2 process. The inhibitory effect is mainly attributed to the scavenging capacity of these ions. Interestingly, the reaction of phosphate ions with hydroxyl radicals resulted in the production of a more selective hydrogen phosphate radical, which enhanced the degradation rate. Humic acid was observed to have an inhibitory impact on the degradation rates in both processes. This inhibition can be attributed to its high UV absorption and radical scavenging effect.

The significant variation in degradation rate constants highlights the pronounced influence of the water matrix in AOPs. Although the exact mechanisms are not fully understood, it is evident that AOPs exhibit high efficiency in removing persistent water pollutants.

In conclusion, the study demonstrates the successful degradation of pantoprazole in the UV/H_2O_2 and UV/$S_2O_8^{2-}$ processes, with UV/$S_2O_8^{2-}$ exhibiting higher degradation rates. Factors such as inorganic salt ions and humic acid were found to affect the degradation rates, emphasizing the importance of considering the water matrix in AOPs. The findings contribute to our understanding of the efficacy of AOPs in the removal of persistent water pollutants.

7. References

[1] https://unesdoc.unesco.org/ark:/48223/pf0000384655_eng (accessed on 13 April 2023)

[2] World Health Organization and United Nations Children's Fund (UNICEF), Progress on sanitation and drinking water: 2014 update. World Health Organization, 2014

[3] UNESCO and WHO, "World Water Assessment Programme, Water for People Water for Life The United Nations World Water Development Report Executive Summary, Paris, 2003.

[4] M. Patel, R. Kumar, K. Kishor, T. Mlsna, C. U. Pittman, and D. Mohan, Pharmaceuticals of Emerging Concern in Aquatic Systems: Chemistry, Occurrence, Effects, and Removal Methods, *Chem. Rev.*, **119** (2019) 3510–3673

[5] B. Gworek, M. Kijeńska, M. Zaborowska, J. Wrzosek, L. Tokarz, and J. Chmielewski, Occurrence of pharmaceuticals in aquatic environment – a review, *Desalin. Water Treat*, **184** (2020) 375–387

[6] J. L. Wilkinson, D. Kolpin, C. Teta, K. Leung et al., Pharmaceutical pollution of the world's rivers, *Proc. Natl Acad. Sci*, **119** (2022) e2113947119

[7] R. K. Szabó, C. S. Megyeri, E. Illés, K. Gajda-Schrantz, P. Mazellier, and A. Dombi, Phototransformation of ibuprofen and ketoprofen in aqueous solutions, *Chemosphere*, **84** (2011) 1658–1663

[8] M. Stefan, *Advanced Oxidation Processes for Water Treatment*. IWA Publ., London, 2018, ch. 2,10

[9] K. Yamakawa, Historical sketch of modern pharmaceutical science and technology (Part 3). From the second half of the 19th century to World War II, *Yakushigaku Zasshi*, **30** (1995) 1–10

[10] D. Taylor, The pharmaceutical industry and the future of drug development, in R. E. Hester and R. M. Harrison (Eds.) Pharmaceuticals in the Environment, R. Soc. Chem., 2015, pp. 1-33.

[11] https://www.statista.com/statistics/263102/pharmaceutical-market-worldwide-revenue-since-2001/ (accessed on 26 April 2023)

[12] M. Caban and P. Stepnowski, How to decrease pharmaceuticals in the environment? A review, *Environ. Chem. Lett.*, **19** (2021) 3115–3138

[13] https://www.iqvia.com/insights/the-iqvia-institute/reports/the-global-use-of-medicines-2022 (accessed on 17 April 2023)

[14] https://www.efpia.eu/media/602709/the-pharmaceutical-industry-in-figures-2021.pdf (accessed on 28 April 2023)

[15] M. Mezzelani, S. Gorbi, and F. Regoli, Pharmaceuticals in the aquatic environments: Evidence of emerged threat and future challenges for marine organisms, *Mar. Environ. Res.*, **140** (2018) 41–60

[16] https://www.umweltbundesamt.de/en/publikationen/the-database-pharmaceuticals-in-the-environment (accessed on 21 May 2023)

[17] K. Kümmerer, Pharmaceuticals in the environment, *Annu. Rev. Environ. Resour.*, **35** (2010) 57–75

[18] M. Stuart, and D. Lapworth, Emerging Organic Contaminants in Groundwater: A review of sources, fate and occurrence, Environ. Pollut., **163** (2013) 259–284

[19] BIO Intelligence Service, Study on the Environmental Risks of Medicinal Products, Final report prepared for Executive Agency for Health and Consumers, Paris, 2013.

[20] OECD, Management of Pharmaceutical Household Water: Limiting Environmental Impacts of Unused or Expired Medicine, *OECD Publishing*, 2022.

[21] L. Santos, M. Gros, S. Rodriguez-Mozaz, C. Delerue-Matos, A. Pena, D. Barcelo, M. Conceicao, B.M. Montenegro, Contribution of hospital effluents to the load of pharmaceuticals in urban wastewaters: Identification of ecologically relevant pharmaceuticals, *Sci. Total Environ.*, **461–462** (2013) 302–316

[22] J. Wang and S. Wang, Removal of pharmaceuticals and personal care products (PPCPs) from wastewater: A review, *J. Environ. Manage.*, **182** (2016) 620–640

[23] K. Kümmerer, Pharmaceuticals in the Environment Sources, Fate, Effects and Risks, Springer-Verlag Berlin Heidelberg, Berlin, 2008, p. 1-8

[24] J. Wang, L. Chu, L. Wojnárovits, and E. Takács, Occurrence and fate of antibiotics, antibiotic resistant genes (ARGs) and antibiotic resistant bacteria (ARB) in municipal wastewater treatment plant: An overview, *Sci. Total Environ.*, **744** (2020) 140997

[25] F. Kaczala and S. E. Blum, The Occurrence of Veterinary Pharmaceuticals in the Environment: A Review, *Curr. Anal. Chem.*, **12** (2016) 169–182

[26] A. Jelić, M. Gros, M. Petrović, A. Ginebreda, and D. Barceló, Occurrence and Elimination of Pharmaceuticals During Conventional Wastewater Treatment, vol. 19, Springer, Berlin, Heidelberg 2012, 1–23

[27] J. R. Masoner, D. W. Kolpin, E. T. Furlong, I. M. Cozzarelli, J. L. Gray, and E. A. Schwab, Contaminants of emerging concern in fresh leachate from landfills in the conterminous United States, *Environ. Sci. Process Impacts*, **16** (2014) 2335–2354

[28] J. R. Masoner, D. W. Kolpin, E. T. Furlong, I. M. Cozzarelli, and J. L. Gray, Landfill leachate as a mirror of today's disposable society: Pharmaceuticals and other contaminants of emerging concern in final leachate from landfills in the conterminous United States, *Environ. Toxicol. Chem.*, **35** (2016) 906–918

[29] B. O. Clarke, T. Anumol, M. Barlaz, and S. A. Snyder, Investigating landfill leachate as a source of trace organic pollutants, *Chemosphere*, **127** (2015) 269–275

[30] M.-C. Lu, Y. Y. Chen, M.-R. Chiou, M. Y. Chen, and H.-J. Fan, Occurrence and treatment efficiency of pharmaceuticals in landfill leachates, *Waste Management*, **55** (2016) 257–264

[31] Q. Sui *et al.*, Pharmaceuticals and personal care products in the leachates from a typical landfill reservoir of municipal solid waste in Shanghai, China: Occurrence and removal by a full-scale membrane bioreactor, *J. Hazard. Mater.*, **323** (2017) 99–108

[32] OECD, Pharmaceutical Residues in Freshwater Hazards and Policy Responses Pharmaceutical Residues in Freshwater Hazards and Policy Responses Contents, *OECD Publishing*, 2019

[33] S. Jobling, M. Nolan, C. R. Tyler, G. Brighty, and J. P. Sumpter, Widespread Sexual Disruption in Wild Fish, *Environ. Sci. Technol.*, **32** (1998) 2498–2506

[34] N. J. Efosa, W. Kleiner, W. Kloas, and F. Hoffmann, Diclofenac can exhibit estrogenic modes of action in male Xenopus laevis, and affects the hypothalamus-pituitary-gonad axis and mating vocalizations, *Chemosphere*, **173** (2017) 69–77

[35] C. S. Martinez, D.A. Feas, M. Siri, D.E. Igartua, N.S. Chiaramoni, S. Del V Alonso, M. J. Prieto, In vivo study of teratogenic and anticonvulsant effects of antiepileptics drugs in zebrafish embryo and larvae, *Neurotoxicol. Teratol.*, **66** (2018) 17–24

[36] R. A. Brain, M. L. Hanson, K. R. Solomon, and B. W. Brooks, Aquatic Plants Exposed to Pharmaceuticals: Effects and Risks, Rev. Environ. Contam. Toxicol., **192** (2008) 67-115

[37] C. Roose-Amsaleg and A. M. Laverman, Do antibiotics have environmental side-effects? Impact of synthetic antibiotics on biogeochemical processes, *Environ. Sci. and Pollut. Res.*, **23** (2016) 4000–4012

[38] M. Desai, A. Njoku, and L. Nimo-Sefah, Comparing Environmental Policies to Reduce Pharmaceutical Pollution and Address Disparities, *Int J Environ. Res. Public Health*, **19** (2022) 8292

[39] C. Loures, M. Alcantara, H. Izairo Filho, A. Teixeira, F. Silva, T. Paiva, G. Samanamud Advanced Oxidative Degradation Processes: Fundamentals and Applications, *Int. Rev. Chem. Eng.*, **5** (2013) 2035-1755

[40] A. Ledezma Estrada, Y. Y. Li, and A. Wang, Biodegradability enhancement of wastewater containing cefalexin by means of the electro-Fenton oxidation process, *J. Hazard Mater.*, **227–228** (2012) 41–48

[41] Y. Deng and R. Zhao, Advanced Oxidation Processes (AOPs) in Wastewater Treatment, *Curr. Pollut. Rep.*, **1** (2015) 167–176

[42] M. Verma and A. K. Haritash, Degradation of amoxicillin by Fenton and Fenton-integrated hybrid oxidation processes, *J. Environ. Chem. Eng.*, **7** (2019) 102886

[43] M. v. Bagal and P. R. Gogate, Wastewater treatment using hybrid treatment schemes based on cavitation and Fenton chemistry: A review, *Ultrason Sonochem*, **21** (2014) pp. 1–14

[44] V. Kavitha and K. Palanivelu, The role of ferrous ion in Fenton and photo-Fenton processes for the degradation of phenol, *Chemosphere*, **55**, (2004) 1235–1243

[45] V. J. P. Vilar, F. C. Moreira, A. C. C. Ferreira, M. A. Sousa, C. Gonçalves, M. F. Alpendurada, and R. A. R. Boaventura, Biodegradability enhancement of a pesticide-containing bio-treated wastewater using a solar photo-Fenton treatment step followed by a biological oxidation process, *Water Res*, **46** (2012) 4599–4613

[46] A. Sharma, M. Verma, and A. K. Haritash, Degradation of toxic azo dye (AO7) using Fenton's process, *Adv. Environ. Res.*, **5** (2016) 189–200

[47] A. Sharma, M. Verma, and A. K. Haritash, Photocatalytic degradation of Acid Orange 7 (AO7) dye using TiO_2, Int. J. Eng. Res. Technol., **4** (2015) 2278-0181

[48] E. S. Elmolla and M. Chaudhuri, Comparison of different advanced oxidation processes for treatment of antibiotic aqueous solution, *Desalination*, **256** (2010) 43–47

[49] L. C. Almeida, S. Garcia-Segura, N. Bocchi, and E. Brillas, Solar photoelectro-Fenton degradation of paracetamol using a flow plant with a Pt/air-diffusion cell coupled with a compound parabolic collector: Process optimization by response surface methodology, *Appl. Catal. B*, **103** (2011) 21–30

[50] E. Brillas, I. Sirés, and M. A. Oturan, Electro-Fenton Process and Related Electrochemical Technologies Based on Fenton's Reaction Chemistry, *Chem. Rev.*, **109** (2009) 6570–6631

[51] A. Kudo and Y. Miseki, Heterogeneous photocatalyst materials for water splitting, *Chem. Soc. Rev.*, **38** (2009) 253–278

[52] T. Oppenländer, *Photochemical Purification of Water and Air*, Wiley-VCH Weinheim, 2002, ch. 5-6

[53] G. H. Safari, M. Hoseini, M. Seyedsalehi, H. Kamani, J. Jaafari, and A. H. Mahvi, Photocatalytic degradation of tetracycline using nanosized titanium dioxide in aqueous solution, *Int. J. Environ. Sci. Technol.*, **12** (2015) 603–616

[54] C. V. Rekhate and J. K. Srivastava, Recent advances in ozone-based advanced oxidation processes for treatment of wastewater- A review, *Chem. Eng. J. Adv.*, **3** (2020) 100031

[55] Y. Rao, H. Yang, D. Xue, Y. Guo, F. Qi, J. Ma, Sonolytic and sonophotolytic degradation of Carbamazepine: Kinetic and mechanisms, *Ultrason. Sonochem.*, **32** (2016) 371–379

[56] S. Parsons, Advanced Oxidation Processes for Water and Wastewater Treatment, IWA Publ., London, *2005.*, 8-34

[57] Z. Eren, Ultrasound as a basic and auxiliary process for dye remediation: A review, *J. Environ. Manage*, **104** (2012) 127–141

[58] M. Matouq, T. Tagawa, High frequency ultrasound waves for degradation of amoxicillin in the presence of hydrogen peroxides for industrial pharmaceutical wastewater treatment, *Global NEST J.*, **16** (2014) 805–813

[59] R. F. Dantas, O. Rossiter, A. K. R. Teixeira, A. S. M. Simões, V. L. da Silva, Direct UV photolysis of propranolol and metronidazole in aqueous solution, *Chem. Eng. J.*, **158** (2010) 143–147

[60] S. Guerra-Rodríguez, E. Rodríguez, D. Singh, J. Rodríguez-Chueca, Assessment of Sulfate Radical-Based Advanced Oxidation Processes for Water and Wastewater Treatment: A Review, *Water (Basel)*, **10** (2018) 1828

[61] B. A. Wols and C. H. M. Hofman-Caris, Review of photochemical reaction constants of organic micropollutants required for UV advanced oxidation processes in water, *Water Res.*, **46** (2012) 2815–2827

[62] S. Hou, L. Ling, C. Shang, Y. Guan, J. Fang, Degradation kinetics and pathways of haloacetonitriles by the UV/persulfate process, *Chem. Eng. J.* **320** (2017) 478–484

[63] R. F. Nunes, F. K. Tominaga, S. I. Borrely, A. C. S. C. Teixeira, UVA/persulfate-driven nonylphenol polyethoxylate degradation: effect of process conditions, *Environ. Technol.*, **43** (2022) 286–300

[64] A. Tsitonaki, B. Petri, M. Crimi, H. Mosbaek, R. L. Siegrist, P. L. Bjerg, In Situ Chemical Oxidation of Contaminated Soil and Groundwater Using Persulfate: A Review, *Crit. Rev. Environ. Sci. Technol.*, 40 (2010) 55–91

[65] W. Li, T. Jain, K. Ishida, H. Liu, A mechanistic understanding of the degradation of trace organic contaminants by UV/hydrogen peroxide, UV/persulfate and UV/free chlorine for water reuse, *Environ. Sci. (Camb.)*, **3** (2017) 128–138

[66] M. Kwon, S. Kim, Y. Yoon, Y. Jung, T. Hwang, J. Lee, J. Kang, Comparative evaluation of ibuprofen removal by UV/H_2O_2 and UV/$S_2O_8^{2-}$ processes for wastewater treatment, *Chem. Eng. J.*, **269** (2015) 379–390

[67] A. R. Lado Ribeiro, N. F. F. Moreira, G. Li Puma, A. M. T. Silva, Impact of water matrix on the removal of micropollutants by advanced oxidation technologies, *Chem. Eng. J.*, **363** (2019) 155–173

[68] J. Ma, H. Li, Y. Yang, X. Li, Influence of water matrix species on persulfate oxidation of phenol: reaction kinetics and formation of undesired degradation byproducts, *Water Sci. and Technol.*, **2017** (2018) 340–350

[69] J. R. Wagner, E. M. Mount, and H. F. Giles, Design of Experiments, in *Extrusion*, Elsevier (2014) 291–308

[70] A. Freddi and M. Salmon, Design of Experiment, Design Principles and Methodologies: Springer Cham, 2019, pp. 127-158

[71] M. Cavazzuti, Design of Experiments, in *Optimization Methods*, Spriger, Berlin, Heidelberg, 2013, pp. 13–42

[72] R. K. Roy, *A primer on the Taguchi method*, Society of Manufacturing Engineers, 2010, 9-10

[73] G. Der, An Overview of Proton Pump Inhibitors, *Gastroenterology Nursing*, **26** (2003) 182–190

[74] C. Lenoir, M. El Biali, C. Luthy, O. Grosgurin, J. A. Desmeules, and V. Rollason, Snapshot of proton pump inhibitors prescriptions in a tertiary care hospital in Switzerland: less is more?, *Int. J. Clin. Pharm.*, **41** (2019) 1634–1641

[75] C. I. Kosma, D. A. Lambropoulou, and T. A. Albanis, Analysis, occurrence, fate and risks of proton pump inhibitors, their metabolites and transformation products in aquatic environment: A review, *Sci. Total Environ.*, **569–570** (2016) 732–750

[76] https://pubchem.ncbi.nlm.nih.gov/compound/Pantoprazole (accessed on 28 May 2023)

[77] P. Poole, Pantoprazole, *Am. J. of Health-Syst. Pharm.*, **58** (2001) 999–1008

[78] M. Yibirin, D. De Oliveira, R. Valera, A. E. Plitt, and S. Lutgen, Adverse Effects Associated with Proton Pump Inhibitor Use, *Cureus*, **13** (2021) e12759

[79] L. Bijlsma, E. Pitarch, E. Fonesca, M. Ibanez, A. Botero, J. Claros, L. Pastor, F. Hernandez, Investigation of pharmaceuticals in a conventional wastewater treatment plant: Removal efficiency, seasonal variation and impact of a nearby hospital, *J. Environ. Chem. Eng.*, **9** (2021)105548

[80] J. A. Luque-Espinar, N. Navas, M. Chica-Olmo, S. Cantarero-Malagón, L. Chica-Rivas, Seasonal occurrence and distribution of a group of ECs in the water resources of Granada city metropolitan areas (South of Spain): Pollution of raw drinking water, *J. Hydrol.*, **531** (2015) 612–625

[81] O. Zenita Devi and K. Basavaiah, Validated spectrophotometric determination of pantoprazole sodium in pharmaceuticals using ferric chloride and two chelating agents, *IOSR J. Appl. Chem.*, **8** (2015) 15-23

[82] D. G. Della Rocca, H. Victoria, C. Moura-Nickel, G. Scaretti, K. Krambrock, A. De Noni, V. Vilar, H. Jose, R. Moreira, Peroxidation and photo-peroxidation of pantoprazole in aqueous solution using silver molybdate as catalyst, *Chemosphere*, **262** (2021) 127671

[83] N. Sadeghpour, M. Vadi, N. Bagheri,Utilizing Carbon Nanotubes as Efficient Nanoadsorbent for Pantoprazole removal from aqueous samples : Kinetics Isotherm and thermodynamic studies, *J. Chil. Chem. Soc.*, **66** (2021) 5324–5331

[84] X. Liu, L. Fang, Y. Zhou, T. Zhang, and Y. Shao, Comparison of UV/PDS and UV/H_2O_2 processes for the degradation of atenolol in water, *J. Environ. Sci.*, **25** (2013) 1519–1528

[85] Y. Zhang, Y. Xiao, Y. Zhong, and T.-T. Lim, Comparison of amoxicillin photodegradation in the UV/H_2O_2 and UV/persulfate systems: Reaction kinetics, degradation pathways, and antibacterial activity, *Chem. Eng. J.*, **372** (2019) 420–428

[86] K. Arman, M. Baghdadi, and A. Pardakhti, Photochemical degradation of dexamethasone by UV/Persulphate, UV/Hydrogen peroxide and UV/free chlorine processes in aqueous solution using response surface methodology (RSM), *Int. J. Environ. Anal. Chem.* (2022)

[87] Y. Ji, L. Wang, M. Jiang, J. Lu, C. Ferronato, and J.-M. Chovelon, The role of nitrite in sulfate radical-based degradation of phenolic compounds: An unexpected nitration process relevant to groundwater remediation by in-situ chemical oxidation (ISCO), *Water Res.*, **123** (2017) 249–257

[88] P. Neta, R. E. Huie, and A. B. Ross, Rate Constants for Reactions of Inorganic Radicals in Aqueous Solution, *J. Phys. Chem. Ref. Data*, **17** (1988) 1027–1284

[89] S. Goldstein and J. Rabani, Mechanism of Nitrite Formation by Nitrate Photolysis in Aqueous Solutions: The Role of Peroxynitrite, Nitrogen Dioxide, and Hydroxyl Radical, *J. Am. Chem. Soc.*, **120** (2007) 10597-10601

[90] H. Herrmann, On the photolysis of simple anions and neutral molecules as sources of O^-/OH, SO_x^- and Cl in aqueous solution, *Phys. Chem. Chem. Phys.*, **9** (2007) 3935–3964

[91] G. Mark, H.-G. Korth, H.-P. Schuchmann, and C. von Sonntag, The photochemistry of aqueous nitrate ion revisited, *J. Photochem. Photobiol. A. Chem.*, **101** (1996) 89–103

[92] W. Zhang *et al.*, Impact of Chloride Ions on UV/H_2O_2 and UV/Persulfate Advanced Oxidation Processes, *Environ. Sci. Technol.*, **52** (2018) 7380–7389

[93] D. O. Mártire and M. C. Gonzalez, Aqueous Phase Kinetic Studies Involving Intermediates of Environmental Interest: Phosphate Radicals and Their Reactions with Substituted Benzenes, *Prog. React. Kinet. Mech.*, **26** (2001) 201–218

[94] J. Ma, H. Li, Y. Yang, and X. Li, Influence of water matrix species on persulfate oxidation of phenol: reaction kinetics and formation of undesired degradation byproducts, *Water Sci. Technol.*, **2017** (2018) 340–350

[95] J. Wang and S. Wang, Effect of inorganic anions on the performance of advanced oxidation processes for degradation of organic contaminants, *Chem. Eng. J.*, **411** (2021) 128392

[96] S. Wang and J. Wang, Radiation-induced degradation of sulfamethoxazole in the presence of various inorganic anions, *Chem. Eng. J.*, **351**, (2018) 688–696

[97] C. Duca, G. Imoberdorf, and M. Mohseni, Effects of inorganics on the degradation of micropollutants with vacuum UV (VUV) advanced oxidation, *J. Environ. Sci. Health, Part A*, **52** (2017) 524–532

[98] P. Westerhoff, G. Aiken, G. Amy, and J. Debroux, Relationships between the structure of natural organic matter and its reactivity towards molecular ozone and hydroxyl radicals, *Water Res.*, **33** (1999) 2265–2276

[99] H. V. Lutze, S. Bircher, I. Rapp, N. Kerlin, R. Bakkour, M. Geisler, C. von Sonntag, T. C. Schmidt , Degradation of Chlorotriazine Pesticides by Sulfate Radicals and the Influence of Organic Matter, *Environ. Sci. Technol.*, **49** (2015) 1673–1680

[100] H. Yuan, X. Zhou, and Y.L. Zhang, Degradation of Acid Pharmaceuticals in the UV/H_2O_2 Process: Effects of Humic Acid and Inorganic Salts, *Clean (Weinh)*, **41** (2013) 43–50

[101] Y. Zhang, J. Zhang, Y. Xiao, V. W. C. Chang, and T.-T. Lim, Kinetic and mechanistic investigation of azathioprine degradation in water by UV, UV/H_2O_2 and UV/persulfate, *Chem. Eng. J.*, **302** (2016) 526–534

BIOGRAPHY

Ana Krpina, [redacted] completed primary school in Biograd na Moru in 2011 and graduated from the IV Gymnasium Highschool in Zagreb in 2015. In 2017, she enrolled Chemical Technology undergraduate study with a focus on Environmental Protection at the University of Split, earning her bachelor's degree in 2020. In the same year, she pursued a graduate study of Chemical and Environmental Technology at the University of Zagreb. During her undergraduate studies, she gained practical experience through an internship at a municipal wastewater treatment plant in Biograd na Moru.