

École polytechnique de Louvain

Treatment of Nanofiltration or Reverse Osmosis Concentrates by UV/H₂O₂ Indirect Photolysis for the Removal of Anti-Cancer Drugs from Real Secondary Wastewater Effluents

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Abstract

Anti-cancer drugs have been detected in the aquatic environment due to their poor elimination in current wastewater treatment plants. These drugs pose a potential risk to aquatic organisms and humans once they have entered the water cycle. This work studies the UV/H₂O₂ treatment of nanofiltration (NF) and reverse osmosis (RO) retentates of secondary wastewater effluent (WWeff) for the removal of anti-cancer drugs and toxicity. This treatment was compared to the direct treatment of WWeff by UV photolysis and by UV/H₂O₂ treatment. The filtration of 5 selected anti-cancer drugs by a RO-SE membrane showed high rejections (>88%) for all drugs, while the NF-DL membrane provided poor rejections (<45% for most drugs). Therefore, only the RO retentate treatment by UV/H₂O₂ (RO-UV/H₂O₂) was tested. The degradation efficiency of the drugs by UV, UV/H₂O₂ and RO-UV/H₂O₂ was compared using a pseudo-first order degradation rate constant. Degradation rates of all drugs significantly increased with the addition of H₂O₂ due to HO· radicals generation. The rates for RO-UV/H₂O₂ were lower than direct WWeff treatment by UV/H₂O₂ due to an increased concentration of organic matter and ions in the retentate stream which inhibited the drug degradation. Acute toxicity on *V. fischeri* was assessed for the feed and all treated effluent streams. The feed showed no toxicity because the concentration of drugs was too small. The stream treated by direct UV photolysis showed no increase in toxicity. Conversely, the effluent streams treated by UV/H₂O₂ showed higher toxicity which was attributed to the formation of toxic by-products that were different than the UV by-products. Finally, a comparison of operating costs for four different treatments (UV, UV/H₂O₂, NF-UV/H₂O₂ and RO-UV/H₂O₂) was done through a basic economic analysis. The UV/H₂O₂ treatment showed the lowest operating costs. The RO-UV/H₂O₂ showed comparable costs due to the reduction in volume that needs to be treated by UV/H₂O₂.

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Contents

List of Figures	i
List of Tables	ii
List of Abbreviations	iii
Introduction	1
1 Literature Review	2
1.1 Anti-Cancer Drugs	2
1.2 Advanced Oxidation Processes	5
1.2.1 Ozonation	6
1.2.2 Fenton and Photo-Fenton Oxidation	6
1.2.3 Electrochemical Oxidation	6
1.2.4 Photocatalysis	7
1.2.5 Direct UV and Indirect UV/H ₂ O ₂ Photolysis	8
1.3 Membrane Filtration	12
1.3.1 General Mechansism	12
1.3.2 Operating Mode	13
1.3.3 Performance	14
1.3.4 RO and NF Membrane Filtration for Wastewater Treatment	15
1.4 NF and RO Membrane Retentate Treatment by AOPs	19
1.5 Ecotoxicity of Anti-Cancer Drugs	21
2 Objectives	23
3 Materials and Methods	24
3.1 Materials	24
3.1.1 Water Matrices	24
3.1.2 Anti-cancer Drugs and Chemicals	24
3.1.3 Membranes	25
3.2 Experimental Procedures	25
3.2.1 Membrane Characterization	25
3.2.2 Membrane Filtration Experiments	26
3.2.3 UV/H ₂ O ₂ Experiments	27
3.2.4 Retentate Treatment by UV/H ₂ O ₂	28
3.3 Analytical Methods	28
3.3.1 HPLC-UV	28
3.3.2 UPLC-MS	28

3.3.3	COD Test	29
3.3.4	Toxicity Assays	29
3.4	Economic Analysis	30
4	Results and Discussions	32
4.1	pCBA Degradation by UV/H ₂ O ₂	32
4.2	RO and NF Membrane Filtration	34
4.2.1	Pure Water Permeability	34
4.2.2	Anti-Cancer Drug Rejection by RO and NF Filtration	34
4.3	RO Retentate Treatment by UV/H ₂ O ₂	37
4.4	Toxicity Assessment	41
4.5	Economic Analysis	44
	Conclusions	48
	Recommendations for Future Research	50
	Bibliography	52

List of Figures

1.1	Input and transport route of cytostatic pharmaceuticals in the aquatic environment	3
1.2	Water absorbance, H ₂ O ₂ absorbance and MP and LP UV mercury lamp emissions. Data not scaled. Reprinted from Ijpelaar et al., 2010	10
1.3	Functioning of pressure driven membrane processes.	12
1.4	Overview of the different pressure-driven membrane processes. Modified from Van der Bruggen et al., 2018	13
1.5	Dead-end and cross-flow filtration mode.	14
1.6	Polyamide thin film composite membranes.	15
1.7	Coupling of membrane filtration and AOP.	19
3.1	Membrane filtration experimental set-up.	26
3.2	UV/H ₂ O ₂ indirect photolysis experimental set-up.	27
3.3	Considered configurations for the economic analysis: a UV photolysis, b UV/H ₂ O ₂ photolysis, c combination of NF with UV/H ₂ O ₂ , d combination of RO and UV/H ₂ O ₂	30
4.1	Concentration of pCBA over time in wastewater effluent.	32
4.2	Degradation rates of pCBA as a function of H ₂ O ₂ dose in LGW and WWeff.	33
4.3	Pure water permeability of NF-DL and RO-SE membranes before and after filtration.	34
4.4	Scheme of the three considered treatments a UV, b UV/H ₂ O ₂ , c RO-UV/H ₂ O ₂	37
4.5	Degradation rate constants of the three selected anti-cancer drugs for the three treatments. n.d. = not determined due to detection error.	38
4.6	COD removal and drug removal of the four effluents after the different treatments. *= data missing for IMT due to detection error.	39
4.7	% Inhibition on <i>V. fischeri</i> as a function of concentration for the three studied anti-cancer drugs after a 15 minute exposure time.	41
4.8	Toxicity assay with <i>V. fischeri</i> after 15 minute exposure of a feed containing IMT, CAP and CP at 0.5mg/L and of the effluents after treatment: RO filtration, UV, UV/H ₂ O ₂ and RO-UV/H ₂ O ₂	42
4.9	Contribution of each item to the total cost of the four treatments to decrease the CP concentration by one order of magnitude in 1L.	46

List of Tables

1.1	Classification of anti-cancer drugs according to the WHO. Modified from Toolaram et al., 2014	2
1.3	Physico-chemical properties of 9 of the most used anti-cancer drugs. Modified from Zhang et al., 2013. Predicted environmental concentrations in France according to Besse et al., 2012 are also included.	4
1.5	MWCO range for MF, UF, NF and RO filtration processes	13
3.1	Secondary effluent composition from Louvain-la-Neuve wastewater treatment plant.	24
3.2	Anti-cancer drugs and their physico-chemical properties.	25
3.3	RO and NF membrane properties.	25
3.4	Solvent composition for UPLC-MS analysis.	28
3.5	Retention times and m/z ratios of analyzed drugs.	29
4.1	Rejection and adsorption values of five selected anti-cancer drugs by NF-DL and RO-SE membranes.	35
4.2	Total drug removal for the NF-DL and RO-SE membranes during filtration of five selected anti-cancer drugs.	36
4.3	Rejection of COD and ions during RO-SE membrane filtration. n.d. = not detected in the permeate. Results obtained from the master thesis of Juline Gillard	39
4.4	Unit prices and lifetime of the items considered in the economic analysis. .	44
4.5	Parameters considered to evaluate the cost of the four different treatments in order to decrease the CP concentration by one order of magnitude in 1L. Also included are the costs for each item and the total cost of the treatment. Costs are expressed in euro/L/order.	45

List of Abbreviations

AOP	Advanced Oxidation Process
CAP	Capecitabine
COD	Chemical Oxygen Demand
CP	Cyclophosphamide
IMT	Imatinib
LGW	Laboratory Grade Water
LP	Low Pressure
MP	Medium Pressure
MTX	Methotrexate
MW	Molecular Weight
MWCO	Molecular Weight Cut-Off
NF	Nanofiltration
NOM	Natural Organic Matter
RO	Reverse Osmosis
TFC	Thin Film Composite
WWeff	Secondary Wastewater effluent
WWTP	Wastewater Treatment Plant
5FU	5-Fluorouracil

Introduction

Pharmaceutical compounds have been used in large quantities for a long time now and their consumption increases every year [1]. A fraction of these pharmaceuticals are not metabolized after the patient's intake and are thus excreted in intact form or as metabolites [2]. Therefore, these metabolites or parent drugs end up in wastewater treatment plants (WWTP). Since currently applied methods are inefficient at removing those pharmaceuticals, they remain in the WWTP effluents which are then discharged in water bodies [1].

Anti-cancer drugs are a subgroup of those pharmaceuticals found at concentrations of ng/L in the environment. They are one of the main chemotherapeutic agents used for cancer treatment [3] and since the number of cancer cases increases every year, the demand for chemotherapy treatments increases as well [4]. For instance, the International Agency for Research on Cancer (IARC) [5], reported 18.1 million new cases of cancer worldwide in 2018 compared to 14.1 million new cases in 2012. As a result, always more drugs are discharged in the environment. The risk of these drugs and their metabolites in the environment on wildlife and human health is not well known because the amount of robust ecotoxicological risk assessments in the literature is limited [6]. However, anti-cancer drugs are meant to kill or reduce proliferating cells by interacting with DNA and are non-specific which means they can also have unwanted effects on non-cancerous cells [3]. Pharmaceutical compounds have been classified as emerging contaminants due to the increase in consumption, hence their accumulation in the environment and their potential toxicity [7]. Moreover, detection methods have improved so they can now be detected in the environment at ng/L levels [8].

Only less than 3% of earth's water is freshwater and this water is being contaminated by WWTP effluents. Consequently, it is important to eliminate those pharmaceuticals from the wastewater before discharging it into water bodies or reuse it for irrigation [9]. Therefore, there has been an increase in the research for solutions that could efficiently remove these persistent and toxic pharmaceuticals from wastewater. Among those solutions, advanced oxidation processes (AOPs) present a great alternative for treating a wide range of pharmaceuticals. These technologies generate highly reactive oxygen species with low selectivity to degrade the pollutants in order to completely mineralize them. Besides AOPs, membrane separation is another treatment technique used for the abatement of pharmaceuticals in wastewater. However, AOPs or membrane separation applied alone still present challenges related to incomplete removal of pollutants, formation of toxic by-products, and high energy or reagent costs [9].

The objective of this work is to combine membrane processes with AOPs for the removal of anti-cancer drugs from a wastewater effluent. More specifically, this thesis will study the removal of anti-cancer drugs by a UV/H₂O₂ treatment of reverse osmosis (RO) or nanofiltration (NF) concentrates. This allows to combine the advantages of both technologies and cancel out the drawbacks of one another. Indeed, the concentrate stream of the membrane can be treated by AOP before disposal, which is advantageous for the AOP because it has to treat a lower volume with a higher concentration of pollutants.

Chapter 1

Literature Review

1.1 Anti-Cancer Drugs

Anti-cancer drugs are one of the main chemotherapeutic agents used to fight cancer and are meant to kill or control proliferating cells through different mechanisms of action [3]. They have thus been classified by the World Health Organization (WHO) in the Anatomical Therapeutic Classification (ATC) system according to their therapeutic action and chemical structures. Antineoplastic drugs belong to the class L01 of the ATC and can be subdivided into five groups: alkylating agents, antimetabolites, plant alkaloids, cytotoxic antibiotics and other antineoplastic agents [10]. Table 1.1 shows the classification and the mode of action of these drugs as well as some examples.

Table 1.1: Classification of anti-cancer drugs according to the WHO. Modified from [3].

Antineoplastic agents L01		Examples	Mode of action
L01A	Alkylating agents	Cyclophosphamide, Ifosfamide	Replaces a hydrogen atom with an alkyl group that can slow or block DNA replication.
L01B	Antimetabolites	Metothrexate, Fluorouracil	Structurally similar to endogenous nucleic acids and can be incorporated into the metabolic pathways instead of the endogenous purine and pyrimidines, thereby affecting the enzyme dependent synthesis of DNA and cell reproduction.
L01C	Plant alkaloids and other natural products	Vinblastine, Paclitaxel	Interacts with the microtubules or the tubulins leading to inhibition of synthesis of proteins and nucleic acids, disruption of the mitotic spindle and eventually cell death.
L01D	Cytotoxic antibiotics and related substances	Dactinomycin, Doxorubicin	Mechanism of action involves direct toxic action on cellular DNA, interfering with DNA replication and protein synthesis.
L01X	Other antineoplastic agents	Imatinib, Procarbazine	E.g. Imatinib as a protein kinase inhibitor can block the breakpoint cluster region-Abl tyrosine kinase and therefore inhibit proliferation and induces apoptosis of chronic myelogenous leukemia cells.

The detection of human pharmaceuticals in the environment has led to increased concerns on their occurrence, fate and potential risks [6]. Body metabolization and excretion followed by wastewater treatment is considered to be the primary pathway of pharmaceuticals to the environment [1]. Anti-cancer drugs are administered at hospitals and now at increasing levels at home by out-patients so they end up in hospital effluents but also municipal wastewater [3]. For instance, according to Kümmerer et al. [11], around 80% of the antineoplastic agents consumed in Germany are prescribed by office-based practitioners and are mostly excreted at home. Figure 1.1 shows typical ways through which the drugs can enter and be transported in the water cycle. The primary sources being household wastewater, hospital effluents, drug waste disposal and also anti-cancer drugs administered to animals [6].

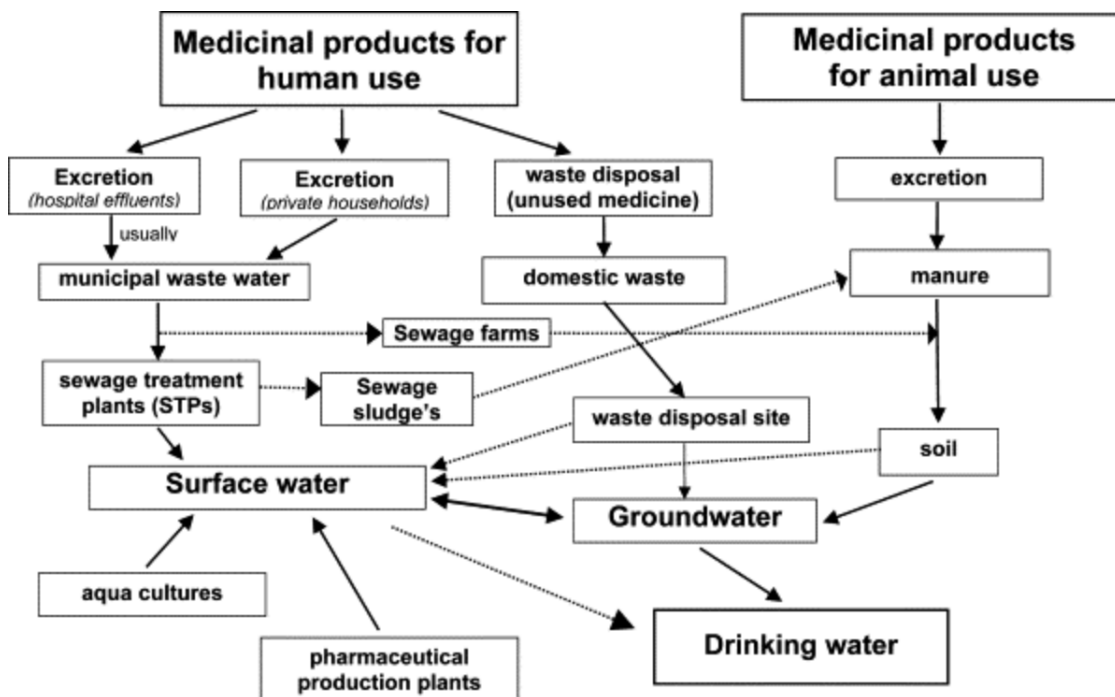


Figure 1.1: Input and transport route of cytostatic pharmaceuticals in the aquatic environment [9].

It is important to know the nature of these drugs to understand the impact they can have on the environment. Their physico-chemical properties such as the dissociation constant (pK_a), octanol-water partition coefficient (K_{ow}), solubility, bio-concentration factor (BCF) and maximum UV absorption, can help understand their behavior in the aquatic environment [6]. Table 1.3 shows the physico-chemical properties for some of the most commonly used anti-cancer drugs. For instance, 5-fluorouracil (5-FU) has a low K_{ow} which suggests that it will not adsorb on suspended solids in water. A low BCF means that the drug is unlikely to accumulate in aquatic organisms. The maximum absorption of UV spectrum will predict if they are susceptible to direct photolysis by natural sunlight, thus 5-FU would not be degraded by natural sunlight [6]. The pK_a of the drug will determine their charge in the water. Furthermore, most cytostatic drugs have extremely low vapor pressures [6]. Clearly, the concentration of the drugs in water bodies should also be known

in order to assess their risk. Table 1.3 also includes predicted environmental concentrations (PEC) for 2008 in France according to Besse et al. [12].

Table 1.3: Physico-chemical properties of 9 of the most used anti-cancer drugs. Modified from [6]. Predicted environmental concentrations in France according to Besse et al. [12] are also included.

Anti-cancer drug	pKa	Solubility [mg/mL]	Log K_{ow}	BCF ^a	UV _{max} [nm]	PEC 2008 [ng/L]
Alkylating Agents						
Cyclophosphamide	2.84	40	0.63	2.1	200	6.98
Ifosfamide	1.45	3.8	0.86	2.2	<290	2.35
Antimetabolites						
Methotrexate	4.70	insol.	-1.85	3.2	290	1.71
5-Fluorouracil	8.02	11.1	-0.89	3	266 39.57	
Capecitabine	1.9	26	1.04	1.9	310	117.24
Cytarabine	4.22	17.6	-1.82	1	281	3.05
Plant Alkyls						
Paclitaxel	11.99	insol.	3.95	591	227/273	0.88
Cytotoxic antibiotics						
Doxorubicin	8.2	2.6	1.27	1	485	0.38
Others						
Imatinib	8.07	insol.	2.89	1	n.a.	19.95

^a BCF indicates biomagnification risk: BCF<30: low, 30-100: moderate, 100-1000: high, >1000 very high

n.a. = data not available

So far, only a few environmental risk assessments have been carried out on a small number of drugs. Moreover, these compounds can be transformed by the human body to create metabolites. Other transformation products can result from treatment processes such as advanced oxidation processes that are also present in the environment [3].

1.2 Advanced Oxidation Processes

Anti-cancer drugs are inefficiently removed by currently applied wastewater treatment plants because of their persistence. Therefore, to remove those pharmaceuticals from the water, advanced oxidation processes have been studied throughout the last decades and have already been applied in some cases. These processes include ozonation, photo-Fenton, electrochemical oxidation, photocatalysis, etc. All of these processes are based on the use of highly reactive and non-selective radicals, such as hydroxyl radicals ($\text{HO}\cdot$), superoxide anion radicals ($\text{O}_2^{\cdot-}$), hydroperoxyl radicals ($\text{HO}_2\cdot$) or alkoxy radicals ($\text{RO}\cdot$) to progressively oxidize organic compounds to non-toxic and biodegradable products [8]. Among these radicals, $\text{HO}\cdot$ is thought to play the most important role in the AOPs for WW treatment [13]. Three types of reactions with hydroxyl radicals can occur in order to degrade organic compounds. The first one is hydrogen abstraction from C-N, N-H or O-H groups (1.1). The second one is through electrophilic addition, which leads to the formation of an organic radical (1.2). The last type is through direct electron transfer (1.3). The products of these reactions are oxidized intermediates or, in the case of complete mineralization, CO_2 , H_2O and inorganic acids [14].



Degradation kinetics The degradation of anti-cancer drugs by advanced oxidation processes generally follows a pseudo-first order kinetic model [15]:

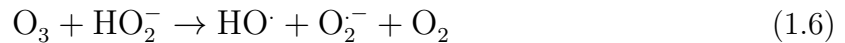
$$-\frac{d[C]}{dt} = k[C] \Rightarrow \ln\left(\frac{C_0}{C}\right) = kt \quad (1.4)$$

where C_0 and C are the initial pollutant concentration and the concentration at time t , t is the time of reaction and k the degradation rate constant. This constant is convenient to compare degradation rates of different processes or at different operating conditions.

An overview of the different AOPs mentioned above will be done in this section and then, more in depth, the UV/ H_2O_2 process, which is the main focus in this work. The different AOPs used for pharmaceutical wastewater treatment can be divided into three types: photochemical processes (e.g. UV and UV/ H_2O_2 , photocatalysis, photo-Fenton), non-photochemical processes (e.g. Fenton, ozonation, electrochemical) and hybrid processes (e.g. photocatalytic ozonation, photoelectrolysis) [8].

1.2.1 Ozonation

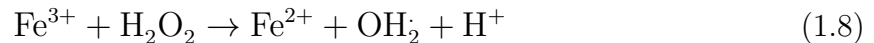
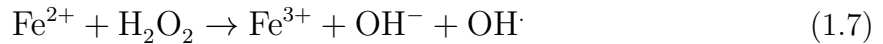
Ozonation is the process through which the organic pollutants are degraded by the addition of ozone. Ozonation and combinations of ozonation with H_2O_2 and/or UV has been used either as a single oxidation step or as pre-oxidation step before other treatments such as a biological treatment [8]. The reaction of ozone with contaminants can occur by two oxidation mechanisms; direct attack of O_3 on the acidic sites or indirect attack through the formation of a variety of radicals such as $\text{HO}\cdot$ [16]. The reaction mechanism for the formation of $\text{OH}\cdot$ from ozone decomposition is the following [17]:



The conversion of pharmaceuticals through ozonation can be influenced by various parameters such as pH, ozone dose and temperature. The advantage of ozonation is that a small dose of ozone provides a high removal efficiency. However, studies have shown that the mineralization by ozonation is limited and persistent by-products are formed [16]. Moreover, as for all AOPs, it is an expensive and energy consuming method [8]. Addition of H_2O_2 and irradiation have been suggested to enhance the degree of mineralization [8].

1.2.2 Fenton and Photo-Fenton Oxidation

Fenton and photo-Fenton oxidation is based on the use of a mixture of iron salts (Fe^{2+}) to transform H_2O_2 into $\text{HO}\cdot$ radicals (reaction 1.7). The Fe^{2+} catalyst can then be regenerated through reaction 1.8.

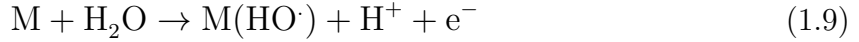


The Fenton reactions can be enhanced by UV or UV-Vis radiation to initiate additional $\text{HO}\cdot$ radicals, hence, improving the rate of removal compared to without radiation. This is referred to as the photo-Fenton process [14]. In addition to the reactions 1.7 and 1.8, photolysis of H_2O_2 occurs with UV light and the photoreduction of Fe^{3+} to Fe^{2+} [13]. The main drawbacks of the Fenton process is that it requires low acidic pH (3–5) conditions and that the iron sludge has to be disposed of. However, the use of iron as reactant is attractive since it is an abundant, inexpensive and a non-toxic metal [18].

1.2.3 Electrochemical Oxidation

Electrochemical oxidation is a process in which reactive species are generated via electricity and without the need for chemicals so without secondary waste [8]. Two oxidation mechanisms occur; the first one is a direct oxidation at the anode in which direct charge transfer occurs between the pharmaceutical compound and the anode surface. The second is an indirect oxidation via generation of reactive oxygen species (mostly $\text{HO}\cdot$ radicals) by oxidants at the surface of the anode.

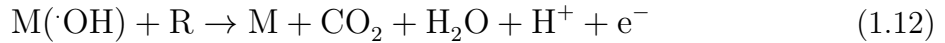
The first step in oxygen transfer reaction is the discharge of water molecules to form adsorbed HO $\cdot$:



The next step depends on the electrode material, there are two classes, active or non-active electrodes. If the electrode is active (e.g. RuO₂, IrO₂, Pt and doped Ti electrodes), the adsorbed radicals interact strongly with the anode and form chemisorbed active oxygen or higher oxide. Then, the chemisorbed redox pair MO/M acts as a mediator for the selective oxydation of the organic compound:



If the anode is non-active (e.g. boron doped diamond electrodes, SnO₂, PbO₂), the surface of the electrode interacts weakly with the hydroxyl radicals so they non-selectively oxidize the organics to CO₂ [9]:



This process has been shown to be efficient and have relatively low energy consumption. However, it is less viable than ozonation or photolysis for the treatment of large wastewater volumes with low pollutant concentration [9].

1.2.4 Photocatalysis

Photocatalysis is a process in which photocatalysts are excited by the absorption of light which has an energy equal or higher than the band gap energy of the photocatalyst. This leads to the excitation of an electron from the valence band to the conduction band.



This creates an electron-hole pair and these charge carriers migrate to the surface of the catalyst to react with surface adsorbed oxygen and water to produce highly reactive oxygen species such as HO $\cdot$ and O₂⁻. Several semiconductors have been evaluated for photocatalysis (TiO₂, ZnO, Nb₂O₅, WO₃ and V₂O₅) but TiO₂ still remains the most used due to its multifaceted functional properties such as good chemical and thermal stability, strong mechanical properties, super-hydrophilicity, low excitation energy, good performance and low cost [9]. Numerous parameters affect the degradation kinetics of the pharmaceuticals by photocatalysis, these include catalyst loading, initial concentration of substrate, pH of the solution, water matrix, wavelength and light intensity and temperature [19].

The suspended photocatalytic process can be combined with membrane filtration to form a hybrid system called photocatalytic membrane reactors (PMR). Degradation of drugs occurs in the photocatalytic reactor and is combined with the membrane module to separate the catalyst and/or improve the effluent quality by rejecting some pollutants. There are

two classes of PMRs, in the first one, the photocatalyst is suspended in the reaction mixture and in the second class, the photocatalyst is immobilized on the membrane surface [2]. Some advantages of PMRs are that the photocatalyst can mineralize organics that cause membrane fouling, it keeps the catalyst in the reaction chamber and there can be control on the contact time between the molecules and the photocatalyst in the reactor [9].

1.2.5 Direct UV and Indirect UV/H₂O₂ Photolysis

After reviewing ozonation, Fenton oxidation, electrochemical oxidation and photocatalysis, the AOP used for this study, which is UV photolysis and UV/H₂O₂ indirect photolysis, will be introduced. Photolysis is the process by which molecules are degraded into smaller units through absorption of light. It has been shown to degrade many emerging contaminants [20]. There are two types of photolysis, direct and indirect.

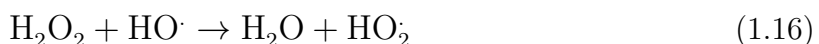
In direct photolysis, the contaminant itself absorbs the photons and is degraded. Therefore, the rate of direct photolysis strongly depends on the light absorption properties of the pharmaceutical, which depends on their chemical structure [21]. Important parameters which determine the efficiency of direct UV photolysis are the degradation rate constant, the molar absorption (or molar extinction) coefficient (ϵ) and the quantum yield (ψ) of the pharmaceutical compounds. The molar extinction coefficient represents the probability that a chemical species absorbs light at a given wavelength [21]. Therefore, a component with a higher molar extinction coefficient will be degraded more by direct photolysis than a component with a lower extinction coefficient. The quantum yield of a compound is the ratio between the number of molecules of that compound degraded and the number of photons absorbed by the solution [21].

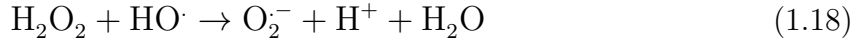
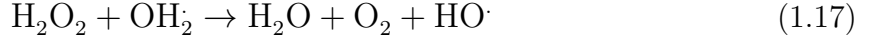
In indirect photolysis, degradation happens through reaction of the pollutant with a highly reactive species generated by photosensitizers. These are species which can absorb radiation to reach an excited state [22]. The most commonly used photosensitizer is hydrogen peroxide (H₂O₂). The addition of peroxide increases the amount of active radicals which increases the removal efficiency for species with poor UV absorption [8]. The addition of H₂O₂ has also allowed to reduce the required UV energy to degrade pharmaceuticals since the degradation is not dependant only on direct absorption by the pharmaceuticals [21].

During UV/H₂O₂ photolysis, peroxide linkage undergoes homolytic cleavage when it is irradiated by UV light having wavelength smaller than 280 nm to form HO $\cdot$ radicals [19]:



These hydroxyl radicals in turn react with the pollutants (1.15) to degrade them. However, these radicals can also react with hydrogen peroxide if it is in excess and create less reactive HO₂ $\cdot$ radicals (1.16) which appear to not contribute to pollutant degradation [14]. The following reactions can occur during H₂O₂ photooxidation [23][24].





The radical recombination reactions produce H_2O_2 which can be photolyzed again:



Several characteristics of H_2O_2 indirect photolysis make this AOP attractive compared to the previously discussed AOPs. First, UV/ H_2O_2 has been shown to have higher degradation efficiency than photocatalysis. Perisic et al. [25] showed that the complete degradation of 29.62mg/L of diclofenac was done in 2 min by UV/ H_2O_2 ($[\text{H}_2\text{O}_2]=16.78\text{mM}$) compared to 156 min for UV/ TiO_2 ($[\text{TiO}_2]=1.3\text{g/L}$). In another study, Miklos et al. [26] compared different AOPs based on electrical energy per order (E_{EO}) values (i.e. the electrical energy required to degrade a contaminant by one order of magnitude in 1m^3). They found that UV/ H_2O_2 and O_3 were less energy intensive ($< 1\text{kWh/m}^3$) than photo-Fenton (3kWh/m^3), electro-oxidation (40kWh/m^3) and photocatalysis ($> 100\text{kWh/m}^3$). Furthermore, UV and UV/ H_2O_2 systems have been successfully coupled with membrane filtration processes [8]. However, several factors have to be considered to optimize the process.

Factors Influencing the UV/ H_2O_2 Indirect Photolysis

The following factors can influence UV/ H_2O_2 treatments: the water composition, the UV light type and intensity, the H_2O_2 concentration, the rate of $\text{HO}\cdot$ radical formation, the chemical structure of the pollutants and the pH of the solution [27].

Water matrix The water matrix can influence the UV/ H_2O_2 process because it can contain substances such as dissolved organic matter (e.g. humic acids) and ions which can react with the $\text{HO}\cdot$ radicals. This is known as radical scavenging and causes a decrease in the amount of radicals available to react with the pollutants [14]. Organic matter, HCO_3^- and Cl^- are known radical scavengers [28] so they react with $\text{HO}\cdot$ and form less reactive species [29]. Besides the scavenging effect, organic matter can also hinder the direct photolysis of peroxide or pollutants by acting as an optical filter and absorbing the available UV light [15]. However, some matrix substances can also have positive effects because they could also act as photosensitizers. Nitrate and sulfate have been recognized as photosensitizers, meaning they can be photoexcited to generate additional $\text{HO}\cdot$ radicals [22][15].

Lamp type The type of lamp used during UV or UV/ H_2O_2 is another important parameter. The most commonly used UV lamps are low pressure (LP) and medium pressure (MP) mercury vapor lamps. LP lamps emit at 254nm and MP lamps emit a broad spectrum of light between 200-800nm. MP lamps have greater potential to directly degrade a broader range of pharmaceuticals because of their wide emission range [30].

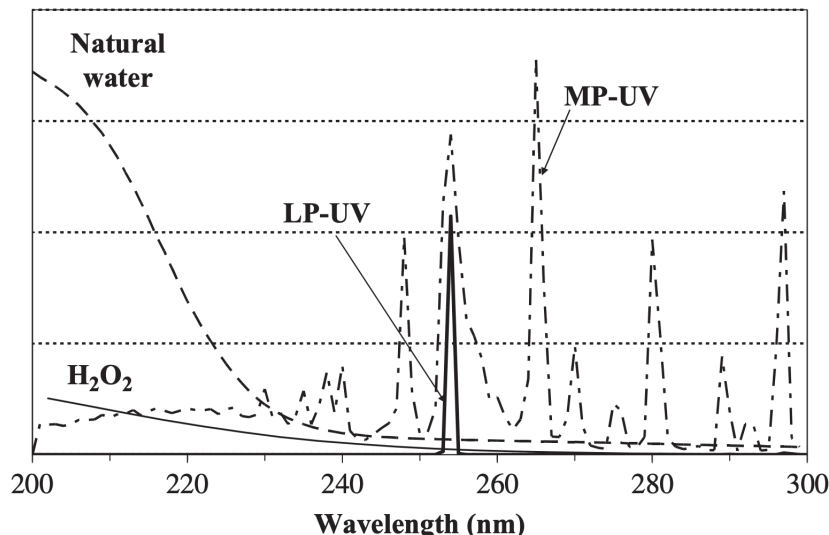


Figure 1.2: Water absorbance, H_2O_2 absorbance and MP and LP UV mercury lamp emissions. Data not scaled. Reprinted from [28].

However the issue with MP lamps is that they have a low efficiency, only about 12% of the input energy is converted to UV light [28]. LP lamps have higher energy efficiency than MP lamps however power output is lower so it requires more LP lamps for the same UV output as MP lamps [30]. In a UV/ H_2O_2 process, the efficiency depends on the homolysis of H_2O_2 . As can be seen on figure 1.2, the molar absorption coefficient of H_2O_2 at 254nm is low ($18.6\text{M}^{-1}\text{cm}^{-1}$ compared to $179\text{M}^{-1}\text{cm}^{-1}$ at 200nm) but because the background absorbance for natural waters at 254nm is also low, H_2O_2 absorbs light very efficiently at 254nm [28]. Moreover, the H_2O_2 absorbance is the highest at 200-230nm but it is also highest for background matter where the emission of MP is relatively low. This is why there is a higher hydroxyl radical yield with LP lamps than MP lamps in natural water. For high quality water, the amount of light absorbed by H_2O_2 is reported to be approximately equal for LP and MP lamps [28].

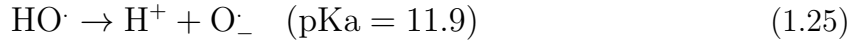
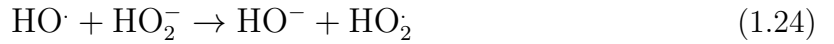
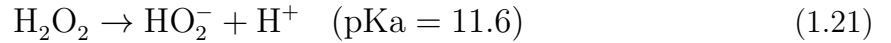
Other than mercury lamps, UV LEDs have emerged as new source for UV radiation. Their advantages compared to mercury lamps is that there is no need for toxic mercury disposal, they have unique peak emission wavelengths, they have a longer lifetime and a lower energy consumption [31].

H_2O_2 concentration By increasing the concentration of H_2O_2 , the oxidation process is improved up to a certain point. However, an excessive amount of H_2O_2 can inhibit the photolytic degradation of the organic compounds because of a competition between the hydroxyl radicals and the peroxide [13][32]. In this case, the scavenging reaction (equation 1.16) may become dominant. Zhang et al. [15] studied the influence of the H_2O_2 dose on the degradation of cyclophosphamide and 5-fluorouracil. They found that the degradation rate increased proportionally with the H_2O_2 dose until a concentration of 0.2mM but after this threshold the rates showed a plateau.

The degradation efficiency of the pollutants by $\text{HO}\cdot$ radicals depends on the second-

order reaction rate between the pollutant and $\text{HO}\cdot$ (k_{OH}), and the $\text{HO}\cdot$ exposure [26]. The exposure to $\text{HO}\cdot$ radicals depends on the concentration of radicals present in the water which is a function of the radical production rate and radical scavenging rate [33]. *para*-chlorobenzoic acid (pCBA) has been widely used as molecular probe to evaluate the exposure of pollutants to $\text{HO}\cdot$ radicals. The reason for this is because it essentially does not undergo direct photolysis at 254nm (LP lamp emission) [27]. Therefore, this molecule allows to optimize the H_2O_2 concentration because it is only degraded by $\text{HO}\cdot$ radicals.

pH Zhang et al. [15] reported that the degradation rates of cytostatic drugs is significantly decreased in a basic solution while there were no significant variations in the degradation efficiency in acidic, neutral and slightly basic conditions (pH 3-8). The decrease of degradation efficiency in high pH could be attributed to three reasons [15][34]. First, H_2O_2 dissociates to HO_2^- and H^+ (reaction 1.21) or self-decomposes to H_2O and O_2 (1.22) at high pH. Second, the high concentration of OH^- as well as HO_2^- can scavenge $\text{HO}\cdot$ radicals (1.23 and 1.24). Third, $\text{HO}\cdot$ radicals can dissociate to H^+ and less reactive $\text{O}\cdot^-$ (1.25).



As was described above, one of the drawbacks of UV/ H_2O_2 process is that H_2O_2 has a small extinction coefficient 254nm [18]. Therefore, the concentration of peroxide has to be quite high for an efficient generation of $\text{HO}\cdot$ radicals but not all of it is photolyzed. As a consequence, 75 to 90% of the influent H_2O_2 remains after UV photolysis. This residual H_2O_2 should be quenched since it can cause toxicity or create toxic by-products [35]. A quenching agent which is widely used is catalase [36]. Catalase is a liver enzyme which breaks down the hydrogen peroxide into water and oxygen.

1.3 Membrane Filtration

Another technology that has been widely studied for the removal of micro-pollutants from wastewater is membrane filtration.

1.3.1 General Mechanism

Pressure-driven membranes are an interesting wastewater treatment technology due to their efficiency from a technical, economical and ecological point of view [37]. The general working principle is shown on figure 1.3. The water to be treated (feed) is separated into the permeate stream which goes through a semi-permeable membrane and the retentate stream which contains the rejected components from the water.

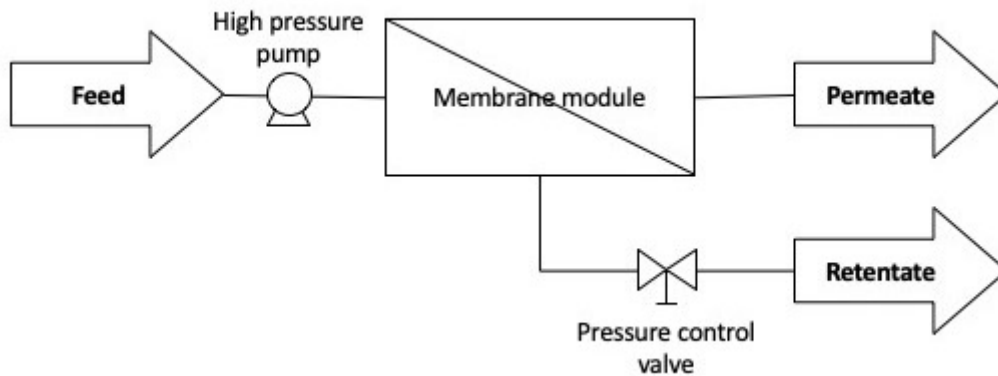


Figure 1.3: Functioning of pressure driven membrane processes.

Porous membranes use pressure as driving force and operate on a size exclusion mechanism. This means that at least one component is rejected and the others pass through the membrane. Pressure-driven membrane processes include four major processes which can be divided by the pore sizes, namely, microfiltration (MF), ultrafiltration (UF), nanofiltration (NF) and reverse osmosis (RO). Figure 1.4 provides an overview of these different processes.

Microfiltration is the least restrictive membrane filtration process. It uses porous membranes with pore sizes in the range of 0.1 to 1 μm and the operating pressure is below 1 bar. Microfiltration membranes are often used as pretreatment before other membranes to avoid fouling [38]. They can remove nondissolved matter such as suspended solids, large macromolecules and bacteria. Ultrafiltration membranes have a pore size between 2 and 100nm and the operating pressure can go up to 6 bar. Ultrafiltration is competitive with microfiltration because it can operate at similar flux but with better removal [38]. Nanofiltration membranes have pore sizes of 1nm and below. They operate on size exclusion but also on a solution diffusion principle, for instance, monovalent ions will diffuse through the membrane and dissolved organic matter and divalent ions will be blocked. The operation pressure is 5-15 bar. Reverse osmosis membranes are non-porous membranes and thus they on a solution diffusion principle. RO membranes can reject

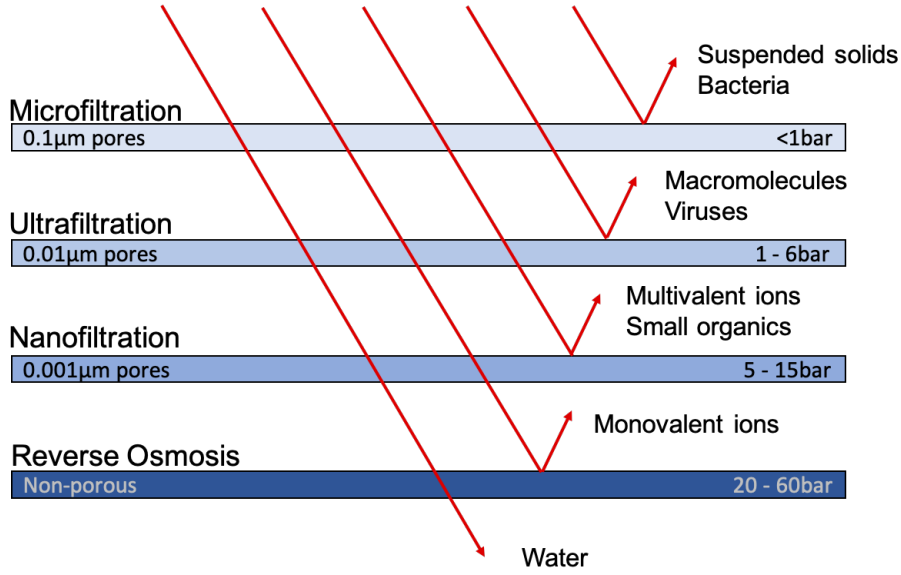


Figure 1.4: Overview of the different pressure-driven membrane processes. Modified from [38].

monovalent ions and are highly used for desalination of water. Their operating pressure is around 40-60 bar and up to 100 bar for high pressure reverse osmosis systems [37].

Since it is difficult to obtain an accurate pore size distribution of the membranes, they are often characterized by their molecular weight cut-off (MWCO) which is the smallest molecular weight (MW) of a solute that is rejected at 90% by the membrane. Table 1.5 summarizes the range of MWCO for each membrane process.

Table 1.5: MWCO range for MF, UF, NF and RO filtration processes [39].

Membrane process	MF	UF	NF	RO
MWCO [kDa]	100-1,000	1-300	0.2-1	0.05-0.5

1.3.2 Operating Mode

Pressure driven membranes can be operated in a dead-end mode or a cross-flow mode (see figure 1.5). In the dead-end mode, the feed stream enters vertically towards the membrane surface. In cross-flow mode, the feed flows tangentially to the membrane surface, and there are two streams leaving the membrane module, one is the retentate flow and the other is the permeate flow (figure 1.3). For most applications, especially nanofiltration and reverse osmosis, the dead-end mode is impractical and uneconomical because rejected solutes accumulate on the membrane surface (fouling) which decreases the flux. The tangential flow in the cross-flow mode can help to shear away the accumulated rejected species to limit the cake layer and hence maintain the permeate flux. [40]. However, the dead-end mode is simple to set-up so it is highly used for lab applications to characterize the membranes.

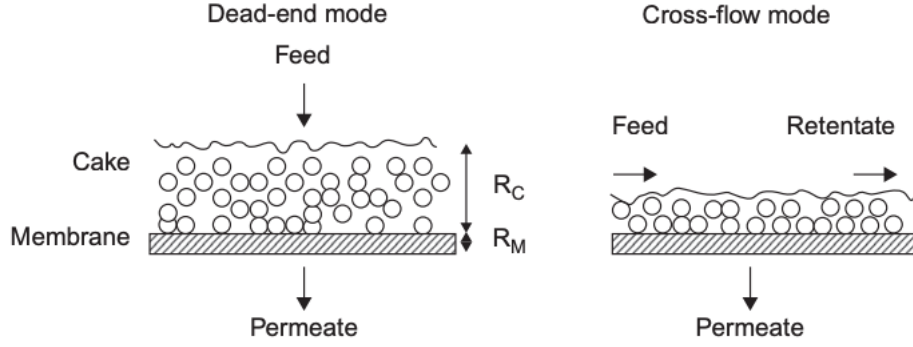


Figure 1.5: Dead-end and cross-flow filtration mode. Reprinted from [40].

1.3.3 Performance

Membrane properties can be evaluated by different parameters: the rejection (%), the recovery rate (or water yield) (%), the permeate flux ($\text{L}/\text{m}^2\text{h}$) and the permeability of the membrane ($\text{L}/\text{m}^2\text{hbar}$). The rejection (R) is the amount of solids in the feed that is rejected and is an intrinsic property of the membrane [41]. The rejection for a component is calculated as follows:

$$R(\%) = \frac{C_F - C_P}{C_F} \cdot 100 \quad (1.26)$$

where C_F is the initial concentration of the component in the feed and C_P the concentration of the component in the permeate.

The recovery is the amount of feedwater that passes through a membrane and is defined as:

$$Recovery(\%) = \frac{Q_P}{Q_F} \cdot 100 \quad (1.27)$$

where Q_P and Q_F are the permeate and feed volumetric flowrates.

The permeate flux (J) is the volume of permeate that passes through a unit area of membrane per unit time:

$$J[\text{L}/\text{m}^2\text{h}] = \frac{\Delta V}{\Delta t} \frac{1}{A} \quad (1.28)$$

where A [m^2] is the active area of the membrane, ΔV the amount of volume that passes during a time Δt .

Finally the permeability (P) is the permeate flux (J) divided by the transmembrane pressure (TMP):

$$P[\text{L}/\text{m}^2\text{hbar}] = \frac{J}{TMP} \quad (1.29)$$

1.3.4 RO and NF Membrane Filtration for Wastewater Treatment

It has been shown that the most efficient membranes to remove pharmaceuticals and other contaminants from water are nanofiltration and reverse osmosis membranes [42] because the size and molecular weight of most pharmaceuticals is smaller than the molecular weight cut-off of UF and MF membranes. Reverse osmosis and nanofiltration membranes are semi-permeable membranes which retain certain solutes depending on the pore size, surface charge and chemical affinity [43].

Reverse osmosis membranes can reject low molecular weight organics and other small uncharged compounds as well as monovalent and divalent ions. The pressure applied needs to be higher than the osmotic pressure. Indeed, the water flux through the membrane is given by [38]:

$$J_v = L_p(\Delta P - \Delta\pi) \quad (1.30)$$

Where L_p is the water permeability of the membrane, ΔP is the applied pressure difference and $\Delta\pi$ the osmotic pressure difference.

Nanofiltration membranes differ from reverse osmosis because they have larger pores than reverse osmosis membranes. They are designed to remove compounds such as multivalent ions or organic contaminants but only partially retain monovalent ions. NF membranes can work at lower pressure because the components that pass through the membrane do not add to the osmotic pressure [42]. They can also operate at higher transmembrane flux. The rejection of the pharmaceuticals during NF and RO membrane filtration is quite complex, thus, there are several variables that influence the separation.

Membrane Materials

Today, RO and NF membranes are usually asymmetric polymeric membranes [40]. Asymmetric membranes have a selective skin layer on top of the membrane body. The membrane body is there just as a support layer and is usually void [40]. Polymeric membranes are relatively cheap, easy to manufacture and available in a wide range of pore sizes. However, they cannot resist to extreme operating conditions. The most widely used NF and RO membranes are polyamide thin film composite (TFC) membranes [44]. As illustrated on figure 1.6, such membranes consist of a top active layer made of polyamide and a microporous support layer typically made of polysulfone [45].

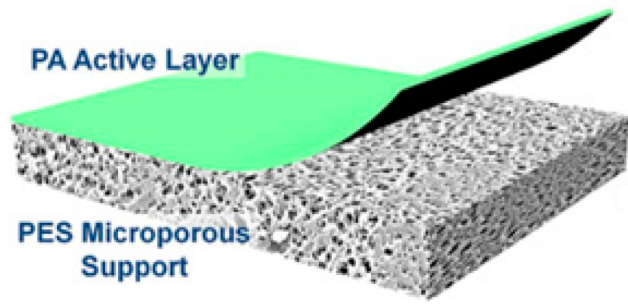


Figure 1.6: Polyamide thin film composite membranes [45].

Rejection Mechanisms

Three different rejection mechanisms in nanofiltration and reverse osmosis membrane filtration have been identified, these are size exclusion (or steric hindrance effect), hydrophobic interaction and electrostatic interaction [9].

Size exclusion (steric hindrance) Size exclusion is simply a sieving mechanism where the components that are larger than the membrane's pore size are removed. High MW compounds should therefore be highly rejected. However, the hydrophobicity and the charge of the solutes and the membrane may influence the rejection. Hydrophobic solutes can interact and adsorb on the hydrophobic membrane surface. Thus organics with MW higher than MWCO of the membrane could diffuse through the membrane. [46]. Also, if a compound is negatively charged, it is rejected by the negatively charged membrane and thus the rejection is considered electrostatic [47]. For these reasons, only hydrophilic neutral and positively charged pharmaceuticals are rejected by size exclusion in NF and RO membranes [9].

Hydrophobic interactions Most polymeric NF and RO membranes are hydrophobic in nature, characterized by their large contact angles [9]. Hence, hydrophobic pharmaceuticals and other organics can be rejected due to adsorption onto those membranes. However, this is a temporary mechanism for low MW solutes because after saturation, they can still diffuse through the membrane pores whereas high MW solutes would not. Therefore, hydrophobic solutes are ultimately still rejected by a size exclusion mechanism. The affinity of the solute for the membrane can be expressed through the octanol-water distribution coefficient (K_{ow}). If the K_{ow} value increases, the hydrophobicity of the compound increases so the interactions are stronger [42].

Electrostatic interactions Polymeric TFC membranes have been shown to be negatively charged at neutral pH due to deprotonation of acid or amine functional groups at the membrane surface [9]. These functional groups are intentionally incorporated during the manufacturing stage to enhance the selectivity and permeability of NF and RO membranes [47]. Negatively charged solutes are therefore highly rejected due to electrostatic repulsion. For positively charged hydrophilic solutes, the rejection is governed by the electrostatic attraction between the membrane and the solute. Electrostatic attraction between the positively charged solute and negatively charged membrane can create a concentration polarization layer. Concentration polarization is an accumulation of retained solutes at the membrane surface [41]. Again, as for hydrophobic solutes, adsorbed positively charged solutes on the membrane surface can still diffuse through the membrane if their MW is smaller than the MWCO.

Factors Affecting the Rejection of Pharmaceuticals

The main factors that influence the rejection mechanisms of NF and RO membranes are the chemistry of the feedwater, of the solute and the membrane properties.

Feedwater chemistry The characteristics of the feedwater that influence the rejection efficiency are the pH of the water, the amount and nature of the natural organic matter and the ionic strength of the feedwater [48]. The pH of the water will determine the charge of the membrane surface and of the pharmaceuticals which can lead to rejection due to electrostatic repulsion. The presence of NOM can increase fouling of the membrane. Thus, it can affect the rejection by changing the morphology of the membrane, acting as an additional barrier or bond with solutes to increase their size [9]. Lastly, the presence of divalent inorganic cations such as Ca^{2+} was shown to alter the membrane surface charge, hence the rejection of pollutants [48].

Solute properties The molecular weight, size, geometry, hydrophobicity, charge and acid-base character of the solute will affect the rejection during the NF or RO process due to the rejection mechanisms discussed above.

The molecular weight of a solute can predict the rejection only if it is non-charged and hydrophilic. However, several studies have shown that molecular size parameters (i.e. molecular width, Stokes radii, molecular mean size) and the geometry are better predictors of steric hindrance effects for the rejection of solutes by NF membranes than their molecular weight [42]. The charge of the solute can be expressed by the acid dissociation constant (pKa) of the solute. Consequently, the charge depends on the pH of the water. Hydrophobic compounds will adsorb onto the hydrophobic membrane surface. The octanol-water distribution coefficient (K_{ow}) best describes the hydrophobicity of a component, a solute with a $\log K_{ow} < 2$ is considered to be hydrophobic [49].

Membrane properties Several membrane properties have been found to influence the rejection of a solute including the molecular weight cut-off, the desalting degree, porosity, hydrophobicity and surface charge [9]. The MWCO concept means that larger molecules will be rejected more often than a smaller molecule. Moreover, a bigger molecule will diffuse through the pores more slowly than a smaller molecule [42]. However, the MWCO of a NF membrane only poorly correlates with the rejection of compounds studied [38]. Therefore, another parameter used to describe the membrane is the salt rejection. The desalting degree is the percent rejection of a 500–2000 mg/L sodium chloride or magnesium sulfate solution [42]. Porosity, expressed as pore density or effective number of pores, has also been used as parameter to determine membrane performance [48]. The surface charge of TFC membranes is usually negative due to the functional groups on the membrane. A change in pH can dissociate functional groups and thus have an effect on the charge of the surface. Most membranes become more negative as the pH increases [50].

Fouling

Fouling is defined as the process which results in a loss of performance of the membrane due to deposition or adsorption of foulants on the membrane surface or pores. It is one of the main drawbacks of membrane filtration [41]. Fouling rate can depend on the nature and concentration of solutes and solvents, the membrane type, pore size distribution, surface characteristics and the operating conditions (recovery rate and cross flow velocity)

[51]. Fouling can happen through adsorption, chemical interactions, cake formation, or pore blocking by particles [40].

Because of the presence of colloids and natural organic matter (NOM) in municipal wastewater, there can be an important amount of fouling. Fouling decreases the permeate flow which requires an increase in feed pressure to compensate [38]. A mitigation strategy is regular physical or chemical cleaning. This is why pre-treatments are done in order to decrease the quantity of organic matter in the membrane feedwater [9]. Fouling is usually divided into 4 categories: organic fouling, colloidal fouling, scaling and biofouling [51].

Fouling of organic matter is thought to be mainly caused by the adsorption of organic matter on the membrane [52]. NOM can either change the properties (charge, hydrophobicity, morphology) of the membrane surface, they can act as additional barrier or bond with solutes and increase their size [53]. Fouling due to colloids happens either by the accumulation of the colloidal particles on the membrane which creates a cake layer, or by pore blocking. Scaling (inorganic fouling) is the precipitation of salts on the membrane surface. Since NF and RO membranes retain ions, their concentration increases at the feed side which can exceed the solubility limit, leading to precipitation on the membrane [52]. Biofouling is the fouling of a membrane due to organisms such as bacteria and fungi. It is a process which involves the formation of a biofilm on the surface of the membrane [52]. It can also reduce the permeate flux. Even though a fouling layer decreases the water flux, it has been shown that it can result in an increase or a decrease in retention of solutes [54]. In fact, since fouling alters the membrane surface characteristics, such as charge and hydrophobicity, the rejection mechanisms can change.

NF and RO for Cytostatic Drug Removal

The use of NF and RO membranes to remove pharmaceuticals has been investigated, however not many focused on anti-cancer drugs. Wang et al. [49] studied the removal of cyclophosphamide by NF and RO from a secondary effluent. They found that the rejection for the RO membrane was more than 90% but much lower for the NF membrane (20-40% in milli-Q water). The rejection increased when the matrix was a membrane bioreactor effluent (60%) due to fouling and interaction between CP and water components. Verliefde et al. [55], found removals of more than 75% for a great number of pharmaceuticals with two different NF membranes. They reported that rejection was mainly influenced by charge effect, negatively charged solutes being better removed than uncharged solutes, which are, in turn, better removed than positively charged solutes. Acero et al. [56] studied the removal of 11 emerging contaminants by NF membranes and found a retention above 70% for most of the pollutants. They reported that size exclusion and electrostatic repulsion of negative species were responsible for the rejection. The rejection values were similar in ultrapure water and in a secondary effluent. In a work from our team accepted for publication to Separation and Purification Technology, Cristovao et al. [57] studied the removal of four anti-cancer drugs in laboratory grade water, synthetic urine and real secondary effluent by two different NF membranes (Desal 5DK and NF270). They found that the Desal 5DK membrane presented the highest rejections (>89% for all drugs) and that there was no significant influence of the water matrix.

1.4 NF and RO Membrane Retentate Treatment by AOPs

The use of membrane processes to remove pharmaceuticals from wastewater has rapidly increased because a high quality permeate stream is obtained. However, membrane filtration generates a secondary stream which has a high pollutant concentration and hence needs additional treatment. Therefore, the treatment of membrane retentates by advanced oxidation processes has been studied. This combines the advantages of each technology and removes the drawbacks of one another [9]. Membrane filtration is an affordable and sustainable technology for water reuse and does not degrade the pollutants so no byproducts are created. However, its main problem is membrane fouling. Moreover, the concentrate needs to be properly treated before disposal [9]. On the other hand, AOPs degrade the pollutants and are versatile. However, they do not work as efficiently for the treatment of large volumes with a low concentration of pollutants [58]. Furthermore, AOPs can generate intermediates that can be more harmful than the parent compound [59]. Membranes and AOPs can be coupled in different ways. AOPs can be used as pretreatment to degrade organic matter in order to minimize membrane fouling. They can also be used as post-treatment to remove the non rejected pollutants from the permeate and the pollutants in the retentate stream.

This work will focus on the use of AOPs as post-treatment for membrane filtration. As figure 1.7 illustrates, the membrane concentrates the pollutants to a level that can be efficiently treated by AOPs.

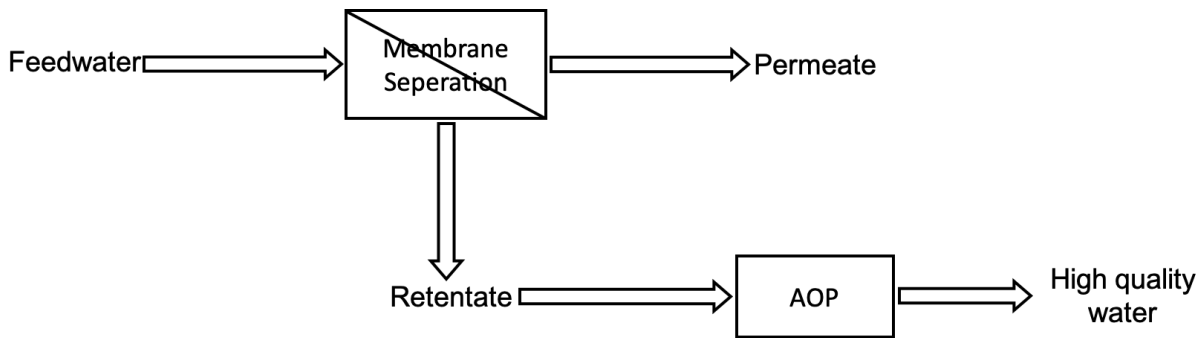


Figure 1.7: Coupling of membrane filtration and AOP.

Several AOPs have been studied as post-treatment stage to complement the membrane filtration process in order to treat the membrane retentate stream. These AOPs include ozonation, Fenton oxidation, photocatalysis, electrochemical oxidation and UV/H₂O₂ photolysis.

Miralles-Cuevas et al. [60] studied the treatment of NF retentate by advanced oxidation processes, including photo-Fenton and ozonation for removal of microcontaminants. They compared the ozonation of the direct WWTP effluent to the ozonation of the concentrated NF retentate. The main difference was that there was a higher ozone consumption and treatment time due to higher dissolved organic matter and salt concentration in the

NF retentate. Also the rate constants of the contaminants were slower in the retentate. However, the volume to be treated by ozonation is 75% less when combined with NF filtration which overpowered the detrimental effects. They concluded that membranes and ozonation could be combined to completely degrade microcontaminants. In another study, Bagastyo et al. [61] studied the removal of organics and organic nitrogen by UV/H₂O₂ from an RO concentrate. They found that a high removal of COD (50-55% removal) was obtained but there was no complete mineralization. The low mineralization was attributed to the fact that there was more inorganic carbon and salt in the RO retentate which reduced the oxidation rate of organics to the final products. The residual organics that were left had small molecular weight and were more biodegradable. Justo et al. [62] studied the removal of 11 pharmaceuticals detected in an RO brine from a municipal WWTP by UV/H₂O₂. They found that a dose of 0.54 mg_{H₂O₂}/mg_{TOC} was able to completely eliminated the pharmaceuticals after 61.7 min. The biodegradability ratio (BOD₅/COD) of the treated effluent was 0.3. Therefore, they suggested that adding a biological treatment to remove the remaining organic matter after chemical oxidation would be cost-effective.

1.5 Ecotoxicity of Anti-Cancer Drugs

Anti-cancer drugs are designed to kill cancerous cells by interacting directly or indirectly with the DNA. Therefore, the presence of these genotoxic drugs in the environment presents a risk to animals and humans. However, the risks are not very clear because of the limited toxicological and ecotoxicological data for long-term exposure to trace amounts of anti-cancer drugs on non-target organisms [3]. Certainly, given the purpose of anti-cancer drugs, genotoxicity assessments should be incorporated into environmental risk assessments [3]. Furthermore, many anti-cancer drugs are also transformed through human metabolism so there is a wide mixture of drugs and their metabolites in the environment. Also, transformation products can be present in treatment effluents [12] since a complete mineralization of the pharmaceuticals is not always achieved or can be uneconomical [27]. Some strategies have been developed to assess the toxicity of drugs, their metabolites and their transformation products in the environment but they are usually lab-scale simulations. The issue with the current strategies is that metabolites and transformation products are usually not identified and characterized so it is not possible to determine which compound is responsible for the toxicity [3].

In order to compare the toxicity of different AOP effluents, acute toxicity tests have been used. Even though the existing requirements for performing the environmental risk assessment of human pharmaceuticals favor chronic toxicity assessments [63][64], the basic knowledge about pharmaceuticals' acute toxicity is crucial [65]. Acute toxicity assessments have been carried out on aquatic organisms such as marine bacteria (*Vibrio fischeri*), algae (*Raphidocelis subcapitata*), crustaceans (*Daphnia magna*) and higher plants (*Lemna minor*). They have multiple advantages including a short test duration, they are sensitive, cost-effective and easy to operate. These tests allow measuring the EC_{50} values of the compounds that are evaluated. The EC_{50} is the concentration of the drug which induces a response halfway between the baseline and maximum after a specified exposure time [66]. The EC-Directive 93/67/EEC [67] states that, regarding aquatic organisms, compounds with $EC_{50} < 1\text{mg/L}$ are considered very toxic; EC_{50} between 1 and 10mg/L are considered toxic; EC_{50} between 10 and 100mg/L are considered harmful and $EC_{50} > 100\text{mg/L}$ are considered not harmful [57].

Bialk-Bielinska et al. [65] performed acute toxicity assessments of six among the most used anti-cancer drugs (5-fluorouracil, ifosfamide, cyclophosphamide, methotrexate, imatinib and tamoxifen) on different aquatic organisms. They found that the most toxic compound towards the tested aquatic organisms were 5-FU (highly toxic to algae, $EC_{50} = 0.075\text{mg/L}$), MET and TAM (highly toxic to duckweed; $EC_{50, \text{MET}} = 0.08 - 0.16\text{mg/L}$, $EC_{50, \text{TAM}} = 0.18 - 0.23\text{mg/L}$). They found that imatinib was the only one that was toxic to *V. fischeri* with an EC_{50} value of 23.06mg/L . Other studies have evaluated the acute toxicity of effluents after advanced oxidation processes. Plahuta et al. [68] studied the efficiency of AOPs to remove bisphenol A. They found that 6 hours of $\text{UV}/\text{H}_2\text{O}_2$ photolysis was the most efficient to remove bisphenol A compared to a 6-hour treatment by photolysis and photocatalysis with TiO_2 . However, the $\text{UV}/\text{H}_2\text{O}_2$ effluent showed the highest inhibition to *V. fischeri*. On the other hand, Governo et al. [69] found that after treating a solution containing 0.38mM of 5-fluorouracil by $\text{UV}/\text{H}_2\text{O}_2$ during 8h, the effluent became less toxic

to *V. fischeri* than the feed. Miralles-Cuevas et al. [60] found that the treatment of an NF concentrate by ozonation increased the acute toxicity on *V. fischeri* and *D. magna*, which could be due to toxic by-products or other wastewater components. Chronic toxicity was evaluated as well. *D. magna* adaptation was observed and reduction of toxicity was shown in *S. capricornutum*.

Chapter 2

Objectives

Now that the issue about the presence of anti-cancer drugs in the environment and some solutions have been addressed, the objectives of this master thesis can be described. In this section, the research questions for this work will be defined.

The general objective of this master thesis is to study the performance and feasibility of coupling membrane filtration with an advanced oxidation process. More precisely, the treatment of reverse osmosis and nanofiltration retentates by a UV/H₂O₂ treatment. In order to evaluate this technology, the following research questions were established and will be answered throughout the rest of this work.

Regarding the UV/H₂O₂ part of the treatment:

1. What is the optimal concentration of H₂O₂ to degrade anti-cancer drugs in a UV/H₂O₂ photoreactor in laboratory grade water (LGW) and secondary WWTP effluent (WWeff) matrices?

For the membrane filtration part of the treatment:

2. Do nanofiltration and reverse osmosis membrane filtration efficiently reject anti-cancer drugs from a WWeff matrix?

For the combination of membrane filtration and UV/H₂O₂ indirect photolysis:

3. Is the degradation of anti-cancer drugs by UV/H₂O₂ treatment of a NF or RO retentate efficient compared to UV photolysis and UV/H₂O₂ treatment of the direct secondary WWTP effluent?
4. Do these treatments decrease the acute toxicity on *V. fischeri* of the treated water compared to the feedwater?
5. Based on experimental results, what is the most economical solution between four different configurations: UV photolysis, UV/H₂O₂ indirect photolysis, the combination of RO with UV/H₂O₂ and the combination of NF with UV/H₂O₂? In other words, for these four configurations, what is the cost required to decrease the drug concentration by one order of magnitude in 1L?

Chapter 3

Materials and Methods

3.1 Materials

3.1.1 Water Matrices

The experiments done in pure water were done in laboratory grade water which came from a Milli-Q system. The other experiments were conducted in a wastewater effluent which was a secondary effluent from the Louvain-la-Neuve WWTP. The characterization of this water is given in table 3.1 and its pH was measured to be 7.5. This water was stored in a refrigerator at 4°C and used within 10 days after sampling.

Table 3.1: Secondary effluent composition from Louvain-la-Neuve wastewater treatment plant.

Compound	BOD	DOC	SO ₄ ²⁻	Cl ⁻	NO ₃ ⁻	PO ₄ ³⁻	HCO ₃ ⁻	Ca ²⁺
Concentration [mg/L]	0.5	10.7	63.4	444.3	2.1	2.6	265	101

3.1.2 Anti-cancer Drugs and Chemicals

The different anti-cancer selected for the experiments are presented in table 3.2 along with their physico-chemical properties. They are among the most used anti-cancer drugs in Europe [12]. All drugs were purchased by Sigma-Aldrich.

Table 3.2: Anti-cancer drugs and their physico-chemical properties.

Drug	Abbreviation	Mechanism of action	Molecular weight [g/mol]	Charge at pH 7.5 [70]	log K_{ow} [71]
Methotrexate	MTX	Antimetabolite	454.44	Negative	-1.85
Capecitabine	CAP	Antimetabolite	359.35	Neutral	1.04
5-Fluorouracil	5-FU	Antimetabolite	130.08	Neutral, Negative	-0.89
Imatinib	IMT	Protein-tyrosine kinase inhibitor	493.60	Positive	3
Cyclophosphamide	CP	Alkylating agent	261.09	Neutral	0.63

The H_2O_2 (30% wt in H_2O) and pCBA for the UV/ H_2O_2 experiments were purchased from Sigma-Aldrich. The enzyme catalase which was used to quench H_2O_2 before toxicity experiments was also purchased from Sigma-Aldrich.

3.1.3 Membranes

Nanofiltration and reverse osmosis membranes were used for the filtration experiments and were provided by Sterlitech and manufactured by GE Osmonics [72]. Both were flat-sheet membranes of size 305 x 305mm. Their properties are summarized in the following table.

Table 3.3: RO and NF membrane properties.

Membrane	Abbreviation	Material	MCWO [Da]	Effective Area [m ²]
Nanofiltration	NF-DL	Polyamide-TFC	150-300	0.0025
Reverse Osmosis	RO-SE	Polyamide-TFC	-	0.0025

3.2 Experimental Procedures

3.2.1 Membrane Characterization

The permeability of a membrane is an important parameter to evaluate the efficiency of the filtration process. The permeability was measured through a gravimetric method. The flux of the permeate was determined by measuring the weight of permeate collected in a beaker during a certain amount of time. The weight was converted in volume using the density of water (1kg/L). The volume flow of the permeate is thus given by the following relation:

$$\dot{V}_P[\text{L/h}] = \frac{m_w \cdot 3600}{1000 \cdot \rho_w \cdot t} \quad (3.1)$$

where m_w [g] is the weight of permeate measured during a time t [s], ρ_w is the water density, 3600 is the conversion factor from s to h and 1000 to convert g to kg. The permeability can then be calculated through equation 1.29.

3.2.2 Membrane Filtration Experiments

For the filtration experiments, the Armfield FT17 Cross Flow Membrane Filtration system was used and is presented on figure 3.1. The filtration module consists of a feed vessel of a capacity of 1L (1) and a high-pressure piston pump (3) which brings the feed to the filtration assembly (2). The pressure can be regulated with a backpressure valve (V1). The retentate is recirculated in the feed tank and the permeate is collected in a beaker. The retentate can be collected at the drain valve (V2). The temperature was kept at a constant temperature with a cooler which was connected to the feed tank. The pressures for the NF and RO membranes were set to 15bar and 35bar respectively.

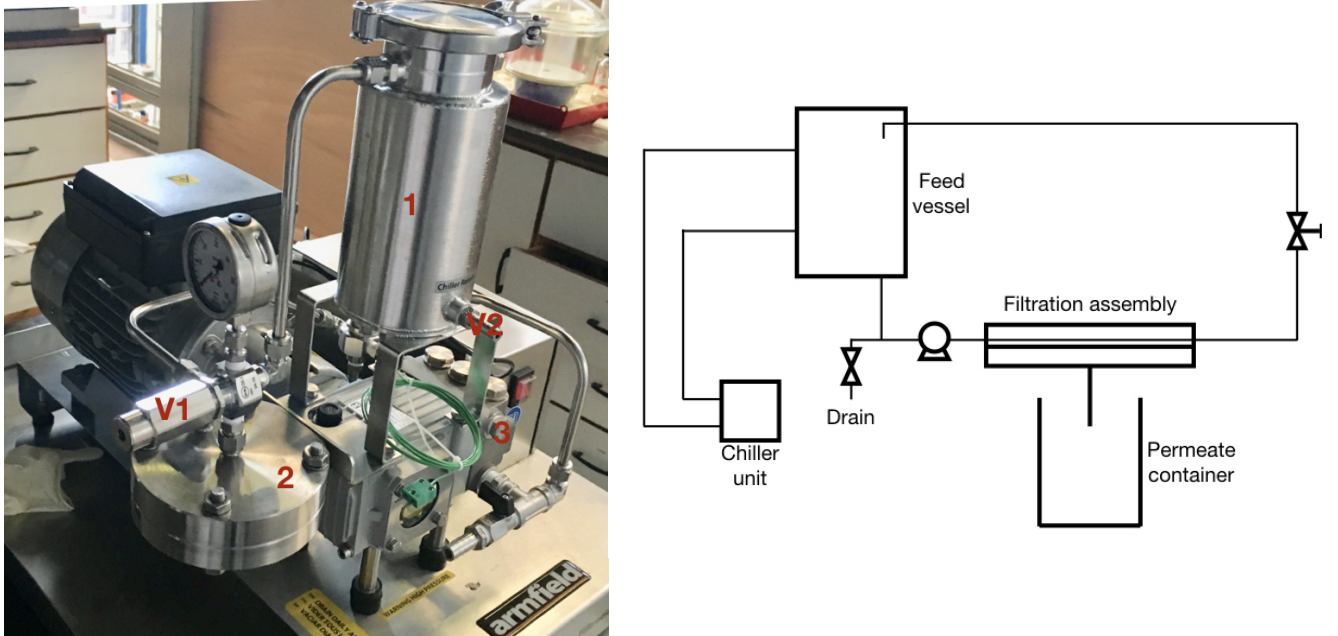


Figure 3.1: Membrane filtration experimental set-up.

For the drug filtration experiments, a 1L feed solution was prepared by spiking the different drugs at $500\mu\text{g/L}$ in a wastewater matrix. The solution was added progressively to the feed tank and filtered through the membrane with a recovery rate (Q_P/Q_F) of 80%. Before and after each drug filtration experiment, the pure water permeability was measured to delineate the influence of fouling on the membrane filtration. A new membrane was first always filtered with LGW until the permeate flux was stable. Samples of the feed, permeate and retentate were collected in order to determine the rejection of the different drugs and also analyze their toxicity. The rejection of the drugs was calculated as follows:

$$R(\%) = 1 - \frac{C_P}{C_F} \cdot 100 \quad (3.2)$$

The percentage of adsorbed drugs on the membrane was also calculated and was determined from a mass balance:

$$\text{Adsorbed}(\%) = \frac{C_F \cdot V_F - (C_P \cdot V_P + C_R \cdot V_R)}{C_F \cdot V_F} \cdot 100 \quad (3.3)$$

3.2.3 UV/H₂O₂ Experiments

The experimental set-up for the advanced oxidation experiments consists of an annular batch photoreactor of a capacity of 1.2L covered in aluminum foil to prevent exposure of personnel to harmful UV rays. Two LP mercury UV lamps (Helios Quartz 10W), which essentially emit monochromatic UV light at 254nm were symmetrically placed at the center of the reactor. LP lamps were used for the reasons described in section 1.2.5, namely the LP lamps efficiently produce HO[•] radical in natural water and pCBA is not degraded by UV-254nm light. The reaction solution was mixed using a magnetic stirrer at a rate of 500rpm. A cooler was connected to the reactor to keep the temperature at 20±1°C. A temperature probe was placed in the reactor to monitor the temperature.

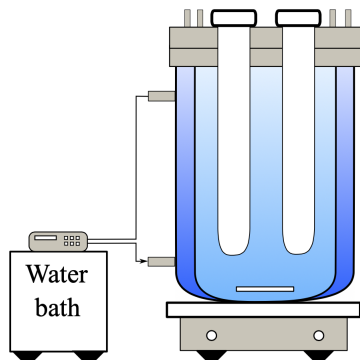


Figure 3.2: UV/H₂O₂ indirect photolysis experimental set-up.

H₂O₂ Concentration Optimization

The first experiments used pCBA in order to optimize the H₂O₂ concentration in pure water and wastewater needed for the anti-cancer drug degradation. Both H₂O₂ and pCBA were stored in the dark at 4°C and -20°C respectively. A 1.2L reaction solution was prepared in the photoreactor. The pCBA concentration was 50μM and the peroxide dose varied as follows: 0, 25, 50 and 100mg/L. First 1.1L of LGW was added in the reactor, then the H₂O₂ and the pCBA, and lastly the remaining 0.1L of water was added. The lamps were switched on right at the start of each experiment. Samples of 1mL were collected with a syringe at times 0, 3, 6, 9, 12, 15 min and a control sample at 15 minutes. The control sample corresponds to a sample of the feed solution which was kept in the dark throughout the duration of the experiment. The syringe was rinsed 3 times between each sample. Samples were stored in the dark at -20°C before the HPLC-UV analysis was performed.

Anti-Cancer Drug Degradation

To study the photo-degradation of antineoplastic drugs, a similar experimental methodology was done as for pCBA degradation. The drugs were spiked in a wastewater effluent at 500μg/L and the optimal H₂O₂ concentration was added. Samples were collected at times 0, 2.5, 5, 7.5, 10, 15, 30, 45 and 60 minutes, as well as a control sample after 60 minutes.

Those samples were stored at -20°C before analysis by the UPLC-MS and assessment for toxicity.

3.2.4 Retentate Treatment by UV/ H_2O_2

When combining membrane filtration with UV/ H_2O_2 degradation, the retentate of the membrane filtration was collected and this retentate was treated in the photoreactor by a UV/ H_2O_2 treatment. A 6L feed solution was prepared with drugs spiked at $500\mu\text{g/L}$ in WWeff. The recovery rate was set to 80% in order to collect 1.2L of retentate. Feed, retentate and permeate samples were taken to be analyzed. The collected retentate was then put in the photoreactor and H_2O_2 was added. The oxidation experiment lasted for 1 hour and samples were taken at 0, 2.5, 5, 7.5, 10, 15, 30, 45 and 60 minutes as well as a control sample at 60 minutes.

3.3 Analytical Methods

3.3.1 HPLC-UV

The analysis and quantification of pCBA in the collected samples was done by High Performance Liquid Chromatography (HPLC) coupled with UV detection. This was done using the Agilent 1200 series HPLC system. The column used was a C-8 (4.6x150mm, $3.5\mu\text{m}$). $5\mu\text{L}$ of the sample is taken and sent the elution column at a speed of $0.6\mu\text{L/s}$. The column was set at a temperature of 30°C and the pressure in the column was 90bars. The mobile phase was a combination of 2 solvents: 20% of solvent A (NaH_2PO_4 25mM) and 80% of solvent B (MeOH 95% in H_2O). The detection of pCBA was done with UV at 240.8nm. When the samples to be analyzed were in a WWeff matrix, they were centrifuged in order to remove the organic matter which can interfere for the detection.

3.3.2 UPLC-MS

For the quantification of anti-cancer drugs in the samples, the Ultra Performance Liquid Chromatography coupled with mass spectrometry (UPLC-MS) system was used. This was done with the Agilent 6100 series single quadrupole LC/MS system. The column used was the HSS5. $5\mu\text{L}$ of sample is extracted and sent to the column with a speed of 0.3mL/s . It is then sent to the elution column which is kept at 30°C and 500bar. The mobile phase was composed of the two following solvents: solvent A (5% CH_3CN in water) and solvent B (100% CH_3CN). The ratio of these samples varied through time in order to detect the various drugs and is shown in the table 3.4. Again, WWeff samples were centrifuged before analysis.

Table 3.4: Solvent composition for UPLC-MS analysis.

Time	0	3	9	12.5	15	17.5	20	22	25
A%	100	100	65	65	50	5	5	100	100
B%	0	0	35	35	50	95	95	0	0

Table 3.5 shows the retention time for each drug and their m/z ratio.

Table 3.5: Retention times and m/z ratios of analyzed drugs.

Drug	Retention time	m/z ratio
Methotrexate	7.2	455
Capecitabine	10.6	360
5-Fluorouracil	1.6	129
Imatinib	8.6	494
Cyclophosphamide	9.9	261

Calibration curves were determined in order to obtain the relation between the peak area given by spectrometer and the concentration of drug contained in the sample. Therefore, standard samples with known concentrations were also analyzed (10, 50, 100, 250, 500, 1000, 2500 and 5000 μ g/L).

3.3.3 COD Test

The chemical oxygen demand (COD) is the amount of oxidizable pollutants found in wastewater, or in other words, the amount of organic matter in water. It is measured as the mass of oxygen consumed to oxidize the organic compounds over the volume of the solution (mg/L).

The COD was measured by adding 3mL of the sample to be tested to 2mL of a solution containing potassium dichromate. The cells were heated for 2 hours at 148°C and then cooled down to room temperature. The potassium dichromate which has oxidized a substance is converted to Cr^{3+} . A spectrophotometer measured the concentration of Cr^{3+} which was converted to the concentration of COD (mg/L).

3.3.4 Toxicity Assays

The toxicity of the effluents of the different experiments was assessed and compared to the toxicity of the feed solution. Therefore, a basic standardized bioluminescence assay with *V. fischeri* (Hach Lange Luminescent bacteria test LCK, 487-DIN/EN/ISO 11348-2) was applied to these samples in order to evaluate their acute toxicity. All samples were carried out in triplicate. The luminescent bacteria were stored at -20°C until usage. They were reactivated in 5mL of a reactivation solution and diluted 100 times in a 2% NaCl solution. 150 μ L of bacteria solution was added to a 96-well microplate which was set at 15°C for 30 minutes. After 30 minutes, the luminescence was measured (I_0). Then, 150 μ L of toxic samples with 2% NaCl and catalase were added to the bacteria and the luminescence was measured again after an exposure time of 15 minutes at 15°C (I_t). The positive controls consisted of a 2% NaCl solution and the negative control samples consisted of a 7.5% NaCl solution which should result in a 40 to 60% inhibition after the incubation time. For the tests in which H_2O_2 was added, the residual H_2O_2 had to be quenched before doing toxicity tests. In fact, it was found that H_2O_2 was toxic to the bacteria. Therefore, 0.2mg/L of catalase was added to the samples before the toxicity test in order to quench

the H_2O_2 . Liu et al. [36] showed that this concentration of catalase could quench 100mg/L of H_2O_2 in less than 10min.

The bioluminescence of the samples was measured with the ThermoScientific Varioskan Flash. The toxicity was expressed as the percentage inhibition luminescence relative to the control samples. It was calculated as follows:

$$\% \text{ Inhibition} = \frac{I_{ct} - I_t}{I_{ct}} \cdot 100 \quad (3.4)$$

where I_{ct} is the I_0 value adjusted by the correction factor: $I_{ct} = \text{average value} \cdot fK \cdot I_0$ and fK is the temporary correction factor determined from the control measurements: $fK = I_t/I_0$.

The linear measuring range of the test lies between 10% and 90%. The higher the inhibition percentage, the more harmful the sample is to the bioluminescent bacteria.

3.4 Economic Analysis

The adaptability of a new treatment process to industrial scale depends not only on technical performance but also on its economic feasibility. Therefore, a basic economic analysis was performed to determine the cost to treat 1L of wastewater in order to reduce the concentration of the slowest degrading drug by one order of magnitude in a continuous process in the 1.2L pilot-scale reactor. Four different cases were considered as presented in figure 3.3: UV photolysis; UV/ H_2O_2 photolysis; the combination of NF with UV/ H_2O_2 , the combination of RO with UV/ H_2O_2 , where, the retentate of the membrane module is treated by advanced oxidation.

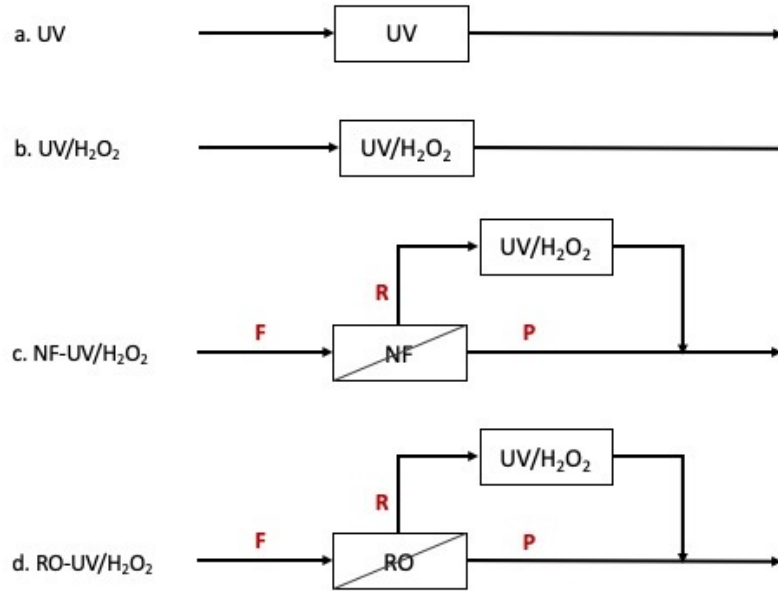


Figure 3.3: Considered configurations for the economic analysis: **a** UV photolysis, **b** UV/ H_2O_2 photolysis, **c** combination of NF with UV/ H_2O_2 , **d** combination of RO and UV/ H_2O_2 .

This economic evaluation was based on the experimental reaction rates of the slowest degrading drug in wastewater determined in the pilot-scale reactor and on the rejection

values determined by membrane filtration. It is necessary to make some considerations and define boundaries for this analysis. Here, only operating costs were considered and were calculated based on the time needed to treat 1L of wastewater. The costs that were taken into account included the cost of the hydrogen peroxide, the cost of the energy needed for the pump and the lamp and the cost of the membrane replacement and lamp replacement.

The time of the treatment was calculated by considering that the UV/H₂O₂ reactor operates as a continuous flow stirred tank reactor (CSTR). The mean residence time of the drugs in a CSTR can be calculated from the continuity equation. This is written as follows for a CSTR in steady state with constant density [73]:

$$C_{A0} - C_A^{OUT} = \frac{V}{F} r_A = \tau r_A \quad (3.5)$$

Where C_{A0} and C_A^{OUT} are the initial and outlet concentrations, V the volume of the reactor, r_A the reaction rate, F the volumetric flow rate at the inlet and τ the mean residence time. The reaction rate for a first order reaction is given by:

$$r_A = kC_A = kC_{A0}(1 - x_A) \quad (3.6)$$

Where k [1/min] is the degradation rate constant of the drug and x_A the conversion. Replacing this expression for r_A in equation 3.5, a relationship between the inlet and outlet concentrations, rate constant and the residence time can be obtained:

$$\frac{C_A^{OUT}}{C_{A0}} = \frac{1}{1 + k\tau} \Rightarrow \tau = \frac{1}{k} \left(\frac{C_{A0}}{C_A^{OUT}} - 1 \right) \quad (3.7)$$

In this equation the inlet and outlet concentrations of the UV/H₂O₂ reactor are needed. For the UV and UV/H₂O₂ processes, C_A^{OUT} is simply the $C_{A0}/10$ and for the membrane-UV/H₂O₂ processes they were calculated from a mass balance knowing the rejection and recovery rate for the membrane process. The rate constant k of the slowest degrading drug was determined from the experimental measurements.

Then, the flow rate (F) needed to treat 1L can be determined from the residence time in the UV/H₂O₂ reactor through the following relation:

$$\tau[\text{h}] = \frac{V[\text{L}]}{F[\text{L/h}]} \Rightarrow F = \frac{V}{\tau} \quad (3.8)$$

Finally, the time needed to treat 1L was then determined based on the flow rate:

$$\begin{aligned} & \frac{1\text{L}}{F} \text{ for the UV and UV/H}_2\text{O}_2 \text{ processes} \\ & \frac{1\text{L-recovery}}{F} \text{ for the membrane-UV/H}_2\text{O}_2 \text{ processes} \end{aligned}$$

Note that it is 1L-recovery for the membrane-UV/H₂O₂ processes because only the retentate needs to be treated by the photoreactor. This time is the duration of the treatment which was used to determine the costs of the lamp, membrane and pump.

Chapter 4

Results and Discussions

4.1 pCBA Degradation by UV/H₂O₂

This section contains the results for the optimization of H₂O₂ concentration. This was found by analyzing the pCBA degradation rates at different H₂O₂ concentrations (0, 25, 50 and 100 mg/L). The influence of the water quality on the degradation was also evaluated by performing the same experiments in LGW and WWeff. The degradation of pCBA by UV/H₂O₂ followed a pseudo-first order degradation rate as can be seen on figure 4.1 for the WWeff matrix. Indeed, the pCBA concentration followed this equation:

$$\log\left(\frac{C}{C_0}\right) = kt \quad (4.1)$$

with a linearity coefficient $R^2 \geq 0.96$. C_0 is the initial concentration of pCBA, C the concentration of pCBA at time t , t the time of the reaction and k the degradation rate constant. This constant can then be determined by calculating the slope of the linear regression.

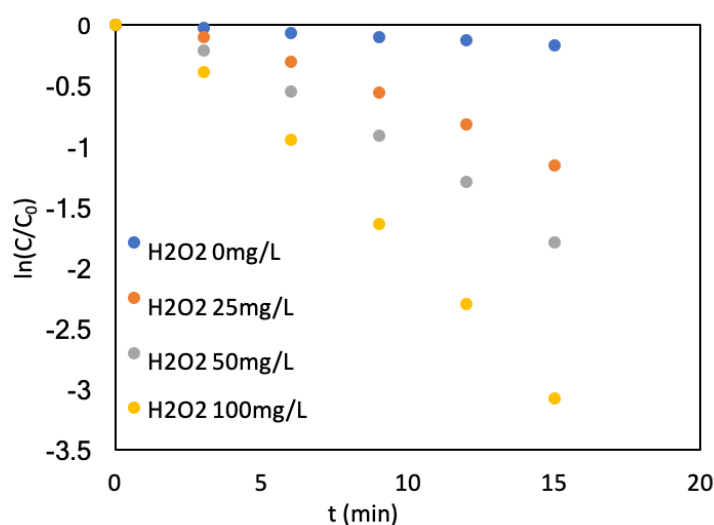


Figure 4.1: Concentration of pCBA over time in wastewater effluent.

Figure 4.2 shows the values of k as a function of the H₂O₂ dose in laboratory grade

water compared to wastewater.

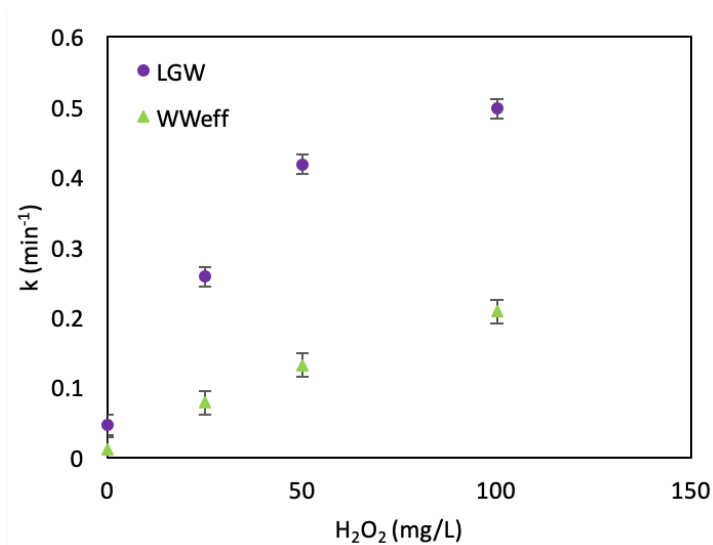


Figure 4.2: Degradation rates of pCBA as a function of H₂O₂ dose in LGW and WWeff.

First of all, figure 4.2 shows that for both laboratory grade water and wastewater effluent, when the concentration of hydrogen peroxide increases the degradation rates of pCBA improve. When no H₂O₂ was added, the degradation rates are negligible (0.046 min⁻¹ in LGW and 0.012 min⁻¹ in WWeff), which confirms that pCBA is not degraded by direct photolysis but rather through indirect photolysis [33]. Indeed the addition of H₂O₂ leading to the formation of $\cdot\text{OH}$ radicals (reaction 1.14) did improve the degradation kinetics. The reason for this is that the reaction of pCBA with $\cdot\text{OH}$ radicals becomes the dominant mechanism for pCBA degradation [27]. Moreover, it can be observed that the degradation rates in LGW are overall higher than in WWeff. This means that the compounds present in the wastewater matrix had a detrimental effect on pCBA degradation and caused hydroxyl radical scavenging. In fact, the organic matter and ions, especially HCO₃⁻ and Cl⁻, which are in the wastewater effluent in high concentrations compared to other ions (cfr. table 3.1) can react with the radicals that are produced which decrease the amount that is available to react with pCBA [29].

Furthermore, it can be seen that for a H₂O₂ dose up to 50mg/L the degradation constants increase linearly with the H₂O₂ concentration. After that, the degradation rates increase more slowly probably due to a self-scavenging effect of the $\cdot\text{OH}$ radicals by the excess hydrogen peroxide (reaction 1.16) and it is expected to reach a plateau [15]. Therefore, in order to avoid excess hydrogen peroxide, the H₂O₂ concentration for the following UV/H₂O₂ experiments were set to 50mg/L. Moreover, for that concentration, a high pCBA degradation was observed after 15 minutes (86% removal). Also, the subsequent experiments will be performed in a wastewater matrix since the goal is to remove the anti-cancer drugs from the secondary effluent of a wastewater treatment plant.

4.2 RO and NF Membrane Filtration

4.2.1 Pure Water Permeability

The pure water permeability was determined for the RO membrane and NF membranes through the gravimetric method (cfr. section 3.2.1). The RO membrane was operated at 35 bars and the NF at 15 bars. The pure water permeability values obtained were 7.4L/m²hbar and 46L/m²hbar for the RO and NF membrane respectively which is quite high compared to values reported in literature. After the filtration of anti-cancer drugs in wastewater, the pure water permeability was measured again and were 3.4L/m²hbar for the RO and 25L/m²hbar for the NF membrane. As shown on figure 4.3, a decrease was observed, meaning there was some permanent fouling on the membrane which can be caused by components from the wastewater matrix, but also from the drugs that were filtered.

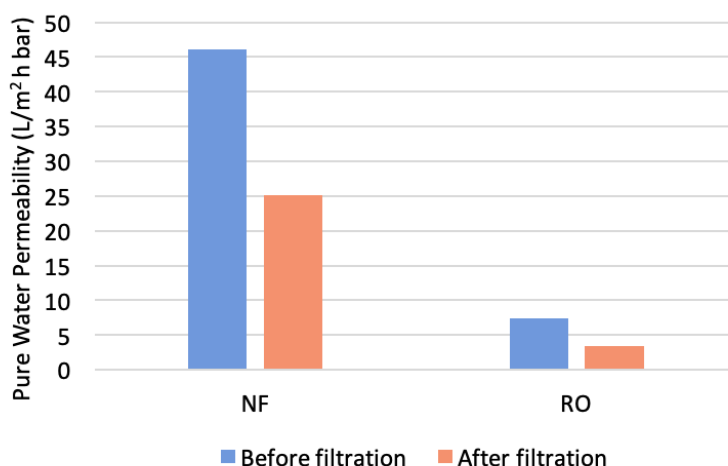


Figure 4.3: Pure water permeability of NF-DL and RO-SE membranes before and after filtration.

4.2.2 Anti-Cancer Drug Rejection by RO and NF Filtration

This section contains the results of the anti-cancer drug membrane filtration experiments in wastewater. The rejection and adsorption of six different anti-cancer drugs for the NF and RO membranes were determined and are summarized in table 4.1.

Rejection values for the NF membrane are relatively low. The rejection by the RO membrane is much higher for all drugs, ranging from 88% to 99%. These drugs are rejected by different mechanism (cfr. section 1.3.4) based on their different physico-chemical properties (table 3.2). The adsorption values were determined based on a mass balance (equation 3.3). The percentage of drugs that was adsorbed is part of the rejection percentage. For instance, for IMT, 85.6% was rejected of which 72.3% was adsorbed on the membrane.

Imatinib which has the highest molecular weight (493.8g/mol) shows the highest rejection for both NF and RO membranes. This molecular weight is higher than the

Table 4.1: Rejection and adsorption values of five selected anti-cancer drugs by NF-DL and RO-SE membranes.

Anti-cancer drug	Nanofiltration - DL		Reverse Osmosis - SE	
	Rejection (%)	Adsorption (%)	Rejection (%)	Adsorption (%)
Imatinib	85.6	72.3	99.7	76.3
Methotrexate	44.5	0	94.1	0
Cyclophosphamide	10.5	8.6	94.6	20.5
Capecitabine	10.8	8.1	93.0	7.9
5-Fluorouracil	27.6	25.6	88.1	48.3

MWCO of both membranes. It also has the highest adsorption values. This means that IMT strongly interacts with the membrane. In fact, IMT is positively charged in the neutral pH range and is a hydrophobic compound ($\log K_{ow} > 2$). Hence, there are strong electrostatic and hydrophobic interactions with the negative and hydrophobic membrane surface. Therefore, although IMT is highly adsorbed on the membrane, it is ultimately rejected due to size exclusion because its MW is too high to diffuse through the membrane.

Methotrexate, which also has a high molecular weight (454.44g/mol), is highly rejected by the RO membrane and has the second highest rejection for the NF membrane, after IMT. It was not adsorbed on any membrane because MTX is negatively charged at pH 7.5 and is a hydrophilic compound ($\log K_{ow} = -1.85$) and the membrane surface is negative and hydrophobic. MTX is therefore highly rejected due to electrostatic repulsion.

Cyclophosphamide is a hydrophilic and neutral compound at the experimental pH conditions so interactions with the membrane should be weak, which is the case as can be seen by the low adsorption values. The main rejection mechanism for CP should therefore be size exclusion which explains its low rejection by the NF membrane and high rejection by the RO membrane, considering its low molecular weight (161.1g/mol) and the MWCO of the NF membrane (150-300g/mol). Similar results were also observed by Wang et al. [49] who studied the removal of CP by NF and RO membranes.

Capecitabine shows similar rejection and adsorption values as CP. Indeed, it is also a neutral and hydrophilic compound so again, it is rejected due to size exclusion and shows low adsorption values.

5-Fluorouracil mainly exists in neutral form until pH 6, but at pH 7.5, its negatively charged conjugate is also present. Also, it is a hydrophilic compound so its main rejection mechanism is size exclusion. Taking into account that 5FU has the smallest molecular weight (130.1g/mol) out the studied drugs, it explains its lower rejection by the RO membrane. The higher rejection by the NF membrane, even though 5FU has a smaller MW than the MWCO, can be due to electrostatic repulsion.

The total drug removal for RO and NF filtration have been determined through equation 4.2 and the values are summarized in table 4.2.

$$\text{Total drug removal (\%)} = \frac{C_{tot,F} - C_{tot,P}}{C_{tot,F}} \cdot 100 \quad (4.2)$$

where $C_{tot,F}$ is the total initial drug concentration in the feed and $C_{tot,P}$ the total drug concentration in the permeate.

Table 4.2: Total drug removal for the NF-DL and RO-SE membranes during filtration of five selected anti-cancer drugs.

Membrane	Drug removal (%)
NF - DL	25
RO - SE	95

Based on these results, it can be concluded that the RO-SE membrane more efficiently removes the anti-cancer drugs from the WWeff. Therefore, the RO-SE membrane has been chosen for the following experiments.

4.3 RO Retentate Treatment by UV/H₂O₂

The results in the previous section showed that the RO membrane removed the anti-cancer drugs efficiently. This means that it creates a high quality permeate, however it also creates a stream that is highly concentrated in cytostatics. Therefore, an experiment was carried out to evaluate the performance of treating an RO retentate by UV/H₂O₂. The technical performance of this treatment was compared to the performance of directly treating the WWeff by UV photolysis alone and UV/H₂O₂ photolysis alone. Figure 4.4 schematically illustrates these three experiments. All oxidation treatments lasted for 1 hour and the three drugs analyzed for these experiments were imatinib, capecitabine and cyclophosphamide. A 50mg/L dose of H₂O₂ was added for the UV/H₂O₂ experiments based on the results from section 4.1. The recovery rate for the RO filtration was 80%.

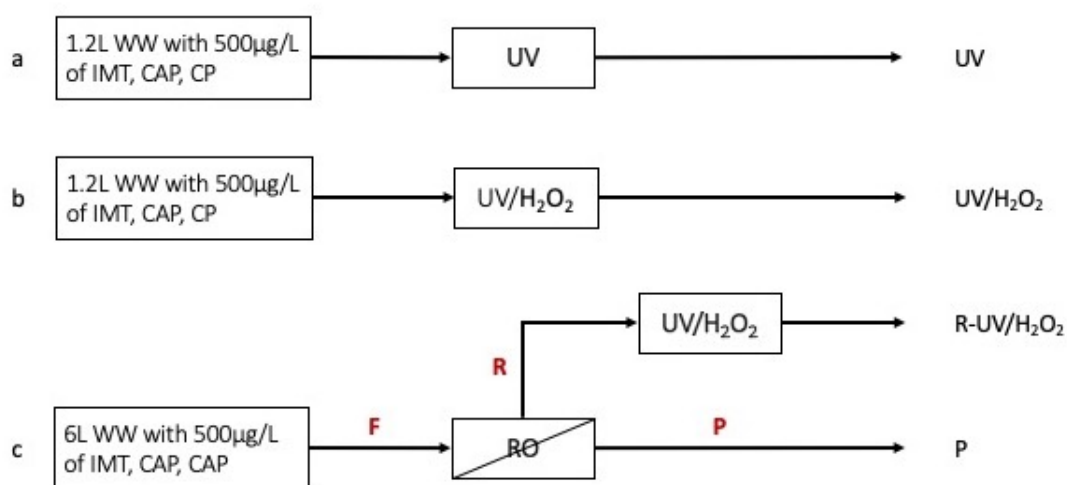


Figure 4.4: Scheme of the three considered treatments **a** UV, **b** UV/H₂O₂, **c** RO-UV/H₂O₂.

The degradation of the three drugs followed a pseudo-first order degradation rate therefore the rate constants could be determined through equation 4.1. Figure 4.5 shows the degradation rate constants of three selected anti-cancer drugs for the three different treatments.

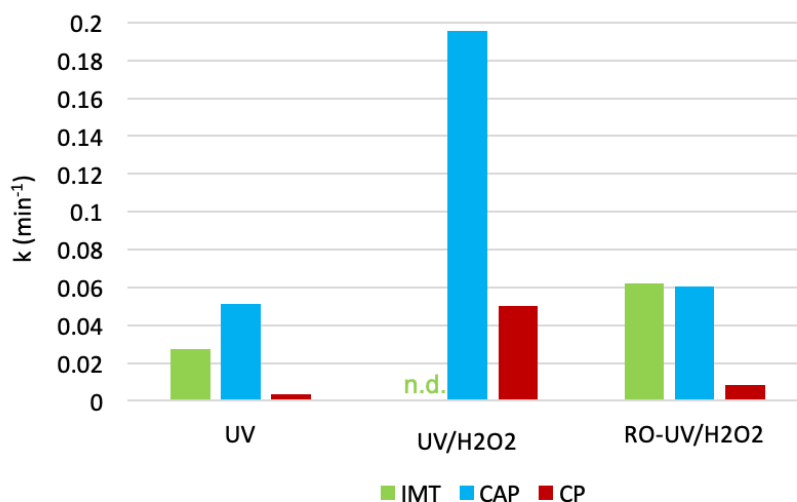


Figure 4.5: Degradation rate constants of the three selected anti-cancer drugs for the three treatments. n.d. = not determined due to detection error.

First, the degradation rate constants for the UV process were lower than the UV/H₂O₂ rate constants for all cytostatic drugs. It shows that the contribution of indirect photolysis by the addition of hydrogen peroxide is significant for drug degradation, especially for CP. In fact, the first-order rate constants are 3.8 and 13.2 times higher for CAP and CP respectively in the UV/H₂O₂ process. This is because CP is not photosensitive (its molar extinction coefficient very small: $7M^{-1}cm^{-1}$ at 254nm [15]) so it is barely degraded by direct photolysis which makes indirect photolysis the primary photodegradation pathway for CP. These results are consistent with literature data, which state that CP shows negligible UV-254 light absorption and hence is very poorly degraded by direct photolysis [15][74]. For CAP, both direct and indirect photolysis contributed to its degradation.

However, the degradation rate constants in the retentate treated by UV/H₂O₂ were much lower than for the UV/H₂O₂ process but still higher than the UV treatment. During membrane filtration, not only were the drugs retained but also other species present in the WWeff matrix such as natural organic matter and ions, increasing their concentration in the retentate stream and inhibiting the degradation of the drugs. The rejection values of COD and the different ions by the RO membrane are summarized in table 4.3 [75]. The rejection for all species was high but it does not mean that all the rejected species are present in the retentate because a certain amount may be adsorbed on the membrane. Nevertheless, organic matter, HCO_3^- and Cl^- have been shown to have a negative effect on anti-cancer drug degradation because of radical scavenging and light absorption (cfr. section 1.2.5) and those were the species present at the highest concentration in the wastewater effluent (table 3.1). The presence of nitrate has been shown to increase degradation rates of anti-cancer drugs [15] however it was present at a low concentration compared to the other species (table 3.1). The rate constant for IMT in the UV/H₂O₂ treatment was not determined due to detection error, but an increase in the rate constant for the RO-UV/H₂O₂ process compared to the UV process is observed which means that $HO\cdot$ radicals contributed to its degradation.

Table 4.3: Rejection of COD and ions during RO-SE membrane filtration. n.d. = not detected in the permeate. Results obtained from the master thesis of Juline Gillard [75].

Species	COD	SO ₄ ²⁻	Cl ⁻	NO ₃ ⁻	Ca ²⁺	PO ₄ ³⁻	HCO ₃ ⁻
Rejection (%)	74.6	83	79	81	88	n.d.	n.d

The COD removal for the four effluents after the different treatments was measured to assess the removal of organic matter. This measure of COD concentration also includes the drugs and their degradation products. The four effluents correspond to the ones depicted on figure 4.4, which includes the permeate of the membrane filtration and the three effluents after oxidation. Figure 4.6 shows the COD removal and the drug removal. These are defined as follows:

$$\text{COD reduction (\%)} = \frac{COD_0 - COD_f}{COD_0} \cdot 100 \quad (4.3)$$

$$\text{Total drug removal (\%)} = \frac{C_0 - C_f}{C_0} \cdot 100 \quad (4.4)$$

Where COD_0 and COD_f are the initial and final (after 1 hour) COD concentrations and C_0 and C_f are the total initial and final drug concentrations. For the RO process it is defined as the removal between the feed and the permeate (see equation 4.2).

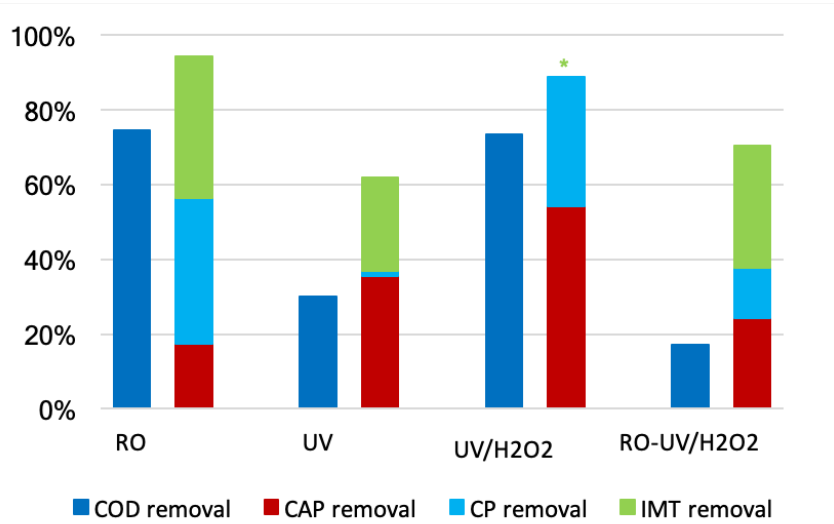


Figure 4.6: COD removal and drug removal of the four effluents after the different treatments. *= data missing for IMT due to detection error.

The RO filtration shows the highest removal for both drugs and COD which shows that it is an efficient way to remove anti-cancer drugs. Within the oxidation processes, it is the UV/H₂O₂ treatment that shows the highest removal for COD and drugs, which means that it degrades the most organic matter (which includes the drugs) and drugs in one hour. This is in accordance with the degradation rates. The removal of COD by

direct UV photolysis is low meaning that organic matter is not efficiently degraded by UV light alone. The drug removal by UV alone is nevertheless non-negligible, even though CP was almost not degraded, IMT and CAP were appreciably removed after one hour. While the degradation rate constants for RO-UV/H₂O₂ were quite low, the amount of drugs removed after one hour remains significant (70%). However, the COD removal is much lower (17%) which can be due to the fact that the initial concentration was higher.

It should be noted that if a same amount of feed is used for each experiment, the amount of retentate that has to be treated by oxidation would only be 20% of the total feed. Whereas, for the UV or UV/H₂O₂ processes alone, the whole feed has to be treated by oxidation. So, even though the degradation rates are slower, the volume of retentate to be treated by oxidation would be much lower since 80% is high quality permeate. The influence of this volume reduction will be assessed in the economic part.

4.4 Toxicity Assessment

The acute toxicity of the effluents after the 3 one-hour treatments and the permeate was evaluated by bioluminescence inhibition using *V. fischeri*. The anti-cancer drugs were first tested separately at different concentrations in order to determine their individual toxicity as well as the mixture of the three drugs. These are shown on figure 4.7.

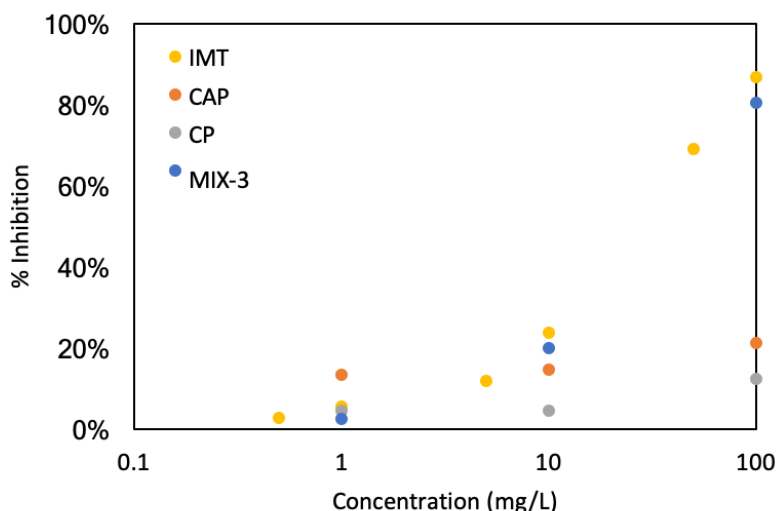


Figure 4.7: % Inhibition on *V. fischeri* as a function of concentration for the three studied anti-cancer drugs after a 15 minute exposure time.

Concentrations higher than 100mg/L were not tested since the concentration of the drugs in the environment is much lower (at the order of the ng/L [12]). In addition, according to the EC-Directive 93/67/EEC [67], compounds with EC_{50} values higher than 100mg/L are considered not harmful to aquatic organisms. This figure shows that, for imatinib, the toxicity on *V. fischeri* depends on the concentration. The EC_{50} value for IMT was found to be around 25mg/L and for the 2 other drugs it is higher than 100mg/L. Therefore, imatinib is the only one that is considered toxic to *V. fischeri*. These results are in agreement with those of Bialk-Bielinska et al. [65]. The toxicity of the mixture of the three drugs does not exceed that of the most toxic drug alone (imatinib) so there appears to be no additive effects for the selected drugs at those concentrations.

Furthermore, the toxicity of the effluents after the treatments was evaluated. Figure 4.8 compares the toxicity, calculated as the percent inhibition, of the 4 effluents after each treatment along with the drug removal and COD removal which was defined by equations 4.3 and 4.4.

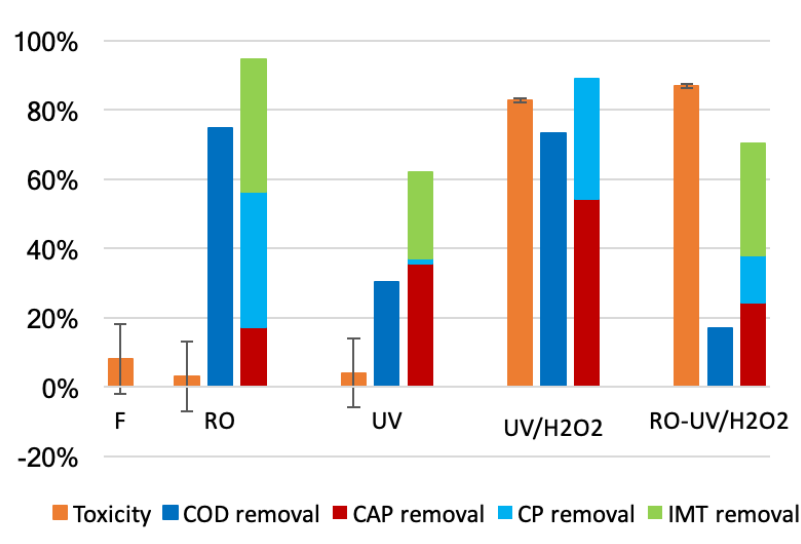


Figure 4.8: Toxicity assay with *V. fischeri* after 15 minute exposure of a feed containing IMT, CAP and CP at 0.5mg/L and of the effluents after treatment: RO filtration, UV, UV/H₂O₂ and RO-UV/H₂O₂.

Figure 4.8 shows that the feed, which was a mixture of 0.5mg/L of the 3 drugs, was not toxic to *V. fischeri*. Indeed, this concentration is too little to be toxic to the bacteria as can be seen on figure 4.7. The permeate of the membrane filtration and the effluent after UV treatment showed no toxicity. For the permeate, the drug concentration and the COD significantly decreased meaning that no toxic compound was left in the permeate. The UV effluent showing no toxicity to *V. fischeri* means that, even though it had the lowest drug removal, no toxic degradation products were formed during this treatment. Besides, there was no complete mineralization of the drugs as can be seen from the COD measurements (only 30% COD removal) meaning that by-products were, in fact, still present. For the UV/H₂O₂ and RO-UV/H₂O₂ effluents, the toxicity increased, showing a 82.6% and 86.8% inhibition respectively. However, these treatments provided high drug removals after one hour. This should mean that the remaining organic matter in the RO-UV/H₂O₂ and UV/H₂O₂ effluents contained by-products which were toxic. Moreover, the UV direct photolysis and UV/H₂O₂ indirect photolysis of only WWeff during one hour showed no toxicity meaning that no toxic by-products was formed from the WWeff components. Hence, the toxicity of the UV/H₂O₂ effluents did come from anti-cancer drug degradation products. Since the degradation products were not identified, it is not known which ones or which combination caused the toxicity. However, several reasons could be attributed the formation of toxic by-products. First, while CP was not degraded by UV photolysis, it is degraded by UV/H₂O₂, therefore, the CP degradation products could cause the toxicity. In fact, Burleson et al. [76] showed that the CP transformation product by ozonation, which was proven to be a CP metabolite (4-keto-CP), was more mutagenic than the parent compound. Moreover, other CP metabolites (4-OH-peroxy-CP, phosphoramidate mustard and nor-nitrogen-mustard) have been shown to be more cytotoxic at lower concentrations than CP itself [3]. Furthermore, the degradation products from IMT and CAP could be different for the UV and UV/H₂O₂ process. In fact, Zhang et

al. [15] proposed two different degradation pathways for two anti-cancer drugs for direct photolysis and UV/H₂O₂ photolysis creating two different by-products. Lastly, Yuan et al. [27] reported that a certain dosage of H₂O₂ could hinder the UV direct photolysis to achieve a higher mineralization of pharmaceuticals that are considerably degraded by direct UV due to a competition for UV light between H₂O₂ and the drug.

Some authors who have studied the treatment of pharmaceuticals by UV/H₂O₂, found that it increased the toxicity of the effluent because toxic degradation products were created [68][24][77]. For instance, Ocampo-Pérez et al. [24] found that the UV/H₂O₂ degradation of cytarabine (anti-cancer drug) during 120 minutes created more toxic photodegradation products to *V. fischeri* than the parent chemical.

It should be noted that, since the concentration in the environment of these 3 drugs studied is predicted to be 100ng/L or less [12], it is not likely there be any acute toxicity. However, the long-term effects of the mixture of drugs in the environment on non-target organisms should be considered as well by performing chronic toxicity and genotoxicity assays [6].

4.5 Economic Analysis

An economic analysis was performed to compare the costs of four different treatments which were depicted on figure 3.3: UV photolysis, UV/H₂O₂ photolysis, the combination of NF with UV/H₂O₂ and the combination of RO and UV/H₂O₂.

In order to do so, it was necessary to calculate the time of the treatment, which was taken as the time needed to treat 1L. First the residence time (τ) was calculated (equation 3.7). This requires the knowledge of the degradation rate constant of the slowest degrading drug which was cyclophosphamide and were determined experimentally (see figure 4.5). Moreover, the inlet and outlet concentrations were determined through a mass balance knowing the rejection and the recovery rate.

The rejection of CP by the RO-SE membrane was 95%. The NF membrane used in this work poorly rejected CP (table 4.1), however, some studies have shown higher rejection of CP with different NF membranes. For instance, Cristovao et al. [57] found 90% rejection for CP in a WWeff matrix with a Desal 5DK membrane. Therefore, this rejection value was considered for the economic analysis. The recovery rate for both NF and RO was set at 80%. This is because no significant decrease in the permeability was observed while filtering the drugs so this recovery rate was possible for both membranes without having significant fouling.

From the residence time, the flow rate that goes in the UV/H₂O₂ reactor can be determined from equation 3.8. Finally, the time to treat 1L can be determined. All of these values are summarized in table 4.5. This table also includes the cost of each element of the treatment which were based on the unit prices and lifetime of each item summarized in table 4.4.

Table 4.4: Unit prices and lifetime of the items considered in the economic analysis.

Item	Price	Lifetime
LP lamp	67 euro/lamp	8000h [23]
H ₂ O ₂	0.24 euro/kg _{H₂O₂} [23]	-
NF membrane	3022 euro/m ² [78]	8600h [79]
RO membrane	2586 euro/m ² [78]	8600h [79]
Electricity cost	0.1142 euro/kWh	-

Table 4.5: Parameters considered to evaluate the cost of the four different treatments in order to decrease the CP concentration by one order of magnitude in 1L. Also included are the costs for each item and the total cost of the treatment. Costs are expressed in euro/L/order.

	UV	UV/H ₂ O ₂	NF-UV/H ₂ O ₂	RO-UV/H ₂ O ₂
k_{CP} [min^{-1}]	0.0034	0.0499	0.0084 ^a	0.0084
R (%)	/	/	90	95
Y (%)	/	/	80	80
τ [h]	39.91	3.01	89.15	26.22
Time to treat 1L [h]	33.26	2.51	14.86	4.37
H ₂ O ₂		0.00001	0.00001	0.00001
Lamp replacement	0.55712	0.04198	0.24887	0.07320
Lamp electricity	0.07597	0.00572	0.03394	0.00998
Pump electricity			0.00005	0.00011
Membrane replacement			0.00041	0.00093
Total cost [euro/L/order]	0.633	0.048	0.283	0.084

^a The degradation rate constant for the NF retentate treatment was considered to be the same as for the RO retentate degradation constant

The cost of the lamps needed for the treatment was calculated based on the price per lamp and their lifetime. Since they are used only for the time of the treatment, this price has to be multiplied by $\frac{\text{time of treatment}}{\text{lifetime}}$. This was also done for the membrane. The cost of the membranes was determined from its area and its lifetime. The area was determined from the transmembrane flux, transmembrane pressure and pure water permeability as follows:

$$P\left[\frac{L}{m^2 h bar}\right] = \frac{F[L/h]}{p[bar]A[m^2]} \Rightarrow A = \frac{F}{pP} \quad (4.5)$$

The electricity cost includes the cost of energy to power the lamps and to power the pump during the treatment time. No pump was considered for the UV and UV/H₂O₂ as it was negligible compared to the pump power needed for the membranes. The power to provide to the pump for the filtration was calculated based on the transmembrane pressure and transmembrane flux. For the lamps, a power of 10W per lamp has to be provided, so a total of 20W for both lamps.

From the total costs, it can be seen that the UV photolysis process is the most expensive treatment and the UV/H₂O₂ is the cheapest one. Figure 4.9 details how the different items contribute to the total costs.

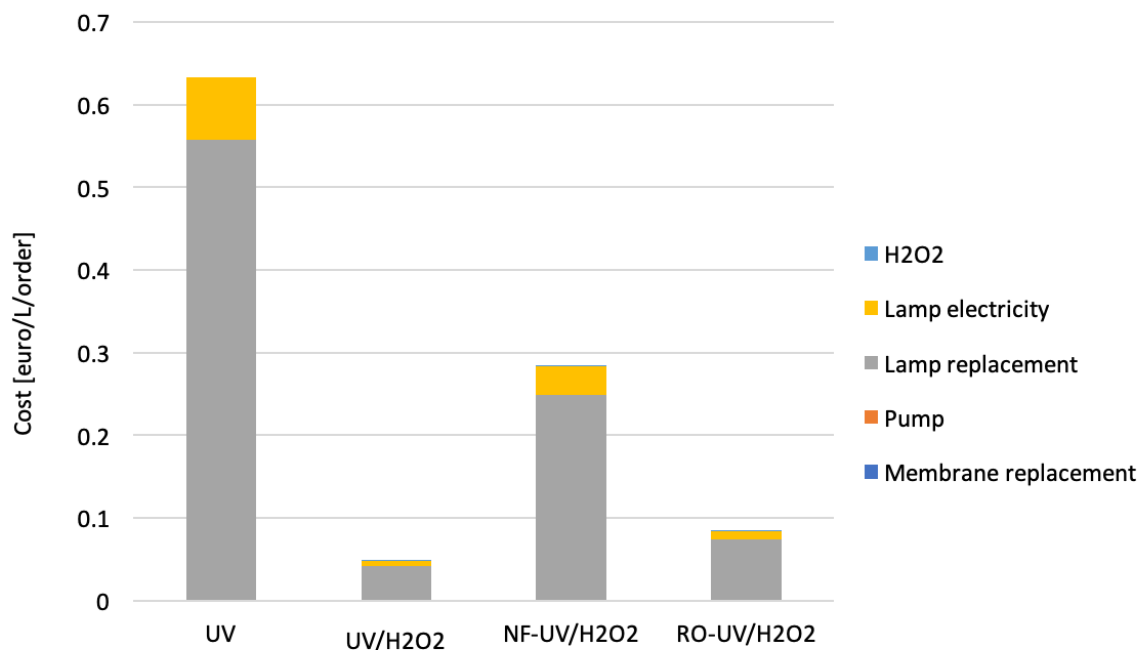


Figure 4.9: Contribution of each item to the total cost of the four treatments to decrease the CP concentration by one order of magnitude in 1L.

The addition of H_2O_2 to the UV process significantly reduces the cost of operation because it reduces the time of operation from 33.26 minutes to 2.5 minutes due to the increase in degradation rate. Moreover, the hydrogen peroxide represents only 0.03% of the total cost for UV/ H_2O_2 . In both cases, it is the cost of the lamp replacement which shows the highest contribution to the total cost. Thus, between UV and UV/ H_2O_2 , the UV/ H_2O_2 process is the cheapest, although it creates a more toxic effluent.

Next, for the NF-UV/ H_2O_2 and RO-UV/ H_2O_2 processes, it is clear from this figure that the photo-oxidation part (lamp electricity, lamp replacement and H_2O_2) of the process has the highest impact on the total operating costs. The cost of the membrane filtration part is only 0.1% of the total cost for NF-UV/ H_2O_2 and 1.2% for RO-UV/ H_2O_2 . Between these two processes, it is the RO-UV/ H_2O_2 combination which is the least expensive. Even though the energy cost to power the pump for the RO treatment is twice as high as for the NF membrane (which is in accordance with other studies [80][81]), the lamp costs are much higher for the NF-retentate treatment. The main reason for this is the lower rejection value for the NF membrane, which creates a permeate with a higher drug concentration. Therefore, the UV/ H_2O_2 part of the process has to compensate and operate much longer to decrease the drug concentration even more so that the permeate stream and the UV/ H_2O_2 effluent combined reach the desired concentration (which is 1 order of magnitude lower than the feed). This means that the rejection efficiency of the membrane is an important parameter when combining membrane filtration with AOP. The cost decreases when the rejection efficiency increases.

The two cheapest treatments are the UV/ H_2O_2 process and the RO-UV/ H_2O_2 process due to their low treatment times. Even though the rate constant for the UV/ H_2O_2 process

is 6 times higher than the rate constant for RO-UV/H₂O₂, the treatment time is only 1.7 times lower (2.5h for UV/H₂O₂ and 4.37h for RO-UV/H₂O₂). Moreover, the cost of the membrane part is negligible. This proves that concentrating the drugs by membrane filtration in a retentate stream, and thus reducing the volume that has to be treated by oxidation, can significantly reduce the cost. In our experiments, the gain of treating a smaller volume by oxidation was lost in the HO· radical scavenging by organic matter and ionic content of the water matrix. However, this can be remedied by increasing the H₂O₂ dose. Consequently, a higher degradation rate would be obtained in the RO-UV/H₂O₂ and would reduce the cost.

Clearly, the cost of all of these treatments could be reduced by decreasing the price of the light source. In some cases LED lights have been used which are less energy consuming than mercury low pressure lamps [31]. Another alternative is, of course, the use of sunlight [2].

Conclusions

This work focused on the feasibility of removing anti-cancer drugs from a secondary wastewater effluent by combining membrane filtration with an advanced oxidation process. More specifically, by first filtering the feed by pressure-driven membrane and then treating the membrane retentate by UV/H₂O₂ photolysis. The performance of the combination of membranes with AOP was compared to the performance of direct UV photolysis and UV/H₂O₂ indirect photolysis.

The rejection efficiency of an RO-SE and NF-DL membranes was assessed. The removal of anti-cancer drugs by the RO-SE membrane was highly efficient. Indeed the RO membrane provided great rejection for all drugs (>88%). Conversely, the rejection by the NF-DL membrane was poor (<45% for most drugs). Therefore, only the retentate of the RO membrane was treated by UV/H₂O₂.

In terms of degradation rates, the UV/H₂O₂ treatment showed higher efficiency than UV photolysis due to the formation of HO[•] radicals to degrade the drugs. For the RO-UV/H₂O₂ treatment, the degradation rates were much slower than for UV/H₂O₂ because of an increased concentration of organic matter and ions in the retentate. However, the drug removal from the retentate stream after one hour was still quite high in which case 70% drug removal was obtained.

Then, these processes were compared based on acute toxicity to *V. fischeri* of the treated effluents. First of all, the feed showed no toxicity because the drug concentration was too low. Naturally, the permeate stream was also non-toxic since the drugs were highly removed. Among the oxidation processes, the UV process showed no toxicity after the treatment. On the other hand, the treatment by UV/H₂O₂ showed an increase in toxicity which was attributed to the formation of toxic by-products because of the UV/H₂O₂ degradation path and the degradation products of CP which weren't present in the UV treatment.

Lastly, the operating costs of 4 different treatments were compared (UV, UV/H₂O₂, NF-UV/H₂O₂ and RO-UV/H₂O₂). The cost of the UV/H₂O₂ process was the lowest. It was shown that the addition of H₂O₂ significantly reduced the cost compared to direct UV photolysis due to the increase in the degradation rates. The cost of RO-UV/H₂O₂ was slightly higher than UV/H₂O₂. Although, the RO-UV/H₂O₂ reaction rates were much lower than for UV/H₂O₂, the costs were comparable due to the smaller volume to be treated by AOP for the RO-UV/H₂O₂ process. The gain of treating a smaller volume was lost in the radical scavenging by the WWeff components. Finally, the reduced rejection efficiency of the NF membrane significantly increased the treatment cost of NF-UV/H₂O₂ compared to RO-UV/H₂O₂.

To conclude, this study showed that the treatment of membrane retentates by UV/H₂O₂ is technically possible although it formed toxic by-products. The UV/H₂O₂ treatment

was shown to be the least expensive. However, this should be taken with caution since it was a basic economic analysis and the membrane retentate-UV/H₂O₂ processes can still be optimized. The UV treatment alone was shown to be the least efficient because not all drugs can be directly photolyzed, or the degradation rates were slow. However, it did not generate toxic by-products.

Recommendations for Future Research

It has been shown in this study that the removal of anti-cancer drugs by a combination of membrane filtration and AOP is feasible. However, some operating conditions can still be improved. Optimizing operating conditions can improve the quality of the effluent and decrease operating costs.

First, since the retentate stream contained a higher concentration of organic matter and other wastewater components, there was probably a higher H_2O_2 consumption. Therefore, it would be necessary to do an optimization of the H_2O_2 dose in a retentate stream in order to obtain optimal reaction rates. Also, an optimization of the treatment time (or residence time) should be considered in order to improve the mineralization of the anti-cancer drugs which was not achieved after one hour. However, this treatment time optimization should be considered together with the economic aspect because increased treatment times can significantly increase costs.

Then, for the experiments in this work, LP UV mercury vapour lamps were used as light source. However, as mentioned earlier, LED lamps have now been studied which have many advantages including longer lifetimes and lower energy consumption. As the lamp operation had the highest impact on operating costs, studying the possibility of using LED lamps for the UV/ H_2O_2 process could reduce costs. Another possibility is the use of natural sunlight. Wang et al. [20] showed that the direct and indirect photolysis of seven micropollutants using a sunlight simulator was feasible.

Concerning the membrane filtration part, it was shown that the RO-SE membrane was highly efficient at removing drugs from 6L of wastewater. However, the evolution of the rejection efficiency over time should be studied if higher volumes of water have to be treated. Moreover, the studied NF membrane showed a poor removal efficiency, but some NF membranes in the literature have shown removal performances that approach that of RO [78]. Therefore, other NF membranes should be tested because the use of NF filtration, if they are efficient, can reduce the cost due to higher LGW permeabilities.

Regarding the evaluation of the toxicity of treated effluents, several suggestions can be made. First of all, it is important to identify and characterize the transformation by-products in order to determine exactly which degradation pathways cause toxicity. Also, if the transformation products are not toxic, it should be proven that they are biodegradable or even that they could be easily degraded by natural microorganisms present in the water and soil after disposal. Since the UV/ H_2O_2 effluents were toxic because of the formation of by-products, the toxicity of the effluent could be measured over time to assess how the toxicity evolves when mineralization increases. Although acute toxicity tests were useful to see the difference in toxicity between a feed solution and the treated effluent, it is important to evaluate the chronic toxicity. Besse et al. [12] stated that it would be

more relevant to perform full-life cycle or multigenerational assays on fish, molluscs or invertebrates to assess environmental chronic effects of drugs and their metabolites. They also stated that *in vivo* tests would be more representative to assess genotoxicity than *in vitro* tests. They suggested that the *in vivo* comet assay (which is a method that measures DNA damage) to assess genotoxicity in organisms can be a suitable tool. Moreover, there is a wide mixture of drugs which co-exist in the environment at much lower concentrations than those studied here. These drugs as well as their human metabolites and degradation products could have additive effects which need to be assessed.

Finally, to assess the possibility of this treatment at larger scale, a full economic analysis should be performed which would include capital costs, operating costs and maintenance costs. Furthermore, a life cycle analysis could be performed to review the environmental impact that this treatment would have.

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