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Andreas Søyland

Stavanger, June 2020

Preface

Originally this thesis was supposed to go in another direction. In the beginning, the potential for ozone production in water using a medium-pressure UV (MP-UV) lamp in a pilot testing facility for the treatment of ballast water was to be studied. This plan was abandoned quite early after some research revealing the high cost associated with the necessary equipment to carry out the testing. After this, the revised plan was to study the removal of pharmaceuticals in water at the same pilot testing facility with the same MP-UV lamp. To make it cost-efficient, aspirin, also known as acetylsalicylic acid, was chosen as the pharmaceutical to use in the study.

The MP-UV lamp can operate between 3-35 kW. For the experimental work, it was to be run at 3 kW, 19 kW, and 35 kW, in order to compare if there was a difference in the removal of aspirin with different power outputs. As the amount of aspirin removed by UV light is vital, the dilution of the system had to be tested. The standard curve for the later analyzes was prepared before the direction of the thesis had to change. Due to Covid-19, the laboratories and the university closed for all students and employees indefinitely. Therefore, the thesis had to go in a theoretical direction.

For this final revision, it was decided to conduct a literature review to determine the removal efficiencies of pharmaceuticals in different types of wastewater treatment plants (WWTPs) and emerging treatment technologies.

Abstract

The global consumption of pharmaceuticals is increasing, and in recent years there has been a growing concern surrounding the release of pharmaceuticals to the environment. Wastewater treatment plants (WWTP) have been identified as one of the sources for this release. Since this is a more recent concern, the WWTPs were not built for the removal of pharmaceuticals. This study evaluates the removal efficiency (RE) for pharmaceuticals in WWTPs with differing treatment technologies to find the most efficient treatment. Emerging technologies are presented and compared to the established processes. A review literature was conducted with the search terms “occurrence pharmaceuticals wastewater” focusing on newer articles published between 2016 and 2020. The review showed a correlation between the RE of pharmaceuticals and the level of treatment in use. Primary, secondary, and tertiary treatment showed an average RE of 16.3%, 40.1%, and 61.6%, respectively. The emerging technologies were found to have a RE of over 90%. Effluents from WWTPs are a source for the release of pharmaceuticals in the environment, and upgrades to the treatment processes are necessary to ensure a better removal.

Selected Abbreviations

A2/O	Anaerobic-anoxic/oxic
ACT	Assisted chemical treatment
AOP	Advanced oxidation process
AS	Activated sludge
CAS	Conventional activated sludge
CBT	Chemical/biological treatment
CBZ-Glu	Carbamazepine *N*-glucuronide
DBP	Disinfectant by-products
DDD	Defined daily dose
DiOH-CBZ	Dihydroxycarbamazepine
DOC	Dissolved organic carbon
DP 252	Drain pump
GC	Gas chromatography
GC-MS	Gas chromatography-mass spectrometry
GLSS	Gas-liquid-solid separator
HNO_3	Nitric acid
HOBr	Hypobromous acid
HP	High pressure
HPLC	High performance liquid chromatography
HRT	Hydraulic retention time
IMS Institute	Intercontinental Medical Statistics Institute
LC	Liquid chromatography
LC-MS/MS	Liquid chromatography-tandem mass spectrometry

LOD	Limit of detection
LOQ	Limit of quantification
LP	Low pressure
m/z	Mass to charge ratio
MBBR	Moving bed bioreactor
MBR	Membrane bioreactor
MBT	Mechanical/biological treatment
MP	Medium pressure
MP-UV	Medium-pressure UV
MS	Mass spectrometry
n.d.	Not detected
NSAID	Nonsteroidal anti-inflammatory drug
PPCP	Pharmaceuticals and personal care products
RE	Removal efficiency
RO	Reverse osmosis
SRT	Solid retention time
SS	Suspended solids
UASB	Upflow Anaerobic Sludge Blanket
UHPLC	Ultra-high performance liquid chromatography
VUV	Vacuum-UV
WWTP	Wastewater treatment plant

1. Introduction

The global use of pharmaceuticals is increasing. In a study done by the Intercontinental Medical Statistics Institute (IMS Institute) in 2015, the global medicine use was predicted to pass 4.5 trillion doses in 2020, up 24% from the levels in 2015 (*Global Medicines Use in 2020*, 2015). When measuring an increase in the use of pharmaceuticals, annual sales are not a preferred measurement as prices may differ. Instead, a measurement called "defined daily dose" (DDD) is used. DDD is defined as the daily average dose for a drug used on its main application in adults (Sakshaug et al., 2019). Antibiotics are a group of pharmaceuticals that have been the focus of many studies much due to the concern for the development of antibiotic-resistant bacteria (Kümmerer and Henninger, 2003; Le-Minh et al., 2010). Between 2000-2015 the antibiotic consumption measured in DDD increased by 65% in a study where 76 countries from around the world were represented, including Norway. (Klein et al., 2018). Low- and middle-income countries were the main drive behind this increase as the use went down in some of the high-income countries. However, even though the antibiotic use went down in some high-income countries, the overall use of antibiotics went up.

In Norway, the sales of prescription drugs increased by 63% from 2004-2018 when measured in DDD ("Reseptregisteret," n.d.). At the same time, the population only increased by 16%, which shows that there is a general increase in the use of pharmaceuticals ("Statistikkbanken," 2020). In the United States, there was a significant increase in the use of prescription drugs from 1999-2012 (Kantor et al., 2015). When we use pharmaceuticals, the body only metabolizes a small amount of the substance. However, large variations occur depending on the type of drug. On average, 30% is metabolized, and 70% of the compound is excreted and goes into the wastewater unchanged (Kümmerer and Henninger, 2003). Since wastewater treatment plants (WWTP) are not designed to remove pharmaceuticals, the compounds can go through the treatment plant without being removed and enter the environment.

Numerous studies have been conducted on the occurrence of pharmaceuticals and personal care products (PPCP) in wastewater (Miège et al., 2009; Wang and Wang, 2016). There has been a growing concern for the release of pharmaceuticals into the environment in recent years. Several studies have examined the effects of pharmaceuticals on different forms of aquatic wildlife, including; daphnia, rainbow trout, marine clams, and mussels. (Cleuvers, 2003; Santos et al., 2010; Fabbri, 2015; Gworek et al., 2019). Generally, the concentrations found in the

aquatic environment are too low for acute toxic effects on wildlife, but there is a lack of studies concerning the long-term chronic impact (Cleuvers, 2003; Corcoran et al., 2010).

Pharmaceuticals have been found all around us in the environment and has led to concerns for not only the environmental impact, but also how it might affect human health (Boxall, 2004). Studies have shown the presence of pharmaceuticals in drinking water, groundwater, and soil (Stackelberg et al., 2004; D'Alessio, 2009; D'Alessio et al., 2018). Even vegetables that have been irrigated with treated wastewater have contained pharmaceuticals (Christou et al., 2017). Even though there is much uncertainty surrounding the impact on human health, no limit for the release of pharmaceuticals has been set (Rivera-Utrilla et al., 2013).

There are many different treatment technologies and local differences in the composition of wastewater. Therefore, it is hard to get an overview of which treatment technologies is best at removing pharmaceutical compounds. This thesis will be a review of articles that study the occurrence of pharmaceuticals in wastewater. In the review, several WWTPs with different technologies are compared, to try to discover which method that has the highest removal efficiency (RE). All the data for influent and effluent concentrations of pharmaceuticals was extracted and sorted by the drug class they belong to. New emerging technologies for the removal of pharmaceuticals will also be presented and compared to the treatment methods in use today.

The objective of the thesis is to identify the best treatment technology for the removal of pharmaceuticals that is widely used today. Identify which pharmaceuticals that are most commonly found in WWTPs and which ones that are most resistant to degradation. Emerging technologies that have been tested in lab-scale will be presented and compared to the removal efficiency of technology in use today. It will be related to the environmental problems that are occurring from the release of pharmaceuticals into the waterways. From this information, promising methods will be identified, and processes that need more investigation will be proposed.

1.1 Wastewater treatment

The treatment of wastewater is not a new exercise. It was introduced in the late 19th century, where one started to see the development of treatment methods that are still in use today (Lofrano and Brown, 2010). Today wastewater treatment can be divided into three different degrees of treatment, viz. primary, secondary and tertiary treatment. These divisions indicate

the type of technology that is used in the treatment plant and what kind of treatment level one can expect to reach.

In developed countries, WWTPs, which only utilize a primary treatment, are not widely in use anymore and reserved for small towns and gatherings of cabins. When a primary treatment is used, the recipient of the treated wastewater must be resistant to the increased loads of organic matter, and nutrients received. The primary treatment is a mechanical treatment for the removal of solids, particles, and suspended solids (SS). A typical primary treatment plant consists of screens, a grit chamber, and a primary settler (Figure 1.). The screens have varying slit sizes to remove smaller and smaller solids gradually. At this stage, all the larger solids are removed. After the removal of solids, the wastewater flows into the grit chamber. In the grit chamber, particles like sand are removed, this chamber is often combined with a fat remover as well. Fat will float to the top and then be scraped off. From here, the wastewater enters a primary sedimentation tank. In the sedimentation tank, SS sink to the bottom where they can be easily removed. The treated water is then released into a recipient.

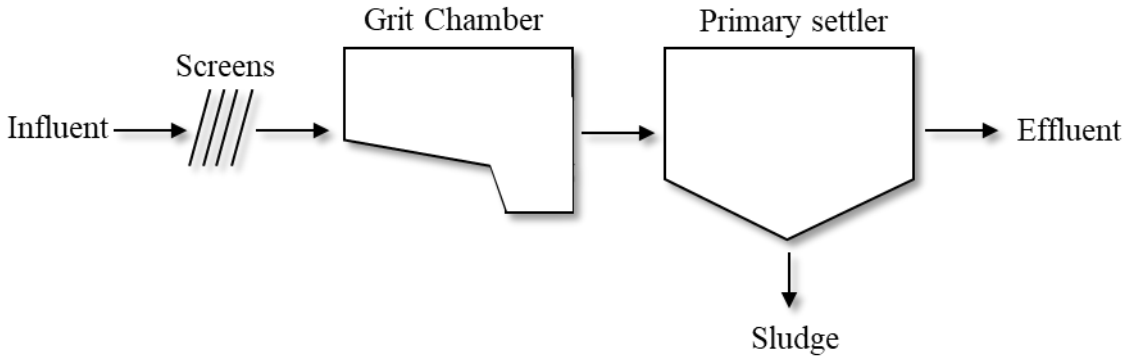


Figure 1. *Overview of a primary treatment plant.*

In the reviewed literature, two different primary treatments are reported, mechanical treatment and assisted chemical treatment (ACT). The plant with a mechanical treatment is operating in the same way as the plant seen in Figure 1. For the ACT plants, chemicals are added to the wastewater before the primary settler. These chemicals are usually inorganic salts, like iron (III) chloride, or polymers with charged functional groups. When added, they help the suspended solids in the wastewater to stick together. They flocculate and become more susceptible to sedimentation. As there are no stages for biodegradation, gravity is the main removal mechanism for both the treatment plants.

In secondary treatment plants, the goal is to remove as much as possible of the organic matter by using a biological or chemical process, or a combination of both. The technology for secondary treatment has been around since the early 20th century. However, it did not start to be widely implemented until the 1970s (Lofrano and Brown, 2010). The secondary treatment can be divided into two main types, fixed growth and suspended growth systems. Some examples of fixed growth technology include moving bed bioreactor (MBBR) and membrane bioreactor (MBR). Activated sludge and upflow anaerobic sludge blanket (UASB) are examples of suspended growth systems. There is not an easy answer to what technology is best, as it depends on the composition of the wastewater and local conditions, like temperature and flow rates. However, activated sludge is one of the most used secondary treatment processes (van Loosdrecht and Brdjanovic, 2014). This is a biological process that utilizes bacteria for the removal of organic matter. Secondary treatment is utilizing the same steps as a primary treatment, but also includes a treatment step for the removal of organic matter, a second settling tank, and some form of sludge treatment (Figure 2).

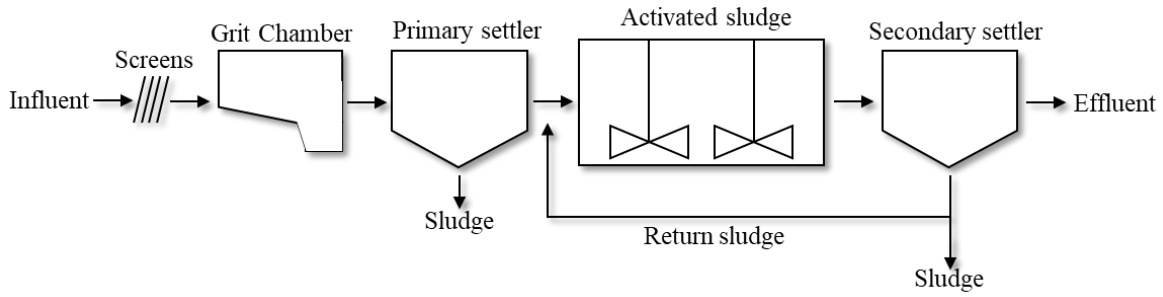


Figure 2. *Overview of a secondary treatment plant.*

There are several different types of secondary treatment processes, and the processes reported in the reviewed literature include; Bardenpho, conventional activated sludge (CAS), chemical/biological treatment (CBT), and mechanical/biological treatment (MBT). One of the tertiary treatment plans utilize a secondary treatment, the UASB, as a step in the process, which will also be presented here. The Bardenpho process is a biological treatment method that can have a varying amount of stages. In the reviewed literature, three stages are utilized. However, both processes with four and five stages exist (Sattayatewa et al., 2009; Banayan Esfahani et al., 2019). The three-stage process consists of an anaerobic zone, followed by an anoxic zone and then an aerobic zone (de Jesus Gaffney et al., 2017).

The CAS process is, as mentioned, one of the most commonly used treatment processes. There exist some different configurations for the activated sludge processes, but they all operate based

on the same principle. A suspended aerobic bacteria culture is responsible for the degradation of the organic compounds. The tank is supplied air from the diffusers at the bottom, which evenly spreads the bubbles and keep the environment oxic. For a CAS process, the tank is narrow and long with the influent at one end to get as close to a steady flow as possible. The treatment plant with a CBT process implemented is utilizing both a chemical and biological process for the treatment. In the reviewed literature, there is not reported any information as to what type of chemical and biological treatment that are in use. Therefore, the most common types will be presented. The chemical process usually comes first. In this process, chemicals are introduced to the wastewater, just like in the ACT process, to promote flocculation of the suspended solids. After the chemical treatment, the wastewater goes into biological treatment, which likely is a form of activated sludge process. Two of the treatment plants utilize a conventional MBT process. It is not specified any closer what type of configuration that is in use. The mechanical step at least consists of screens and, most likely, a grit chamber as well. For the biological step, there is a broader selection of technologies to choose from. However, since it is a conventional MBT process, a form of activated sludge treatment is likely implemented.

Upflow anaerobic sludge blanket (UASB) is a biological process that utilizes anaerobic degradation. Here the influent is at the bottom of the tank, and the wastewater flows upwards through a mix of aggregated granules. When organic matter is degraded in this process, biogas is formed. The biogas tends to stick to the granules. The gas is separated from the water and solids in a gas-liquid-solid separator (GLSS) at the top of the tank. This type of treatment is effective for wastewater with a high carbohydrate content, which has made them useful for the treatment of wastewater from food processing industries (Daud et al., 2018).

In the later years, with an increased focus on the removal and reuse of nutrients in wastewater, tertiary treatment has become more and more common. For tertiary treatment, in addition to the removal of suspended solids and organic matter, the goal is to remove nitrogen and phosphorus. Specially designed biological and chemical processes are used to achieve this. They are often based on the same principles as the technology used in secondary treatment but tweaked for the removal of nutrients. This is done by increasing the solid retention time (SRT) and alternating between aerobic and anaerobic tanks.

Many treatment plants also implement a disinfection step, as seen in Figure 3. UV and chlorination are two of the more common methods in use. The disinfection step is mostly used when the effluent either goes into a river, which may be used for tap water further downstream,

or if the treated water will be reused for irrigation. If a secondary treatment plant has a disinfection step before release, it will count as a tertiary treatment plant even though nitrogen and phosphorus are not removed (Sonune and Ghate, 2004).

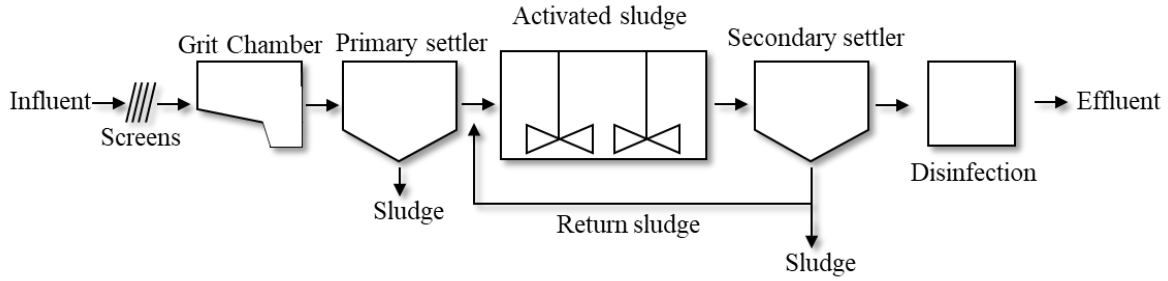


Figure 3. *Overview of a tertiary treatment plant that uses disinfection.*

In the reviewed literature, the reported tertiary treatment processes and disinfection stages, include; anaerobic-anoxic/oxic (A2/O), chlorination, hydrogen peroxide (H_2O_2) treatment, reverse osmosis (RO) and UV. The A2/O process is a suspended growth system, with an anaerobic, anoxic, and oxic tank. Chlorination, H_2O_2, RO, and UV are all disinfection methods for wastewater and will be presented briefly. For chlorination, chlorine is added to the wastewater as the last step after primary and secondary treatment to kill or inactivate pathogens. Chlorination will give a lasting disinfection effect as the chlorine will follow the water stream, and the pathogens will be exposed over a longer time. There are, however some concerns surrounding this method due to the formation of disinfectant by-products (DBP) like trihalomethanes and haloacetic acid (Yang et al., 2005), which are shown to have an acute toxic effect on aquatic wildlife including *Daphnia Magna* (Du et al., 2017). Hydrogen peroxide treatment is used in the same way as chlorination, as a chemical disinfection step. Reverse osmosis membranes are widely used in the treatment of wastewater and was suggested as an important technology for this use as early as the 1970s (Cruver and Nusbaum, 1974). A RO membrane acts as a physical barrier for the removal of pathogens and dissolved solids. It is a very effective treatment, given the right process conditions are in place to lessen the biofouling of the membrane (Bartels et al., 2005).

UV-light has been studied and used in different applications for the last century. In other words, it is a well-studied and well-known technology (Oppenländer, 2003). UV light is divided into four classes based on the wavelength, UV-A (380-315 nm), UV-B (315-280 nm), UV-C (280-200 nm), Vacuum-UV (VUV) (200-100 nm). The different wavelengths have different properties and different effects on organisms. Therefore, it is essential to choose a light source

fitting for the intended application. In general, UV-lamps can be divided into three types; low pressure (LP), medium pressure (MP), and high pressure (HP), where low pressure is the most common source of UV-light (Zoschke et al., 2014).

Low-pressure mercury UV lamps, herby referred to as LP-UV lamps, are used in a wide range of applications. These lamps emit a well-defined spectrum with a peak at 254 nm and another minor peak at around 185 nm (Zoschke et al., 2014). In modern LP-UV lamps, around 40% of the electric power is converted to UV-C light, and only 6-9% is converted to VUV (Liao et al., 2011). The wavelength of 254 nm is absorbed by nucleic acids, which causes DNA damages in organisms (Olsen et al., 2016; Sun and Blatchley, 2017). Because of this peak, the LP-UV lamps are used a lot in water treatment facilities as a disinfectant. Another reason for the LP-UV lamp's popularity is the low power consumption compared to a medium pressure mercury UV lamp or HP-UV lamp.

The spectrum of an MP-UV lamp is much broader than for an LP-UV and consists of several peaks and is, therefore, a polychromatic light. The light from an MP-UV lamp has been shown to have a better, longer-lasting effect on the breakdown of bacteria and other lower-level organisms (IJpelaar et al., 2010). DNA building blocks can reverse the DNA damages created by LP-UV lamps. This means that organisms can be deactivated and seem dead for a while, but later repair the damages and be active again. Compared to LP-UV lamps, MP-UV lamps have more prominent wavelengths present below 200 nm. These wavelengths can damage proteins and enzymes, which, combined with the DNA damage from 254 nm, will lead to irreversible effects on an organism (Olsen et al., 2016). The drawback with MP-UV lamps is the high energy consumption. An MP-UV lamp is typically operating with a power output between 1-30 kW and can be even higher at times (IJpelaar et al., 2010).

Another disinfection treatment step that was not reported in the reviewed literature was the use of ozone. Even though it was not in the reported literature, ozone as a treatment will be presented to provide context for later. The disinfection properties of ozone have been known and used for water treatment purposes since the late 19^{th} century (Gottschalk et al., 2010). Ozone used today, both as a disinfectant and in other uses in the industry, is usually produced by a corona discharge ozone generator. This works by releasing an electric discharge in an environment of oxygen gas. The electric discharge carries enough energy to split oxygen molecules. The split oxygen molecule creates two lone unstable oxygen atoms, which quickly reacts with other available oxygen molecules to form ozone, as seen in equation 1.

(1) $$O\cdot + O_2 \rightarrow O_3$$

(2) $$O_3 + H_2O \overset{UV}{\leftrightarrow} H_2O_2 + O_2$$

(3) $$H_2O_2 \overset{UV}{\leftrightarrow} 2\,OH\cdot$$

Ozone is a highly unstable gas and must be created "in situ" instead of being supplied by a gas tank. The fact that ozone is highly reactive is necessary for its disinfection properties, but it also means that other potentially harmful by-products can be created (Gottschalk et al., 2010). Ozone has the potential to oxidize organic matter, either directly or indirectly. Both the direct and indirect oxidation processes can lead to the formation of DBPs. The creation of DBPs is inevitable but can be reduced if the direct reactions of ozone are favored over hydroxyl radical reactions during ozonation (De Vera et al., 2015). The direct oxidation of organic matter with ozone is a selective reaction where ozone reacts with an unsaturated bond. In general, ozone will react faster with a molecule, the more nucleophilic it is. This means ozone will react faster with aromatic and aliphatic compounds that have electron-supplying substituents, like amine or hydroxyl groups (Gottschalk et al., 2010). One of the potential reaction mechanisms for ozone in water is the creation of hydroxyl radicals. This is one of the most prominent indirect oxidizing pathways of ozone. When only ozonation is applied, the creation is happening via a complicated pathway, and the generation is limited. However, when UV light is added, the creation of hydroxyl radicals is promoted via a hydrogen peroxide pathway (eq. 2 and 3) (Denkewicz, 2015; Gligorovski et al., 2015). This relationship between ozone and UV light will be more investigated in the next subsection.

Wastewater in coastal areas and from industry may contain a higher concentration of bromide (Br^-) compared to inland and domestic wastewater. Ozone will be affected by this as bromide is highly reactive with ozone (Penru et al., 2013). The reactions that occur between ozone and bromide has the potential to form bromate (eq. 4 and 5), which is a known carcinogenic.

(4) $$Br^- + O_3 \rightarrow BrO^- + O_2$$

(5) $$BrO^- + 2O_3 \rightarrow BrO_3^- + 2O_2$$

However, it has been shown that the ozonation of seawater with a concentration of up to 5 mg O_3/L did not form any bromate (Penru et al., 2013). Seawater has a bromide content of 62 mg/L, the highest concentrations found in WWTPs with specific bromide sources, like the chemical industry, was 50 mg/L. Therefore, it is reasonable to assume no formation of bromate in wastewaters either. Instead, the ozonation of water with high bromide concentrations lead to bromide being oxidized into secondary oxidants, mainly hypobromous acid (HOBr) (eq. 6).

From a water treatment perspective, the generation of hypobromous acid is interesting as it has been shown to have an inhibitory effect on bacterial regrowth (Penru et al., 2013). This means it may act as a more long-term disinfectant and prevent microorganism activity further down the line in, for example, a drinking water distribution system.

(6) $$Br^- + O_3 + H_2O \rightarrow HOBr + O_2 + OH^-$$

The tertiary treatment plants have come a long way when it comes to treating wastewater and making it reusable. However, pharmaceuticals are still a concern and not removed sufficiently with the widely used treatment processes today.

1.2 Emerging treatment technologies

Due to the increasing concern surrounding pharmaceuticals in the wastewater, there has been numerous research articles about new treatment technologies capable of degrading pharmaceuticals. Advanced oxidation processes (AOP) seem to be some of the most prominent methods in the research. Treatment processes that involve the formation of hydroxyl radicals in high enough quantities to affect water purification are referred to as AOPs (Glaze et al., 1987; von Sonntag, 2008). Hydroxyl radicals are extremely unstable compounds that will react unselectively and immediately. Since ozone itself is selective in its reaction mechanisms, hydroxyl radicals may further help the oxidation processes to remove organic matter and other more complex compounds (Gligorovski et al., 2015). The formation of hydroxyl radicals can be promoted via several different methods, but the most interesting in a wastewater treatment perspective is O_3, UV/O_3, UV/H_2O_2, and O_3/H_2O_2. Both ozone and UV light are in use today in WWTPs and was presented in the previous section. However, they have not been implemented with the degradation of pharmaceuticals in mind, but rather to act as a disinfectant. These methods have shown potential to degrade pharmaceuticals in their current implementation. They are therefore included in the results and discussion for emerging treatment technologies since the operational parameters may be optimized for the degradation of pharmaceuticals.

Even though ozone and UV work well on their own, a study done by Magbanua et al. (2006) showed a massive improvement in the disinfection effect when combined. They studied the effect of UV and ozone against *E. Coli* and the synergistic disinfectant effect when both where combined. When combined, they achieved the same result with an 18 times lower UV dose and a 4 times smaller ozone dose. Even though this study only looks at *E. Coli*, it still shows the

potential that the combination of UV and ozone has for an enhanced disinfection effectiveness. This may mean that one can expect to see an increased RE for pharmaceuticals as well when UV light and O_3 are combined. This combined effect makes the use of UV/O_3 in a water treatment application very interesting.

What gives the synergistic effect of UV/O_3 combined extra attention is the possibility for photochemical generation of ozone. Therefore, the UV light can be used for both disinfection or removal of pharmaceuticals and the production of ozone. UV light consists of a broad wavelength spectrum, and it is the wavelengths below 200 nm that are interesting for the photochemical generation of ozone. The generation of ozone by exposing oxygen to UV light has been known since 1900 (Gottschalk et al., 2010). The generation of ozone by using UV light have generally given low yields per kWh compared to other more established methods of ozone production. This has led to a lack of progress in lamp development and reactor design (Dohan and Masschelein, 1987). The lamps that emit wavelengths in this ozone generating spectrum are often referred to as VUV (Zoschke et al., 2014). A wavelength of 185 nm is optimal for the formation of ozone. In theory, one photon with a wavelength of 185 nm has the potential to create two molecules of ozone when irradiating oxygen or a gas mixture containing a sufficient amount of oxygen (Dohan and Masschelein, 1987). This wavelength is absorbed by an oxygen molecule, which splits the molecule into two oxygen atoms, where in turn, the separate oxygen atoms react with other oxygen molecules.

$$O_2 + h\nu\ (185\ nm) \rightarrow 2\ O\cdot$$

$$O\cdot + O_2 + M \rightarrow O_3 + M$$

In the last reaction, M is a molecule used to absorb excess kinetic energy (Dohan and Masschelein, 1987).

By using the Planck-Einstein relation to calculate the photon energy at 185 nm, the theoretical production of ozone per kWh can be calculated.

$$E = h\nu = h\frac{c}{\lambda} = 6.63 * 10^{-34} Js * \frac{3 * 10^{8}\ m/s}{185 * 10^{-9} m} = 1.07 * 10^{-18} J$$

This is the energy of a single photon at 185 nm. This then gives the following calculation for the number of photons per second:

$$\frac{1\ J/s}{1.07 * 10^{-18} J} = 0.93 * 10^{18}\ s^{-1}$$

Since one photon can generate two molecules of ozone, we then have $1.86*10^{18}$ molecules of ozone per second. This amounts to $14.8*10^{-5}$ g of ozone per second or a theoretical production of 534 g/kWh for UV light at 185 nm. In a study by Dohan and Masschelein (1987), they achieved an ozone production of 16-27 g/kWh with pure oxygen and 7 g/kWh when using dry air.

There are several studies where LP-UV lamps have been used to produce ozone (Bolton and Denkewicz, 2007; Briner, 1959; Dohan and Masschelein, 1987; Liao et al., 2011; Zoschke et al., 2014). All the studies researched used the same experimental approach for the formation of ozone. Air or oxygen was passed between the UV-lamp and the surrounding quartz glass where ozone was generated. This flow of newly generated ozone gas is then injected into the water again upstream of the UV-lamp (Liao et al., 2011; Zoschke et al., 2014). There are many factors that influence how much ozone will be generated, and reactor diameter and gas flow rate has been shown to largely affect the ozone production (Liao et al., 2011). If air is used instead of oxygen, it is essential to ensure the air is dry as water vapor in the gas will always affect the production of ozone negatively. For a gas mixture containing 0.5 mole water/$m^{3,}$ it was observed a decrease in ozone yield by a factor of 0.55-0.6 (Dohan and Masschelein, 1987). In an ordinary LP-UV lamp, the most prominent wavelength is 254 nm. This wavelength leads to the photolysis of ozone and, as such, affects the photochemical generation of ozone from the 185 nm light.

1.3 Analytical methods and sampling methods for pharmaceuticals in wastewater

From the reviewed literature, gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) were the main types of methods used to analyze pharmaceuticals in the wastewater. Some different configurations of LC-MS/MS were used, including high performance and ultra-high performance, liquid chromatography (HPLC, UHPLC).

The GC-MS consists of two separate units. There is the gas chromatography (GC), which vaporizes the samples and separates the compounds in a column. The mass spectrometry (MS) ionizes them and detects the compounds as they come off the column. Since the samples need to be vaporized, GC is best suited for volatile substances. In the column, there is a stationary phase which retains some compounds while others pass with ease. The sample is carried through the column by a carrier gas, which need to be an inert or unreactive gas, helium is

commonly used, but hydrogen and nitrogen can be used as well. Through the column, the different pharmaceuticals will be separated and have different retention times. At the end of the column, the compounds can be detected. If standard solutions of the pharmaceuticals of interest have been run in the GC beforehand, the retention times give what type of pharmaceutical it is, and the area below the peak gives the amount present. However, if two pharmaceuticals have the same retention time, it would not be possible to differentiate between them. When a GC is coupled to an MS, the accuracy is better than each method on their own. The MS work by converting compounds to an ionized state. The ions are then sent through an electric or magnetic field where they will be detected and measured by the mass to charge ratio (*m/z*).

An LC-MS/MS is utilizing three stages for the detection of compounds. These three stages are the liquid chromatography (LC), which separates the compounds dissolved in a liquid phase using a column, and two mass spectrometers lined up after each other that ionizes and detects the compounds. The LC works by the same principle as a GC, except the mobile phase is now a liquid instead of a gas. The volatility of the compounds to be analyzed are not a concern either for LC. As mentioned, two different configurations were used in the literature reviewed herein, HPLC and UHPLC. Both operate under high pressure to ensure the flow of the sample through the column. UHPLCs benefit over HPLC is more rapid flow rates leading to a shorter analysis time. When two mass spectrometers are lined up after each other, the sensitivity and accuracy increases, this is due to the possible fragmentation of the molecules when exposed to two ionization processes. In the first MS, the molecule is ionized and detected, and in the next, the ionization might lead to the fragmentation of the molecule. These fragments will be detected and can be related to the parent compound. GC and LC both have their advantages and disadvantages over each other. For GC, there is a weak matrix effect, and the analytical cost is low compared to LC. However, LC has a shorter analytical duration and easier sample preparation (Hao et al., 2007).

When it comes to sampling methods, at the highest level, only two different approaches exist, grab sampling or composite samples. The most widely used sampling method today is the 24-h composite sample. When used, a mechanical sampler is set up that samples a given volume per hour for 24-h. This takes more time but is preferred over grab sampling. A grab sample is highly susceptible to fluctuations in the concentration and does not represent what the average concentrations coming into the WWTPs are. As the name suggests, a grab sample is filling the sample container in one go. This might lead to significant differences for the influent and effluent samples. 5- and 18-h composite samples have also been reported. In general, the most

accurate sampling method would be the 24-h composite samples, that have been adjusted for the hydraulic retention time (HRT) of the WWTPs (Rodayan et al., 2014). This means that if the HRT is ten hours, effluent sampling should be initiated ten hours after the influent sample was started.

2 Results and discussion

In this work, the removal efficiencies for pharmaceuticals in different WWTPs have been studied. The results are divided by the different pharmaceutical groups that have been detected in the WWTPs. Each pharmaceutical group is then presented by the treatment method, and the removal efficiency is compared between the different methods when possible. The WWTPs are from different locations around the world (Europe, Asia, Africa, North/South America), and differ in both size and treatment methods used. An overview of the different wastewater treatment plants presented are listed in Table 1.

Table 1. *Overview of the wastewater treatment plants with the chosen sample and analytical method.*

Country	Treatment level	Size (PE/ m^3/day)	Sample period	Analytical method	References
China	Tertiary	-/-	Seven days, spring, 24-h composite samp.	HPLC- MS/MS	Ashfaq et al., 2017
Poland	Secondary	-/-	One year, grab samp.	HPLC-MS/MS	Kot-Wasik et al., 2016
Portugal	Primary/ Secondary	213,500/ 54,500	2013/2014, 24-h composite samp.	UHPLC-MS/MS	de Jesus Gaffney et al., 2017
Algiers	Secondary	250,000/ 50,400	November 2014, 24-h composite samp.	GC-MS	Kermia et al., 2016
France	Tertiary	93,000/-	April-August 2015, 24-h composite samp.	GC-MS	Thiebault et al., 2017
Brazil	Tertiary	600,000/ 194,400	November 2017, March/April 2018, 5-h composite samp.	UHPLC-MS/MS	Bisognin et al., 2019
Czech Republic	Secondary	1000/-	Grab samp.	UHPLC-MS/MS	Rozman et al., 2017
Mexico	Tertiary	-/-	April 2015/2016, 24-h/18-h composite samp.	HPLC-MS/MS	Rivera-Jaimes et al., 2017
Saudi-Arabia	Tertiary	-/300,000	24-h composite samp.	HPLC-MS/MS	Shraim et al., 2017
Spain	Tertiary	-/18,000	Six months, grab samp.	HPLC-MS/MS	Afonso-Olivares et al., 2017
USA	Secondary	-/136,000	Twice per season in 2010, 24-h composite samp.	HP-LC/MS/MS	Mohapatra et al., 2016
Italy	Secondary	600,000/-	May 2016, 24-h composite samp.	UPHLC-MS/MS	Palli et al., 2019
Colombia	Primary	2,500,000 /350,000	March 24-h composite samp.	UPHLC-MS/MS	Botero-Coy et al. 2018

HPLC-MS/MS: High-performance liquid chromatography-tandem mass spectrometry. UHPLC-MS/MS: Ultra high-performance liquid chromatography-tandem mass spectrometry. GC-MS: Gas chromatography-mass spectrometry. Samp.: samples.

2.1 Antibiotics

Antibiotics is the pharmaceutical group with the most detected compounds. The high interest for antibiotics is due to the increasing concern surrounding the development of antibiotic-resistant bacteria (Kümmerer and Henninger, 2003; Le-Minh et al., 2010). In the reviewed literature, twenty-eight different types of antibiotics were detected in the wastewater samples. The data from primary treatment is presented in Table 2. The WWTP with a mechanical treatment process is equipped with a secondary treatment, but samples were taken after the primary treatment. The removal efficiency (RE) for antibiotics in a primary treatment plant ranged from -24.0 to 66.7%. For some of the compounds, the concentrations increased in the effluent. The average removal for all the compounds were 21.7%. Two types of primary treatment have been included, assisted chemical treatment (ACT) and mechanical treatment.

Table 2. *Overview of antibiotic concentrations in influent and effluent found in WWTPs with primary treatment.*

Antibiotics	**Influent** (µg/L)	**Effluent** (µg/L)	**Treatment process**	**Removal Efficiency** (%)	**References**
Azithromycin	6.32	3.99	ACT	36.9	Botero-Coy et al., 2018
Ciprofloxacin	2.29	0.81	ACT	64.6	Botero-Coy et al., 2018
	2.0	1.6	Mechanical	20.0	de Jesus Gaffney et al., 2017
Clarithromycin	0.32	0.31	ACT	3.1	Botero-Coy et al., 2018
Clindamycin	0.02	0.018	ACT	10.0	Botero-Coy et al., 2018
Doxycycline	0.12	0.066	ACT	45.0	Botero-Coy et al., 2018
Erythromycin	0.04	0.044	ACT	-10.0	Botero-Coy et al., 2018
	0.5	0.62	Mechanical	-24.0	de Jesus Gaffney et al., 2017
Metronidazole	0.31	0.32	ACT	-3.2	Botero-Coy et al., 2018
Norfloxacin	1.37	0.47	ACT	65.7	Botero-Coy et al., 2018
Sulfadiazine	n.d.	n.d.	Mechanical	-	de Jesus Gaffney et al., 2017
Sulfamerazine	n.d.	n.d.	Mechanical	-	de Jesus Gaffney et al., 2017
Sulfamethazine	n.d.	n.d.	Mechanical	-	de Jesus Gaffney et al., 2017
Sulfamethoxazole	0.63	0.65	ACT	-3.2	Botero-Coy et al., 2018
	2.2	1.2	Mechanical	45.5	de Jesus Gaffney et al., 2017
Sulfapyridine	0.5	0.43	Mechanical	14.0	de Jesus Gaffney et al., 2017
Sulfathiazole	n.d.	n.d.	Mechanical	-	de Jesus Gaffney et al., 2017
Tetracycline	0.33	0.11	ACT	66.7	Botero-Coy et al., 2018
Trimethoprim	0.32	0.34	ACT	-6.3	Botero-Coy et al., 2018

n.d.: Not detected. ACT: Assisted chemical treatment

As primary treatment is the most basic form of wastewater treatment, the removal of pharmaceuticals was not expected to be high. Several of the detected antibiotics even showed an increase in concentration from the influent to the effluent. This was the case for erythromycin, metronidazole, sulfamethoxazole, and trimethoprim. Erythromycin is especially interesting as the effluent concentrations were higher for both WWTPs studied and had the most significant difference from inlet to outlet. The higher concentrations in the effluent might be explained by desorption of erythromycin from the particulate phase during the treatment, or due to particulate matter containing erythromycin being filtered out in the sample preparation. (Lindberg et al., 2005; Gulkowska et al., 2008). Not all the detected compounds showed a low removal. For ciprofloxacin, norfloxacin, and tetracycline, the removal was around 65%. In an ACT, there is not much biodegradation taking place, as mentioned earlier. The removal of particles is based on sedimentation. Ternes et al. (2004) have found that ciprofloxacin adsorbs significantly to suspended solids. Ciprofloxacin and norfloxacin have a similar structure and are part of the group of antibiotics called fluoroquinolones. For this group of antibiotics, the primary removal mechanism in wastewater treatment is adsorption to sludge (Golet et al., 2003). Tetracyclines are a group of antibiotics including, doxycycline, oxytetracycline, and tetracycline, which, as the name suggests, consist of four cyclic rings with different functional groups attached. In a study about the fate of tetracyclines in wastewater, no evidence of biodegradation was found, but rather a significant adsorption to sludge (Kim et al., 2005). As mentioned, the most removed antibiotics in primary treatment, had a removal efficiency of around 65%. The SS removal for the plant in question was reported to be 60% (Botero-Coy et al., 2018). Therefore, it is likely that these antibiotics are removed by sorption to the sludge and SS.

When secondary treatment is implemented, the overall removal of pharmaceuticals is expected to increase compared to a primary treatment. The pharmaceutical concentrations in the influent and effluent for secondary treatment plants can be found in Table 3. The average removal for all the antibiotics detected in the plants with secondary treatment is 35.3%. This is not much higher than what was found for the primary treatment. However, for sulfapyridine, Rozman et al. (2017) found a negative RE of -836.8% in one of the WWTPs. If we exclude this from the calculation, then the average RE is 70.2%. Sulfapyridine was detected in two WWTPs. Rozman et al. (2017), with the mechanical/biological treatment (MBT), reported an effluent concentration eight times higher than in the influent. The other was a Bardenpho process WWTP, with a RE of 44.0%. Rozman et al. (2017) does not comment on possible explanations

for the high effluent concentrations of sulfapyridine. One flaw with the experimental design is that grab samples were used for sampling, which can lead to significant concentration fluctuations in the samples. The flow of pharmaceuticals into and out of the WWTP is not likely to be homogenous; it will fluctuate with time of day. This can result in more substantial fluctuations for the influent and effluent samples than when 24-h composite samples are used (Clara et al., 2004). However, the difference for sulfapyridine is so significant that other explanations need to be considered. Sulfasalazine is a drug used for inflammatory bowel diseases, and it is metabolized by bacteria into sulfapyridine and 5-aminosalicylic acid (Weber-Schöndorfer, 2015) (Figure 4). The bacteria responsible for this metabolization contain azoreductases, which is a group of enzymes that facilitate the cleavage of azo bonds (-N=N-) (Claus et al., 2016).

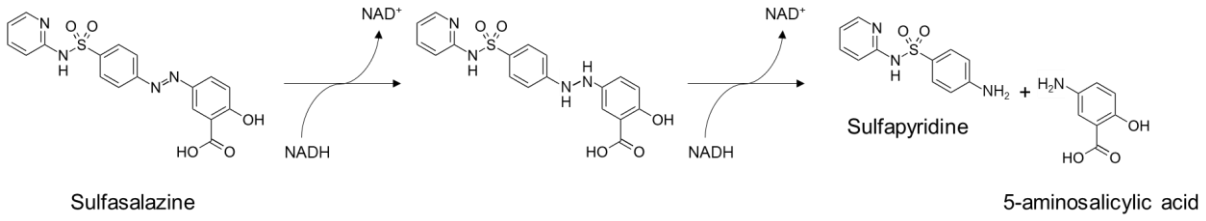


Figure 4. *The basic mechanism for the azoreduction of sulfasalazine into sulfapyridine and 5-aminosalicylic acid.*

Numerous bacteria contain azoreductase activity, including, *Clostridium, Pseudomonas, Bacillus, Geobacillus, Lysinibacillus, Enterococcus*, and *Escherichia* (Misal and Gawai, 2018). In similar treatment plants like the one in this case, both *Bacillus*, *Clostridium*, and *Pseudomonas* have been found as some of the most prominent genera's (Bitton, 2011; Cyprowski et al., 2018). Sulfasalazine is not one of the studied pharmaceuticals, but it is a widely used pharmaceutical in the Czech Republic with over 500,000 DDDs issued in the 4th quarter of 2019 ("SÚKL," 2020). According to the National Cancer Institute, the manufacturing and use of sulfapyridine were discontinued in 1990 (NCI, 2020). All the above makes the azoreduction of sulfasalazine into sulfapyridine a viable explanation for the large effluent concentration of sulfapyridine. For many of the antibiotics, the RE was below 50%, including erythromycin, sulfamerazine, sulfamethoxazole, and sulfapyridine. These compounds had the lowest RE, but cephalexin with a RE of 70.4% still had the highest effluent concentration with 1.751 µg/L.

Table 3. *Overview of antibiotic concentrations in influent and effluent found in WWTPs with secondary treatment.*

Antibiotics	**Influent** (µg/L)	**Effluent** (µg/L)	**Treatment process**	**Removal Efficiency** (%)	**References**
Amoxicillin	0.813	0.000813	CAS	99.9	Palli et al., 2019
Cephalexin	5.912	1.751	CBT	70.4	Mohapatra et al., 2016
Chloramphenicol	0.022	0.0059	MBT	73.2	Kot-Wasik et al., 2016
	0.009	<0.02	MBT	100.0	Rozman et al., 2017
Ciprofloxacin	2.0	0.35	Bardenpho	82.5	de Jesus Gaffney et al., 2017
	2.789	0.257	CBT	90.8	Mohapatra et al., 2016
Clarithromycin	2.035	0.084	MBT	95.9	Rozman et al., 2017
	0.18	0.079	CAS	56.1	Palli et al., 2019
	0.136	0.066	CBT	51.5	Mohapatra et al., 2016
Doxycycline	0.176	<LOD	CAS	100.0	Palli et al., 2019
Erythromycin	0.0756	0.0399	MBT	47.2	Kot-Wasik et al., 2016
	0.152	0.006	MBT	96.1	Rozman et al., 2017
	0.5	0.51	Bardenpho	-2.0	de Jesus Gaffney et al., 2017
	0.143	0.072	CBT	49.7	Mohapatra et al., 2016
Levofloxacin	1.178	0.105	CBT	91.1	Mohapatra et al., 2016
Ofloxacin	0.1257	0.0352	MBT	72.0	Kot-Wasik et al., 2016
Penicillin G	0.015	>0.01	MBT	100.0	Rozman et al., 2017
Sulfadiazine	n.d.	n.d.	Bardenpho	-	de Jesus Gaffney et al., 2017
Sulfamerazine	0.012	<0.010	MBT	16.7	Rozman et al., 2017
	n.d.	n.d.	Bardenpho	-	de Jesus Gaffney et al., 2017
Sulfamethazine	0.053	0.007	MBT	86.8	Rozman et al., 2017
	n.d.	n.d.	Bardenpho	-	de Jesus Gaffney et al., 2017
Sulfamethoxazole	0.621	0.633	MBT	-1.9	Rozman et al., 2017
	2.2	0.69	Bardenpho	68.6	de Jesus Gaffney et al., 2017
	2.007	0.342	CBT	83.0	Mohapatra et al., 2016
Sulfapyridine	0.057	0.534	MBT	-836.8	Rozman et al., 2017
	0.5	0.28	Bardenpho	44.0	de Jesus Gaffney et al., 2017
Sulfathiazole	n.d.	n.d.	Bardenpho	-	de Jesus Gaffney et al., 2017
Trimethoprim	0.25	0.003	MBT	98.8	Rozman et al., 2017
	0.992	0.149	CBT	85.0	Mohapatra et al., 2016

n.d.: Not detected. LOD: Limit of detection. CAS: Conventional activated sludge. CBT: Chemical/biological treatment. MBT: Mechanical/biological treatment.

The WWTPs in Table 4 with tertiary treatment all have a disinfectant treatment implemented. Also, one of the plants has reverse osmosis (RO) filtration as well. Again, with an extra treatment step implemented, the logical conclusion would be that the overall removal would be higher than for both primary and secondary treatment. This is not the case, at least not when all the detected antibiotics are included. The RE for antibiotics in tertiary treatment is then 52.5%,

which is almost 20% lower than the RE for secondary treatment when sulfapyridine is excluded. Two compounds have a high negative RE in the tertiary treatment. These are clindamycin and danofloxacin with a removal efficiency of -153.8% and -113.9%, respectively. If these are excluded, the average RE for tertiary treatment increases to 65.5%, which still is not as high as the average removal in secondary treatment when sulfapyridine is excluded.

Table 4. *Overview of antibiotic concentrations in influent and effluent found in WWTPs with tertiary treatment.*

Antibiotics	**Influent** (µg/L)	**Effluent** (µg/L)	**Treatment process**	**Removal Efficiency** (%)	**References**
Cephalexin	1.88	1.53	Chlorination	18.6	Shraim et al., 2017
Ciprofloxacin	0.0272	0.00871	A2/O + UV	68.0	Ashfaq et al., 2017
	0.385 ± 0.534	0.064 ± 0.029	UASB/AS + H_2O_2	83.4	Bisognin et al., 2019
	1.97 ± 1.05	0.065 ± 0.010	CAS/Chlorination/RO	96.7	Afonso-Olivares et al., 2017
Clindamycin	0.039 ± 0.023	0.099 ± 0.039	UASB/AS + H_2O_2	-153.8	Bisognin et al., 2019
Danofloxacin	0.000	0.001	A2/O + UV	-113.9	Ashfaq et al., 2017
Doxycycline	n.d.	n.d.	UASB/AS + H_2O_2	-	Bisognin et al., 2019
Enrofloxacin	0.00117	0	A2/O + UV	100.0	Ashfaq et al., 2017
	0.037*	n.d.	UASB/AS + H_2O_2	100.0	Bisognin et al., 2019
Erythromycin	0.076 ± 0.036	n.d.	CAS/Chlorination/RO	100.0	Afonso-Olivares et al., 2017
Metronidazole	0.023*	n.d.	UASB/AS + H_2O_2	100.0	Bisognin et al., 2019
	0.168 ± 0.209	n.d.	CAS/Chlorination/RO	100.0	Afonso-Olivares et al., 2017
Norfloxacin	0.485	0.0781	A2/O + UV	83.9	Ashfaq et al., 2017
	n.d.	n.d.	UASB/AS + H_2O_2	-	Bisognin et al., 2019
Ofloxacin	0.495	0.129	A2/O + UV	73.9	Ashfaq et al., 2017
	0.281 ± 0.320	0.034 ± 0.008	UASB/AS + H_2O_2	87.9	Bisognin et al., 2019
	1.15 ± 0.409	<LOQ	CAS/Chlorination/RO	100.0	Afonso-Olivares et al., 2017
Oxytetracycline	0.293	0.0227	A2/O + UV	92.3	Ashfaq et al., 2017
	0.641*	1.154*	UASB/AS + H_2O_2	-80.0	Bisognin et al., 2019
Sarafloxacin	0	0.000431	A2/O + UV	-	Ashfaq et al., 2017
Sulfadiazine	0.0106	0.00295	A2/O + UV	72.2	Ashfaq et al., 2017
	0.057 ± 0.027	0.051 ± 0.029	UASB/AS + H_2O_2	10.5	Bisognin et al., 2019

Sulfadimethoxine	0	0	A2/O + UV	-	Ashfaq et al., 2017
Sulfamethazine	0.00132	0.000805	A2/O + UV	39.0	Ashfaq et al., 2017
Sulfamethoxazole	0.0479	0.0231	A2/O + UV	51.8	Ashfaq et al., 2017
	1.48	0.695	CAS/UV	53.0	Rivera-Jaimes et al., 2018
	0.980 ± 0.466	0.301 ± 0.181	UASB/AS + H_2O_2	69.2	Bisognin et al., 2019
	0.748 ± 0.350	n.d.	CAS/Chlorination/RO	100.0	Afonso-Olivares et al., 2017
Sulfathiazole	0.049*	0.070*	UASB/AS + H_2O_2	42.9	Bisognin et al., 2019
Tetracycline	0.179	0.018	A2/O + UV	89.9	Ashfaq et al., 2017
	n.d.	n.d.	UASB/AS + H_2O_2	-	Bisognin et al., 2019
Trimethoprim	0.68	0.338	CAS/UV	50.3	Rivera-Jaimes et al., 2018
	0.042 ± 0.025	0.050 ± 0.001	UASB/AS + H_2O_2	-19.0	Bisognin et al., 2019
	0.201 ± 0.121	0.031	CAS/Chlorination/RO	84.6	Afonso-Olivares et al., 2017
Tylosin	<LOQ	0.051*	UASB/AS + H_2O_2	-	Bisognin et al., 2019

n.d.: Not detected. *Only detected in one sample. LOQ: Limit of quantification. A2/O: Anaerobic-anoxic/oxic. UASB: Upflow anaerobic sludge blanket. AS: Activated sludge. CAS: Conventional activated sludge. RO: Reverse osmosis.

When comparing the RE of the same antibiotics in both primary, secondary, and tertiary treatment plants, it shows that in general, a higher treatment level leads to a better RE. In Figure 5, ciprofloxacin, erythromycin, and sulfamethoxazole are compared. Ciprofloxacin showed better removal in the secondary treatment plants compared to the tertiary. However, the difference is only around 3%. For erythromycin and sulfamethoxazole, tertiary treatment performed significantly better than both primary and secondary treatment.

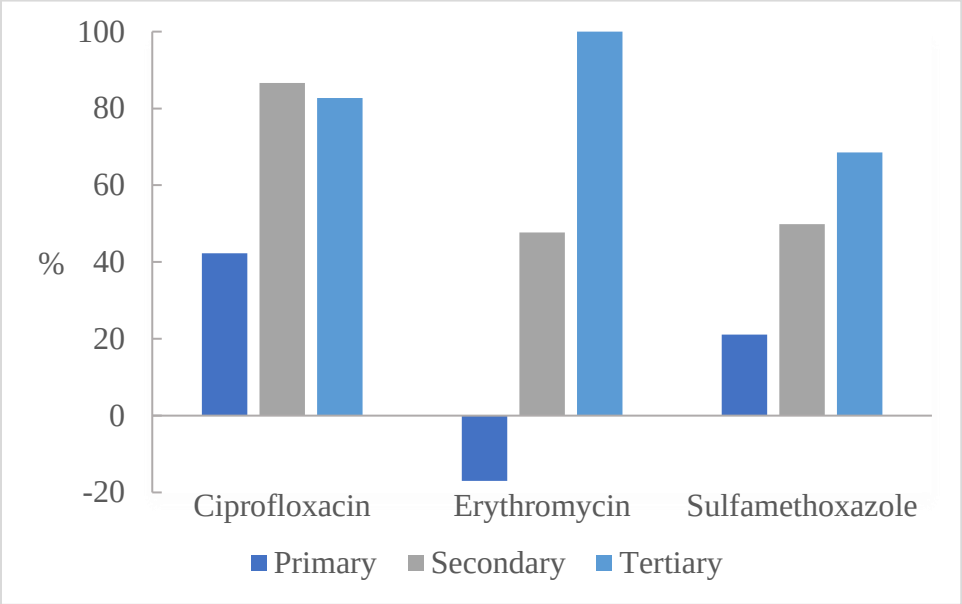


Figure 5. *Comparison of the RE of antibiotics for different treatment levels.*

Even though there are many different antibiotics, several of them share the same core structure. One could presume they would behave similarly in the treatment plants and have a similar removal efficiency. This does not seem to be the case. Antibiotics with the suffix -floxacin are part of quinolone antibiotics which are based around the structure for 4-quinolone, as seen in Figure 6 (Heeb et al., 2011).

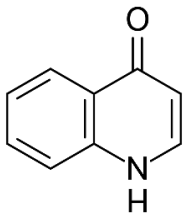


Figure 6. *Structure of 4-quinolone, which quinolone antibiotics are based around.*

Both ciprofloxacin, norfloxacin, levofloxacin, ofloxacin, enrofloxacin, danofloxacin, sarafloxacin are all built around this structure. Additionally, these are part of a more specific group called fluoroquinolones, which have a fluorine atom and a carboxyl group attached to the bicyclic ring structure (Figure 7) (Fedorowicz and Sączewski, 2018).

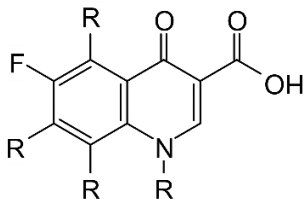
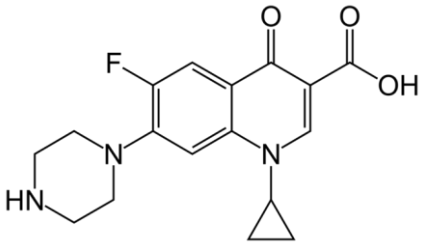
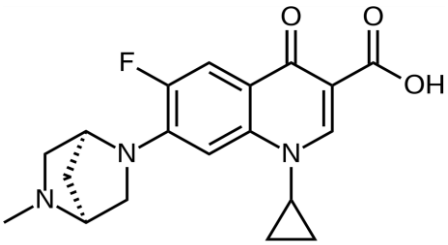
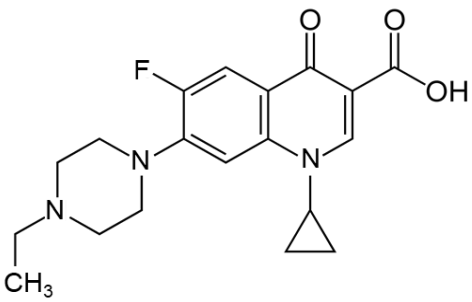


Figure 7. *The base structure for all fluoroquinolones.*

Ciprofloxacin, danofloxacin, and enrofloxacin are suitable for comparison as they all share the same core structure (Figure 7) and have similar side chains. Ashfaq et al. (2017) detected all these compounds in a tertiary treatment plant with UV-light as a disinfection step. Even though they have similar structures, vastly different removal efficiencies were observed (Table 5).

Table 5*. Structures and removal efficiencies of selected fluoroquinolones.*

Name	**Structure**	**Removal efficiency (%)[a]**
Ciprofloxacin		68.0
Danofloxacin		-113.9
Enrofloxacin		100.0

[a]Ashfaq et al., 2017.

Both ciprofloxacin and enrofloxacin have a decrease in concentration from influent to effluent, while the concentration of danofloxacin more than doubles. Enrofloxacin is removed entirely

during the treatment, and ciprofloxacin is a known metabolite of enrofloxacin (Maggs, 2008). This might explain why there is found a lower removal for ciprofloxacin. The mechanisms behind the biodegradation of enrofloxacin in wastewater are not well known. However, in a study done by Alexandrino et al. (2017), the concentration of microorganisms belonging to the phyla *Proteobacteria* and *Bacteroidetes* increased over time when exposed to enrofloxacin—suggesting that they are important in the degradation process. An increase in the effluent concentration can be explained by pharmaceuticals being enclosed in feces particles, which is first released in the biological treatment (Gobel et al., 2007). This may be the case for danofloxacin as the concentrations of unchanged danofloxacin in the excreta of chickens and cows were 85% unchanged (Heitzman, 1998).

2.2 Nonsteroidal anti-inflammatory drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are some of the most commonly used pharmaceuticals, which is reflected in the detected influent concentrations. The highest detection was found for ibuprofen with 37.25 µg/L. Most of the compounds have a high removal rate in secondary and tertiary treatment plants, with some exceptions. One of these exceptions is diclofenac.

Table 6. *Overview of NSAID concentrations in influent and effluent found in WWTPs with primary treatment.*

NSAIDs	**Influent** (µg/L)	**Effluent** (µg/L)	**Treatment process**	**Removal Efficiency** (%)	**References**
Acetylsalicylic acid	17	1.8	Mechanical	89.4	de Jesus Gaffney et al., 2017
Diclofenac	0.40	0.34	ACT	15.0	Botero-Coy et al. 2018
	2.5	1.9	Mechanical	24.0	de Jesus Gaffney et al., 2017
Ibuprofen	22	16.0	Mechanical	27.3	de Jesus Gaffney et al., 2017
Indomethacin	0.15	0.12	Mechanical	20.0	de Jesus Gaffney et al., 2017
Ketoprofen	0.10	0.04	Mechanical	82.0	de Jesus Gaffney et al., 2017
Naproxen	2.98	2.40	ACT	19.5	Botero-Coy et al. 2018
	7.9	8.20	Mechanical	-3.8	de Jesus Gaffney et al., 2017
Nimesulide	n.d.	n.d.	Mechanical	-	de Jesus Gaffney et al., 2017

n.d.: Not detected. ACT: Assisted chemical treatment.

When only primary treatment is in use, the removal efficiency of NSAIDs is low (Table 6). For all the detected compounds, the average removal is 34.2%. Acetylsalicylic acid and ketoprofen

have the highest removal, with 89.4% and 82.0%, respectively. Naproxen showed a slight increase in concentration from the influent to the effluent for the plant with a mechanical treatment process. A possible explanation is that during the sample preparation, naproxen adsorbed to particulate matter have been filtered out, leading to the detection of a lower influent concentration (Lindberg et al., 2005).

Table 7. *Overview of NSAID concentrations in influent and effluent found in WWTPs with secondary treatment.*

NSAIDs	**Influent** (µg/L)	**Effluent** (µg/L)	**Treatment process**	**Removal Efficiency** (%)	**References**
Acetylsalicylic acid	17	0	Bardenpho	100.0	de Jesus Gaffney et al., 2017
Diclofenac	0.9905	2.7107	MBT	-173.7	Kermia et al. 2016
	2.1380	3.0184	MBT	-41.2	Kot-Wasik et al., 2016
	1.237	0.500	MBT	59.6	Rozman et al., 2017
	1.957	2.364	CAS	-20.8	Palli et al., 2019
	2.5	1.5	Bardenpho	40.0	de Jesus Gaffney et al., 2017
	0.067	0.021	CBT	68.7	Mohapatra et al., 2016
Ibuprofen	8.6129	0.4313	MBT	95.0	Kermia et al. 2016
	6.5861	0.1417	MBT	97.8	Kot-Wasik et al., 2016
	37.25	0.042	MBT	99.9	Rozman et al., 2017
	22	0	Bardenpho	100.0	de Jesus Gaffney et al., 2017
	14.333	0.040	CBT	99.7	Mohapatra et al., 2016
Indomethacin	0.15	0.12	Bardenpho	20.0	de Jesus Gaffney et al., 2017
Ketoprofen	0.5652	1.0345	MBT	-83.0	Kermia et al. 2016
	2.7004	0.1593	MBT	94.1	Kot-Wasik et al., 2016
	0.393	<0.01	MBT	97.5	Rozman et al., 2017
	0.819	0.182	CAS	77.8	Palli et al., 2019
	0.1	0.01	Bardenpho	90.0	de Jesus Gaffney et al., 2017
Naproxen	1.2197	0.3337	MBT	72.6	Kermia et al. 2016
	1.054	<0.05	MBT	95.2	Rozman et al., 2017
	7.9	0.95	Bardenpho	88.0	de Jesus Gaffney et al., 2017
	11.912	0.053	CBT	99.6	Mohapatra et al., 2016
Nimesulide	n.d.	n.d.	Bardenpho	-	de Jesus Gaffney et al., 2017

n.d.: Not detected. MBT: Mechanical/biological treatment. CAS: Conventional activated sludge. CBT: Chemical/biological treatment.

When secondary treatment is implemented, the overall removal efficiency increases significantly for most of the NSAIDs (Table 7). For diclofenac, it is the opposite. Now it has an average negative removal of -11.2%. If diclofenac is included, the overall average RE is 53.5%. If it is excluded, the RE increases to 77.8%. Six different treatment plants detected diclofenac in their influent and effluent. Of these, the distribution was 50/50 between negative and positive removal efficiency. Treatment plants with seemingly the same treatment method detect quite different removal rates. The removal efficiency of diclofenac for plants with a mechanical/biological treatment range from -173.7% to 59.6%. The design parameters of the wastewater treatment plants are not reported. These parameters would be valuable information to discover why there are such significant differences, since the solid retention time (SRT) has been shown to have a strong correlation with the treatment efficiency (Kreuzinger et al., 2004). When the SRT is increased, there is room for more diverse microbiology to establish itself in the treatment. To see significant removal of diclofenac, according to Ternes et al. (2004), the SRT needs to be between 5-15 days. Another study, however, got contradictory results on how the SRT affected the removal of diclofenac and suggested there were other influences of importance (Clara et al., 2005). For one WWTP, ketoprofen was detected with a higher effluent than influent concentration. The other treatment plants showed high removal for the same compound, with an average RE of 89.8%. It is the same case here as with diclofenac that the treatment plants seem to be operating similarly. Kermia et al. (2016), reported negative removal for both diclofenac and ketoprofen. The explanation given for the increase in effluent concentration is that conjugated metabolites are deconjugated in the treatment process.

Table 8. *Overview of NSAID concentrations in influent and effluent found in WWTPs with tertiary treatment.*

NSAIDs	**Influent** (µg/L)	**Effluent** (µg/L)	**Treatment process**	**Removal Efficiency** (%)	**References**
Diclofenac	0.0218	0.0260	A2/O + UV	-19.3	Ashfaq et al., 2017
	1.0900	0.5930	CAS/UV	45.6	Rivera-Jaimes et al. 2017
	0.245	0.079	Chlorination	67.8	Thiebault et al. 2017
	0.207±0.127	n.d.	CAS/Chlorination/RO	100.0	Afonso-Olivares et al. 2017
Ibuprofen	0.219	0.0201	A2/O + UV	90.8	Ashfaq et al., 2017
	0.81	n.d.	CAS/UV	100.0	Rivera-Jaimes et al. 2017
	2.27	0.038	CAS/Chlorination	98.3	Thiebault et al. 2017
	20.8±3.20	0.071±0.055	CAS/Chlorination/RO	99.7	Afonso-Olivares et al. 2017
Indomethacin	0.00924	0.0112	A2/O + UV	-21.2	Ashfaq et al., 2017
	0.066	0.056	CAS/UV	15.2	Rivera-Jaimes et al. 2017
Ketoprofen	0.0582	0.00937	A2/O + UV	83.9	Ashfaq et al., 2017
	1.70	0.047	CAS/Chlorination	97.2	Thiebault et al. 2017
	0.991±0.169	0.178±0.037	CAS/Chlorination/RO	82.0	Afonso-Olivares et al. 2017
Naproxen	0.00788	0.00117	A2/O + UV	85.2	Ashfaq et al., 2017
	2.4	0.077	CAS/UV	96.8	Rivera-Jaimes et al. 2017
	1.33	0.058	CAS/Chlorination	95.6	Thiebault et al. 2017
	2.51±0.605	0.111±0.043	CAS/Chlorination/RO	95.6	Afonso-Olivares et al. 2017

A2/O: Anaerobic-anoxic/oxic. CAS: Conventional activated sludge. RO: Reverse osmosis.

When tertiary treatment is in use, one starts to see overall a high removal efficiency, with an average of 71.4% (Table 8.). Diclofenac is, in general, removed at a higher rate with tertiary treatment than with secondary treatment, but still an increase in concentration from influent to effluent is detected for one of the treatment plants. For indomethacin, the removal efficiency has even become worse with tertiary treatment compared to secondary treatment. Ashfaq et al. (2017) found that there was a release of diclofenac from SS during the anoxic process, which can explain the negative removal. According to Kimura et al., (2005), the presence of chlorine in the structure of diclofenac and indomethacin is the reason for the reduced degradation.

Overall there seems to be an increasing trend of higher removal efficiencies for NSAIDs with an increasing level of treatment. However, when we look at selected NSAIDs, there are some interesting differences (Figure 8). Ibuprofen and naproxen show a high removal with both secondary treatment and tertiary treatment. The secondary treatment barely has a better removal for ibuprofen compared to tertiary, with a 1% difference. Where the interesting results occur are for diclofenac and ketoprofen. For these pharmaceuticals, the removal efficiency decreases significantly from a primary treatment to secondary treatment. The explanation for this might be that diclofenac and ketoprofen in primary treatment adsorb to the SS, and are removed through the sludge (Lindberg et al., 2005). Remaining SS in the primary treatment effluent will have diclofenac and ketoprofen adsorbed to it, which will be removed in the filtration of the samples, thus giving a low effluent concentration (Gulkowska et al., 2008).

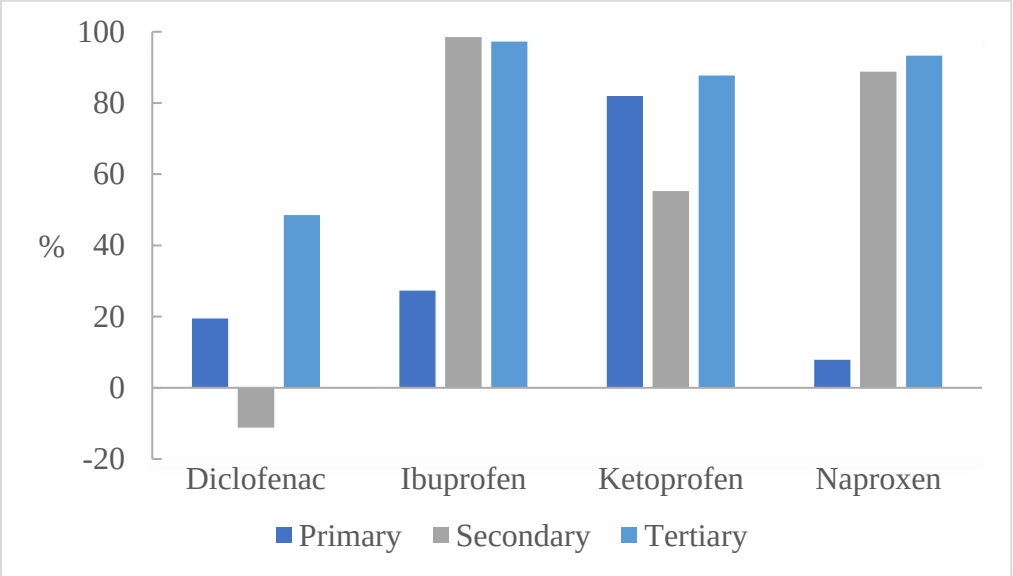


Figure 8. *Comparison of the RE of selected NSAIDs for different treatment levels*

When a secondary treatment is in place, the biological treatment may release the NSAIDs adsorbed to SS, but not further degradation takes place (Gobel et al., 2007), which leads to an increase in the detected effluent concentration. This is likely the fate for diclofenac, but for ketoprofen, only one out of the five secondary treatment plants had a negative removal rate. The rest showed an average removal efficiency of 89.8%, which is even 2% higher than the tertiary treatment was able to achieve. The low removal of ketoprofen is, therefore, probably caused by the local composition of the wastewater or particular operational parameters in this one treatment plant. It cannot be generalized for the removal efficiency of ketoprofen in secondary treatment as a whole.

2.3 Analgesics, anticonvulsants, and antidepressants

The following pharmaceutical groups do not contain as many different compounds as antibiotics and NSAIDs. Therefore, several different groups are presented in Table 9, with vastly different applications. Analgesics are pain relievers, anticonvulsants are used to treat epileptic seizures, and antidepressants are used, as the name suggests, against symptoms of depression.

***Table 9**. Overview of analgesic, anticonvulsant, and antidepressant concentrations in influent and effluent found in WWTPs with primary treatment.*

Pharmaceuticals	**Influent** (µg/L)	**Effluent** (µg/L)	**Treatment process**	**Removal Efficiency** (%)	**References**
Analgesic					
Paracetamol	39.25	29.66	ACT	24.4	Botero-Coy et al. 2018
	118.00	74	Mechanical	37.3	de Jesus Gaffney et al. 2017
Anticonvulsant					
Carbamazepine	0.07	0.065	ACT	7.1	Botero-Coy et al. 2018
	1.5	0.88	Mechanical	41.3	de Jesus Gaffney et al. 2017
Antidepressant					
Fluoxetine	0.003	0.01	Mechanical	-233.3	de Jesus Gaffney et al. 2017

ACT: Assisted chemical treatment.

Since these compounds are not in the same pharmaceutical group and do not share the same structural core, the average removal efficiency for all of them will not be relevant. The general removal is low as expected in a primary treatment plant. Paracetamol showed an average removal rate of 30.9%. Carbamazepine showed an average removal rate of 24.2%, which was the highest average observed for all the treatment levels. This is still a low removal efficiency, but it might be higher than for the other treatment levels since carbamazepine shows a low affinity for sorption to sludge, which is the main removal mechanism in primary treatment (Ternes et al., 2004). Fluoxetine was only detected in one treatment plant, where a negative removal of -233.3% was observed. This means that the effluent concentration was three times higher than the influent. Such a significant increase from influent to effluent with only primary treatment applied is not expected. There are no explanations provided by de Jesus Gaffney et al. (2017) for why this occurs. A possible explanation, as mentioned for earlier compounds, is that they are adsorbed to solids, which are broken down through the silts and mechanical treatment. Thereby making the compounds available for detection.

When secondary treatment is implemented, there is a major increase in the removal efficiency of paracetamol and a huge decrease for carbamazepine, respectively, an average RE of 99.8% and -95.2% (Table 10). Paracetamol is removed close to completion when secondary treatment is in use. All the treatment processes have a biological step in common, which is where the bulk of the degradation is probably happening, since paracetamol is easily biodegradable (Zhang et al., 2013).

***Table 10**. Overview of analgesic, anticonvulsant, and antidepressant concentrations in influent and effluent found in WWTPs with secondary treatment.*

Pharmaceuticals	**Influent** (µg/L)	**Effluent** (µg/L)	**Treatment process**	**Removal Efficiency** (%)	**References**
Analgesic					
Paracetamol	9.3917	0.1124	MBT	98.8	Kot-Wasik et al. 2016
	39.225	0.025	MBT	100.0	Rozman et al. 2017
	0.74	<LOD	CAS	100.0	Palli et al. 2019
	118	0.01	Bardenpho	100.0	de Jesus Gaffney et al. 2017
	37.690	n.d.	CBT	100.0	Mohapatra et al. 2016
Anticonvulsant					
Carbamazepine	2.0719	3.5086	MBT	-69.3	Kot-Wasik et al. 2016
	2.85	2.725	MBT	4.4	Rozman et al. 2017
	0.205	0.247	CAS	-20.5	Palli et al. 2019
	1.5	0.63	Bardenpho	58.0	de Jesus Gaffney et al. 2017
	0.033	0.181	CBT	-448.5	Mohapatra et al. 2016
Antidepressant					
Fluoxetine	0.003	0.01	Bardenpho	-233.3	de Jesus Gaffney et al. 2017
	0.029	0.025	CBT	13.8	Mohapatra et al. 2016

MBT: Mechanical/biological treatment. CAS: Conventional activated sludge. CBT: Chemical/biological treatment. LOD: Limit of detection.

Carbamazepine show varying removal efficiencies when secondary treatment is implemented, from a negative removal of -448.5% to 58.0%. The concentrations coming into the wastewater treatment plant are of interest. Mohapatra et al. (2016) detected the overall lowest influent and effluent concentrations but had the most negative removal efficiency. In a lab-scale test, no biological degradation or adsorption of carbamazepine could be detected (Clara et al., 2004). The increase in concentration is likely due to the cleavage of carbamazepine glucuronides

which have been proposed as an explanation for the increase in effluent concentration of carbamazepine by numerous studies (Ternes, 1998; Vieno et al., 2007; Zhang et al., 2008; Zorita et al., 2009). However, it was not until recently, in a study done by He et al. (2019), that the concentration of carbamazepine *N*-glucuronide (CBZ-Glu) in wastewater, was reported. They examined for carbamazepine and its metabolites, including; carbamazepine *N*-glucuronide, 2-hydroxycarbamazepine, 3-hydroxycarbamazepine, 10-hydroxycarbamazepine, carbamazepine 10,11-epoxide, and 10,11-dihydroxycarbamazepine (Figure 9).

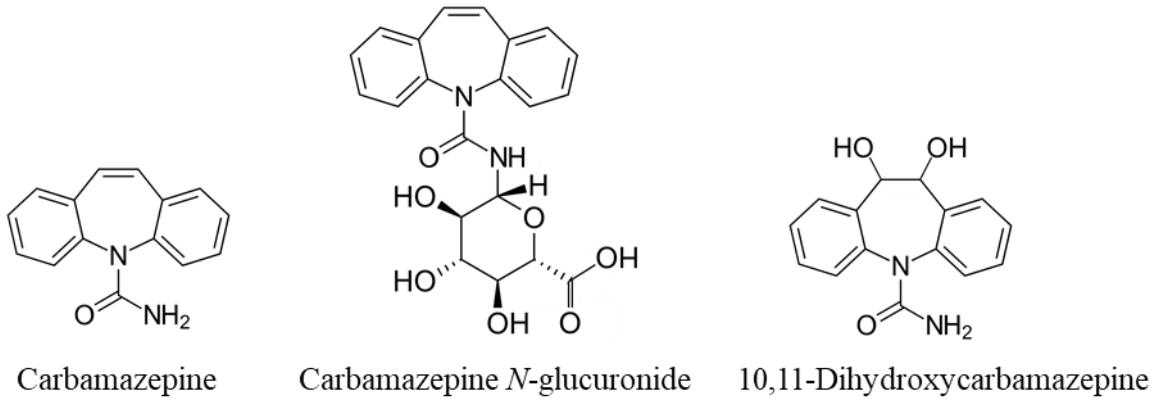


Figure 9. *Carbamazepine with two of its most common metabolites.*

When He et al. (2019) carried out the analysis, they found that the concentration of carbamazepine metabolites exceeded the concentration of carbamazepine in wastewater. In the influent, carbamazepine only made up 20.38% of the total concentration when the main metabolites were included, CBZ-Glu and 10,11-dihydroxycarbamazepine (DiOH-CBZ) stood for 16.25% and 47.27%, respectively. DiOH-CBZ, with the other hydroxylated carbamazepine metabolites, showed no sign of reforming carbamazepine during biodegradation (Brezina et al., 2015). An increase in the effluent concentration can, therefore, be attributed to the cleavage of the carbamazepine glucuronide. However, if the concentration proportions He et al. (2019) reported are representative, one should maximum see a negative removal for carbamazepine of around -75%.

For fluoxetine, no increase in removal was reported by de Jesus Gaffney et al. (2017), when secondary treatment was implemented. However, the reported data from de Jesus Gaffney et al. (2017) in Table 10 are median concentrations, the max concentrations detected showed a difference from 0.05 µg/L in primary, to 0.03 µg/L in secondary treatment.

Table 11. *Overview of analgesic, anticonvulsant and antidepressant concentrations in influent and effluent found in WWTPs with tertiary treatment.*

Pharmaceuticals	**Influent** (µg/L)	**Effluent** (µg/L)	**Treatment process**	**Removal Efficiency** (%)	**References**
Analgesic					
Paracetamol	13.640±2.136	0.417±0.652	UASB/AS + H_2O_2	97.0	Bisognin et al. 2019
	5.65	0.01	A2/O + UV	99.9	Ashfaq et al. 2017
	7.88	n.d.	CAS/UV	100.0	Rivera-Jaimes et al. 2017
	38.90	31.20	Chlorination	19.8	Shraim et al. 2017
	55.8	0.013	CAS/ Chlorination	100.0	Thiebault et al. 2017
Anticonvulsant					
Carbamazepine	0.00217	0.00524	A2/O + UV	-141.5	Ashfaq et al. 2017
	0.29	0.188	CAS/UV	35.2	Rivera-Jaimes et al. 2017
	0.215	0.163	CAS/ Chlorination	24.2	Thiebault et al. 2017
	0.443±0.164	0.016±0.007	CAS/RO	96.4	Afonso-Olivares et al. 2017
Antidepressant					
Fluoxetine	0.000346	0	A2/O + UV	100.0	Ashfaq et al. 2017
	0.205±0.024	0.063	CAS/RO	69.3	Afonso-Olivares et al. 2017

UASB: Upflow anaerobic sludge blanket. AS: Activated sludge. A2/O: Anaerobic-anoxic/oxic. n.d.: Not detected. CAS: Conventional activated sludge. RO: Reverse osmosis.

It is first when tertiary treatment is implemented that one starts to see significant removal of carbamazepine (Table 11.). The average RE of carbamazepine for all the examined tertiary wastewater treatment plants is only 3.4%. However, Afonso-Olivares et al. (2017) reported a removal of 96.4%. This treatment plant implemented a reverse osmosis (RO) filtration before the effluent. In this study, samples were taken from several parts of the treatment process, and they found that the carbamazepine concentration was not decreased before the RO filtration. Even though the carbamazepine was removed from the effluent, it was not degraded. Instead, it went into the RO concentrate, which means the problem will be more isolated, but some form of treatment for the degradation of carbamazepine still needs to be applied. Paracetamol still has a removal efficiency close to 100% for the reported numbers, except for a study conducted by Shraim et al. (2017), which reported a low removal rate of 19.8%. There are given no comments about this deviation in removal efficiency in the report, and there is a lack of information about the sampling time and treatment process that was used in the study. A lack

of information surrounding the treatment process in the WWTPs reported on is occurring in several of the studies. This makes it harder to compare the different treatment processes, and a flowchart of the processes used in the plant should be a minimum of information given in the article.

Fluoxetine also has a considerable increase in RE compared to secondary treatment. The average removal is now 84.65%.

2.4 Beta-blockers, lipid regulators, and psychostimulants

In this chapter, several different pharmaceutical groups are merged, as there were not that many detected pharmaceuticals from each group. The presented pharmaceuticals consist of beta-blockers, lipid regulators, and caffeine. They are used to treat abnormal heart rhythms and lower blood pressure, treat high lipid levels in the blood, and as a central nervous system stimulant that increases the mental alertness, respectively. The most prominent source of caffeine is from coffee and tea, and it is also added to some medications for headaches as well.

Table 12. *Overview of beta-blockers, lipid regulators, and psychostimulants concentrations in influent and effluent found in a WWTP with primary treatment.*

Pharmaceuticals	**Influent** (µg/L)	**Effluent** (µg/L)	**Treatment process**	**Removal Efficiency** (%)	**References**
Beta-blockers					
Atenolol	1.1	0.78	Mechanical	29.1	de Jesus Gaffney et al. 2017
Metoprolol	0.06	0.04	Mechanical	33.3	de Jesus Gaffney et al. 2017
Propranolol	0.21	0.19	Mechanical	9.5	de Jesus Gaffney et al. 2017
Lipid regulators					
Clofibric acid	n.d.	n.d.	Mechanical	-	de Jesus Gaffney et al. 2017
Bezafibrate	1.1	0.5	Mechanical	54.5	de Jesus Gaffney et al. 2017
Gemfibrozil	0.5	0.39	Mechanical	22.0	de Jesus Gaffney et al. 2017
Psychostimulant					
Caffeine	117	83	Mechanical	29.1	de Jesus Gaffney et al. 2017

n.d.: Not detected.

For the primary treatment, only one of the two studies examined reported on the detection of beta-blockers, lipid regulators, and psychostimulants (Table 12). Therefore, the different primary treatment processes cannot be compared. The low removal efficiencies seen are

expected as neither the beta-blockers, lipid regulators, or caffeine has been reported to have significant sorption to SS or sludge (Wick et al., 2009; Sui et al., 2010; Huang et al., 2011).

Table 13. *Overview of beta-blockers, lipid regulators, and psychostimulant concentrations in influent and effluent found in WWTPs with secondary treatment.*

Pharmaceuticals	**Influent** (µg/L)	**Effluent** (µg/L)	**Treatment process**	**Removal Efficiency** (%)	**References**
Beta-blockers					
Atenolol	0.2821	0.0949	MBT	66.4	Kot-Wasik et al. 2016
	0.643	<0.01	MBT	98.4	Rozman et al. 2017
	0.561	0.058	CAS	89.7	Palli et al. 2019
	1.1	0.28	Bardenpho	74.5	de Jesus Gaffney et al. 2017
	1.552	0.707	CBT	54.4	Mohapatra et al. 2016
Metoprolol	1.98	0.029	MBT	98.5	Rozman et al. 2017
	0.06	0.05	Bardenpho	16.7	de Jesus Gaffney et al. 2017
	0.107	0.061	CBT	43.0	Mohapatra et al. 2016
Propranolol	0.21	0.22	Bardenpho	-4.8	de Jesus Gaffney et al. 2017
Lipid regulators					
Clofibric acid	n.d.	n.d.	Bardenpho	-	de Jesus Gaffney et al. 2017
Bezafibrate	1.1	0.15	Bardenpho	86.4	de Jesus Gaffney et al. 2017
Gemfibrozil	0.5	0.09	Bardenpho	82.0	de Jesus Gaffney et al. 2017
	0.824	0.243	CBT	70.5	Mohapatra et al. 2016
Psychostimulant					
Caffeine	11.4899	0.1335	MBT	98.8	Kot-Wasik et al. 2016
	185	0.038	MBT	100.0	Rozman et al. 2017
	117	0.49	Bardenpho	99.6	de Jesus Gaffney et al. 2017
	19.582	0.006	CBT	100.0	Mohapatra et al. 2016

MBT: Mechanical/biological treatment. CAS: Conventional activated sludge. CBT: Chemical/biological treatment. n.d.: Not detected.

In the secondary treatment, the effect of biological degradation is shown. The removal efficiencies increase for all the compounds compared to primary treatment, except for metoprolol and propranolol (Table 13.). de Jesus Gaffney et al. (2017), reported a RE of 33.3% and 9.5% for metoprolol and propranolol after primary treatment. After going through the secondary treatment, the RE was decreased to 16.7% and -4.8% for metoprolol and propranolol, respectively. The other studies reported much higher removal for metoprolol, with an average

of 70.8%. de Jesus Gaffney et al. (2017) utilizes a three-stage Bardenpho process, with an anaerobic, anoxic and aerobic treatment stage. The degradation of metoprolol under anaerobic and anoxic conditions was shown to be minimal. The major removal came from aerobic conditions (Rubirola et al., 2014). Since the Bardenpho process used, only has one stage were the biodegradation of metoprolol takes place, this might lead to the lower removal efficiency reported. The information about what type of biological treatment process that is used in the other treatment plants is not given, but as mentioned in the introduction, activated sludge is one of the most used treatment processes, and the chances that this is what they are using is high. That would also make sense as to why one see a higher removal of metoprolol reported from these treatment plants as the activated sludge process is aerobic. Of the beta-blockers, propranolol showed the highest sorption to sludge (Scheurer et al., 2010), which might help explain the negative removal efficiency reported in the secondary treatment. In the primary treatment, propranolol might stay adsorbed to the solids, but when entering the secondary treatment, desorption can occur, leading to an increased effluent concentration.

Clofibric acid was not detected in the wastewater, but bezafibrate and gemfibrozil showed a removal of over 70%. Aerobic biodegradation was reported as the main removal mechanism in wastewater treatment for the mentioned beta-blockers (Huang et al., 2011). However, with a RE of just above 70%, there is still room for improvement. The RE for caffeine is 100% or close to it for all the WWTPs, likely due to microbial activity as caffeine is readily biodegradable (Sui et al., 2010).

Table 14. *Overview of beta-blockers, lipid regulators, and psychostimulant concentrations in influent and effluent found in WWTPs with tertiary treatment.*

Pharmaceuticals	**Influent** (µg/L)	**Effluent** (µg/L)	**Treatment process**	**Removal Efficiency** (%)	**References**
Beta-blockers					
Atenolol	0.08	0.045	CAS/UV	43.8	Rivera-Jaimes et al. 2017
	2.04	0.545	Chlorination	73.3	Shraim et al. 2017
	16.4	0.893	CAS/ Chlorination	94.6	Thiebault et al. 2017
	1.27±0.342	0.039±0.027	CAS/RO	96.9	Afonso-Olivares et al. 2017
Metoprolol	0.0144	0.0416	A2/O + UV	-188.9	Ashfaq et al. 2017
	1.26	0.121	CAS/ Chlorination	90.4	Thiebault et al. 2017
Propranolol	0.00808	0	A2/O + UV	100.0	Ashfaq et al. 2017
	0.425±0.149	<LOQ	CAS/RO	100.0	Afonso-Olivares et al. 2017
Lipid regulators					
Clofibric acid	0.000713	0.000152	A2/O + UV	78.7	Ashfaq et al. 2017
	0.005	0.004	CAS/RO	20.0	Afonso-Olivares et al. 2017
Bezafibrate	1.58	0.31	CAS/UV	80.4	Rivera-Jaimes et al. 2017
	0.253±0.212	n.d.	CAS/RO	100.0	Afonso-Olivares et al. 2017
Gemfibrozil	0.001	0.000	A2/O + UV	86.7	Ashfaq et al. 2017
	0.045	0.023	CAS/UV	48.9	Rivera-Jaimes et al. 2017
	n.d.	n.d.	CAS/Chlorination	-	Thiebault et al. 2017
	5.41±2.45	0.021±0.049	CAS/RO	99.6	Afonso-Olivares et al. 2017
Psychostimulant					
Caffeine	2.837	0.0229	A2/O + UV	99.2	Ashfaq et al. 2017
Caffeine	32.189±5.458	0.341±0.542	UASB/AS + H_2O_2	98.9	Bisognin et al. 2019
Caffeine	49.1±7.72	0.098±0.114	CAS/RO	99.8	Afonso-Olivares et al. 2017

CAS: Conventional activated sludge. RO: Reverse osmosis. A2/O: Anaerobic-anoxic/oxic. LOQ: Limit of quantification.

When tertiary treatment is applied, one starts to see significant variations in the removal efficiencies, especially for the beta-blockers (Table 14). Metoprolol was detected in two WWTPs with a RE of -188.9% and 90.4%, respectively. The treatment facility with a negative removal utilized an A2/O process with UV light as a disinfectant. This process is similar to the

Bardenpho process in the sense that it consists of three stages were two of them are anaerobic and anoxic, and only one stage with oxic conditions, which, as mentioned, is needed for the biodegradation of metoprolol. The degradation of metoprolol with UV-light is not efficient, as only 7% were transformed after a contact time of 10 minutes (Šojić et al., 2012). The treatment with a CAS has a very high removal degree, and it seems like this process is the most efficient for the removal of metoprolol. In both secondary and tertiary treatment, when the RE has been low or negative, the influent concentration of metoprolol has been low as well.

With the tertiary treatment, lipid regulators were, in general, removed to a high degree. The RE of clofibric acid was only 20% for the CAS/RO process; this was surprising. RO filtration has been shown to remove other pharmaceuticals well from the effluent and a study done by Díaz et al. (2017), found that clofibric acid was removed completely when RO was applied.

Caffeine is still experiencing a removal close to 100% with tertiary treatment. The small variations are likely due to differences in the local conditions.

2.5 Pharmaceuticals in wastewater sludge

One of the removal mechanisms for pharmaceuticals in wastewater treatment is adsorption to sludge. Even though this is a known removal pathway, there is a lack of studies sampling and examining sludge for the content of pharmaceuticals. In the literature reviewed, there were only two studies that reported on the concentrations of pharmaceuticals in sludge (Table 15.).

Table 15. *Concentration of selected pharmaceuticals in influent and sludge*

Pharmaceuticals	Influent (µg/L)	Sludge (µg/kg)	Treatment process	References
Caffeine	2.837	0.551	A2/O + UV	Ashfaq et al. 2017
	32.189±5.458	635±858	UASB/AS + H_2O_2	Bisognin et al. 2019
Ciprofloxacin	0.0272	313	A2/O + UV	Ashfaq et al. 2017
	0.385±0.534	2217±2451	UASB/AS + H_2O_2	Bisognin et al. 2019
Enrofloxacin	0.00117	23.6	A2/O + UV	Ashfaq et al. 2017
	0.037*	n.d.	UASB/AS + H_2O_2	Bisognin et al. 2019
Norfloxacin	0.485	5320	A2/O + UV	Ashfaq et al. 2017
	n.d.	271±176	UASB/AS + H_2O_2	Bisognin et al. 2019
Ofloxacin	0.495	4870	A2/O + UV	Ashfaq et al. 2017
	0.281±0.320	1142±365	UASB/AS + H_2O_2	Bisognin et al. 2019
Oxytetracycline	0.293	1710	A2/O + UV	Ashfaq et al. 2017
	0.641*	n.d.	UASB/AS + H_2O_2	Bisognin et al. 2019
Sulfadiazine	0.0106	0.687	A2/O + UV	Ashfaq et al. 2017
	0.057±0.027	n.d.	UASB/AS + H_2O_2	Bisognin et al. 2019
Sulfamethoxazole	0.0479	2.85	A2/O + UV	Ashfaq et al. 2017
	0.980±0.466	n.d.	UASB/AS + H_2O_2	Bisognin et al. 2019
Tetracycline	0.179	1030	A2/O + UV	Ashfaq et al. 2017
	n.d.	62±29	UASB/AS + H_2O_2	Bisognin et al. 2019

A2/O: Anaerobic-anoxic/oxic. UASB: Upflow Anaerobic Sludge Blanket. AS: Activated sludge. *Only detected once.

The pharmaceutical concentrations in sludge are reported for dry sludge. Several of the analyzed pharmaceuticals have a high affinity for adsorption to sludge. Fluoroquinolones is a group of antibiotics that are removed primarily through the adsorption to sludge (Golet et al., 2003). The reported concentrations in the reviewed literature substantiate this as the removal pathway. Ciprofloxacin, norfloxacin, and ofloxacin are all fluoroquinolones, and are detected with some of the highest concentrations in sludge compared to the other pharmaceuticals. Even when not detected in the influent Bisognin et al. (2019) still found a concentration of 271±176 µg/kg of norfloxacin in the sludge. Both Ashfaq et al. (2017) and Bisognin et al. (2019) carried out mass balance calculations for the wastewater treatment plants studied. Ashfaq et al. (2017), found that the influent load of pharmaceuticals was 352 g/d, the effluent load 14.5 g/d, and in

the sludge 58.1 g/d. Bisognin et al. (2019) showed much higher loads of 9,401.77±1,044.64 g/d in the influent, 511.47±56.83 g/d in the effluent, and 130.56±38.53 g/d in the sludge. This shows that high amounts of pharmaceuticals are present in the sludge and cannot be overlooked as a source for the release of pharmaceuticals to the environment. In a recent study by Ivanová et al. (2018) occurrence of pharmaceuticals in sludge was for the first time studied in Slovakia, where 65% of the wastewater sludge is utilized indirectly (as compost) for soil improvement. There have been detected pharmaceuticals in vegetable samples, which definitely should raise concerns (Christou et al., 2017). The potential effects use of wastewater sludge in agriculture might have, has not received enough attention and needs to be examined closer.

2.6 Emerging technology for the removal of pharmaceuticals in wastewater

Since the removal of numerous pharmaceuticals in conventional WWTPs are not complete and even negative in some cases, research into alternative treatment technologies capable of degrading pharmaceuticals has been prominent. The different treatment methods reviewed are UV, O_3, UV/O_3, UV/H_2O_2, and O_3/H_2O_2. These are all considered advanced oxidation processes apart from UV.

When UV-light is used as a disinfectant in the wastewater treatment, the UV-dose is usually around 40-140 mJ/cm^2 (Kim et al., 2009). Diclofenac was one of the pharmaceuticals reported with a negative removal efficiency in some WWTPs and seemed not to be easily degradable. However, diclofenac and ketoprofen showed a degradation of over 90% when exposed to the highest UV disinfectant dose of 140 mJ/cm^2. The UV dose needed to be as high as 5644 mJ/cm^2 for the 90% removal of all the examined pharmaceuticals (Kim et al., 2014). For the degradation of carbamazepine and clofibric acid, a study found the necessary UV dose for 90% removal to be 1378 and 601 mJ/cm^2, with a contact time of 81.7 and 35.6 minutes respectively (Afonso-Olivares et al., 2016). These doses and contact times are very high, and other more efficient methods need to be evaluated.

Ozone is used in wastewater treatment but do not see the same extensive use as UV-light. The removal efficiencies of these emerging technologies are most relevant for the pharmaceuticals that show low removal with conventional treatment technologies. From the reviewed literature, clindamycin, danofloxacin, diclofenac, indomethacin, carbamazepine, clofibric acid, and metoprolol are some of the pharmaceuticals that stand out, with removal efficiencies below 50% for secondary and tertiary treatment. Carbamazepine and diclofenac showed good removal with O_3, with a 90% removal when exposed to 0.61-0.66 g O_3/g DOC, where DOC is dissolved organic carbon. In the same study, wastewater from six different treatment plants were used,

and they found that the composition of the wastewater had a significant impact on the removal efficiencies (Antoniou et al., 2013). In a recent lab-scale test, wastewater with a composition of almost 100 different pharmaceuticals were subjected to an ozone flow of 50 mg O_3/min in a reactor tank of 1 L. With these parameters the observed removal efficiency after the first minute was reported to be 97.2% (Szabová et al., 2020). If the same RE can be reached in a full-scale WWTP, ozonation of the wastewater for removal of pharmaceuticals seems to be very efficient.

The synergistic effect of UV/O_3 when it comes to efficiency as a disinfectant is well-known (Magbanua et al., 2006). The interesting next question is if it may be more efficient for the removal of pharmaceuticals than UV or ozone on its own. In a recent study done by Yao et al. (2018), the removal of some selected pharmaceuticals was compared between O_3 and UV/O_3. UV/O3 showed removals comparable or slightly higher than O_3 on its own. However, the UV/O_3 process had a significantly higher energy consumption compared to O_3, which makes it less favorable. There are some other studies suggesting the use of this treatment technology for the removal of pharmaceuticals. Lester et al. (2011) compared the degradation of ciprofloxacin by UV/O_3 over time with UV and UV/H_2O_2/O_3. UV/O_3 performed much better than UV and degraded at the same rate as UV/H_2O_2/O_3. According to Gomes et al. (2017), the method has potential but needs to be thoroughly compared with other methods to conclude on its competitiveness.

The removal efficiency with UV/H_2O_2 treatment have been reported by Rosario-Ortiz et al. (2010), for selected pharmaceuticals, with different UV and H_2O_2 conditions present. Wastewater from three different WWTPs were used in the analysis. The RE of the pharmaceuticals varied significantly between the different wastewater samples (Table 16.).

Table 16. *Difference in removal efficiency for carbamazepine with UV/H_2O_2 treatment for different wastewater compositions.*

	Carbamazepine removal efficiency (%)[a]	
	UV: 500 mJ/cm^2 H_2O_2: 20 mg/L	UV: 700 mJ/cm^2 H_2O_2: 20 mg/L
1	95	95
2	57	78
3	44	50

[a]Data from Rosario-Ortiz et al., 2010.

This variation in removal is due to the amount of effluent organic matter (EfOM) present and its properties. The formation of hydroxyl radicals and their non-selective oxidation properties are the main mechanism for the removal of pharmaceuticals with this treatment process. When EfOM is present, scavenging of the hydroxyl radicals occurs, leading to a lower RE (Rosario-

Ortiz et al., 2010). Proper treatment before the UV/H_2O_2 process is essential to ensure good removal of pharmaceuticals from the wastewater. Kim et al. (2009) reported a removal efficiency of 90% for 39 out of 41 studied pharmaceuticals with a UV dose of 923 mJ/cm^2, H_2O_2 concentration of 7.8 mg/L, and HRT of 5 minutes. The pharmaceuticals with removal below 90% were norfloxacin and caffeine, which is not too much of a concern as they are reported with high RE in conventional WWTPs.

When O_3 and H_2O_2 are combined as a treatment process, the formation of hydroxyl radicals is promoted. O_3/H_2O_2 was determined to be the most energy-efficient treatment method when compared to UV, UV/H_2O_2, UV/O_3, O_3, and UV/H_2O_2/O_3. The degradation rate of ciprofloxacin was also measured for the same methods, and O_3/H_2O_2 had the highest degradation rate (Lester et al., 2011). If the pharmaceuticals to be removed already have a high affinity for ozonation, the addition of H_2O_2 will not make a significant difference to the removal (Akmehmet Balcıoğlu and Ötker, 2003).

3 Conclusion

When looking at the overall removal in the reviewed literature, it has been found that tertiary treatment processes are more efficient at removing pharmaceuticals compared to secondary treatment processes, and the secondary treatment processes are again better than the primary treatment processes. The average removal efficiency for all the pharmaceuticals presented at each treatment level, were 16.3%, 40.1%, and 61.6% for primary, secondary, and tertiary treatment, respectively. This shows that the general tendency is better removal when a higher degree of treatment is implemented. However, when looking at individual pharmaceuticals, the situation is more nuanced. Diclofenac is an example were the removal efficiency was highest with primary treatment and even showed negative removal with secondary and tertiary treatment. Some of the most persistent pharmaceuticals include; clindamycin, danofloxacin, diclofenac, indomethacin, carbamazepine, clofibric acid, and metoprolol which all had an average RE below 50% for all the treatment plants.

Amongst emerging technologies, ozone and UV/H_2O_2 seems to be the most promising new treatment processes for implementation in WWTPs. Carbamazepine and diclofenac, some of the most persistent pharmaceuticals in commonly used treatment plants, show a RE of 90% when exposed to 0.61-0.66 g O_3/g DOC. The UV/H_2O_2 process managed to get a RE of at least 90% for 39 out of 41 pharmaceuticals with a UV dose of 923 mJ/cm^2, H_2O_2 concentration of 7.8 mg/L, and HRT of 5 minutes. When compared to the 61.6% RE for tertiary treatment, implementation of these emerging technologies to WWTPs would drastically decrease the release of pharmaceuticals into the environment.

When future studies on the removal of pharmaceuticals in wastewater are initiated, more information should be provided about the different stages present in the WWTPs. A schematic of the process would go a long way, but an increased focus needs to be put on the operational parameters. This is needed to get a better understanding of how differences in, for example, HRT and SRT, affect the removal of pharmaceuticals. If all the studies presented the WWTPs in a similar fashion, comparisons of treatment plants between studies would become more manageable.

The way the removal efficiency usually is presented in current studies is giving a false idea of what the total removal rate is. Most of the literature is only concerned with the influent and effluent concentrations in the treatment plant. Everything that happens in between is ignored. In the reviewed literature, only two of the articles reported on the pharmaceutical concentrations

in the sludge. This is a significant removal pathway for pharmaceuticals, and every analysis for pharmaceuticals in wastewater should include sludge samples. The concentrations of pharmaceuticals in sludge should be known since sludge from wastewater treatment can be used as fertilizer for agricultural purposes. This raises another concern that should be investigated in future studies; have the use of sludge from WWTPs as fertilizer in agriculture led to increased or detectable levels of pharmaceuticals in the surrounding environment or even in the produce grown in the fields? In addition to just taking sludge samples, samples between each treatment stage would be useful to understand the different pathways of the pharmaceuticals better. With this information, mass balances could be presented to show where the different pharmaceuticals end up.

A more focused view on what is going on inside WWTPs is not only important for the main pharmaceuticals, the metabolites of pharmaceuticals cannot be ignored either. When the only concern is surrounding the parent compound, a removal efficiency of 100%, might not mean much. The parent compound is removed, but metabolites that potentially are even more toxic than the parent compound may have taken its place. Due to this possibility, more research needs to be done to map out potential toxic metabolites.

4 Experimental design

Experimental procedures for the preliminary experimental work conducted at the start of this project are presented here. The methods used in the final plan are also presented.

4.1 Dilution measurements

First, the flow of the system was set to 20 m^3/h, the pump was at 6% power, and the pressure in the system was 0.4 bar. A saline solution was prepared in a 10 L bucket. NaCl was used as the salt, and the amount added varied from each test. To see how much salt was added, the conductivity was measured with a WTW Multi 340i conductivity meter with a TetraCon® 325 electrode. A drain pump (DP 252) was lowered into the 10 L bucket with the salt solution. The pump was connected with a hose to a valve that led to the system. There was an inlet on one side of the chamber and an outlet on the other side (Figure 10.). The pump was activated, the inlet valve opened, and the saline solution was pumped into the chamber. When a steady flow was established, after about 15 seconds, the outlet valve was opened. When 20 seconds had passed, the first sample was taken from the outlet. Every five seconds, a new sample was poured

20 m^3/h

into a beaker until five samples were taken, covering an interval of 20 seconds. The conductivity and temperature of all the samples were measured. This procedure was repeated four times.

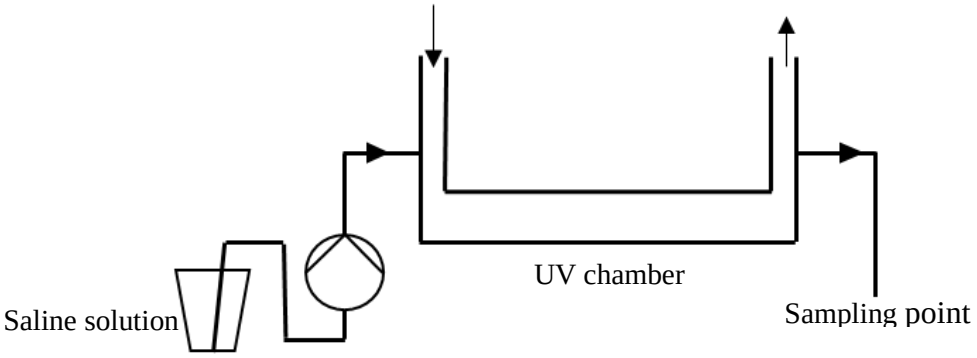


***Figure 10**. Simple schematic of the experimental setup.*

4.2 Analytical method

Testing at the facility were never carried out, but the MP-UV lamp was supposed to be run at 3 kW, 19 kW, and 35 kW to determine differences in removal with different power outputs. However, analytical methods for determination of the supposed results were planned and tested. Spectrophotometry was chosen as the method to analyze the results. HPLC was considered as the results likely would have been more precise, but the higher cost and complexity made the method less preferred. There was found no method to determine aspirin photometrically when dissolved in a tap water matrix. The closest approach, which was discovered and thought possible to adapt, was the method used by (da Silva and Borges, 2019). Since aspirin does not absorb light when dissolved, it is necessary to change the aspirin into salicylic acid. Salicylic acid can form a purple complex with a ferric ion (Fe^{3+}), which is easy to analyze with a spectrophotometer. When aspirin is dissolved in water, some of it will also react to form salicylic acid (Figure 11.).

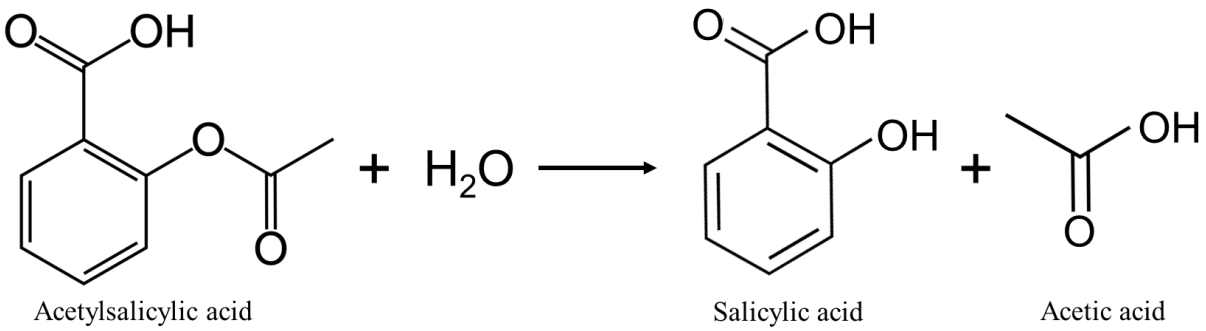


***Figure 11**. Reaction equation for acetylsalicylic acid in the presence of water.*

Because of these factors, it will only make sense to measure the salicylic content and then calculate that into the corresponding amount of aspirin. This is by no means the most precise way to perform an analysis of the aspirin but seems to be the most viable option given the conditions.

Some solutions were prepared to make a standard curve. A 50 mmol/L salicylic acid solution was prepared by weighing in 0.6990 g of salicylic acid. This was then added to a 100 mL volumetric flask with some distilled water in it. 0.9880 g of sodium hydroxide was added, and then the flask was filled with distilled water to the 100 mL mark.

A 0.2 M ferric solution was prepared by dissolving 3.9237 g of $(NH_4)_2Fe(SO_4)_2$, in a 50 mL volumetric flask. The salt was dissolved in a solution of 5 mL nitric acid (HNO_3) and some distilled water. When the salt was dissolved, distilled water was added to the 50 mL mark in the volumetric flask.

The 50 mmol/L salicylic acid solution was diluted to concentrations between 0.133-1.33 mmol/L. This was done directly into test tubes using automatic pipettes. All the dilutions that were analyzed can be found in Table 17. In each dilution, 2 mL of the 0.2 M ferric solution was added to form the purple complex.

Table 17. *Preparation of standard solutions for the calibration plot*

#	Salicylic acid (50 mmol/L), mL	Distilled water, mL
1	0.1	0.9
2	0.2	0.8
3	0.3	0.7
4	0.4	0.6
5	0.5	0.5
6	0.6	0.4
7	0.7	0.3
8	0.8	0.2
9	0.9	0.1
10	1	0

The spectrophotometer was set to 535 nm as the complex formed between salicylic acid and Fe^{3+}, absorbs well at this wavelength (da Silva and Borges, 2019; Reid et al., 2008). The prepared standard solutions were transferred from the test tubes into cuvettes used for the absorbance measurements. The spectrophotometer was set to zero with a blank consisting of distilled water.

Due to Covid-19, this original plan never saw the light of day. The thesis, therefore, had to be converted to a theoretical one, with no experimental work.

4.3 Literature review

A literature review was conducted for articles published between 2016 and 2019. Peer-reviewed articles were found through google scholar. All relevant publications were categorized and organized according to the treatment grade of the WWTP in the study, then added to Zotero. The search term used in Google Scholar was "occurrence pharmaceuticals wastewater"; this gave very relevant results. A subjective judgment was then used to choose the articles most suitable for this review.

Many of the studies sampled over long time periods and often in different seasons. When reported, the average concentration of pharmaceuticals at the influent and effluent was extracted and used in this review. If the data were presented with standard deviation, that was included as well. Not all the articles presented the removal efficiency, and they had to be calculated from the reported influent and effluent concentrations using equation 7.

(7) $\left(\frac{Cinf-Ceff}{Cinf}\right) * 100\% =$

Where C_{inf} is the concentration in the influent and C_{eff} is the concentration in the effluent.

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