# Optimizing Pharmaceutical Wastewater Treatment: A Comprehensive Review and Unique Experimental Insight

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## Abstract

The increased production and consumption of pharmaceuticals to combat evolving diseases, bacterial infection, and generally as a treatment for elusive ailments (i.e. psychiatric treatments for Alzheimer's), results in higher concentrations of pharmaceuticals in the natural environment both from production processes and human waste. This issue, while seen at a greater effect on a local level (concerning the production facility), can potentially become a global issue through the alteration of ecosystems. Here, we analyze conventional treatments for pharmaceutical wastewater treatment, which are classed under Advanced Oxidation Processes, Bio-activated methods, and treatments that involve separation methods. These treatments are then evaluated for their pros and cons when dealing with pharmaceutical wastewater. We conclude by creating an experimental treatment solution after we evaluate the standard wastewater treatment solutions that are considered staples and proven to work in breaking down organic compounds.

## Introduction

Medicine as we know it has evolved to not only better human ailments but also advance human health, leading to transformations in the medical field. However, the impact medicines and pharmaceuticals can have on the environment is often overlooked. Pharmaceuticals, such as antibiotics and steroid hormones, are chemical compounds that are produced to be used as medicinal drugs, and their environmental effects are becoming rapidly well-known [1,2]. It has been revealed that 3000 different (i.e. not natural) chemical substances are used in medicines. When those are exposed to the environment they can have toxic effects, such as behavioral changes or immune system compromisation, on most organisms, from humans to fish. They cannot be removed by traditional wastewater treatment methods [3].

Figure 1 below shows how pharmaceuticals enter the environment [4]. Regardless of the route of pharmaceuticals into the environment, the presence of pharmaceutical waste in the environment has detrimental effects on environmental and human health, in the forms of antibiotic resistance and behavioral changes for aquatic organisms.

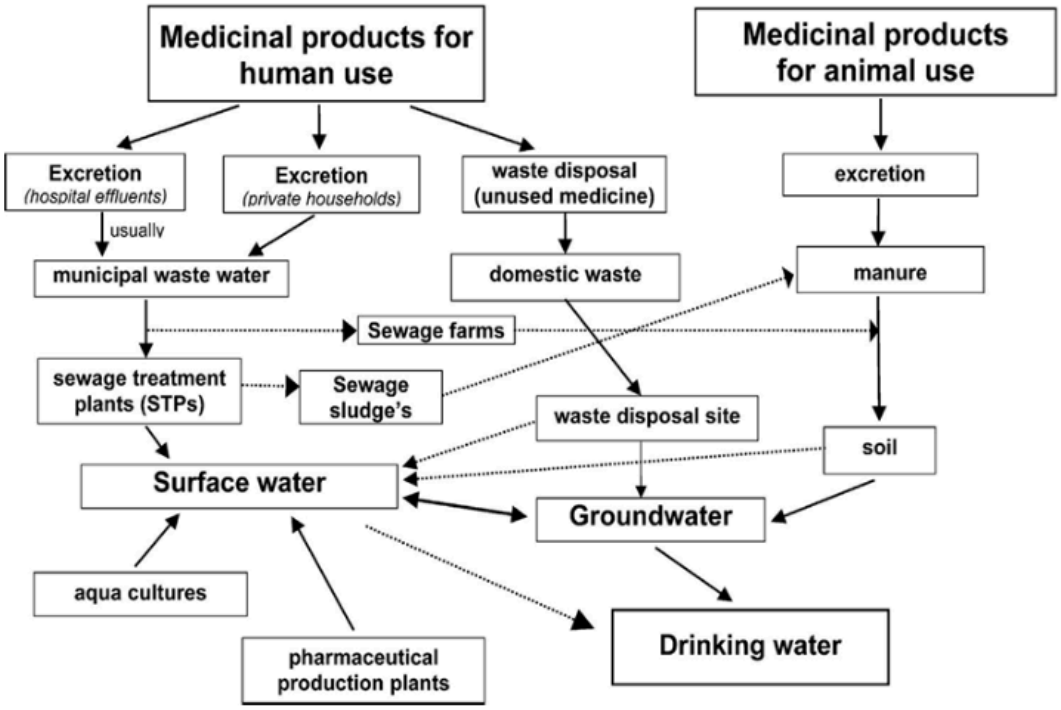


Fig 1. Routes of Pharmaceutical Waste into the Environment, taken from Ganiyu et al. (2015)

Pharmaceutical waste arises largely from pharmaceutical production plants, wastewater treatment plants (WWTPs), and landfills [5]. Due to the avenues of exposure, Active Pharmaceutical Ingredients (APIs) have become widespread in waterways, and are present in 80% of 47 groundwater sites and 139 surface water sites, found and researched across the United States [6]. Contrary to earlier research findings on the environmental impact of pharmaceuticals [7,8], recent studies have delved deeper into their effects, especially in aquatic environments. This newer literature emphasizes the tangible effects in these settings, highlighting the influence of pharmaceutical waste. The connection lies in molecular pathways shared between the environment and humans, revealing how pharmaceuticals affect both [9].

Pharmaceutical contamination has been shown to damage aquatic ecosystems [10]. Aquatic life, primarily fish, that has been exposed to pharmaceutical waste show changes in behavior, such as inhibitions of reproductive activity and reduction in activity necessary for survival, subsequently leading to a decrease in feeding [11,12]. In a different study, various fish species have exhibited inhibitions of cardiovascular systems (at greater than 10 µg/L) and reproductive functions (between 1–100 µg/L) due to ibuprofen throughout their habitat, with sub-lethal effects occurring within measured concentrations at 0.37–0.85 µg/L [11,13]. Prozac, an antidepressant, was found to have behavior changes in freshwater fish, such as territorial aggression, decreases in growth, feeding rate inhibition, and inhibition of predatorial activities at low concentrations [13]. These studies show that, even though the effects are not lethal, even at low

concentrations (environmental concentrations of “acceptable” pharmaceutical waste typically being at 0.1 –185 µg/L [11]) of pharmaceutical entry (through hospitals, production plants, households, all viable sources) into aquatic life behavioral changes like these are prevalent, which can lead to a disruption of ecosystems and long-term potential of environmental devastation.

It’s been discovered that aquatic life and ecosystems are affected by pharmaceutical deposits, but that water is also fed on by other organisms, which are affected as well. Organisms reliant on open water sources (e.g. lakes, rivers) affected by pharmaceutical waste, experience antibiotic resistance to viruses [14]. Antibiotic-resistant genes (ARG) will proliferate in humans in the event of exposure to high non-lethal concentrations of pharmaceutical wastewater and pharmaceutical compounds [15,16]. Antibiotic resistance will affect the immune systems of organisms at a local level, preventing them from fully fighting common diseases, as those diseases will be able to resist the medicine that is meant to eradicate them.

Given the negative impacts of pharmaceutical contamination of waterways, treatment methods to break down or remove pharmaceuticals are required. Advanced Oxidation Processes (AOPs) and Bio-activated methods are commonly used to break down pharmaceutical compounds. AOPs generate radicals that break down APIs while Bio-activated methods use bacteria and other microorganisms to facilitate oxidative breakdown.

A possible solution to pharmaceutical wastewater treatment would be combining various types of established treatments, possibly including their complementary treatments (should they be necessary for requirements), and establishing them together so that these combined treatments complement each other well. Simultaneously, I will be theorizing how best to alter these already-established treatments so that their drawbacks are mitigated or completely eliminated.

## Section 2- Types of Waste Treatment Solutions

For wastewater treatments to be successful in removing APIs, the treatment must be economical, non-toxic, and have versatile scalability. Current methods, while effective across a wide range of pharmaceutical compounds, fail in their applicability on target sources, either due to issues with versatility, purification effectiveness, or the production of toxic byproducts. In the following subsections, I will explain the working principles and highlight the effectiveness and limitations of radical-based, bio-, and separation-based treatments.

### Radical-Involved Treatments

AOPs are oxidation reactions that make use of radicals, specifically the hydroxyl radical, to oxidize and aid in the breakdown process of biochemical molecules [17]. Hydroxyl radicals (·OH),

differ from hydroxide ions ($OH^-$) primarily in their electron configuration. Hydroxide ions possess an overall charge of -1, whereas an unpaired electron on the oxygen atom characterizes ·OH. This characteristic makes radicals extremely reactive, which makes them an excellent species for pharmaceutical wastewater treatments due to their effectiveness in dealing with wastewater. Figure 2 below, which is adapted from[18] gives a general overview of radicals' effects on Pharmaceutical and Personal Care products (PPCPs) and pharmaceutical compounds. The diagram shows the different types of AOPs and how they are applied to the breaking down of pharmaceuticals. These different treatments are applied to wastewater samples to make pharmaceutical degradation more efficient.

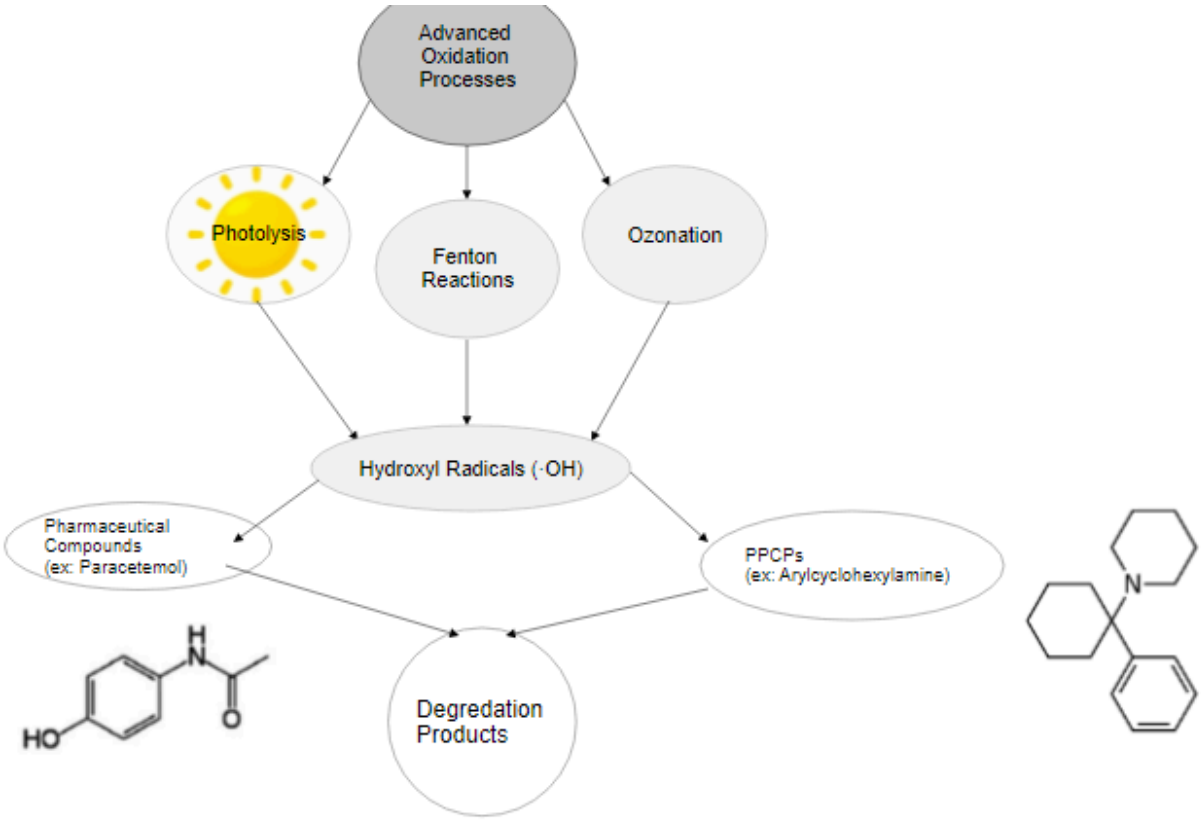


Figure 2: Process flow of pharmaceuticals and PPCPs through AOPs, adapted from Krishnan et al

Photolysis is a stable staple in wastewater treatment of organic and/or pharmaceutical compounds. There are two types of photolysis, direct and indirect. Direct photolysis involves the degradation of a compound through direct absorption of UV light (either direct sunlight or a UV lamp), while indirect photolysis occurs when the compound reacts with another substance that has absorbed light, leading to degradation. Direct photolysis, which is particularly effective for APIs, is the preferred approach [19]. It's demonstrated by a successful experiment using an ultraviolet lamp to break down 2-chloropyridine, a pharmaceutical effluent component, in just 20

minutes [20]. A general direct photolysis treatment starts with an entrance of influent through a reactor with a UV lamp and is pumped into a biological aerating filter (BAF), then through a filter and into a water tank [21].

Photolysis has a low efficiency in breaking down APIs. For example, indirect photolysis accounted for 38% of the degradation of sulfamethoxazole, while direct accounted for 48% [22]. Given the higher degradation efficiency of direct photolysis, this is more useful for the proposed solution than indirect photolysis. To combat the low efficiency of direct photolysis, photolysis needs to be catalyzed/paired with a complementary reaction such as the Fenton reaction.

Fenton reactions are the involvement of an iron catalyst in a solution of hydrogen peroxide ($H_2O_2$) to create radicals. Photolysis when coupled with Fe (III) and $H_2O_2$ or $TiO_2$ can be more efficient than the treatment on its own, as it's shown to remove over 98% of pharmaceuticals including estrogens [23,24]. Fenton reaction mechanisms involve, in the presence of excess iron, the following reactions:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + HO\bullet$$
$$Fe^{3+} + H_2O_2 \rightarrow HOO\bullet + Fe^{2+} + H^+$$
$$2H_2O_2 \rightarrow HOO\bullet + HO\bullet + H_2O$$

Here, excess $H_2O_2$ following the reaction is decomposed into diatomic oxygen and water, which is later converted into hydroxyl radicals to break down APIs. Superoxide molecules ($O_2^-$), which are formed via partial reduction of molecular oxygen ($O_2$), can recycle $Fe^{3+}$ back to $Fe^{2+}$ at the reaction's end by donating its electron to $Fe^{3+}$ in the following reaction:

$$Fe^{3+} + O_2^- \rightarrow Fe^{2+} + O_2$$

This makes Fenton reactions reusable. Fenton involves the preparation of $Fe(ClO_4)_2$ under molecular nitrogen ($N_2$) [25].

The photoreduction of Fe (III) to Fe (II) is aided by UV, which is helpful for water treatment due to the non-toxic nature of iron. Complete oxidation does not require UV, enabling the procedure to work without sunlight as well, but it does help enhance Fenton reactions [26]. This works on a larger scale since the conditions can be met without a complicated setup that simulates specific pressure and temperature conditions, implying that this can work at normal pressure and room temperature [27]. The downside is that there is a need for an aqueous solution system with a pH requirement between 2-4 to make hydroxide radicals, as well as a need to regulate and control the concentrations of hydrogen peroxide & ferrous ions, as well as facilitate the disposal of the iron sludge [28]. Fenton reactions can be used partially to make a non-toxic biodegradable intermediate and then treated with another biological step for complete oxidation [29].

An example of the efficiency of Photo-Fenton (PFP) reactions is in an experiment to break down the analgesic drug Dipyrone (DIPY), which quickly hydrolyzes to 4-methylaminoantipyrine (4-MAA), where Photo-Fenton reactions on 4-MAA had a 96.4% removal, which lasted around

45 minutes after an 83.2% removal rate after 2.5 minutes [30]. The setup involved a large 1.0 L reaction vessel in which 400. mL of DIPY (later hydrolyzed to 4-MAA) was added, afterward $Fe^{2+}$ ions were added & following 5 minutes of magnetic stirring, the $H_2O_2$ was added. For the PFP experiment, the reaction vessel was put under a UV lamp to activate the peroxide and enhance the formation of radicals [30]. This experiment concluded that the technology and processes used for pharmaceutical wastewater treatment and mineralization are promising [30]. The versatility in these experiments can, as well, be applied to different targets of organic waste in water.

Ozonation works as a treatment due to its strong disinfection and sterilization properties [31]. The hydroxide radicals and the ozone ($O_3$) molecules that help in a chemical attack increase the oxidation capacity of the wastewater [32]; thus making ozonation a staple for wastewater treatment. A general ozone wastewater treatment starts with the entrance of wastewater to an ozone contact column where it is met with ozone. Following the reaction the water is transported to a tank, and then the effluent is filtered out following a biofilter, while the ozone is released into the atmosphere [33]. Fig. 3 below shows the system, with a granular activated carbon (GAC) filter that helps to eliminate compounds contributing to the further mutagenicity of the water [34].

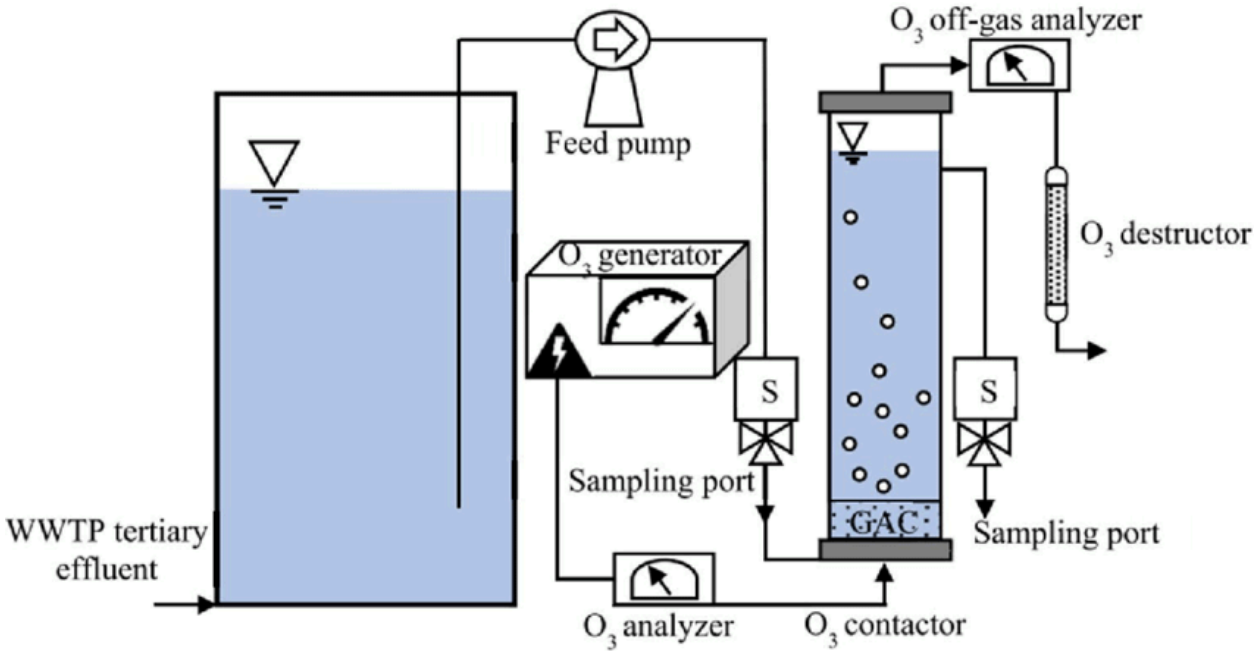


Fig. 3- Wastewater treatment via ozonation mechanism, taken from Uddin et al. 2021

Complementary reactions can be added onto the main treatment to either make the process more efficient or counteract any toxic byproducts as a result of the treatment [35]. Even with the addition of complementary reactions that will provide depth and safety to the treatment, organic compounds containing amides remain resistant to the treatment(s), as only aromatic compounds, amino groups, and other compounds containing a double carbon bond (C=C) are

susceptible [36]. A study of ozonation attacks on amoxicillin showed that the phenolic ring was broken down, causing the formation of hydroxyl derivative intermediates. Sulfur, an element present in amoxicillin, was not oxidized in the treatment of amoxicillin [37]. Ozonation's limitation is that the compounds being treated are not fully oxidized, which provides a route for harmful byproducts to be created, such as bromate. By-product bromate is formed when the water source contains a source of bromine, which is a possible carcinogen [38]. Other harmful byproducts, such as *N*-nitrosodimethylamine, and *N*-nitrosodimethylamine (NDMA), was also reported in drinking water ozonation [39]. This results in the need for an additional treatment, such as sand filtration, to deal with the harmful products. Due to ozone causing the reduction of the microbial count, odor, color, and foam, this causes multiple reactive oxidation products to be generated, meaning ozonation as a whole is expensive, as the detoxifying treatments following are additional costs [40]. Overall, while ozonation is effective as a treatment, it is not what we want for an experimental solution to wastewater treatment, due to the need to be paired with other treatments to be effective (which means higher costs), the incapability to attack amides, and the toxic byproducts that are a result of the treatment.

## Bio-Activated Treatments

Activated sludge is a form of treatment where excretion and waste products are related to the target effluent. The downside to this treatment is the inability for the treatment to be done on-site, leading to multitudes of wastewater effluent being shipped to activated sludge plants, causing operational issues such as color, foaming, and bulking in secondary clarifiers, which separate the suspended solids from the wastewater [41]. This also requires high energy consumption and the tons of sludge produced for this purpose [42]. Efficiency is also inhibited by temperature or pH changes, dissolved oxygen, organic load, microbial community, and toxic or recalcitrant substances [43,44]. Figure 4 provides an overview of how activated sludge treatment works. Wastewater is fed through a grid, as solids are removed and the sludge is added to the water to rid it of organic compounds, and following filtration and disinfection, the effluent is released [45].

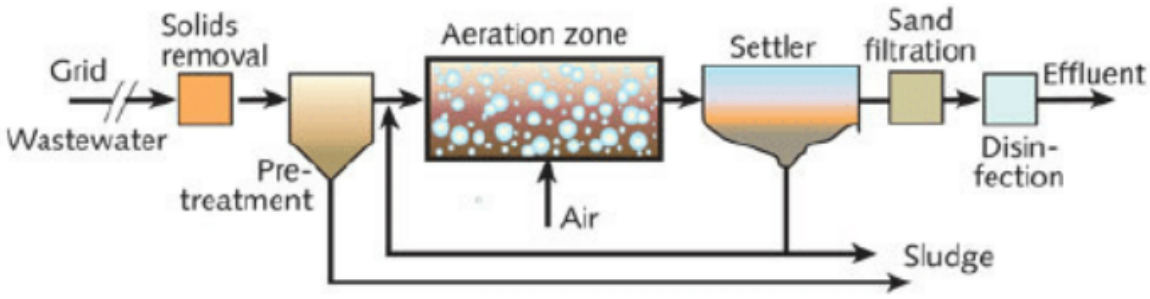


Fig. 4 A simplification of Activated Sludge Procedures taken from Pandey and Singh

This was seen in a wastewater treatment plant in India, called Patancheru Enviro Tech Ltd (PETL), where activated sludge was used on pharmaceutical water samples [14]. Overall, activated sludge is neither sanitary when the water source is for sustenance, nor is it good enough to remove APIs and other pharmaceutical constituents in water [1]. Activated sludge works by utilizing the bacteria in the biomass (feces, scat, etc.) to break down organic molecules in a biologically friendly way. Moreover, the treatment cannot work on-site, as large amounts of activated sludge will need to be transported or transportation of sludge to the target water source to WWTPs would be required [41]. Moreover, the pharmaceutical compounds (in general) that are not broken down in the WWTPs are released back into the environment via the plants, as seen with PETL which shows that the facility is not the only environmental source for poorly treated effluents containing high levels of APIs [14]. All this makes activated sludge and other bio-activated methods a poor option for the experimental solution to pharmaceutical wastewater treatment.

Separation-Based Treatments

Separation-based treatments involve the use of highly packed filters to separate organic molecules and compounds from water. Adsorption is a separation-based treatment where organic pollutants (even at the trace level) bind to the adsorbent surface. This is becoming a widely used method for sterilizing [3]. Meanwhile, membrane treatments act as filters. Figure 5 below shows a general process flow of separation treatments being used, where separation is being used to treat wastewater [46].

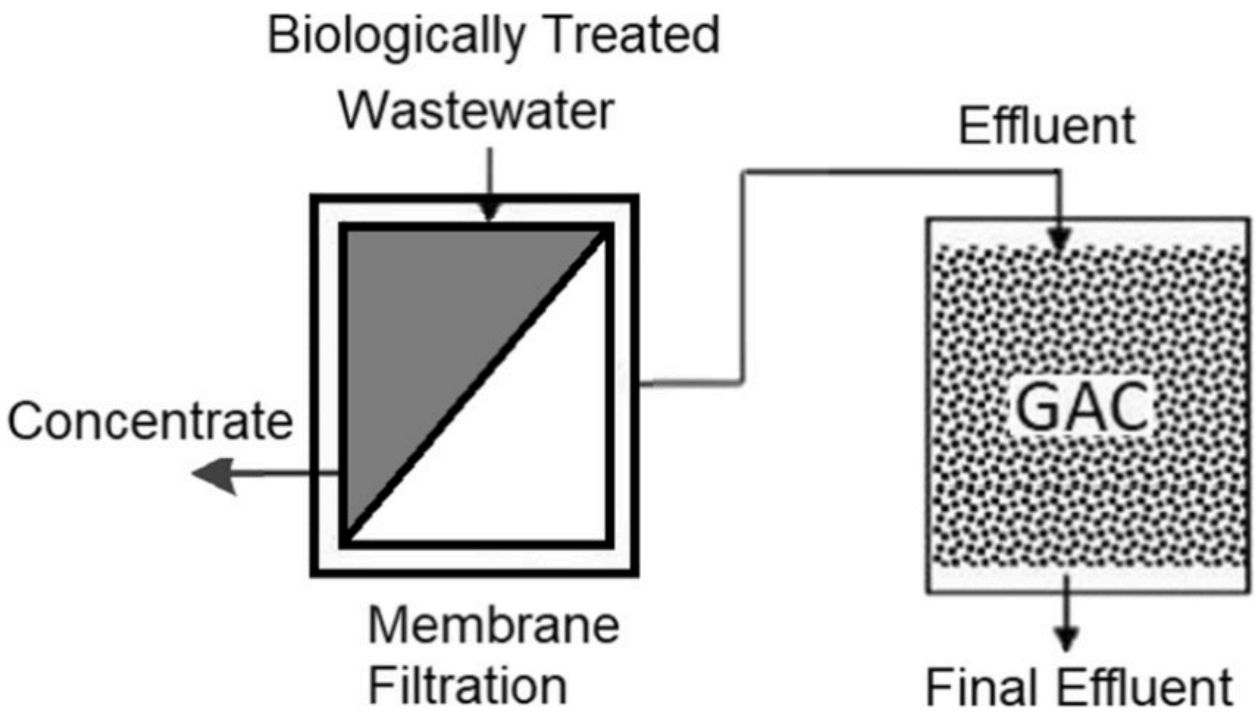


Fig. 5: Membrane Filtration generalized to treat wastewater, taken from [46]

A general schematic of adsorption treatment involves waste being fed into the column, where waste is treated. Following that, the water exits the process [47]. A form of adsorption treatment is called activated carbon, which involves a carbon that has been processed to have low-volume pores for greater adsorption of pharmaceuticals [3]. There are two main types of activated carbon classifications, granular activated carbon (GAC), which excels at continual contact and pollution treater, whereas powdered activated carbon (PAC) while having less contact time, is cheaper and still effective [3]. GACs and PACs target different pharmaceutical compounds, for example, GACs excel at filtering pharmaceutical compounds and endocrine-disrupting substances (EDS) [48]. Overall, adsorption is an effective removal agent and can be reusable, but the cons of this process are the high costs and oftentimes the need for specialized adsorptive materials, which can be as expensive as $200/mol of substance (and perhaps more expensive), with cheaper and perhaps ineffective ones being as cheap as $1/mol of substance [49].

Membrane treatments are done under the driving force of water, components within the water are driven through a membrane filter and, as a result, the permselective membrane leaves behind the components while the water goes through [50]. A general membrane treatment solution has the wastewater being pumped through a filter, and the purified water exits the process while another round of wastewater is cycled back again through the process [51].

There are four broad types of membrane filtration: microfiltration (MF), ultrafiltration (UF), nanofiltration (NF), and reverse osmosis (RO); these different kinds of membranes differ in filter-pore size (as seen in Fig. 5 below) [52]. NF/RO membranes are efficient in rejecting pharmaceutical particles and substances in the micro size due to the smaller pore structure [52] [53]. MF and UF methods are ineffective for smaller particles but are comparable with a larger concentration of pharmaceuticals in the target area [54] [53].

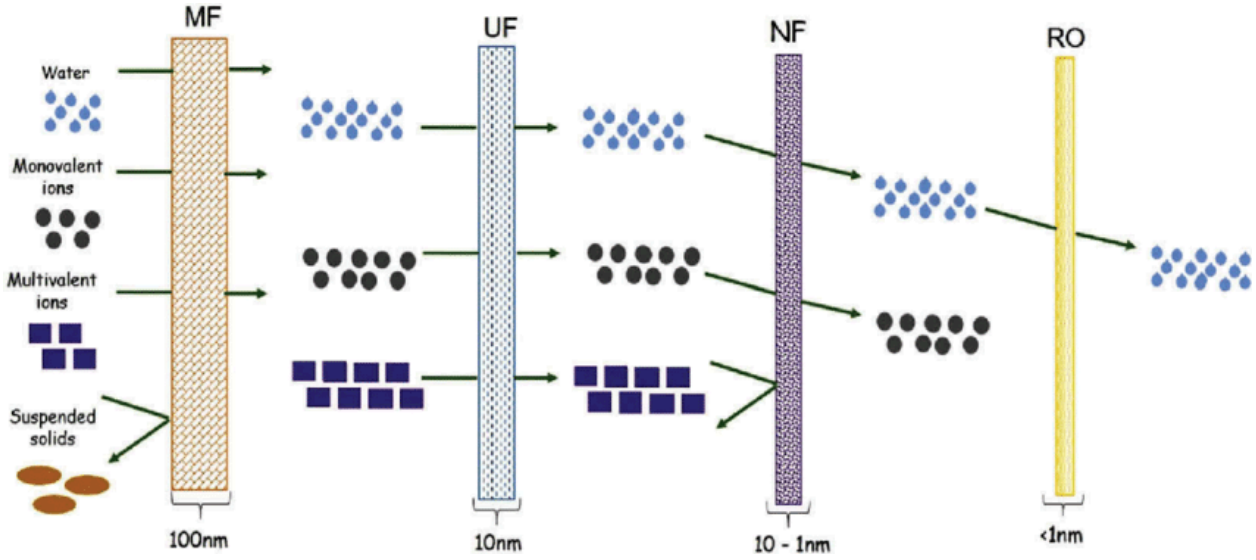


Fig. 5 taken from Syafiqah et al. 2019 depicts the filtration differences between various membranes.

Section 3- Next Steps in R&D

I am seeking an efficient and cost-effective solution that can offer a more generalized approach to API treatment, to reduce resource utilization and mitigate the expense associated with the prolonged practice of transporting wastewater via trucks between the site and WWTPs. Past research done on measuring the effectiveness of pharmaceutical wastewater treatments, as covered above, has been done in isolation, instead of coupling these treatment technologies together. Moreover, this solution must minimize the generation of hazardous sludge. In the following subsections, I will describe the more common wastewater treatment solutions and their implementation for pharmaceutical wastewater. Here, I will propose further research to test coupling these processes to develop a more effective pharmaceutical wastewater treatment procedure.

An example of this is combined photolysis and Fenton reactions. Direct photolysis plus Fenton reactions involve the use of either sunlight or UV lamp-light. How this experiment works is that, either in the open or in a large reaction vessel, the target water source can have hydrogen peroxide ($H_2O_2$) plus ferrous salt added, and later can be exposed to sunlight. This can also involve the addition of a UV lamp-light, in case the sunlight procedure either takes too long or is too weak on its own. The process works through the activation of the peroxide by UV light and coupled with the breakdown of the ferrous salt, both reactions begin to form radicals, which aid in the breakdown process.

Utilizing radicals from other AOP treatments to combine with photolysis, which unfortunately does not break down all the organic compounds in the target water source [22]. Prior research has shown that AOPs are non-selective, and are versatile at treating a variety of wastewater (pharmaceutical, activated sludge, etc.). However, a limitation of AOPs is that they perform only at low pH, and when isolated from each other, they are not efficient Including a separation process following AOP treatment could address this limitation. Given that the main goal of this experimental solution is for it to be implemented on-site instead of resources being diverted to factories, adding more strain to an already complicated process. A downside to photo-Fenton procedures is that they perform only at low pH, but this can be combated by using chelating agents to raise the reaction pH of the photo-Fenton radicals to be produced at neutral [55]. Beforehand, the use of photo-fenton would have been ineffective for pharmaceutical wastewater treatment, but with chelating agents such as ethylenediaminetetraacetic acid (EDTA), the reaction can proceed at a neutral pH.

Membrane technology already has made an impact in filtering pharmaceutical waste products out, converting it into reusable water [56]. Moreover, membrane separation can make use of effluent feeding repeatedly through the membranes. However, the problem is with fouling and subsequent cleaning and maintenance of membranes. The most effective and relevant methods for pharmaceutical wastewater treatment are certain physical cleanings, such as pneumatic cleaning (involving air) or ultra-sonic cleaning, which dislodges the particles at the molecular level from the membrane [57]. Biochemical cleaning is also useful, involving enzymes and enzymatic mixtures to stir up and dislodge the particles, but in the case of permanent fouling, chemical cleaning, using various chemical agents, is best used; chemical cleaning can be combined with physical methods as well, seeing enhancements of flux recovery up to 95% [58,59].

Given the past research discussed, I've proposed the following solution to pharmaceutical wastewater treatment:

1. Transfer the water that needs to be treated to transparent reaction vessels via pipes as normal.
2. Add the required concentration of hydrogen peroxide to the vessels, along with ferrous ions as catalysts for the radical production phase.

3. Add chelator agents to the vessels to enable the reaction to occur at a neutral pH instead of an acidic pH as is typical of photo-Fenton reactions.
4. Expose the vessels to sunlight and stir the contents of the vessels with a magnetic stirring rod so that the contents generate hydroxyl radicals for the breakdown of the pharmaceutical compounds in the water.
5. Monitor the mixture via chromatography to see if the reaction has proceeded to completion. Once it has, filter out the water using ultrafiltration membranes or activated carbon membranes.
6. Filter out this water with more membrane filters until it arrives at a small tank for observation purposes.
7. Examine the concentration of this final tank to see if it's as close to purity as possible. If so put it through one more filter and observe the purity again. If not, return it to the reaction vessels for further examination and treatment.

Wastewater treatment solutions are similar to what I have proposed, but they are less sustainable than traditional solutions like activated sludge factories or chlorination. The proposed treatment involves a sustainable energy source, either in the form of sunlight or UV-powered lights that can work efficiently and without mess. The average wastewater treatment plant uses either chlorination (primarily seen in the US) or activated sludge (as seen in India), and while they work, they require shipment of wastewater to a plant instead of being done on-site. Furthermore, not enough wastewater treatment plants use Photo-Fenton reactions due to the acidic pH requirement and the high input of chemicals and iron into the reaction. I address these issues in my experimental solution while providing an avenue for efficiency and sustainability.

We can change the source of hydroxyl radical production by instead having a 10 to 100 W UV lamp (on average) shining directly downwards into the vessel. The lamp will be more useful than sunlight in a lab setting, as it takes around 20-45 minutes to break down an API for a 400 mL aliquot.

The ferrous sludge is a semi-solid that contains ferrous compounds/ions, water, contaminants, pH adjusting agents, and other biological compounds that were initially in the vessels. The superoxide molecules for the Fenton reactions will be an aid in repurposing the ferrous sludge for $Fe^{2+}$ catalysts. The sludge will be difficult to deal with post-repurposing, as it serves no purpose despite its nontoxicity due to the iron. Overall, this is the proposed solution, based on past research, to pharmaceutical wastewater.

Limitations to this solution could possibly be the addition of the chelating agent and maintaining the other pieces of equipment used. While the chelating agent is beneficial, the addition of another chemical to the process (and subsequently the sludge) may have an impact on cleanup.

The maintenance of the equipment and potential concerns about reusability will cause the processes to be slow. To begin with, the requirement of sunlight, as this renewable source of energy is limited depending on seasons and time, and this affects efficiency. Another limitation is the purity of the treated water, as the goal is to make this water safe for drinking, but after going through a chemical-heavy process, the amount of materials and effort involved calls the proposed treatment into question. A final limitation is a cost, as such a proposed experiment will be expensive as an on-site solution, as more conventional treatments can cost 9.56-16.88 €/m³ and 13.46–20.13 €/m³ for Fenton and PFP respectively for the $Fe^{2+}/H_2O_2$ ratio [60]. The criteria for success are mainly in attaining purity in an efficient process over a certain period of time.

Methods

My approach for research regarding the literature search was specific toward pharmaceutical wastewater treatment. However, initially, I focused on wastewater treatment of organic solvents and compounds due to the conventional treatments that are applied to this issue. Since wastewater treatments are largely applicable across both areas, I saw it best to start researching the less complex scenario before moving to pharmaceuticals, which can contain inorganic substances as well. The system of researching shifted from the effects of pharmaceutical wastewater on wildlife and the environment to the effects of their treatments in solving the issue. By mainly focusing on how pharmaceutical wastewater treatments have evolved, starting from using conventional methods to adding complementary reactions to make the solutions work, I was able to construct this paper. My data was collected based on the effectiveness of physical experiments, which were based on hypotheses on how different solutions would work. This is best seen with PFP, and its effectiveness at only acidic pH levels, but the addition of chelating agents such as EDTA enables PFP to work at a neutral pH, thus allowing a wider variety of pharmaceutical wastewater to be purified. These experiments were conducted based on previous experiments when organic wastewater was an issue in Asian countries. These studies first replicated older experiments to test for viability, then tweaked them to minimize the drawbacks of various treatments. This was best seen with EDTA to PFP. The papers chosen are a mix of old and new, which helps me better understand how the research has evolved over time. Overall, my methodology was choosing a mix of old and new papers that established the problem from organic wastewater to pharmaceutical wastewater, while simultaneously building up research from the past to better show how experiments and treatments have evolved.

Conclusion/Discussion

Past wastewater treatment solutions have been effective in curbing the amount of organic waste being released back into the environment, with sources being from pharmaceutical plants and even wastewater treatment plants, primarily in activated sludge. Having gone through the previously established treatment methods for APIs, the proposed experimental solution, which

involves an on-site PFP solution that includes chelating agents to bring the reaction pH to neutral, seeks to combine the positives of all treatment methods mentioned while cutting back on their drawbacks by improving efficiency and lowering the time taken for reactions. The main goal is to figure out a way to curb organic waste in the environment and in water sources, and the best way to do this is, in the long term, to make pharmaceuticals more environmentally appropriate.

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