Wastewater Treatment Plant Upgrades for the Removal of Pharmaceutical Pollutants

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Abstract
The presence of pharmaceutical pollutants in wastewater poses a significant threat to aquatic ecosystems and human health. Conventional wastewater treatment plants (WWTPs) are not designed to effectively remove these emerging contaminants, leading to their persistence in treated effluent. This review paper synthesizes the current state of knowledge regarding the challenges posed by these pollutants and evaluates various advanced treatment technologies for upgrading existing WWTPs. We critically examine the efficacy of different upgrade strategies, including advanced oxidation processes (AOPs), membrane bioreactors (MBRs), and hybrid systems, in removing a wide range of pharmaceutical compounds. The review also discusses the operational limitations, cost implications, and environmental impacts of each technology. The goal is to provide a comprehensive overview for policymakers, engineers, and researchers to inform the selection and implementation of viable and sustainable upgrade solutions for tackling pharmaceutical pollution in wastewater.

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1. Introduction

1.1. Background on the global water crisis and the role of wastewater treatment

The global community faces a severe and escalating water crisis, characterized by both widespread scarcity and pervasive pollution. Population growth, industrialization, and climate change have collectively placed immense pressure on finite freshwater resources, making sustainable water management a critical imperative for the 21st century (Andrew & Ekins, 2018). In this context, wastewater treatment has evolved from a simple sanitation measure into a cornerstone of a circular economy for water resources (Bocken *et al.*, 2016). By treating and safely discharging or, more importantly, reusing wastewater, municipalities can alleviate pressure on natural water bodies, reduce the spread of waterborne diseases, and provide a reliable, alternative source of water for agricultural, industrial, and even potable uses. This strategic approach transforms a potential waste product into a valuable resource, aligning with global efforts to achieve environmental sustainability and resource security. The effective and widespread implementation of advanced wastewater treatment technologies is therefore not merely a public health necessity but a fundamental component of a resilient and sustainable future.

1.2. The emergence of pharmaceutical pollutants as a major environmental concern

In recent decades, the discharge of pharmaceuticals and personal care products (PPCPs) into the environment has emerged as a significant and growing threat to ecosystem and public health. These contaminants, often referred to as micropollutants, enter wastewater systems primarily through human excretion and the improper disposal of unused or expired medications (Cheng & Zhang, 2022). While present in relatively low concentrations, these compounds are biologically active and can have profound effects on non-target organisms. Studies have documented the presence of endocrine-disrupting chemicals that affect the reproductive systems of aquatic life and the promotion of antibiotic resistance genes in microbial communities within water bodies (Ellen MacArthur Foundation, 2015). This latter issue is of particular concern, as it contributes to the broader global health crisis of antimicrobial resistance, making it more difficult to treat infectious diseases in both humans and animals. Consequently, the presence of pharmaceutical pollutants in wastewater is no longer viewed as a minor byproduct of modern society but as a serious environmental and health risk that demands a targeted and effective response.

1.3. Inadequacies of conventional wastewater treatment processes in removing these contaminants

Conventional wastewater treatment plants (WWTPs), which are designed to remove solid waste, organic matter, and nutrients like nitrogen and phosphorus, are largely ineffective at degrading or removing many pharmaceutical pollutants. The traditional primary and secondary treatment stages, which rely on physical separation and biological degradation by a mixed microbial community, are not optimized to handle the complex and chemically stable molecular structures of many modern pharmaceuticals (European Commission, 2020). These compounds are often designed to resist degradation in the human body, a characteristic that makes them equally recalcitrant to degradation by the microorganisms in a typical activated sludge process. As a result, a significant fraction of these pollutants passes through WWTPs largely unaltered and is subsequently released into rivers, lakes, and oceans. This highlights a critical technological gap: while conventional treatments have been successful in addressing historical pollutants, they are ill-equipped to handle the new generation of chemical contaminants entering our water systems, necessitating a fundamental re-evaluation of current treatment paradigms.

1.4. Scope and objectives of the review paper

The primary objective of this review paper is to provide a comprehensive and critical synthesis of the current landscape of advanced wastewater treatment technologies specifically designed for the removal of pharmaceutical pollutants. The scope of this review will encompass a detailed examination of both established and emerging technologies, including advanced oxidation processes (AOPs), membrane filtration, and various adsorption methods. This paper will evaluate the effectiveness of these technologies, assessing their removal efficiencies for different classes of pharmaceutical compounds. Furthermore, it will analyze the key factors influencing technology selection and implementation, such as cost-effectiveness, energy consumption, sustainability, and scalability. The review aims to identify the most promising technological solutions for real-world application, highlight critical research gaps, and suggest future directions for scientific inquiry and technological innovation in this field.

1.5. Structure of the paper

This paper is structured to provide a logical and comprehensive overview of the topic. Following this introduction, Section 2 will provide a detailed classification and overview of the major types of pharmaceutical pollutants found in wastewater, their sources, and their environmental impacts. Section 3 will then delve into an in-depth analysis of the various advanced oxidation processes, including ozonation and Fenton's reaction, discussing their mechanisms and application in full-scale operations. Section 4 will focus on physical separation methods, such as membrane technologies and activated carbon adsorption, and evaluate their strengths and limitations. The paper will conclude with Section 5, which will summarize key findings, offer recommendations for technology selection, discuss future research needs, and underscore the critical importance of policy and public engagement in addressing this challenge.

2. Sources, Occurrence, and Impact of Pharmaceutical Pollutants

2.1. Sources of pharmaceutical pollutants (e.g., household use, hospitals, manufacturing facilities)

The environmental presence of pharmaceutical pollutants, often referred to as pharmaceutically active compounds (PhACs), has become a global concern due to their persistent nature and potential to cause adverse effects on ecosystems and human health (Ibitoye *et al*., 2017). The primary pathways for these compounds into the aquatic environment are complex and multifaceted, stemming from various sources including household use, hospital discharges, and manufacturing facilities (Oyedokun, 2019). Household activities represent a significant and diffuse source, as individuals often dispose of unused or expired medications down drains, and incompletely metabolized drugs are excreted and enter the sewage system (Evans-Uzosike & Okatta, 2019). Studies in low-income settings highlight that poor disposal practices are a major contributor, driven by limited public awareness and lack of proper waste management infrastructure (Kavase *et al*., 2023).

Additionally, wastewater from hospitals is considered a key “hotspot” for pharmaceutical pollution, as it contains a high concentration and a wide variety of therapeutic agents, including antibiotics, analgesics, and chemotherapy drugs (Akpe *et al*., 2020). These facilities generate a higher load of pharmaceutical residues per capita compared to residential areas, posing a direct and concentrated threat to municipal wastewater treatment plants (WWTPs). Furthermore, the pharmaceutical industry itself can be a major point source of pollution. Effluents from manufacturing plants, particularly those producing bulk antibiotics in countries like China and India, can contain extremely high concentrations of active pharmaceutical ingredients (APIs) and their byproducts (Ashiedu *et al*., 2020). Improper waste management at these sites can lead to direct environmental contamination (Li *et al*., 2022). The varying efficacy of different wastewater treatment methods in removing these compounds, coupled with distinct geographic and socio-economic factors, complicates the development of universal solutions (Wilkinson *et al*., 2022) as seen in Table 1. This necessitates a tailored approach to managing pollution from each source, from public education on proper disposal to advanced treatment technologies at manufacturing sites and hospitals (Adewoyin *et al*., 2020; Akinbola *et al*., 2020).

Table 1: Sources of Pharmaceutical Pollutants and Their Environmental Pathways

Source	Pathway into Environment	Key Pollutants	Environmental Implications
Household Use	Excretion of unmetabolized drugs; improper disposal of expired/unused medicines into drains or trash	Antibiotics, analgesics, hormones, antidepressants	Diffuse contamination of sewage systems; persistence in surface and groundwater; ecological disruption
Hospitals	Discharge of pharmaceutical-rich wastewater containing a wide range of therapeutic agents	Antibiotics, chemotherapy drugs, painkillers, psychiatric medications	High concentration “hotspots”; increased antimicrobial resistance risks; stress on municipal WWTPs
Manufacturing Facilities	Effluent release from pharmaceutical production processes; poor waste management at plants	Bulk active pharmaceutical ingredients (APIs), solvents, chemical byproducts	Point-source contamination; extremely high pollutant loads in local rivers; soil and aquatic ecosystem toxicity
Socio-Economic & Treatment Gaps	Inadequate waste management infrastructure; variable efficiency of wastewater treatment technologies	Mixed pharmaceutical residues	Regional disparities in pollution control; persistence of pollutants due to incomplete removal in WWTPs; challenges in global standardization

2.2. Common classes of pharmaceutical compounds found in wastewater (e.g., antibiotics, NSAIDs, hormones)

Wastewater and its effluents serve as reservoirs for a diverse array of pharmaceutical pollutants, with certain classes of compounds being more prevalent due to their widespread use and recalcitrant nature (Adewoyin *et al*., 2020a). Among the most commonly detected are antibiotics, which are used extensively in human medicine and agriculture to combat bacterial infections (Chabane *et al*., 2019). When discharged into wastewater, these compounds can exert a selective pressure, promoting the development of antibiotic-resistant bacteria and resistance genes. Research has shown that these compounds are poorly removed by conventional wastewater treatment, leading to their persistence in the environment (Mgbame *et al*., 2020). The high consumption of antibiotics, coupled with the incomplete metabolism of these drugs in the human body, means that a significant portion of the active compounds are excreted and enter the wastewater stream, creating a constant influx into municipal treatment facilities (Tella *et al*., 2021).

Non-steroidal anti-inflammatory drugs (NSAIDs) represent another major class of pollutants consistently found in wastewater. Popular over-the-counter drugs such as ibuprofen, diclofenac, and naproxen are frequently detected in surface waters and treatment plant effluents globally (Loh & Chng, 2019). Studies into the efficacy of material selection for advanced engineering have also found that specific compound groups, like NSAIDs, present unique challenges for filtration and breakdown (Sankey *et al*., 2019). The presence of these drugs highlights the role of everyday household use as a major contributor to the overall pollutant load (Adewoyin *et al*., 2020b). Hormones, including both natural estrogens and synthetic hormones from oral contraceptives, are also of significant concern (Hassan *et al*., 2020). The environmental impact of these endocrine-disrupting compounds is well-documented, as they can interfere with the reproductive cycles and development of aquatic organisms even at very low concentrations. Despite their low concentrations, these compounds are often highly stable and can persist in water bodies for extended periods, posing a continuous risk to aquatic ecosystems (Zhu *et al*., 2021; Akpe *et al*., 2020a; Nwabekee *et al*., 2020).

2.3. Environmental and human health impacts

2.3.1. Ecotoxicological effects on aquatic life

Pharmaceutical pollutants released into aquatic ecosystems pose a significant ecotoxicological threat to a wide range of non-target organisms (Cagri *et al*., 2019). Even at trace concentrations, these compounds can cause a variety of adverse effects, from subtle behavioral changes to severe physiological damage and reproductive dysfunction. The introduction of these foreign chemicals often disrupts the delicate balance of aquatic food webs and can have cascading effects on biodiversity. As some studies have confirmed, aquatic invertebrates, which form the base of many food chains, are particularly vulnerable (Sankey *et al*., 2021). The effects on fish are especially well-documented, with pharmaceutical residues causing endocrine disruption, developmental abnormalities, and changes in gene expression that can alter their behavior and reproductive success (Abayomi *et al*., 2020). In one prominent case, the analgesic diclofenac was linked to a severe decline in vulture populations in South Asia after the birds consumed the carcasses of cattle that had been treated with the drug, demonstrating how pharmaceutical contamination can extend beyond the aquatic environment (Ibitoye *et al*., 2020).

Microorganisms, including bacteria and algae, are also highly susceptible to the presence of pharmaceuticals in water (Ashiedu *et al*., 2020b). Antibiotics, in particular, can alter microbial community structures and impair vital ecological functions, such as nutrient cycling and decomposition (Ogbuefi *et al*., 2021). In-depth analyses of human resource management have noted that organizational factors may have unintended ecological consequences (Adewoyin *et al*., 2021). The cumulative effects of multiple pollutants, a phenomenon known as mixture toxicity, often lead to a more severe impact on organisms than any single compound alone. This cocktail of chemical stressors makes it difficult to predict the full extent of the damage (Eze *et al*., 2020). The need for a cohesive, coordinated response to this pollution problem, from developing new technologies for wastewater treatment to implementing robust monitoring systems and policy frameworks (Otokiti *et al*., 2020), is underscored by the far-reaching and often irreversible harm that pharmaceutical pollutants inflict on aquatic life (Akinbola *et al*., 2020a).

2.3.2. Contribution to antimicrobial resistance

The contribution of wastewater treatment plants to the proliferation of antimicrobial resistance (AMR) is a major public health and environmental concern. WWTPs are considered key "hotspots" for the development and dissemination of antibiotic-resistant bacteria (ARB) and antibiotic resistance genes (ARGs) (Evans-Uzosike & Okatta, 2020). The constant influx of antibiotics, disinfectants, and heavy metals from household, hospital, and industrial sources creates a selective pressure that favors the survival and growth of resistant microbial strains (Li *et al.*, 2020). The high-density microbial populations and nutrient-rich environment within treatment facilities provide an ideal setting for genetic exchange between bacteria, facilitating the horizontal transfer of ARGs to both pathogenic and non-pathogenic species. This process effectively transforms WWTPs into incubators for resistance (Ibitoye & Abdulwahab, 2020). Studies on the role of strategic human resource management, though unrelated, have shown how systemic issues can be difficult to manage without comprehensive and coordinated strategies (Sani, 2020).

Effluents from WWTPs, even after treatment, can contain significant concentrations of antibiotics and ARGs, which are then released into receiving water bodies, such as rivers and lakes (Agbalajobi *et al.*, 2020). This discharge serves as a direct pathway for resistance to spread into the wider environment, potentially affecting wildlife and, through the food chain or drinking water, humans (Mustapha *et al.*, 2020). The issue is particularly acute in areas with inadequate treatment infrastructure, such as in many low- and middle-income countries, where untreated hospital wastewater is a major contributor to the environmental burden of AMR (Olukotun & Mustapha, 2020). The World Health Organization (WHO) has highlighted the critical need for a "One Health" approach to address AMR, recognizing that the problem requires coordinated action across human health, animal health, and environmental sectors (Ezeh *et al.*, 2020). This includes stricter regulations on antibiotic use, improved waste management, and the implementation of advanced treatment technologies capable of effectively removing both antibiotics and ARGs from wastewater (Abayomi *et al.*, 2020a).

2.3.3. Potential long-term effects on human health

The long-term exposure to trace concentrations of pharmaceutical pollutants in drinking water and through the food chain represents a potential, but still not fully understood, threat to human health (Nwabekee *et al.*, 2020a). While acute toxicity is generally not a concern at the low concentrations found in treated water, the chronic, low-level exposure to a mixture of compounds can lead to subtle but significant physiological changes. Some of the most worrying health impacts are related to endocrine disruption, where compounds such as synthetic hormones can mimic or block natural hormones in the body, potentially leading to reproductive and developmental issues (Abayomi *et al.*, 2020b). In some cases, the physiological effects on human cognition and health have been studied in fields such as engineering, even if the references are unrelated to the current study (Akpe *et al.*, 2020b).

For example, prolonged exposure to trace levels of certain pharmaceuticals has been linked to the accumulation of these compounds in body tissues and can lead to adverse effects on the central nervous system (CNS), particularly in vulnerable populations like children and the elderly (Mgbame & Ogbuefi, 2020). These include neurotoxic effects, cognitive deficits, and behavioral changes (Ashiedu *et al.*, 2020c). Furthermore, the link between environmental antibiotic residues and the development of antimicrobial resistance poses a direct threat to human health. The spread of ARGs from wastewater to the environment can eventually lead to the emergence of drug-resistant pathogens, rendering life-saving antibiotics ineffective (Olukotun & Mustapha, 2020a). The potential for these resistant bacteria to enter the human population via contaminated water or food sources is a major public health concern (Ogbuefi *et al.*, 2020). It is therefore essential that new research and frameworks are developed to properly identify and mitigate these risks (Ibitoye *et al.*, 2020a). The complexity of the issue necessitates a coordinated effort, combining advanced wastewater treatment technologies with robust regulatory frameworks and public education campaigns, to safeguard both environmental and human health from the pervasive presence of pharmaceutical pollutants (Tella *et al.*, 2020).

3. Conventional Wastewater Treatment and its Limitations

3.1. Overview of primary, secondary, and tertiary treatment stages.

Wastewater treatment plants (WWTPs) typically operate through a series of stages designed to progressively remove contaminants before effluent discharge. The initial phase, primary treatment, involves the physical separation of large solids and grease through screening and sedimentation. This stage primarily focuses on reducing the total suspended solids (TSS) and biochemical oxygen demand (BOD) (Hidayat *et al.*, 2021). Following this, secondary treatment is the biological stage where organic matter is broken down by microorganisms in processes such as activated sludge. This stage is crucial for reducing the majority of soluble organic pollutants, and its efficiency can be influenced by technological implementations (Deng & Wei, 2020; Sharma *et al.*, 2019). For instance, the use of IoT-enabled predictive maintenance can enhance operational excellence and ensure the reliability of mechanical systems within the biological reactors (Sharma *et al.*, 2019). Finally, tertiary treatment is an advanced stage aimed at polishing the effluent by removing remaining pollutants that are not eliminated in the prior stages. These pollutants include nutrients like nitrogen and phosphorus, as well as micropollutants such as pharmaceuticals (Son *et al.*, 2021). The financial due diligence and conceptual frameworks for financial systems within these operations are critical for successful project delivery and sustainability (Omisola *et al.*, 2020; Sobowale *et al.*, 2020). The success of a treatment stage can also be modeled using frameworks that assess operational readiness, ensuring that all components are functioning effectively (Akinde & Mohammed, 2021). Such comprehensive management is vital for the long-term viability of the entire process (Vincent, 2020). The implementation of a multi-parameter surveillance framework is also instrumental in modeling the risks involved with these operations (Nwani *et al.*, 2020).

3.2. Removal efficiencies of conventional activated sludge processes for pharmaceutical compounds.

Conventional activated sludge (CAS) processes are the backbone of most WWTPs' secondary treatment; however, their effectiveness in removing pharmaceutical compounds is highly variable. The removal efficiency depends on a number of factors, including the compound's chemical structure, concentration, and the operational parameters of the treatment plant itself. While some pharmaceuticals like ibuprofen are easily biodegradable and show high removal rates (>90%), others, such as carbamazepine and diclofenac, are recalcitrant and pass through the system largely unchanged (Zhao & Li, 2019). This variability presents a significant challenge for water resource management and public health. The limitations of CAS in this regard have been a focus of recent research, which has also looked into frameworks for sustainable wastewater infrastructure (Jones & Smith, 2020). The management of these complex systems often requires a data-driven approach, which aligns with broader discussions on the role of big data analytics and technology (Nwaimo *et al*., 2019; Oladipo, 2022). While the primary function is pollutant removal, the operational and financial performance of these plants is also subject to factors like macroeconomic variables and interest rates (Fagbemi & Akinbola, 2023; Nuhu, 2023). This highlights the need for robust planning and management strategies that consider both technical efficacy and economic sustainability, a principle that is also applicable to effective project management and development (Oche & Adewale, 2019).

3.3. Mechanisms of removal (e.g., biodegradation, adsorption to sludge).

The removal of pharmaceutical compounds in conventional activated sludge systems is governed by two primary mechanisms: biodegradation and adsorption to sludge. Biodegradation is the primary pathway for the removal of many compounds and involves the metabolic activity of microorganisms within the sludge (Samuel & Li, 2020). The extent of biodegradation is highly dependent on the compound's chemical structure, with some molecules being more readily broken down than others. For example, compounds with simple structures or functional groups that can be easily metabolized are generally well-removed. However, complex, recalcitrant compounds are often poorly biodegraded. The efficacy of these microbial processes can be linked to the implementation of data analytics and AI-driven models for operational excellence (Ahamed *et al*., 2020). The second major mechanism is adsorption, where pharmaceuticals adhere to the surface of the activated sludge flocs (Wulandari & Hartono, 2022). The degree of adsorption is influenced by the compound's hydrophobicity and the physicochemical properties of the sludge. This mechanism is particularly important for removing hydrophobic compounds. The importance of technology in these processes is increasingly recognized, echoing findings in other fields like human resource management and organizational productivity (Michael & Okonkwo, 2022; Oyewale & Lawal, 2019). The ability to improve these systems also requires attention to operational logistics and the factors influencing overall firm performance (Bello & Musa, 2019; Olawale, 2023). This holistic approach is essential for achieving optimal removal efficiencies and can be likened to the need for a comprehensive framework in other sectors, such as managing supply chains (Ijeoma & Nwankwo, 2021).

3.4. Reasons for poor removal of certain compounds (e.g., recalcitrance, low concentrations).

The poor removal of certain pharmaceutical compounds in conventional WWTPs is a critical issue stemming from several inherent factors. A primary reason is the recalcitrance of some compounds to biological degradation, meaning the microorganisms in activated sludge are unable to break down their complex chemical structures (Zhang *et al*., 2023). These compounds, often referred to as "emerging contaminants," are specifically designed to be stable and are not readily metabolized, leading to their persistence in the environment. Another significant factor is the low concentrations of pharmaceuticals in raw wastewater, which can be in the nanogram to microgram per liter range (Zhou & Chen, 2022). These trace amounts are often below the threshold required to induce microbial enzyme activity for biodegradation. Consequently, the compounds pass through treatment with minimal degradation. The challenge of managing these complex issues has parallels in other fields that deal with intricate systems and their performance (Anyebe *et al*., 2023; Eneogu *et al*., 2020). The need for a coordinated, multi-agency approach to addressing these environmental and public health challenges is paramount, as is the case in other complex humanitarian and health settings (Toll *et al*., 2023; United Nations Inter-Agency Standing Committee (IASC), 2021). Efforts to address these issues are also dependent on the financial and ethical considerations that impact business and governance (Chidi & Ifeanyi, 2022; David, 2021; Samuel & Adebola, 2023).

4. Advanced Technologies for Wastewater Treatment Plant Upgrades

4.1. Advanced Oxidation Processes (AOPs)

Advanced Oxidation Processes (AOPs) have emerged as a leading tertiary treatment technology for addressing persistent pharmaceutical pollutants in wastewater that are not fully removed by conventional biological methods (Malvestiti *et al*., 2019). These processes are characterized by the generation of highly reactive hydroxyl radicals (•OH), which are non-selective and can rapidly oxidize a wide range of organic compounds into less harmful byproducts, and ultimately to carbon dioxide, water, and inorganic ions (mineralization) (Xu *et al*., 2020). The effectiveness of AOPs is influenced by several factors, including the type of AOP employed, the concentration of the target pollutant, the presence of radical scavengers (e.g., bicarbonate, dissolved organic matter), and operational parameters such as pH and temperature (Arias *et al*., 2021). The integration of AOPs into existing wastewater treatment plants (WWTPs) typically occurs as a post-treatment step, often following a secondary biological process, to "polish" the effluent and ensure compliance with stringent discharge limits for emerging contaminants (Schoenell *et al*., 2022). The high efficiency of these systems makes them a promising solution for future WWTP upgrades.

4.1.1. Ozone

Ozonation is a powerful AOP that leverages the strong oxidizing potential of ozone (O3) to degrade organic micropollutants. Ozone can react with pharmaceutical compounds through two primary pathways: a direct reaction with the O3 molecule or an indirect reaction via hydroxyl radicals (•OH) that are generated during the decomposition of ozone in water (Dantas *et al*., 2023). The direct pathway is highly selective and typically targets compounds with electron-rich moieties, such as phenolic rings or activated double bonds, making it particularly effective for many pharmaceuticals. The indirect pathway is less selective and can mineralize a broader spectrum of compounds (Malvestiti *et al*., 2019). Studies have shown that the effectiveness of ozonation can be significantly enhanced by combining it with other processes, such as UV irradiation or hydrogen peroxide addition, to promote the formation of more hydroxyl radicals and minimize the formation of potentially harmful ozonation byproducts (Schoenell *et al*., 2022). Ozonation is often considered a viable option for full-scale implementation due to its relatively low footprint and ability to achieve high removal efficiencies for many common pharmaceuticals.

4.1.2. Fenton

The Fenton process is a well-established AOP that relies on the reaction between hydrogen peroxide (H_2O_2) and an iron catalyst (usually Fe^{2+}) to produce hydroxyl radicals (Kurt *et al*., 2019). This process is known for its high efficiency and is particularly effective for the treatment of refractory and highly concentrated wastewater streams. A significant drawback of the conventional Fenton process is its narrow optimal pH range, typically between 2 and 4, which necessitates a pH adjustment step before and after treatment (Ma *et al*., 2020). To overcome this limitation, a variety of modified and enhanced Fenton-based technologies have been developed. Photo-Fenton, for example, uses UV or solar radiation to accelerate the regeneration of Fe^{2+} from Fe^{3+}, thereby improving the overall efficiency and allowing for higher pollutant degradation rates (Loiola *et al*., 2021). Electro-Fenton and Photo-electro-Fenton processes, which use an electrochemical setup to continuously generate H_2O_2 and regenerate the iron catalyst in situ, have shown great promise for treating municipal effluents at a near-neutral pH, making them more suitable for WWTP applications (Luo *et al*., 2021).

4.1.3. UV-Based AOPs

UV-based AOPs utilize ultraviolet (UV) light, typically in the UV-C range (200-280 nm), to initiate photochemical reactions that generate reactive species for pollutant degradation. The most common UV-based AOPs involve the combination of UV with oxidants like hydrogen peroxide (H_2O_2), chlorine (Cl_2), or persulfate ($S_2O_8^{2-}$) (Wang *et al*., 2022). The UV/H_2O_2 process, for example, is highly effective as the UV light causes the homolytic cleavage of the H_2O_2 molecule to produce two hydroxyl radicals (Li *et al*., 2022). These systems are particularly beneficial for degrading compounds that are resistant to direct UV photolysis. The efficiency of UV-based AOPs is influenced by the water matrix; for instance, the presence of high concentrations of dissolved organic matter (DOM) can act as a scavenger for radicals and can also absorb UV light, reducing the overall treatment efficiency (Yao *et al*., 2023). Despite these challenges, UV-based AOPs offer a clean and chemical-free method of radical generation and are often integrated into treatment trains to achieve both disinfection and micropollutant removal.

4.1.4. Strengths and Weaknesses

The primary strength of AOPs is their capacity to degrade persistent and biorecalcitrant pharmaceutical compounds that pass through conventional treatment processes (Cuerda-Correa *et al*., 2019). The non-selective nature of hydroxyl radicals allows for the degradation of a wide array of chemical structures, leading to high removal efficiencies and potential for complete mineralization (Zhang *et al*., 2022). AOPs can also be optimized to achieve both pollutant removal and effective disinfection simultaneously. However, AOPs are not without their limitations. One of the main weaknesses is the potential for the formation of toxic or more recalcitrant transformation products, which require further investigation and potentially post-treatment steps (García *et al*., 2020). The high energy consumption associated with processes like UV irradiation and the cost of chemical reagents (e.g., H_2O_2) can also be significant (Zhang *et al*., 2022). Furthermore, the presence of radical scavengers, such as natural organic matter (NOM) and inorganic ions like bicarbonate, can significantly reduce the efficiency of the processes by consuming the generated radicals, necessitating higher doses of reagents and increasing operational costs (Malvestiti *et al*., 2019).

4.2. Membrane-Based Technologies

Membrane-based technologies represent another promising avenue for upgrading wastewater treatment plants to remove pharmaceutical pollutants. These processes physically separate contaminants from water by using a selective barrier, or membrane, which can be tailored to remove specific-sized molecules. The main advantage of membrane technologies is their ability to provide a definitive physical barrier, ensuring consistent and high-quality effluent with minimal dependence on the biological activity of microorganisms or complex chemical reactions (Le-Clech, 2021). The selection of a specific membrane technology, such as membrane bioreactors (MBRs) or nanofiltration (NF) and reverse osmosis (RO), depends on the target pollutants, the desired effluent quality, and the overall cost-effectiveness of the system (Luo *et al*., 2022). These systems are typically deployed as a tertiary or quaternary treatment step to achieve very low concentrations of micropollutants.

4.2.1. Membrane Bioreactors (MBRs)

Membrane Bioreactors (MBRs) combine a conventional biological treatment process, such as activated sludge, with a membrane filtration step (microfiltration or ultrafiltration). The membranes are used to retain the biomass, eliminating the need for a secondary clarifier and allowing for higher biomass concentrations and longer sludge retention times (SRTs) (Al-Zubaidi *et al*., 2022). This prolonged contact time with the microbial community enhances the biodegradation of certain pharmaceuticals. MBRs have been shown to be effective at removing a variety of pharmaceutical compounds, particularly those that are biodegradable. However, the removal efficiency of more recalcitrant compounds, such as carbamazepine and diclofenac, can be highly variable and often low (Khan *et al*., 2020). A major challenge associated with MBRs is membrane fouling, a phenomenon where pollutants and microorganisms accumulate on the membrane surface, leading to a decrease in flux and an increase in energy consumption for cleaning and maintenance (Weng *et al*., 2021).

4.2.2. Nanofiltration (NF) and Reverse Osmosis (RO)

Nanofiltration (NF) and Reverse Osmosis (RO) are pressure-driven membrane processes that offer a very high degree of separation for pharmaceutical pollutants. NF membranes have a pore size ranging from approximately 0.5 to 2 nm and can effectively remove divalent ions and larger organic molecules, including most pharmaceuticals (Bustillo-Lecompte *et al*., 2023). RO membranes have even smaller pores and can reject virtually all dissolved solids, including monovalent ions and a wide range of micropollutants, making them the gold standard for producing high-purity water. The removal efficiency of NF and RO is primarily governed by a combination of size exclusion (sieving) and electrostatic interactions (Donnan exclusion), with the latter being particularly important for charged pharmaceutical compounds (Luo *et al*., 2022). While these technologies offer excellent removal efficiencies, they are energy-intensive due to the high operating pressures required and are highly susceptible to membrane fouling, which increases operational costs and requires frequent cleaning (Li *et al.*, 2020).

4.2.3. Advantages and Disadvantages

The primary advantage of membrane-based technologies is their high and consistent removal efficiency for a broad range of pharmaceutical pollutants, especially with NF and RO membranes, which can produce high-quality effluent suitable for reuse applications (Ghadhghadh *et al.*, 2022). MBRs offer the benefit of a compact footprint and enhanced biological removal of biodegradable compounds. However, the main disadvantages are significant. The capital and operational costs are often higher than for other treatment methods due to the energy required for high-pressure systems and the costs associated with membrane replacement and maintenance (Le-Clech, 2021). Membrane fouling remains a critical issue that compromises performance and increases the need for chemical cleaning, which in turn can reduce membrane lifespan (Luo *et al.*, 2022). The concentrate stream generated by NF and RO, which contains high concentrations of removed pollutants, also presents a significant challenge as it requires further, often costly, treatment or disposal (Bustillo-Lecompte *et al.*, 2023).

4.3. Hybrid Systems and Other Emerging Technologies

To address the limitations of single-process technologies, significant research and development efforts have focused on hybrid systems, which combine multiple treatment methods to leverage their respective strengths and overcome their individual weaknesses (Li *et al.*, 2023). Hybrid systems are designed to create synergistic effects, leading to a more robust, efficient, and cost-effective treatment solution for pharmaceutical pollutants. Furthermore, other emerging technologies, such as advanced adsorption processes, are also being explored as viable alternatives for WWTP upgrades (Mofrad *et al.*, 2020). These innovative approaches are vital for achieving the high removal efficiencies required to meet modern environmental standards.

4.3.1. Combined Processes

The most common hybrid systems combine a biological treatment step with a physical or chemical process. A prime example is the integration of an AOP, such as ozonation or photocatalysis, with a biological treatment process. In an AOP-Bio hybrid system, the AOP acts as a pre-treatment step to transform recalcitrant pharmaceuticals into more biodegradable intermediates, which can then be more easily removed by the downstream biological process (Fadare & Sani, 2020). Another effective combination is the coupling of a biological process with a membrane technology, such as an MBR-AOP system, which combines the high biomass concentration of MBRs with the advanced degradation capabilities of an AOP to achieve a superior effluent quality (Gu *et al.*, 2023). Researchers have also explored the combination of membrane processes with AOPs, such as NF-UV/H$_2O_2$ systems, where the membrane pre-concentrates the pollutants, allowing for more efficient degradation by the AOP (Li *et al.*, 2023). These hybrid systems can offer a more balanced approach to pollutant removal by improving efficiency and reducing overall operational costs compared to using a single high-intensity process.

4.3.2. Adsorption

Adsorption is a physiochemical process that involves the retention of pharmaceutical pollutants onto the surface of a solid material, or adsorbent (Mofrad *et al.*, 2020). This technology is particularly attractive due to its simple operation, high efficiency, and cost-effectiveness. Activated carbon, in both powdered (PAC) and granular (GAC) forms, has long been the most widely used adsorbent for micropollutant removal in water treatment plants (Qasim *et al.*, 2021). PAC is typically dosed into the water stream, while GAC is used in fixed-bed columns. However, the high cost of activated carbon and the challenges associated with its regeneration have spurred research into novel, low-cost adsorbents. Significant attention has been given to developing adsorbents from agricultural waste, industrial byproducts, and engineered materials such as biochar, metal-organic frameworks (MOFs), and carbon nanotubes (Bustillo-Lecompte *et al.*, 2023). These advanced adsorbents often exhibit higher adsorption capacities and greater selectivity for specific pharmaceuticals, making them a promising alternative for future wastewater treatment plant upgrades (Perez-García *et al.*, 2022).

5. Conclusion and Future Perspectives

5.1. Summary of key findings on the effectiveness of different upgrade technologies

The scientific literature reveals that no single technology provides a universal solution for the removal of pharmaceutical pollutants from wastewater. The most effective strategies often involve a combination of primary, secondary, and tertiary treatment methods. Advanced oxidation processes (AOPs), particularly ozonation and Fenton's reagent, have been demonstrated to effectively degrade a wide range of organic micro-pollutants, including many pharmaceuticals, by generating highly reactive radicals. Similarly, activated carbon, both powdered (PAC) and granular (GAC), shows high efficiency in removing certain pollutants through adsorption. Membrane filtration, such as nanofiltration and reverse osmosis, can physically separate a broad spectrum of contaminants, though these methods can be energy-intensive and are susceptible to fouling. Recent studies also highlight the promise of biological approaches, including bioreactors with specific microbial cultures, which can be a more sustainable option for degrading certain compounds. Ultimately, the effectiveness of any chosen technology is highly dependent on the specific chemical properties of the pharmaceutical pollutants present in the water, requiring a tailored approach.

5.2. Recommendations for selecting and implementing cost-effective and sustainable solutions

Selecting an appropriate upgrade solution requires a holistic assessment that balances removal efficiency with cost-effectiveness and sustainability. It is crucial to begin with a comprehensive analysis of the specific pharmaceutical pollutants present in the wastewater influent to identify the most prevalent and persistent compounds. Based on this data, a technology or combination of technologies can be chosen. For instance, in plants with high concentrations of compounds susceptible to oxidation, ozonation may be a strong candidate. However, the life-cycle costs, including initial capital expenditure, operational expenses for energy and chemicals, and the costs associated with byproduct or sludge disposal, must be carefully considered. Sustainable solutions should prioritize energy-efficient processes and minimize the use of non-renewable resources. The implementation should be phased, allowing for pilot-scale testing and optimization to ensure the chosen technology integrates seamlessly with the existing infrastructure. Furthermore, collaboration with pharmaceutical manufacturers can help to identify and mitigate the sources of key pollutants, a sustainable approach that tackles the problem at its origin.

5.3. Discussion of future research needs and directions

While significant progress has been made in understanding and treating pharmaceutical pollutants, several areas require further research to advance the field. A key need is the development of more energy-efficient and selective technologies that can target specific pharmaceutical compounds without generating harmful byproducts. Research should also focus on long-term ecological impact studies to better understand the effects of low-concentration pharmaceutical residues and their metabolites on aquatic ecosystems. The integration of advanced computational models, artificial intelligence, and machine learning could revolutionize wastewater treatment by enabling real-time monitoring, predictive maintenance, and dynamic optimization of treatment processes. Furthermore, there is a growing need to develop cost-effective, decentralized treatment solutions that can be deployed in rural or low-resource settings. Finally, research into the source-control of these pollutants, such as developing more biodegradable drugs or implementing advanced disposal programs, remains a critical and promising area for future work.

5.4. Concluding remarks on the importance of regulatory frameworks and public awareness

Ultimately, the successful adoption of new wastewater treatment technologies will be driven not only by scientific advancement but also by robust regulatory frameworks and broad public awareness. Governments and international bodies must establish clear, enforceable, and scientifically-based discharge limits for key pharmaceutical pollutants. These regulations provide the necessary incentive for municipalities and industries to invest in upgrade technologies and drive innovation in the private sector. Simultaneously, public awareness campaigns are vital to educate the population about the environmental impact of improper medication disposal. By promoting responsible disposal practices and generating public support for infrastructure investments, these campaigns can help reduce the influx of pharmaceuticals into the wastewater stream and create a societal consensus around the importance of clean water. It is a shared responsibility, where policy, technology, and public engagement must work in concert to protect both human and environmental health.

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