The Persistence of Refractory Pharmaceuticals in Aquatic Systems and Their Environmental Impacts

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Abstract. The persistence of pharmaceutical residues in aquatic environments has emerged as a pressing global concern, as conventional wastewater treatment plants were not designed to remove such micropollutants. This review investigates both the occurrence of refractory pharmaceutical compounds in wastewater and the treatment strategies available to mitigate their impacts. Four representative methods are examined: nanofiltration, microbial biodegradation, constructed wetlands, and titanium dioxide (TiO_2) photocatalysis. Nanofiltration membranes have demonstrated consistent removal efficiencies above 90% for a wide range of pharmaceuticals, yet they require high operational costs and generate concentrated waste streams. Microbial biodegradation provides an environmentally friendly option, but its effectiveness is highly sensitive to natural factors such as temperature, pH, and nutrient levels, resulting in fluctuating performance across seasons and locations. Constructed wetlands represent a cost-effective and sustainable solution, though their efficiency is limited for highly persistent pharmaceuticals. TiO_2 photocatalysis achieves high degradation rates by generating strong oxidizing radicals under UV excitation, but its application is hindered by light scattering, shielding effects, and interference from natural organic matter and inorganic ions. Overall, while each method shows promise and can achieve removal rates above 70% for certain compounds, significant challenges remain in ensuring stability, scalability, and cost-effectiveness. These findings highlight the urgent need for integrated, hybrid approaches and policy-driven frameworks to safeguard aquatic ecosystems from pharmaceutical contamination.

Keywords: Pharmaceutical removal, waste water, TiO_2.

1. Introduction

Pharmaceutical residues have become a class of emerging micropollutants in aquatic systems, largely because conventional wastewater treatment plants (WWTPs) were designed to remove only bulk organic matter rather than complex synthetic chemicals. These compounds enter the environment through multiple pathways, including excessive prescribing, expired household drugs, clinical and hospital waste, improper disposal, and metabolites excreted by patients. Due to their chemical stability, water solubility, and resistance to degradation, they often persist through treatment processes and accumulate in rivers, lakes, groundwater, and even drinking water sources [1-5]. Alarmingly, drug residues have been detected at concentrations as low as nanograms per liter in raw water supplies, raising precautionary concerns for human health despite the absence of confirmed adverse effects at these levels [1]. Groundwater contamination can also result from landfill leakage and sewer infiltration, while biotechnological pharmaceutical production introduces auxiliary substances such as buffers, chelators, and antibiotics. Recent studies indicate that 15–20% of medicines used in hospitals are potentially bioaccumulative, further exacerbating environmental risks [6–8].

The persistence of pharmaceuticals poses multifaceted ecological threats. Aquatic organisms exposed to these compounds may experience subtle but serious disruptions: endocrine interference in fish and amphibians has led to feminization, reduced fertility, or altered sex ratios, while psychotropic residues can cause behavioral changes. Small rivers and streams are particularly vulnerable due to high proportions of untreated wastewater inputs, and groundwater contamination represents an additional long-term risk. Despite the growing recognition of these issues, relatively few studies have systematically addressed the removal of pharmaceuticals in wastewater treatment. Existing research

often evaluates isolated technologies under laboratory conditions, leaving critical gaps in understanding their efficiency, stability, and scalability in real-world contexts.

This study aims to address these gaps by evaluating advanced treatment methods for pharmaceutical removal, with particular focus on nanofiltration, microbial biodegradation, constructed wetlands, and titanium dioxide (TiO_2) photocatalysis. The objectives are threefold: (1) to identify the most efficient techniques for removing pharmaceutical contaminants from wastewater, (2) to compare their effectiveness under varying environmental conditions, and (3) to assess their potential for large-scale application. Studying this problem is significant for two main reasons. First, it highlights a critical flaw in modern water treatment systems, which are ill-equipped to filter out persistent micropollutants such as pharmaceuticals. Second, it underscores the lack of public awareness and regulatory frameworks around pharmaceutical waste disposal. Without targeted research and informed intervention, these contaminants will continue to accumulate in aquatic environments, silently undermining ecosystem stability and posing long-term risks to human and environmental health.

2. Methodology

This review was conducted through a systematic search of four major scientific databases: Web of Science, Scopus, ScienceDirect, and Google Scholar. The search period was restricted to publications between 2000 and 2025, ensuring coverage of both foundational studies and the most recent advances. The search strategy employed the following keywords: “pharmaceutical removal” AND “drinking water” AND (biodegradation OR constructed wetlands OR TiO_2 OR nanofiltration).

To ensure relevance and quality, studies were selected based on predefined inclusion and exclusion criteria. Inclusion criteria required that articles be peer-reviewed, present original experimental data, and focus on pharmaceutical removal in water or wastewater treatment systems. Exclusion criteria involved studies that lacked empirical data, were unrelated to drinking water contexts, or were limited to meeting abstracts or reviews without primary findings.

The initial database search yielded 20 articles. After removing duplicates, 12 studies remained. Screening of titles and abstracts further reduced this number to 10. Following a thorough full-text review and application of the inclusion and exclusion criteria, a final set of 9 articles was selected for detailed analysis in this review. These studies collectively provide insights into the performance, limitations, and scalability of advanced treatment methods for pharmaceutical removal.

3. Results

3.1. Presentation of key findings

1. Conventional biological methods

Traditional approaches to handling pharmaceutical wastewater have long relied on biological treatment methods, both aerobic and anaerobic microorganisms are involved in breaking down pharmaceuticals and their byproducts through degradation processes [9-10].

Biodegradation by Microbial Cultures. Microbial communities are crucial to ecosystems, decomposing organic matter and xenobiotics like pharmaceuticals. Environmental biodegradation is especially key for pharmaceutical breakdown, particularly when WWTPs and STPs are inefficient. [11]. Naturally occurring bacteria, fungi, and algae degrade medicines through two complementary routes. In metabolic degradation, specialist bacteria such as Pseudomonas putida import the drug, employ cytochrome P450 enzymes to cleave its structure, then funnel the fragments into the tricarboxylic-acid (TCA) cycle, ultimately releasing carbon dioxide, water, and energy (ATP). When the compound cannot sustain growth, cometabolic degradation takes over: fungi like Trametes versicolor consume simple sugars and simultaneously secrete laccases and ligninolytic peroxidases that oxidise the drug extracellularly, breaking it into small, harmless molecules such as CO_2, ammonia,

and sulfate. Together, these microbial strategies provide an enzyme-driven polishing step that markedly reduces pharmaceutical residues in treated effluents.

Constructed Wetlands. Constructed wetlands offer effective, reliable, and sustainable wastewater treatment. They have a long history of wastewater treatment, characterized by low costs, simple operation, easy maintenance, environmental friendliness, and their potential as an alternative to wastewater treatment plants [12]. Upon entry, suspended solids and hydrophobic APIs (Active Pharmaceutical Ingredient) are rapidly removed by sedimentation and sorption to organic substrates and biofilms; ionizable species are simultaneously retarded via pH-dependent electrostatic interactions with negatively charged soil particles and root surfaces. A vertical redox gradient then governs subsequent fate: oxic microzones surrounding the rhizosphere sustain aerobic bacteria that deploy extracellular oxidases (e.g., laccases, peroxidases) to cleave aromatic moieties, while deeper anoxic layers harbour denitrifiers and sulfatereducers that cometabolise nitro- or azo-substituted pharmaceuticals using root exudates as electron donors. Concurrent phyto-transformation involves root uptake of hydrophilic residues followed by intracellular phase-I/II enzymatic reactions and sequestration within vacuoles or lignin matrices. Supplementary photolytic degradation occurs at the water– biofilm interface, enhancing removal of recalcitrant species such as ketoprofen and diclofenac. Integrated performance data indicate >70 % elimination of readily degradable pharmaceuticals (e.g., tetracycline, sulfamethoxazole), confirming the system's reliability as a sustainable tertiary treatment option [13]. Biological treatments can be valueable ideas for people to dispose of pharmaceutical wastewater; However, these methods are susceptible to fluctuations due to natural factors such as temperature, pH, and nutrient levels. Consequently, their effectiveness will vary with the seasons and across different geographical locations. Thus, more improvements should be made to make those treatments more reasonable and usable [3].

2. Chemical methods

Titanium Dioxide (TiO2) Photocatalysis Heterogeneous photocatalysis using the semi-conductor titanium dioxide (TiO2) has proven to be a promising treatment technology for water purification. The effectiveness of this oxidation technology for the destruction of pharmaceuticals has also been demonstrated in numerous studies. For example, the most commonly investigated antiepileptic is the dibenzoazepine derivative, carbamazepine (CBZ; 5H-diben-zo[b,f]-azepine-5-carboxamide). CBZ, also used assedative for numerous mental disorders, can cause toxic effects in the liver and is a hematopoietic. Studies have reported the removal efficiency of CBZ in WWTPs as below 10 %. The degradation efficiency of UV/TiO2 for CBZ has reached 70.4% [4]. So I think it would be a good idea to put it into sewage treatment. Because when TiO2 is excited by ultraviolet light, strong oxidizing hydroxyl radicals (HO*) are produced. Their oxidation potential is as high as 2.8V, and they can selectively attack the benzene ring and amide group of CBZ [2,9].

3. Physical methods

Physical removal methods separate pharmaceutical residues from wastewater by using physical forces instead of chemical reactions. Common tools are membranes and solid materials such as activated carbon or resins. These methods do not change the drug molecules; they simply move them from water to another phase, so the water becomes cleaner.

Removal using Nanofiltration membranes consistently eliminate over 90 % of pharmaceuticals from water and wastewater by simultaneously acting as a three function barriers: their nanometre-scale pores physically exclude larger molecules, their negatively charged surfaces electrostatically repel anionic drugs, and their polymeric matrix adsorbs hydrophobic species. The overall rejection for any given compound is therefore a composite of these effects and varies with the drug's physicochemical attributes (molecular size, charge, hydrophobicity, solubility), the membrane's characteristics (pore size, surface charge, hydrophobicity, permeability), and operating conditions (transmembrane pressure, flux, pH, and feed composition). A clear illustration is the behaviour of sulfamethoxazole and carbadox: as the pH rises above 5.6, both antibiotics deprotonate and acquire a net negative charge, resulting in increased electrostatic repulsion by the negatively charged membrane and a corresponding rise in rejection efficiency from 90 % to 95 % [2] [5].

4. Conclusion

4.1. Summary of key findings

Wastewater treatment traditionally employs primary and secondary systems to remove contaminants from sewage. However, these conventional methods often fall short in completely eliminating pharmaceutical residue. To solve this problem, a range of alternative treatment approaches has been developed that may offer enhanced removal capabilities. These include biological methods, chemical methods such as titanium dioxide (TiO_2) photocatalysis and Fenton's oxidation, as well as physical methods like nanofiltration. Each of these methods aims to improve the overall efficiency of wastewater treatment and reduce the environmental impact of these pharmaceutical contaminants.

4.2. Comparison with previous studies

Previous methods such as autoclaving have also been tested for the degradation of pharmaceutical contaminants. High-pressure sterilization involves subjecting waste to high-temperature treatment to degrade the harmful chemicals and microorganisms present. Antibiotic residues are typically high in organic content and can be treated using high-pressure sterilization methods. Although highly efficient (>98%), high-pressure sterilization or supercritical carbon dioxide fluid sterilization requires subsequent processing. Currently, due to the high cost, it is not feasible. Therefore, the main challenge lies in developing an economically viable and practically feasible technology. Without consideration of economic feasibility, these methods remain impractical for developing countries, where medical waste volumes are significantly higher [6]. Compared with recently developed alternatives, these approaches are prohibitively expensive and require stringent operational conditions, which limits their current application. However, what is common among these methods is that their removal efficiency is very high.

4.3. Limitations of the study

Although almost all of them can reach a elimination rate of over 70% towards some specific pharmaceuticals, there are several concerns: for example, the microbes adopting in the biodegradation process are easily affected by natural factors like temperature, pH, and nutritious level etc, so its effectiveness may varies along with season and locations. Although TiO_2 photocatalysis shows high efficiency in degrading carbamazepine, several drawbacks limit its practical large-scale application. For instance, NOM in wastewater will compete with it for free radicals. And it needs to be used together with UV light. However, in actual wastewater, UV light often fails to reach all parts of the water due to the presence of many opaque substances in the wastewater that prevent it from passing through. This will also lead to a decrease in processing efficiency. The process is sensitive to pH and control of simultaneously occurring reactions is quite difficult. A robust system is yet to be developed for large scale successful demonstration.

4.4. Suggestions for future research

Future research needs to focus on methods that combine low cost with effectiveness. For instance, further research is required to improve photocatalytic systems so that they remain effective in the presence of impurities commonly found in natural water bodies. Another priority is to develop photocatalytic processes that can operate efficiently under visible light rather than relying solely on ultraviolet irradiation. Future research must prioritize field validation of hybrid technologies, sludge stabilization, and green manufacturing to mitigate pharmaceutical persistence. Policy-driven integration of source control, advanced treatment, and monitoring is essential for sustainable water resource management.

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