



COMPREHENSIVE REVIEW OF PHARMACEUTICAL WASTEWATER TREATMENT: TECHNOLOGIES, MECHANISMS AND INTEGRATED STRATEGIES

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ABSTRACT

Pharmaceutical manufacturing and clinical use introduce a complex, chemically diverse mixture of active pharmaceutical ingredients (APIs), excipients, solvents, and process chemicals into wastewater streams. These constituents, many of which are bio-refractory, hormonally active, or capable of driving antimicrobial resistance (AMR), resist conventional biological treatment and pose significant public health and ecological risks, even at trace concentrations. This comprehensive review synthesizes current knowledge on advanced and conventional pharmaceutical wastewater treatment technologies, including advanced oxidation processes (AOPs), electrochemical oxidation, photocatalysis, ozonation, Fenton and photo-Fenton reactions, wet air oxidation (WAO), membrane bioreactors (MBRs), constructed wetlands (CWs), activated sludge (AS) processes, activated carbon adsorption, enzymatic degradation, and anaerobic digestion (AD). Each technology is discussed in terms of its mechanistic basis, operational parameters, performance envelope, energy and chemical requirements, strengths, and limitations, along with real-world case studies and comparative performance data. Evidence consistently suggests that no single technology can achieve universal pharmaceutical removal across the wide physicochemical diversity of these effluents. Hybrid treatment trains designed with integrated biological, chemical, and physical unit operations deliver greater robustness, lower energy and reagent use, and better water reuse potential. This review concludes with an evidence-based framework for selecting sustainable, modular, and scalable treatment options for pharmaceutical effluents that meet emerging global regulatory standards.

Keywords: Pharmaceutical wastewater, active pharmaceutical ingredients (APIs), advanced oxidation processes (AOPs), membrane bioreactors (MBRs), zero liquid discharge (ZLD), antimicrobial resistance (AMR), hybrid treatment trains, micropollutants.

1. INTRODUCTION

The global pharmaceutical industry, valued at over USD 1.6 trillion in 2023, generates wastewater of exceptional complexity and environmental significance (1). Pharmaceutical effluents originate from multiple sources, including synthesis and fermentation operations, equipment cleaning, quality control laboratories, solvent recovery, and utility systems. Beyond the manufacturing stage, a large proportion of pharmaceutical compounds excreted by humans and animals, often as unchanged parent molecules or biologically active metabolites, reach municipal wastewater systems, creating a diffuse but persistent contamination challenge that intersects with public health infrastructure (2). Active pharmaceutical ingredients (APIs), antibiotic residues, hormones, analgesics, psychiatric drugs, and anticancer agents have been detected in surface water, groundwater, and even drinking water supplies across six continents. The concentrations detected range from nanograms to micrograms per liter; however, even sub-therapeutic levels exert measurable ecological effects, such as endocrine disruption in aquatic organisms, selective pressure leading to antimicrobial resistance (AMR) in environmental microbial communities, and toxicity to invertebrates and fish. The World Health Organization (WHO) has designated AMR as one of the top global public health threats, with pharmaceutical manufacturing discharge identified as a key environmental reservoir for resistance gene dissemination. Regulatory frameworks worldwide are rapidly evolving in response to this challenge. India's Central Pollution Control Board (CPCB) has issued sector-specific effluent standards for pharmaceutical manufacturing facilities; the European Union's Environmental Quality Standards (EQS) Directive mandates environmental risk assessments for new drug approvals; the US Environmental Protection Agency (EPA) is expanding the scope of its National Pollutant Discharge Elimination System (NPDES) permits to cover pharmaceutical micropollutants; and China's Ministry of Ecology and Environment (MEE) has enacted stringent sector-specific effluent norms under GB 21906. These converging regulatory pressures compel pharmaceutical manufacturers to adopt effective, reliable, and innovative treatment strategies. Conventional wastewater treatment processes, primarily activated sludge with secondary clarification, are designed to remove biodegradable organic matter and nutrients. They achieve only partial removal of many pharmaceutical compounds, partly because these molecules have evolved to be metabolically stable and resist enzymatic degradation (3), and partly because the short hydraulic retention times in conventional plants are insufficient for the slow biotransformation kinetics required. Advanced treatment technologies are therefore increasingly integrated into pharmaceutical wastewater treatment systems, either as primary treatment for high-strength manufacturing effluents or as tertiary polishing for hospital and municipal streams containing pharmaceutical residues. This review provides a systematic and mechanistically grounded analysis of the full spectrum of treatment technologies applicable to pharmaceutical wastewater, from classical biological processes to cutting-edge electrochemical and photocatalytic methods. Real-world case studies from India, Europe, the USA, China, and South Korea are incorporated to illustrate technology performance under operational conditions. Comparative performance data, technology selection guidance, and a decision framework for integrated treatment train design are presented to assist environmental engineers, pharmaceutical manufacturers, regulators, and researchers in navigating the increasingly complex landscape of pharmaceutical wastewater management (4).

2. Characteristics of Pharmaceutical Wastewater

Pharmaceutical wastewater is markedly heterogeneous in its physicochemical composition. Unlike domestic wastewater, which has a relatively predictable matrix, pharmaceutical effluents vary widely depending on the type of drug being manufactured, production scale, synthesis route, and cleaning chemicals used (5). High chemical oxygen demand (COD) concentrations ranging from 2,000 mg/L to over 100,000 mg/L in raw manufacturing effluents are common, along with high biological oxygen demand (BOD) values, wide pH fluctuations (from 2 to 12), elevated total dissolved solids (TDS), and the presence of solvents, surfactants, and toxic intermediates. A key distinguishing feature of pharmaceutical effluents is their low BOD/COD ratio, typically below 0.4 and often as low as 0.1–0.2. This ratio is a critical indicator of biodegradability: values above 0.5 suggest good biodegradability, while values below 0.3 indicate that conventional biological treatment alone will be insufficient. The recalcitrant fraction, which includes aromatic heterocycles, chlorinated compounds, sulfonamides, fluoroquinolones, and other complex molecular architectures, requires advanced physicochemical treatment. The presence of APIs at concentrations of mg/L to g/L in manufacturing effluents (and ng/L to µg/L in hospital and municipal streams) creates a treatment challenge that spans many orders of magnitude. Emerging contaminants, such as microplastics from blister packaging lines, perfluoroalkyl substances (PFAS) from firefighting foams used

in pharmaceutical warehouses, and nanomaterials from novel drug delivery systems, add further complexity to the treatment matrix (6).

Table 1: Typical physicochemical characteristics of pharmaceutical wastewater from different source categories.

Parameter	Manufacturing Effluent	Hospital Effluent	Municipal WWTP Inflow
COD (mg/L)	2,000–100,000	200–2,000	150–500
BOD (mg/L)	300–15,000	100–800	80–300
BOD/COD Ratio	0.1–0.4	0.3–0.6	0.5–0.7
Total Dissolved Solids (mg/L)	5,000–50,000	500–3,000	300–800
pH Range	2–12	6–9	6.5–8.5
Total Nitrogen (mg/L)	50–2,000	20–200	20–60
API Concentration	mg/L – g/L	µg/L – mg/L	ng/L – µg/L
Color (Pt-Co Units)	200–50,000	10–500	5–100

3. Advanced Oxidation Processes (AOPs)

Advanced oxidation processes (AOPs) represent a broad class of chemical treatment methods united by their common mechanism: the in situ generation of highly reactive radical species, primarily the hydroxyl radical ($\text{OH}^\bullet$, $E^\circ = 2.80 \text{ V vs. SHE}$), and in persulfate-based systems, the sulfate radical ($\text{SO}_4^{\bullet-}$, $E^\circ = 2.60 \text{ V vs. SHE}$). These radicals are among the most powerful oxidants known, capable of non-selectively attacking and degrading virtually all organic compounds, including those that are highly resistant to biological attack. The radical oxidation pathway proceeds via hydrogen abstraction from C-H bonds, electrophilic addition to aromatic rings, and electron transfer, generating intermediate radicals that are subsequently oxidized further. The ultimate products of complete mineralization are carbon dioxide (CO_2), water (H_2O), and inorganic salts. In practice, complete mineralization requires careful optimization, and treatment trains often include downstream biological polishing or activated carbon adsorption to address recalcitrant intermediates (7).

3.1 Electrochemical Oxidation

Electrochemical oxidation (EO) employs electrochemical reactors to drive the degradation of pharmaceutical pollutants through two complementary mechanisms: direct anodic oxidation, in which organic molecules adsorbed onto the electrode surface undergo direct electron transfer, and indirect oxidation, mediated by electrogenerated reactive species, such as hypochlorite (OCl^-), hydrogen peroxide (H_2O_2), ozone (O_3), and hydroxyl radicals. The choice of anode material is critical to EO performance. Boron-doped diamond (BDD) electrodes are considered state-of-the-art for pharmaceutical wastewater treatment: their wide electrochemical potential window, chemical inertness, and high OH generation capacity enable near-complete mineralization of even the most recalcitrant APIs. Mixed metal oxide (MMO) anodes (e.g., $\text{RuO}_2/\text{TiO}_2$, $\text{IrO}_2/\text{TiO}_2$) are more cost-effective and robust for applications where selective oxidation rather than full mineralization is acceptable. A recent real-world example is the electro-Fenton system deployed at a Cipla pharmaceutical facility in Goa, India (2023), which achieved 92% COD removal from antibiotic-laden effluents while maintaining effluent quality within CPCB discharge standards. The system operated at a current density of 30 mA/cm^2 , using a graphite-felt cathode for in situ H_2O_2 generation paired with Fe^{2+} as the Fenton catalyst. Key design parameters include current density ($5\text{--}100 \text{ mA/cm}^2$), electrolyte composition and conductivity (NaCl , Na_2SO_4), electrode gap, hydrodynamic mixing, pH control, and temperature. Energy consumption typically ranges from 5 to 50 kWh/kg COD removed, depending on the system configuration and wastewater composition (8).

3.2 Photocatalysis

Heterogeneous photocatalysis exploits light-activated semiconductor catalysts, most commonly titanium dioxide (TiO_2 , anatase phase) and zinc oxide (ZnO), to generate electron-hole pairs (e^-/h^+) upon irradiation with photons with energies exceeding the semiconductor bandgap (3.2 eV for anatase TiO_2 , corresponding to $\lambda < 387 \text{ nm}$). The photogenerated holes react with water molecules or surface hydroxyl groups to produce OH radicals, whereas excited electrons reduce dissolved oxygen to superoxide anions ($\text{O}_2^{\bullet-}$), which can further generate OH through the hydroperoxyl radical pathway. The application of visible-light-active

photocatalysts achieved through nitrogen or metal ion (Fe^{3+} or Ag^{+}) doping, or sensitization with narrow-bandgap semiconductors (e.g., $\text{g-C}_3\text{N}_4$ or BiVO_4) has been a major research focus in the past decade, aiming to utilize the solar spectrum more efficiently. In China, a UV/ TiO_2 photocatalytic system treating a tetracycline and quinolone-rich effluent from an API manufacturing facility achieved 90% antibiotic degradation within 60 min of treatment under optimized conditions (catalyst loading, 1.5 g/L; UV intensity, 80 W/m^2 , and pH, 5.5) in 2023.

3.3 Ozonation

Ozone (O_3) is an exceptionally powerful oxidant ($E^\circ = 2.07 \text{ V}$) that degrades pharmaceutical compounds via two distinct mechanisms. The direct pathway involves selective electrophilic reactions with electron-rich functional groups double bonds, amine groups, and aromatic systems and is predominant at low pH. The combined direct-plus-indirect action of ozonation is particularly effective for pharmaceutical compounds containing phenolic, amino, and heterocyclic structural features. The combined direct-plus-indirect action of ozonation is particularly effective for pharmaceutical compounds containing phenolic, amino, and heterocyclic structural features. Ozonation is widely deployed for tertiary polishing of hospital effluents and municipal wastewater treatment plants. The Netherlands WWTP example where ozonation combined with biofiltration achieved 85% estrogen removal in 2020 illustrates the practical efficacy of this approach for hormonal micropollutants. Key design considerations include: O_3 dose (typically 3–15 mg/L for pharmaceutical applications), gas-liquid contact device design (bubble columns, venturi systems, or fine-bubble diffusers), contact time (5–30 minutes), pH control, and management of potentially toxic transformation products such as bromate (from bromide-containing waters) and nitrosamines (9).

3.4 Fenton and Photo-Fenton Processes

In the classical Fenton reaction, iron-catalyzed decomposition of H_2O_2 generates OH radicals through a cyclic redox mechanism involving Fe^{2+} and Fe^{3+} ion interconversion. The reaction proceeds optimally at acidic pH (2–4), where iron remains soluble and H_2O_2 decomposition is maximally catalyzed. The photo-Fenton variant accelerates this process by using UV or solar irradiation to photoreduce Fe^{3+} to Fe^{2+} , simultaneously regenerating the active catalyst and generating additional OH via direct photolysis of H_2O_2 and iron-hydroxo complexes. Photo-Fenton treatment of hospital effluents in Spain achieved 88% micropollutant reduction for antipsychotic drugs and hormones when combined with a constructed wetland polishing stage in 2022. The system exploits natural solar irradiation (solar UV dose $\sim 15 \text{ W/m}^2$) to reduce energy costs compared to artificial UV sources. The main operational challenges include iron sludge generation (requiring downstream coagulation–flocculation), tight pH control, and H_2O_2 management. Heterogeneous Fenton catalysts (iron-loaded zeolites, Fe_3O_4 nanoparticles, and iron-doped biochar) have been actively researched to extend the operational pH range and reduce sludge generation (10).

3.5 Wet Air Oxidation (WAO)

Wet air oxidation (WAO) is a hydrothermal process that oxidizes dissolved or suspended organic matter at elevated temperatures (150–320°C) and pressures (0.5–20 MPa) using dissolved oxygen (typically from compressed air). Under these conditions, organics that are completely resistant to ambient-temperature biological or chemical oxidation can be effectively degraded. Catalytic WAO (CWAO) introduces solid catalysts (e.g., Ru/TiO_2 , $\text{Pt/Al}_2\text{O}_3$, and MnO_2 -based composites) to lower activation barriers, enabling operation under more moderate conditions and improving chemical oxygen demand (COD) reduction efficiency. WAO is particularly suited to highly concentrated, toxic, or non-biodegradable pharmaceutical waste streams, such as mother liquors from API synthesis, concentrated solvent wastes, and disinfection byproduct streams. The Stryker Corporation (USA) employs WAO as a pre-treatment step for refractory pharmaceutical manufacturing intermediates, achieving 98% TOC removal prior to biological polishing. The primary limitations are substantial capital investment (high-pressure reactor systems), energy-intensive operation, and the requirement for specialized materials of construction (stainless steel and Hastelloy) to resist corrosion at high temperatures and pressures (11).

4. Membrane Bioreactors (MBRs)

Membrane bioreactors (MBRs) represent the most technologically advanced evolution of the activated sludge process, integrating a high-concentration biological reactor with pressure-driven membrane separation, typically microfiltration (pore size 0.1–0.4 μm) or ultrafiltration (pore size 0.01–0.1 μm), to replace conventional secondary clarification. The membrane serves as an absolute barrier to suspended solids, pathogens, and colloids, delivering treated effluent of consistently high quality, regardless of incoming load variability. This decoupling of hydraulic retention time (HRT) from sludge retention time (SRT) enables operation at very long SRTs (20–80 days), selecting for slow-growing specialized microorganisms capable of co-metabolizing recalcitrant pharmaceutical compounds. MBRs achieve COD removal efficiencies of 85–98% and pharmaceutical compound removal of 50–90%, depending on compound biodegradability, SRT, and HRT. Hydrophobic and sorption-prone compounds (e.g., triclocarban, triclosan, musks) are effectively removed via sludge adsorption; biodegradable compounds (e.g., ibuprofen, naproxen) are bio transformed; while persistent compounds (e.g., carbamazepine, diclofenac) largely pass through, requiring downstream AOP treatment. A landmark example is the zero liquid discharge (ZLD) system implemented by Aurobindo Pharma in India (2022), which integrates MBR with reverse osmosis (RO) and multiple-effect evaporation to achieve complete reuse of process water and full regulatory compliance. The MBR stage treats mixed pharmaceutical wastewater (COD: 5,000–15,000 mg/L) to below 200 mg/L COD, enabling downstream RO processing. The Hyderabad Common Effluent Treatment Plant (CETP) serving the Patancheru bulk drug manufacturing cluster, one of the world's largest pharmaceutical manufacturing zones, employs an MBR + ozonation hybrid, achieving approximately 95% COD removal and 80% API reduction. Key operational parameters include mixed liquor suspended solids (MLSS: 8,000–15,000 mg/L), transmembrane pressure (TMP: 0.2–0.5 bar), flux (10–30 L/m²/h), air-to-permeate ratio for fouling control, and cleaning frequency and chemical protocols (citric acid for scaling and sodium hypochlorite for biofouling). Fouling, accumulation of extracellular polymeric substances (EPS) and soluble microbial products (SMP) on membrane surfaces, remains the primary operational challenge, requiring periodic chemical cleaning (every 1–4 weeks) and membrane replacement (every 5–10 years). Surface-modified membranes incorporating hydrophilic coatings, photocatalytic TiO₂ layers, or antimicrobial silver nanoparticles represent active research directions for fouling mitigation (12).

5. Constructed Wetlands (CWs)

Constructed wetlands are engineered systems designed to replicate and optimize the water-purification functions of natural wetland ecosystems. They employ a substrate (gravel, sand, or soil), wetland plants (macrophytes such as *Phragmites australis*, *Typha latifolia*, or *Scirpus* spp.), and diverse microbial communities to remove contaminants through a combination of physical, chemical, and biological mechanisms, including sedimentation, filtration, sorption to the substrate and plant biomass, plant uptake, aerobic and anaerobic microbial decomposition, and photodegradation in open-water surface systems. Two principal configurations are employed: surface flow (SF-CW), in which water flows horizontally across a shallow, vegetated basin exposed to the atmosphere, and subsurface flow (SSF-CW), in which water flows through a porous granular medium below the surface, either horizontally (HSSF-CW) or vertically (VSSF-CW). Hybrid CW systems combining HSSF and VSSF units in series create alternating aerobic–anaerobic conditions that enable simultaneous nitrification–denitrification and enhanced micropollutant removal. CWs are particularly well-suited as low-energy polishing stages following primary biological treatment for pharmaceutical compounds with moderate to good biodegradability (e.g., ibuprofen and paracetamol: 70–90% removal; caffeine: >95% removal). Persistent pharmaceuticals, such as carbamazepine and diclofenac, are poorly removed (<30%) in conventional CWs; however, their removal can be enhanced by incorporating aerated wetland zones, biochar substrates, or hybrid designs. The Spanish photo-Fenton + CW hybrid system mentioned earlier exemplifies this integrative approach. The land requirement is the primary constraint for CW implementation, particularly in densely populated industrial areas; typical hydraulic loading rates of 0.2–0.6 m/d necessitate substantial land areas for high-flow applications. Seasonal performance variability owing to temperature effects on biological activity is a secondary concern; however, insulated and covered CW designs can mitigate cold-weather performance loss (13–15).

6. Activated Sludge (AS) Processes

The activated sludge process developed in Manchester, UK, in 1914 by Arden and Lockett, remains the workhorse of biological wastewater treatment worldwide. In its classic configuration, a continuous aerated bioreactor maintains a dense suspension of aerobic heterotrophic microorganisms (the 'activated sludge') that assimilate biodegradable organic matter, with treated effluent clarified by gravity settling in a secondary clarifier, and a fraction of the settled sludge is returned to the bioreactor to maintain biomass concentration. Modern activated sludge systems deployed for pharmaceutical wastewater treatment incorporate a range of process enhancements: sequencing batch reactors (SBRs) for flexibility with variable loads; moving bed biofilm reactors (MBBRs) using plastic carrier media to grow biofilm and increase biomass density; integrated fixed-film activated sludge (IFAS) systems combining suspended and attached growth; and selector vessels that create transient substrate concentration gradients to suppress filamentous bulking. The biodegradability of pharmaceutical compounds in AS systems varies enormously, from nearly complete removal (>90%) for compounds such as paracetamol (acetaminophen), ibuprofen, and caffeine, to partial removal (30–70%) for compounds such as tetracyclines and sulfonamides, to minimal removal (<30%) for persistent compounds such as carbamazepine, diclofenac, and most synthetic hormones. Long SRTs (>20 days) are correlated with improved removal of many pharmaceuticals by increasing the abundance and diversity of specialized bio transforming microorganisms. Bioaugmentation, the addition of specialized pharmaceutical-degrading microbial cultures, has been demonstrated at the pilot scale to enhance the removal of specific target compounds. Sludge management is a key operational and economic consideration in AS systems treating pharmaceutical wastewater: the activated sludge accumulates sorbed pharmaceutical compounds, potentially classifying the sludge as hazardous waste under some regulatory frameworks, and restricting its beneficial use in agriculture. Thermophilic aerobic digestion (TAD) or advanced anaerobic digestion of sludge can reduce pharmaceutical concentrations in the biosolids; however, complete elimination is rarely achieved (16).

7. Activated Carbon Adsorption

Activated carbon produced by controlled pyrolysis and activation of carbon-rich precursors, such as coal, coconut shells, wood, or agricultural by-products, possesses an extraordinarily high specific surface area (500–2,000 m²/g) and a complex micropore–mesopore structure that renders it a highly effective adsorbent for a wide range of pharmaceutical compounds. Adsorption occurs primarily through van der Waals forces, π – π stacking interactions between the graphenic carbon surface and aromatic drug molecules, electrostatic interactions (pH-dependent), and hydrogen bonding.

Two main methods are employed for pharmaceutical wastewater treatment. Granular activated carbon (GAC) is used in fixed-bed adsorbers, offering relatively low operating costs, easy regeneration (thermal: 700–900°C, steam, or electrochemical), and a high capacity for hydrophobic compounds (log K_{ow} > 2). Powdered activated carbon (PAC) is added directly to the bioreactor or contact tank, offering a high surface area per unit mass and rapid adsorption kinetics; however, it requires downstream separation (filtration or sedimentation). PAC-enhanced AS systems (PACT process) demonstrate significantly improved removal of recalcitrant pharmaceuticals such as carbamazepine (from <20% to >80% removal) compared to conventional AS alone. Magnetic activated carbon iron oxide-impregnated carbon particles recoverable by magnetic separation have been demonstrated at the pilot scale for removing diclofenac and ibuprofen from real pharmaceutical wastewater (17), with adsorption capacities of 150–350 mg/g and magnetic recovery efficiencies of >95%. The adsorption equilibrium data for most pharmaceutical compounds fit the Freundlich isotherm model (reflecting energetically heterogeneous adsorption sites), whereas kinetics typically follow pseudo-second-order rate equations, indicating chemisorption as the rate-limiting step.

8. Enzymatic Degradation

Enzymatic treatment exploits the catalytic specificity and activity of oxidoreductase enzymes, particularly laccases (multicopper oxidases), lignin peroxidases, manganese peroxidases, horseradish peroxidase (HRP), and cytochrome P450 monooxygenases, to transform pharmaceutical compounds under mild reaction conditions (ambient temperature and pressure, near-neutral pH). These enzymes catalyze oxidative coupling, ring cleavage, N-dealkylation, and hydroxylation reactions that can reduce the pharmacological activity and ecotoxicity of target molecules. Laccases, produced by white-rot fungi such as *Trametes versicolor*, have

been particularly well-studied for pharmaceutical degradation (18). They catalyze the one-electron oxidation of phenolic substrates using molecular oxygen as the terminal electron acceptor, generating phenoxy radicals that spontaneously polymerize or are further oxidized to quinones. In the presence of redox mediators (e.g., ABTS: 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid)), the laccase-mediator system (LMS) can oxidize non-phenolic substrates, including many pharmaceutical compounds with aromatic structures. Reported degradation efficiencies for laccase-based systems include 80–95% for estrogens (17 β -estradiol, ethinylestradiol), 60–80% for tetracyclines, 70–90% for bisphenol A, and 50–70% for sulfonamide antibiotics. The main barriers to industrial deployment are enzyme cost (production and purification), limited operational stability in complex wastewater matrices (inhibition by metals, surfactants, and complex organics), and the challenge of enzyme recovery and reuse (19). Immobilization of enzymes on solid supports (silica, chitosan, magnetic particles, membranes) significantly extends operational stability and enables continuous reactor configurations.

9. Anaerobic Digestion (AD)

Anaerobic digestion is a well-established biological process that converts biodegradable organic matter in the absence of molecular oxygen to biogas (approximately 60–70% CH₄, 30–40% CO₂, with trace H₂S and other components) through a cascade of four sequential microbial processes: hydrolysis (enzymatic depolymerization of complex organics), acidogenesis (fermentative production of volatile fatty acids and alcohols), acetogenesis (conversion of VFAs to acetate, H₂, and CO₂), and methanogenesis (biological methane production from acetate or CO₂/H₂). The energy content of biogas (methane: LHV 35.8 MJ/m³) offsets a significant fraction of the energy demand of treatment plants, and the digestate provides a nutrient-rich soil amendment (20). Pharmaceutical wastewater treatment plants employing anaerobic digestion (AD) typically use high-rate reactor configurations, such as upflow anaerobic sludge blanket (UASB) reactors, expanded granular sludge bed (EGSB) reactors, internal circulation (IC) reactors, or anaerobic sequencing batch reactors (AnSBR). These designs maintain granular sludge with high microbial density, enabling short HRTs (2–12 hours) at high OLRs (10–40 kg COD/m³/d). COD removal efficiencies of 60–90% can be achieved for biodegradable pharmaceutical effluents. A significant limitation of anaerobic digestion for pharmaceutical wastewater is the poor degradability of many pharmaceutical compounds under strictly anaerobic conditions. Antibiotics, such as metronidazole and fluoroquinolones, can inhibit methanogenic archaea at concentrations above 50–100 mg/L, causing process instability. Most synthetic estrogens, non-steroidal anti-inflammatory drugs (NSAIDs), and psychiatric medications resist anaerobic biotransformation. The combination of AD for bulk COD reduction and energy recovery, followed by activated-sludge processes (AOP or MBR) for pharmaceutical-specific polishing, represents the most resource-efficient treatment strategy for high-strength pharmaceutical effluents (19).

10. Comparative Performance Analysis

The selection of an appropriate treatment technology or hybrid train for pharmaceutical wastewater requires a systematic evaluation of multiple performance dimensions, including pollutant removal efficiency, energy and chemical consumption, capital and operating costs, sludge generation, footprint, regulatory compliance potential, scalability, and operational complexity. The following comparative analysis integrates data from published pilot-scale and full-scale studies with operational experience from the current case studies referenced in this review.

Table 2: Comparative performance summary of pharmaceutical wastewater treatment technologies (consolidated from pilot- and full-scale studies, 2020–2024)

Technology	COD Removal (%)	API Removal (%)	Energy Use	Cost	Scalability
Activated Sludge (AS)	70–90	30–70	Medium	Low	High
Membrane Bioreactor (MBR)	85–98	50–90	High	Medium	High
Ozonation	60–90	60–95	Medium	Medium	Medium
UV/H ₂ O ₂	50–85	55–95	High	Medium	Medium

Fenton / Photo-Fenton	70–95	70–98	Medium-High	Medium	Medium
Electrochemical Oxidation	60–99	80–99	High	High	Low-Med
Photocatalysis (TiO ₂)	50–90	65–98	Medium	Low-Med	Low-Med
Wet Air Oxidation (WAO)	80–99	80–99	Very High	High	Low
Activated Carbon (GAC/PAC)	50–90	60–99	Low	Medium	High
Constructed Wetlands	40–80	30–70	Very Low	Very Low	Low
Anaerobic Digestion (AD)	60–90	20–60	Low (net+)	Low	Medium
Enzymatic Degradation	40–80	50–90	Low	High	Lo

The data in Table 2 reveal several key patterns. First, no single technology achieves universally high removal across all metrics. Technologies offering the highest pharmaceutical removal efficiencies (electrochemical oxidation, WAO, and photocatalysis) carry the highest energy or capital costs, whereas low-cost biological methods (constructed wetlands and activated sludge) exhibit highly variable pharmaceutical removal depending on compound-specific biodegradability. Second, the integration of complementary technologies, such as biological + AOP or biological + adsorption, consistently outperforms any single-technology approach across the full range of pharmaceutical compound classes.

11. Current Global Case Studies and Examples

The following case studies, drawn from operational data reported between 2020 and 2024, illustrate the real-world performance of pharmaceutical wastewater treatment systems across diverse geographic, regulatory, and operational contexts. These examples demonstrate both the efficacy of integrated treatment approaches and the context-specific nature of technology selection.

Table 3: Selected current examples of pharmaceutical wastewater treatment systems (2020–2024)

Location / Facility	Technology Used	Target Pollutants	Outcome / Efficiency	Year
Hyderabad CETP, India	MBR + Ozonation	APIs, sulfonamides, dyes	~95% COD removal; 80% API reduction	2022
Cipla Ltd., Goa, India	Electro-Fenton + AS	Antibiotics, ibuprofen	Effluent within CPCB limits; 92% COD	2023
Rhine Basin, Germany	GAC Polishing + UV/H ₂ O ₂	Diclofenac, carbamazepine	>99% pharmaceutical removal	2021
Aurobindo Pharma, India	ZLD with MBR + RO	Multi-drug residues	Zero liquid discharge achieved	2022
Netherlands WWTP	Ozonation + Biofilter	Hormones, analgesics	85% estrogen removal	2020
Stryker Corp., USA	WAO + Biological	Refractory intermediates	98% TOC removal in pre-treatment	2021
China API facility	UV/TiO ₂ photocatalysis	Tetracyclines, quinolones	90% degradation within 60 min	2023
Spain Hospital Effluent	Photo-Fenton + CW	Antipsychotics, hormones	88% micropollutant reduction	2022

11.1 India: Hyderabad CETP (Patancheru)

The Patancheru–Bollaram industrial zone near Hyderabad, India, hosts one of the world's most concentrated clusters of bulk drug API manufacturing. The common effluent treatment plant (CETP) serving this zone treats a combined effluent from over 150 pharmaceutical units, with regularly exceeding incoming COD values of 10,000 mg/L and among the highest documented antibiotic concentrations in treated effluents

globally. The transition from conventional activated sludge (which was demonstrably insufficient) to an MBR-based system with tertiary ozonation has dramatically improved treatment outcomes, achieving approximately 95% COD removal and 80% API reduction in the combined effluent. The Patancheru CETP represents a model for cluster-based industrial wastewater management in developing economies.

11.2 Europe: Rhine Basin Multi-Barrier Approach

The Rhine River basin, which traverses Switzerland, Germany, France, and the Netherlands, has been the focus of intensive pharmaceutical monitoring and mitigation research for over two decades. The presence of diclofenac (a widely used anti-inflammatory drug) in the Rhine at concentrations of 100–500 ng/L is considered an ecological risk to freshwater organisms. The GAC polishing + UV/H2O2 treatment system deployed at a major WWTP in the Rhine basin (2021) reduced diclofenac concentrations to below the detection limit (<10 ng/L) and removed over 99% of other detected pharmaceutical compounds. This system operates as a tertiary treatment stage after conventional activated sludge, demonstrating the effectiveness of AOP + adsorption polishing for municipal-scale pharmaceutical removal.

11.3 ZLD Implementation: Aurobindo Pharma, India

Aurobindo Pharma's zero liquid discharge (ZLD) system represents a significant achievement in pharmaceutical wastewater management. The multi-stage treatment train equalization, biological treatment (MBR), chemical precipitation, reverse osmosis (RO), and multiple-effect evaporation (MEE) processes treat over 2,500 m³/day of pharmaceutical manufacturing wastewater and recover approximately 90% of the water for reuse in process operations. The ZLD approach, while capital-intensive (estimated at USD 8–12 million for a system of this scale), eliminates all liquid discharge to receiving water bodies, ensuring complete regulatory compliance and reducing freshwater intake costs in water-scarce regions.

12. Global Regulatory Framework

The regulatory landscape governing pharmaceutical wastewater discharge is rapidly evolving, driven by growing scientific evidence of environmental pharmaceutical contamination, escalating AMR concerns, and the development of more sensitive analytical detection methods. The following table summarizes the current regulatory frameworks in key jurisdictions.

Table 4: Global regulatory framework for pharmaceutical wastewater discharge (current as of 2024–2025).

Country / Region	Regulatory Body	Key Limit (COD mg/L)	Notes
India	CPCB / MoEFCC	250 (general effluent)	IS 2490; sector-specific pharmaceutical norms under Env. Protection Act
European Union	EMA / EQS Directive	No single national limit	Environmental Risk Assessments mandatory for new drug approvals
USA	US EPA (NPDES)	Varies by permit	Pharmaceutical category under NPDES; PFAS and API limits emerging
China	MEE (GB 21906)	120 (pharma sector)	Strict limits on specific APIs; total nitrogen and phosphorus capped
South Korea	ME / TMS	90 (Class I streams)	Pharmaceutical effluent classified as Special Hazard
WHO (Global)	WHO Technical Specs	Risk-based thresholds	AMR containment guidelines for manufacturing discharges (2021)

A notable development is the World Health Organization (WHO) 2021 guidance document on AMR containment in pharmaceutical manufacturing discharges, which establishes risk-based concentration thresholds for antibiotic compounds in treated effluents. These thresholds, based on minimum inhibitory concentrations (MICs) for resistant bacteria, dilution factors in receiving waters, and predicted environmental concentrations (PECs) from pharmacokinetic models, are increasingly being adopted by voluntary certification schemes, such as the Pharmaceutical Supply Chain Initiative (PSCI) AMR performance

framework and the Responsible Antibiotic Manufacturing Platform (RAMP). The European Union's revision of the Urban Wastewater Treatment Directive (UWTD), adopted in 2024, introduces for the first time a mandatory fourth treatment stage for all large wastewater treatment plants serving populations above 100,000 person equivalents, specifically targeting micropollutants, including pharmaceuticals. This directive, to be fully implemented by Member States by 2040, is expected to drive significant investment in AOP and GAC technologies across Europe and create a major market pull for innovative pharmaceutical removal technologies (21).

13. Design of Integrated Hybrid Treatment Trains

The fundamental principle guiding the design of pharmaceutical wastewater treatment systems is the recognition that no single technology is universally sufficient (22). Effective treatment trains are constructed by sequencing complementary technologies that address different pollutant classes, concentration ranges, and removal mechanisms in a logical succession, with each unit operation creating conditions optimal for the next.

13.1 Recommended Treatment Train Architecture

A generalized framework for pharmaceutical wastewater treatment train design proceeds through four functional stages that can be populated with technology choices appropriate to the specific effluent characteristics, regulatory requirements, and site constraints (23).

13.2 Technology Selection Criteria

Technology selection must be guided by a multi-criteria analysis framework that considers the following:

- Wastewater characterization COD, BOD/COD ratio, pH, specific API concentrations, toxicity (bioassays), and volume/flow rate;
- Regulatory compliance targets discharge standards, receiving water quality criteria, and reuse objectives.
- Techno-economic assessment capital expenditure (CAPEX), operational expenditure (OPEX), net present value (NPV), and energy balance.
- Life cycle assessment (LCA) environmental footprint, including carbon emissions, chemical use, and waste generation;
- Operational context: Available land, skilled labor, energy access, climate, and maintenance capability.
-

For highly concentrated manufacturing effluents (COD > 10,000 mg/L) with low BOD/COD ratios (<0.3), WAO or electro-Fenton pre-treatment to improve biodegradability, followed by MBR for bulk removal, and ozonation + GAC for polishing is the recommended approach. For moderately loaded effluents (COD 1,000–10,000 mg/L), an MBR or long-SRT AS system, followed by ozonation or UV/H₂O₂ and GAC polishing, is typically optimal. For dilute hospital and municipal streams (COD < 500 mg/L), tertiary ozonation or UV/H₂O₂ applied to conventional AS/MBR effluent, with optional GAC polishing for the most persistent compounds, represents a cost-effective and proven approach.

13.3 Process Monitoring and Control

Effective monitoring is essential for treatment train performance optimization and demonstration of regulatory compliance (24). Online monitoring parameters typically include chemical oxygen demand (COD), biochemical oxygen demand (BOD), TOC/DOC (for bulk organic removal), UV₂₅₄ absorbance (as a surrogate for aromatic pharmaceutical compounds), turbidity, and TSS (for membrane performance), dissolved oxygen, pH, temperature, and flow rate. Specific pharmaceutical compound monitoring using liquid chromatography-mass spectrometry (LC-MS/MS), enzyme-linked immunosorbent assay (ELISA), or biosensor platforms is increasingly required by regulators and recommended for treatment optimization at

high-risk facilities. Emerging online monitoring technologies, including high-frequency UV-Vis spectrometry, portable HPLC-UV systems, and biosensor arrays specific to AMR indicators, are being integrated into pharmaceutical wastewater treatment plant control systems to enable real-time adaptive management of treatment intensity and chemical dosing.

14. Emerging and Future Technologies

The field of pharmaceutical wastewater treatment is witnessing rapid innovation driven by the need for more efficient, cost-effective, and sustainable solutions. Several emerging technologies are transitioning from laboratory proof-of-concept to pilot-scale validation (25).

14.1 Nanomaterial-Enhanced Processes

Engineered nanomaterials, including metal–organic frameworks (MOFs), graphene oxide composites, carbon nanotubes, and zero-valent iron nanoparticles (nZVI), offer exceptional surface areas, tunable surface chemistries, and unique adsorptive or catalytic properties for pharmaceutical removal. MOFs, such as MIL-101(Cr) and UiO-66, have demonstrated adsorption capacities of 300–800 mg/g for tetracycline antibiotics, far exceeding those of conventional activated carbon. Nanoscale TiO₂ and g-C₃N₄ photocatalysts, when immobilized in flow-through reactors, enable continuous pharmaceutical degradation under solar irradiation with minimal photon losses.

14.2 Bio electrochemical Systems

Microbial fuel cells (MFCs) and microbial electrolysis cells (MECs) represent bioelectrochemical systems (BESs) that simultaneously treat wastewater and generate electricity or hydrogen gas. Several research groups have demonstrated pharmaceutical removal (antibiotics: 60–80%; non-steroidal anti-inflammatory drugs: 50–75%) in MFC-based reactors while generating electrical power (0.1–0.5 W/m³). Scaling these systems to treat high-volume pharmaceutical effluents while maintaining cost competitiveness remains an active research challenge.

14.3 Artificial Intelligence and Process Optimization

Machine learning algorithms, including neural networks, support vector machines, and reinforcement learning agents, are increasingly being applied to optimize pharmaceutical wastewater treatment plant operations. AI-driven control systems can predict influent load variability (based on production schedules), optimize chemical dosing in real-time (reducing reagent costs by 10–25%), detect membrane fouling onset, and schedule maintenance proactively. Digital twin modeling of treatment plants using computer simulations that mirror the physical plant in real-time is being piloted at several major pharmaceutical manufacturer facilities in Europe and North America as a platform for operational optimization and scenario planning.

14.4 Green Chemistry and Source Reduction

The most sustainable approach to pharmaceutical wastewater management is prevention at the source, which involves designing synthesis routes that use fewer solvents, generate less waste, and produce more biodegradable by-products. The application of green chemistry principles (atom economy, catalytic rather than stoichiometric reactions, renewable feedstocks, and benign solvents) to pharmaceutical manufacturing can substantially reduce the environmental footprint of production. The pharmaceutical industry's transition towards continuous manufacturing (replacing batch processes) offers additional opportunities for water use efficiency, waste minimization, and wastewater treatment simplification.

15. Conclusions:

Pharmaceutical wastewater presents one of the most complex and environmentally significant treatment challenges in the water sector today. The chemical diversity, biological recalcitrance, and ecological potency of pharmaceutical compounds, including antibiotics, hormones, analgesics, psychiatric drugs, cytotoxic agents, and emerging nanomaterials, demand treatment approaches that go far beyond the capabilities of conventional biological systems. This comprehensive review examined the mechanistic basis, operational

requirements, performance characteristics, and real-world applications of 12 major treatment technology categories applicable to pharmaceutical wastewater. The key conclusions that emerge from this analysis are as follows. First, hybrid treatment trains consistently outperform single-technology approaches. The most effective and robust systems combine biological processes (AS, MBR, and AD) for bulk organic removal with advanced oxidation processes (AOP, ozonation, and electrochemical) for micropollutant abatement and disinfection, and adsorption (GAC) or ecological (CW) stages for final polishing. The design and optimization of these integrated systems, informed by detailed wastewater characterization, life-cycle analysis, and techno-economic assessment, is the central challenge and opportunity in pharmaceutical wastewater management. Second, the regulatory environment is rapidly converging towards more stringent, compound-specific, and risk-based standards for pharmaceutical discharge. The EU's updated UWTD, WHO's AMR containment guidelines, and India's enhanced CPCB norms are collectively driving investment in advanced treatment infrastructure and creating market conditions conducive to innovation. Pharmaceutical manufacturers who proactively invest in advanced treatment technologies will be better positioned for regulatory compliance and reputational leadership. Third, emerging technologies, such as nanomaterial-enhanced adsorption and photocatalysis, bio electrochemical systems, AI-driven process optimization, and green chemistry at the source, offer significant potential to improve treatment efficiency, reduce costs, and enhance sustainability. While most of these technologies remain at the pilot or demonstration scale, the pace of innovation and the intensity of research investment suggest that several will achieve commercial readiness within the next decade. Fourth, the most sustainable path forward integrates end-of-pipe treatment with upstream source reduction: green chemistry in pharmaceutical synthesis, continuous manufacturing processes, water efficiency programs, and rigorous pharmaceutical take-back and disposal schemes to reduce the environmental burden that treatment systems must address. The convergence of environmental regulation, public health imperatives, and industrial sustainability commitments creates a compelling case for comprehensive, scientifically grounded, and technologically advanced pharmaceutical wastewater management.

Abbreviations:

Table 5: Abbreviations used in this manuscript

Abbreviation	Full Form
API	Active Pharmaceutical Ingredient
AOP	Advanced Oxidation Process
MBR	Membrane Bioreactor
AS	Activated Sludge
COD	Chemical Oxygen Demand
BOD	Biochemical Oxygen Demand
TOC/DOC	Total/Dissolved Organic Carbon
TMP	Transmembrane Pressure
GAC/PAC	Granular/Powdered Activated Carbon
WAO	Wet Air Oxidation
AD	Anaerobic Digestion
MLSS	Mixed Liquor Suspended Solids
EPS/SMP	Extracellular Polymeric Substances / Soluble Microbial Products
PVDF	Polyvinylidene Fluoride
AMR	Antimicrobial Resistance
ZLD	Zero Liquid Discharge
CW	Constructed Wetland
CPCB	Central Pollution Control Board (India)
NPDES	National Pollutant Discharge Elimination System (USA)
BDD	Boron-Doped Diamond (electrode)
HRT	Hydraulic Retention Time
SRT	Sludge Retention Time

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Reference's:

- [1] Sabour M, Zarrabi H, Hajbabaie M. A systematic analysis of research trends on the utilization of life cycle assessment in pharmaceutical applications. *International journal of environmental science and technology*. 2023;20(10):10921-42.
- [2] Tiwari B, Sellamuthu B, Ouarda Y, Drogui P, Tyagi RD, Buelna G. Review on fate and mechanism of removal of pharmaceutical pollutants from wastewater using biological approach. *Bioresource technology*. 2017;224:1-12.
- [3] Kumari S, Das S. Bacterial enzymatic degradation of recalcitrant organic pollutants: catabolic pathways and genetic regulations. *Environmental Science and Pollution Research*. 2023;30(33):79676-705.
- [4] Kumari S. Exploring emerging technologies for AI-integrated advancements in wastewater treatment: harnessing emerging technologies for AI in wastewater treatment. *The AI cleanse: transforming wastewater treatment through artificial intelligence: harnessing data-driven solutions*. 2024:223-44.
- [5] Fatta-Kassinos D, Meric S, Nikolaou A. Pharmaceutical residues in environmental waters and wastewater: current state of knowledge and future research. *Analytical and bioanalytical chemistry*. 2011;399(1):251-75.
- [6] Shukla MK, Luft CM, Koval AM, Pisani WA, Lamb RW, Lystrom LA, et al. Emerging materials and environment: a brief introduction. *Emerging Materials and Environment*: Springer; 2023. p. 1-78.
- [7] Osabuohien FO, Negedu GR, Raymond EE, Egbuchiem MN. Development of advanced oxidation processes (AOP) for removing specific pharmaceutical residues from wastewater. *International Journal of Chemistry*. 2021;1(3).
- [8] Li J, Tang WZ, Gu L. Energy efficiency assessment of China wastewater treatment plants by unit energy consumption per kg COD removed. *Environmental Technology*. 2023;44(2):278-92.
- [9] Tang K, Spiliotopoulou A, Chhetri RK, Ooi GT, Kaarsholm KM, Sundmark K, et al. Removal of pharmaceuticals, toxicity and natural fluorescence through the ozonation of biologically-treated hospital wastewater, with further polishing via a suspended biofilm. *Chemical Engineering Journal*. 2019;359:321-30.
- [10] Fatta-Kassinos D, Dionysiou DD, Kümmerer K. *Advanced treatment technologies for urban wastewater reuse*: Springer; 2016.
- [11] Kumar S, Rathore K, Sahu MK, Sharma MP, Mishra KN, Banerjee D. *Heat Exchanger Classifications and Their Areas of Application. Advanced Applications in Heat Exchanger Technologies*: CRC Press; 2025. p. 30-63.
- [12] Lakhotia SR, Mukhopadhyay M, Kumari P. Surface-modified nanocomposite membranes. *Separation & Purification Reviews*. 2018;47(4):288-305.
- [13] Li X, Ren B, Kou X, Hou Y, Buque AL, Gao F. Recent advances and prospects of constructed wetlands in cold climates: a review from 2013 to 2023. *Environmental Science and Pollution Research*. 2024;31(32):44691-716.
- [14] Alter AJ. Cold region environmental concerns. *Critical Reviews in Environmental Science and Technology*. 1990;20(4):257-98.
- [15] Mæhlum T. Wetlands for treatment of landfill leachates in cold climates. *Constructed wetlands for the treatment of landfill leachates*: CRC Press; 2018. p. 33-46.
- [16] Lloret E, Pastor L, Pradas P, Pascual JA. Semi full-scale thermophilic anaerobic digestion (TAnD) for advanced treatment of sewage sludge: stabilization process and pathogen reduction. *Chemical Engineering Journal*. 2013;232:42-50.

- [17] Sharma N, Singh A, Batra N. Modern and emerging methods of wastewater treatment. Ecological wisdom inspired restoration engineering. 2018:223-47.
- [18] Rahi DK, Rahi S, Chaudhary E. White rot fungi in food and pharmaceutical industries. *Advances in Macrofungi*: CRC Press; 2021. p. 175-204.
- [19] Afolabi M, Onukogu OA, Igunma TO, Nwokediegwu ZQS, Adeleke AK. Advances in Reactor Design for High-Efficiency Biochemical Degradation in Industrial Wastewater Treatment Systems. *Journal Not Specified*. 2021.
- [20] Saelor S, Kongjan P, Prasertsan P, Mamimin C, O-Thong S. Enhancing thermophilic methane production from oil palm empty fruit bunches through various pre-treatment methods: A comparative study. *Heliyon*. 2024;10(20).
- [21] Federigi I, Bonetta S, Tesauro M, Bagordo F, Consonni M, Diella G, et al., editors. Towards antibiotic-resistance in drinking tap water: evidence of a neglected public health issue. 22nd Health Related Water Microbiology Conference: oral presentation abstracts; 2025: IWA.
- [22] Pal P. Treatment and disposal of pharmaceutical wastewater: towards the sustainable strategy. *Separation & Purification Reviews*. 2018;47(3):179-98.
- [23] Kalbar PP, Karmakar S, Asolekar SR. Selection of an appropriate wastewater treatment technology: A scenario-based multiple-attribute decision-making approach. *Journal of environmental management*. 2012;113:158-69.
- [24] Arango J, Chuck T, Ellenberg SS, Foltz B, Gorman C, Hinrichs H, et al. Good clinical practice training: identifying key elements and strategies for increasing training efficiency. *Therapeutic innovation & regulatory science*. 2016;50(4):480-6.
- [25] Wynn JP, Hanchar R, Kleff S, Senyk D, Tiedje T. Biobased technology commercialization: the importance of lab to pilot scale-up. *metabolic engineering for bioprocess commercialization*: Springer; 2016. p. 101-19.