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A Comprehensive Review on the Occurrence, Toxicity, and Microbial Degradation of Pharmaceutical Compounds in Industrial Waste

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Abstract

Pharmaceutical compounds (PCs) have emerged as significant environmental contaminants due to their widespread use, persistence, and potential adverse effects on ecosystems and human health. These compounds enter the environment through various pathways, including wastewater treatment plant effluents, improper disposal, and agricultural practices. Despite their therapeutic benefits, PCs pose substantial ecological risks, exhibiting toxic effects across multiple trophic levels. This review comprehensively examines the classification, characteristics, and environmental occurrence of pharmaceutical compounds, with particular emphasis on non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen. The toxicological impacts on bacteria, algae, invertebrates, and vertebrates are discussed, highlighting the need for effective removal strategies. Biodegradation, particularly by bacteria, fungi, and algae, presents a promising and environmentally friendly approach for pharmaceutical removal. Process optimization using experimental design methodologies, including the Taguchi approach, offers opportunities to enhance degradation efficiency. Advanced analytical techniques for monitoring pharmaceutical degradation are also reviewed. This synthesis of current knowledge provides a foundation for developing sustainable strategies to mitigate pharmaceutical pollution in industrial waste.

Keywords: Pharmaceutical compounds, biodegradation, ibuprofen, emerging contaminants, wastewater treatment, toxicity assessment

1. Introduction

Pharmaceutical compounds (PCs) represent a diverse assemblage of chemicals utilized for the diagnosis, treatment, and prevention of diseases in both human and veterinary medicine (Li et al., 2014). These compounds encompass a broad range of active ingredients with complex molecular structures, varying physicochemical properties, and specific biological activities. The global consumption of pharmaceuticals has increased dramatically over recent decades,

driven by advances in medical science and increased life expectancy. However, this widespread use has created an unintended consequence: the continuous release of these biologically active compounds into the environment (Kummerer, 2009).

Pharmaceuticals are increasingly recognized as emerging environmental contaminants due to their pseudo-persistence and potential to cause adverse effects in non-target organisms. Despite their beneficial therapeutic properties, these compounds possess characteristics similar to conventional pollutants, including persistence, bioaccumulation potential, and toxicity (Santos et al., 2010). The environmental occurrence of pharmaceuticals has been documented globally in surface waters, groundwater, soils, and sediments, with concentrations typically ranging from nanograms to micrograms per liter (Kolpin et al., 2002; Castiglioni et al., 2006).

The presence of pharmaceutical residues in the environment is particularly concerning because conventional wastewater treatment plants (WWTPs) were not designed to remove these compounds effectively. Consequently, pharmaceuticals and their metabolites often pass through treatment processes and enter receiving waters, where they may exert chronic effects on aquatic organisms (Zuccato et al., 2005). Additionally, the application of biosolids and reclaimed water to agricultural lands introduces pharmaceuticals into terrestrial ecosystems, potentially leading to groundwater contamination (Fent et al., 2006; Gottschall et al., 2013).

Among the various classes of pharmaceuticals, non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen have received considerable attention due to their high consumption rates and frequent detection in environmental matrices. Ibuprofen, a propionic acid derivative, is one of the most widely used over-the-counter medications globally, with annual production reaching several kilotons (Zwiener et al., 2002). Its presence in water bodies has been associated with various toxicological effects, including reproductive impairment in fish and growth inhibition in plants (Han et al., 2010; Rede et al., 2016).

Biodegradation by microorganisms offers a promising approach for the removal of pharmaceutical contaminants from the environment. Various bacteria, fungi, and algae have demonstrated the capacity to degrade or transform pharmaceutical compounds through metabolic and co-metabolic pathways (Tran et al., 2014; Ding et al., 2017). The isolation of indigenous microorganisms from contaminated sites, coupled with process optimization strategies, can enhance degradation efficiency while providing an eco-friendly and cost-effective treatment alternative.

This review aims to synthesize current knowledge on the environmental occurrence, toxicity, and microbial degradation of pharmaceutical compounds, with particular focus on industrial wastewater. The classification and characteristics of pharmaceuticals, their fate in aquatic and terrestrial ecosystems, toxicological impacts on various organisms, and biodegradation strategies are comprehensively reviewed. Additionally, the application of experimental design methodologies for process optimization and advanced analytical techniques for monitoring pharmaceutical degradation are discussed.

2. Classification and Characteristics of Pharmaceutical Compounds

Pharmaceutical compounds can be classified according to several criteria, including biological activity, chemical structure, mode of action, and therapeutic effects (Halling-Sørensen et al., 1998; Jones et al., 2001). On the basis of biological activity and purpose, pharmaceuticals include antibiotics for bacterial infections, analgesics for pain relief, anti-neoplastics for cancer treatment, and hormones for endocrine disorders. Classification by chemical structure encompasses diverse groups such as β-lactams, quinolones, tetracyclines, and macrolides, each with distinct molecular architectures that influence their environmental behavior and persistence.

The therapeutic classification of pharmaceuticals provides insight into their usage patterns and potential environmental sources. Major therapeutic classes frequently detected in the environment include analgesics (paracetamol, ibuprofen, diclofenac), antibiotics (sulfonamides, fluoroquinolones, tetracyclines), antiepileptics (carbamazepine), beta-blockers (atenolol, metoprolol), hormones (17α-ethinylestradiol), and psychiatric medications (Halling-Sørensen et al., 1998; Jones et al., 2001).

Pharmaceutical compounds exhibit several distinctive physicochemical characteristics that differentiate them from conventional industrial pollutants. Most pharmaceuticals have molecular masses ranging from 200 to 500/1000 m/z, making them relatively large and chemically complex molecules (Lipinski et al., 1997; Kummerer, 2009). They are typically polar molecules containing ionizable functional groups, and their degree of ionization depends on the pH of the surrounding medium. This property influences their solubility, sorption behavior, and mobility in environmental compartments. Additionally, many pharmaceuticals demonstrate high persistence in the environment, resisting degradation through various abiotic and biotic processes (Kummerer, 2009).

3. Sources and Occurrence of Pharmaceuticals in the Environment

3.1 Pharmaceutical Manufacturing and Wastewater Generation

The pharmaceutical industry employs diverse manufacturing processes that generate significant quantities of complex wastewater. Four primary manufacturing methods are commonly utilized: chemical synthesis, natural product extraction, fermentation, and formulation (Gadipelly et al., 2014). Chemical synthesis involves various reactions and recovery processes using organic and inorganic reactants, producing wastewater with high biological oxygen demand (BOD), chemical oxygen demand (COD), and total suspended solids (TSS), with pH ranging from 1 to 11 (USEPA, 1983).

Fermentation processes, employed for producing antibiotics and other biologically derived compounds, generate substantial waste including spent aqueous fermentation medium and solid cell debris. The wastewater from fermentation typically exhibits high COD, BOD, and TSS levels with pH ranging from 4 to 8 (USEPA, 1983). Formulation processes, involving the preparation of final dosage forms such as tablets and capsules, also contribute to wastewater generation through equipment cleaning and compounding operations (Gadipelly et al., 2014).

3.2 Occurrence in Aquatic Ecosystems

Pharmaceutical residues have been detected in various aquatic environments worldwide, including wastewater treatment plant effluents, surface waters, groundwater, and even drinking water supplies. Wastewater treatment plants represent significant point sources for pharmaceutical contamination, as conventional treatment processes achieve incomplete removal of many compounds (Zuccato et al., 2005; Sui et al., 2010). Influent concentrations of pharmaceuticals in WWTPs vary widely depending on usage patterns, with typical ranges from ng L^{-1} to low μg L^{-1} (Santos et al., 2007).

Surface water contamination by pharmaceuticals has been extensively documented across multiple continents. In India, river water concentrations of acetaminophen reached 11.55 μg L^{-1}, while cetrazine was detected at 41.84 μg L^{-1} (Archana et al., 2016). In China, diclofenac concentrations in rivers reached 67.0 μg L^{-1} (Dai et al., 2015). Groundwater contamination also occurs, with pharmaceuticals such as carbamazepine, clofibratic acid, and diazepam detected in various regions (Fram & Belitz, 2011; López-Serna et al., 2011). The transport of pharmaceuticals to groundwater occurs through leaching from contaminated surface waters, septic systems, and land application of biosolids or reclaimed water (Heberer, 2002; Lapworth et al., 2012).

3.3 Occurrence in Terrestrial Ecosystems

Soil and sediment contamination by pharmaceuticals results from multiple pathways, including land application of biosolids and manure, irrigation with reclaimed water, and direct disposal of pharmaceutical waste (Topp et al., 2008; Carter et al., 2014). Concentrations of pharmaceuticals in solid matrices typically range from ng g^{-1} to μg g^{-1} levels, with variation depending on compound properties and application practices (Wilga et al., 2008).

Ibuprofen has been detected in sludge at concentrations up to 96 ng g^{-1} in Poland (Kumirska et al., 2015) and in soil at 75.93 μg g^{-1} in the United States (Karnjanapiboonwong et al., 2011). Diclofenac, carbamazepine, and ciprofloxacin have also been detected in agricultural soils and sediments at varying concentrations (Biel-Maeso et al., 2018; Dalkmann et al., 2012; Li et al., 2012). The persistence of pharmaceuticals in soil depends on their binding capacity, photostability, adsorption characteristics, and susceptibility to microbial degradation (Koba et al., 2018). Compounds with strong sorption tend to accumulate in sediments and soils, while more mobile compounds may leach into groundwater.

4. Toxicological Impacts of Pharmaceuticals

4.1 Effects on Bacteria

The release of antibiotics into the environment poses particular concerns due to the potential for promoting antibiotic resistance in bacterial communities. Antibiotic-resistant bacteria and resistance genes can spread through aquatic environments, potentially compromising the effectiveness of antimicrobial therapies (Jones et al., 2003; Kümmerer, 2004). Conjugation, transduction, and transformation mechanisms facilitate the transfer of resistance genes among bacteria in environmental compartments such as rivers and streams (Baker et al., 2018).

Various bacterial species, including Acinetobacter, Escherichia coli, Pseudomonas aeruginosa, and members of the Enterobacteriaceae family, have demonstrated resistance to multiple antibiotic classes, including β-lactams, quinolones, sulfamethoxazole, and tetracyclines (Kümmerer, 2004). The presence of these resistant bacteria in drinking water sources poses potential risks to public health, particularly when treated water is reused for various purposes.

4.2 Effects on Algae and Higher Plants

Algae are commonly employed in aquatic toxicity assessments due to their sensitivity to various pharmaceuticals. Sensitivity varies among algal species, with microalgae and

cyanobacteria often showing greater responsiveness to antibiotics compared to standard test species such as Pseudokirchneriella subcapitata (Halling-Sørensen, 2000). Acute toxicity endpoints for algae typically include growth inhibition and photosynthetic activity.

Pharmaceuticals can affect higher plants through soil contamination, particularly when biosolids or reclaimed water are used for agricultural purposes. Adverse effects on plant growth, nitrogen fixation, and heterocyst frequency have been documented at appropriate exposure concentrations (Forni et al., 2002; Carter et al., 2014). Ibuprofen contamination in soil has been shown to reduce seed germination and decrease root elongation (Rede et al., 2016).

4.3 Effects on Invertebrates

Aquatic invertebrates demonstrate varying sensitivity to pharmaceutical compounds. Studies have reported physiological changes in aquatic mussels exposed to morphine, including relaxation state induction (Gagné et al., 2010). Cocaine and its metabolites have shown negative impacts on zebra mussel physiology at environmentally relevant concentrations, with evidence of DNA damage (Binelli et al., 2012; Parolini et al., 2013).

Standard toxicity tests using Daphnia magna have revealed acute effects for various pharmaceuticals. The 48-hour EC50 values for immobilization include 34.99 mg L^{-1} for acetaminophen, 80.28 mg L^{-1} for diclofenac, and 5.91 mg L^{-1} for fluoxetine (Minguez et al., 2016). Chronic exposure studies have demonstrated reproductive effects in invertebrates at lower concentrations, highlighting the importance of long-term toxicity assessments.

4.4 Effects on Vertebrates

Vertebrates are also susceptible to pharmaceutical contamination. The most notable example involves diclofenac toxicity to vultures, which caused catastrophic population declines in South Asia. The drug induces severe kidney failure in Gyps species, with lethal doses as low as 0.1-0.2 mg kg^{-1} (Sumpter, 2010). This discovery led to the ban of diclofenac in India and neighboring countries.

Endocrine-disrupting effects have been documented in fish exposed to estrogenic compounds. The synthetic hormone 17α-ethinylestradiol (EE2), commonly used in contraceptive pills, causes feminization of male fish at ng L^{-1} concentrations, with significant impacts on reproduction and population sustainability (Desbrow et al., 1998; Kidd et al., 2007). Ibuprofen

has also been associated with reproductive damage in medaka fishes at concentrations ranging from 0.1-1 μg L^{-1} (Han et al., 2010).

5. Biodegradation of Pharmaceutical Compounds

5.1 Bacterial Degradation

Bacteria play a crucial role in the environmental degradation of pharmaceutical compounds through metabolic and co-metabolic pathways. Metabolic degradation involves the utilization of pharmaceuticals as sole carbon and energy sources, while co-metabolism refers to the transformation of compounds by enzymes produced for other substrates (Tiwari et al., 2017). Numerous bacterial strains have been isolated and characterized for their ability to degrade various pharmaceuticals.

Pseudomonas aeruginosa TJ1 utilizes 17β-estradiol as a carbon and energy source (Zeng et al., 2009), while Stenotrophomonas maltophilia KB2 demonstrates metabolic degradation of naproxen (Wojcieszyńska et al., 2014). Ibuprofen degradation has been achieved by Variovorax Ibu-1 through metabolic pathways (Murdoch & Hay, 2015). Cefalexin-degrading bacteria isolated from activated sludge achieved over 90% degradation within 24 hours (Lin et al., 2015).

The efficiency of bacterial degradation depends on various factors, including compound structure, environmental conditions, and the presence of additional carbon sources. Some bacteria, such as Pseudomonas spp. and Achromobacter denitrificans, require supplementary carbon sources to support pharmaceutical degradation (Shourian et al., 2009; Nguyen et al., 2017). Enzymatic degradation using β-lactamase produced by Bacillus subtilis has proven effective for cephalexin degradation across a range of pH and temperature conditions (Al-Gheethi & Ismail, 2014).

5.2 Fungal Degradation

White-rot fungi (WRF) and their oxidoreductase enzymes have received considerable attention for pharmaceutical biodegradation due to their broad substrate specificity and ability to degrade recalcitrant compounds. Extracellular enzymes, including lignin peroxidase, manganese peroxidase, versatile peroxidase, and laccase, catalyze the transformation of various pollutants (Garcia-Ruiz et al., 2014).

Phanerochaete chrysosporium has demonstrated high removal efficiencies for various pharmaceuticals, including diclofenac (>99%), ibuprofen (75-90%), and naproxen (>99%) in spiked water (Rodarte-Morales et al., 2012). Trametes versicolor effectively removed multiple pharmaceutical compounds from wastewater, achieving 100% removal for acetaminophen, ketoprofen, sulfamethoxazole, and tetracycline (Cruz-Morato et al., 2013, 2014). The degradation mechanisms involve both extracellular enzymatic activities and biosorption onto fungal biomass.

5.3 Algal Degradation

Algal-based technologies offer sustainable approaches for pharmaceutical removal, combining wastewater treatment with carbon sequestration and bioenergy production potential (Park et al., 2011). Algae remove pharmaceuticals through multiple mechanisms, including biosorption, biodegradation, photodegradation, and volatilization (Padmavathiamma & Li, 2007; Zhang et al., 2012).

Chlamydomonas reinhardtii achieved 100% removal of 17β-estradiol through biodegradation (Hom-Diaz et al., 2015). Chlorella sorokiniana demonstrated degradation of paracetamol and salicylic acid, with diclofenac removal reaching 29.99% (Escapa et al., 2015, 2016). Chlamydomonas mexicana showed enhanced ciprofloxacin degradation through co-metabolism, with degradation rates increasing from 13% to 56% within 11 days when electron donors were supplemented (Xiong et al., 2017b). Algae are increasingly recognized as "green livers" capable of detoxifying xenobiotic compounds (Torres et al., 2008).

6. Process Optimization for Biodegradation

Design of Experiments (DOE) provides statistical approaches for planning, conducting, and interpreting control tests to identify influencing factors in degradation processes (Peixoto et al., 2017). Various optimization techniques, including Response Surface Methodology (RSM), Central Composite Design (CCD), Box-Behnken Designs (BBD), and Taguchi methods, have been applied to biodegradation studies.

The Taguchi method, developed by Dr. Genichi Taguchi in the late 1940s, employs orthogonal arrays (OA) to reduce experimental runs while maintaining statistical validity. This approach uses signal-to-noise (S/N) ratios to identify optimal process parameters and analysis of variance (ANOVA) to determine the significance of factors (Athreya & Venkatesh, 2012; Krishankant et al., 2012). The method significantly reduces experimental effort; for example, a full factorial

design requiring 128 experiments for seven factors at two levels can be reduced to eight experiments using L-8 orthogonal array. This efficiency makes Taguchi's approach particularly valuable for environmental applications where resources and time constraints exist (Daneshwar et al., 2007; Kaushik & Thakur, 2009).

7. Analytical Techniques for Pharmaceutical Monitoring

7.1 High-Performance Liquid Chromatography

High-performance liquid chromatography (HPLC) is widely used for quantitative and qualitative analysis of pharmaceuticals in environmental samples. The method offers high accuracy and precision when appropriate method development and suitability tests are performed. Photodiode array (PDA) detectors enable detection of UV-absorbing analytes through wavelength scanning (Tekkeli, 2013).

7.2 Mass Spectrometry

Mass spectrometry techniques, particularly liquid chromatography-tandem mass spectrometry (LC-MS/MS), are preferred for pharmaceutical analysis due to their sensitivity, selectivity, and versatility (Nikolaou, 2013). Quadrupole-time of flight (Q-ToF) mass spectrometry enables structural elucidation of transformation products and facilitates the proposal of degradation pathways. Gas chromatography-mass spectrometry (GC-MS) is also employed for volatile and non-polar pharmaceuticals, though derivatization steps may be required (Kolpin et al., 2002).

7.3 Nuclear Magnetic Resonance Spectroscopy

Nuclear magnetic resonance (NMR) spectroscopy allows quantitative determination and structural characterization of pharmaceutical compounds in both solid and liquid states. Recent applications include drug impurity analysis, formulation characterization, and degradation product identification (Reinscheid et al., 2006; Chachibai & Pastor, 2017).

7.4 Ultraviolet-Visible Spectrophotometry

UV-visible spectrophotometry is employed for determining functional groups and conducting assays of pharmaceutical compounds. The technique measures absorption of electromagnetic radiation in the 200-800 nm range, corresponding to electron excitation to higher energy states (Kumirska et al., 2010).

8. Ibuprofen as a Case Study

Ibuprofen ($C_{13}H_{18}O_2$) is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. As a propionic acid derivative, it inhibits cyclooxygenase enzymes, reducing prostaglandin synthesis (Vincenteno et al., 2010). The compound has a pKa of 4.59, water solubility of 0.021 mg L^{-1}, and exists as a racemic mixture (Wong, 2006).

Environmental concentrations of ibuprofen range from low ppt to low ppb levels, with detection in surface waters, wastewater, and biosolids globally (Santos et al., 2010). In South Korea, ibuprofen was detected at 0.03 μg L^{-1} in major rivers (Kim et al., 2007), while concentrations in South Wales surface waters averaged 0.1 μg L^{-1} (Kasprzyk-Hordern et al., 2008). Biosolids contain ibuprofen at 24-548 μg kg^{-1} (Nieto et al., 2010).

Toxicological effects of ibuprofen include reproductive damage in medaka fish at 0.1-1 μg L^{-1} (Han et al., 2010), oxidative stress in mussels at 250 ng L^{-1} (Gonzales-Rey & Bebianno, 2012), and genotoxicity in tilapia (Ragunetti et al., 2010). Biodegradation of ibuprofen has been demonstrated by various microorganisms, with removal efficiencies exceeding 90% in mixed cultures (Radjenovic et al., 2009; Langenhoff et al., 2013). S-enantiomer degradation typically occurs faster than R-enantiomer, indicating stereoselective biodegradation (Winkler et al., 2001).

9. Conclusions and Future Perspectives

Pharmaceutical compounds represent a significant class of emerging environmental contaminants, with widespread occurrence documented across aquatic and terrestrial ecosystems. Despite their therapeutic benefits, these compounds pose risks to non-target organisms across multiple trophic levels, from bacteria to vertebrates. The incomplete removal of pharmaceuticals by conventional wastewater treatment processes necessitates the development of effective remediation strategies.

Biodegradation by microorganisms offers a promising approach for pharmaceutical removal, with bacteria, fungi, and algae demonstrating the capacity to degrade or transform various compounds. Process optimization using experimental design methodologies, particularly the Taguchi approach, can enhance degradation efficiency while reducing experimental costs and resource requirements. Advanced analytical techniques enable comprehensive monitoring of pharmaceutical degradation and identification of transformation products.

Future research should focus on several key areas: (1) isolation and characterization of novel microbial strains with enhanced degradation capabilities; (2) elucidation of degradation

pathways and identification of transformation products; (3) development of combined treatment processes integrating biological and advanced oxidation methods; (4) assessment of chronic toxicity of degradation products; and (5) implementation of sustainable strategies for pharmaceutical waste management. Additionally, understanding the natural variation in biodegradation potential across different environmental compartments and the influence of microbial community diversity on degradation efficiency will be crucial for developing effective bioremediation strategies.

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