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Case Report

A critical assessment of technical advances in pharmaceutical removal from wastewater – A critical review

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ABSTRACT

Use of pharmaceutical products has seen a tremendous increase in the recent decades. It has been observed that more than thirty million tons of pharmaceuticals are consumed worldwide. The used pharmaceutical products are not completely metabolized in human and animal body. Therefore, they are excreted to the environment and remain there as persistent organic chemicals. These compounds emerge as toxic contaminants in water and affect the human metabolism directly or indirectly. This literature review is an endeavour to understand the origin, applications and current advancement in the removal of pharmaceuticals from the environment. It discusses about the pharmaceuticals used in medical applications such diagnosis and disease treatment. In addition, it discusses about the recent approaches applied in pharmaceutical removal including microbial fuel cells, biofiltration, and bio nanotechnology approaches. Moreover, the challenges associated with pharmaceutical removal are presented considering biological and environmental factors. The review suggest the potential recommendations on pharmaceutical removal.

1. Introduction

Pharmaceuticals are defined as biologically active compounds with diverse mode of actions. Pharmaceuticals are administered to human and animals to treat curable diseases.

Emergence of new and uncurable diseases has led to the development of new and effective pharmaceutical compounds [1]. At present, Pharmaceuticals play a key role in modern medicine. During the 19th

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and 20thcenturies, along with the progression of medical sciences, a huge number of new synthetic pharmaceuticals were introduced in to the market and their number is still growing [2].

As defined by the USA Geological Survey, contaminants are synthetic or natural compounds which are likely to enter the environment while mostly remain unmonitored and exert an adverse effect on human health [3]. A part or portion of pharmaceuticals cannot be digested by humans and excreted into the environment, which are transported to Wastewater Treatment Plant (WWTP). Veterinary administration, washing and waste disposal are also identified as prominent sources of pharmaceutical contamination [4]. From WWTP, these pharmaceuticals are discharged into the environment [5]. The unregulated use of pharmaceutical compounds and their disposal into the water bodies such as reivers and lakes cause the water contamination [6]. The pharmaceutical active compounds such as antibiotics and hormone receptors cause toxicity to the marine organisms [7]. A study reported reduced reproduction and feminization of fish in water polluted with biologically active compounds [8] Unfortunately, very less information is available about their origin, fate or toxic effects on the environment [6].

The occurrence of antibiotics, analgesics, antidepressant drugs, chemotherapy medicines, antipyretics and hormones in municipal wastewater treatment plant at a concentration of 0.05–6.3 μg/L has been documented repeatedly. A study reported the presence of tamoxifen (anticancer drug) and ciprofloxacin at a concentration of 24–37 and 8–100 ng/L respectively [1]. Other pharmaceuticals such as metformin, carbamazepine, clarithromycin, atenolol and trimethoprim were also present at a considerable concentration (≥500 ng/L). Different analytical methods and instrumentation techniques are invented to identify the occurrence of a wide range of pharmaceuticals and quantify their concentration in wastewater treatment plants, municipal sewage, rivers, water bodies, ground water sediment, manure and soil. [9] According to Strategic Approach to International Chemical Management, the occurrence of pharmaceuticals is a global issue [10].

Over the years, several studies reported different methods for the removal of pharmaceuticals from the environment. These methods are broadly divided into physical, chemical, biological and hybrid processes [11]. The physical methods include conventional activated sludge (CAS) treatment, activated carbon treatment and membrane filtration. The latter two processes showed higher removal efficiency of pharmaceuticals than the CAS process. The absence of toxic by-products is considered the main advantage of the physical treatment procedures. But several disadvantages are associated with the processes such as waste disposal, energy consumption, foul smell, and reduced adsorption capacity. A wide variety of pharmaceuticals can be treated with high removal efficiency by chemical procedures such as advanced oxidation process (AOP), UV and ozone treatment. The main disadvantage of the chemical process is the generation of toxic by-products and high energy consumption [6]. The biological processes have low to moderate removal efficiency and include membrane bioreactor, bio-filtration, microbial and enzymatic processes. Biological processes are less energy intensive and generates less or no residues. but these processes are selective and produces toxic by-products [12]. This review focuses on the different techniques used for the removal of pharmaceuticals. Microbial engineering approaches for different pharmaceuticals are also explored widely.

2. Occurrence of pharmaceuticals

Pharmaceuticals are very diverse biologically active compounds including analgesics, anti-inflammatory, antibiotics, and anti-epileptics. To understand the origin and source of pharmaceuticals, the various types of pharmaceuticals found must be explored and discussed.

2.1. Origin of pharmaceuticals

2.1.1. Antibiotics

Overall consumption of antibiotics has increased by more than 30% since the last decade. Antibiotics are considered as pseudo-persistent compounds as they are continuously released in environment at low concentration. It has been observed that with the time microorganisms have evolved to develop resistance mechanism against the antibiotics [1]. A study reported that the presence of various antibiotics including fluoroquinolone, sulfonamide, tetracycline and chloramphenicol in both surface and wastewater [13]. Their concentration ranges from 0.06 to 23.4 ng/L. Epitetracycline, a member of tetracycline group of antibiotic is reportedly present in both treated and untreated water at 80–100 ng/L concentration [14]. Importantly, tetracycline and fluoroquinolone form more complex compounds when reacts with metal cations [1].

2.1.2. Therapeutic hormones

Estrogen is the most common hormone found in environment as it is widely used as birth control agent. Different metabolites of estrogen like estrone and estradiol are detected in aquatic environment and reported to have adverse developmental and reproductive effect on aquatic organisms [15]. According to a study it has been observed that a women excrete and 10–100 μg and this concentration may increase during pregenancy [1,16]. Estrogen detection has been reported in influent and effluent at a concentrations of 5–187 ng/L and 0.3–11.6 ng/L respectively [17,18].

2.1.3. Analgesic pharmaceuticals

Drugs such as acetaminophen, naproxen, iboprufen, diclofenac and meprobamate belong to analgesic pharmaceuticals which are widely used for inflammation and pain relief. Due to their long persistence in surface and ground water, these molecules are considered as potential pollutants [17]. In recent time, significant rise in the use of ibuprofen has been reported and about 15% of this drug remain un-metabolized and excreted. Out of this 26% is released as metabolite [19]. The ibuprofen metabolites are reported highly toxic to the aquatic organisms. A research group reported the occurrence of iboprufen, naproxen, diclofenac, gemfibrozil, furosemide and hydrochlorothiazole at a concentration of 3–18 μg/L [20]. An anxiolytic drug, meprobamate is also detected in tap water [21]. The presence of these drugs in water bodies delivers great concern to the human health.

2.1.4. Pharmaceutical metabolites

During digestion in human and animal systems, the pharmaceutical compounds are transformed into hydrophilic, polar and biologically active metabolites which are excreted through urine and faeces to the environment. Accumulation of metabolitessuch as 10,11-dihydro −10,11-epoxy carbamazepine, 4-hydoxydiclofenac, N4-acetylsulfamethoxazole in aquatic organism's tissues were reported by a study [1]. These contaminants represent potential threat to evoke immune response as well as exert adverse effects on aquatic life. Sertraline and fluoxetine produce highly toxic metabolites (desmethyl sertraline and norfluoxetine respectively) and their presence is reported in the aquatic fishes at a higher concentration then reported level of toxicity. Due to their weak interactions with materials, their capture by adsorption is limited, making them persistent in the environment. After release, these metabolites are transformed and affect the microbial community present in WWTPs [22]. Hence continuous release of the pharmaceuticals raises a concern regarding their fate and their eco-toxicological effect on different aquatic organisms due to their analogues formation.

2.2. Sources of pharmaceuticals and ecosystems penetration pathways

Pharmaceutical compounds have various routes of applications such as topical, ingestion, and pulmonary [23]. The compounds are released

or excreted to the environment based on their application routes. The excreted compounds include undigested drug components, active and inactive metabolites, and parent drug-metabolite conjugates [24]. The excretion route and forms can be different based on the health, disease status, gender, age genetics and pharmacokinetics of the drugs [25,26].

2.2.1. Consumers

The primary routes for entry of pharmaceutical are sewage households and through direct disposal of pharmaceuticals. Storage and accumulation of the expired pharamceuticals is the major cause for their unwanted disposal. A survey found that nearly half of the patients who were consuming the drugs did not finish their medication course [27]. Nearly 65% of them has disposed the drugs to trash and one tenth of them has discarded in sewage. Once the pharmaceutical is disposed into sewage, it enters the wastewater treatment facilities, leaches to the ground, enters directly to water bodies. Raw sewage enters the environment through instances like overflowing, storm or system failures of the sewage treatment plants. Damage to the infrastructure and active recharge of groundwater with reclaimed water can promote the introduction of biologically active compounds into ground waters [28].

The liquid effluent resulted from the sewage treatment is usually discharged into water bodies and used for irrigation. According to a study, pharmaceuticals can migrate and accumulate through irrigated soil at ng/L level of concentration [29]. The solid effluent from the sewage treatment plant is known as sludge. Sludge can be simply disposed or can be used as fertilizer through which the residues can leach through the soil to enter and contaminate the ground water. It is also reported that plants can absorb pharmaceutical residues. Another major source is wastewater treatment plant. A large concentration of pharmaceuticals may be released in the effluent rejection stream from membrane filtration technique which is directly dumped in environment without any treatment [30,31].

2.2.2. Hospitals and healthcare providers

Medications in hospitals differ than other facilities in respect to their doses, types, per capita consumption and quantities. The drugs are prescribed based on their toxicity and term of prescription. It leads to entry of different drugs in varrying quantity to the environment in comparison to other sources. Long-term care facilities contribute mainly from healthcare community and contribute to entry of pharmaceuticals to the environment. The patients in those facilities often require multiple medications. Change in the prescription and doses is another reason for disposal of pharmaceuticals in these fascilities. This results in accumulation of medication in large amounts which is then disposed into sewage. Physicians and pharmacists also sometimes dispose their expired medications to trash. Computerized unit dose dispensing can be solution to the disposal of drugs [32].

2.2.3. Veterinarians

The list of veterinary drugs approved by Food and Drug Association (FDA) has reported to have no impacts of environment. But there is significant number of drugs which are used for both animals and humans [33,34]. The drugs used for pet animals results into deposition in environment through excretion which can enter the water bodies by run off. This leads to cases of poisoning in wildlife. One of the examples is wide use of pentobarbital for euthanasia in animals. Improper deposition of euthanized animals leads to entry of residues at high concentration into the environment. Also, if not properly disposed, it can be scavenged by wild animals and leads to wildlife poisoning. Diclofenac is another widely used drug for animals in Southeast Asia. Improper deposition of animal bodies who were treated with high doses of diclofenac result into transmission of the drug to different wild animals causing poisoning in them. These two instances proves that pharmaceuticals and enter the environment through unexpected an unusual routes [32].

2.2.4. Agriculture and aquaculture

Pharmaceuticals are widely used in agriculture and aquaculture. Antibiotics and steroids hormones are most widely used in agriculture and aquaculture. Though the pharmaceuticals used for humans are similar to that of used for animals, but the quantity of drugs used in agriculture is huge [8]. Thus the residues entering the environment at higher concentration have potential for ecological damage. In aquaculture, the drugs are introduced to the environment directly. Highly toxic drugs like chloramphenicol, nitrofurazone and furazolidone are used at high concentration which results in accumulation in sea-foods. These antibiotics can easily enter the food chain if consumed by human and they exert adverse effect [35]. Antibiotics treated animals excretory products are used as manure and pharmaceutical residues enter through soil. These residues are accumulated in roots and stems of the plants [36].

2.2.5. Miscellaneous sources

Apart from major routes, there are numerous insignificant pathways through which pharmaceuticals enter the environment. These include raw or treated sewage from cruise ships. Humanitarian relief camps are one of the unusual source of pharmaceutical pollution. Large proportions of different drugs are stored for distribution among people who need them which are discarded to the environment. The poorly equipped manufacturing labs can be a considerable source of contamination [32].

3. Pharmaceutical applications

The demand for the drugs has influenced by various circumstances. For example, the most prominent pain killer was discovered and used widely used during the World war to ease pain of the wounded soldiers. Similarly, pandemics such as small pox, rabies, influenza, Cholera, H1N1, SARS, and COVID-19 has urged the scientists to find the cure and prevention of the diseases. The pharmaceutical companies have played a major role in developing drugs which are potential enough to fight against the deadly diseases. The emerging technologies has given wings to pharmaceutical companies by which they they explore new methods to treat deadly diseases. The pharmaceuticals can be classified as pharmaceuticals used in diagnosis and pharmaceuticals used in treatment of diseases.

3.1. Pharmaceutical products adding in the diagnosis

Early diagnosis of the disease helps the clinicians identify the root cause of the illness and prescribe the appropriate treatment [37]. Before the advancement in the field of research and technology, the physicians would diagnose the patient mainly based on the physical symptoms of the disease The newer pharmaceuticals aid in early detection as well as prognosis of the diseases [38]. Diagnosis can be categorized as invasive and non-invasive. Most commonly used approved oral administration is the barium-based contrast medium and Small iodinated agents which are introduced into patient intravenously [39,40]. sSme of these contrast agents for CT Scan have been approved by the FDA and their application are mentioned in Table 1.

Most of the radiotracer used in the therapy or diagnosis decays rapidly having a half-life of few hours and causing less or no harm to the patient [41]. The use of radiotracer depends upon the type of diagnosis to be performed. Radiotracers along with their diagnosis has been listed in Table 2.

3.2. Pharmaceutical products aiding in treatment of disease

Now current era of pharmaceutical research has leaped forward more specific in action and target oriented such as proteins and peptides, nucleic acids and live cells [51]. For an example, ritonavir is used for the treatment of HIV was conjugated with thiazole so that it increased

Table 1
Applications of important contrast agents.

Drug name	Applications
Iodipamide meglumine	Hepatobiliary imaging agent
Iothalamate meglumine	Brain and body CT, urography, angiography
Diatrizoate meglumine	Retrograde cystourethrography
Ethiodized oil	Hysterosalpingography and lymphography
Ioxaglate meglumine; Ioxaglate sodium	Pediatric angiocardiography, urography, contrast CT of brain and body imaging, arthrography and hysterosalpingography.
Iopamidol	Disorders of the heart, brain, blood vessels, and nervous system
Iohexol	Myelography, cisternography, ventriculography, Angiography, urography, contrast CT of brain and body imaging
Ioversol	Cerebral angiography, peripheral arteriography, urography, Angiocardiography, urography in children, Peripheral and coronary arteriography, left ventriculography,
Ioxilan	Angiography, urography, brain and body imaging

Information Obtained from: https://www.ncbi.nlm.nih.gov/books/NBK5330/bin/fdaApprovedContrastAgents.xlsx.

Table 2
Utilization of radiotracers towards diagnosis.

Radiotracers	Diagnosis	References
Fluoride F-18 (sodium fluoride F-18)	Diagnosis of bone and joint diseases, and prostate cancer patients.	[42,43]
Fludeoxyglucose F18	Neoplastic diseases, epilepsy, alzheimer disease, myocardial viability, atherosclerosis, infectious, inflammatory processes, and tumors	[44]
Ammonia N13	Tumour imaging of myocardium, liver, kidneys and brain	[45]
Amyvid florbetapir F18, Neuraceq florbetaben F18	Neuropathological diagnosis such as Alzheimer's Disease	[46,47]
Choline C 11, Axumin fluciclovine F18	Tumour especially prostate cancer	[48,49]
NETSpot Ga 68 dotatate	Somatostatin-receptor positive neuroendocrine tumors (NETs)	[50]

metabolic stability and aqueous stability [52,53]. Small molecules drugs provided efficacy against a wide variety of diseases. But could have targeted only 2–5% of human genome. Therefore the next generation of therapeutic drugs focused on protein and peptides. Some of the currently used drugs associated with proteins and peptides include: "Insulin" for Type 2 Diabetes, "Gonadotropin-releasing hormone (GnRH) receptor" for prostate cancer, endometriosis, assisted in reproduction, "Glucagon" for Hypoglycemia, "Vasopressin" for vasodilatory shock; bleeding esophageal varices, "Oxytocin" for Labor induction; postpartum hemorrhage; lactation etc [54,55].

4. Microbial technologies for pharmaceutical removal

The growth of pharmaceutical industries results in usage of various kinds of drugs used in a variety of sectors such as agriculture, poultry, human health and fisheries. Several natural trace organic and anthropogenic pollutants are contaminating the water bodies across the world. Pharmaceutical waste enters the water cycle either as original compound or as metabolized form (in low loads). The maximum concentration of pharmaceuticals waste is generated from the so called hotspots such as 'elderly houses or hospitals'. Though these compounds are present in low concentrations, studies indicated that these chemicals form a potential new problem due to their estrogenic and carcinogenic toxicity [56].

4.1. Treatment of pharmaceutical wastewater

Pharmaceutical waste water (PWW) has a complicated composition that includes microbial toxicity, high level organic components and salt contents. The conventional biological approaches include anaerobic, aerobic and anaerobic – aerobic processes for PWW treatment. Recently, treatment strategies are mainly focused on employing physico-chemical technology as the primary technique that includes conventional (adsorption, coagulation, floatation and ozonation) and advanced oxidation processes.

Advanced oxidation process (AOP), utilizes free radicals for oxidizing the contaminants. Recently, Fenton's oxidation is considered as a useful AOP, that works by the incorporation of Fe as the catalyst, to catalyze the formation of OH-. Fenton's reaction is mainly operated at room temperature without any environmental impact. It produced around 80% degradation of contaminants with effective mineralization efficiency with the help of Fe based catalyst [57].

The main biological treatment processes for antibiotics removal include biodegradation and sludge adsorption. Biological Aerated Filter system (BAF) comes under aerobic treatment while up flow anerobic sludge blanket (UASB), anaerobic digestion (AD), anaerobic filter (AF) and anerobic baffled reactor (ABR) processes belongs to anaerobic methods. The sequencing batch reactor (SBR) and membrane bioreactor (MBR) processes are the two most common combined aerobic and anaerobic methods. The most predominant processes currently used in antibiotics removal in breeding waste water are MBR, SBR, AD and BAF (Huang et al., 2021). The antibiotics removal rates by various biological treatment methods are summarized in Table 3.

4.2. Microbial fuel cells

Over the past decade, Microbial Fuel Cells (MFC) have been explored extensively as a route to not only produce electricity but also support semi-selective contaminants metabolization [58]. A typical two chambered microbial cell consists of a cathode set-up, anode chamber and a membrane for isolating both cathode and anode. Generation of electricity in the MFCs occurs in the anodic compartment by the oxidation of biodegradable waste. It is a bio-electrochemical system which converts the chemical energy into electrical energy with the help of catalytic actions of the microorganisms [59].

Pharmaceutical wastewater mainly consists of high levels of organic materials, microbial toxic compounds and salt content, which will be metabolized by microorganisms and mineralized into small organic molecules, water, carbon dioxide as well as potentially ammonia. MFCs are adopted as remediation method which speeds up the deterioration of pharmaceutical wastes and reduces the reaction time because of the

Table 3
Removal of antibiotics from breeding wastewater using biological processes **(Huang *et. al.*, 2021)**.

Processes	Biological Treatment	Antibiotics	Removal efficiency (in percentages)
Anaerobic method	AD	Tetracycline	65
Aerobic method	BAF	Sulfamonomethoxine, Sulfachloropyridazine, Trimethoprim, Norfloxacin, Lincomycin, Leucomycin.	89–91 (Total antibiotics)
Aerobic–anaerobic combined methods	SBR	Sulfamonomethoxine, Tetracycline	88–96
	MBR	Sulfamonomethoxine, Tetracycline	>90
	IAMBR	Tetracycline, Chlortetracycline, Doxycycline, Roxithromycin, Norfloxacin,	4–53 (Total Antibiotics)

driving power of cathode processes [60].

Antibiotics discharged from pharmaceutical industries cannot be entirely degraded by traditional physiochemical and biochemical methods, due to the stability of these chemicals and their relative low concentrations within the streams. Recently, with glucose as fuel, MFCs possessing air cathode were successfully used in the degradation of antibiotic penicillin. Also, this glucose – penicillin combination was used in the generation of power [61]. Constructed wetlands with MFCs were utilized in the degradation of several antibiotics (Figure-1). The impact of concentrations, external resistance, aeration periods and carbon sources on the TC (Tetracycline) and SMX (Sulfamethoxazole) removal have been studied. The studies with Microbial Fuel Cell – Constructed Wetlands (MFC-CWs) microcosms were reported and the results showed that MFC-CWs with low permeate glucose concentrations exhibited the SMX and TC removal.

Aromatic compounds are a common contaminant released by the pharmaceutical industries. Phenol, nitrobenzene, benzene and their derivatives are listed as the major contaminants by the US Environmental Protection Agency (USEPA). MFCs were employed in decontamination of PWW rich in these aromatic compounds conducted in the decontamination of PWW in an Air Cathode Microbial Fuel Cell (ACMFC), in saline condition by bio-augmentation of halophilc consortia [63]. The results indicated that significant removal of TSS, SCOD and TCOD were achieved with an energy production of 895 mV. *Rhodococcus*, *Marinobacter*, *Bacillus*, and *Ochrobactrum* were the most common halophilic strains in ACMFC. In another study, Wu et al., (2018) used a two-chambered MFC for treating PWW which contains acetone or phenol and generate electricity simultaneously which resulted in perfect pollutant removal rate with no traces of acetone or phenol [64].

MFC can be combined with the Fenton technique for the removal of BPA (Bisphenol A), TCC (Triclocarbon), Estrone and sulfamethazine. Wang *et. Al.,* (2017) compared MFCs in both batch and continuous flow modes and stated that, OH radical oxidation and permeation on the graphite material are the main reason for the efficiency of MFC –Fenton technique for the removal of TCC, BPA, Estrone and sulfamethazine [65] (Fig. 2).

4.3. Bioremediation

Bioremediation is a well-established technology that has been used for decades as an effective method in the degradation of petroleum hydrocarbons and chlorinated solvents. The bioremediation techniques commonly employed are applications of biomimetic membranes, photocatalysis and ultrafiltration membranes [67]. Bioremediation is mainly achieved by biostimulation, bioaugmentation and natural attenuation. The biostimulation corresponds to the addition of electron acceptors or nutrients for encouraging the growth of microorganisms, which in turn enhances the rate and extent of biodegradation of the pollutants. The natural attenuation is the natural remediation capability of a particular microbial community present in a polluted site for achieving pollutant removal. Finally, bioaugmentation is a strategy of inoculation of a particular contaminated site with microbial consortia (group of different microbial species) which possess biodegrading capacity, when an appropriate microbial community does not exist or it is considered to be too slow for the complete degradation of the pollutants [68].

Various studies have documented the application of bioremediation in breaking down of pharmaceutical wastes. A study was conducted which focused on the treatability of bulk pharmaceutical waste water with the help of activated sludge reactor with acclimatized mixed microbial consortia. An 86.6%f reduction in the COD value was achieved by the bioremediation process. In another study, multi-biofilm consisting of bacteria and fungi was used in treating pharmaceutical wastewater. But, though most of the pharmaceutical compounds (such as ibuprofen) are biodegradable, other compounds such as trimethoprim and carbamazepine are recalcitrant. Also, these biological treatment methods are mostly sensitive to environmental changes such as oxygen, temperature, pH and nutrient levels. These environmental conditions play a huge role in the efficiency and stability of bioremediation process, thus it should be monitored and optimized carefully [69].

Bacterial remediation and myco-remediation are the two new aspects of bioremediation. The bacterial remediation has been used in degrading xenobiotic compounds and has been used in activated sludge process [67]. Most of the bacterial remediation are focused on the aerobic degradation of the pharmaceuticals by either individual bacteria or bacterial consortia in which oxygenases are involved. The bacterial remediation is commonly employed in activated sludge process, but due to certain operational issues associated with the generation of large quantities of sludge, development of bacterial consortia is preferred, including micro-algae and bacteria – microalgae consortia [69].

In nature, fungi are excellent decomposers possessing intracellular and extracellular enzymes that exhibit significant capabilities for degrading organic material. Specifically, cytochrome P450 systems and ligninolytic enzymes, which includes both laccases and peroxidases, has been proven to possess exceptional capacity to white rot fungi for the degradation of recalcitrant pollutants. Due to the nonspecific nature of

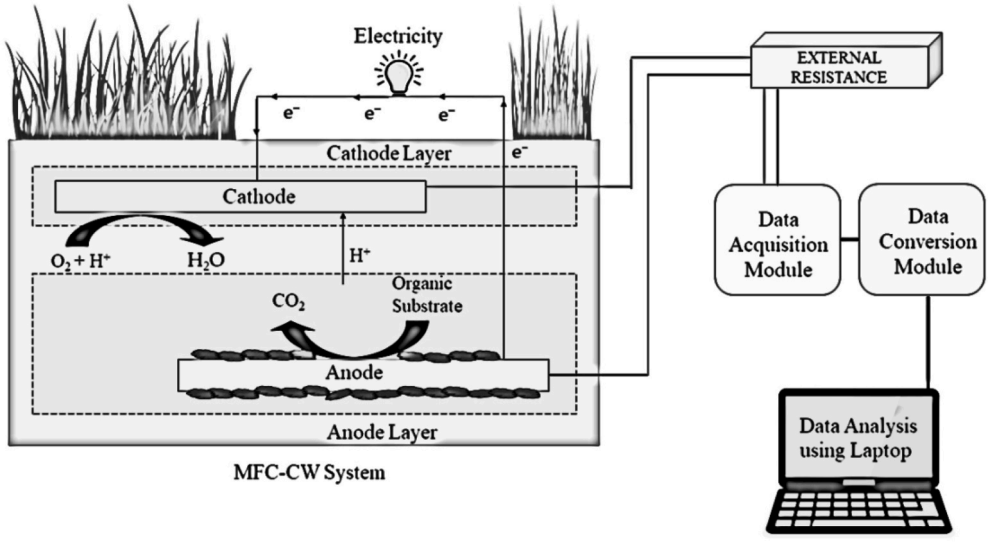

Fig. 1. MFC- constructed wetland system's schematic representation [62].

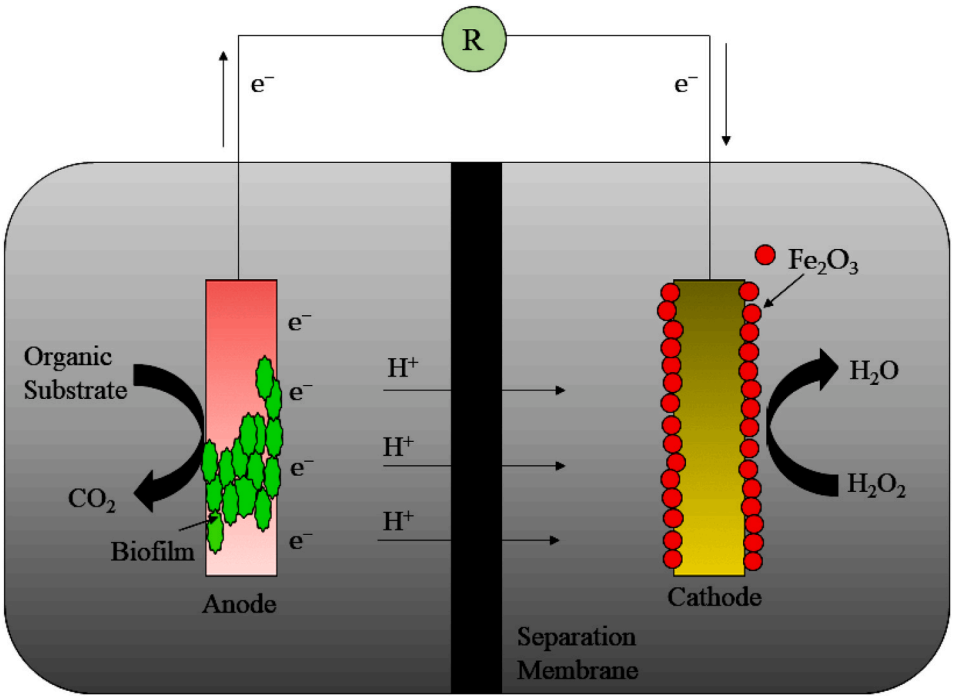

Fig. 2. MFC – Fenton system's schematic representation [66].

these enzymes to deal with diverse chemical compounds, it can be used to degrade various classes of pharmaceuticals. Also, several fungal species are considered to be hyper-accumulators, that are capable of bioaccumulation of xenobiotic compounds [70]. Thus, mycoremediation is considered to be eco-friendly, cost effective and effective approach for pharmaceutical treatment [71].

Macromycetes (polypores or mushrooms) are proven to remediate antibiotics, hormones, beta-blockers, anti-inflammatory drugs and psychoactive drugs. Experiments with *Trametes versicolor* in flask batch, shows that the fungi possess impressive capacity for the degradation of vast number of pharmaceuticals. In case of bioreactor-based studies, *Trametes versicolor* was capable of degrading pharmaceuticals such as diazepam, codeine, metoprolol and carbamazepine. *Trametes versicolor* was employed in the 94% degradation of carbamazepine (9mg/L) after six days in the flask experiment. Also, fungus remediation efficiency of carbamazepine in fluidized bed bioreactor operated in both continuous and batch mode was operated. The results showed that, around 96% of the drug was degraded in two days in batch mode, whereas only 54% was degraded in continuous mode [69].

Trametes versicolor has shown promising remediation of NSAIDs (Non steroid Anti-inflammatory drugs), whereas bioremediation of NSAIDs using bacterial monoculture has not been successful. Moreover, Olicón-Hernández et al., (2020) conducted the study on the degradation of a mixture of diclofenac, acetaminophen, ketoprofen, ibuprofen and naproxen with *P. oxalicum*, using bench fluidized bioreactors. *P. oxalicum* indicated higher degradation percentage in the bioreactor than at the flask [72].

Also, *Trametes versicolor* is employed in degradation of antibiotic ofloxacin with about 80% efficiency. When the same experiment was conducted in fluidized air-pulse bioreactor, remediation of ofloxacin rich hospital waste was done with 99% efficiency. About 50 fungal isolates were isolated from salmon hatcheries having oxytetracycline remediation ability. The filamentous fungi *Epicoccum nigrum*, *Penicillium commune*, *Aspergillus terreus*, *Beauveria bassiana* and *T. harzianum* were recognized to generate preferable remediation rates amounting to about 78% [73].

Some of the potential microbial technologies that can be successfully used for removal of pharmaceuticals from waste stream are constructed wetlands, microalgae-based systems, microbial fuel cell based approach, biofiltration, bio-nanotechnology approach and arbuscular fungal treatment.

4.4. Constructed wetlands

Constructed wetlands (CWs) are artificial systems that integrate natural wetlands with eco-friendly treatment methods for achieving pharmaceutical waste management [74]. CWs employ the microbial route of pharmaceutical waste management in amalgamation with phytoremediation. CWs employed for pharmaceutical waste treatment may employ free surface flow, subsurface flow or hybrid flow type CWs [75]. Pharmaceuticals often do not have specific receptors in the plants present in CWs and are transported and translocated by means of simple diffusion mechanisms. The rate of this diffusion is affected by multiple factors like hydrophobicity, solubility and other physicochemical properties of pharmaceutical compounds [76]. Despite the basic understanding that the plant-microbe interaction plays a key role in the treatment of pharmaceutical waste in a CWs, the molecular mechanism behind this potential strategy is still unexplored [77]. Research studies have shown that the species diversity of macrophytes in CWs has a direct effect on the type of microbial consortium associated with it. Another major factor determining the microbial assemblage in CWs is the composition of pharmaceutical wastewater in these systems that changes relatively with the products produced by a pharmaceutical industry. The presence of certain chemical compounds (like organophosphate flame retardants) in the pharmaceutical waste water can act as stimulatory for microbial growth whereas some inhibitory substances like dibutyl phthalate may prove detrimental to the microbial richness as evident from the literature [78,79]. Nature of filtering materials added to CWs has a potential role in controlling the diversity of microbes and their interaction with macrophytes thereby controlling the overall rate of treatment process [80]. Addition of biochar and intertidal wetland sediments was reported to enhance the performance of CWs in treating pharmaceuticals [81]. The rate of aeration also determines the diversity of microbial community in various zones of CWs (surface, middle and bottom) [82]. Fig. 3 presents the process of pharmaceutical degradation in constructed wetlands.

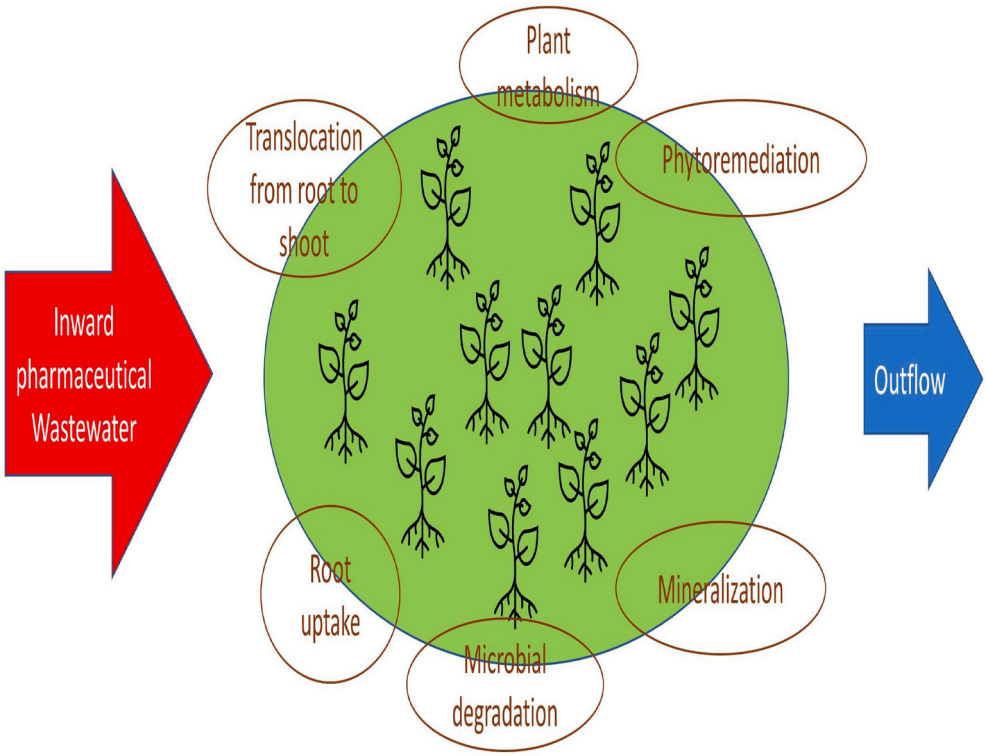

Fig. 3. Pharmaceutical removal in constructed wetland.

Basic mechanism of degradation of pharmaceuticals in CWs involves sequences of interdependent events like photodegradation, sorption, sedimentation, phytodegradation and microbial degradation [75]. In the photodegradation mechanism, the pharmaceutical compounds based on their functional group may either directly absorb solar radiation or indirectly produce photo induced intermediates that are highly reactive [74]. Sorption of the pharmaceuticals occurs through combination physical and chemical changes whereby the degradation products attach to a substrate or biofilm propelling further degradation. The sorption and sedimentation process acts as a key factor in determining the bioavailability of pharmaceuticals for photodegradation and microbial breakdown [83].

Phytoremediation mechanisms involve phytostabilization or phytodegradation. The uptake and translocation of pharmaceuticals is driven by non-receptor mediated simple diffusion mechanisms [84]. The metabolism of the pharmaceuticals within plants is accompanied by phytodegradation, phytotransformation and breakdown by endophytic microbes. The data about the intermediate formation and fate of metabolic intermediates within plant cells is rarely reported in the literature [85]. The contribution of microbial mechanisms associated with rhizosphere remediation has a significant role in the biodegradation of pharmaceuticals in CWs [86]. The molecular mechanism behind the plant-microbe interaction associated with microbial breakdown of pharmaceuticals is still unclear. The degradation of pharmaceuticals by microbes is primarily an enzyme catalysed process that is specific to the chemicals present in pharmaceutical waste [87]. Despite its potential application of CWs in pharmaceutical waste management, its scaling up (most studies in literature is limited to lab scale) and performance analysis over a long period of time are still the major challenges that need to be resolved for its successful commercialization [75].

4.5. Microalgae based systems

Microalgae based degradation of pharmaceuticals are gaining enormous interest recently due to its sustainable and eco-friendly nature. This method can be coupled with the removal of other nutrients present in pharmaceutical wastewater, which provides an innovative cost effective solution for efficient removal of the pharmaceuticals against the conventional treatment practices [88]. The pharmaceuticals have different physicochemical properties which can alter the parameters of the water by making it uninhabitable. This forces the microalgae to take up and valorises the pharmaceuticals to ensure its survival. The removal and degradation of these pollutants by microalgae happens in three steps [89]. At first the compound is adsorbed rapidly through physicochemical interaction between the cell wall and pollutant. Next the compound undergoes slow transference through the cell wall and at last, the compound ends up in the algal cells as bioaccumulation or gets biodegraded [90].

In bio-sorption, the pharmaceutical compounds get distributed onto the microalgal surface through hydrophobic and ionic interactions. The compounds get dispersed between the liquid phase and cell wall. The process of biosorption is passive and requires no energy. Bioaccumulation, however, is an active process which utilizes energy and is slower than biosorption. The pharmaceuticals are taken up by the microalgae along with nutrients [91]. The process of bioaccumulation can take place against the concentration gradient between the external environment and cytoplasm. Both processes functions by employing different mechanisms, but due to their continuous nature, the quantification of pharmaceuticals undergoing each process cannot be measured. Hence they are measured under a combined name of biosorption [92].

Biodegradation of the pharmaceutical compounds in micro algae is catalysed by different enzymatic reactions. The enzymatic reactions depend on the nature of pharmaceutical compounds and micro algae used. The biodegradation of these compounds in microalgae follows three phases. At first the pharmaceuticals undergo detoxification by the action of Cytochrome P450. The lipophilic compounds are converted to hydrophilic compounds by the addition of hydroxyl groups. In the next phase the enzyme glucosyltransferases or glutathione-S-transferases acts on the electrophilic groups ($CONH_2$,COOH) to form a conjugate bond with glutathione to protect the algal cells from oxidative damages [93].

The last phase executes the bio-transformation of the pharmaceuticals into simpler detoxified compounds by the influence of various enzymes like, dehydrogenase, transferase, dehydratase, laccases, mono(di)oxygenase, hydrolases, glutamyl-tRNA reductase, decarboxylase, carboxylase and pyro-phosphatase. Other than biodegradation many pharmaceuticals can undergo photo-degradation or photolysis once it is accumulated in microalgae.

Photolysis process is an effective, economical, environment friendly process which is comparatively easy to optimize. Direct photolysis and indirect photolysis can contribute to the breakdown of pharmaceuticals. In direct photolysis the pharmaceuticals absorb the UV-range from sunlight and degrade itself without the participation of microalgae. In indirect photolysis the compounds are broken down by the generation of free radicals from the exposure of sunlight. Here microalgae is involved to suppress the free radicals and convert the energy to useable form for the cells [94]. Singh et al. (2020) cultivated *Chlorella* sp., SL7A, *Chlorococcum* sp., SL7B and *Neochloris* sp., SK57 in river water contaminated with pharmaceutical waste for biomass and lipid production. *Neochloris* sp., SK57 showed high growth rate, biomass yield and lipid production. The lipid yield was 28% of cell dry weight. An 84% reduction of BOD in the pharmaceutical contaminated river water was reported. The study suggests that the high lipid yield produced by algae after the valorization of pharmaceuticals can be further used for food and fuel applications [89]. In the study conducted by Chen et al. (2021) revolving algal biofilm reactor was used to remove pharmaceutical and personal care products from water. The compounds used for the study were ibuprofen, oxybenzone, triclosan, bisphenol A and N, N-diethyl-3-methylbenzamide. It was reported that the revolving algal biofilm reactor degraded more than 90% of the compounds and the rest 10% was removed by the accumulation in the formed algal biomass.

4.6. Biofiltration

Biofiltration method for pharmaceutical waste management employs the oxidation mechanism of microbial biofilm attached to a filter media to achieve the biodegradation of pharmaceutical pollutants [95]. The pharmaceutical waste present in the wastewater is made to flow over a filter containing microbial biofilm. The bacterial biofilm utilizes the pharmaceutical residues as their prime source of carbon and oxidizes them through their enzyme driven central metabolism [96]. The biomass, treated wastewater and carbon dioxide produced as result of bacterial oxidation process are further tuned for various applications [97]. The biofilters used for pharmaceutical waste treatment can be submerged type or fixed bed reactors. A uniform distribution of the pharmaceutical waste water over the filter matrix is the major attribute of fixed bed type. In the submerged type the filter matrix is suspended and acts as a support to the oxidizing microbial biofilm [98].

In principle the biofiltration combines sorption followed by biodegradation (based on the nature of the pharmaceutical contaminant). Both bacteria and fungi are majorly employed as potential candidates for biofiltration of pharmaceutical wastewater [99]. Biofilm formation over the biofilter bed can occur either through natural attachment aided by the exopolysaccharide production by biofilm forming bacteria [100]. Artificial immobilization of biofilm into biofilter beds may involve cross linking between bacteria, covalent bonding to the filter matrix, entrapment, encapsulation and membrane separation [96]. The filter used in the biofiltration process should be eco-friendly, economically feasible, highly porous, intrinsic nutrients, greater water retention capacity and improved material properties. The rate of the biofiltration process is influenced by multiple factors like pH, moisture content, pressure, temperature and nutrient supply [101].

The integration of microbial enzymes (either direct or immobilized form) to the biofilters was observed to enhance the degradation of pharmaceuticals in a biofiltration assembly [102]. The confirmation of the biofiltration unit may be rotating drum type, submerged aerated type and hybrid systems. Although an excellent method for pharmaceutical waste bioremediation, biofiltration has not yet achieved commercial success due to major challenges associated with this method [103]. The problems associated with scaling up of this microbial process, lack of proper understanding about the metabolic pathways associated with pharmaceutical waste degradation, clogging of biofilters by high concentration of pollutants, overall maintenance cost and issues associated with proper discharge of treated wastewater needs critical attention in future for the success of this method on a larger scale [96].

4.7. Bio-nanotechnology approaches

Treatment using bio-nanotechnological approach provides a sustainable, ecological, and clean alternative to conventional treatment approaches on pharmaceutical wastes. In this approach engineered or natural biosynthesised nanomaterials (nanoparticles) of size less than 100 nm are used. The bio-nanomaterials are produced from bacteria, fungi, yeast, algae and plants. The microbes will grow and produce extracellular enzymes and other compounds, which bio mineralization and synthesis of bionanomaterials. Among all the microbes, fungal nanoparticles are intensely studied because of their higher accumulation of metals and better tolerance towards the toxic effect of metals and their oxides. These nanomaterials are easy to synthesize when compared to the chemical synthesis of similar nanomaterials. Some of the commonly used nanomaterials for the synthesis of bio-nanomaterials are carbon base, graphene, polymeric solvents, metal oxides, nanocomposite and different nanoadsorbents [104].

Generally, microbes will take up the metal ions and convert it to elemental metal which can bind to different cell structures. Fungal cells take up the heavy metal ions and the putative mechanisms occurring during intracellular synthesis binds the metal ion to the fungal cell wall via electrostatic interactions. This metal ion is further reduced by fungal enzymes and results in bionanoparticle synthesis [105]. Such particles possess distinctive qualities like high photosensitivity, large surface area, magnetic properties, size effect, catalytic activity and quantum confinement effect. The advantage of using bio-nanomaterials over the conventional techniques is that it is cheap and the nanomaterials can be easily disposed of or reused, hence providing a sustainable approach [106,107]. They have a defined chemical composition, size and morphology; the biosynthesis of the bionanoparticles requires very mild physicochemical conditions, which makes them easy to handle. Biosynthesis provides another advantage of in-vivo tuning of the required characteristics by altering the cells at gene level.

The pharmaceutical waste management by employing the bionanoparticles are facilitated by the combination of adsorption of the compound to the nanoparticle and degradation by the biomaterial. Other than pharmaceutical waste the bionanomaterials are used to treat wastewater containing other organic pollutants like pesticides and dyes [108]. The biodegradation efficiency of bionanomaterials depends on the properties of the pharmaceutical waste, the microorganism used to produce the nanomaterial and the environmental factors (light, temperature and climate).

Wang et al. (2022) reported that suspended biofilms containing Mn-oxidizing bacteria are used for the treatment of different pharmaceutical compounds. The Mn-oxidizing bacteria ensured a continuous formation of biogenic manganese oxides when a spiked Mn(II) concentration was maintained in the reactor. It was reported that there was a 36% degradation of diclofenac and 80% degradation of sulfamethoxazole when compared to the degradation percentages of normal moving bed biofilm reactors without biogenic manganese oxides. However, when municipal wastewater is used instead of synthetic sewage there was a significant decrease in the degradation of diclofenac degradation and a shift in the microbial community of the biofilm over long term treatment was observed. It was due to high pH of the municipal wastewater. The degradation of 17α-ethinyl estradiol in the secondary wastewater treatment effluent using immobilized biogenic manganese oxide and *Pseudomonas putida* MnB1 was conducted by Tran et al., 2020 [109].

Pseudomonas putida MnB1 and biogenic manganese oxide was packed using modified granular activated carbon, which formed the biofilm. This biofilm was compared against the conventional biofilm for its removal efficiency and feasibility. The conventional biofilm employs adsorption to grab the pollutants and proceeds with the degradation. The newly synthesized biofilm was reported to have a degradation efficiency greater than 95%, which suggests that the degradation was due to a combined effect of microbial degradation and chemical oxidation by the biogenic manganese oxide.

4.8. Arbuscular fungal treatment

Among the soil microbial community one of the most important components are the arbuscular mycorrhizal fungi. They are known to form a mutualistic symbiosis with around 80% of the terrestrial plants. The arbuscular mycorrhizal fungi are present mainly in terrestrial environment, however recently the evidence related to their presence in the wetland environments is growing. More than 99 families of wetland plants were reported to have mutualistic symbiosis with the fungi [110]. These fungi help the host plants in an efficient absorption of nutrients and in the transfer of fatty acids and photosynthetic products to the root system [111,112]. The arbuscular mycorrhizal fungi association also enhances the biotic and abiotic stress tolerance for the host plant. It is reported that plants showed stress resistance against droughts, organic contaminants and heavy metal [113–115]. The mycorrhizal network also acts as a network between plants in the cycles of the ecosystem and promotes healthy and rich plant growth. The arbuscular fungal treatment has been reported to enhance the contaminant degradation enzyme activity of the plants. They tend to increase the bioavailability of the contaminants by altering the soil conditions resulting in sequestration of the pharmaceuticals present in soil [115]. The mycorrhizal structures span a large area in the soil and accumulate the contaminants which are either broken down by the fungi or transferred right into the plant roots [116,117].

A study was conducted [115] on the treatment performance of a constructed wetland using *Glyceria maxima* (wetland plant) colonized by an arbuscular mycorrhizal fungi, *Rhizophagus irregularis* BEG140. The wetland was constructed in order to provide the plant with stress from the pharmaceutical compounds ibuprofen and diclofenac. It was observed that the association of the fungi had a positive effect on the plant, as it enhanced the plant growth, protein content and activities of the antioxidant enzymes (superoxide dismutase and peroxidase). The ibuprofen degradation efficiency was increased from 6% to 14% and diclofenac degradation efficiency was increased from 2% to 21% after the association with *Rhizophagus irregularis*. It was also reported that the content of their metabolic process in the effluent was reduced.

Although pharmaceutical compounds are developed for the well-being of humans, indiscriminate use of these can lead to environmental problems. Table 4 represents Treatment efficiency (%) of various biological methods. New promising approaches such as genetic engineering are still at infancy, but application of new editing tool such as CRISPR-Cas9 may help for the introduction of metabolic genes that are focused on the target compounds. Thus, many more studies are required to deal with removal of pharmaceutical wastes.

5. Challenges in pharmaceutical removal

Pharmaceutical wastes (PWs) produced encompass-used and unused, expired prescription pharmaceuticals, including antibiotics and hormones, over-the-counter medicines, blood samples, needles, syringes, swabs, histo-pathological samples, fecal specimens, surgical tools, personal care products, along with some radioactive products [131]. Among these, many recalcitrant compounds have emerged as new contaminants in the environment, and are detrimental to both public health and ecology [132]. PW includes raw materials, by-products, and end products, which can be contagious, toxic, harmful, genotoxic, and radioactive. Disposal of PWs is quite challenging, as these comprise both solid and liquid waste, produced mainly from healthcare facilities, including-hospitals, nursing homes, medical stores, diagnostic labs, etc. These may also result in antibiotic resistance, which can create havoc in the future [133]. Commonly referred to as 'medical waste,' these remain challenging for both developed and developing economies. Other than that, waste has the possibility of being abused or diverted for illicit use.

PWs are frequently dumped in landfills, resulting in possible leaks

Table 4
Treatment efficiency (%) of various biological methods with process conditions.

S. No	Target pharmaceutical	Source	Microbial treatment method	Process conditions	Treatment efficiency (%)	Reference
1	Carbamazepine	Synthetic water	Constructed wetlands	0.5–2.0 mg/L of pharmaceutical, *Scirpus validus*	74	[118]
2	Naproxen	Synthetic water	Constructed wetlands	plant, cultivated under hydroponic conditions, 21 days.	98	[118]
3	Ibuprofen, paracetamol, and caffeine	Rural waste water	Constructed wetlands	Plant of *Phalaris arundinacea* and *Phragmites australis*, beds filled with 0.8 m of gravel, 10 cm of water.	75–99	[119]
4	Triclosan	Synthetic water	Microbial fuel cell	5.8 mg/L of pharmaceutical, 96 h	79	[120]
5	Ciprofloxacin	Artificial wastewater	Microbial fuel cell	10 mg/L of pharmaceutical, temperature at 25 °C, K3[Fe(CN)6] Cathode, 7 pH and 88 h	99	[121]
6	Estrone, lamivudine, trimethoprim and levofloxacin	Urine samples added with pharmaceuticals	Microbial fuel cell	2 g m/L of initial concentration, 30 h treatment,	96	[122]
7	Catechol	Synthetic water	Bacterial bioremediation	500 mg/L of pharmaceutical, *Pseudomonas putida* and 94 h.	97	[123]
8	Azithromycin	Waste water from hospital	Fungal bioremediation	4.31 of Azithromycin, 10 L reactor, 25 °C, *Trametes versicolor,* 4.5 pH and 8 days	100	[124]
9	Acetaminophen	Synthetic water	Fungal bioremediation	1.56 μg/L of Acetaminophen, *Trametes versicolor,* 120 h. 25 °C, 8 days, 4.5 pH	100	[124]
10	Ketoprofen	Waste water from hospital	Fungal bioremediation	2.17 μg/L of Ketoprofen, *Trametes versicolor,* 25 °C, 4.5 pH and 8 days	95	[125]
11	Ibuprofen	Waste water from hospital	Fungal bioremediation	0.9 μg/L of Ibuprofen, *Phanerochaete chrysosporium*, L of reactor, 30 °C, 4.5 pH and 200 rpm	90	[126]
12	Cephalexin	Synthetic water	Nanotubes	Method of chemical vapour deposition	96	[127]
13	Acetaminophen	Synthetic water	Nanotubes	Technique of chemical vapour deposition using a catalytic catalyst H_2SO_4 oxidation	74	[128]
14	Diclofenac sodium	Synthetic water	Bionanomaterials	Selenium NPs	97	[129]
15	Caffeine	Synthetic water	Bionanomaterials	Co-precipitation, $AgFeO_2$ NPs	95	[130]

into aquifers from rivers and lakes, negatively affecting aquatic and terrestrial ecosystems. Any malpractice permissible in their disposal and treatment results in the discharge of infectious agents and poisonous chemicals into the surroundings and creates environmental and social health risk. Looking at the variety of PW, different components require separate disposal approaches. The

It is observed that wastewater treatment plants (WTTs) are one of the primary sources of PWs dispersal in the environment [134]. However, it is reported that the majority of PWs toxic components are not eliminated by waste treatment, resulting in polluting the environment. Reportedly, the concentration of PWs in Indian water is 40 times higher, than that of Europe and the United States [135]. Other options for elimination of biomedical waste also include-landfilling, incineration, mechanical, autoclave, microwave treatment, and chemical recycling [136]. Some of these technologies can effectively reduce the PWs effectively. But may not be friendly to the ecosystem. This led to drafting of new waste classifications, disposal strategies, making PWs remediation a complex process. Further, it is agreeable that vast amounts of PWs produced, include many compounds with complicated, highly stable chemical structures, sometimes toxic molecules. Policymakers, medical professionals, and members of the recycling industry, face challenges during handling of PWs matter. This is the reason that several nations still lack the necessary regulations, or often fail to enforce them [136].

5.1. Bioremediation

Biodegradation of PWs by microbes (or enzymes) has untapped potential for treatment of waste, referred to as 'Bioremediation'. It refers to the use of living organisms, generally microbes to deal with contaminants for their degradation or at least reducing their toxicity, resulting in the ecosystem restoration, without disruption to local environment [137]. Bioremediation is relatively affordable, eco-friendly, and economical. Many bacterial species tested for remediation, include-*Pseudomonas* sp., *Rhodococcus* sp., *Clostridium* sp. etc. Similarly, fungal cultures of *Aspergillus* sp., *Bjerkandera adusta*, *Penicillium* sp. etc. have also shown promising results. Biotechnological advances led to alteration in these microorganisms, involving unique genes and enzymes with superior degradation potential, commonly grouped as genetically engineered microorganisms (GEMs) [138]. During recent times, case studies carried out suggested incorporation of modified microbes in waste biorefineries [139]. The vast diversity of microbes can be employed for effective disposal of PWs. Although, it requires toolkits with standardized genetic components for *in-vitro* creation of mutant libraries, followed by selection of mutant with desired phenotype [140]. Here, a lack of knowledge and expertise on parameters influencing growth and metabolism of microorganisms in contaminated environments frequently restricts their application. Along with this, environmental variables need to be taken in to account in use of GEM as well. This requires improvement in effectiveness, addressing wide range of complicated chemical structures, making remediation to be complex and generally low [141]. In the next section, we have discussed these challenges in detail in a systematic manner.

5.2. The GEMs in the PWs treatment

At first, the GEMs usage in the pharmaceutical digestors sounds lucrative; however, the success rate from the lab to the real world is still low. Advances in recombinant DNA technology, led to creation of different strains of microbes, that can break-down otherwise unbreakable contaminants in a petri dish, or lab conditions, However, practical application of this knowledge into genuine *in-situ* bioremediation techniques offers many obstacles. The scale-up of technologies, with a higher level of predictability is needed which might be more difficult to achieve, since it involves employment of live organisms. The significant challenges in GEMs-assisted remediations of PWs are compiled in Fig. 4 and discussed in detail below-

5.3. Biological factors

There is no doubt that employing GEMs is some-what low-cost remedial scheme in getting rid of PWs. However, many biological factors affect the microbial degradation of organic molecules in PWs. It includes direct inhibition of enzyme activity due to multiple factors. First, different microbial species could compete for nutrition sources, exhibit antagonism or predatory behaviors [142]. In addition, the stability of recombinant plasmid is affected by various parameters, such as copy number, growth rate, insert type, etc. (Rebello et al., 2021). Microbes generally are unstable and may quickly mutate with xenobiotics and

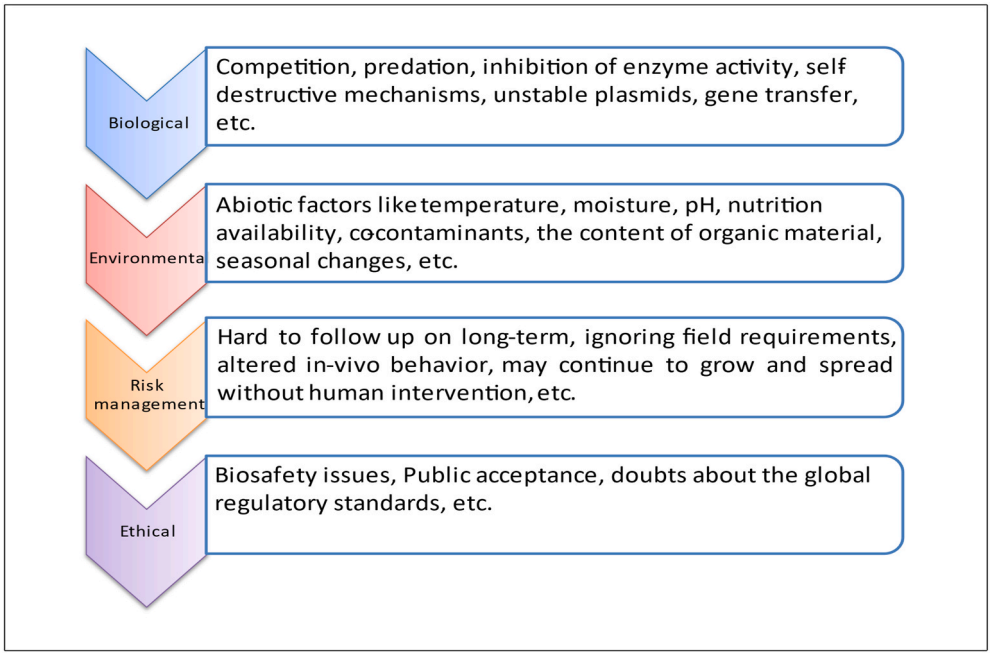

Fig. 4. Different challenges ahead of the GEMs usage in the biorefineries.

toxic molecules. Even creating genetically altered microorganisms for bioremediation is difficult and often plasmids carrying the newly introduced gene are unstable. This may lead to environmental and biosafety concerns in future. Further, some GEM exhibit self-destructive mechanisms (vectors or genes for suicide), or may function only under specific environmental circumstances (e.g. growth rate, abiotic factors, inoculum size, unique distribution etc.) and thus, needs to be under control [143]. Currently, molecular applications involve a small-restricted number of well-studied bacteria, like *E. coli, P. putida, B. subtilis*, etc. More research is needed for exploring different species, strains and their compatible vectors with safer selection markers for cloning and expression.

5.4. Environmental factors

These factors include-temperature, moisture, pH, nutrition availability, co-contaminants, the content of organic material, and others [144]. It is already known that appropriate environmental conditions are crucial for microbial growth and survival, thus these parameters ultimately influence the rate of microbial degradation. Studies suggest that these environmental factors regulate the rates of enzyme-dependent processes. This alters the microorganism's assisted biodegradation, which may not proceed at the required optimum rates. The degradation, although can happen at a variety of range; still pH of 6.5–8.5 have been found to be most appropriate [145].Other parameters, like temperature modulate the solubility; which tends to rise with increasing temperature. It ultimately augment the bioavailability of PWs molecules for effective degradation [145]. Excess moisture creates somewhat anaerobic conditions, which result in manifestation of undesirable products and foul odor [146]. For optimal microbial utilization, sufficient nutrients and oxygen must be present in a useable form and appropriate proportions. The nutrients influence the balance of vital nutrients for microbial growth, ultimately their efficiency and pace of biodegradation. Usually, seasonal changes, abiotic factor fluctuations, and delays in substrate breakdown have an adverse impact microbial activity. Thus, effective degradation of organic contaminants requires a thorough understanding of the process and its mechanism of action.

Additionally, a possibility of horizontal gene exchanges/transfer (including selection markers) between native microbes and GEMs may result in creation of resistant varieties [147]. The gene transfer could involve insertion in an endogenous gene, as well as at different locations, resulting in unforeseen and unexpected outcomes. Thus, effective bioremediation technology requires prior due diligence over the adverse effects.

5.5. Risk management and ethical concerns

It is important to study GEM impact on ecosystem's stability and functionality [148]. The field release of GEMs for bioremediation can create havoc on environment. There is a high probability of releasing toxic undigested organic material in the environment after the breakdown of PWs by GEMs. As GEMs are designed for higher affinity for organic matter, they exhibit faster growth rate than natural species, giving the former an edge to dominate in an environment. Ultimately, they might become invasive in new ecosystems and detrimental to environment and economy [149]. Thus, the challenge is to research for GEM resulting in complete breakdown of contaminants from the environment.

Further, it is difficult to follow-up the GEMs impact and getting rid of them might become impossible, once introduced into the ecosystem. It is a possibility that GEMs may continue to grow and spread, even without human intervention. Even the recent developments in meta-omics approaches, like-genomics, transcriptomics, proteomics etc., did not completely unravel the possible role of enzymes and signaling networks in GEMs mediated degradation pathways [139]. Thus, it is very challenging to certify that the application of these engineered microbes does not affect the environment or human health. The after-effects of DNA alteration might not be restricted to the specific traits of the gene being replaced, and the long-term effects of GEMs could be more detrimental than predicted [149].

Various ethical concerns rose regarding waste degrading GEMs involving perceived dangers to the integrity and intrinsic ecosystem and organisms. Public acceptance of GEMs is another critical obstacle ahead to their broad commercialization. An ethical debate over the potential consequences of utilizing GEMs in open environments was sparked over surge in designing GEMs for waste treatment programs. Generally, the microbes designed for bioremediation techniques are developed in laboratories under controlled settings, ignoring field requirements and other challenging scenarios [150]. The Environmental Protection Agency of the United States (EPA) did authorize first GE strain of *Pseudomonas fluorescens* HK44, for degradation of soil organic compounds. However, since then, no new GEMs were commercialized. One major factor behind that is lack of risk assessment in releasing GMOs. Enough precautions are required to evaluate the environmental dangers brought by release of recombinant organisms into the environment. Thus, global regulatory organizations and national and international agencies are paying more attention to biosafety issues related to the marketing of GEMs. The advantages and challenges related with GEMs are compiled in Table 5.

5.6. Potential recommendations

Now a days, designing and improving the GEMs in removal of toxic PWs is one of the frontier research areas in environmental biotechnology. Researchers are developing potential solutions to overcome the challenges, ahead of using GEMs in remediation purpose. GEMs essentially need to be studied for a longer time, as their genome is comparatively unstable and vulnerable in environments changes. Different substrates and microbial interactions are possible modulators of genome expression [151]. The studies on other parameters, including-temperature, pH, hydraulic retention duration, dosage, and their performance in aerobic and anaerobic settings, are frequently being carried out [152]. Although, repetition of controls sometimes does not work during scale-up from laboratory-scale results, and the scientific community still lacks expertise to troubleshoot that, limiting the commercial application of PWs bioremediation. This requires collaboration of industries and academic research, which would enable a seamless transfer from laboratory to the field scale.

It has been quite common that a single microbe lacks some genes, necessary for complete mineralization of organic contaminant in PWs. Thus, it becomes imperative to immobilize toxic organic contaminants

Table 5
List of advantages and challenges of using GEMs in PWs degradation sector.

Advantage	Challenges
Rapid degradation of contaminants	Limited availability of molecular toolkit to improve the rate of degradation and storage of GEMs
Multifunctional microbes can be engineered for multi-types of degradations at the same time	Unexpected variations in the lab environment
The expression of various degrading enzymes can be regulated by induction	The recombinant's plasmid stability might be affected
Cost-effective method	Mutations might affect the activity of these microbes
Ecological safe and sustainable	Horizontal gene transfer can occur between indigenous microbial species
Ease of practical treatment	Doubts on their long-term sustainability and relations with other microorganisms
High efficiency with a small amount of cell culture	Various regulatory and legal criteria have to be resolved before practical application
Avoid the use of harsh chemicals and high temperature and pressure	Safety concerns of the release of these engineered microbes

and regulate their bioavailability, resulting from uncomplete breakdown of pharmaceuticals by GEMs. This can be improved by creating a co-microbial consortium for complete degradation of such complex contaminants. Each microbe in these consortia would have a distinct role in particular degradation step, without overlap with other members [145]. The organic matter degradation requires hydrolytic microorganisms, i.e., bacteria rich in production of lipases, amylases, and protease; as candidates for bioremediation agents. The potential of hydrolytic bacteria is widely accepted in lowering the pollution parameters in liquid organic wastes [137].

The metagenomics library has led to the identification of additional or novel genes, which can be exploited in developing GEMs. These studies provide an in-depth understanding of microbial activities and their relation with different genes, mRNA and proteins expression levels, enzymes and metabolic pathways in challenging surroundings [153]. This offers an insight into the evolution of degradative pathways. Advanced effective learning methods about genetic diversity and microbial community architecture are required for the hour. Thus, the time is not far from when creation of different GEMs would be feasible by introducing new function genes, effective in contaminants degradation, with robust fecundity and good adaptability. This would considerably increase the efficiency of microbes in PWs treatment.

The development of novel gene editing methods, such as CRISPR/Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats) endonuclease system and homologous recombination, ease the process of targeting genes for insertion and deletion [148]. For instance, a single-plasmid CRISPR interference system with dead Cas9 (dCas9) and single-guide RNA (sgRNA) was built in *Aeromonas hydrophila*, and used for silencing a variety of genes. *A. hydrophila* ability to reduce Arsenic (V) was hampered when ArsB or ArsC-2 were suppressed using the CRISPR technique, indicating that ArsB is the main arsenic efflux pump and ArsC-2 is a significant arsenate reductase in this bacterium [154].

The suicide systems can neutralize the adverse impacts of GEMs on native microbial community. The production and accumulation of harmful compounds, after the depletion of pollutants, cause the extermination of the recombinant strain. This prevents horizontal gene transfer into the wild type strains [155]. Several bioinformatics databases are being created for in-depth analysis of biodegradation process. Since 1995, the University of Minnesota Biocatalysts/Biodegradation Database (UM-BBD) has provided data on microbial catabolism and related biotransformation, biodegradation processes, catabolic enzymes, pathways for xenobiotics and other potentially harmful pollutants produced by various microorganisms. In order to gather more information and maintain data on gene structure and enzymes, involved in biodegradation of environmental pollutants; this database is already linked to numerous other databases, including BRENDA, ENZYME, ExPASy, and NCBI [156].

Public awareness/access to information could be one of the strategies that might be useful to tap the advantages and minimize the risks of layman outcry against use of contemporary biotechnology. This would ensure public access to relevant information. This is a crucial component of public engagement. The scientific community should develop pilot scale testing to demonstrate the operational expenses and complexities [157]. This is required for investment and infrastructure setup, making it accessible for commercialization.

The remediation needs to be carried out in accordance with current legal license requirement, ecological and environmental security criteria. The regulatory agencies advise that before a changed microbe is released, its genetic destiny should be compared to the native microbial strains, under all vital field settings [158].

Three international accords and conventions are particularly relevant to PWs management, environmental protection, and sustainable development. These include Stockholm Convention on Persistent Organic Pollutants (POPs), the Basel Convention on Hazardous Waste, and the Minamata Convention on Mercury [159]. The GEMs undoubtedly pose ecological risks, but by means of technological advancement and innovation. It is possible to find a practical approach in future, that satisfies the needs of low-risk and high-efficiency bioremediation of PWs. Thus, employing these suggestions, the waste management using GEMs can be made appropriate for adoption by small and medium-sized firms. At the end, it is imperative to mention that we need to expand the understanding on scope and characteristics of modified microbial strain's efficiency in the breakdown of contaminants. The development of appropriate inoculants and the evaluation of their effects on the environment could be helpful in reaching closer to the goal. It is agreeable that despite advances in research, the vast majority of beneficial species and their potential has not yet explored. The rules and standards must be enforced to guarantee GEMs innovation in controlled manner and progress in the right direction.

Metagenomics have been explored extensively for screening of genes and enzymes capable of pharmaceutical wastes degradation [160]. These enzymes can be categorized in different categories such as lipases, carboxylases, reductases, carboxylases, etc [161–163]. These enzymes can be used for degradation of potential pharmaceutical compounds.

6. Future technologies for pharmaceutical waste removal

Rapid urbanization and modernization has triggered a logarithmic increase in the accumulation of pharmaceuticals and personal care products (PPCP) in the soil and aquatic environments. Conventional methods of pharmaceutical waste management often fail to achieve targeted success as they are not effective in complete degradation of PPCP or their breakdown products leaving a significant proportion of pharmaceutical residues in the environment. The future of pharmaceutical removal from soil and aquatic environments majorly targets integrated strategies, novel bioremediation methods and improved engineering methods that are eco-friendly as well as economically feasible. Previous studies have mostly focused on finding ways to increase efficiency of removal of pharmaceuticals from the environment. Microbial technologies integrated with renewable energy sources like wind and solar could make a considerable contribution to pharmaceutical waste treatment. However their effectiveness may be tied to environmental and climatic factors. Green-based pharmaceutical treatment methods should be developed in future considering with current advances in science and technology.

7. Conclusion

Fast growth of population, widespread industry, urbanisation and intensive agricultural methods are all driving up the worldwide need for safe and clean water. Removal of pollutants from pharmaceutical wastes necessitates the creation of new treatment approaches. In the last few years, it was observed that the newer technologies such as microbial fuel cells which not only degrade the pharmaceutical waste but also convert into useful energy. In addition, wastewater treatment technologies such as advanced oxidation process proved efficient in the treatment of pharmaceutical wastewater. It is concluded that although efficient technologies are already invented but their development to industrial scale is the utmost requirement of the current scenario. Integrated treatment approaches can create tremendous promise and may have a bright future and it can only succeed with the full commitment of present scientific community and governing agencies.

Declaration of competing interest

It is declared that all the co-authors are mutually agreed to submit this manuscript to the journal.

Data availability

No data was used for the research described in the article.

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