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REVIEW ARTICLE

A REVIEW ON COMPARATIVE STUDY BETWEEN THE PHYSICOCHEMICAL AND BIOLOGICAL PROCESSES FOR PARACETAMOL DEGRADATION

Wadhah Hassan Ali Edrees[1*], Qais Yusuf Mohammed Abdullah[1], Ali Gamal AL-Kaf[2], Khalid Mohamed Naji[3]

[1]*Microbiology Division, Biology Department, Faculty of Science, Sana'a University, Yemen.*
[2]*Medicinal Chemistry Department, Faculty of Pharmacy, Sana'a University, Yemen.*
[3]*Chemistry Department, Faculty of Science, Sana'a University, Yemen.*

ABSTRACT
Paracetamol has emerged as one of the most frequent pharmaceuticals that found in natural waters and even in drinking water due to its high consumption and therefore deserves a review on the possible treatments for its remediation. The purpose of this review work is to give a compare between the physicochemical and biological processes for removing paracetamol from aquatic environment. Different types of processes are described in this review: from physicochemical process such as membrane filtration, chlorination, activated carbon, and advance oxidation, which applied for pracetamol degradation, to biological process such as microbial, membrane bioreactor, aerobic and anaerobic degradation, which are more recently focused on the degrading paracetamol. Physical processes, that eliminate the pollutant without degrade it, are not efficient enough to completely remove paracetamol from aquatic environment. While the chemical processes that are shown to be fast and efficient to remove paracetamol substance possess some drawbacks representing in high operational cost which make them not a desirable choice for treating wastewater. Biological process receives currently a significant attention for the removal of pollutants because it is found to be the most efficient technology which can be applied in degrading different pollutants. Regardless of its disadvantages, it has been found more efficient on degrading the paracetamol when compared to physicochemical processes. Furthermore, the combination between the biological and physicochemical processes overcomes all of the problems of processes that presented during treatment. Also, the combined processes improve the paracetamol degradation rate and reduce the treatment costs.
Keywords: Biodegradation, biological and physicochemical process, Paracetamol.

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Address for Correspondence:
Wadhah Hassan Ali Edrees, Microbiology Division, Biology Department, Faculty of Science, Sana'a University, Yemen, E-mail: *edress2020@gmail.com*

INTRODUCTION
Paracetamol, also known as acetaminophen, 4-acetamidophenol, N-(4-hydroxyphenyl) acetamide ($C_8H_9NO_2$) Figure 1, and consists of a benzene ring core substituted by one hydroxyl group and the nitrogen atom of an amide group in the *para* (1, 4) pattern. It is very common over the counter analgesic used for fever, headaches, and other minor pain[1].
Paracetamol is one of the most frequently used drugs worldwide[2]. In Yemen, it is ranked as first of top ten drugs produced by local industrial and one of the top ten drugs imported[3]. Also, it was consumed as the second pharmaceutical products in the year 2008 in Kuwait[4]. Paracetamol has been found with a concentration from 0.101–20.86 µg/l in the wastewater in Kuwait[4]. In the UK more than 65 µg/l in Tyne river[5], and 0.211 µg/l detected in a well supplying drinking water[6]. Frequent occurrence of this compound in environment and drinking water has raised a concern about their potential effects on environment and human health[7]. Previous studies on removal of paracetamol from wastewater mainly focused on chemical methods which may be undesirable choice method due to their generation of secondary pollutants, and the high operational cost[8,9]. The objective of this review work is to compare between physicochemical and biological treatment methods efficiency for paracetamol remove and degradation in aquatic environment. Moreover, it

will serve as a valuable source of data and literature for paracetamol degradation and remove from aquatic environment.

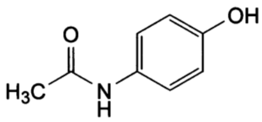


Figure 1: Chemical structure of paracetamol

Meanwhile this review will open the door to meaningful discussion on the application of physicochemical and biological methods in removing paracetamol from environment as well as advantages and disadvantages, and degradation routes for paracetamol.

Paracetamol degradation by physicochemical processes

The physicochemical treatment technologies have been explored with the intention of finding suitable for polishing techniques to further remove paracetamol concentrations from aquatic environment. These technologies include sand filtration, membrane separation, activated carbon, chlorination and oxidation processes[8,10,11]. The physical methods are losing acceptance since their main drawbacks are the transfer of pollutants from the liquid phase to a new phase instead of their elimination. These methods require post-treatments to remove the pollutant from the newly contaminated environment, enhancing in this way operational costs and diminishing effective viability[12]. It was reported that the paracetamol was removed by 57%, with mean and median concentrations in the sand filtration effluent of 8.58 ng/l and 4.5 ng/l, respectively[4].

Membrane processes

The use of membrane technology, particularly in wastewater treatment and reuse has received much attention since early 1990s. Four types of membrane processes are reverse osmosis (RO), ultrafiltration (UF), microfiltration (MF), and nanofiltration (NF) that were evaluated for removing the paracetamol from wastewater treatment plant (WWTP) and drinking water treatment plant (DWTP)[13,14]. The retention of micro pollutants in membrane processes can generally achieved by size exclusion, adsorption onto membrane, and charge repulsion[15]. The RO membrane was employed on WWTP and found that the more than 70% of paracetamol was removed[16]. The UF membrane was recorded to decrease the paracetamol from 0.018 µg/l to 0.017 µg/l from WWTP[10]. Another study applied the NF and UF membrane to retention the paracetamol and found that the <10% of paracetamol was retained by NF and UF[17]. The sand filtration was recorded to remove the paracetamol with efficiency 8.7% of paracetamol from WWTP. In contrast, the sand filtration was applied to remove paracetamol from WWTP and found that the paracetamol was decreased from>500µg/l to 1.3µg/l with efficiency 99% remove[18]. Also, the dioxychlorination and sand filtration was used as a conventional treatment and UF, UV and RO as an advanced treatment to remove the paracetamol from DWTP (0.26µg/l). It was 14% removal of paracetamol found by conventional treatment and 99% by advanced treatment[14]. However, the studies on the use of RO/NF for pharmaceutical removal is limited and most of the studies employed NF and RO membranes for tertiary treatment in WWTP or for treating saline ground water[10]. However, the membrane processes such as OR and NF could in theory remove all pollutants, including dissolved organics, their operational costs are high because of high-energy requirements and membrane fouling. MF and UF are cost-effective options. Therefore, in water-reuse applications, UF or MF needs to be combined with biological processes[13].

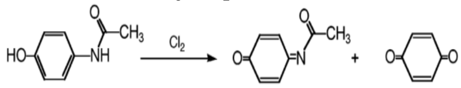
Activated carbon (AC)

AC is a recognized conventional technology for the removal of both natural and synthetic organic contaminants and commonly employed for controlling taste and odor in drinking water[19]. It is most commonly applied as a powdered activated carbon (PAC) or in granular activated carbon (GAC) form in packed bed filters[20]. The AC was employed the adsorb and remove the paracetamol compound from wastewater, surface water, and drinking water[21,22]. The PAC was applied to remove the paracetamol from wastewater and found that the >90% of paracetamol was reduced by PAC[10]. While, the AC was observed to remove 72% of paracetamol from DWTP after 4h[21]. Similarly, it was observed that the 58% of paracetamol (0.200µg/l) was removed by the AC from surface water[22].

However, it was pointed out that the decrease rate of paracetamol was 38% by a chemical flocculation system and 74% by a sand/activated carbon filter recorded in hospital WWTP. Also, the paracetamol (0.26 µg/l) which detected in source water was 69% removed by GAC filtration in DWTP[14]. The catalytic wet air oxidation of paracetamol on AC was reported that the 126.1 mg of paracetamol was removed completely after 2 h[23]. The main advantage of using AC to remove pharmaceuticals is that it does not generate toxic or pharmacologically active products[24]. It enhances the buffer capacity of a biological treatment system due to adsorption of the toxic compounds present, thereby decreasing the toxicity toward the microorganisms. Despite the effectiveness of AC, the major drawbacks for the use of AC is a quite expensive, non-selective, ineffective against certain pollutants, poor economic feasibility required a lot of energy and short lifetime, often due to low and expensive regeneration capacities. The regeneration of adsorbent after its use has several problems as it doesn't cost effective and not a straight forward method which results in loss of adsorbent[25].

Chlorination

Chlorination is one of the most common treatment processes for disinfecting wastewater and drinking water. Therefore, many pharmaceutical compounds are further subjected to chlorination treatment processes. Chlorine is strong oxidant on pharmaceutical compounds containing aromatic like paracetamol that rapidly react to form chlorinated compounds by the other substituents on the ring[26]. The presence of paracetamol in wastewater and drinking water raises the concern of whether or not the compound persist during chlorination treatment. It was reported that during chlorination of paracetamol, 11 different chlorination products were observed including the toxic substances N-acetyl-p-benzoquinone imine and 1,4-benzoquinone Figure 2, the latter being a toxicant associated with lethality in paracetamol overdoses[26].



I II III

Figure 2: Effect of chlorination on paracetamol

[(I)Paracetamol (II) N-acetyl-p-benzoquinone imine (III)1,4-benzoquinone.]

The study recorded that the 76.2% of paracetamol was degraded during the chlorination treatment[27]. Also, the 0.12 µg/l of paracetamol which found in water source in the DWTP was greater than 90% removed of these concentration by chlorination methods[28]. Similarly, the 70% of paracetamol was removed by using the free chlorine (3.5 mg/l dose)[11].

Advanced oxidation processes (AOPs)

Advanced oxidation processes (AOPs) are relatively new and effective technologies which have gained a lot of attention in the field of water and wastewater treatment in the past 30 years. AOPs are oxidation methods which degrade a wide range of pollutants by in situ formation of highly reactive radicals such as hydroxyl radical[29]. The major advantage of AOPs is their capability to destroy the organic pollutants completely without transferring them to another phase or producing secondary waste disposal troubles. AOPs consist of four main groups; (1) photochemical processes such as UV/H_2O_2, UV/O_3, and $UV/O_3/H_2O_2$, (2) photocataytic processes such as photo-Fenton and UV/TiO_2, (3) chemical oxidation such as ozonation (O_3), O_3/H_2O_2 and H_2O_2/Fe^{2+}, and (4) sonolytic processes such as ultrasound (US)[30,31]. Furthermore, several previous publications have been devoted to the study of paracetamol degradation in water using different AOPs.

Ozonation

Ozone technology has been employed to the treatment of waters primarily due to its strong disinfection and sterilization properties. The main mode of action in the ozonation process is the formation of OH **-**radicals due to ozone decay in the water, but there is also ozone molecules present for chemical attack which increases the oxidation capacity[32]. The use of ozone as a means of breaking down paracetamol in water has been the subject of numerous studies over the last ten years[8,11,14]. The ozonation and H_2O_2/UV systems were applied for the complete mineralization of paracetamol (5.0×10^{-3} mol dm^{-3}) in aqueous solutions. After 120 min, the paracetamol mineralization was 30% by ozonation at pH 2.0 and 40% by H_2O_2/UV at pH 7.0 recorded[8]. In similar, it was recorded that the 94% of paracetamol was degraded in 24 h by the oxidizing system in the drinking water treatment[21]. The oxidative removal of paracetamol (0.117 µg/L) from Colorado River water was evaluated by using O_3 (2.5 mg/L) and O_3 combined with H_2O_2 (0.5 mg/L) and found that the >99% of paracetamol was removed after 24 min by O_3/H_2O_2[31]. Also, the mineralization of paracetamol (157 mg/L) in pH 3.0 by the use O_3, O_3/UV,$O_3/Fe^{2+}/UV$ and $O_3/Fe^{2+}+Cu^{2+}/UV$ systems was studied. The paracetamol was completely degraded in 6 min by this oxidation process[34]. The degradation of paracetamol (157 mg/L) by direct ozonation and ozonation catalyzed with Fe^{2+}, Cu^{2+} and/or UV light at pH 3.0 was studied and found that the 83% of paracetamol was mineralized in 4 h[35]. Similarity, it was observed that the more than 70% of paracetamol was removed by using the ozone (2.5 mg/l dose)[11]. Also, it was found that the paracetamol was removed from DWTP after ozonation with a varying efficiency 68%[14]. The main disadvantage of ozonation is that in general the target compounds are not completely mineralized, but merely transformed, and so even more harmful substances can be produced as a result[36].

Fenton reactions

The Fenton and photo-Fenton process involves the reaction of ferrous ions (Fe^{2+}) as a catalyst and hydrogen peroxide (H_2O_2) as an oxidizing agent under UV/visible radiation to form active oxidant species, mainly hydroxyl radical, which oxidize organic compounds when they are present in aqueous solution. Compared to other oxidants, hydrogen peroxide is not expensive, not dangerous, easy to handle and poses no lasting environmental threat since it readily decomposes to water and oxygen[37]. Fenton process has been used and applied for the degradation and mineralization the paracetamol in aquatic and wastewater. The electro-Fenton and photoelectro-Fenton processes were applied to remove the treatment of wastewater containing 5 mM of paracetamol and recoreded that the 89% of paracetamol was removed by the electro-Fenton and 97% by photoelectro-Fenton method[38]. However, the ultrasound process was evaluated for degradation of paracetamol. After 4 h of sonolysis, the extent of degradation was 95%, 82%, 70% and 56%, respectively, for the reaction mixture initially containing 25, 50, 100 and 150 mg/l of paracetamol[31]. Similarity, it was observed that the 5 mM of paracetamol was 72% degraded by Fenton at pH 2.0 and 74% by electro-Fenton processes at pH 2.0 in aerator reactor in wastewater[39]. Recently, studies aiming at the application of Fenton's oxidation process into pretreatment of non-biodegradation industrial wastewaters have been reported[40]. In a Fenton's oxidation pretreatment process, the initially non-biodegradable organic compounds can be converted into more biodegradable intermediates, thus greatly enhancing the biodegradability of raw wastewaters[41].

In the Fenton's oxidation followed by biological oxidation process, non-biodegradable organic compounds can be partially oxidized to easy biodegradable organic intermediates and then be completely degraded in biological treatment system[42].

A further economic evaluation shows how the proposed treatment strategy markedly increases plant efficiency, resulting in an 83.33% reduction in reagent cost and a 79.11% reduction in costs associated with reaction time. Total cost is reduced from 3.4502 €/m^3 to 0.7392 €/m^3.

The electrochemical and photoelectrochemical process were applied to degrade the paracetamol (96 mg/l) in aqueous solution using reticulated vitreous carbon electrodes (RVC) at pH 5.0. The paracetamol concentration was 90% degraded by the electrolysis RVC in 4 h, 90% by the electrolysis with the modified electrode TiO_2/RVC in 2 h, and 98% by the electricatalysis ($CuO/TiO_2/Al_2O_3$/RVC) in 1 h[43]. The ultrasound/H_2O_2 and ultrasound/Fenton processes were investigated for the paracetamol degradation (100 mg/L) in aqueous solution. The optimal conditions of sono-Fenton process guarantee a mineralization higher than 60% are 4.7 mmol/l of Fe^{2+} and 14.4 mmol/l of H_2O_2[44]. Despite the effectiveness of Fenton and photo-Fenton, the main drawbacks of these technologies as a wastewater treatment system are mainly related to the need for pH control and the problem of sludge generation[45].

TiO_2 photocatalysis

Photocatalysis is the acceleration of a photochemical transformation by the action of a catalyst such as titanium dioxide (TiO_2) or Fenton's reagent. TiO_2 photocatalysis, one of the most promising AOPs, receives significant attention for the treatment of contaminated streams because of its chemical stability, nontoxicity, and low[46]. The major disadvantage of using TiO_2 in photocatalysis is its applicability to UV irradiation (λ <380 nm) only due to its wide band gap (3.2 eV). Sunlight is composed of 2% ultra-violet light, hence expensive light sources are often needed to activate TiO_2 and enable oxidation[47]. This type of treatment has been applied to remove the paracetamol from aquatic environment. The photocatalysis (TiO_2/UV) system was evaluated in promoting the degradation of paracetamol (1.0×10^{-4} mol/L) in aqueous solution. It was about 90% of paracetamol removed after a reaction time of 160 min[48]. The photo/photocatalytic oxidation of paracetamol (2.0 mM) was studied in aqueous TiO_2 suspension using UV and it was found that more than 95% of paracetamol was degraded within 80 min[30]. Also, the photodegradation of paracetamol was investigated in 1.0g/l TiO_2 suspended solution and found that the 95% of paracetamol was removed in 100 min[49]. Similarity, the photocatalysis (UV/TiO_2) was applied to remove the paracetamol (4 mM) and found that more than 80% of paracetamol was degraded after 30 min[50]. Also, the influences of dosage TiO_2 on paracetamol degradation was investigated and found that the degradation of paracetamol were 100%, 80% and 50% observed at initial concentration of paracetamol 100, 200, and 500 mg/l respectively at 240 min[51].

Electrochemical treatment

Electrochemical technology can be defined as an anodic oxidation that is able to attain the oxidation of pollutants from water or wastewater, either by direct or by mediated oxidative processes originated on the anode surface of an electrochemical cell[52]. The treatment of paracetamol using anodic oxidation with a Boron-doped diamond (BDD) electrode has been successful investigated in small scale on the oxidation of paracetamol. It was found that anodic oxidation with BDD was a very effective method for the complete mineralization of paracetamol up to 1 g/l in aqueous medium within the pH range 2.0–12.0[9]. Also, the electrochemical was applied for paracetamol degradation from water by using a catalytic action of Fe^{2+}, Cu^{2+}, and UV light on electro generated H_2O_2. Total mineralization of paracetamol (157 mg/L) is achieved when Fe^{2+}, Cu^{2+}, and UV light are combined at pH 3.0 and 35°C in 6 h[53]. Also, the paracetamol (157 mg/l) mineralization was carried out at pH 3.0 using a Pt anode and an O_2-diffusion cathode in the presence and in the absence of Fe^{2+}, Cu^{2+} and/or UV light as catalysts. It was observed the complete (100%) degradation of paracetamol in 75 min[33].

Paracetamol degradation by biological processes

Biological processes most frequently use microorganisms, plants, and adsorption on living or dead biomass. Microbes degrade or convert the pollutants in an effective way. In both cases, whether it is a degraded or converted product, it is very important to confirm that the end product is more stable than the parent compound and less toxic[54,55]. Biodegradation will generally occur during secondary treatment in the WWTP. The biodegradation of compound depends on a number of factors, such as: stereochemistry, toxicity, structure, and concentration of the compound, efficiency of the microbial strain, conditions during degradation, retention time, and presence of other compounds and their concentration[54]. The advantage of biological treatment is the enormous adaptability of microorganisms to a wide variety of substrate media, but this is a long term treatment in large physical areas and leads to the generation of non-biodegradable, soluble, and cellular residues, and also the high salinity of the effluent inhibit the microbial growth[56]. A few researches on the removal of paracetamol in WWTPs have been focused on biological treatment processes. According to this research, the paracetamol is known to show good removal efficiencies by biological treatment processes due to its high biodegradability[7,57,58]. Biological degradation of paracetamol can be achieved by anaerobic, aerobic, microorganisms (bacteria and fungi), membrane bioreactor, and phytoremediation.

Anaerobic treatment

Anaerobic technology was used earlier for treating wastewaters of different industries. In anaerobic treatment, the high organic content in industrial wastewater decomposes into methane and CO_2 with the help of microorganisms. The advantages of anaerobic treatment are very little sludge production, with lower energy inputs, operation at high organic loading rate, operating cost, need of low nutrient amount and production of biogas[59]. High bacterial sensitivity to some environmental conditions, long starting processes, not good at removing non-organic pollution within wastewater, and the production of malodorous compounds, have been commonly cited as disadvantages of anaerobic treatment[60].

The anaerobic biodegradation of paracetamol was studied by using sludge enriched with humic acid in WWTP and found that the 90% of paracetamol was degraded in six months with pH (7.0)[61]. Also, it was reported that the 87.8% of paracetamol (2.70µg/L) was removed by anaerobic fluidized bed reactor and 97.9% by anaerobic fluidized membrane bioreactor[62]. Similarly, it was found that the anaerobic packed-bed reactor has a good ability to treatment the brewery wastewater containing paracetamol concentration from 5 to 15 mg/l[63].

Aerobic treatment

Aerobic condition accelerate biodegradation at a much faster rate and to a greater than anaerobic condition in a given time period. Advantages of aerobic systems include higher ability of elimination of soluble biodegradable organic matters and lower suspended solid concentration in the effluent[64]. The aerobic treatment in WWTP was recorded to reduce the paracetamol concentration form 1000 µg/l to less than 0.010µg/l from wastewater[18]. Also, the treatment of paracetamol was achieved by sequencing batch reactor (SBR) with aerobic granular sludge that consisted of a wide variety of bacteria, mainly including coccoid-like and rod-shaped bacterium and found that the paracetamol was removed by SBR[65]. However, the biodegradation of paracetamol was carried out by aerobic granules using SBR which are consisted of consortia of coccus and bacillus bacteria. The granular sludge on day 80 and 200 degraded paracetamol (1000 mg/l) completely in 48 h and 28 h, respectively, indicating that granulation contributed to paracetamol degradation. The specific paracetamol degradation rate was observed to increase with increasing paracetamol initial concentration from 500 to 5000 mg/l. Paracetamol up to 1000 mg/l could be effectively degraded and mineralized by this consortium[66]. In aerobic processes, the disadvantages are: (1) usually produce a digested sludge with very poor mechanical dewatering characteristics, (2) have high power costs to supply oxygen, even for very small plants, (3) are significantly influenced in performance by temperature, location, and type of tank material, (4) no heavy metal removal, and (5) lack of useful by-product[67].

Activated sludge (AS) process

This process is the most common one utilized biological process in many WWTPs as a secondary treatment. It is capable of converting most organic wastes to stable inorganic forms by oxidizing organic matter into CO_2 and H_2O, NH_4 and new biomass under aerobic conditions. The new biomass production excess is the main drawback of biological treatment since a posterior management is required prior to its disposal[56]. A number of reports have been published about the degradation rate and remove of paracetamol by AS in WWTP and sewage treatment plant (STP). The paracetamol concentration between (0.96 µg/l to 100 mg/l) have been removed completely (100%) or more than 90% by AS process[57]. In similar, it was recorded that the paracetamol was reduced from 246 µg/l to 4.3µg/l by AS process in STP[58]. Also, it was reported that the paracetamol (69.57 µg/l), which presented in the raw effluent, was completely eliminated by AS[5]. Similarly, the paracetamol concentration was 100% removed in WWTP by AS system[68,69].

Membrane bioreactor (MBR)

The MBR has been used for the large-scale wastewater treatment of industrial wastewater and have become an alternative to conventional AS processes for wastewater treatment. MBR technology is considered the most promising development in biological wastewater treatment[70]. The advantages of MBR are full removal of suspended solids, compact plant size, efficiently in degradation, flexibility in operation, little sludge production, disinfection and odor control, prolonged microorganisms retention time and treatment of toxic organic and inorganic contaminants[55]. The main disadvantage of MBR is high energy usage to reduce the fouling problem. Coupling of fluidized bed reactor with membrane reactor was found to potentially reduce the membrane energy cost[71]. Several reports have explored the removal of paracetamol from WWTP or STP to evaluate the MBR system efficiency. It was found that the biodegradation of paracetamol was completely degraded by MBR[31]. Similar result was also reported that the paracetamol was decreased from 0.015µg/l in source drinking water to 0.0003µg/l in finished drinking water with the efficiency 98% removal[28]. Also, it was recorded that the paracetamol was reduced from 43.223µg/l to 0.031µg/l in WWTP[72]. Biological treatment combined with membrane filtration is also employed for treating wastewater. The combined between the MBR equipped with hollow-fibre (HF) UF membrane in in WWTP with using pilot-scale was applied to remove the paracetamol from the aqueous phase. It was showed that the paracetamol was completely removed from wastewater[68].

Microorganism's degradation of paracetamol

Microorganisms play a vital role in the degradation of xenobiotics and in maintaining the steady-state concentration of chemicals in the environment[54]. Microorganisms have established effective strategies involving specialized enzyme systems and metabolic pathways to access paracetamol as a carbon and energy source. Thus, such microorganisms are capable of degrading paracetamol and converting them to easily metabolizable substrates[7].

The essential characteristics of aerobic microorganisms degrading organic pollutants are:

1. Metabolic processes for optimizing the contact between the microbial cells and the organic pollutants.
2. The initial intracellular attack of organic pollutants is an oxidative process, the activation and incorporation of oxygen is the enzymatic key reaction catalyzed by oxygenases and peroxidases.
3. Peripheral degradation pathways convert organic pollutants step by step into intermediates of the central intermediary metabolism.
4. Biosynthesis of cell biomass from the central precursor metabolites[73].

Some of bacteria and fungi which are capable of using paracetamol as carbon and energy source have been described. Further, a microbial consortia involving fungal and bacterial cultures for treatment were found effective in removing the paracetamol[65,74]. The advantages of microbial degradation and mineralization of paracetamol are representing in the producing nontoxic byproducts and reducing the environmental impact of the treated water on the receiving surface and drinking water supplies[75].

Bacterial treatment

Some bacteria have been reported to use the paracetamol as the sole carbon, nitrogen, and energy resource for growth as well as capable of degrading and converting it to nontoxic compounds. Also, the biodegradation performance of patacetamol by bacterial consortia were much better than any pure bacterial strain due to a potential complementary interaction among the different bacterial strains[65,74]. The first study was aimed to isolate and characterize of a new paracetamol and 4-aminophenol degrading microorganism from wastewater contaminated site of a pharmaceutical plant. Detailed studies identified the organisms as *Pseudomonas* sp. strain ST-1 and capable of using phenol 4-aminophenol (4000 mg/l) and paracetamol (4000 mg/l) as sole source of carbon and energy. The optimal conditions for growth were recorded at 30°C and pH 7. Non growing suspended cells of strain degraded 68% of 4-aminophenol and 76.8% of paracetamol in 72 h. This strain may contribute to efforts on phenolic bioremediation, particularly in an environment with very high levels of paracetamol and 4-aminophenol[76]. However, it was recorded that the *Pseudomonas* sp. strain ST-4 was grown on mineral salt media plates containing 400 ppm of 4-aminophenol as growth substrate and found to be able to degrade it up to 84%. Biodegradation was found to be more effective than autoxidation of 4-aminophenol, indicating bioremediation as main process to eliminate aromatic amines[77]. Also, it was reported that two paracetamol degrading strains were isolated from the membrane bioreactor biomass and identified as *Delftia tsuruhatensis* and *P. aeruginosa*. It was found that the 97% and 40% of paracetamol concentration were removed by *D. tsuruhatensis* and *P. aeruginosa*, respectively, in 48 h[75].

Furthermore, three bacterial strains which capable of degrading paracetamol were isolated from a high efficiency paracetamol degrading aerobic granules. These strains were identified and assigned to be *Cupriavidus* sp. strain F1, *Lysobacter* sp. strain F2 and *Pseudomonas* sp. strain Fg-2. The optimal conditions for the growth of the strains were all at 25~35℃ and pH 7~8. The strains F1, F2, and Fg-2 were able to degrade paracetamol up to 400 mg/l, 2500 mg/l and 2000 mg/l, respectively. The hydroquinone 1,2-dioxygenase and catechol 1,2-dioxygenase enzyme were found with high activities in all strains extracts which suggested these enzymes might play important roles in degrading paracetamol. It was suggested that the synergistic effect exerted by different strains in the microbial consortia possibly strengthened biodegradation of paracetamol[65]. Moreover, it was isolated the paracetamol degrading bacteria from activated sludge samples and identified as *Cupriavidus necator*. The optimal pH 7.0 and temperature 30℃ were found for *C. necator* biodegradation in shaking flasks. This strain was found completely degrading of paracetamol at the initial concentration of 400 mg/l in 48 h. The maximum specific growth rate and yield coefficient were 0.097 h^{-1} and 0.21 mg/mg recorded, respectively. The results indicated that this strain had a high mineralization extent for paracetamol[78]. *Pseudomonas aeruginosa* strain HJ1012 was isolated from stable microbial aggregate in a sequencing batch reactor treating paracetamol contaminated wastewater. This organism could completely degrade paracetamol as high as 2200 mg/l within 75 h of reaction. It is degraded predominantly via p-aminophenol to hydroquinone with subsequent ring fission, suggesting partially new pathways for paracetamol degrading bacteria[79]. Three bacterial strains were isolated from a paracetamol degrading aerobic aggregate, and assigned to species of the genera *Stenotrophomonas* sp. strain Fg-2 and *Pseudomonas* sp. strain F1 and F2. The *Stenotrophomonas* sp. was found the first time known to be as the paracetamol degraders. In batch cultures, the strain F1, F2, and Fg-2 could perform complete degradation of paracetamol at concentrations of 400, 2500, and 2000 mg/l or below in 116 h, 60 h, 45 h, respectively. A combination of three microbial strains resulted in considerably enhanced degradation and mineralization of paracetamol. These strains were able to use up to 4000 mg/l, and mineralized 87.1% of the added paracetamol at the initial of 2000 mg/l[74]. Mixed microbial communities have the most powerful biodegradative potential because the genetic information of more than one organism is necessary to degrade the complex mixtures of organic compounds present in contaminated areas. The genetic potential and certain environmental factors such as temperature, pH, and available nitrogen and phosphorus sources, therefore, appear to determine the rate and the extent of degradation[73]. Therefore, the synergistic effects on the paracetamol degradation in the co-culture of microorganisms may be attributed to their metabolic products in the consortia. The synergistic enhancement of degradation efficiency in consortia can result from the cooperative effects as a result of different complementary biochemical compound degradation pathways in the strains, assimilation of compound onto cell membrane and changes of cell hydrophobicity by excreted substances, removal of compound metabolites by one strain that inhibit other strains, and significant increase of biomass using surfactants as a primary carbon source. *Pseudomonas mendocina* was isolated from wastewater and applied to degrade the paracetamol. It was found that this strain able to grow in paracetamol concentration from 500 to 1000 mg/l and degraded it in 48 h[80]. *Pseudomonas* species are environmental organisms known for their ability to degrade aromatic compounds of environmental concern[81]. The adaptability of *Pseudomonas* species to different organic compounds makes it an attractive organism for its use in biodegradation for wide ranges of organic substances that present in WWTP.

Fungal treatment

Fungi are known to degrade a wide variety of materials and compounds, process known as mycodegradation. Living fungi are employed in degradation of persistent organic pollutants due to their unspecific oxidative enzymatic system, which includes ligninolytic extracellular enzymes as laccase and peroxidases, as well as intracellular enzymes as the cytochrome P450 system[82,83]. Few studies up to now have been reported about the use of fungi and their enzymes to remove or degrade the paracetamol. It recorded the first studies of paracetamol removal with fungi strains which isolated from a solution of paracetamol and identified as a *Penicillium* sp. This strain was found to possess the ability to utilize a paracetamol as sole carbon sources for growth. Studies with washed-cell suspensions indicated that growth of the *Penicillium* sp. isolate in the presence of paracetamol induced the respective enzyme systems for the degradation of this compound to acetate and 4-aminophenol[84]. However, the study was carried out the treatment paracetamol using a *Trametes versicolor* pellets fungi in a batch fluidized bed bioreactor under sterile and non-sterile conditions. The initial total amount of paracetamol into the reactor was between 109.3 µg/l–114.4 µg/l. The paracetamol concentration was completely removed after 8 days[85].

Also, the two fungal enzymes, laccase (*Trametes versicolor*) and tyrosinase (mushroom) were combined into crosslinked enzyme aggregates by using a chitosan. The crosslinked enzyme was applied for the paracetamol transformation from wastewater samples. The paracetamol transformation was achieved of more than 80% to nearly 100% from the municipal wastewater and of more than 90% from the hospital wastewater by crosslinked enzyme[86].

Phytoremediation

Phytoremediation technology, green bioremediation, is a developing low-cost technique for removal of heavy and hazardous metal ions from industrial wastewater. In such case, phytoremediation that use the natural or transgenic plants proves a better treatment tool for bio-treatment is able to bioaccumulate the toxins[87]. Phytoremediation techniques are relatively manageable and allow a fast adaption to a specific area as well as not require large investment to be practically introduced. Furthermore, they are cost friendly as they are able to remove several pollutants at once and can be applied at a small as well as at a large scale[88]. In the study that was used a hairy root culture of horseradish (*Armoracia rusticana* L.) to remove the paracetamol with concentration 1 mM in the growth medium. The result showed that 70% of paracetamol was decreased after 3 h of incubation[89]. However, it was carried out the treatment of paracetamol with the help of *Armoracia rusticana* and *Linum usitatissimum* in hairy root cultures and hydroponically cultivated with the *Lupinus albus*, *Hordeum vulgaris*, and *Phragmites australis* plants in laboratory conditions. It was found that the 100% (160 mg/l) and 50% (30 mg/L) of starting amount were removed during 8 days by *A. rusticana* and *L. usitatissimum*, respectively. *A. rusticana* have been found the ability to remove paracetamol (600 mg/L) completely from the medium. The paracetamol in concentrations of 0.1 mM (15.12 mg/L) was 100% by *L. luteolus*, 83% by *H. vulgare* and 16% by *P. australis* removed from media during 4 days[88].

In the case of Hordeum, paracetamol was fully removed during 2 days and partially released back to the media at the end of experiment. Based on this observation, it is possible to suppose, that paracetamol is stored in vacuole and released because of toxic effect of paracetamol to Hordeum plant[88]. The experiment was evaluated the efficiency of sugar cane bagasse (SCB) and vegetable sponge (VS) (*Luffa cylindrica*) plants and compared with AC for removing paracetamol (100 µM) from aqueous media. The results showed that SCB was more attractive than AC in terms of price and efficiency (60% against 45% adsorption, respectively), while VS was responsible for removing 40% of paracetamol dissolved in the enriched water samples[90]. Similarly, it was carried out the remove of paracetamol from contaminated water with the help of plants duckweeds, *Lemna minor* and *Spirodela polyrhizza*. There was totally (100%) removed of the paracetamol after 7 days by duckweed plants[91].

CONCLUSION

The physical processes described previously have shown limited success for the treatment of paracetamol from aquatic environment. The regeneration of membrane filtration and activated carbon after use has several problems representing which affect on efficiency to reject and adsorb the paracetamol and disposable it again to environment as parent compound without degradation. The chemical processes such as advanced oxidation processes have effectively degraded paracetamol from the aquatic environment in few hours. The cost of chemical agents and the energy sources are the major disadvantage on using chemical methods to remove the paracetamol from wastewaters. Methods which produce fewer intermediates must to allow for effective modeling and application are being developed to implementation the industrial wastewater treatment. However, the combination between physicochemical processes accelerates the paracetamol degradation and reduces the cost of the treatment process. Biological process is considered to be the most crucial process for the removal of paracetamol present to a large extent in the dissolved phase in WWTP. It is showing higher removal rates of paracetamol. In the biological process, the use microorganisms exhibited a highly selective removal efficiency towards the target pollutants and it can be stated that is more appropriate for environment cleanup of pollutants. So by developing an understanding of microbial communities and their response to the natural environment and pollutants, expanding information of genetics of the microbes to increase capabilities to degrade pollutants, researching for new biodegradation techniques which are cost effective, these opportunities offer potential for significant advances. The drawbacks of use biological process are take more period for degradation, seasonal variation of the microbial activity as a result by direct exposure to changes in environmental factors that cannot be regulated and problematic application of treatment additives. However, the biological process is often highly specific and limited to some compounds that are biodegradable.

Regardless of which aspect of biodegradation that is used, this technology offers an efficient and cost effective way to treat contaminated ground water and soil. Its advantages generally outweigh the disadvantages, which is evident by the number of sites that choose to use this technology and its increasing popularity. The combination between the physicochemical and biological processes has increased attention recently. The combined process enhances the degradation rate and complete degradation the non-biodegradability as well as reduce the treatment process cost.

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