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Occurrence, ecotoxicology, removal of diclofenac by adsorption on activated carbon and biodegradation and its effect on bacterial community: A review

D. Cherik, M. Benali, K. Louhab*

Research Laboratory of Alimentary Technology, Faculty of Engineering Sciences, University of Boumerdes, Boumerdes 35000, Algeria

*E-mail address: louhab_ka@yahoo.fr

ABSTRACT

This paper reviewed the occurrence of diclofenac in the ecosystem, its ecotoxicology and its removal. Treatment technologies were based on two methods. Firstly, the physicochemical process namely adsorption on activated carbon thanks to its economic benefits. At the other end, the second method is biological process as biodegradation by activated sludge and membrane bioreactor. In this latter process diclofenac can affect the bacterial community in sludge and influence the efficiency of treatment or biodegradation.

***Keywords*:** diclofenac; adsorption; membrane bioreactor; conventional activated sludge; bacterial community

Contents

1. INTRODUCTION

Today, the occurrence of drugs in the aquatic environment has become a worldwide issue of increasing environmental concern [107]. Pharmaceutical products are consumed in very big quantity and present at very low concentrations (µg/L to ng/L range) [1-4,69]. They are presented in the environment via various human activities, including direct discarding of unused medication, liberates from pharmaceutical manufacturing plants [4], human and veterinary drug use [5,6]. Furthermore, PCs are also introduced to the environment as they are excreted from humans as unchanged compounds, metabolites or conjugates via urine and feces and enter the municipal sewage system [7,8,65,79,93] and are not eliminated in wastewater treatment plants [9,78,109]. They represent a threat to both public health and the environment [10-13] due to their physicochemical properties, particularly polarity, water solubility, persistence, microbial resistance [14,15] and bioaccumulation in the food chain [16]. Sewage treatment plays an important part in removing contaminants from reclaimed water but it's known that conventional wastewater treatment plants (WWTP) do not remove all the pollutants [98], especially the persistent polar pollutants due to their physicochemical properties [25,90,91].

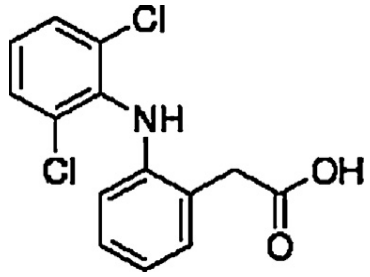
Most treatment methods of pharmaceuticals wastewater are physicochemical and conventional biological processes [17]. Activated carbon adsorption is frequent examples of physicochemical mechanisms [18-21]. Currently there are many adsorbents developed and reported for the removal of drugs pollutants from aqueous solutions and industrial effluents [22]. Biological wastewater treatment is one of the main important biotechnological processes [23,24] in which microorganisms are applied for removal of organic contaminants [4] and of which activated sludge Process [26,66] and membrane bioreactors are the most frequently used [83,85,89]. Most WWTPs use activated sludge processes where in microorganisms are utilized to mineralize the pollutants, or degrade them to acceptable forms. Pollutants can also be eliminated from water by denudation into air or by sorption onto sludge that is regularly discharged. Membrane bioreactors (MBR) combine the biological degradation of waste products with membrane filtration [84]. The use of MBR in wastewater treatment is becoming increasingly important, since their various benefits; high biodegradation efficiency, smaller footprint and less sludge production [87].

In these biological processes (activated sludge and membrane bioreactor) using microorganisms [145,147] such as ammonia-oxidizing bacteria for the removal of ammonium [151], Escherichia coli [155], Methanogens [156] and nitrite-oxidizing bacteria [140] and as micropollutants may affect the ecosystem and human health [10-13], they can also affect these bacterial communities as well as their microbial diversity [142-144,155] and thus this impact affects the proper functioning of the wastewater treatment plant [147], which explains the occurrence of micropollutants such as pharmaceutical residues in effluents of these treatment plants [9, 78 and 109], but unfortunately, there are few studies concerning the impact of micropollutants on the bacterial community.

Diclofenac (DCF), a non-steroidal anti-inflammatory drug [27,81] is one of the most extensively studied pharmaceuticals, for his potential toxic effects on no-target organisms [28]. Diclofenac was detected in wastewater [94,86] in a number of countries. According to published documents, the concentrations of this drug varied in a range from 0.01 to 8.5 µg/l [38,16] the rate of his elimination in sewage treatment plants is low (up to 40%) [29,123]. Table 1 present physicochemical properties and molecular structure of Diclofenac.

In this context, the objective of this study is to write a review of the literature by recent publications and studies in full and small scale between 2008s and 2015 on the presence of diclofenac in water, his toxicity, removal and effects on bacterial community. We inspect the performance of different water treatment systems in the elimination of this drug, particularly technologies that use adsorption on activated carbons and biodegradation with biological processes as well as activated sludge and membrane bioreactor plus an analysis of the influence of pharmaceutical residues and diclofenac on bacterial diversity in the sludge during its removal.

Table 1. Main characteristics of diclofenac.

Structure [a]	Molecular weight (g/mol) [a]	Log K_{OW} [a, b]	pKa [a]
	296.14	0.7-4.51	4.15

[a]; [30]
[b]; [156]

2. OCCURRENCE OF DICLOFENAC

The non-steroidal anti-inflammatory; diclofenac is the most habitually identified in the aquatic environment [31,80], including drinking water [32] and that is usually used to treat rheumatoid arthritis [31,33]. The occurrence of Diclofenac in wastewaters was observed in Asia countries such as Korea and Taiwan with concentration of up to 1 µg l^{-1} [54-57]. [34] Investigated the spatial distributions and seasonal variations of diclofenac (DFC) in the Huangpu River system (a drinking water source for Shanghai in China) over a period of practically two years and the concentration was 13.6 ng/l. [101] also investigated the occurrence of diclofenac in surface water (Beiyun River) of Beijing in three sampling events representing different seasonal flow conditions, diclofenac was detected with detection frequencies 100%, this high detection of diclofenac reflect his extensive use in Beijing.

The levels were the same in two seasons (March and June) with median concentrations 67 ng/l and 67.8 ng/l, respectively and 57.3 ng/l in September. This difference due to the period of seasons, where period from March to June is an arid season and the flow was low causal a higher levels and in September the season is moist and the flow was high causal a lower levels.

Table 2. Diclofenac concentrations detected in environment of various countries.

Country	Samples	Concentration (ng/l)	References
USA	drinking water	0.25	**[99]**
	effluent	<10	**[96]**
Taiwan	Drug production facilities	20733	**[54]**
	Hospitals	286	
	effluent	61	
	Regional discharges	84	
	Animal husbandries	4	
	Aquacultures	4	
	Hospital	10	**[55]**
	Influent	58-367	**[105]**
	Effluent	25-182	
China	River system (drinking water)	13.6	**[34]**
	Pearl Rivers water	1.1	**[100]**
Korea	Influent	131	**[57]**
	Effluent	24	
Spain	Urban wastewater	570	**[59]**
	Industrial wastewater	140	
	Effluent	<15	**[60]**
Serbia	Municipal waste water	1338	**[64]**
	Surface water	<324	
Greece	Influent wastewaters		**[62]**
	- Ioannina City	100.8	
	- Ioannina hospital	180.7	
	- Arta	106.9	
	- Preveza	1346.0	
	- Agrinio	98.8	
	- Grevena	78.3	
	- Kozani	83.1	
	- Veroia	-	
	Effluent wastewaters		
	- Ioannina City	98	
	- Ioannina hospital	63.2	
	- Arta	162.5	
	- Preveza	56.1	
	- Agrinio	154.9	
	- Grevena	-	
	- Kozani	97.1	
	- Veroia	145.6	
Portugal	Seawater	30.6	**[58]**

These results confirm the results found by [119] where they observed that concentrations average of diclofenac is bigger in the dry season than the wet. In Western Balkan Region such as Serbia [64] studied the occurrence of 81 pharmaceuticals drugs using solid-phase extraction and the presence of this pharmaceuticals compounds was analyzed by Ultra-High Performance Liquid chromatography coupled to mass spectrometry with hybrid triple quadrupole–linear ion trap (UPLC–QqLIT–MS/MS), Results shown the presence of Diclofenac with concentration of 1.34 µg/l in Danube River with frequency of occurrence 11.11%. [96] Were surveyed monthly for 12 months the presence of this drug after different steps of treatment in an advanced wastewater reclamation plant in Gwinnett County, GA, U.S.A. The results show that diclofenac was detected in primary effluent with 220 ng/l of average concentration, 99 ng/l in membrane effluent, granular active carbon effluent and final effluent with average concentrations below 10 ng/l. Diclofenac was also detected in Spain [59,60,73], in Greece [62,110], in USA [97], in Sweden [63], Portugal [58,67], Rio de Janeiro in Brazil [88] and in South Wales region of the United Kingdom (UK) [61,95]. In the African continent diclofenac was detected in the concentration range of 1.1-15.6 µg/l in South Africa [152]. Table 2 shows the concentrations of diclofenac detected in WWTPS of various countries. Note that concentrations in WWTPS effluents in Asia countries such as Taiwan [54,105] (from 25 ng/l to 182 ng/l) are more than in Europe [60] (<10 ng/l) and America [96] (<15 ng/l) countries.

3. ECOTOXICOLOGY OF DICLOFENAC IN

The removal percentage of DCF during wastewater treatment processes typically ranges from 21% to 40% [29], which justifies their occurrence in surface water, groundwater and even in drinking water at very low concentration [34, 35] and adverse effects in different organisms were observed with high BOD, COD [106]. It has considered being a very toxic anti-inflammatory due to the recorded death of birds shortly after scavenging on contaminated livestock in India and Pakistan [35, 36]; it has showed a potential endocrine disrupting influence by delaying and reducing hatching success of fish eggs and low concentrations damage digestive organs [36]. [92] Suggested that the anti-inflammatory drug diclofenac caused oxidative stress and reduced testosterone level that can has a negative impact in aquatic organisms. [111] explained the effects of three drugs, diclofenac, ibuprofen and propanol on Baltic Sea blue mussels using Mytilus edulis trossolus as a model organism.

The uptake and stress engendered in Mytilus edulis trossolus from exposure to diclofenac was studied using the two physiological indicators; strength and abundance of byssus threads, and scope for growth (SFG). Results shows that exposure to diclofenac would lead to bio concentration in the mussels, and negatively affect the regeneration of the byssus threads (weaker and lower abundance of threads) and decrease the scope for growth. [112] studied the effect of diclofenac exposure over 15 days (250ng/l) in mussel Mytilus galloprovincialis and evaluated the responses of biomarkers in the mussel tissues; this study show that mussel were affected during initial days.

The antioxidant system was rapidly triggered, mostly in the gills; evidence of damage was observed in digestive glands. DCF made a direct relationship between the acetylcholinesterase activity and the vitellogenin-like protein levels in females. [113] also studied the effect of diclofenac exposure on the marine mussel (Mytilus spp.) and results

shows a lower response in the biomarker approach but with an induction of lipid peroxidation (LPO) after 96 h diclofenac potential in tissue damaging has been seen. [114] investigated the Toxicological effects of clofibric acid and diclofenac on plasma thyroid hormones of an Indian major carp, Cirrhinus mrigala during short (96 h) and long-term (35 days) exposures to different concentrations (1, 10 and 100 µg/l), this study demonstrated that diclofenac has a profound effect on plasma thyroid hormones an Indian major carp, Cirrhinus mrigala in short and long term. [118] evaluated also the effects of diclofenac on early life stages of common carp (Cyprinus carpio) during 30 days and the progress of carp performed to be delayed at the beginning of the test and any damaging impact was observed on the hatching and viability of carp embryos. [115] studied the consequences of exposure to diclofenac up to 3 months on two freshwater cladocerans (Daphnia magna and Moina macrocopa) and Japanese medaka (Oryzias latipes). Clear diminution of reproduction was observed at 25 mg/l for Daphnia magna, and at 50 mg/l for Moina macrocopa.

For fish (Oryzias latipes), the chronic exposure for 3 months of diclofenac at 0,001-10 mg/l causes an important reduction in hatching success and delay in hatch and at 10mg/l the hatching of eggs was completely interfered and Gonadosomatic index (GSI) of female fish was affected also, whereas fertility of the parent generation was not affected. [116] also evaluated the Toxicity screening of Diclofenac, Propranolol, Sertraline and Simvastatin using zebrafish (Danio rerio) and sea-urchin (Paracentrotus lividus) embryo bioassays, results show that effects of diclofenac has a delicate endpoints on hatching, 75% epiboly-stage, abnormal cellular growth and yolk-sac abnormalities these results were observed in [117], this consequence contributed to a significant rise of total abnormalities and high sensitivity of sea urchin embryos to diclofenac.

Diclofenac also has effects on the soil [120] studied his time dissipation and the consequences of exposure on Folsomia candida. The results indicated that diclofenac can exert severe effects on the survival of adult F. candida, so limiting the reproductive potential of the population and the impact of diclofenac on the neural system may be different in soil invertebrates compared to vertebrates.

4. CONVENTIONAL WASTEWATER TREATMENT OF ANTI-INflAMMATORY DICLOFENAC

4. 1. Adsorption on activated carbon

The adsorption process on activated carbon is most commonly used to remove diclofenac present in the aquatic environment thanks to its economic benefits to have an effective treatment of polluted waters [37,39,42,82].

The activated carbon is most collectively used thanks to his high surface area and its superficial chemical properties. The surface of the activated carbon is hydrophobic can contain functional groups. The latter contains heterosexuals-atoms to know l-hydrogen, the oxygen, nitrogen, chlorine and sulfur [40]. They depend on the nature of the activation and contribute to the acid or basic character of the surface [41]. By-products such as olive nuts [44], carbon nanotube [46], mesoporous silica functionalized with different organic moieties [74] and zeolite [51] can be valued and testified for the removal of diclofenac from aqueous solutions.

The activated carbon can be used in two forms; powder (PAC) and granular (GAC), activated carbon's ability to remove the pollutant depends on its properties as pH of point of

zero charge (pH_{pzc}) and the properties of diclofenac as its solubility in water and also the reaction parameters namely the contact time, the dose of activated carbon, reaction temperature and the pH of solution [40]. Several studies have demonstrated the efficiency of the elimination of diclofenac on the activated carbon powder (PAC) or granular (GAC) (Table 3). [1] investigated the efficiency removal of diclofenac by two commercially available activated carbon; Clarimex 061 CAE and Epibon YM 12X40.

This study showed that the increase in concentration of diclofenac from 10 mg/ l to 50 mg/ l promotes the elimination rate of 68% to 99%, respectively for Clarimex 061 CAE, by against in the case of the use of Epibon the elimination rate the rate of elimination decreased from 82.70 % to 70.20 %. [157] exanimated the correlation between the coefficient of partition octanol-water ($\log K_{ow}$) and the adsorption, they found that by increasing the concentration of diclofenac which is a hydrophobic compound, the adsorption was better presented by the Freundlich isotherm ($R^2 > 0.92$) which is positively correlated with $\log K_{ow}$ ($R^2 = 0.8397$).

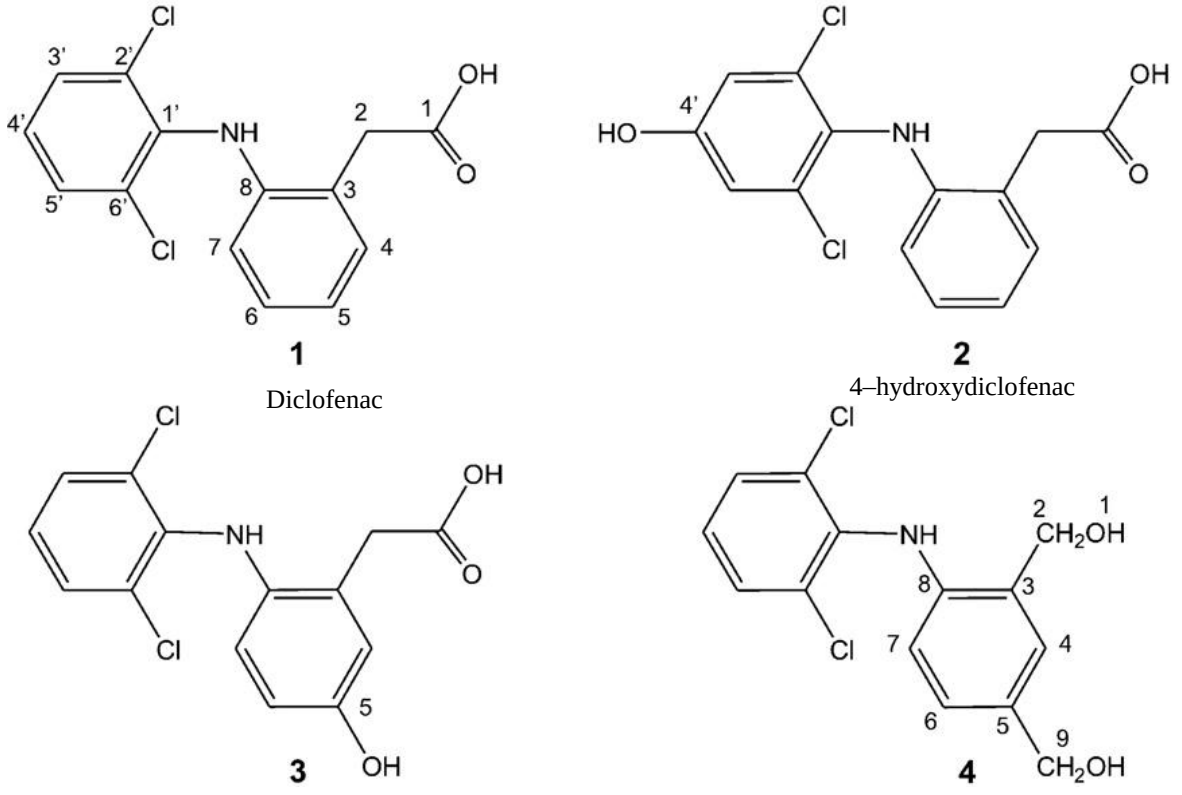


Fig. 1. Structures of diclofenac and the degradation products identified by NMR [70].

Table 3. Key publications on diclofenac adsorption on activated carbons.

Reference	Adsorbent	Experimental conditions	Observations	Adsorption capacity
[43]	Isabel grape bagasse	$[C_0]$ = 5-30 mg l^{-1} T = 22°C V = 25ml Carbone dose = 5mg pH = 5 time contact = 72h	Isabel grape bagasse before being crushed and sieved to a particle size less than 150 µm. After this procedure, the adsorbent was used without any physical or chemical pretreatment.	q_e= 5.12-23.77mg g^{-1}
[44]	GAC (from exhausted olive-waste cake)	$[C_0]$ = 14.8 mg l^{-1} T = 25°C V = 300ml Carbone dose = 100-450 mg pH = 4.1 time contact = 26h	Activated carbon was produced via chemical activation using phosphoric acid	q_e= 13.776 mg g^{-1}
[45]	functionalized silica-based porous materials	$[C_0]$ = 100 µg l^{-1} T = 25°C Carbone dose = 2 g l^{-1} time contact = 4 h pH = 7	Modification of HMS with either aminopropyltriethoxy or 3 mercaptopropyltrimethoxy (for amine- or mercapto- modification, respectively) was performed by a co- condensation method following the procedure described by Lee et al. [20]. SBA-15 was prepared under acidic conditions according to the synthesis procedure described by Zhao et al. [27], whilst MCM-41 was synthesized under basic conditions following the procedure described by Kim et al. [28]. The procedures for synthesis of the adsorbents used in this study were described in Supplementary information, pages 10–11.	q_{eHMS} = 31.93 mg g^{-1} q_{eM-HMS} = 35.59 mg g^{-1} q_{eA-HMS} = 5.89 mg g^{-1} $q_{eSBA-15}$ = 34.18 mg g^{-1} $q_{eMCM-41}$ = 32.64 mg g^{-1} q_{ePAC} = 40.55 mg g^{-1}
[46]	granular carbon nanotubes/alumina hybrid	$[C_0]$ = 15.5 µmol l^{-1} T = 25°C Carbone dose = 25mg time contact = 72 h pH = 6	The granular CNTs/Al2O3 hybrid adsorbents with the CNTs/Al2O mass ratios of 1:1, 1:3, 1:5, 1:7 and 1:9 were prepared by a solegel method (granular adsorbent cannot be prepared at less alumina content than 1:1). A certain amount of pseudo boehmite predetermined according to the mass ratio of CNTs/Al2O3 was adde. In to 10 mL of diluted nitric acid solution containing 0.04 g Brij 35.	$q_{max(CNTs/Al2O3)}$= 106.5µmol/g

Reference	Adsorbent	Experimental conditions	Observations	Adsorption capacity
[47]	activated biochars	$[C_0]$= 20 µM T= 25°C Carbone dose= 2g l^{-1} time contact= 72 h pH= 7	After stirring for 10 min, 0.2 g MWCNTs was slowly added into the mixture with vigorous 3 stirring for 10 min, and then five drops of diluted aqueous ammonia were added into the mixture to form the gel. The gel was dried for about 15 min at 80°C to remove the extra ammonia on the surface and then was granulated in the size of about 3 mm. The granules were aged at 25°C for 8 h, followed by drying at 50°C for 12 h. Finally, the dried granules were calcined at 450°C for 4 h with a heating rate of 2°C/min.	$q_{N\text{-}biochar}$ = 372 mg g^{-1}
[53]	GAC and PAC	$[C_0]$= 20 µM T= 25°C Carbone dose= 2g l^{-1} time contact= 72 h	Biochars produced by pyrolyzing torrefied loblolly pine chip (15*6 mm) at 300°C for 15 min were classified as either N-biochar or O-biochar in terms of pyrolysis with pure nitrogen or 7% oxygen with 93% nitrogen gas, respectively. Both biochars were activated by NaOH to increase the surface area and pore volume of the biochars. Biochars were milled and passed through a 200-mesh (74lm) sieve, and then stored with ultrapure water (2000 mg/L) for 24 h as a stock solution to hydrate prior to use; the designed dosages of biochar were confirmed by measuring control samples. Three NSAIDs One granular activated carbon and two powdered activated carbons	$q_{O\text{-}biochar}$ = 214 mg g^{-1} q_e = 87.4 µg g^{-1}
[49]	trimethylsilylated mesoporous SBA-15	$[C_0]$ = 100 µg/l T = 25°C Carbone dose = 1g l-1 time contact = 24 h pH = 5.5	Calcined SBA-15 (1.0 g) was Heated at 150°C in vacuo for 6 h and then slurried in anhydrous toluene (100 mL) for 1 h. Next, a five-fold excess amount of HMDS (3.0ml) in anhydrous toluene (50 ml) was added and stirring was continued at room temperature [21] for 24 h. The resulting product was filtered and washed with different solvents in the following order: toluene, acetone, ethanol, ethanol/water (50:50, v/v), water, ethanol, and acetone. The sample was then dried in vacuo at 150°C for 4 h and stored in a desiccator.	q_e= 87.40µg/g

Reference	Adsorbent	Experimental conditions	Observations	Adsorption capacity
[48, 50]	Carbone Xerogels	$[C_0]$ = 100 mg/l T = 31°C Carbone dose = 60 mg	A Carbon Xerogel (CX) was prepared by polycondensation of resorcinol with formaldehyde (with a molar ratio of 1:2). The original CX material was modified by	q_{eCX}= 32.4 mg g^{-1} q_{eCXN}= 33.8 mg g^{-1}

[51]	magnetic nanoparticles coated zeolite (MNCZ)	V = 25ml $[C_0]$ = 100 µg/l T= 31°C Carbone dose= 1g l-1 pH = 7 contact time=300 min	liquid phase, thermal and hydrothermal resulting in this production of 3 additional materials: - CX with Sulfuric acid resulting in the CXS material -CX with Nitric acid resulting in the CXN material -CXN with Urea solution (1mol l-1) resulting in the CXNUT material 0.5 g of zeolite was mixed with a 6.1 g FeCl3.6H2O and 4.2 g $FeSO_4.7H_2O$ and then dissolved in 100 mL using ultrasonication, as well as, the pH of the mixture was adjusted to 10.0 using 0.1 M NaOH. The mixture was agitated in a rotary shaker at 160 rpm for 24 h. Thereafter 25 mL of the 6.5 M NaOH was then slowly added and mixed with the above solution. The system was mixed for an hour following the addition of NaOH. The formed black precipitates were washed with ultrapure water several times; an external magnetic field was used to enhance the washing process. This procedure leads to form αFe_3O_4-Zeolite anoparticles with a size of around 10–20 nm. The αFe_3O_4-Zeolite was then oxidized at 300°C for 3 h to obtain YFe_2O_3-Zeolite (MNCZ).	q_{eCXNUT}= 38.7 mg g^{-1} q_{eCXS}= 40.2 mg g^{-1} q_e= 95.56 mg g^{-1}
[52]	the tissues of Cyclamen persicum tubers	$[C_0]$ = 70 mg/l T = 25°C Carbone dose = 0.7g pH = 4 contact time=120 min	the tissues of Cyclamen persicum tubers was prepared by the physical and chemical activation with Zncl2, H3PO4 and KOH	q_{max}= 22.22 mg/g

[43] studied the adsorption of diclofenac sodium on Isabel grape bagasse as adsorbent; the results showed that the percentage of elimination was from 16.4 % to 22.8 % and independent from the initial concentration of diclofenac sodium. The kinetics of adsorption have follows the model of pseudo second order and isotherms were presented by the model of freundlich, study thermodynamics showed that the process of adsorption was produced by an exothermic process accompanied with a reduction in the randomness at the solid/solution interface. [44] Also studied adsorption of diclofenac onto a low-cost activated carbon prepared from olive-waste cakes and the influence of reaction parameters such as pH and temperature. In this study the adsorption process also followed the pseudo-second-order kinetic and the increase of the pH of the solution influenced inversely on the rate of adsorption, on the other hand the temperature had no effect on the process. [53] Investigated the adsorption of diclofenac sodium onto three different commercial activated carbons (one granular carbon denoted C1 and two powdered activated carbon (denoted C2 and C3) possessing ~651, 1470 and 913 m^2g^{-1} surface areas, respectively at 303 K using batch adsorption experiments.

The characteristics of these materials were estimated; their textural, surface features and points of zero charge and the obtained results enabled to estimate the possibility to use the

activated carbons in the removal of diclofenac by adsorption. [45] Estimated the mechanism of adsorption of diclofenac on various types of adsorbents with mesoporous silicates and the commercial activated carbon, the adsorption process followed the pseudo-second-order kinetic and the adsorption isotherm was best described by a linear isotherm model. The modification of the hexagonal mesoporous silicates adsorbent (HMS) with mercapto functional caused an increase of the adsorption capacity and they explained this increase through improved hydrogen bonding between the hydrophobic interactions. [74] studied the adsorption of many pharmaceutical residues among them the anionic compound; diclofenac on mesoporous silica SBA-15 and its postfunctionalized counterparts with hydroxymethyl (HM-SBA-15), aminopropyl (AP-SBA-15) and trimethylsilyl (TMS-SBA-15) and found that its adsorption rate was not significant at pH = 5.5 on SBA-15, these results are similar to those of AP-SBA-15. For HM-SBA-15 the adsorption rate is improving slightly and with TMS-SBA-15 the rate exceeded 70%.

4. 2. Biodegradation of diclofenac

Biodegradation is the most commonly used to eliminate persistent pharmaceutical residues process. This process breaks down and mineralizes these pollutants by either bacteria or fungi in simpler compounds [149,150].

[68] investigated the transformation of diclofenac by pellets of Phanerochaete chrysosporium in fed-batch bioreactors operating under continuous air supply or periodic pulsation of oxygen. The performance of the fungal reactors was steady over a 30-day treatment and the effect of oxygen pulses on the pellet morphology was evidenced. Complete elimination of diclofenac was achieved in the aerated and the oxygenated reactors, even with a fast oxidation rate in the presence of oxygen (77% after 2 h), reaching a total removal after 23 h. [70] Assessed the degradation of diclofenac sodium using the white-rot fungus Trametes versicolor. The use of T. versicolor pellets to degrade diclofenac led to an unusual fast degradation rate at concentrations in the range of μg/l to mg/l in a defined liquid medium. In vivo and in vitro experiments using the cytochrome P450 inhibitor 1-aminobenzotriazole and purified laccase, respectively, suggested at least two different mechanisms employed by T. versicolor to initiate diclofenac degradation.

Two hydroxylated metabolites, 4-hydroxydiclofenac and 5-hydroxydiclofenac, were structurally elucidated by nuclear magnetic resonance as degradation intermediates in fungal cultures spiked with diclofenac. Both parent compound and intermediates disappeared after 24 h leading to a decrease in ecotoxicity calculated by the Microtox test. Laccase-catalyzed transformation of diclofenac led to the formation of 4-(2,6-dichlorophenylamino)-1,3-benzenedimethanol, which was not detected in in vivo experiments probably due to the low laccase activity levels observed through the first hours of incubation. Figure 1 shows the structure of diclofenac and its metabolites.

Biodegradation is considered the most important process for eliminating the majority of pharmaceuticals [68]. Sewage sludge is divided into two types; primary sludge after primary treatment [153] and secondary sludge after biological secondary treatments [23,24,76] in which microorganisms play a key role in removal of organic contaminants [4] and of which activated sludge Process (CAS) [26, 66] and membrane bioreactors (MBR) are the most frequently used [77] under aerobic or anaerobic condition [151].

Diclofenac is a polar pharmaceutical compound mostly used as the sodium salt diclofenac-Na in human and veterinary medicine to reduce inflammation and pain

[88,94,102]. Many studies have evaluated the biodegradation of diclofenac by conventional activated sludge and membrane bioreactors.

Diclofenac biodegradability in activated sludge and the membrane bioreactor process is influenced by various factors [149]; namely physicochemical properties of diclofenac and the operational parameters of wastewater treatment process including temperature, pH, concentration of biomass, hydraulic retention time (HRT), sludge retention time (SRT), biodegradation kinetics (K_{biol}) and redox conditions [79,130,132] and hydrophobic interactions [146]

Sorption of pharmaceutical residues on solid depends on the hydrophobicity of the molecule to be eliminated according to its coefficient octanol-water K_{ow} where when log K_{ow} <2.5 sorption is considered low and when logK_{ow} is between 2.5 and 4 is estimated an average sorption and a high sorption when logK_{ow} >4 [131,154]. Certainly, a long retention time (HRT) allows a very good interaction between diclofenac and polluted water [133].

4. 2. 1. Conventional activated sludge

In conventional activated sludge (CAS) the aeration tank and the final clarifier form one process unit. The separation of treated sewage and sludge happens in the clarifier via sedimentation. Therefore the capability to sediment is an important selection criterion. The biomass concentration in the mixed liquor is limited by the capacity of the clarifier [88].

Microbial degradation of diclofenac by activated sludge does not lead to its complete elimination but produces other metabolites which are also considered such as pollutants [139], these authors investigated the repartition of diclofenac in activated sludge, they detected 7 diclofenac transformation products among them 1-(2,6-dichlorophenyl)-1,3-dihydro-2H-indol-2-one and 2,3-dichloro-N-(phenyl)aniline.

Activated sludge is the most used in the biological treatment and the rate of elimination of diclofenac by this process was insignificant and does not exceed 50 % [122, 129 and 130]. [86] Confirmed this results when they investigated the performance of activated sludge to remove diclofenac and the results showed that this drug was not completely eliminated (21.8±28.5%). These results are in accordance with [108] who demonstrated that the removal of diclofenac was 48%. [24] studied the elimination of diclofenac by activated sludge in three WWTP and they showed that the removal rate was 60% for activated sludge presented by tertiary treatment in WWTP1, while for the other two stations the removal rate was <25%.

[75] Studied the biodegradability of the diclofenac on two types of sludge; sterilized and activated. Results of batch adsorption experiments via sterilized sludge showed that the removal efficiency was 40.1% at 6 hours and 19.7% for activated sludge where the contributions of sludge adsorption and biodegradation were 14.9% at 6 hours and 4.8%, respectively, The authors suggested that this difference in removal efficiency by sterilized and activated sludge is due probably by the sterilizing effect of the activated sludge which can be caused changes in the characteristics of the sludge and improves the elimination of diclofenac and also suggested that the structure of diclofenac (the electronic withdrawing groups) namely its functional groups (amine, halogen, and carboxylic groups) causes the resistance of diclofenac in its biodegradation.

[124] found that the biodegradation kinetics of diclofenac with activated sludge follows the pseudo first order model with a 0.87% correlation coefficient (R^2). These authors also confirmed the persistence of diclofenac to biodegradation. [125] investigated the biodegradation of diclofenac by nitrifying activated sludge and established the no removal of

diclofenac with this process, these results are consistent with those of [126] who have studied the removal of diclofenac by nitrifying activated sludge in large scale (WWTP) and small scale (laboratory level) at a temperature of 12 °C, the authors found that diclofenac is not biodegradable in large scale and the reaction rate constant (k′) and biodegradation constant (k_{biol}) were 1.7 d^{-1} and 0.6 l $g_{ss}^{-1}d^{-1}$, respectively in WWTP. In laboratory scale the biodegradation rate showed a difference between the reactors where with 10 µg / l of diclofenac the biodegradation rate was 86% in the reactor 1, whereas in the other reactors was 90%. The authors explained this difference by the amount of active nitrifying bacteria in the reactors which was influenced by temperature.

4. 2. 2. Membranes bioreactors

In membrane bioreactor the clarifier used in activated sludge is replaced by a membrane [85]. So, the plant can be operated at higher biomass concentrations resulting in smaller plant sizes [87,104]. The most essential benefit of MBR is the complete retention of suspended solids, thus decreasing emissions to the dissolved fractions [103]. The sorption can be estimated by the K_d value which is the ratio between the concentration of compound in the solid and in the aqueous phase in equilibrium conditions [121], this parameter indicates the sorption efficiency of the sludge, wherein when the K_d value is less than 500 L/kg, the efficiency of the sorption is considered negligible [104].

Recently, the membrane bioreactor process has become the most effective process for the removal of diclofenac compared to activated sludge [86], where the authors have demonstrated a low eliminating for diclofenac by the activated sludge process with a rate of (21.8 ±28.5%), as against the disposal of this waste was 65% for the membrane bioreactor process. On the other hand anaerobic MBR system has not shown an effective elimination rate for diclofenac (<10%) [127], these results are consistent with those of [71] these authors worked on a process of anaerobic / anoxic / aerobic membrane bioreactor in a large scale and observed removal rate below 20% for diclofenac.

In contrast in another study [90] where they used a anaerobic system by anaerobic fluidized membrane bioreactor (AFMBR) using granular activated carbon (GAC) as carrier medium, 78% was the removal rate of diclofenac and the elimination rate of COD was 95% at total HRT of 5 h. It can be concluded that the use of GAC helps eliminate diclofenac in the anaerobic system.

[72] investigated the degradation of diclofenac by a white-rot fungus-augmented membrane bioreactor (MBR) with and without addition of a redox mediator (1-hydroxy benzotriazole, HBT); the results showed that the addition of a redox mediator (1-hydroxy benzotriazole, HBT) improve the removal efficiency of diclofenac from 70% to 95%. In non-sterile conditions studied by [138] the removal rate of diclofenac was 55% in an MBR system with a hydraulic retention time of two days. [134] have shown that increasing the biomass concentration in the MBR system due to the long retention time favors the elimination of diclofenac and can be influenced by microbial activity according to [135]. These authors found that the reduction of microbial activity in the MBR system induces a decrease in the rate of elimination of diclofenac which indicates that the latter is eliminated by biological degradation and not by the sorption process only. [136] investigated the elimination of diclofenac by MBR under different temperature (10-45 °C) in laboratory-scale and demonstrated that the temperature has an effect on the microbial activity. The results showed that the maximum and minimum removal rate were at 10 °C and 20 °C, respectively.

The full-scale MBR showed significantly better removal of hydrophilic compound (log D < 3) [141]; they explained the greater removal by the existence of preand post-anoxic tanks and the combination of aerobic zones with different levels of DO (Dissolved Oxygen) relative to a pre-anoxic and one aerobic tank in the pilot MBR.

The molecular features of diclofenac can affect the rate of his elimination by membrane bioreactor on the scale of laboratory [77]. In this study, the authors observed a very low rate of elimination (17 %) and they justified this behavior of diclofenac in the MBR system by the presence of chlorine group and also the electron withdrawing functional groups generates an electron deficiency and thus renders the drug less susceptible to oxidative catabolism.

As regards the influence of pH, [137] explain the relationship between physicochemical properties of diclofenac and his efficiency removal by a laboratory scale MBR at mixed liquor pH values of 5, 6, 7, 8, and 9. At pH 5 the rate of removal was highest; this result is due to the physicochemical properties of this ionisable compound under acidic conditions wherein the pK_a value is 4.15 [30] so at pH 5 diclofenac is neutral which makes it a hydrophobic compound. The change in pH causes a variation in the hydrophobicity of diclofenac what gives us a log D. The increase of the made pH decreases log D and consequently the hydrophobicity of diclofenac what makes decrease also the efficiency elimination.

5. EFFECT OF DICLOFENAC ON BACTERIAL COMMUNITY

Sludge from sewage treatment plants is rich in microorganisms responsible for removing contaminants. Consequently, these micro pollutants can have an impact on these bacterial communities and affect the efficiency of biological treatment, namely activated sludge and membrane bioreactor process [142-145 and 147]. These effects are studied by tests of inhibition of development of the bacterial culture [155].

[152] studied the effect of four pharmaceuticals residues (Ketoprofen, naproxen, carbamazepine and gemfibrozil) on the ammonia oxidizing bacterium Nitrosomonas europaea at concentrations of 1 and 10 μM. They suggested that the presence of these pharmaceutical residues can affect the activity of the bacterial community and the elimination of nitrogen. [148] used the molecular-based method, fluorescent in situ hybridisation (FISH) to study the effect of organic loads on the structure of the bacterial community and estimated the stability of the anaerobic reactor by measuring the rate of elimination of DCO, the results showed that the rate of elimination of DCO decrease with the increase of the organic load in the reactor and a change was observed in the populations microbial.

Only a few studies evaluated effects of diclofenac on the bacterial community in activated sludge or membrane bioreactor system. Diclofenac can affect bacterial community used for its removal in the activated sludge process [140]; these authors demonstrated that diclofenac affects the structure of the sensitive nitrite-oxidizing bacterial community. [129] found that exposure of microbial community used in the activated sludge treatment causes a strong influence on this community after two months of exposure. This influence on the microbial diversity may affect the wastewater treatment plants. [128] studied this effect in laboratory scale and found that the increasing of concentration of pharmaceutical residues among them diclofenac caused a larger structural divergence on bacterial population and reduced bacterial diversity may affect the essential functions of activated sludge wastewater

treatment systems compared to the reactor which was operated without the addition of pharmaceutical residues.

The abundance of the methanogenic populations on anaerobic digestion (AD) process with regard to the pharmaceutical residue; diclofenac was studied by [156]. The authors compared the effect of diclofenac on biomass using a mesophilic wastewater treatment plant sludge-based (SI) and a thermophilic manure-based inoculum (MI) and they found that, SI inoculum were more resistant to the effect of diclofenac compared to the MI inoculum as regards the production of methane then the increase in biomass caused a decrease of this production until 31% and provoke an increase of the effect of diclofenac. This study demonstrated that hydrogenotrophic methanogens are more resistant than methanogens aceticlastic to the inhibitory effect of diclofenac via the method city by [148].

6. CONCLUSIONS

Diclofenac is the most pharmaceutical residue detected in the environment following its extensive human and veterinary use; it may be outcome of drug manufacturing plants and discharges from hospitals and domestic. This anti-inflammatory drug residue pollutes the aquatic environment and cause harmful effects on the human being, flora and fauna of the ecosystem.

The elimination of diclofenac was demonstrated to large and small scale with two process treatment of polluted water; physicochemical process such as activated carbon adsorption thanks to its advantages economic and biological process or biodegradation using conventional activated sludge (CAS) and membrane bioreactor (MBR) where the microorganisms are responsible for its degradation. Discussion of studies and publications used in this review demonstrated that biodegradation by membrane bioreactor is the most effective process for the removal of a resistant and persistent contaminant such as diclofenac with complete retention of suspended solids, thus reducing emissions to the dissolved fractions, but this removal may be influenced by factors such as the HRT where the increase increases the time of the contact of water with biomass and improves elimination of diclofenac and even an increase in biomass and even the increase in biomass can promote this removal. To see the efficiency of the biological treatment we studied the relationship between diclofenac and the bacterial community of sludge. After this review we find that there is not a lot of research concerned with the effect of diclofenac on biomass but little found in the literature allows us to conclude that the DCF has an influence on the growth of the bacteria sludge and consequently on their diversity.

In summary, to improve biodegradation diclofenac we need to deepen and develop methods to study the impact of pharmaceutical residues as diclofenac on bacterial community of sludge to understand the process of biodegradation and therefore improvement of its removal.

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