



## Review article

## Ibuprofen as an emerging organic contaminant in environment, distribution and remediation

Sunil Chopra, Dharmender Kumar\*

Department of Biotechnology, Deenbandhu Chhotu Ram University of Science and Technology, Murthal 131039 Sonapat, Haryana, India

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## ABSTRACT

Pharmaceutical and personal care products (PPCPs) are the one of sub-class under emerging organic contaminants (EOCs). Ibuprofen is the world's third most consumable drug. This drug enters into our water system through human pharmaceutical use. It attracts the attention of environmentalist on the basis of risk associated, presence and transformation in the environment. The detection and removal are the two key area where we need to focus. The concentration of such compounds in waterbodies detected through conventional and also by the advanced methods. This review we described the available technologies including chemical, physical and biological methods, etc used the for removal of Ibuprofen. The pure culture based method, mixed culture approach and activated sludge culture approach focused and pathway of degradation of ibuprofen was deciphered by using the various methods of structure determination. The various degradation methods used for Ibuprofen are discussed. The advanced methods coupled with physical, chemical, biological, chemical methods like ozonolysis, oxidation and adsorption, nanotechnology based methods, nanocatalysis and use of nonosensors to detect the presence of small amount in waterbodies can enhance the future degradation of this drug. It is necessary to develop the new detection methods to enhance the detection of such pollutants. With the developments in new detection methods based on GC-MS//MS, HPLC, LC/MS and nanotechnology based sensors makes easier detection of these compounds which can detect even very minute amount with great sensitivity and in less time. Also, the isolation and characterization of more potent microbial strains and nano-photocatalysis will significantly increase the future degradation of such harmful compounds from the environment.

## 1. Introduction

Water is the essential substance in our ecosystem and it is required to fulfill the basic needs of all organisms from drinking, bathing, transportation, etc (Yu et al., 2006). We cannot imagine life without water but the water quality is decreasing day by day. There are various artificial and natural causes behind the declining of the water quality but one of the major reasons is human interference. From basic need to industrial needs humans required water. But due to human interference many new pollutants are entering in our water resources which causes the declining in the rate of water quality increased many fold. The increase in world population, industrialization, increased in the area under agricultural sector and declining of green cover are the major reason behind the drastically declining water quality (Jurado et al., 2012). The entry of inorganic and organic pollutants in water bodies lead to deterioration in the water quality. Emerging organic pollutants (EOCs) are some of the artificial organic substances which are not present in the environment

naturally, cause maximum damage to the ecosystem and introduced in the environment due to industrialization and manmade activity. Pharmaceutical and personal care products (PPCPs) are the one of sub-class under EOCs. The PPCPs are considered to be having more potential to degrade the environment and water quality than any other pollutants due to their bioactive nature and hazardous toxic metabolites (Chopra and Kumar, 2018, 2020). A large number of PPCPs are consumed every day, these compounds and their partial metabolic products enter into water bodies via the sewage system. However, the traditional water waste treatments plants (WWTPs) are not efficient to remove these compounds. Due to these facts such types of pollutants are frequently observed in the WWTPs and also in surface water. Due to leaching of water, these compounds reached to the groundwater and thus may even present in drinking water (Tambosi et al., 2010).

The Ibuprofen is the third most popular, highly prescribed and most saleable over the counter medicine in the world (Marchlewicz et al., 2015). It is one of the drug listed in Essential Drugs list 2010 made by

\* Corresponding author.

E-mail address: [dkbiology@gmail.com](mailto:dkbiology@gmail.com) (D. Kumar).

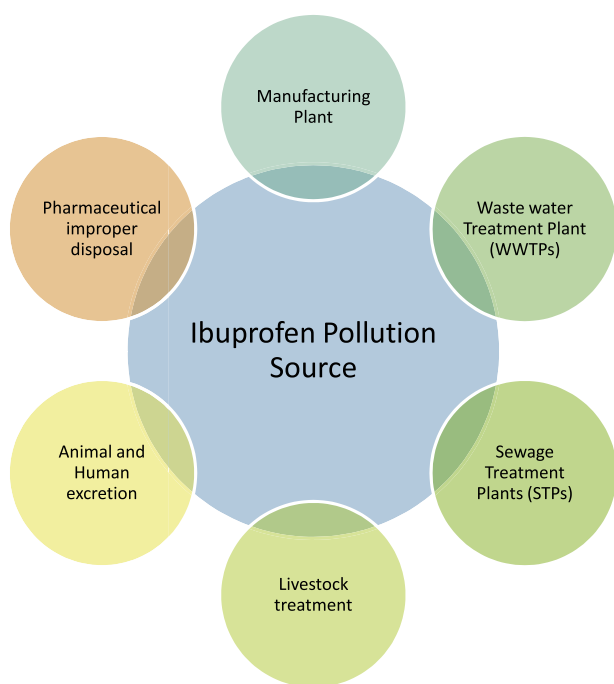


Figure 1. Source of occurrence of Ibuprofen.

World Health Organization (WHO). The toxicity and concentration of Ibuprofen in waste water treatment plants (WTPs) and water bodies are increasing day by day due to increased rate of consumption due to population pressure. This might pose a hazardous impact on the environment due to its bioactive nature. This is becoming ubiquitous to water bodies because it cannot be effectively removed by conventional water treatment methods. In recent years, its intake is increased as reported in many European Union (EU) countries (Hudec et al., 2012; Parolini et al., 2011). The therapeutic doses of Ibuprofen are ranging from 600 to 1200 mg/day. The oral dose of ibuprofen is completely (~99%) form the bond with plasma albumin rapidly and almost 15% of it is excreted by humans as unchanged molecule (conjugated with glucuronide and thiol) and also its metabolites like carboxyibuprofen, hydroxyibuprofen and carboxyhydratropic acid. The conjugates are further hydrolyzed in environment (Marchlewicz et al., 2015; Murdoch and Hay, 2015). While in WWTPs and sewage wastewater contain metabolite like 4-isobutyricbenzaldehyde, 1-(4-isobutylphenyl)-1-ethanol, 2-[4-(1-hydroxyisobutyl) phenyl] propionic acid, 4-ethylphenol, 4-ethylbenzaldehyde and 1-ethyl-4-(1-hydroxy) isobutylbenzene (Rácz et al., 2012; Zheng et al., 2011). Currently, research conducted in different parts of the world using techniques like the based on biosensors including the enzymatic biosensors, microbial biosensors and immune-sensors etc. The surface plasmon resonance (SPR) bases methods are emerging as promising technique to analyze the concentration of various emerging pollutants in various water bodies, due to their better efficiency, in real time monitoring, and economical benefits (Boruah and Biswas, 2018; Sanvicens et al., 2011). These techniques attract the attention of environmentalists for pharmaceutical and personal care products (PPCPs), a subcategory of EOCs. The PPCPs are bioactive in nature and their presence caused vast damage to water quality and adverse effect on life. The world third most consumable drug Ibuprofen is a non-steroidal anti-inflammatory drugs (NSAIDs; a subclass of PPCPs) detected in many water bodies. Presently, the concentration is varies from *ppb* to *ppt* range as per load on ecosystem (Murdoch and Hay, 2015). Ortiz de García et al. (2014) studied the ecotoxicology of 26 PPCPs drugs in aquatic systems in Spain and their environmental risk assessed. They reported that ciprofloxacin, acetaminophen, clofibrate, ibuprofen, clarithromycin, triclosan, parabens, omeprazole, and 1,4-benzoquinone has d some type of risk to the aquatic environments and/to

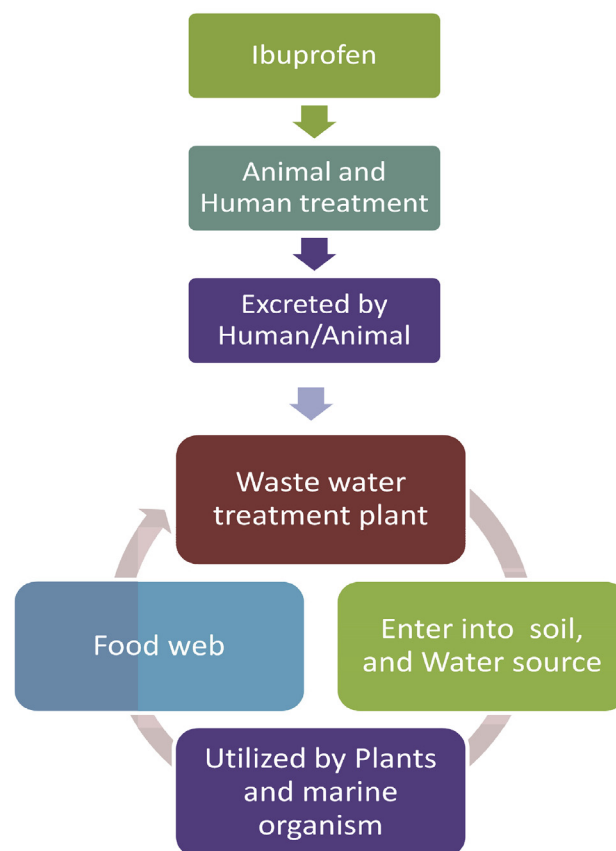


Figure 2. Pathway of Ibuprofen entering into food web.

WWTPs. This review is on the attempt for the use of current approaches for removal of Ibuprofen by various methods. The use of analytical techniques also discussed for the removal of Ibuprofen present in the environmental sources.

## 2. Source, occurrence and toxicity of Ibuprofen

The anthropogenic activity are responsible for increasing of concentration of this drug into the environment. Although, its improper disposal, manufacturing plants, WWTPs, sewage treatments plants (STPs), livestock treatments etc., are also the reason behind the entering of Ibuprofen into environment (Figure 1). After consumption by the humans and animals, it didnot completely metabolized and gets excreted. The enzymes present in human and animals metabolize it into various metabolites. The excretion product contains both Ibuprofen and its metabolites. Its metabolites are more toxic than it parent molecule. After excretion, it enters into WWTPs, STPs, river, lake, oceans, soil, ground water etc. Further it is consumed by plans and the aquatic organisms. This gave a path it to entering into our food web (Figure 2). The main sources for monitoring it are STPs and WWTPs (Daughton and Ternes, 2001). But, it does not mean that the Ibuprofen is present only in STPs and WWTPs. Now days, it is more frequently detected in many water bodies like rivers, lake, coastal areas, ground water etc. Different technologies were used to identify the Ibuprofen in different water bodies and concentration detected different types of environmental samples (Tables 1 and 2). The concentration and its effect on aquatic organisms like adult Zebrafish (*Danio rerio*) studied by using UPLC-TOF/MS (Song et al., 2018).

Their toxicity study is mainly conducted on daphnia and fish to determine the acute and chronic toxic effect. This allows identifying it's no observed effect concentration (NOEC), which used further to calculate predicted no-effect concentration (PNEC). The estimated real risk ratio of

**Table 1.** Source of occurrence and detecting methods used to identify Ibuprofen in water bodies.

| Sr. No. | Location  | Concentration         | Technique Used  | Reference                     |
|---------|---|-----------------------|---|-------------------------------|
| 1.      | South Africa  | 19.2 µg/L             | HPLC equipped with photo diode array detector   | (Madikizelaand Chimuka, 2017) |
| 2.      | Macherey& Nagel, Düren, Germany                       | 3.5 µg/L              | solid phase microextraction (SPME)combined with gas chromatography/mass spectrometry (GC/MSD) | (Huppert et al., 1998).       |
| 3.      | River Mississippi, USA                                | 34 ng/L               | solid phase extraction using two-layer disks consisting of C18 and SDB-XC                     | (Zhang et al., 2007).         |
| 4.      | Lake Erie basin, North Ohio, USA                      | 1.2 µg/L              | LC-MS/MS  | (Wu et al., 2009)             |
| 5.      | Tula Valley, Mexico                                   | 1406 ng/L             | GC-MS   | (Gibson et al., 2010)         |
| 6.      | River Mankyung, South Korea                           | 414 ng/L              | LC-MS/MS  | (Kim et al., 2009)            |
| 7.      | Pearl River Delta in South China                      | 1417 ng/L             | HP 6890 GC with a Micromass Platform II massdetector  | (Peng et al., 2008)           |
| 8.      | STP-influent stream in Taiwan                         | 2200 ng/L             | LC/MS/MS  | (Fang et al., 2012)           |
| 9.      | 6 WWTPs   | 7800–8600 ng/L        | LC/MS/MS  | (Guerra et al., 2014)         |
| 10.     | DosacoChowk, 9–10 km Sheikhpura Road, Lahore-Pakistan | 610 µg/kg-6046 µg/kg, | LC-20A system (Shimadzu, Japan) equipped with UV detector; HPLC                               | (Ashfaq et al., 2017)         |
| 11.     | South China, the Pearl River Delta                    | -                     | Stereoisomeric profiling  | (Wang et al., 2013)           |

**Table 2.** Ibuprofen detection in various types of environmental samples.

| S.No. | Samples                  | Location and concentration  | Reference   |
|-------|--------------------------|---|---|
| 1.    | Wastewater               | Canada (45 µg/L)<br>Pakistan (703–1673 µg/L)<br>South Africa (1.38 µg/L)<br>Belgium (5.78 µg/L)                                       | Guerra et al., (2014); Vergeynst et al., (2015);<br>Ashfaq et al., (2017); Matongo et al., (2015) |
| 2.    | Sludge                   | South Africa (0.009 µg/kg)<br>Pakistan (2053–6064 µg/kg).   | Matongo et al., (2015); Ashfaq et al., (2017)   |
| 3.    | WWTPs                    | Greece, Sweden, Switzerland, United Kingdom, Bosnia and Herzegovina, Croatia, Serbi, China and Korea (0.004 and 603 µg/L)             | Luo et al., (2014)  |
| 4.    | Soil and soil irrigation | Soil in Pakistan (321–610 µg/kg)<br>Soils irrigation in eastern Spain (0.213 µg/L)  | Ashfaq et al., (2017); Vazquez-Roig et al., (2012)  |
| 5.    | Surface waters           | Canada (0.98 µg/L)<br>Greece (1.0–67 µg/L)<br>Korea (<15–414 µg/L)<br>Taiwan (5.0–280 µg/L)<br>France (8.0 µg/L)<br>China (1417 µg/L) | Almeida et al., (2013); Luo et al., (2014)  |
| 6.    | Groundwater              | Europe is 3 ng/L–395 ng/L   | Luo et al. (2014)   |

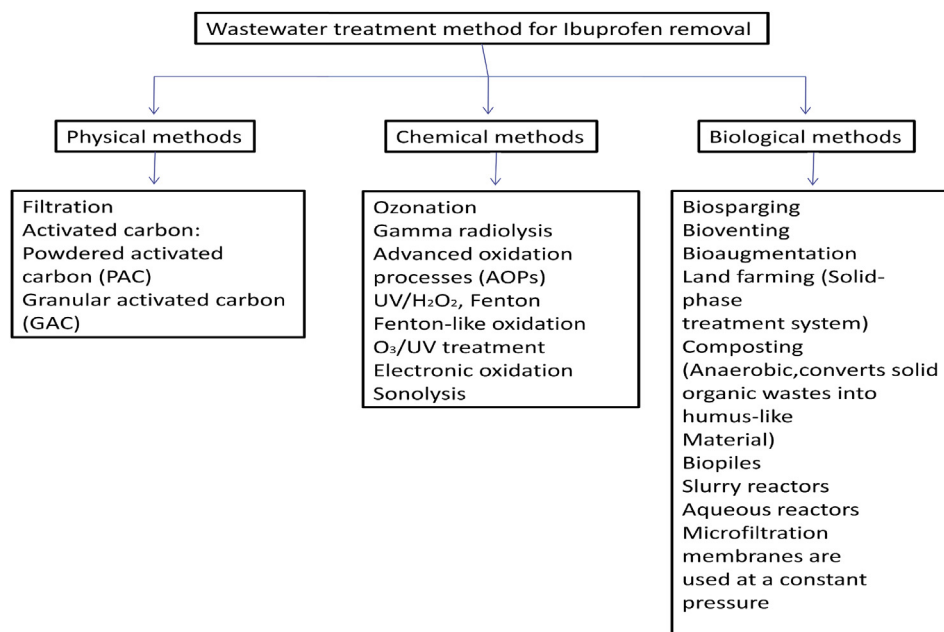


Figure 3. Different methods for Ibuprofen removal.

ibuprofen was  $\leq 1$ , this suggested that it was an environmental risky substance (Bouissou-Schurtz et al., 2014). Its toxic effects was shown on various model organisms like *Asterias rubens*, *Psammochinus miliaris*, *Arenicola marina*, *Allivibrio fischeri*, *Navicula* sp., *Chlorella vulgaris*, *Acetabularia obliquus*, *Chlamydomonas reinhardtii*, *Nannochloropsis limnetica*, *Daphnia magna*, *Oryzias latipes*, *Oncorhynchus mykiss*, *Neocaridina denticulata*, *Scenedesmus subspicatus*, *Daphnia magna*, *Pseudokirchneriella subcapitata*, *Danio rerio*, *Rutilus rutilus*, *Pimephales notatus*, *Daphnia longispina*, *Menidia beryllina*, *Oreochromis niloticus* and *Mytilus galloprovincialis* (Mohd Zanuri et al., 2017; Di Nica et al., 2017; Ding et al., 2017; Geiger et al., 2016; Grzesiuk et al., 2016; Du et al., 2016; Jeffries et al., 2015; Sung et al., 2014; González-Naranjo and Boltes, 2014; Brozinski et al., 2013; Gonzales-Rey and Bebianno, 2012; Ragugnetti et al., 2011; Flippin et al., 2007; Fent et al., 2006). It also decreases the fish spawning and simultaneously increased the eggs number in *Oryzias latipes*; Japanese medaka (Flippin et al., 2007). It also caused the endocrine disruption in *Mytilus galloprovincialis* while present in low concentration (250 ng/L). Moreover, its presence caused the induction of antioxidative stress. It also increased the activity of catalase, superoxidase dismutase, phase II glutathione S-transferase and glutathione reductase after exposure (within 7 days). The membrane damage in digestive gland and lipid oxidation level increased in mussels was observed (Gonzales-Rey and Bebianno, 2012). The genes down regulation caused aerobic respiration, skeletal development and immune function damage at concentration 11.5  $\mu\text{g/L}$  while at higher concentrations increased expression of arachidonic acid metabolism pathway by regulatory genes and inflammatory response by immune genes (Jeffries et al., 2015). After considering these facts, it is very necessary to build up the more effective method and advance technologies for Ibuprofen removal from environment.

The acute toxicity of pharmaceutical pollutants (Ibuprofen) is calculated by short-term EC50 (10 and 100 mg/L); cyto- and genotoxic effects are analyzed with prolonged exposure to analgesics. The long exposure is mainly concerned with cell oxidative status imbalance (Parolini and Binelli, 2012). Furthermore, all additional consequences like changes in growth rate, behavior, reproduction and alterations at biochemical level are observed. Kayani et al. (2009) observed that conjugation of Ibuprofen and diacylglycerol (ibuprofen-DG) was accountable for the inhibition of cell division and non-disjunction of chromosomes to several pairs. Han et al. (2010) investigated the chronic toxicity of ibuprofen by hormonal

balance under *in vitro* condition using the H295R cell line on *Oryzias latipes*, *Moina macrocopa* and *Daphnia magna*. They revealed that Ibuprofen increased the 17- $\beta$  estradiol production, decreased testosterone production and aromatase activity. In addition to this the 0.1  $\mu\text{g/L}$  ibuprofen has resulted in delayed hatching process. Lange et al. (2006) showed that 1–100 ng/L of ibuprofen was responsible for decrease the activity of amphipod crustacean in *Gammarus pulex*.

### 3. Removal methods of Ibuprofen

The various advance techniques such as adsorption (powdered activated carbon (PAC), granular activated carbon (GAC) etc.), biofiltration (trickling filter, sand filters, biological activated carbon (BAC) filter etc.), reverse osmosis, attached growth technology, membrane bioreactors, nanofiltration, carbon nanocomposites and magnetic nanoparticles ((AC)/CoFe2O4) are used for the removal for PPCPs (Saucier et al., 2017; Luo et al., 2014). These types of techniques are in developing phase and lot more avenues are available for research in these directions. But, due to lack of optimal treatment methods lead to release of many pollutants (PPCPs, pesticides, hydrocarbons etc.) and their metabolites into environment (Rozas et al., 2016). The entry of these compounds into various water bodies leads to long-term adverse effects on aquatic life (primary producers, cnidarians, cladocerans, mussels, or fish) (Parolini and Binelli, 2012; Grujić et al., 2009). In addition to this, these drugs are biological active molecules which were designed to cure disease and slowly metabolized. Oliveira et al. (2015) identified the negative impacts of the drug in the form of biocoenosis, low biodegradability and pseudo-persistence.

The detection of EOCs in waste water is carried out with automatic methods which are highly sensitive, precise and selective to the many compounds (Lorenzo et al., 2018). Currently, new contaminants are entering in wastewater which led to increase or suppress the detection signals. This limits the quantification and detection of contaminants in analysis. Therefore, it is necessary to improve the technologies and pre-treatment method of samples (pure extract) to detect pollutants in waste water by easy methods (Khan et al., 2020). In the water bodies such type of pollutants makes a complex mixture along with other pollutants present in water. The techniques used to measure the water quality are based on the parameters viz. electrical conductivity, pH, turbidity, chemical oxygen demand (COD), biochemical oxygen

**Table 3.** Different selective advance wastewater treatment methods for Ibuprofen removal.

| Technology used  | Condition and Uses of chemicals/radiation/strains  | Removal efficiency (%)                                       | Reference   |
|--|--|--|---|
| Coagulation-flocculation   | Chemical: FeCl <sub>3</sub> /Al <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub> ;<br>Concentration: 25, 50 mg/L   | 12.0 ± 4.8%  | Suárez et al. (2009), Luo et al. (2014)                                   |
| Ozonation/AOPs   | Radiation: UV <sub>254</sub><br>Time: 10 min   | 34%  | Luo et al. (2014)   |
| Ozonation/AOPs   | Combine method: UV <sub>254</sub> and H <sub>2</sub> O <sub>2</sub> (50 mg/L)<br>Time: 10 min, 30 min  | Almost 100%  | Luo et al. (2014)   |
| Ozone oxidation  | Concentration: 1 mg/L, 160 mg/L for 20 min,  | 99%  | Wang and Wang (2016)  |
| Membrane processes   | Material: PES flat-sheet of 100 kDa<br>Pressure = 0.5 ± 0.01 bar   | 7%   | Jermann et al. (2009), Luo et al. (2014)                                  |
| Membrane processes   | Material: Filmtec TW30<br>Pressure: 9.5–10.2 bar   | >99%   | Sahar et al. (2011), Yangali-Quintanilla et al. (2011), Luo et al. (2014) |
| Membrane bioreactor  | Module: Full-scale HF (Koch Puron)<br>MAB: 235 m <sup>2</sup><br>pore size: 0.1–0.2 µm   | ~100%  | Trinh et al. (2012), Luo et al. (2014)                                    |
| Membrane bioreactor  | Module: Lab-scale submerged HF UF module<br>MA: 0.047 m <sup>2</sup><br>Pore size: 0.04 µm<br>SRT: 70 days<br>HRT: 24 h<br>MLSS: 8.6–10 g/L                      | 96.7 ± 0.7%  | Tadkaew et al. (2011), Luo et al. (2014)                                  |
| Membrane bioreactor  | Module: Lab-scale polyvinylidene fluoride HF<br>MA: 0.2 m <sup>2</sup><br>Pore size: 0.4µm<br>HRT: 1 or 3 days<br>MLSS: 2.3–4.6 g/L                              | Almost 100%  | Bo et al. (2009), Luo et al. (2014)                                       |
| Attached growth treatment processes  | Media: bioplastic-based biofilm carriers<br>volume: 2.5 L  | Almost 100%  | Falás et al. (2012), Luo et al. (2014)                                    |
| Activated sludge with high nitrifying activity in sequencing batch reactor (SBR) | Biodegradation time: after 24 h in water   | 76%  | Kruglova et al. (2016)  |
| Grit channels, primary clarifies and conventional activated sludge               | Initial concentration: 4500 ng/L   | 99.7%  | Blair et al. (2015)   |
| Primary treatment + Orbal oxidation ditch + UV disinfection                      | Initial concentration: 130–450 ng/L  | 60–90%   | Sun et al. (2014)   |
| Fenton oxidation   | Initial concentration: 0.87 mM<br>Temp: 30 °C<br>pH: 3<br>Time: 2h<br>Concentration: Fe <sub>2</sub> : 25% (1.2 mM), H <sub>2</sub> O <sub>2</sub> 25% (0.32 mM) | >50%   | Wang and Wang (2016)  |
| Microbial biodegradation   | <i>Bacillus thuringiensis</i> B1(2015b)  | 20 mg/L in 6 days  | Marchlewicz et al. (2017a, 2017b)<br>Marchlewicz et al. (2016)            |
| Microbial biodegradation   | <i>Patulibacter</i> sp. I11  | 125 µg/L, 31 µg/L, 46 µg/L in 300 h, 90 h, 90 h respectively | Almeida et al. (2013)   |
| Microbial biodegradation   | <i>Variovorax</i> sp. Ibu-1  | 200 mg/L in 75 h   | Murdoch and Hay (2015)  |
| Microbial biodegradation   | <i>Nocardia</i> sp. NRRL 5646  | 1000 mg/L in 120 h   | Chen and Rosazza (1994)   |

demand (BOD), total suspended solids (TSS), total dissolved solids (TDS) and coliform count. The environmentalists major thrusts are on the nutrient load, presence of heavy metals, microbes, and other types of priority pollutants present in water (Daughton and Ternes, 2001; Daughton et al., 2009; Rodriguez-Narvaez et al., 2017). The identification of these pollutants are not possible through conventional detection methods. It is necessary to develop the new detection methods to enhance the detection of such pollutants. Therefore, new detection methods based on techniques such as GC-MSMS, HPLC, and LCMS etc deploying nanotechnology based sensors makes easier detection of these compounds. The Ibuprofen concentrations in the water bodies are low and it has been observed that their low concentration does not indicates its safe status to living system. The continuous interaction of these molecules with the living system causes the long term adverse effect. Presently, the removal method of Ibuprofen has increased attention of researcher around the world. Their r removal based methods are divided into three categories: physical, chemical and biological methods (Figure 3). There are various advanced technology

are available, such as advanced oxidation processes (AOPs), coagulation-flocculation, membrane processes, membrane bioreactor (MBR), biodegradation by strain and microbial consortium for removal of Ibuprofen (Table 3). More recently, Sharma B. et al. (2019) reviewed that the organic waste including the municipal solid waste (MSW) containing diverse types of EOCs, pesticides, PPCPs, and xenobiotics. To increase the removal efficiency of Ibuprofen there are e following points which need to give attention.

1. The effect of concentration of Ibuprofen on the removal efficiency of microbes. Because different microbes take different route for degradation of Ibuprofen.
2. The role of microbial community in Ibuprofen degrading is accounted. It is still not clear in activated sludge system which microbial community degrades Ibuprofen.
3. Biodegradation of Ibuprofen is an effective and low cost method. While removal of Ibuprofen by activated sludge biodegradation and biosorption contributed simultaneously.

**Table 4.** Selective biological techniques for Ibuprofen degradation.

| Technique           | Techniques  | Applications  |
|---------------------|---|---|
| In Situ degradation | Biosparging<br>Bioventing<br>Bioaugmentation  | Biodegradative abilities of indigenous microorganisms in presence of Ibuprofen within environmental parameters<br>Biodegradability of pollutants ibuprofen solubility with geological factors   |
| Ex situ degradation | Land farming (Solid-phase treatment system)<br>Composting (Anaerobic, converts solid organic wastes into humus-like material)<br>Biopiles | Surface application, aerobic process, application of to natural soils followed by irrigation and tilling<br>To make plants healthier good alternative to land filling or incinerating practical and convenient.<br>Surface application, agricultural to municipal waste |
| Bioreactors         | Slurry reactors<br>Aqueous reactors   | Bioaugmentat Toxicity of amendments<br>Toxic concentrations of contaminants   |
| Microfiltration     | Microfiltration membranes are used at a constant pressure   | Waste water treatment; recovery and reuse of more than 90% of original waste water  |

4. The intermediate compounds produced during degradation seems to be more toxic than the parent compound. The pathway of degradation and the intermediates produced during degradation need to be detected

### 3.1. Removal of Ibuprofen by chemical methods

The advanced chemical processes are mainly focused on wastewater treatments. The advanced chemical processes include ozonation, gamma radiolysis, advanced oxidation processes (AOPs), UV/H<sub>2</sub>O<sub>2</sub>, Fenton and Fenton-like oxidation, O<sub>3</sub>/UV, electronic oxidation and sonolysis (Wang and Xu, 2012) and degradation of Ibuprofen from the liquid system using electro-Fenton process (Loaiza-Ambuludi et al., 2013). In ozonation the ozone is used for oxidation method for the removal of Ibuprofen. Ozone is mainly depends on the strong non-selective oxidizing activity of hydroxyl radicals (Bai et al., 2016). The mechanism behind the ozonation is the formation of hydroxyl radicals. The ultra-pure water was produced from 160 mg/L to 1 mg/L and 0.1 mg/L to 12 g/L of Ibuprofen removed in 20 min at pH 9, 25 °C by ozonation (Quero-Pastor et al., 2014a, 2014b). Ozonation is an oxidation process shows efficient removal of Ibuprofen. One of the popular methods for portable water disinfection is Ultraviolet (UV) treatment. UV light disrupts the bonds of the chemical present in waterbodies so method used for removal of PPCPs (Kim et al., 2009). The gamma irradiation is one of the AOPs, rising as efficient technology for the removal of EOCs in wastewater. The removal efficiency of Ibuprofen was decreased with the increase in pH from 1.45 to 11.0 this indicating that it involved H ion radical reaction (Zheng et al., 2011). Mendez-Arriaga et al., in 2010 used Fenton technology at pH 3; 30 °C temperature for 2 h with use of Fe<sup>2+</sup>-1.2 mM, H<sub>2</sub>O<sub>2</sub>-0.32 mM for the removal of 0.87 mM Ibuprofen with >50% removal efficiency. While with Photo-Fenton at 30 °C, pH 3 for 2 h with Fe<sup>2+</sup>-1.2 mM, H<sub>2</sub>O<sub>2</sub>- 0.32 mM achieved almost 100% removal efficiency of 0.87 mM of Ibuprofen (Mendez-Arriaga et al., 2010).

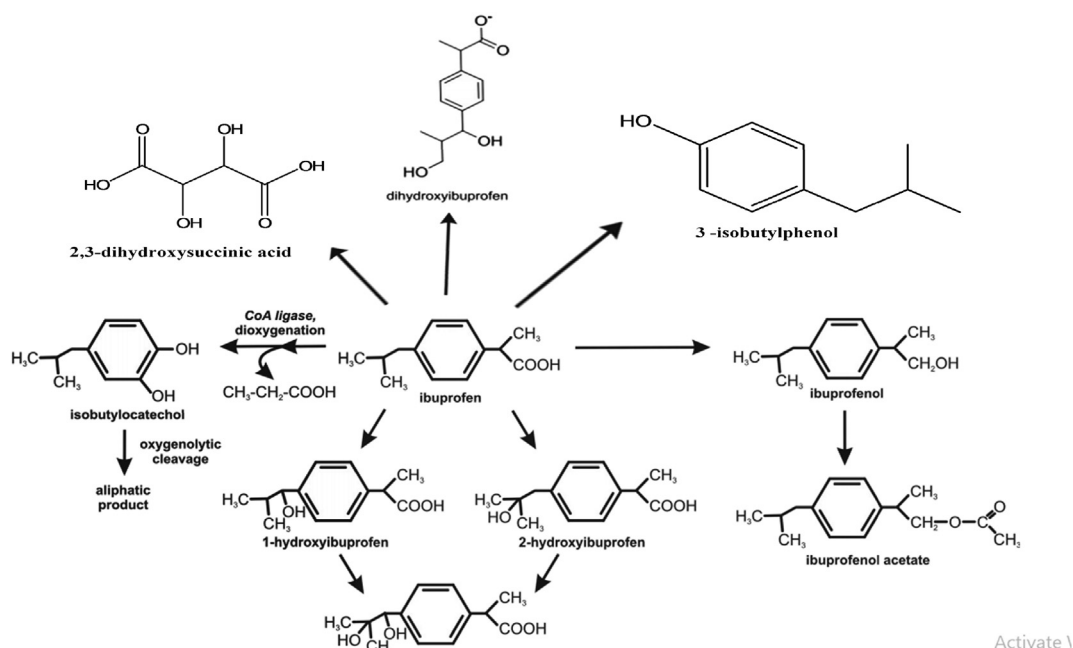
Ibuprofen is more effectively removed by AOPs sub-class under physicochemical methods (Góngora et al., 2017; Iovino et al., 2016; Huang and Liu, 2015). The oxidation of Ibuprofen is started by the high reactive hydroxyl radicals during the AOPs (Góngora et al., 2017; Li et al., 2015; Braz et al., 2014). Metabolites like 4-isobutylphenol, Hydratropic acid, 4-(1- carboxyethyl) benzoic acid, 4-ethylbenzaldehyde, 2-[4-(1-hydroxy-2-methylpropyl) phenyl] propanoic acid, 1-(4-isobutylphenyl)-1-ethanol, 4-acetylbenzoic acid 1-isobutyl-4-vinylbenzene and 4-isobutylacetophenon are produced during this process (Ruggeri et al., 2013; Sabri et al., 2012; Caviglioli et al., 2002). However, these metabolites possess more toxicity than Ibuprofen identified in many studies (Huang and Liu, 2015; Braz et al., 2014; Quero- Pastor et al., 2014). Du et al. (2019) used multi-walled carbon nanotubes (MWCNTs) as catalyst and ibuprofen and acetylsulfamethoxazole removal enhanced due to higher OH formation.

### 3.2. Removal of Ibuprofen by physical method

The adsorption is most used physical process, which offers the removal of organic pollutants in wastewater. Various adsorbents are used to enhance the efficiency of removal of Ibuprofen. In tradition adsorbent the activated carbon is widely used for water treatment, it can also remove the partial concentration of Ibuprofen from waste water. The activated carbon was categorized into: powdered activated carbon (PAC) and granular activated carbon (GAC). The PAC concentration of 5 g/L and 10 mg/L was used to remove Ibuprofen concentration of 100 ng/L and 40 mg/L from surface and synthetic water respectively (Snyder et al., 2007; Mestre et al., 2007). The graphene was used by Rizzo et al., in 2015 for removal of 10 mg/L of Ibuprofen from synthetic water with the efficiency of approximate 95%. Wang et al. (2016) reported the Ibuprofen removal via multi-nanotube method from the mixture or various drugs from the river water. Hydrocar (Coal-like product) also known as hydrothermally carbonized material made by transformation of biomass through thermo-chemical process (Titirici et al., 2008). The hydrothermal carbonization (HTC) or hydrous pyrolysis is made through the decomposition of biomass in presence of subcritical water (Funke and Ziegler, 2010). The HTCs and its composites are used in Li/Na ion batteries electrodes, fuel cells and super capacitors for the adsorption, catalysis, environmental science etc (Deshmane et al., 2013; Qu et al., 2013; Titirici, 2012; Dong et al., 2011; Rillig et al., 2010). It is also potential used as contaminant remediation and soil improvement (Alatalo et al., 2016; Shi et al., 2015; Malghani et al., 2013). Previously, PPCPs removal was performed by the use of hydrocar made from sucrose or carbon products like orange peel and cork granules (Fernandez et al., 2015; Mestre et al., 2014, 2015). Plósz et al. (2012) suggested a modeling framework approach using activated sludge for trace substances; which enhances the degradation of carbamazepine and diclofenac by activated sludge. The degradation of Ibuprofen can also enhance by assessing the factors which influence the degradation. Nanophoto-catalytic reactor for degradation is one of future technology for real-time degradation of pollutants (Shankar et al., 2004).

### 3.3. Removal of Ibuprofen by biological methods

In many toxicological studies, it is found that the intermediates formed during the advance chemical treatment pose more toxicity than parent compounds (Quero-Pastor et al., 2014). Therefore, the biodegradation of Ibuprofen seen as a future alternative for the removal of Ibuprofen from the waterbodies. The use of biodegradation provided advantages over conventional and AOC methods like an economical, natural process and wide optimal conditions. Microbes used Ibuprofen in their metabolism as a carbon and energy source. Various microbes each other to remove the pollutants present in waterbodies. Various methods were proposed for bioremediation of various pollutants showed in Table 4. Biological treatment is considered as an important method for



**Figure 4.** Pathway of degradation of Ibuprofen purposed by different researchers ((adapted from Murdoch and Hay, 2005, 2013, 2015; Hanlon et al., 1994; Zwiener et al., 2002; Quintana et al., 2005; Marco-Urrea et al., 2009; Chen and Rosazza, 1994; Salgado et al., 2020, Sharma K et al., 2019, Huang et al., 2020).

the micro pollutants removal (Falás et al., 2012). Although, bioremediation processes has been identified as an efficient cleaning technology. But they are characterized by some disadvantages. Such as: (1) the possible effect of bioremediation technology on the native microenvironment, (2) some xenobiotics have lower susceptibility rate during biodegradation, (3) genetics modified microbes are impossible to remove after biodegradation (4) intermediates produced during biodegradation having more toxic impact on system then their parent molecule and (6) contamination present in soil, water and gases are more frequent. The microorganisms which are able to degrade are often exposed to vibrating temperatures and pH. Although, environmental and economical conditions such as availability of additional carbon sources, high levels of xenobiotics required and price (Kumar et al., 2011; Sharma, 2012). There are many microorganisms having the capability to use Ibuprofen as carbon and energy sources. But the metabolic pathway of degradation and enzymes involved in degradation is poorly characterized. In the recent review by Zur et al. (2018), the authors described the current research and toxicity and biodegradation methods of paracetamol and ibuprofen along with the utility of bioinformatics based approaches to understand the genetic bases of microorganisms involved in degradation of such xenobiotics compounds. Bioremediation and biodegradation based methods seems to be a promising alternative to the chemical methods. But, the presence of ibuprofen in the environment, their toxic effects and mode of action of microbial degradation and as genetic mechanism need to understand in future (Zur et al., 2018).

### 3.3.1. Pure culture approach

There are few studies have been reported on the pure cultures isolated from soil, activated sludge, sediments, and wastewater which can use frequently detected Ibuprofen in waterbodies. Presently, there is little information about the metabolites formed during the biodegradation of Ibuprofen. So there are few pure strains are identified which have potential to degrade Ibuprofen have been described: *Nocardia* sp. NRRL 5646 (Chen and Rosazza, 1994; Li and Rosazza, 1997), *Sphingomonas* Ibu-2 (Murdoch and Hay, 2013), *Bacillus thuringiensis* B1(2015b) (Marchlewicz et al., 2017), *Variovorax* Ibu-1 (Murdoch and Hay, 2005) and *Patulibacter* sp. I11 (Almeida et al., 2013). In the presence of tryptone and yeast extract the *Patulibacter* sp. I11 strain can degrade the Ibuprofen. This suggests that there was involvement of acyl-CoA synthetase iron,

sulphur cluster and enoyl-CoA for the degradation of Ibuprofen (Almeida et al., 2013). During Ibuprofen degradation by *nocardia* sp. NRRL 5646 the intermediate compounds like Ibuprofenol acetate and Ibuprofenol were detected (Chen and Rosazza, 1994). Murdoch and Hay (2005, 2015) proposed the pathway of degradation for Ibuprofen by *Sphingomonas* Ibu-2 and *Variovorax* Ibu-1. They suggested that meta-ring fission enzymes were involved in the degradation *Variovorax* Ibu-1 (Murdoch and Hay, 2015). The *Bacillus thuringiensis* B1(2015b) degrade the Ibuprofen in the presence of glucose. The toxicological studies showed that *B. thuringiensis* B1(2015b) is more resistant to Ibuprofen; The EC50 of Ibuprofen for B1 strain is 809.3 mg L<sup>-1</sup> (Marchlewicz et al., 2017). Marco-Urrea et al., in 2010 suggested that the fungal strain like *Trametes versicolor*, *Irpex lacteus*, *Ganoderma Lucidum* and *Phanerochaete chrysosporium* also having potential to degrade Ibuprofen as a solo source of energy. The key feature for biodegradation of Ibuprofen by pure strain is enzyme induction. The biodegradation of Ibuprofen depends on potential of microbe to produced Ibuprofen degrading specific enzyme.

### 3.3.2. Mixed culture approach

The mixed culture approach is much easier way to achieve degradation as compared to pure culture. Because it's too difficult to isolate pure degrading strain in some; and maintenance of pure strains is also a difficult task. But there are no study is carried out on Ibuprofen degradation by mixed strain approach. But there are few studies available on the mixed culture degradation of PPCPs (Khunjar et al., 2011). The mixed culture possess move capability to remove PPCPs compare to pure culture using mixed media (Khunjar et al., 2011). Zhou et al., in 2014 reported the removal of PPCPs by mixture of culture poured in the activated sludge. Few studies demonstrated that the mixed culture biodegradation rate for removing the PPCPs is higher than the individual strain (Vasiladou et al., 2013). The mixed strain approach is a futuristic approach for the degradation of Ibuprofen.

### 3.3.3. Activated sludge culture approach

The conventional WWTPs use activated sludge process for the removal of PPCPs including Ibuprofen. But, the efficiency and the removal rate of Ibuprofen is low. They remove partial concentration of Ibuprofen. And the intermediate formed during the degradation are toxic then the parent substance. However, adsorption and volatilization by

using activated sludge having low contribution in the degradation of PPCPs (Li et al., 2015).

#### 4. Pathway for ibuprofen biodegradation

There is little information available how the Ibuprofen metabolized by the microbes. However, some microbes having potential to generate hydroxyl-ibuprofen and carboxylated-ibuprofen during degradation were detected (Hanlon et al., 1994; Zwiener et al., 2002; Quintana et al., 2005; Marco-Urea et al., 2009; Salgado et al., 2020). While the Murdoch and Hay tried to describe the metabolic pathway of ibuprofen with the help of *Sphingomonas Ibu-2* (Murdoch and Hay, 2005, 2013, 2015). They observed a novel mechanism which involved coenzyme-A ligase. During degradation deacetylation and dioxygenation transformed into isobutylcatechol after the extradiol ring-cleavage. Chen and Rosazza (1994) reported a fungal *Nocardia* which having potential to transform it into carboxylic acid and further into an alcohol and acetylate.

Almeida et al. (2013) also indicated involvement of this enzyme in ibuprofen decomposition by *Patulibacter* sp. strain I11. Salgado et al. (2020) used *Patulibacter medicamentivorans* strain under aerobic conditions for the degradation of Ibuprofen they suggested the two main intermediates 2-phenylpropanoic acid and isobutylbenzene were produced during the degradation of Ibuprofen. The Ibuprofen was cleaved into extradiol dioxygenase to 5-formyl-2-hydroxy-7-methylocta-2,4-dienoic acid during degradation by *Bacillus thuringiensis* B1(2015b) is hydroxylation of both: aromatic ring and aliphatic chain of ibuprofen (Marchlewicz et al., 2017). The main intermediate metabolites produced during Ibuprofen degradation were hydroxylated in the isopropyl chain from ibuprofen 1 and 2-hydroxyibuprofen after few hours of the experiment, and 1,2-dihydroxyibuprofen as a final metabolite. Hydroxylated and carboxylated derivatives are frequent detected during the microbial metabolism (Zwiener et al., 2002; Quintana et al., 2005). The initiation of degradation was started with 1,4-hydroquinone and the second one to 2-hydroxyquinol. 1,4-hydroquinone is a product of acyl-CoA synthase/thiolase activity and may be transform to 2-hydroxy-1,4-quinol by hydroquinone monooxygenase. Moreover, the activity of hydroxyquinol 1, 2-dioxygenase after the induction by ibuprofen was observed due to presence of glucose alone the enzyme was not active at all. Hydroxyquinol 1,2-dioxygenase favorable binds 2-hydroxy-1,4-quinol and is responsible for ortho cleavage of this compound to 3-hydroxy-cis,cis-muconic acid. While during biodegradation of ibuprofen by *Nocardia* sp. NRRL 5646, there were two main metabolites, ibuprofenol and ibuprofenol acetate, were observed (Figure 4). Finally these products were further mineralized by bacterium (Chen and Rosazza, 1994). Murdoch and Hay (2005, 2013) characterized the most recognized Ibuprofen degradation pathways in *Sphingomonas Ibu-2* bacteria, having potential to utilized Ibuprofen as sole carbon and energy source. They also provided the five-gene cluster (ipf ABDEF) involved in Ibuprofen mineralization. The genes ipfA and ipfB were coded the two subunits of dioxygenases; while the ipfD gene was coded the enzyme for the removal/addition of acyl groups acyl-CoA synthetase; the (ipfF) was coded the coenzyme A ligase gene; and finally gene ipfE function was not describe. The degradation was started with the degradation by strain Ibu-2 with coenzyme A. The enzyme removes the propionic acid chain and further dioxygenation reaction led to isobutylcatechol formation. This compound undergoes oxygenolytic cleavage (Murdoch and Hay, 2005, 2013). Whereas in various experiments, the concentration of Ibuprofen was increased with isobutyl having side-chain of hydroxyl- or carboxyl-group led to decrease in concentration of ibuprofen (Hanlon et al., 1994; Marco-Urea et al., 2009; Quintana et al., 2005; Zwiener et al., 2002). Sharma K et al. (2019) were identified the hydroxyl, demethylation and dehydrogenation derivative during optimized the batch biodegradation using *Micrococcus yunnanensis*. Finally, they identified the monooxygenase enzyme which was responsible for the degradation of Ibuprofen. The degradation of ibuprofen using sludge of hospital, municipal and distillery were produced the hydroxylated ibuprofen and

ibuprofen carboxylic during initial degradation period. Consequently, benzoquinone, quinone and catechol like compounds were produced during the degradation (Huang et al., 2020). Based on these studies, we have designed the pathway for degradation of ibuprofen indicating the various intermediates produced during degradation (Figure 4).

#### 5. Conclusion and future perspective

The conventional wastewater treatment methods are not effective for the removal of the Ibuprofen, the third most consumable drug and frequently detected water system. Moreover, the removal of Ibuprofen by activated sludge system is affected by the various physical and biological factors, such as concentration of Ibuprofen in waste water, pretreatment system, environmental conditions and microbial community present in sludge. Bioremediation based methods seems to be a promising alternative to the chemical methods. But, the toxicity and analysis of various micro-pollutants a promising field of research that needs to give attention. With the advent of nanotechnology based materials and nano-sensors lead to rapid detection of these compounds and catalysis based methods improve the degradation. This can be possible through nano-structures, nanospheres and nanoshell which entrap the compounds in their shell and leads to further progress of the chemical based reactions. The possible reason behind the presence of Ibuprofen in environmental source due to the lack of microbial efficiency of degrading Ibuprofen. Therefore, there is need of more studies which enhance the biodegradation of Ibuprofen in water bodies to make potential strategies against the removal of Ibuprofen from waste water. Advancements in enzyme technology gives the way for the new technology of degradation and which can be preferred over conventional technology. The mixed culture approach used in reactor with nanoparticles can enhance the degradation of Ibuprofen. Therefore, more efficient technology need to be applied for more rapid and cost effective degradation of these compounds from the environment.

#### Declarations

##### Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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