Chapter 1
Introduction

1. Introduction

1.1 Background

Despite the fact that, pharmaceuticals are endorsed as the life savers for millions of people around the globe, they have appeared as an emerging pollutants in last two decades (Dao et al., 2020; Ebele et al., 2017; Klavarioti et al., 2009). PhCs form an integral part of our lives and its extensive use and poor removal by conventional wastewater treatment facilities make them ever-present in the environment (Abdelmelek et al., 2011; Y. Yang, 2020). The PhCs are capable of causing both the long term and short term adverse effects on biotic components of the environment (Scheers et al., 2012; J. Wang & Wang, 2016). The existence of PhCs in surface waters (streams, lakes, and rivers), sea water, ground water, soils, wastewater treatment facilities (influents and effluents), and sludges has been recurrently reported (Dao et al., 2020; Ebele et al., 2017; Klavarioti et al., 2009; M. Yang & Zhang, 2016).

PhCs are chemicals that interrupt or modify the physiology when taken into a living organism (Ficke et al., 2007). The PhCs can either be natural or synthetic. The PhCs generate a biological response by targeting the macromolecules inside the body. The PhCs usually interrupt nervous system (brain) for generation of a needed biological response. They can be grouped into numerous classes based on their pharmacological effects on living beings. Figure 1 elaborates the broad classification of PhCs with the examples of PhCs commonly found in natural waters (Murray et al., 2010; Taheran et al., 2018; Yedhu & Manikandan, 2021).

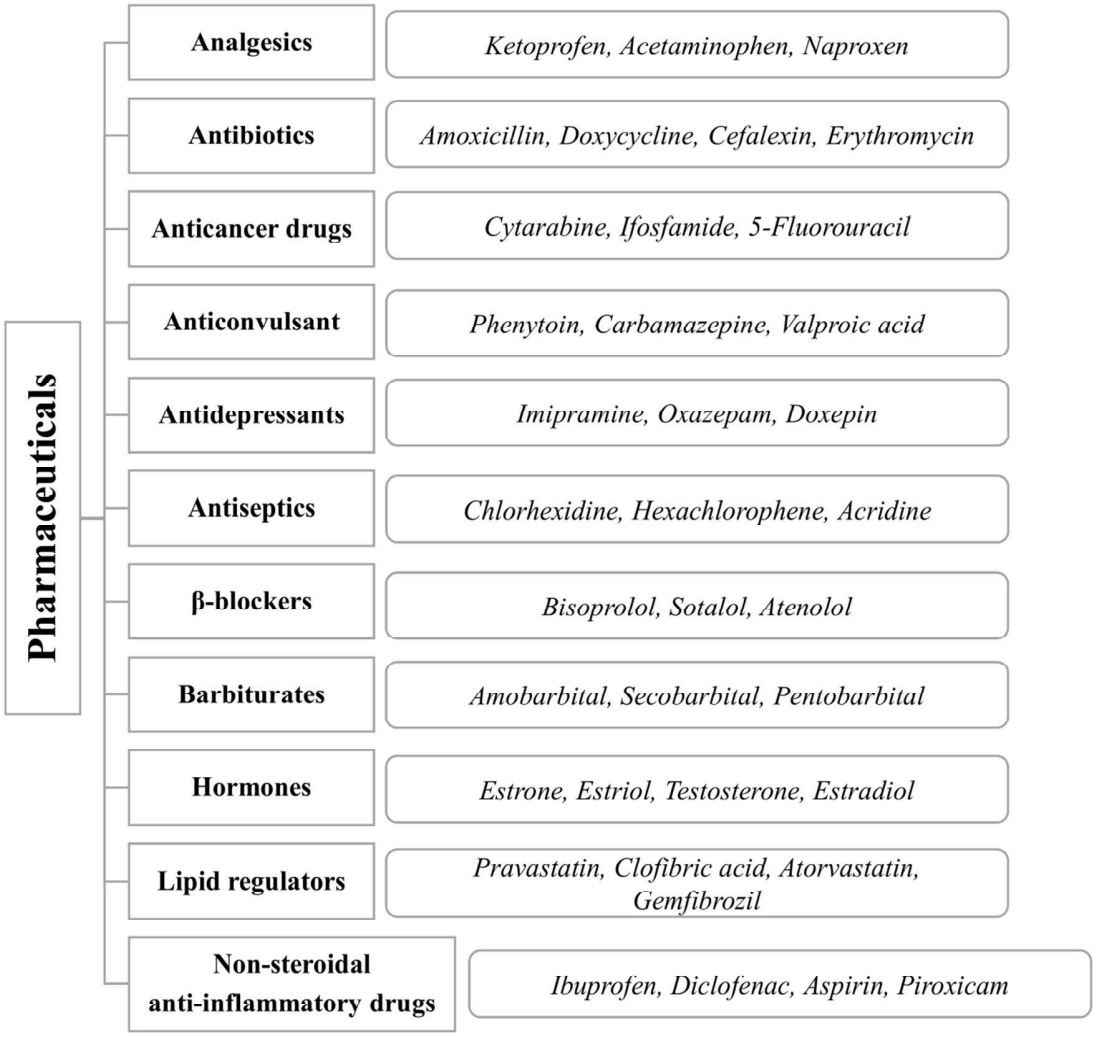

Figure 1: Classification of pharmaceutical compounds with their examples

The major routes of entry for PhCs in environment are individual excretion, discarding the spare PhCs, and agricultural application. Many PhCs are excreted predominantly via feces and urine after being taken into the body; consequently, these PhCs are constituents of domestic and commercial wastewater(Blair et al., 2013; García-Fernández & Roy Editor, 2020; Murray et al., 2010).Conventional treatment methods largely relying on biological treatments, are not efficient enough to degrade these PhCs due to its complex molecular structure (Rathi et al., 2021; Zhai et al., 2021). A wide variety of PhCs related with wastewater discharges were detected in surface

water as well as ground water (Ebele et al., 2017). The PhCs can have an indirect impact on the atmosphere in case of intensified livestock farming, by means of using compost and purines and it can further be transferred to living beings through the food supply chain. The PhCs administered in fisheries are also discarded blatantly into rivers, lakes, and marine waters. Frequently reported PhCs in water having comparatively high concentration (~10 to 100 µg/L) are: acetaminophen, amoxicillin, aspirin, ciprofloxacin, diclofenac sodium, ibuprofen, metronidazole, ofloxacin, oxytetracyclin, sulfamethoxazole, tetracycline, and tinidazol(Patel et al., 2019).Among these, diclofenac and ibuprofen are most commonly detected non-steroidal anti-inflammatory drugs (NSAID) in the aquatic environment and maximum research papers are published on the removal of these NSAIDs (Hama Aziz et al., 2017; Taoufik et al., 2020).

Though PhCs are designed to remain chemically stable, they can be further transformed via hydrolysis, photo-degradation, and sometimes bio-degradation also in the aquatic environment (Dubey et al., 2021; Ebele et al., 2017; Mamy et al., 2015). Though all of the PhCs may not be persistent, their constant discharge to the environment leads to pseudo-persistence (Patel et al., 2019).There are three possibilities for PhCs after entering the environment, first is complete mineralization of parent compound to inorganic compounds i.e. CO_2, water, nitrate, sulfate etc. Second is incomplete removal, which leads to the production of reactive intermediates, which can be more toxic compared to the parent compound. This fate is more common for hydrophilic PhCs. The third possibility is, parent PhC remain as it is because of its strong persistent nature and gets accumulated in environment. This happens with most lipophilic PhCs. Even for the PhCs of the same pharmacological class, the rates of removal in the environment are highly varied without any logical relationship (Patel et al., 2019).

It is difficult to analyze the environmental risk from PhCs, though their persistent nature, potential toxicity, and probable carcinogenic effect on living beings give rise to the need for environmental risk assessment. Researchers have reported that PhCs can pose severe health risk to living beings (micro-organisms and higher animals)even if at low concentration such as µg/L or ng/L (Taoufik et al., 2020; J. Zhang et al., 2021). The adverse effects of PhCs vary from metabolic alterations to hormonal imbalance. The PhCs could adversely affect endocrine system i.e. alteration in salivary gland, change in genetic system, and modifications in thyroid (Redding

et al., 2009; Rodriguez-Narvaez et al., 2017; Snyder et al., 2003). The PhCs also interfere with hormonal activity which alleviate the risk of breast cancer in humans and may act as an anti-androgen causing feminizing effects in males (Blair et al., 2013; Rokhina et al., 2012). Antibiotics which are designed to fight bacterial infections, may influence prokaryotic cells by inhibition of nucleic acid (DNA/RNA) synthesis, protein synthesis, and/or cell envelope synthesis. Furthermore, antibiotic resistance in microbial communities, gene expression alterations, abnormal protein and enzyme activities, and growth malformations in rats, fish, and frogs have all been observed (García-Fernández & Roy Editor, 2020; Patel et al., 2019; M. Yang & Zhang, 2016). Decline in vulture populations in Asiatic countries was due to the pharmaceutic Diclofenac (Cid-Cerón et al., 2016; Hu et al., 2012). Ethinyl-estradiol was found to cause feminizing effects on male fish (Rokhina et al., 2012). Even though at lower most concentrations, the mixture of some PhCs can instigate serious harm which is known as cocktail effect (L. Feng et al., 2013; García-Fernández & Roy Editor, 2020). Therefore, the cumulative effect of such pharmaceutical mixtures in drinking waters is a serious concern (Taheran et al., 2018).

The European Medicines Agency (EMA) issued guidelines in 2006 on Environmental Risk Assessment (ERA) for PhCs on the basis of serious problems they can pose to the environment. Diclofenac, ibuprofen, α-estradiol, and β-ethinylestradiol are included in the list of priority substances issued by The European Water Framework Directives on Priority Substances. Similarly, the United States Environmental Protection Agency (USEPA) added erythromycin, estrogenic hormones, and several other pharmaceutical ingredients in its third Contaminant Candidate List (CCL3). Unfortunately, there are no statutory maximum limits set for active PhCs in aquatic environment.

The best possible way to overcome this problem is to develop efficient treatment methods for the removal of aqueous PhCs. Because of the persistent nature of PhCs, the application of advanced oxidation processes (AOPs) for removal of these compounds is confirmed in past years. AOPs involve in-situ generation of radicals i.e. hydroxyl radical, sulfate radical, chlorine radical and other reactive species which attack recalcitrant PhCs. The PhCs are converted to various intermediate products and eventually to inorganic compounds i.e. water, CO_2, SO_4^{2-}, NO_3^- etc. AOPs have many environmental applications in water and wastewater treatment, especially to

destruct complex organic compound such as PhCs.

1.2 AOPs for the removal of aqueous PhCs

AOPs can be described as aqueous phase oxidation methods which involve generation of highly reactive species such as $^{\bullet}OH$ and $SO_4^{\bullet-}$ in the degradation mechanisms of targeted PhCs (Klavarioti et al., 2009). Basic AOPs include: heterogeneous and homogeneous photo-catalysis (based on near ultraviolet (UV) or solar visible irradiation), electrolysis, ozonation, Fenton processes and Fenton-like processes, ultrasound and wet air oxidation; whereas less conventional processes include: pulsed plasma, microwaves, and ionizing radiation. AOPs can be applied on the basis of targeted pollutants and the objective of treatment. AOPs can either be employed alone or combined with other physicochemical and biological processes. AOPs can also be used as pretreatment to biological processes to increase the biodegradability of waste stream. Conversely, for the waste streams having biodegradable constituents, biological pre-treatment followed by AOP as a post-treatment can work effectively.

Various AOPs have been applied by researchers to degrade or remove pharmaceuticals in water or wastewater. In accordance with the review presented by Kanakaraju et al., 2018, AOPs applied for PhCs removal can be categorized in three types: i. Photochemical processes i.e. photo-catalysis, photo-Fenton, and UV oxidation (UV/H_2O_2, UV/O_3 etc.); ii. Non -photochemical processes i.e. electrochemical oxidation, ozonation, Fenton, sonolysis, ultra-sonication, and irradiation; iii. Combination of AOPs i.e. photo-assisted AOPs, electro-assisted AOPs, sono-assisted AOPs. Though it is apparent from maximum reviewed studies that AOPs can efficiently degrade PhCs, identifying the intermediate products and evaluating toxicity levels are crucial.

1.3 Electrochemical oxidation (EO) for the removal of aqueous PhCs

The general design of EO comprises two electrodes connected to an electricity source through which electric energy is supplied to the supporting electrolyte in the cell containing PhCs. The moment an electric energy is supplied, strong oxidizing species are generated, which interact with the PhCs and degrade them. In the EO, the PhC oxidation can occur by i. direct oxidation, through electron transfer from the PhC to the anode, and/or by ii. indirect oxidation, through

chemical reaction with electro-generated reactive species depending upon the supporting electrolyte (Radjenovic et al., 2011). There are five principal operational parameters which govern the EO process: electrode material, initial pH, initial PhC concentration, current density, and supporting electrolyte(Ahmad et al., 2021; Martínez-Huitle & Panizza, 2018).There are active as well as non-active electrodes on the basis of their oxygen evolution over-potential, and direct or indirect oxidation pathway is related to these electrodes (Brillas et al., 2010). Boron doped diamond (BDD), lead oxides, tin oxides, and antimony oxides are examples of non-active anode, and they are responsible for direct oxidation (Aquino et al., 2012; Qiu et al., 2021).In contrast, active anodes support the formation of higher state oxides because of the strong interaction between $HO^{\bullet}$ and the electrode surface. Here the $HO^{\bullet}$ generated is considered as chemisorbed and interaction is restricted to the anode surface. The most common active anodes are platinum and mixed metal oxides coated anodes which are also called dimensionally stable anodes (DSA). In indirect oxidation, reactive chemical species (reactive oxygen species-ROS and reactive chlorine species-RCS) are electrochemically generated depending upon the supporting electrolyte and type of electrode used (Labiadh et al., 2017; Pointer Malpass & de Jesus Motheo, 2021). With the increase in current density, the PhC degradation rate is usually found to increase. The reason behind is the subsequent production of more $HO^{\bullet}$on the surface of the electrode. Nevertheless, after an optimum value, the PhC degradation rate is not increased consistently with an increase in current, suggesting that the oxygen evolution reaction predominates at higher current density (Palma-Goyes et al., 2018). The initial pH is supposed to play an important role as it affects the oxidation potential of PhCs, however, many researchers have reported highly varying results (Y. Yang, 2020). Because of the difference in organic structures, effect of pH is found to be different in many studies. The presence of inorganic anions (i.e. chloride and sulfate) and natural organic matter in the water matrices have an effect on the PhC degradation using EO (Barazesh et al., 2016).The major benefit of this process is no chemical usage during the process.

1.4 Peroxymonosulfate (PMS) based processes

Peroxymonosulfate (PMS) is a strong oxidizer with redox potential 1.85 V (Ling et al., 2017). PMS does not explicitly react with the organic pollutants and it needs to be activated by various means such as heat, UV, activated carbon, and transitional metals. PMS is readily water soluble (>250 g/L @ 20^0C). PMS is promptly activated because of its asymmetric structure and lesser bond energy requirement for the bond dissociation(Kumar et al., 2021). The general form of PMS used in research studies is Oxone ($2KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$).

For various activation methods, the intermediate oxidative species generated by PMS activation also vary. The sulfate radicals – $SO_4^{\bullet -}$ are common among these oxidative species: $^{\bullet}OH$, $O_2^{\bullet -}$, $^1O_2$, $SO_5^{\bullet -}$. Comparing redox potential of sulfate radicals with others i.e. hydroxyl radicals, chlorine radicals, superoxide radicals, and carbonate radicals; sulfate radicals have equal or even higher redox potential. These oxidative species have the potential for degradation of aqueous PhCs. In last decade, UV and metal oxide activation were the largely studied methods as per published research papers. Carbon-based materials have also been found to have potential for PMS activation. With a view to apply this process on large scale, heat activation and ultrasonic activation are not practical because of high energy demand. Carbon activation and metal oxide activation require more insight robustness. In case of nano composite-based activation, it takes time and effort to synthesize such materials. Among many activation processes, ferrous activation could be a promising process due to high activity, easy availability, cost effectiveness, and unhazardousness. However, for constant activation of PMS and reverse reaction from Fe^{3+} to Fe^{2+} transformation, ferrous salt requirement is high. PMS activation efficiency is adversely affected due to lower ferrous concentration (Du, Yang, et al., 2019; Govindan et al., 2015; Khan et al., 2013). One more disadvantage of using Fe^{2+}/PMS process is iron sludge generation is a considerable amount. Continuous supply of Fe^{2+} for PMS activation (EC/PMS) can solve this problem. Also, using iron as sacrificial anode solves the recycling issue of Fe^{2+} from Fe^{3+} that may occur at cathode (Govindan et al., 2014; N. Yang et al., 2015). By combining electrocoagulation (EC) and Fe^{2+}/PMS as EC/PMS, benefits of both processes can be availed and drawbacks are avoided. In the EC/PMS process, Fe^{2+} dosing can be regulated effectively by regulating the applied current density and this results in much lesser iron sludge generation. The added advantage is that

PMS can directly be activated by electricity as well (Govindan et al., 2014; Sun et al., 2020).

1.5 Need of the study

The Indian pharmaceuticals market is growing at a compound annual growth rate of 15.92 % and expected to touch USD 55 billion by 2022 from USD 36.7 billion in 2017. By 2023, India is expected be one of the top three pharmaceutical markets by incremental growth and sixth largest market globally by absolute size (Pharmaceuticals Industry Report, March 2022, *India Brand Equity Foundation*). Every year, massive amount of pharmaceuticals are released into the environment (Ebele et al., 2017). The presence of these compounds in environment have potential health effects on human i.e. antimicrobial resistance; cancerous, tumors, birth defects, and other developmental disorders because of endocrine disrupting compounds; and also on aquatic life i.e. feminization or masculinization by hormones and xeno-estrogens (J. Wang & Wang, 2016; J. Zhang et al., 2021). Moreover, there is a need of development of environment friendly removal processes which destruct the PhCs instead of separation from one phase to another. For that reason, removal of PhCs is one of the major environmental issues globally and drew special consideration. Even UN sustainable goals have included the removal of trace pharmaceuticals from water environments as one of the goals, which increases the seriousness of this matter.

Literature review shows that most of the studies of EO and EC/PMS for removal of PhCs were carried out in last decade. The volume and extent of these studies are not enough to understand these complex processes, especially for trace PhCs. Factors influencing these processes are mainly: electrodes, electrolyte, targeted PhC and its concentration, applied current density or voltage, and pH. In previous studies, few of these factors were analyzed. However, sparse studies were carried out on real matrices such as ROC. Also, studies were carried out in either sulfate or chloride medium, but in real matrices, both are being present in different amount. Study on the effect of this sulfate to chloride ratio was necessary. Furthermore, effect of applied current density was studied for the removal of targeted compound and not for the extent of overall degradation. Besides, analysis of the targeted PhC and its intermediate products undergoing these removal processes were not given enough consideration in previous studies. The first part of this study involving EO of DCF covered above mentioned all aspects. Likewise, electrocoagulation and PMS

activation, both processes were studied for removal of PhCs. There were previous studies which reported the application of combination of these processes for toxic organic compounds such as chlorophenols, however, this is the first study on application of EC/PMS for PhC removal to the best of our knowledge. In the later part of the present study, factors affecting this EC/PMS is studied using response surface methodology. Continuous flow application was explored as well which was never done before.

Overall, this study would add to the knowledge present in the field of EO and EC/PMS for removal of PhCs. Quenching studies, effect of sulfate to chloride ratio, and continuous flow application – are the most unique parts of this study.

1.6 Aim and objectives of the study

Aim of this research is to study electrochemical and peroxymonosulfate based processes for the removal of aqueous pharmaceutical compounds.

Objectives of this research are as follows:

- To carry out experiments on (i) electrochemical processes, (ii) peroxymonosulfate based processes, and (iii) various combinations of the above processes for removal from a PhC spiked reverse osmosis concentrate
- To understand the effect of various parameters of electrochemical and peroxymonosulfate based processes on PhC removal
- To conduct toxicity test on treated solution to evaluate end-product toxicity
- To identify intermediate products of oxidation for selected pharmaceutical compounds