Chapter 8
Advanced Treatment Methods for the Emerging Contaminants: An Insight into the Removal of Anticancer Drugs

Charulata Sivodia and Alok Sinha

Abstract Emerging contaminants (ECs) are unregulated chemical substances that on account of their persistent nature and high toxicity can cause inimical impact on the ecosystem. ECs occurred as a mixture of complex compounds where an undesirable synergy between them obviate their proper detection and remediation in the environment. Compounds like pharmaceuticals, personal care products, and polyfluoroalkyl substances comprised the major category of ECs. The surge in cancer incidence and chemotherapy treatment has enhanced the application of anticancer drugs (ACDs) which contributed to the existing problem of pharmaceutical pollution. ACDs being one of the major emerging contaminants are frequently detected in surface water, municipal wastewater, and pharmaceutical effluent that substantially causes genotoxic and mutagenic effects on the aquatic environment. Several remediation techniques were reported on the removal of pharmaceutical compounds such as anti-inflammatory, analgesic, and endocrine disruptors however very few studies documented the degradation mechanism of anticancer drugs. Hence, this chapter elucidates the occurrence of ACDs and their major route in the environment. In addition to this, the current treatment technology like ozonation, electrochemical treatment, and membrane bioreactor, employed for the removal of ACDs are also discussed.

Keywords Advanced treatment methods · Anticancer drugs · Emerging contaminants

8.1 Introduction

Emerging contaminants (ECs) are those chemical substances which occur either naturally or anthropogenically and subsists for a long period in the environment (Sauvé

C. Sivodia (✉) · A. Sinha
Department of Environmental Science and Engineering, Indian Institute of Technology (Indian School of Mines) Dhanbad, Dhanbad, Jharkhand 826004, India
e-mail: charu.sivodia@gmail.com

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and Desrosiers 2014; Galindo-Miranda et al. 2019). ECs slowly seek into the environment and trigger negative impacts on human health. Pharmaceuticals compounds are considered as a significant group of ECs, which are frequently detected in various water matrices and can potentially affect the environment (Fent et al. 2006; Marsalek 2008; Feier et al. 2017; Gojkovic et al. 2019). In aquatic environment, pharmaceuticals remain biologically active and resists degradation (Aherne and Briggs 1989; Chen et al. 2002; Cleuvers 2004). Nevertheless, so far research on the fate and removal of anticancer drugs (ACDs) has received very less attention. The surge in cancer patients leads to the increase in the consumption of chemotherapy drugs which become a matter of concern, since these drugs never metabolize completely and ultimately reaches into the water which enhance the water pollution load (Trombini et al. 2016; Gonçalves et al. 2022). The function of the ACDs is to intervene with the cancer cell to prevent the DNA replication (Załęska-Radziwiłł et al. 2011). Hence, these drugs can cause mutations at low level without even killing the cancer cells (O'Keefe 2011). This book chapter compiles the latest updates on the advanced treatment methods applied on the removal anticancer drugs.

8.2 Sources, and Fate of Anticancer in Environment

The fate of cytostatic in environment mainly depends on the factors like dose, category consumption, and excretion rate of drugs from in and outpatients. Hospitals particularly focused on the tumour treatment are also recognized as the alleged source of cytostatic in the environment. As a matter of fact, the rate of excretion is considered as the main source of chemotherapy drugs in the environment. (O'Keefe 2011), detected ACDs in urine (40%), bile (45%), and faeces (50%) samples and advocated that certain amount of unmetabolized ACDs passed through the outpatients to the municipal wastewater. Moreover, effluents from pharmaceutical industries also recognized as a potential source of ACDs which could reach to the aquatic environment (Mahnik et al. 2006; Lenz et al. 2007; Zhang et al. 2013). Kosjek and Heath (2011) stated that most of the ACDs have high solubility which pertains to their high mobility in water, and they possibly pass from the wastewater treatment plant (WWTP) effluent to the surface water. Roberts and Thomas (2006) reported the concentration of tamoxifen up to 694 ng L^{-1} in the wastewater effluent of Tyne catchment in UK. Azuma et al. (2015) detected different ACDs (cyclophosphamide, tamoxifen, doxifluridine, capecitabine, and bicalutamide) in the Yodo river and effluents of sewage treatment plant (STP) of Japan. The concentration of the ACDs were measured up to 55 ng L^{-1} in river and up to 316 ng L^{-1} in STP effluent. The above studies confirmed that apart from hospital effluent, ACDs were also detected in the wastewater effluent which suggests the incapability of the convention methods in removing refractory compounds. Further the occurrence of different ACDs is presented in Table 8.1.

Table 8.1 Most detected anticancer drugs in environment

Drugs	Concentration	Matrix	References
Cyclophosphamide	6–146 10–20; 64 2–43; 20	Hospital effluent Surface water WWTP -effluent	Steger-Hartmann et al. (1996), Steger-Hartmann et al. (1997) Ternes (1998), Moldovan (2006) Negreira et al. (2014) Cristóvão et al. (2021)
Cytarabine	9.9 1.3	WWTP -effluent Surface water	Jureczko and Kalka (2020)
5-fluorouracil	5–124,000	Hospital effluent	Mahnik et al. (2004), Kovalova et al. (2009)
Gemcitabine	0.9–38	Hospital effluent	Kovalova et al. (2009)
Tamoxifen	0.2–8 110–147;143–694	Hospital effluent WWTP-effluent	Liu et al. (2010), Roberts and Thomas (2006), Negreira et al. (2014)
Procarbazine	< 5	Hospital effluent	Yin et al. (2010)
Ifosamide	30–1914 2–27; 30–40	Hospital effluent WWTP-effluent	Kümmerer et al. (1997) Negreira et al. 2014), Cristóvão et al. (2021), Catastini et al. (2008)
Doxorubicin	0.1–10	Hospital effluent	Mahnik et al. (2006), Yin et al. (2010), Mahnik et al. (2007)
	2.7	WWTP-effluent	Negreira et al. (2014)

8.3 Toxicity and Effect of Anticancer Drugs on the Environment

Anticancer drugs are designed to kill the cancer cells by modifying the cell DNA structure. However, upon reaching the aquatic environment, the ACDs interfere with the cells of non-target biota and alter their molecular pathways (Kiffmeyer et al. 1998; Nussbaumer et al. 2011; Russo et al. 2020). The solubility factor is also considered as an important aspect of ACDs in environment which determines the presence of ACDs in water. Most of the ACDs are hydrophilic in nature with negative log Kow value. This blend of low Kow values and high solubility factor leads to the high mobility of ACDs in water (Meylan et al. 1999). Previous studies on the ecotoxicity of the ACDs suggests the potential toxicity of these drugs on the aquatic organisms. (Fonseca et al. 2018) conducted an exposure study of the cyclophosphamide on the ragworm *Nereis diversicolor*. The ragworm was exposed with the drug having concentration of 0.5 μg/L for fourteen days and damaged the DNA of the organisms completely. Liu et al. (2019), reported that cyclophosphamide not only affect the cell DNA but can also inhibit the activity of lactate dehydrogenase enzyme of the non-target organisms. The authors conducted an exposure study of cyclophosphamide with 320 μg/L concentration on the *Megalobrama amblycephala* for 24 h. The applied

dose of the drug results in the elevated levels of peripheral blood leukocytes in the blunt snout bream. ACDs can also induce histopathological modifications in kidney and liver of the aquatic organisms such as zebrafish (Kovács et al. 2015).

8.4 Treatment Techniques for Anticancer Drugs

Anticancer drugs (ACDs) considered as an emerging pollutant in water system and concerns are raised towards this category. Wastewater treatment plant play a crucial role in eliminating such persistent pollutant. However, the conventional processes, viz. adsorption, coagulation, and biodegradation lack complete removal of such compounds. Early studies reported on ACDs degradation were mostly devoted on the photocatalytic and UV-based treatment system.

8.4.1 Biological Treatment

8.4.1.1 Membrane Bioreactor (MBR)

Membrane bioreactor is recently explored as an effective treatment process for the removal of emerging pollutants. In MBR, activated sludge process is combined with the membrane filtration. (Delgado et al. 2009) studied the microbial behaviour of cyclophosphamide (CPH) and its major metabolite in a membrane bioreactor. The reactor run for 70 days along with a control without the drug. The chemical stress caused by CPH might obstruct the rate of sludge production where the energy consumption diverted towards the adaptive response instead of growth. This reflects the toxicity and low biodegradability of cytostatic drugs. In recent years advancement made in membrane technology improve the removal of refractory compounds. (Wang et al. 2018) employed forward osmosis method to enhance the removal efficacy of anaerobic membrane reactor. The anaerobic MBR-FO reactor was applied to eliminate a group of eight ACDs including cyclophosphamide, doxorubicin, and tamoxifen from wastewater. For the concentration of 100 ng/L, 95–97% of drug removed from the wastewater. Such elevated rate of drug removal suggests the high rejection capacity of the FO-MBR. It was also observed that molecular weight and surface charge of the ACDs mainly influenced the rejection capacity of the membrane. However, surge in volatile fatty acids implies the toxicity of ACDs towards the microbes. (Cristóvão et al. 2022), explored the potential of nanofiltration in removing ACDs namely cyclophosphamide, ifosamide, capecitabine, paclitaxel, and etoposide) in domestic wastewater at pilot scale. The removal efficiency of the applied system was maximized through operational parameters, viz. permeate flux, and recovery rates. The applied method results in 96% of rejection with 6 bar of pressure and 73% of recovery rate. Additionally, the samples did not induce any immobilization effect on the *Daphnia magna* species.

8.4.1.2 Fungi-Based Treatment

Besides membrane reactor, fungi-based degradation counts as a non-conventional biological method for the remediation of pharmaceuticals (Ferrando-Climent et al. 2015; Pereira et al. 2020). The enzyme associated with fungi species mainly participate in the degradation process. (Jureczko et al. 2021), used white rot fungi (WRF) for the attenuation of cytostatic drugs, viz. bleomycin and vincristine from conventional wastewater plant. The authors employed five species of WRTF namely *Trametes versicolor and Pleurotus ostreatus* which often used for the pharmaceutical removal. The degradation study was run over a period of 9 days that gives 95% of drug removal efficiency. Their study revealed that laccase and cytochrome P450 were the main enzymes which facilitates the extracellular oxidation and intracellular degradation. However, by-products formed by the parent compound was found as toxic to the fungal strains. Similarly, Yadav et al. (2022) also stated the potential of the WRF in the degradation of anticancer drugs. Their study evaluated three strains of WRF, viz. *Ganoderma lucidum, Trametes versicolor,* and *Phanerochaete chrysosporium*) on the removal of etoposide and cyclophosphamide. The *G.lucidum* strain has shown the highest removal of etoposide (99%) after six days of the treatment. However, only 71% of the cyclophosphamide was removed after treatment.

8.4.2 Advanced Oxidation Process

Advanced oxidation process is the chemical treatment method extensively used fort recalcitrant compounds. In this process factors like heat, catalyst, and light usually applied alone or in a combination to generate reactive oxygen species namely radicals. The high redox potential of these radicals significantly breaks the complex structure of hazardous compounds into non-toxic by-products rather than just a physical transformation (Khan et al. 2016; Zhao et al. 2019). A brief description of the types of AOP is given in Fig. 8.1 and the treatment techniques for the ACDs removal is represented in Table 8.2.

8.4.2.1 Photocatalysis

Photocatalysis is one of the significant AOPs which is widely applied in the wastewater treatment (Hasanpour and Hatami 2020; Sundar and Kanmani 2020). The main reaction in a photocatalytic process is initiated when a photon is absorbed ($h\nu$) in the presence of an incident light and generate electron–hole pairs on the surface of the catalyst. The electron (eCB^-) and holes ($h\nu_B$) thus produced are oxidizing and reducing species, respectively (Zhu and Zhou 2019). The electrons react with the dissolved oxygen and produce superoxide radicals (Eqs. 8.1 and 8.2). On the contrary, water molecules react with the generated holes and produce hydroxyl radicals as the oxidants (Eqs. 8.3–8.4) (Byrne et al. 2018; Wang et al. 2019; Motamedi

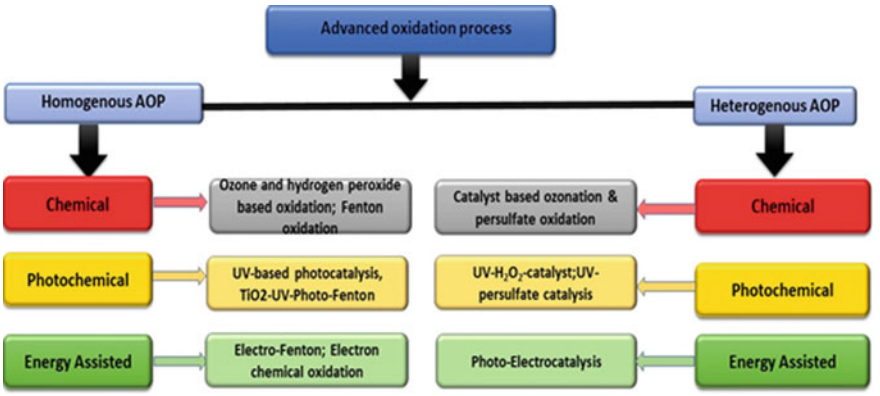

Fig. 8.1 Classification of different AOPs. Adapted and modified from Kim et al. (2022)

Table 8.2 Treatment methods applied on anticancer drugs

Target compound	Process	Matrix	Removal (%)	References
Cyclophosphamide Ifosfamide	Biological	–	59	Česen et al. (2015)
Irinotecan, Ifosfamide Cyclophosphamide Capecitabine	Ozonation	Hospital effluent	97	Ferre-Aracil et al. (2016)
Cyclophosphamide	Photocatalysis	Wastewater	69	Ofiarska et al. 2016)
Ifosfamide, Irinotecan Cyclophosphamide Capecitabine	Ozonation	Hospital effluent	97	Ferre-Aracil et al. (2016)
16 Anticancer drugs	Biological and photodegradation	Ultrapure water	50–90	Franquet-Griell et al. (2016)
Chlorambucil Cyclophosphamide Ifosfamide Decarbazine Tamoxifen Methotrexate	Ozonation	Wastewater	20–70	Li et al. (2016)
Cyclophosphamide	Membrane bioreactor	Wastewater	60	Seira et al. (2016)
Cyclophosphamide	Electrochemical oxidation	Ultrapure water	65–77	Siedlecka et al. (2018)
Doxorubicin	Electrochemical oxidation	Ultrapure water	85–100	Garcia et al. (2020)

et al. 2022).

$$\text{Photocatalyst} + \text{hv} \rightarrow h_{VB^+} + e_{CB^-} \tag{8.1}$$

$$e_{CB^-} + O_2 \rightarrow O_{2\cdot} \tag{8.2}$$

$$h_{VB^+} + H_2O \rightarrow {}^{\cdot}OH + H^+ \tag{8.3}$$

$$H_2O_2 + e_{CB^-} \rightarrow {}^{\cdot}OH + OH^- \tag{8.4}$$

To understand more about the fate and degradation of ACDs, Franquet-Griell et al. (2016) studied the behaviour of 16 ACDs from hospital and wastewater effluent through different treatment process (hydrolysis, aerobic biodegradation, and UV-C photolysis). During hydrolysis process the chemotherapy drugs like doxorubicin, melphalan, and chlorambucil which were stable at pH 4–7 having high dielectric constant removed completely (95%) from the system. While nine drugs out of 16 like cytarabine, etoposide, and cyclophosphamide showed only 50% removal. Later in biodegradation process most the compounds were found to be refractory to the applied process, which suggests process like advanced oxidation was required for further degradation. Lastly, photolysis was applied which gives > 90% of removal, although compounds having chlorine such as cyclophosphamide and ifosfamide still remain that were later removed in a combined UV-H_2O_2 system. At last, the ACDs removal were simulated in surface water by solar photocatalysis. It was observed that most of the drugs circumvents sun's radiation which reflect the stability of such drugs in the environment. The high toxicity of ACDs towards biological system leads to the addition of advanced treatment, hence in later research mostly photocatalysis and advanced oxidation process was applied.

Authors of Ofiarska et al. (2016) reported degradation of two ACDs namely ifosfamide and cyclophosphamide by photocatalysis using TiO_2 and Pt-doped TiO_2 catalyst. It was observed that when undoped TiO_2 was used the removal occurred in the bulk solution while in case of Pt-doped TiO_2, the removal occurred on the surface of the catalyst as well. The addition of platinum at the catalyst surface increased the electron or hole separation that further promote accumulation of the ${}^{\cdot}OH$ radicals at the TiO_2 surface. Apart from TiO_2, oxyhalides of bismuth was also used as photocatalyst in the degradation study of the anticancer drug (Wilczewska et al. 2021). It was established that halogen atom intersects the layer of BiO_2 which facilitate the electric field that eventually enhanced the conduction band of the semiconductor. Unlike other photocatalyst, BiO_2 generate superoxide radicals ${}^{\cdot}O_2^-$ as the main oxidant no matter what light source was used during the photodegradation process. When used for the degradation of 5-FLU, it shows 95% of removal efficiency with 90 min of reaction time.

8.4.2.2 Ozonation

Ozonation process has been significantly applied in the treatment of organic contaminants. Ozone is a strong oxidant which can be generated through pure oxygen by means of different methods like chemical, photocatalytic, and electric discharge (corona) (Joseph et al. 2021; Gorito et al. 2021). Ferre-Aracil et al. (2016) employed ozonation to a hospital wastewater effluent contained with cytostatic drugs. With ozone gas concentration of 43 g m^3 about 97% of the target drugs were eliminated. The key factor of their research was the economic assessment and development of a prediction model to study the behaviour of the ozone reactor. The applied model helps to determine the rate kinetics, total dissolved organic concentration along with chemical ozone demand. These factors later applied to evaluate the cost of the reactor.

8.4.2.3 Electrochemical Advanced Oxidation Processes (EAOPs)

Electrochemical advanced oxidation is associated with the in-situ generation oxidants like $^{\bullet}OH$ and H_2O_2 without adding chemicals as compared to usual AOPs. The mechanism behind the production of oxidant species is driven by the current supply (j) supplied across the anode and cathode that eventually reduce or oxidize the organic components into biodegradable compounds. Further section defines the different types of EAOPs.

Direct Oxidation

When the target compound oxidized at the electrode surface by means of direct electron transfer at anode then it is called as direct oxidation (Eq. 8.5). The direct oxidation depends upon two factors (i) diffusion process where the organic pollutant diffused through the electrolyte bulk solution to the anode surface and (ii) electrocatalytic property of the anode where interaction between the electrons and organic matter depends on the anode oxidation potential (Panizza and Cerisola 2009).

$$R \rightarrow +P + e^{-} \tag{8.5}$$

Indirect Oxidation

Indirect oxidation occurs when intermediate oxidant products generate at the interface of solution or at the anode surface in the presence of the external voltage (Eqs. 8.6 and 8.7) (Cavalcanti et al. 2013; Nidheesh et al. 2018). Whereas the generation of $^{\cdot}OH$ radicals in bulk through water electrolysis is knows as indirect electrode surface oxidation. Here the anode material plays a vital role in forming the oxidant species (Eq. 8.8) (Sánchez et al. 2013) (Paiva Barreto et al. 2015).

$$2H_2O \rightarrow H_2O_2 + 2H^+ + 2e^- \tag{8.6}$$

$$3H_2O \rightarrow O_3 + 6H^+ + 6e^- \tag{8.7}$$

$$M + H_2O \rightarrow M(^{\cdot}OH) + H^+ + e^- \tag{8.8}$$

Based on the formation of $^{\cdot}OH$ radical, oxidation mechanism of an electrochemical cell can be determined. The $^{\cdot}OH$ radicals thus formed get adsorbed at the anode surface either physically or chemically. When a chemical bond is established between the oxygen atom of $^{\bullet}OH$ molecules and anode surface then the radicals are chemically adsorbed (Eq. 8.9) (Panizza and Cerisola 2009; Brillas and Sirés 2015). Anodes like platinum, ruthenium, and graphite produce such radicals and they are known as active anode. On the other hand, radicals formed without any involvement of chemical bond form physiorbed radicals. These types of radicals are formed by electrodes such as boron diamond and are often called as inactive anodes (Escalona-Durán et al. 2020; Malpass and Jesus Motheo 2021). Furthermore, the reactivity of the anode also depends upon the oxygen evolution potential. The OEP of the non-active anode is less as compared to active anode thereby it shows higher reactivity towards organic compound. Moreover, oxidation of electrolytic solution also gives oxidizing radicals like Cl2, H2S2O8, and $HClO^-$ that are not as strong as $^{\bullet}OH$ radicals but can remain for a long time of duration in the system and diffused at the same time in the reaction medium (Eqs. 8.10–8.12) (Neodo et al. 2012; Chanikya et al. 2021).

$$M(^{\cdot}OH) \rightarrow MO + H^+ + e^- \tag{8.9}$$

$$M(^{\cdot}OH) + Cl^- \rightarrow M(HClO) \tag{8.10}$$

$$2Cl^- \rightarrow Cl_{2(aq)} + 2e^- \tag{8.11}$$

$$HClO \rightarrow H^+ + ClO^- \tag{8.12}$$

The structure of cytostatic drugs is complex having purine or pyrimidine rings and are mostly non-biodegradable, hence restrict the performance of conventional wastewater treatment plants. Only few studies were reported on removal of CSTs through electrochemical process. (Siedlecka et al. 2018), removed five cytostatic drugs from aqueous solution through BDD electrode. Their study suggested that compound having more electron donor sites such as cyclophosphamide were more resistant to hydroxyl free radical attack. Though, use of BDD at pilot scale could increase the cost of the electrochemical reactor. Use of inactive anodes like graphite might solve this problem as this electrode is inexpensive and widely used for organic pollutant removal. Graphite in presence of sodium chloride as an electrolyte, generate chlorine oxidants and was reported to eliminate 90% of cytarabine from aqueous

solution (Sivodia and Sinha 2020). The presence of anions in solution matrix also affects the degradation process, as anions like nitrite inhibit the oxidation process, while Cl^- ions accelerate the oxidation rate (Xu et al. 2020). The application of ECPs probably enhanced the biodegradability of such complex compounds.

8.5 Conclusions and Future Prospectus

Anticancer drugs as a group of pharmaceutical compounds become a matter of concern due to increase in the consumption rate, their endurance towards the conventional treatment methods (coagulation, filtration, and biodegradation) and carcinogenic effects on eukaryotic organisms. Besides, the ubiquitous occurrence of anticancer drugs in different water matrix such as surface water, groundwater, and wastewater effluent also reflect the resilience of ACDs against the applied treatment methods because of which they can easily seek into the environment. The chapter gives an insight on the ongoing remediation techniques of ACDs. Cyclophosphamide is the most studied compound of all ACDs because of its high consumption rate and low degradability. Oxidation process is the most effective technique which completely degrade the refractory compounds in a short span of time. The membrane technology also shown effective removal of various ACDs such as cyclophosphamide, capecitabine, and ifosamide, however higher removal efficiency was achieved only after combining other removal techniques. The number of studies reported on biodegradation of ACDs is limited and only white rot fungi has shown an effective degradation of the anticancer drugs. Also, toxicity study of the degradation by-products can also give more insights on the fate of ACDs after treatment. Lastly, removal of anticancer drugs in real water matrix should be explored to comprehend the implementation of the current methods at pilot scale.

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