Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
A sustainable approach for the removal methods and analytical determination methods of antiviral drugs from water/wastewater: A review

Bahriye Eryildiz a, b, Bahar Yavuzturk Gul b, c, Ismail Koyuncu a, b, *

a Istanbul Technical University, Environmental Engineering Department, Maslak 34469, Istanbul, Turkey
b National Research Center on Membrane Technologies, Istanbul Technical University, Maslak 34469, Istanbul, Turkey
c Department of Molecular Biology and Genetics, Istanbul Technical University, Maslak 34469, Istanbul, Turkey

A R T I C L E   I N F O

Keywords:
Antiviral drugs
COVID-19
Determination methods
Removal process
Virus
SARS-CoV-2

A B S T R A C T

In the last years, antiviral drugs especially used for the treatment of COVID-19 have been considered emerging contaminants because of their continuous occurrence and persistence in water/wastewater even at low concentrations. Furthermore, as compared to antiviral drugs, their metabolites and transformation products of these pharmaceuticals are more persistent in the environment. They have been found in environmental matrices all over the world, demonstrating that conventional treatment technologies are unsuccessful for removing them from water/wastewater. Several approaches for degrading/removing antiviral drugs have been studied to avoid this contamination. In this study, the present level of knowledge on the input sources, occurrence, determination methods and, especially, the degradation and removal methods of antiviral drugs are discussed in water/wastewater. Different removal methods, such as conventional treatment methods (i.e. activated sludge), advanced oxidation processes (AOPs), adsorption, membrane processes, and combined processes, were evaluated. In addition, the antiviral drugs and these metabolites, as well as the transformation products created as a result of treatment, were examined. Future perspectives for removing antiviral drugs, their metabolites, and transformation products were also considered.

1. Introduction

Pharmaceutical compounds, such as antiviral drugs, analgesics, antibiotics, anti-inflammatory medicines, beta-blockers, lipid regulators, X-ray contrast media, antidepressants and antipsychotics have become increasingly common in human and animal health care, to improve life quality and extend lifespan [1,2]. This increase in the use of pharmaceutical compounds has emerged as a global environmental problem in recent years [3]. Therefore, the widespread use of pharmaceutical compounds for a variety of purposes across the world needs careful monitoring of their contamination of water sources [2].

Antiviral drugs are a class of pharmaceuticals that are used to treat viral infections by preventing the growth of pathogens [4]. After the approval and distribution of the first antiviral drug, idoxuridine, on the market in 1963, the alarming rate of mortality due to viral infections prompted the creation of an increasing number of antiviral drugs [5,6]. These antiviral drugs are commonly used to treat a variety of viral infectious diseases, including influenza, human immunodeficiency virus (HIV), hepatitis and herpes [5,7]. A novel coronavirus (COVID-19) linked to respiratory diseases in humans was discovered in China, Wuhan in December 2019 [8,9]. COVID-19 as of March 2022 > 462,000,000 people have been infected, and >6, 000, 000 have died according to World Health Organization (WHO) [10]. In March 2020, WHO recognized the new coronavirus (COVID-19), also known as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2), as a worldwide pandemic, based on its fatal effect [11].

These antiviral drugs are common in wastewater due to the use of personal care items and pharmaceuticals in the home, as well as in the pharmaceutical industry and hospital waste [12]. Therefore, the use of these clinically tested antiviral drugs has the potential to pose a significant threat to the water resource quality for human consumption [8]. Parts of antiviral drugs that have not been completely metabolized are extracted by patients in their urine or feces and are then mostly disposed of in the sewage system. It has been found that up to 60 % of an applied dose of antiviral drugs is excreted by patients [4,7]. Eventually, antiviral drugs are discharged into receiving aquatic environment through the effluent release of wastewater treatment plants (WWTPs) because of inadequate removal in WWTPs [7,13].
Continuous drug use has resulted in increased water pollution and may have negative consequences such as aquatic toxicity, development of resistance in pathogenic microbes; genotoxicity and endocrine disruption in the aquatic ecosystem [1,14]. In addition, when an antiviral drug and the virus to be treated co-exist in the same waterbody, vulnerable organisms may acquire resistance. This might lead to the emergence of new antiviral resistance in the environment [15]. Therefore, it is essential to treat these drugs to eliminate the negative effects on the environment. Several treatment technologies including ozonation, photocatalysis, electrochemical advanced oxidation process, photo-catalysis, adsorption, activated sludge process and membrane bioreactor have been used to remove antiviral drugs from water/wastewater up to now. Although these technologies are efficient for removing antiviral drugs from the water supply, they have their drawbacks, including large equipment costs, high energy consumption, secondary contamination and the creation of additional harmful by-products.

There is a shortage of knowledge on the combined evaluation of antiviral drugs and viruses discharged into the environment, determination methods, and their treatment in the water/wastewater using various biological and non-biological processes. Thus, it is crucial to investigate the fate and determination methods in the environment. The goal of this review was to investigate the physicochemical properties, analytical methodologies for viruses and to be treated antiviral drugs and removal methods for antiviral drugs. Furthermore, the research addresses challenges that were faced as well as prospective prospects.

2. Antiviral drugs and virus

There are many viruses and antiviral drugs used in the treatment of these viruses in the literature. These antiviral drugs, their pharmacological and physicochemical properties are presented in Table 1 [16,17].

Antiretroviral drugs (ARVs) are medications that treat retroviral infections, especially human immunodeficiency virus type 1 (HIV-1) [20]. These drugs can significantly prolong the life of people who is HIV-positive. They consist of mainly six subdivisions such as nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase inhibitors, protease inhibitors, entry & fusion inhibitors and p450-3A inhibitors [18,19]. Also, the most commonly used ARVs for retroviral infections are abacavir, zidovudine, lamivudine, stavudine and nevirapine. These drugs can be used together to increase the curability of the HIV viruses [20].

Herpes simplex viruses (HSVs), which are double-stranded, enveloped DNA viruses of the Herpesviridae family, are common pathogens in humans [21,22]. These viruses generally occur in the oral and genital areas. However, while some of them affect children by causing chickenpox, which has possible complications such as encephalitis and pneumonia, some of them are caused by neuralgia and nerve palsy in adults [23,24]. Herpex simplex viruses consist of herpes simplex virus type 1 (HSV-1) which is the most susceptible, herpes simplex type 2 (HSV-2), varicella-zoster virus, cytomegalovirus and Epstein-Barr virus [25]. Acyclovir, one of the antiherpetics, is an antiviral drug used in the treatment of Herpex simplex viruses such as HSV-1, HSV-2 and Varicella-Zoster (VZV) [26]. Also, because of the physicochemical properties of acyclovir such as low water solubility, poor membrane permeability, and low oral bioavailability (15–30 %), its therapeutic properties may be reduced [26,27]. Famiclovir (FCV), is a pro-antiviral drug produced to increase the bioavailability effect of penciclovir. Both penciclovir and famciclovir are antiherpetics that are actively used against HSV-1, HSV-2 and VZV virus [28–30].

Influenza is a respiratory infectious disease that ranks high as one of the deadliest diseases in the category of infectious diseases with its rapid transmission rate [31,32]. Influenza viruses are classified as A, B and C according to their matrix proteins and nucleoproteins [33]. Influenza can be overcome as a very minor disease, in some cases, it can result in hospitalization or even death [34]. It is estimated that approximately 3 to 5 million serious infections are transmitted annually due to the influenza epidemic, resulting in 290,000 to 650,000 deaths from respiratory diseases all around the world [35]. Although vaccination is one of the effective treatments for influenza, it is less effective against special populations such as children, the elderly and people who have a weak immune system. In addition, since the production of the vaccine takes at least 6 months, antiviral drugs become a complement to vaccines [36]. Two groups of anti-influenza drugs, adamantanes (amantadine and rimantadine) and neuraminidase inhibitors (NAI) (oseltamivir and zanamivir) are used for the treatment of influenza infectious disease [33,37].

Due to the rapid spread rate of COVID-19 that firstly appeared in China, Wuhan in December 2019, it reached the status of pandemic disease [38–40]. Although there is no specific drug for the treatment of COVID-19, the drugs favipiravir, remdesivir, hydroxychloroquine, azithromycin and chloroquine have been subjected to clinical testing [41,42]. Favipiravir is an RNA virus polymerase inhibitor showing effective antiviral activity against several RNA viruses [43]. Therefore, favipiravir is treat COVID-19 in several countries such as Japan, Russia, Ukraine, Uzbekistan, Italy, and Turkey [44,45]. Remdesivir, the nucleotide analog of adenosine, is a drug used in the treatment of COVID-19 for people older than 12 years in the USA [46].

3. Occurrence and determination methods in the aquatic environment

3.1. Antiviral drugs

Antiviral drugs have been found in a variety of aquatic environments including raw wastewater, WWTP effluents, surface water and groundwater. Antiviral drugs reaching WWTPs are only partly eliminated, and

---

| Virus            | Antiviral drug | Trade name | Formula     | Molecular weight (MW) (g/mol) | Log Kow | pKa (acidic, basic) | Bioavailability |
|------------------|----------------|------------|-------------|------------------------------|---------|-------------------|-----------------|
| HIV              | Abacavir       | Zidovudine | C9H12N4O2   | 286.33                       | 1.2     | 15.41, 5.8        | 1               |
|                  | Zidovudine     | Retrovir   | C11H12N4O4  | 267.24                       | 0.05    | 9.96, - 3         | 1               |
|                  | Lamivudine     | Epivir     | C11H12N4O2S | 229.26                       | -9.54   | 14.29, -0.16      | 1               |
|                  | Stavudine      | Zerit      | C11H12N4O2  | 224.21                       | -0.72a  | 9.95, - 3         | 1               |
|                  | Nevirapine     | Viramune   | C11H12N4O2  | 266.29                       | 3.89    | 14.98, 3.28       | 1               |
|                  | Abacavir       | Zovirax    | C9H12N4O2   | 225.20                       | 1.56    | 11.98, 3.02       | 1               |
|                  | Famiclovir     | Famvir     | C10H12N4    | 321.33                       | 0.64    | 16.68, 3.65       | 1               |
|                  | Penclovir      | Denavir    | C12H12N4O2  | 253.25                       | -1.14   | 12, 2.88          | 1               |
|                  | Influenza      | Amantadine  | Gocovi      | 151.24                       | 2.44    | - 10.71           | 1               |
|                  | Zanamivir      | Relenza    | C10H12N4O2  | 312.4                        | 0.95    | 14.03, 9.31       | 1               |
| SARSCoV-2        | Favipiravir    | Favipiravir| C2H24N4O2   | 157.1                        | -       | 9.39, -3.7        | 1               |
|                  | Remdesivir     | Veklury    | C2H24N4O6P  | 602.58                       | -       | 10.23, 0.65       | 0               |

* at 37 °C.
they may find their way into the environment through hierarchical levels. Fig. 1 shows the many ways by which antiviral drugs can enter the environment from various sources and eventually reach drinking water sources. Unused antiviral drugs are thrown away in the sewage system, drains, and even in the garbage. Antiviral drugs can reach the environment through three major routes: the pharmaceutical industry’s effluent, medical waste, and medicines that are out of date, unused, or undesirable are disposed of away [13].

Since antiviral drugs are detected at low concentrations in environmental media, pre-concentration is necessary before analysis. Fig. 2 shows the analysis method for the detection of antiviral drugs. Analysis techniques of antiviral drugs are given in Table 2. Solid-phase extraction (SPE) is the most often utilized isolation and enrichment procedure in the literature. The SPE procedure can be performed on-line or off-line [47]. Moreover, suspended substances (SSs) such as colloids, microorganisms, and suspended particles, from aqueous environmental samples (i.e wastewater) are removed by filtering before extraction. Otherwise, SSs can occlude both the SPE cartridges and analysis systems [48]. Several SPE cartridges have been utilized to separate antiviral drugs from aqueous matrices in the literature. In the majority of the SPE procedures mentioned in Table 2, Waters Oasis hydrophilic-lipophilic balance (Oasis HLB, USA) cartridges are employed. Several methods such as liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) [49–58], high-performance liquid chromatography (HPLC) [59–64], ultra-performance liquid chromatography with positive electrospray ionization tandem spectrometry (UPLC-MS/MS) [65] and (ultraviolet) UV–Vis spectrophotometer [66,67] have been used to determine antiviral drugs from aqueous samples. In most cases, liquid chromatography-tandem mass spectrometry (LC-MS/MS) is used to quantify antiviral drugs from environmental waters and wastewaters due to high selectivity, accuracy, sensitivity and flexibility [68,69].

3.2. Viruses

Viruses are common and persistent in raw, treated wastewater and receiving water bodies [92]. Human feces, particularly that of diseased people, is a major source of viruses in wastewater and enteric viruses are discharged in sewage systems by infected people with approximately 105 to 1012 per gram of feces [93]. The bodies that receive treated wastewater are frequently used for recreational activities, agriculture, and as a supply of raw water for the manufacture of drinking water [94]. Pathogenic viruses in wastewater are a concern because of endangering human health [95]. Fig. 3 represents the possible transport ways and the fate of the virus in the environment.

Viral outbreaks are a global problem that has a negative impact on public health and safety. Virus diseases, particularly local influenza epidemics, have prompted researchers to focus on virus detection in wastewater and water [96–98]. COVID-19 has been spreading over the world, infecting millions of people, and causing significant loss of lives and economic damage. The present negative consequences of the COVID-19 pandemic need the development of novel detection tools for future viral outbreaks. Water-based epidemiology (WBE), which monitors viral RNA in wastewater, allows researchers to investigate COVID-
19 prevalence and spread in defined populations, which is useful for guiding public health policies [99]. There are excessive data on water and wastewater-based epidemiology in the literature. Some studies are summarized in Table 3.

Medema et al. (2020) conducted the first investigation on the occurrence of SARS-CoV-2 in sewage samples in the Netherlands. Sewage water samples were obtained from WWTPs in six Dutch towns. The SARS-CoV-2 virus was found in raw wastewater at the Kaatsheuvel WWTP and the Amsterdam Schiphol Airport’s Tilburg WWTP, according to the findings. Notably, the scientists stated that after the first person tested positive for SARS-CoV-2, the first water sample carrying the virus was tracked for 4 days. This was a significant and intriguing discovery in the light of the overall epidemic that is sweeping the globe [101]. Similarly, Ahmed et al. (2020) were the first to report the presence of SARS-CoV-2 in untreated wastewater (sewage) samples taken in Australia at two WWTPs and one suburban pumping station. 22.2 % of the total tested samples were positive. Furthermore, the authors estimated the number of infections using Monte Carlo simulation. If the water samples are found to be positive for SARS-CoV-2, the simulation will be carried out. As a result, the presence of SARS-CoV-2 in raw wastewater can act as an early warning signal in society for COVID-19 infections [100]. Furthermore, Sherchan et al. (2020) collected samples from two WWTPs for four months. The results showed that SARS-CoV-2 RNA was tested positive in roughly 13 % of the raw wastewater samples using RT-qPCR. However, SARS-CoV-2 RNA was not identified in the secondary-treated effluent wastewater or final effluent samples. The findings revealed that the SARS-CoV-2 was eliminated to undetectable levels during wastewater treatment operations [106]. Wu et al. (2020) verified SARS-CoV-2 positivity in Massachusetts. Using RT-qPCR, they evaluated wastewater collected from an urban treatment facility and identified SARS-CoV-2 RNA at 57–303 copies per ml of sewage. The measured viral titers were much greater than predicted based on clinically confirmed cases in Massachusetts at the time [102]. Similarly, Peccia et al. (2020) determined SARS-CoV-2 RNA quantities in primary sewage sludge from the New Haven, Connecticut, metropolitan region. SARS-CoV-2 RNA was found throughout the >10-week research. SARS-CoV-2 RNA concentrations in sludge were 0–2 days ahead of SARS-CoV-2 positive test results by specimen date of collection, 0–2 days ahead of the percentage of positive tests by specimen date of collection, 1–4 days ahead of local hospital admissions, and 6–8 days ahead of SARS-CoV-2 positive test results by reporting date. Their findings demonstrate the value of viral RNA tracking for SARS-CoV-2 infection surveillance at the community level in municipal wastewater [103]. The genome of SARS-CoV-2 was discovered in raw wastewater samples collected in three WWTPs in Italy, according to Rimoldi et al. (2020). The infectivity test, however, proved that the pathogenicity of SARS-CoV-2 coronavirus in wastewater was useless because of the lack of cytopathic impact (CPE). Viruses are frequently destroyed or rendered inactive during water treatment or purification operations [111]. Prado et al. (2021) discussed the results of sanitary sewage monitoring in Rio de Janeiro (Brazil) and its use as an additional indicator in the surveillance of COVID-19 cases, hence helping public health interventions from local authorities. Throughout 20 weeks, 12 composite raw sewage samples were obtained from two WWTPs and alternately from 17 sewer pipes (SP) from nearby neighborhoods. SARS-CoV-2 RNA was identified and quantified using RT-qPCR by the ultracentrifugation-based approach. During the peak of the pandemic, SARS-CoV-2 RNA was found in 84.3 % (188/223) of the samples, with a positive rate ranging from 42 % (5/12) in the first week of monitoring to 100 % and virus concentrations ranged from 3.1 to 7.1 log10 genome copies/100 mL during the investigation. Positive rates in WWTPs were higher than in SP, making them a useful tool for tracking trends in the evolution of the COVID-19 curve, although SP data were more efficient when public health actions were required [104]. The presence of SARS-CoV-2 in Pakistan was investigated by Sharif et al., (2021). A two-phase separation process is utilized for sample extraction and concentration. An additional high-speed centrifugation phase was performed before RNA extraction to increase viral RNA yield. SARS-CoV-2 was found in 78 wastewater samples collected from 38 different locations across Pakistan, as well as 74 wastewater samples from polio monitoring stations. 21 wastewater samples (27 %) from 13 districts tested positive for RT-qPCR. Positive SARS-CoV-2 RNA samples from locations with COVID-19 patients and a quarantine facility support the findings and future application of wastewater surveillance [105]. Recently, Monteiro et al. (2020) conducted the first investigation on the occurrence of SARS-CoV-2 in sewage samples in Portugal. Wastewater samples were obtained from WWTPs in two Portuguese towns. The SARS-CoV-2 virus was found in raw wastewater at the Sousel WWTP in Portugal. The findings demonstrated the value of viral RNA tracking for SARS-CoV-2 infection surveillance at the community level in municipal wastewater [106]. The genome of SARS-CoV-2 was discovered in raw wastewater samples collected in three WWTPs in Italy, according to Rimoldi et al. (2020). The infectivity test, however, proved that the pathogenicity of SARS-CoV-2 coronavirus in wastewater was useless because of the lack of cytopathic impact (CPE). Viruses are frequently destroyed or rendered inactive during water treatment or purification operations [111]. Prado et al. (2021) discussed the results of sanitary sewage monitoring in Rio de Janeiro (Brazil) and its use as an additional indicator in the surveillance of COVID-19 cases, hence helping public health interventions from local authorities. Throughout 20 weeks, 12 composite raw sewage samples were obtained from two WWTPs and alternately from 17 sewer pipes (SP) from nearby neighborhoods. SARS-CoV-2 RNA was identified and quantified using RT-qPCR by the ultracentrifugation-based approach. During the peak of the pandemic, SARS-CoV-2 RNA was found in 84.3 % (188/223) of the samples, with a positive rate ranging from 42 % (5/12) in the first week of monitoring to 100 % and virus concentrations ranged from 3.1 to 7.1 log10 genome copies/100 mL during the investigation. Positive rates in WWTPs were higher than in SP, making them a useful tool for tracking trends in the evolution of the COVID-19 curve, although SP data were more efficient when public health actions were required [104]. The presence of SARS-CoV-2 in Pakistan was investigated by Sharif et al., (2021). A two-phase separation process is utilized for sample extraction and concentration. An additional high-speed centrifugation phase was performed before RNA extraction to increase viral RNA yield. SARS-CoV-2 was found in 78 wastewater samples collected from 38 different locations across Pakistan, as well as 74 wastewater samples from polio monitoring stations. 21 wastewater samples (27 %) from 13 districts tested positive for RT-qPCR. Positive SARS-CoV-2 RNA samples from locations with COVID-19 patients and a quarantine facility support the findings and future application of wastewater surveillance [105]. Recently, Monteiro et al.
Table 2
Determination methods for antiviral drugs in water/wastewater.

| Antiviral drug | Metabolite | Matrix | Extraction | Detection method | Wavelength (nm) | Measuring range | References |
|----------------|------------|--------|------------|------------------|----------------|----------------|------------|
| Acyclovir      | –          | Aqueous solution | –         | UV-Vis spectrophotometer | 760          | –             | [66]       |
| Sofosbuvir     | –          | Aqueous solution | –         | UV-Vis spectrophotometer | 260          | –             | [67]       |
| Oseltamivir    | Oseltamivir carboxylate | Aqueous solution | –         | HPLC system tandem with a triple quadrupole mass spectrometer with electro-spray ionization (ESI) | –             | –             | [59]       |
| Staduvine      | –          | Wastewater treatment plant influent and effluent | –         | HPLC equipped with a fluorescent detector (FLD) | –             | –             | [60]       |
| Acyclovir      | –          | Aqueous solution | –         | High-performance liquid chromatograph equipped with a VP-ODS column and SPD-M20A photodiode array detector | 254          | –             | [70]       |
|                | Oseltamivir carboxylate | Synthetic river water | SPE | LC-MS/MS | – | 2–20 ng/L (LOQ) | [49]       |
| Oseltamivir    | –          | Aqueous solution | –         | HPLC with UV detection | 230          | –             | [71]       |
| Acyclovir      | –          | Aqueous solution | –         | HPLC | 275 | – | [61]       |
| Acyclovir      | –          | Reverse osmosis brine | –    | HPLC with UV detection | 254          | –             | [72]       |
| Lamivudine     | –          | Pure water | –         | Spectrophotometer | 297, 302, 313, 334, 365 and 366 | – | [73]       |
| Oseltamivir    | Oseltamivir carboxylate | River water | SPE | UPCL-MS/MS with electro-spray ionization (ESI) | –             | –             | [65]       |
| Zanamivir      | –          | Artificial fresh water | – | – | – | – | [74]       |
| Zidovudine     | –          | Municipal wastewater | SPE | LC-MS/MS | – | 0.1–0.2 ng/L (LOD) 0.2–0.7 ng/L (LOQ) | [50]       |
| Lamivudine     | –          | Synthetic river water | SPE | LC-MS/MS | – | 0.1–0.2 ng/L (LOD) 0.2–0.7 ng/L (LOQ) | [50]       |
| Nevirapine     | –          | River water | SPE | LC-MS/MS | – | 0.2–0.7 ng/L (LOQ) | [51]       |
| Favipiravir     | Oseltamivir carboxylate | River water | SPE | LC-MS/MS | – | 0.1–0.2 ng/L (LOD) 0.2–0.7 ng/L (LOQ) | [51]       |
| Lamivudine     | –          | Aqueous solution | –         | HPLC | 275 | – | [63]       |
| Lamivudine     | –          | Aqueous solution | –         | HPLC | 215 | 0.2 µM (detection limit) | [64]       |
| Lamivudine     | Oseltamivir carboxylate | Aqueous solution | –         | HPLC with UV detection | 220          | –             | [80]       |
| Zidovudine     | –          | Hospital wastewater | SPE | UPLC-MS/MS | – | – | [81]       |
| Lamivudine     | –          | Pharmaceutical wastewaters | – | HPLC/MS | – | – | [82]       |
| Zidovudine     | Oseltamivir phosphate (Tamiflu) | Oseltamivir carboxylate | Aqueous solution | HPLC with UV detection | 215          | 0.2 µM (detection limit) | [64]       |
| Zanamivir      | –          | Aqueous solution | –         | HPLC | 271 | – | [78]       |
| Lamivudine     | –          | Aqueous solution | –         | HPLC | 215 | 0.2 µM (detection limit) | [64]       |
| Lamivudine     | Oseltamivir phosphate (Tamiflu) | Oseltamivir carboxylate | Aqueous solution | HPLC with UV detection | 220          | –             | [80]       |
| Acyclovir      | –          | Hospital wastewater | SPE | UPLC-MS/MS | – | – | [81]       |
| Acyclovir      | –          | Pharmaceutical wastewaters | – | HPLC/MS | – | – | [82]       |
| Acyclovir      | –          | Wastewater treatment plant influent and effluent | – | LC-MS | – | – | [52]       |
| Acyclovir      | –          | Anaerobic sludge | SPE | LC-ESI-MS/MS | – | – | [53]       |
| Acyclovir      | –          | Synthetic wastewater | SPE | UFLC-4000 QTRAP hybrid triple quadrupole-linear ion trap mass spectrometer (QqLIT-MS) | – | 0.03–50.6 ng/L (LOD) 0.1–167.2 ng/L (LOQ) | [54]       |
| Acyclovir      | –          | Urban and hospital wastewater | SPE | LC-MS/MS | – | 0.03–50.6 ng/L (LOD) 0.1–167.2 ng/L (LOQ) | [54]       |
| Abacavir       | –          | Wastewater treatment plant influent and effluent | – | LC-tandem-MS and HPLC | – | – | [84]       |
| Lamivudine     | –          | Wastewater treatment plant influent and effluent | – | LC-tandem-MS and HPLC | – | – | [84]       |
| Zidovudine     | –          | Wastewater treatment plant influent and effluent | SPE | LC/MS/MS with ESI-positive ion mode | – | 0.30 ng/L (LOD) 0.92 ng/L (LOQ) | [55]       |
| Lamivudine     | –          | Synthetic wastewater | SPE | LC/MS/MS | – | 0.30 ng/L (LOD) 0.92 ng/L (LOQ) | [55]       |
| Lamivudine     | Oseltamivir carboxylate | Municipal wastewater | SPE | LC/MS | – | – | [86]       |

(continued on next page)
(2022) used the Charité assays (E Sarbecco, RdRP, and N Sarbecco) to track the dynamics of SARS-CoV-2 RNA at the five WWTPs that serve over two million people in Portugal over 32 weeks. They also studied raw wastewater from three COVID-19 hospitals. SARS-CoV-2 RNA detection was irregular in the first several weeks, with amounts ranging from $10^3$ to $10^5$ genome copies per liter (GC/L). The synchronicity between trends in SARS-CoV-2 RNA daily new COVID-19 cases highlights the value of WBE as a surveillance tool and in raw wastewater, especially after the epidemiological curve has been phased out and hotspots of disease re-appear in the population, which may be difficult to detect based only on contact tracing and syndromic surveillance.

Besides the studies conducted with wastewater limited research was published about tracking SARS-CoV-2 in water bodies. SARS-CoV-2 pollutes the water in a variety of ways. One method is to transfer SARS-CoV-2 infected untreated wastewater to rivers, lakes, or other bodies of water. Another option is to employ processed wastewater effluents that are infected with SARS-CoV-2 as a result of inadequate virus eradication from wastewater. The most common way in areas with poor basic sanitation is to dump raw sewage directly into bodies of water without treatment [95].

Guerrero-Latorre et al. (2020) reported the first detection of SARS-CoV-2 in a river from Quito, Ecuador. The scientists noted that the presence of SARS-CoV-2 in the river was caused by the city’s direct release of wastewater into river streams without any treatment [110].
Virus detection on water and wastewater.

| Disease | Virus | Source | Concentration method | RNA detection method | Virus concentration | References |
|---------|-------|--------|----------------------|----------------------|---------------------|------------|
| COVID-19| SARS-CoV-2 | Wastewater treatment center aerosols | The Coriolis®F (a liquid cyclone) Amicon 100 kDa tangential flow filtration devices (Millipore) | qPCR, Illumina MiSeq | %3.4-12.1 | [98] |
| | | River delta wetland | NW | qRT-PCR | 0.91 EID50/ml, 0.057 TCID50/ml | [96] |
| | | Fecal and water samples were collected at migratory stopover sites | Filter-concentration through cation charged filters (CCF) | qRT-PCR | 53 % stopover sites, 7 % and 4.8 % of the fecal and water samples | [97] |
| | | WWTP | Electronective membrane, ultrafiltration | qRT-PCR | 22 % | [100] |
| | | WWTP | Ultrafiltration | qRT-PCR | 2.6-2200 gene copies per mL | [101] |
| | | WWTP | Ultracentrifugation-based method | qRT-PCR | 57-303 copies per ml | [102] |
| | | WWTP | Two-phase separation method, high-speed centrifugation | qRT-PCR | 1.7 × 10^5-4.6 × 10^6 ml^-1 copies per ml | [103] |
| | | Raw wastewater | PEG precipitation, centrifugation | qRT-PCR | 3.1 to 7.1 log10 genome copies /100 mL | [104] |
| | | Municipal and hospital wastewater | Filtration 80.45-μm pore size | qRT-PCR | ND | [105] |
| | | River waters | Electronective membrane-vertex (EMV) method | qRT-PCR | ND | [106] |
| | | River waters | Skimmed Milk Flocculation method, centrifugation | qRT-PCR | ND | [107] |
| | | River waters | Real-time RT-PCR and infectivity test on culture cells | Positive nucleocapid (N) gene and the Orf1ab gene | [108] |

Rimoldi et al. (2020) reported a similar discovery of the SARS-CoV-2 virus in the Lambro River in Italy [111]. Furthermore, Haramoto et al. (2020) studied the presence of the SARS-CoV-2 virus in both WWTP and local river surface water in Japan. The SARS-CoV-2 RNA concentration in five secondary-treated wastewater samples (before chlorination) was quantified at 2.4 × 10^3 copies/L, according to the results of RT-qPCR analysis. In contrast, SARS-CoV-2 RNA was not found in the wastewater influent or river samples [109].

Notably, despite the presence of SARS-CoV-2 viral RNA in rivers, an infectivity assay on culture cells revealed that the coronavirus had no infectivity [112].

4. Antiviral drugs treatment technologies

4.1. Non-biological methods

4.1.1. Adsorption

Adsorption processes are used for the treatment of water/wastewater including some pharmaceuticals because of their simple design and low operation cost, low energy requirement and no production of by-products [113-115]. However, expensive adsorbs are a significant disadvantage [114,116]. In the adsorption process, various adsorbents such as activated carbons, clays, silica particles, carbon nanotubes, minerals and hydrous metal oxides [113,117-119]. One of the main challenges is the sustainable management of spent adsorbents [120]. To solve this problem, regeneration is a promising method that restores the adsorption capabilities of depleted adsorbents by desorbing the pollutants that have already been absorbed. Rather than replacing the adsorbents, it is commonly seen to be a less expensive and superior solution [121]. During wastewater treatment, several methods such as sedimentation, filtration, centrifugation, and magnetic separation techniques are utilized to separate and recover wasted adsorbents [120].

There are parameters such as adsorbent amount, pH, contact time and temperature that affect adsorption performance for the removal of antiviral drugs from water/wastewater. Jain et al. (2014) stated that pH, adsorbent amount and temperature considerably affected the removal of acyclovir from water using adsorption. They also reported these parameters according to their degree of impact as follows: adsorbent amount > temperature > pH [66]. In the study of Babas et al. (2020), the effect of operational parameters that consist of pH (3, 6.8 and 11), amount of adsorbent (10, 20 and 30 g/L) and initial concentration of sofosbuvir (0.05, 0.1 and 0.15 mM).

was investigated on the removal of sofosbuvir which is an antiviral drug for the treatment of Hepatitis-C. They discovered that optimum operational parameters were pH 6.8, adsorbent amount 20 g/L and initial sofosbuvir concentration 0.1 mM with the highest removal efficiency of 58.5 % [67].

Wang et al. (2015) investigated the removal of oseltamivir (OE) which is an antiviral drug for the treatment of influenza and oseltamivir carboxylate (OC) which is oseltamivir’s metabolite using adsorption. They concluded that when water/wastewater included initial oseltamivir and oseltamivir carboxylate concentration of 10^-4 mmol/L, the removal efficiency of these compounds was above 90 % using carbon nanotubes [59]. Kebede et al. (2020) searched treatment of wastewater that included some antiretroviral drugs using an adsorption process that its adsorbent is nanofibers produced from Monda whitei root extract. They evaluated the effect of adsorbent dose, initial drug concentration, pH, contact time and temperature on adsorption rate. They observed that most of the interaction of adsorbate-adsorbent occurred in the first 30 min. They stated that temperature and pH have a significant effect on the adsorption rate as they affect the physicochemical structure of the adsorbent and the molecule to be removed [60].
Advantages and disadvantages of removal methods for antiviral drugs are given in Table 4.

4.1.2. Advanced oxidation process

4.1.2.1. Photolysis (UV-based). Photolysis is one of the advanced oxidation processes that causes a chemical compound to decompose by exposure to artificial or natural light [130]. There are two classes of photolysis: direct and indirect. Direct photolysis is caused by UV absorption, whereas indirect photolysis occurs when an organic compound interacts with photosensitizers such as oxygen and hydroxyl or peroxy radicals [131].

Photolysis is used for the treatment of pharmaceuticals that are included in antiviral drugs in water/wastewater [61,132–134]. The efficiency of the photolysis for the removal of antiviral drugs can be affected by the pH, initial concentration of the antiviral drug, chemical properties of the water/wastewater and light source [70,73,135]. Due to the pKa value of each antiviral drug, its dissolution form may change at changing pH values. In the study of Jia et al. (2019), with increasing pH from 5 to 9, the ratio of the molecular form of acyclovir was decreased and the ratio of ion form of acyclovir (ACV) increased. Because of less susceptibility of free radicals to negative form of ACV, the photo degradation rate of ACV was slightly affected by the initial concentration of acyclovir [70].

Blum et al. (2017) examined the treatment of active 30 pharmaceutical ingredients including oseltamivir using photolysis for 28 days in river water. Also, they evaluated the photolysis rate of these compounds in a buffer that included ammonium acetate, filtered river water and unfiltered river water oseltamivir carboxylate was removed 10 to 40 % in three different water content under UV irradiation for 28 days. The different half-life results for the target pharmaceuticals in three different water content reveal the effect of the chemical properties of water sources on the kinetics of the photolysis process [49]. Tong et al. (2011) investigated the treatment of oseltamivir phosphate (Tamiflu) using different combinations of UV-based processes that consist of only UV, UV/H2O2 and UV/H2O2/Fe2+. They reported that since the formation and interaction of hydroxyl ions increases with the addition of H2O2 and Fe2+, the kinetic rate of photolysis to which these chemicals are added increases [71].

4.1.2.2. Ozonation. The breakdown of ozone, which is often used for water/wastewater treatment as a disinfectant and oxidant, leads to the formation of hydroxyl radicals during the ozonation process [136,137]. Pharmaceuticals are removed using an ozonation method with a high oxidation potential (E° = 2.07 V) that targets the oxidation of double bonds, amine groups or aromatic structures in their structures [138,139]. However, more harmful by-products than the original may be generated in water/wastewater treated with ozone treatment, and this toxicity may remain in water/wastewater to some extent [123]. Furthermore, since ozonation generates more biodegradable compounds, it can be used with biological treatment for the elimination of drugs [129,140]. Prasse et al. (2012) studied the removal of acyclovir and carboxy-acyclovir which is acyclovir's biotransformation product in drinking and surface water using the ozonation process. Results showed that the degradation of acyclovir and carboxy-acyclovir were significantly affected by the pH change, especially due to the effect of pH on amine parts in acyclovir and carboxy-acyclovir structures. COFA which is a by-product of ozonation did not oxidize even with increasing ozone dose while COFA found in wastewater treatment plant (WWTP) effluent decreased with rising ozone dose. They stated that there could be two reasons: (I) due to other reagents formed as a result of ozonation in wastewater and (II) increase of OH radicals with the acceleration of ozonation due to organic matter in wastewater. To test the biodegradability of COFA, COFA was added to the WWTP effluent and treated using biological treatment. There was no degradability of COFA in the first 48 h, but 40 % degraded after 14 days [75]. Therefore, intermediate products that may occur during the ozonation removal of antiviral drugs and their effects on the environment should be analyzed in-depth [76].

Table 4 shows non-biological technologies for the treatment of antiviral drugs.

| Methods                          | Advantages                                                                 | Disadvantages                                                                 | References |
|----------------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------|------------|
| Adsorption                       | Easy design                                                               | Expensive adsorbents                                                         | [114,116]  |
|                                  | Low operation cost                                                        |                                                                             |            |
| Photolysis (UV-based)            | Rapid reaction rate                                                       | Transformation products can be more permanent than original               | [50,77,122]|
|                                  | Cost-effective                                                            |                                                                             |            |
|                                  | Easy operation                                                            |                                                                             |            |
| Ozonation                        | Generation of more biodegradable products                                 | Generation of more harmful by-products                                      | [75,87]    |
| Photocatalysis                   | Cost-effective                                                            | Rare applicability in the real system                                     | [122]      |
|                                  | Highly effective                                                          | Expensive electrodes                                                        |            |
|                                  |                                                                           | High energy consumption                                                     |            |
| The electrochemical advanced     |                                                                           |                                                                             |            |
| oxidation process                |                                                                           |                                                                             |            |
| Activated sludge process         | Cheaper investment cost                                                   | Generation of transformation products that can be harmful                  | [123–126]  |
|                                  |                                                                           |                                                                             |            |
| Membrane bioreactor              | High-quality permeate                                                     | Biofouling                                                                  | [122,127–129]|
|                                  | Less sludge production                                                    |                                                                             |            |
|                                  | Lower environmental impact                                                |                                                                             |            |
|                                  | Small footprint                                                           |                                                                             |            |
|                                  | No need chemical                                                          |                                                                             |            |
|                                  | High performance                                                          |                                                                             |            |
was decreased due to the reduction of the TiO$_2$ photon absorption rate by taking more photons into the drug [63].

Reactive species called radical scavengers affect the efficiency of photocatalysis reactions. Wang et al. (2015) examined the effect of radical scavengers such as KI, ISO, and NaF on the removal of oseltamivir phosphate (OP) using photocatalytic degradation. Removal of OP was decreased with increasing potassium iodide (KI) while degradation of OP was enhanced with increasing NaF. The use of ISO did not give considerable effect on the removal of OP until C$_{ISO}$/C$_{OP}$ = 2, while degradation of OP was improved at C$_{ISO}$/C$_{OP}$ > 5. Also, the removal efficiency of OP was >95% with 20 and 100 mg/L P25 which is one of the powdered TiO$_2$ after 80 min of irradiation of UV-A [64].

4.1.2.4. The electrochemical advanced oxidation process. Electrochemical advanced oxidation processes (EAOPs) are alternative technologies for the removal of pharmaceutical compounds such as antiviral drugs [80,154,155]. Electrical current instead of chemicals was used for the production of OH radicals in the electrochemical advanced oxidation process [156]. EAOPs can be applied as two mechanisms for removing target pollutants: (I) direct oxidation is occurred at the surface of an anode or physically and chemically sorbed OH radicals (II) indirect oxidation is defined as the electrochemical production of compounds such as ozone (O$_3$), active bromine or S$_2$O$_5^2^-$, hydrogen peroxide (H$_2$O$_2$), active chlorine [157].

The removal of antiviral drugs by electrochemical degradation is affected by parameters such as pH, current density, initial concentration of antiviral drug and various inorganic ions [78,79]. The degradation of abacavir using electrochemical oxidation was examined by Zhou et al. (2019). They evaluated the effects of current density, pH and some ions on process efficiency for the removal of abacavir. As the electric current density was increased, antiviral drug removal was increased because of the increase in OH radical formation. After the current density was >0.2
mA/cm² of current, almost all of the abacavir was removed. Abacavir removal can be affected by pH because of its pKa and chemical structure containing an amide group, and this effect may not be significant in some pH ranges. Also, among inorganic ions such as NO₃, HCO₃, and Cl⁻, HCO₃ was the most inhibitive ion because of its preventing feature of OH radicals formation [78]. Wang et al. (2019) conducted electro-chemical oxidation experiments with different parameters such as pH, current density, initial antiviral drug concentration, and ions to remove lamivudine. They stated that degradation of lamivudine was improved with increasing electrical current density while removal of lamivudine was decreased with increasing initial lamivudine concentration because of the production of OH radicals on the anode surface. pH change did not considerably affect lamivudine removal. Since CO₂ can occur in the presence of HCO₃ and lamivudine removal was increased because of oxidizing the lamivudine by CO₂. However, NO₃ was an inhibitor for the degradation of lamivudine due to the formation of NH₃ [79].

4.2. Biological methods

4.2.1. Activated sludge processes

Activated sludge processes consist of many physical, chemical and biological processes containing oxidation, sorption, volatilization and mainly biodegradation and can be used for the removal of pharmaceuticals including antiviral drugs [52,158]. Compared to advanced processes, the activated sludge process has cheaper investment cost than most advanced processes and can be easily operated. Pharmaceutical compounds can be transformed into a toxic form as a result of removal using other treatment processes such as chlorination and ozonation while organic and inorganic materials are oxidized and turned into gases and sludge in the activated sludge process [123–126].

The degradation of antiviral drugs by the activated sludge process can be explained by the oxidation of the hydroxyl-moiety to the carboxyl-moiety [84]. Xu et al. (2017) examined the biological degradation of acyclovir using an activated sludge process under different ammonium conditions. Results showed that acyclovir biodegraded to carboxy-acyclovir even with different initial concentrations and different ammonium conditions. Also, the removal of acyclovir was enhanced with an increasing ammonium oxidation rate [83].

There are several parameters such as pH, the amount of dissolved oxygen, hydraulic retention time (HRT), organic loading rate (OLR), solids residence time (SRT), temperature and microbial community that affects on removal performance of the activated sludge process [159–164]. Matsua et al. investigated the biodegradation rate of pharmaceuticals including oseltamivir in wastewater treatment plant using activated sludge process. They stated that oseltamivir was removed at <50 %. Four different wastewater that have different SRT and temperature values were used in their study. The removal efficiency of oseltamivir and other pharmaceuticals was increased when the temperature was high and SRT was long [55]. Treatment of three pharmaceutical wastewaters that have different acyclovir concentrations and other characteristics such as TOC, and COD using aerobic biological process were examined by Mascolo et al. (2010). They found that almost all acyclovir was biologically removed. But acyclovir in wastewater that has the highest TOC and acyclovir concentration was treated slower than the other two wastewater because of the degradation time of the TOC [82]. The removal efficiency of pharmaceutical compounds including antiviral drugs by activated sludge is related to LogKow values which are measures of hydrophobicity. Muriuki et al. (2020) stated that since nevirapine and lamivudine have high hydrophobicity properties, these antiviral drugs can be easily adsorbed to solid. This adsorption capacity was also affected by sludge age. The adsorption capacity decreased with increasing sludge aging [56]. Also, Azuma et al. (2018) stated that the degradation of antiviral drugs in activated sludge is associated with log Kd value which is the solid-water partition coefficient [81].

Biological technologies for the treatment of antiviral drugs are presented in Table 6.

4.2.2. Membrane bioreactor

Membrane bioreactor (MBR), which is a modification of the activated sludge process, is used for the treatment of pharmaceuticals including antiviral drugs and consists of a biological reactor and a membrane module. Membrane filters the particulate from waste in the reactor and ensures the purification of the wastewater [89,165–167]. The membrane bioreactor is operated under two major configurations: submerged MBR and external MBR [168]. Compared to the conventional activated sludge process, the membrane bioreactor has several advantages such as high-quality permeate, less sludge production, operation at higher mixed liquor suspended solids (MLSS) concentrations, lower environmental impact and small footprint [127–129].

Treatment of pharmaceutical wastewater containing acyclovir using membrane bioreactor was investigated by Mascolo et al. (2010). Results showed that the removal efficiency of acyclovir using MBR was approximately 98 %. Some by-products formed as negative ions were found after MBR treatment. These by-products were reduced by 90 % with the MBR treatment method [87]. Arriaga et al. carried out a study about the treatment of organic micropollutants such as acyclovir in the effluent of wastewater treatment plant using MBR. They operated MBR in two stages. Stage 1 operated with continuous feeding that included some pharmaceuticals while stage 2 operated without the addition of pharmaceuticals. Acyclovir removal was approximately 60 % for stage 1 and around 90 % for stage 2 [88]. Performance of two-staged anaerobic fluidized membrane bioreactor (SAF-MBR) with granular activated carbon was compared to activated sludge for treatment of pharmaceutical compounds including some antiviral drugs and their by-products after disinfection by McCurry et al. (2014). They stated that similar to aerobic processes, the anaerobic system occurs as sorption due to hydrophobicity in the removal of pharmaceuticals containing antiviral drugs. It was reported that except for emtricitabine whose removal rate was almost 50 %, acyclovir, abacavir and lamivudine were removed at >80 % using SAF-MBR [86].

4.3. Combined processes

The removal of antiviral drugs in water/wastewater has been investigated by combining processes. Knopp et al. (2016) investigated the removal of micropollutants containing antiviral drugs using biological treatment combined with ozonation. Then, experiments were carried out with two biological filters or granular activated carbon filters. They stated that acyclovir was removed 94 % with only biological treatment and the concentration of carboxy-acyclovir that is transformation product of acyclovir was increased. Acyclovir and carboxy-acyclovir were removed 100 % and carboxy-acyclovir converted into N-(4-carbamoyl-2-imino-5-oxo imidazolidin)-(formamido-N-methoxyacetetic acid (COFA) which is more toxic than acyclovir during ozonation. They reported that both GAC filters and biological filters failed to reduce COFA [91]. Mascolo et al. (2010) examined the treatment of pharmaceutical wastewater that contained acyclovir using a membrane bioreactor coupled with ozonation. Results showed that removal of acyclovir was approximately 100 % using membrane bioreactor-ozonation. Removal of the by-product formed during ozonation has been effectively achieved once it has been re-entered into the MBR system. If this treatment configuration (ozonation after MBR) is used, similar by-product elimination can only be achieved when the ozonation is run for >60 min, resulting in a high operational cost [87]. Schlüter-Vorberg et al. (2015) investigated the degradation of acyclovir by biological treatment integrated ozonation. Also, they evaluated the toxicity of acyclovir and its transformation products for the environment. Acyclovir was completely converted to carboxy-acyclovir which is the only transformation product from acyclovir during biological treatment. During ozonation, carboxy-acyclovir converted to COFA and unidentified transformation products. According to ecotoxicological tests, while the reported toxicity of C-ACV and COFA does not imply an
intolerable environmental risk, the findings highlight the need to research the toxicity of TPs in general, especially if they are generated from parent pharmaceuticals such as ACV that have no aquatic toxicity [56].

5. Future perspectives

In recent years, the occurrence and fate of antiviral drugs in the environment have attracted the attention of scientists, particularly in light of the COVID-19 pandemic. These drugs accumulate in the environment since they are persistent and resistant to biodegradation. Even at low concentrations, they can have negative effects on the aquatic environment. Therefore, various removal processes have been investigated to address environmental pollution issues.

Several antiviral drugs enter the environment and can eventually reach some even drinking water supplies [13]. Therefore, effective antiviral drug treatment in WWTPs is critical. The removal of these pharmaceuticals by most current treatments used in WWTPs (such as coagulation, flocculation, sedimentation, and filtration) can be ineffective [169]. Also, there is a great lack of the removal of antiviral drugs from WWTPs in the literature. Future studies should be performed on the occurrence, removal and mass loads of antiviral drugs in WWTPs.

Advanced oxidation processes (AOPs) have emerged as a viable option because of the resistant nature of effluents containing antiviral drugs. Ozonation and photodegradation that have been mostly used in the literature are successful in removing antiviral drugs in several studies [49,70,71,75,76]. However, these treatment methods can cause the production of more permanent products than the original antiviral drug [65]. Therefore, novel treatment methods for removing antiviral drugs from water/wastewater should be investigated. Adsorption, membrane processes and electrolysis can also be utilized to remove antiviral drugs, their metabolites and transformation products from water/wastewater.

Adsorption can be used as an alternative removal technique for the treatment of antiviral drugs, although it is not commonly employed to remove antiviral drugs. This approach was found to be quite successful (antiviral drug removal efficiency of 58.5–90%) [59,67]. In addition, the adsorbent materials can be fabricated from agricultural residues and

### Table 6

| Antiviral drugs | Matrix | Concentration | Treatment technology | Process conditions | Removal | References |
|----------------|--------|---------------|----------------------|-------------------|---------|------------|
| Oseltamivir    | Municipal sewage treatment plant influent | 5–100 ng/L | Activated sludge process | Effluent quantity; ~49 m³, Temperature: 25 °C, SRT: ~14 day, TOC: 9900 mg/L, COD: 26700 mg/L, pH 6.7, Time: 28 day | <50 % | [55] |
| Acyclovir      | Three pharmaceutical wastewater | 170 mg/L | Activated sludge process | Temperature: 20–25 °C, TOC: 20200 mg/L, COD: 54800 mg/L, pH 6.4, Time: 28 day | >90 % | [82] |
| Acyclovir      | Municipal wastewater | 600 ng/L | Aerobic treatment system | Flow rate: ~27,000 m³/gün, Time: ~70–75 % | <80 % | [86] |
| Acyclovir      | Hospital wastewater | 15 mg/L | Activated sludge treatment | Temperature: 20 °C and dark, Reactor volume: 2 L, HRT: 24 h, SRT: 15 day | >90 % | [81] |
| Acyclovir      | Milli-Q water | 15 μg/L | Activated sludge treatment with the addition of nitrifying culture | Dissolved oxygen concentration: 2.5–3 mg/L, pH: 7.5–8, Initial ammonium: 50 mg/L, Secondary treatment with disinfection, Feed flow rate: 1.6 L/day, Recirculation flow rate: 4.8 L/day | 88.2 % | [83] |
| Acyclovir      | Urban and hospital wastewater | – | Aerobic biological treatment | Secondary treatment with disinfection | 90 % | [54] |
| Acyclovir      | Pharmaceutical wastewater | 154 mg/L | Membrane bioreactor | Membrane module: hollow fiber membrane, Membrane surface area: 0.047 m² | 98 % | [87] |
| Acyclovir      | Wastewater treatment effluent | – | Membrane bioreactor | MBR system volume: 250 L, HRT: 10 h, Flow rate: 5.5 m³/day, Two anaerobic fluidized bed reactor, HRT: 6.8 h, SRT: 36 days | 60–90 % | [88] |
| Abacavir       | Municipal wastewater | 600 ng/L | Staged anaerobic fluidized membrane bioreactor | Two anaerobic fluidized bed reactor, HRT: 9.9–11.4 h, SRT: 24.2–27.7 days, Flow rate: ~27,000 m³/gün | <10 % | [56] |

### Table 6 continued

| Antiviral drugs | Matrix | Concentration | Treatment technology | Process conditions | Removal | References |
|----------------|--------|---------------|----------------------|-------------------|---------|------------|
| Lamivudine     | –      | 90–100 ng/L   | –                    | Effluent quantity; ~49 m³, Temperature: 25 °C, SRT: ~14 day, TOC: 9900 mg/L, COD: 26700 mg/L, pH 6.7, Time: 28 day | <50 % | [55] |
| Penciclovir    | –      | –             | –                    | Temperature: 20–25 °C, TOC: 20200 mg/L, COD: 54800 mg/L, pH 6.4, Time: 28 day | >90 % | [82] |
| Valaciclovir   | –      | 15 mg/L       | –                    | Temperature: 20 °C and dark, Reactor volume: 2 L, HRT: 24 h, SRT: 15 day | >90 % | [81] |
| Acyclovir      | –      | 15 μg/L       | –                    | Dissolved oxygen concentration: 2.5–3 mg/L, pH: 7.5–8, Initial ammonium: 50 mg/L, Secondary treatment with disinfection, Feed flow rate: 1.6 L/day, Recirculation flow rate: 4.8 L/day | 88.2 % | [83] |
| Acyclovir      | –      | –             | –                    | Secondary treatment with disinfection | 90 % | [54] |
| Acyclovir      | –      | 154 mg/L      | –                    | Membrane module: hollow fiber membrane, Membrane surface area: 0.047 m² | 98 % | [87] |
| Acyclovir      | –      | –             | –                    | MBR system volume: 250 L, HRT: 10 h, Flow rate: 5.5 m³/day, Two anaerobic fluidized bed reactor, HRT: 6.8 h, SRT: 36 days | 60–90 % | [88] |
| Abacavir       | Municipal wastewater | 600 ng/L | Staged anaerobic fluidized membrane bioreactor | Two anaerobic fluidized bed reactor, HRT: 9.9–11.4 h, SRT: 24.2–27.7 days, Flow rate: ~27,000 m³/gün | <10 % | [56] |
offer an economical alternative because of their low cost [170]. Therefore, there is a need for more studies on the treatment of antiviral drugs from water/wastewater using an adsorption process with different low-cost adsorbents.

Membrane processes, such as reverse osmosis, nanofiltration and membrane bioreactors, have attracted a lot of attention in the pharmaceutical industry [171–174]. Antiviral drugs can be removed and recovered without any chemical modifications by the use of appropriate membranes. The generated water was quite clean and could be reused without additional treatment in a circular economy approach.

Although combined techniques are not widely used, they are one of the most effective strategies for removing antiviral drugs from water/wastewater and significantly reducing the toxicity of treated water/wastewater. The most common combination approach is an AOPs followed by biological treatment, membrane, or even an adsorption process [56,87,91]. Because of their complexity, high operation costs, and in most cases, inability to operate in a continuous mode, these approaches are rarely used [130].

A wide range of antiviral drugs have been utilized to treat COVID-19 patients. Favipiravir is one of the antiviral drugs used to treat COVID-19. In the literature, there are still few investigations on the presence, removal, fate, and ecotoxicological impacts of favipiravir and other antiviral drugs used to treat COVID-19 [175,176]. Because of the potential negative impacts of these antiviral drugs on the environment, both their transportation and their environmental impact must be thoroughly examined.

6. Conclusions

In recent years, the presence and fate of antiviral drugs in environmental matrices have gotten a lot of interest from the scientific community. These pharmaceuticals are chemically stable and resistant to biodegradation, accumulating in the environment. Even at low concentration levels, they can negatively affect aquatic and terrestrial ecosystems. Therefore, it is of great importance to investigate various degradation/removal methods of these drugs to address environmental pollution concerns. Robust and sensitive analytical approaches are necessary to investigate the risks posed by antiviral drugs in terms of consumption and persistence in the environment. Given the restricted methods for detecting antiviral drugs in an aqueous solution, more accurate detection approaches are required. The majority of the research is focused on the removal of oseltamivir. In recent years, the use of antiviral drugs has increased, especially with COVID-19, and this causes an increase in the concentration of these drugs in the environment. Thus, more study is needed to effectively remove additional antiviral drugs from water/wastewater. However, data on the metabolites of antiviral drugs, their removal products, measurement and fate are largely lacking in knowledge. The gap in this area needs to be filled.

Abbreviations

3TC Lamivudine
ACV Acyclovir
AOPs Advanced oxidation processes
ARVs Antiretroviral drugs
CCF Cation-charged filters
COD Chemical oxygen demand
COFA N-(4-carbamoyl-2-imino-5-oxo imidazolidin)-formamido-N-methoxyacetetic acid
COVID-19 Novel coronavirus
EAOps Electrochemical advanced oxidation process
ED50 Egg infectious doses
EMV Electronegative membrane-vortex
FCV Famiclovir
GC Genome copies
H2O2 Hydrogen peroxide
HIV-1 Human immunodeficiency virus type 1
HIV Human immunodeficiency virus
HPLC High-performance liquid chromatography
HRT Hydraulic retention time
HSV-1 Herpes simplex virus type 1
HSV-2 Herpes simplex type 2
HSVvs Herpes simplex viruses
KI Potassium iodine
LC-MS/MS Liquid chromatography coupled with tandem mass spectrometry
LMV Lamivudine
MBR Membrane bioreactor
MLSS Mixed liquor suspended solids
MW Molecular weight
NAI Neuraminidase inhibitors
ND Not detected
NNRTis Non-nucleoside reverse transcriptase inhibitors
NRTs Nucleoside/nucleotide reverse transcriptase inhibitors
NVP Nevirapine
O3 Ozone
OASIS HLB Oasis hydrophilic-lipophilic balance
OC Oseltamivir carboxylate
OE Oseltamivir
OLR Organic loading rate
OP Oseltamivir phosphate
qPCR Quantitative polymerase chain reaction
qRT-PCR Quantitative reverse transcription-polymerase chain reaction
S2O82– Active bromine
SAF-MBR Staged anaerobic fluidized membrane bioreactor
SARS-CoV-2 Severe acute respiratory syndrome coronavirus
SPE Solid-phase extraction
SRT Solids residence time
SSs Suspended substances
TCID50 Tissue culture infectious dose
TOC Total organic carbon
UPLC-MS/MS Ultra-performance liquid chromatography with positive electrospray ionization tandem spectrometry
UV Ultraviolet
VZV Varicella-Zoster
WBE Wastewater-based epidemiology
WWTPs Wastewater treatment plants
ZDV Zidovudine

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

References

[1] C.F. Couto, I.C. Lange, M.C.S. Amaral, Occurrence, fate and removal of pharmaceutically active compounds (PhACs) in water and wastewater treatment plants—a review, J. Water Process Eng. 32 (2019) August.
[2] M. Bilal, K. Rizwan, M. Adeel, H.M.N. Iqbal, Hydrogen-based catalyst-assisted advanced oxidation processes to mitigate emerging pharmaceutical contaminants, Int. J. Hydrogen Energy (xxxx) (2021).
[3] P. Krasucka, A. Rombel, X.J. Yang, M. Rakowska, B. Xing, P. Oleśczuk, Adsorption and desorption of antiviral drugs (ritonavir and lopinavir) on sewage sludges as a potential environmental risk, J. Hazard. Mater. 425 (November 2021) (2022) 127901.
[4] L. Yao, W.Y. Dou, Y.F. Ma, Y.S. Liu, Development and validation of sensitive methods for simultaneous determination of 9 antiviral drugs in different various environmental matrices by UPLC-MS/MS, Chemosphere 282 (May) (2021), 131047.
S.E. Bear, M.T. Nguyen, J.T. Jasper, S. Nygren, K.L. Nelson, D.L. Sedlak, Removal of pharmaceuticals, toxicants and emerging contaminants from wastewater using advanced treatment processes: a review. J. Hazard. Mater. 270 (2014) 124–132.

S. Jang, H.S. Kim, S.Y. Ham, J.H. Park, H.D. Park, Investigation of critical sludge characteristics for membrane fouling in a submerged membrane bioreactor: role of soluble microbial products and extracted extracellular polymeric substances, Chemosphere 271 (2021), 129879.

V. Homem, L. Samuel, and P. Roberto, Measurement and removal of antibiotics from aquatic matrices – a review. Environ. Manag. 92 (1) (2020) 2304–2347.

D.L. Giokas, A.G. Vlessidis, Application of a novel chemometric approach to the treatment of pharmaceutical wastewater, Environ. Sci. Pollut. Res. 20 (2013) 921–932.

V. Jang, H.S. Kim, and S.Y. Ham, Comparison of photocatalytic activities of photoreactors of different geometric characteristics, Environ. Eng. Sci. 36 (6) (2019) 630–639.

B. Jin, Z. Wang, Y. Chen, Y. Hu, and H. Liu, Photocatalytic degradation of pharmaceuticals in water by oxygenated electrochemical oxidation: parametric optimization, kinetic studies and toxicity assessment, Sci. Total Environ. 691 (2019) 417–429.

Z. Wei, et al., Electrolyte index as a critical indicator for the biodegradation of the pharmaceuticals in aerobic activated sludge processes, Water Res. 160 (2019) 10–17.

B. Hu, J. Quan, K. Huang, J. Zhao, G. Xing, Effects of C/N ratio and dissolved oxygen on aerobic denitrification process: a mathematical modeling study, Chemosphere 272 (2021) 127606.

P. Izadi, P. Izadi, A. Eldyasti, Understanding microbial shift of enhanced biological phosphorus removal process (EBPR) under different dissolved oxygen (DO) concentrations and hydraulic retention time (HRTs), Biochem. Eng. J. 166 (September) (2020) 105550.

K. Kumar, G.K. Singh, M.G. Dastidar, T.R. Sreekishnan, Effect of mixed liquor volatile suspended solids (MLVSS) and hydraulic retention time (HRT) on the performance of activated sludge process during the biotreatment of real wastewater, Water Resour. Ind. 5 (2014) 1–8.

D. Dionisi, A.A. Rasheed, Maximisation of the organic load rate and minimisation of oxygen consumption in aerobic biological wastewater treatment processes by Alzheimers disease and solid residues solid race time, J. Water Process Eng. (2017) 105.

L.M. Pantea, J.E.A. Timothy, M. Lapara, C. Wisniewski, A. Grasmick, Floc size distribution in a membrane bioreactor and performance comparison of phenol biodegradation via suspended biofilm, Chem. Eng. J. 359 (August) (2019) 321–330.

P. Izadi, P. Izadi, and M. Mousavi, Application of a novel hybrid electrochemical reactor for the simultaneous removal of phenol, 1-nitroso-2-naphthol and anionic dyes, Sep. Purif. Technol. 166 (2016) 325–332.

B. Eryildiz et al., Recovery, regeneration and sustainable management of spent pharmaceutical waste, Environ. Chem. Lett. 12 (1) (2014) 24–27.

J. C. Orona-Nadal, F. García, A. González, S. López, M. Álvarez-Torres, and E. Alguacil, Evaluation of the potential of different activated carbons for the adsorption of pharmaceutical pollutants, Sci. Total Environ. 741 (2020) 140321.

A. V. Baskar, et al., Recovery, regeneration and sustainable management of spent pharmaceutical waste, Environ. Chem. Lett. 12 (1) (2014) 24–27.

C. Orona-Nadal, F. Garcia, A. Gonzalez, S. Lopez, M. Alvarez-Torres, and E. Alguacil, Evaluation of the potential of different activated carbons for the adsorption of pharmaceutical pollutants, Sci. Total Environ. 741 (2020) 140321.

K. Tan, et al., Removal of pharmaceuticals, toxicants and emerging contaminants from wastewater using advanced treatment processes: a review. J. Hazard. Mater. 270 (2014) 124–132.

S. Jang, H.S. Kim, and S.Y. Ham, Comparison of photocatalytic activities of photoreactors of different geometric characteristics, Environ. Eng. Sci. 36 (6) (2019) 630–639.
[173] D. Dolar, A. Vuković, D. Asperger, K. Kosutić, Effect of water matrices on removal of veterinary pharmaceuticals by nanofiltration and reverse osmosis membranes, J. Environ. Sci. 23 (8) (2011) 1299–1307.

[174] C.F. Couto, et al., Assessing potential of nanofiltration, reverse osmosis and membrane distillation drinking water treatment for pharmacologically active compounds (PhACs) removal, J. Water Process Eng. 33 (October 2019) (2020) 101029.

[175] S. Allahverdiyeva, O. Yunusoglu, Y. Yardim, Z. Şentürk, First electrochemical evaluation of favipiravir used as an antiviral option in the treatment of COVID-19: a study of its enhanced voltammetric determination in cationic surfactant media using a boron-doped diamond electrode, Anal. Chim. Acta 1159 (2021).

[176] K. Kiyannehr, G. Moussavi, S. Mohammadi, K. Naddaf, Chemosphere the efficacy of the VUV/O₃ process run in a continuous-flow fluidized bed reactor for simultaneous elimination of favipiravir and bacteria in aqueous matrices, Chemosphere 304 (April) (2022), 135307.