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A review of emerging micro-pollutants in hospital wastewater: Environmental fate and remediation options

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ABSTRACT

Hospitals played vital role in the maintenance and sustenance of human health. However, hospital activities generate high volume of toxic solid and liquid containing diverse inorganic, organic and microbial wastes released untreated into the ecosystem. The management of hospital wastewater in particular has been a major source of concern due to the presence of unregulated emerging micro-pollutants at concentrations in the range of ng/L to μg/L. These pollutants at low concentration exert different potential health effects on human and aquatic species. In this review, the formation, composition, properties and ecotoxicology effects of selected emerging micro-pollutants (Norfloxacin, Ofloxacin, Ciprofloxacin, Clofibric acid and Carbamazepine) at different concentrations in hospital wastewater were reviewed. The review also elucidates on detection and quantification of concentration of different emerging micropollutants in hospital wastewater by Spectrophotometry techniques, Gas Chromatography, Ion Chromatography, Gas Chromatography-Mass spectrometry, and High-Performance Liquid Chromatography. Furthermore, treatment of hospital wastewater through physical, biological, chemical, adsorption and advanced oxidation processes such as photocatalysis and photo-Fenton including their operational mechanism were provided. The chemistry and mechanism of degradation of the selected emerging micropollutants into several intermediates were reviewed. It was found that conventional wastewater treatment methods are not designed for effective removal of these unregulated pollutants in hospital wastewater because they exist as mixtures at very high concentrations and exerts different toxicological effects. The review also reveals that no single technology can effectively detoxify the wastewater, instead combination of methods such as (phototcatalytic/adsorption or photo-fenton/adsorption) was found most appropriate for hospital wastewater treatment. Finally, regular monitoring and determination of physicochemical and ecotoxicological parameters and treatment of hospital wastewater are recommended.

1. Introduction

Hospitals played critical role in the maintenance of the health status of a country citizen. On the other hand, hospital activities are often accompanied with the generation of diverse inorganic, organic and microbial components usually released without prior treatment into the environment. Hospital waste management has been a major source of concern to the environmental chemist due to the presence of toxic contaminants that exerts harmful impacts on human and aquatic species. According to Ogwugwa et al. [1], daily wastewater generated in the hospital per bed varies from 40 to 120 L in developed countries and 2–50 L in developing countries like Nigeria [2]. Existing general services namely laundry, kitchen, number and type of wards and units, temperature control systems; numbers of outpatient and inpatients; facility age, number of beds, and maintenance procedures; institutional management practices, geographic location, period of services, and season all have impacts on the volume of wastewater generated in any hospital [3]. The water consumption in hospitals has been estimated between 200 and 1200 L per bed per day, with highest values obtained from developed nations and the lowest from developing countries (200–400 L/bed/day) [4]. In industrialized countries, total hospital wastewater output range from 250 to 570 m^3 per day, with a fraction of hospital wastewater ranging from 0.2 to 65% flown and processed in municipal wastewater treatment facilities [4].

Hospital wastewater is loaded with several emerging micro-

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Abbreviation

AOP	Advanced oxidation processes
BPC	Base Peak Chromatogram
CA	Clofibric Acid
CIP	Ciprofloxacin
CBZ	Carbamazepine,
DNA	Deoxyribonucleic Acid
EC50	Half Maximal Effective Concentration
EIC	Extracted Ion Chromatogram
GC-MS	Gas Chromatography Mass Spectrometry
HPLC	High Performance Liquid Chromatography
NGOs	Non Governmental Organization
NOR	Norfloxacin
NOEC	No Observed Effect Concentration
OFL	Ofloxacin
PEC	Projected Environmental Concentration
pH	Potential Hydrogen
TIC	Total Ion Count
TCS	Triclosan
UTI	Urinary Tracts Infections
UV–Vis	Ultraviolet Visible Radiation

pollutants such as; original or metabolized pharmaceuticals compounds such as anti-inflammatory, anti-diabetic, antiepileptic, pesticides residue, industrial chemicals, perfluorinated compounds, surfactants, personal care products, analgesics, disrupting compounds, endocrine, antibiotics and hormones radioactive elements, and microorganisms such as; fecal coliform, total coliform, pathogens (*E. coli, Vibrion Staphylococcus aureus, Salmonella, and Pseudomonas aeruginosa*), radioelements, and heavy metals [5]. Some of these pollutants are categorized as micro-pollutants (10^{-6} –10^{-3} mgL^{-1}) or macro-pollutants ($>10^{-3}$ mgL^{-1}) based on their measured quantities, and the majority have no regulatory status in the environment [6].

Of particular interest are the emerging micro-pollutants, these are natural or synthetic substances not routinely monitored in the environment but have the potential to infiltrate and exert different health problems [7]. These chemicals enters the ecosystem through different point and non-point sources such as release of untreated wastewater generated, half used and expired products, manufacturing processes and excretion of partially mineralized drugs from the body into sewer system [8]. Drugs with active ingredients are metabolized after administration and the unmetabolized active substances are excreted either unaltered compounds, or conjugated with an deactivating agent or a combination of metabolites linked to the molecule [9], For instance, urine accounts for 55–80% of the total unmetabolized active ingredients [10] and partially in faeces, and thus enter the water cycle. Waste generated from laboratory, diagnostic unit, and operating theater through patients make hospitals key providers of these wide range of micro-pollutants [3]. Chemicals, disinfectants, heavy metals, and sterilizants, iodinated contrast media, and radioactive markers are among the active principles of medications and their metabolites [3].

Hospital effluents have a toxicity that is 5–15 times that of an urban effluent and this constitute serious human and environmental risks following organisms exposure to hazardous substances, or infiltration into groundwater [11,12]. Hospitals, on the other hand, are not the only source of pharmaceutical residues found in all wastewater treatment plants due to their micro properties [6]. Regardless of their variations, in most cases, hospital effluents are categorized as having the same pollution load as sewer wastewaters and are released into public sewage systems, and received as an urban wastewater in treatment facility, and treated in the same manner. The predicted concentrations or observed values of pharmaceutical residues in hospital wastewater are calculated using characteristics such active component intake, water consumption per bed, and percentage excretion [9]. Exposure to these pharmaceutically active residual compounds has contributed to the increasing antibiotic resistance, as most bacteria and fungi have ability to destroy the drugs. For instance in United States of America (USA) alone, approximately 2.8 million antibiotic-resistant infections and 35,000 deaths have been reported yearly, thus considered as emerging areas of concern.

Most municipal wastewater treatment plants are designed for the removal of biodegradable compounds such as, carbon, phosphorus, and nitrogen molecules, as well as microorganisms, but not micro-pollutants such as chemical and pharmaceutical residues, and endocrine disrupting compounds [9]. However, Chlorination is sometimes required for the treatment of the total hospital wastewater, and other times the treatment is just required for the effluent from infectious disease units before being discharged into the municipal sewer [13].

Many authors believe that treating urban and hospital wastewaters in a municipal effluent treatment plant is ineffective because it relies on dilution of diverse outputs and did not allow for pollutant isolation [14,15], particularly emerging micro-pollutants and dangerous compounds, from the liquid phase [16]. Micro-pollutants, particularly pharmaceuticals, are difficult to remove from wastewaters because their concentrations are in the range of 10^{-3}–10^{-6} mg/L, which is significantly lower than that of traditional macro pollutants (COD, BOD_5, phosphorus and nitrogen compounds) [17]. Furthermore, emerging micro-pollutants encompass a wide range of compounds with significant variances in their primary features, which influence their behavior and fate in the wastewater treatment process. The biodegradability and physicochemical qualities such as; water solubility, adsorption, and volatilization of typical pollutants found in hospital wastewater determine their removal effectiveness [18]. The features of wastewater treatment plants (that is, tertiary, secondary and primary treatments), operating circumstances (sludge retention time, temperature, pH and hydraulic), reactor type, and other variables are affected by biodegradability and physicochemical qualities [6]. Since there are new analytical standards which are commercially available; the number of emerging micro-pollutants based on recent investigations continue to increase, and more than 300 pharmaceutical residues and conjugates chemical have been identified. Current researches have been to conduct health risk assessment of number of compounds, because of growing evidence of possible influence on aquatic creatures (such as organ abnormalities, genetic lesions, reproductive abnormalities, and behavioral alterations) and antibiotic-resistant genes and bacteria [19], thus, these pollutants are of special concern.

Owing to various problems of hospital wastewater and its derivative, several conventional methods such as; chlorination [20], ozonation [21], reverse osmosis [22], activated carbon adsorption [23], ultra-filtration [24], electro-coagulation [8] have been applied for their removal from wastewater. However, each of the methods has different associated setbacks. For instance, chlorination technology often lead to formation of disinfection by-products (DBPs) which are very more harmful and carcinogenic to human being [25]. Ozonation, and reverse osmosis are very costly [26]. Adsorption technology always generates toxic sludge which occupies space during processing [27]. All these setbacks make it difficult to achieve the desired treatment of wastewater.

On the contrary, advanced oxidation processes (AOPs) have been found suitable for successful removal and degradation of toxicants/pollutants through generation of oxidizing agent (hydroxyl radicals or other free reactive species) [28]. Different researchers have studied degradation of hospital wastewater and its derivatives (such as tetracycline antibiotic, Phenol Forrnaldehyde, Choramphenicol, Norfloxacin, Ciprofloxacin, Dichlofenac, Acetaminophen and Atenolol) using photocatalytic technology [29], Electro-oxidation [30], Electro-fenton [30], Electrocatalysis [31], Ozonation [26], Photo-Fenton [32], Metallic Nanoparticles [33], and Fenton reaction [34]. Most of these techniques are capable of degrading various pollutants nevertheless their efficiency

is low [35,36].

Recently, research attention has shifted to hybrid/combination of different treatment techniques to achieve the desired degradation efficiency of emerging micro-pollutants in hospital wastewater within short period of time. In this review paper, the following emerging micro-pollutants namely Norfloxacin, Ofloxacin, Ciprofloxacin, Clofibric acid, Carbamazepine were selected due to their increase prevalence in the water bodies across the world coupled with the growing cases of bacterial infections rate among patients. Norfloxacin, Ofloxacin and Ciprofloxacin all belong to quinolone antibiotics family used for the treatment of bacterial related infections especially such as urinary tract infections (UTI). Specifically, Norfloxacin is applied primarily to subdue spontaneous bacterial peritonitis (SBP) in patients with liver cirrhosis while Ciprofloxacin is also known for curing SBP in patients. Studies have shown that UTI is one of the most globally prevalence health problem especially among women and out of 8 million patients in one each year, 10 in 25 women and 3 in 25 men usually have symptoms of a UTI. Clofibric acid is an antilipemic agent used for the treatment of hypertrigly ceridemia and high cholesterol. Carbamazepine is a drug used for the treatment of patients' diagnosed with epilepsy and severe diabetes (peripheral neuropathy). It is estimated that 5 million individuals worldwide are diagnosed with epilepsy each year. Epilepsy is estimated to affect 49 persons out of every 100,000 in high-income nations each year. Each year, 139 people in middle and low-income nations are diagnosed with epilepsy.

Thus, to the best of our knowledge, this is the first review on occurrence, environmental fate, quantification of the selected emerging micro-pollutants in hospital wastewater. The review also provides insight on the different analytical methods for the detection and quantification of the emerging micro-pollutants. The review also provides an overview of the conventional methods of treating hospital wastewater namely: the physical, biological and chemical counterpart. In addition, the review also focus on the theory, mechanism and application of advanced oxidation processes such as photocatalysis, photo-Fenton and combined advanced treatment techniques for the removal of the selected micro-pollutants in hospital wastewater. This state-of-art review also outline new insights on the mechanisms and degradation of the selected emerging micropollutants and formation of various intermediates based on the adopted treatment method.

2. Formation and composition of hospital wastewater

Hospital wastewater encompasses varieties of conventional and non-conventional parameters based on the geographical locations. The formation and compositions (Bacteriological, heavy metals and Pharmaceutical residues) are discussed in this section.

2.1. Bacteriological composition

The evaluation of markers of fecal contamination and pathogens is usually included in the bacteriological composition of hospital wastewater. *E. coli* is generally used to identify fecal coliforms since it accounts for 80–90% of thermo-tolerant coliforms identified [37]. *E coli* is a kind of facultative anaerobic bacterium found in the stomach and feaces. The presence of *E coli* in hospital wastewater indicates fecal pollution, and besides *E coli*, other harmful fecal microorganisms such as spores of sulfite-reducing anaerobes, *Staphylococcus aureus, Salmonella typhii, Pseudomonas aeruginosa;* and pathogenic viruses (rotavirus, norovirus, enterovirus, adenovirus) and hepatitis A virus are also exist in high proportion in hospital wastewater [1]. Thus, Enterovirus concentrations have been shown to be 2–3 times higher in hospital wastewater than in municipal wastewater [38].

2.2. Heavy metal composition

Different heavy metals have been found in hospital wastewater [39], such as platinum via excretion by Oncology patients who have been given *cis*-platinum, carboplatinum, or other cytostatic drugs. [40]; Mercury is widely found in disinfectants, diagnostic agents, and diuretics as active components [5]; and due to gadolinium large magnetic moment, it is often found in iodinated contrast medium used in magnetic resonance imaging [41]. Mercury, and platinum are the most common heavy metals detected in hospital effluents [39]. Other heavy metals, such as copper, lead, cadmium, iron, and nickel, are commonly found in municipal wastewater at similar amounts [39,42–44]. Due to the high magnetic moment imaging of the digestive system, with three magnetic resonance imaging systems serve 15 to 25 patients on a daily basis, spine (MRI), and brain, gadolinium-containing compounds such as gadopentetic acid, gadodiamide, and Gd-diethylenetriamine pentaacetate are delivered (intravenously or orally) regularly. After a few hours of administration, the contrast media are excreted unmetabolized into hospital sewage. It was established that approximately 90% of gadolinium is eliminated during the patient's stay in hospital within 24 h [45], while at home, an excretion rate of 85–98% within 70 min may be achieved. For instance, Oliveira et al. [46], detected gadolinium in effluent from Freiburg University Hospital Germany. Mercury is commonly found in agents of diagnostic, disinfecting active components, and agents of diuretic. In hospital wastewater, mercury contents vary from 0.3 to 7.5 g/L [47]. Since the early 2000s, developed nations have made an attempt to decrease mercury pollution by adopting diagnostic agents without this heavy metal and establishing improved waste management techniques.

Since the mid-1970s, platinum-containing compounds such as; carboplatin and cisplatin, have been utilized as anti-neoplastics in oncology [46]. These antineoplastics are eliminated at various rates after administration (patient dependent). Within the first 24 h following administration, Carboplatin is excreted in 50–75% rate [46]. Cisplatin is excreted between 31 and 85% rate within 51 days after treatment. The two long-term stages of platinum renal excretion have biological half-lives of 160 and 720 days, respectively. 70% of the platinum given is anticipated to be excreted in hospital wastewater [46]. The platinum content was measured by Kümmerer et al. [48], in five European hospitals of various sizes and found to vary between 174 and 2514 beds with concentrations ranging between 3.5 and 0.01 g/L. The authors examined the fluctuation in platinum concentration in the Freiburg University Hospital, Germany over the period of 24 – hour and discovered two concentration maxima at 10 a.m. and 4 a.m. Platinum temporal variability was measured for one week at the main building of the Geneva University Hospital (741 beds – Switzerland) by Daouk et al. [49], who found a significant rise at the end of the week. Platinum concentrations were measured between 0.01 and 2 gL^{-1} and a ranged of 2.0–289 g/L was found in an oncological unit in Vienna, Austria [50]. They carried out a platinum speciation study and discovered that carboplatin was the major cause of Platinum loading.

2.3. Pharmaceutical residues composition

The use of medicines varies greatly amongst healthcare institutions [51]. For instance, the entire pharmaceutical consumption of a nursing home, a mental hospital, and a regular hospital in Germany has been calculated and varied from 32 kg/year (hospital of psychiatric) to 1263 kg per year (general hospital), with yearly average pharmaceutical consumption ranges between 0.1 and 1000 g per bed [5]. Contrast media, analgesics, antibiotics, laxatives, anti-inflammatories, and cytostatic medicines are the most commonly used therapeutic categories in hospitals [52].

Pharmaceutical residues in hospital wastewater are determined by a combination of three primary factors: the amount given, the fraction excreted, and the chemical properties (primarily biodegradability and stability) [53]. In diverse geographic locations, hospital wastewater have been tested for pharmaceutical residues (Asia – [54], Europe – [55], and North America – [56].

Mayoudom et al. [56], reported the analysis of 12 pharmaceuticals in hospital wastewater and found to have the concentration in range of 78 μgL^{-1} and 5 mgL^{-1}. The percentage distribution of therapeutic categories is dependent on the analyte under investigation, which usually account for 94% of the total concentrations tested. The most common treatment groups are contrast media, analgesics, cytostatics, and anti-infective and anti-bacterials, which account for more than 40% of the total concentration observed in hospital wastewater [3]. Other identified classes of pharmaceuticals detected include anti-epileptic, psychoanaleptic, anti-inflammatory, and -blocker medications with a maximum concentration of 20% of the total concentration tested [3].

The majority of pharmaceuticals found in hospital wastewater had maximum values of less than 10 g/L [57]. Higher concentrations are usually detected for particular chemicals (such as; ibuprofen, acetaminophen, ciprofloxacin, caffeine, iomeprol, gabapentin, iopamidol, iopromide, theobromine, metformin), with numerous contrast media agents at the low concentration in mgL^{-1} range [9]. Daouk et al. [49], examined different categories of pharmaceuticals in Geneva University Hospital Switzerland with beds of 741 capacities and calculated mean daily loads to be between 0.1 and 14 g/day for 15 pharmaceuticals, except for piperacillin (0.08 g per day), acetaminophen (143 g per day) and diclofenac (0.04 g per day). The weekly variability of these medicines was explored, and daily load for compounds like morphine, ibuprofen, and acetaminophen, which are often taken on a regular basis, stayed between 50 and 150% of the average [58]. Pharmaceuticals less often used, are mefenamic acid, diclofenac, and the anti-epileptics gabapentin, however have a larger variability, up to 400% of the average value, with the greatest concentrations recorded during the week. Among the medicines studied metronidazole showed more variability than sulfamethoxazole and ciprofloxacin with the greatest amounts of metronidazole detected early in the week.

Compared to general hospitals, specialized wards and hospitals such as; oncologic unit, critical unit, geriatric unit, and psychiatric unit employ a diverse set of medicines. Anti-metabolites and anthracyclines were found in the wastewater of an oncological in-patient care unit (18 beds) at Vienna University Hospital, Austria [50]. In the treatment of lung, bladder, breast, and cutaneous cancer, the anti-metabolite 5-fluorouracil is given in doses ranges between 200 and 1000 mg/m^2 body surface [59]. Within 24 h, around 2–35% of the given medication was found unmetabolized in the patient urine [59]. Epirubicin, doxorubicin, daunorubicin, and anthracyclines, are commonly used to treat solid and hematological tumors, such as high-grade lymphoma, acute leukemia, bladder cancer and breast cancer, at doses ranges between 15 and 120 mg/m^2 body surface [60]. Within 24 h, approximately 3.5–5.7% of doxorubicin, 13–15% of daunorubicin and 11% of epirubicin were found unmetabolized in the urine [61]. 5-Fluorouracil and doxorubicin, which were given as cytostatics, were detected in the wastewater between 8.6 and 124 μg per Lit and 0.26 and 1.35 μg per Lit respectively [62]. The wastewater of the oncological in-patient treatment ward contained 0.5 to 4.5% of the administered quantity of 5-fluorouracil and 0.1 to 0.2% of the administered amount of doxorubicin [63].

de Souza et al. [64], examined intravenous antibiotics used in a Brazilian hospital's intensive care unit (16 beds) and equally estimated the environmental risk and projected environmental concentration (PEC). The usage of antibiotics in the critical care ward is significant because, this unit consumed 25% of all antibiotics even though the unit occupies only 10% of the hospital's entire number of beds are available. Several intravenous antibiotic classes were utilized, with piperacillin, ceftriaxone, ampicillin, meropenem, ceftazidime, cefazolin, sulbactam, clindamycin, trimethoprim, cefepime, and vancomycin having the greatest usage [65]. These researchers computed PECs by taking into account effluent dilution due to surface water flow (10 times) [5]. The estimated concentrations discharged by the critical care unit vary between 1.15 μgL^{-1} for quinolones to 701 μgL^{-1} for cephalosporins, if the dilution effect is ignored [66]. Ceftriaxone (320 μg/L) and cefazolin (280 μg/L) have the highest anticipated concentrations among cephalosporins. Penicillins and carbapens are two more groups with substantial anticipated concentrations with 262 μg/L and 229 μg/L respectively. Ampicillin (222 μg/L) and meropenem (220 μg/L) had the highest anticipated concentrations within these two groups [67]. According to de Souza et al. [64], the majority of the intravenous antibiotics studied pose a significant environmental risk. Some of the hazards associated with antibiotic release are due to the emergence of antibiotic-resistant microorganisms [68].

These antibiotics contain adsorbable organic halides, volatile organic and other organic compounds such as phenol, alcohols, acetates, ketones and acetaldehyde [69]. Adsorbable organic halides can be found in pharmaceuticals and disinfectants formed from chlorine applied in cleaning, halogen-containing solvents, and other forms chemical like ethidium bromide [37]. In hospital wastewater, adsorbable organic halides levels range between 150 and 7760 μgL^{-1}, in contrast to the 0.04 to 0.2 μgL^{-1} range reported in urban wastewaters [37].

2.4. Concentrations of pharmaceutical residues in the hospital wastewater

Predicted and measured concentrations of pharmaceutical residues in hospital wastewater may provide different findings with respect to the time frames used. Projected concentrations are extrapolated from yearly pharmaceutical usage statistics in most circumstances, whereas concentrations are established for a certain time period and at a single point in time [5,70]. Depending on the chemicals, measured concentrations may have more variability than anticipated values. Predicted concentrations are considered by some authors to be a superior choice for determining pharmaceutical discharge over extended time periods [40]. Each technique has advantages and disadvantages that should be considered when building a source characterization attempt. The choice between the two is ultimately determined on access to consumption statistics, cost, and sewage system accessibility, as well as research goals.

Prioritization approaches have been created because the medications are commercially available in hundreds, and many of them can be discovered in the ecosystem as conjugates or parent molecules. These prioritization approaches take into cognizance varieties of parameters such as physico-chemical properties, degradability/persistence, consumption/sales, (eco) toxicity risk, and treatment resistance [6]. Table 1 summarizes various concentration of micro-pollutants (therapeutic drugs) observed in the healthcare facilities effluents. According to this table; there are different classification of pharmaceutical residues such as; Analgesics/inflammatory, antibiotics, anti-hypertensive, psychiatric, beta-blocker, hormones and contrast media. In analgesics, paracetamol was reported to range between 5 and 1,368, ibuprofen between 0.07 and 43, codeine between 0.02 and 50. In antibiotics, ciprofloxacin was reported to range from 0.03 to 125 and norfloxacin between 0.33 and 44.00.

[3].

3. Adverse effects of hospital wastewater on environment

Pharmaceuticals are excreted as a combination of unmodified parent chemicals and their intermediates (that is metabolite) following ingestion. Although it may appear intuitive that a highly degradable substance (one with a low excretion rate) is easier to break down in the ecosystem, studies have found a negative correlation between the proportion of excreted pharmaceuticals and their concentration in the ecosystem, implying that poorly excreted pharmaceuticals may have a low environmental degradability inherently [71]. Pharmaceuticals may, in fact, take a variety of paths once they enter the sewage system, exhibiting great environmental stability and permanence, or volatilization, and chemical or biological degradation. Drugs such as ciprofloxacin and ceftazidime which contain both basic and acidic functional groups exhibited more complex behavior in sewer network, as well as during wastewater treatment. This means that, depending on the

Table 1
Micro-Pollutants: Concentration of Classes of Therapeutic Drugs Measured in Healthcare Facilities wastewater.

Classification/Analyzed compounds	Concentrations (μg/L)
Analgesics/Anti-inflammatories	
Paracetamol	5.00–1368
Ibuprofen	0.07–43.00
Codeine	0.02–50.00
Naproxen	10.00–11.00
Diclofenac	0.24–15.00
Salicylic acid	23.00–70.00
Antibiotics	
Ciprofloxacin	0.03–125
Metronidazole	0.10–90.00
Tetracycline	0.01–4.00
Ofloxacin	0.35–35.00
Clarithromycin	0.20–3.00
Norfloxacin	0.33–44.00
Penicillin	0.85–5.00
Doxycycline	0.10–7.00
Oxytetracycline	0.01–4.00
Erythromycin	27.00–83.00
Sulfamethoxazole	0.04–83.00
Lincomycin	0.3–2.00
Trimethoprim	0.01–15.00
Anti-hypertensive	
Diltiazem	0.71–2.00
Psychiatric	
Carbamezepine	0.54–2.00
Beta – blockers	
Metoprolol	0.45–25.00
Hormones	
Estrone, E1	0.02–0.03
Ethinylestradiol, EE2	0.02–0.02
17β – estradiol, E2	0.03–0.04
Estriol, E3	0.35–0.50
Contrast media	
Iomeprol	0.01–1392
Iopromide	0.2–2500
Anti-cancer	
5 – fluorouracil	5.00–124
Cyclophosphamide	0.008–2.00
Ifosfamide	0.01–2.00
Tamoxifen	0.004–0.17
Anti-diabetics	
Glibenclamide	0.05–0.11
Anti-viral	
Aciclovir	0.02–0.60

ambient conditions, behavior of these molecules can behave as anionic, cationic, neutral, or zwitterionic in the environment [71]. As a result, understanding the physicochemical features of pharmaceutics can aid in predicting the activities that occur during their passage through wastewater treatment plants. These processes may include biodegradation, or chemical transformation, sorption onto solids, and residual pharmaceuticals may be exposed to photolysis and photodegradation following discharge into surface water bodies, potentially reducing their potential environmental impact [72].

Parent chemicals or modified forms of pharmaceuticals are generally conjugated or hydrolyzed in wastewaters. Hydrolyzed derivatives can lead to the formation of parent compounds at a later period, such as after discharge into a receiving body or during sewage treatment, providing another endogenous source of drug release into the environment [73]. Carbamazepine, for example, is discharged as glucuronides, which may act as a storage for the parent material, which will be released later [74]. To make matters even more complicated, concentrations of some pharmaceuticals have been discovered between the technique's limit of quantification and detection, and consistently below the projected concentration of the environment. This happened, for example, with the anti-neoplastic drug tamoxifen [75], and could be attributed to one or many reasons in this case. One theory is that tamoxifen gets deteriorated before being analyzed because the compound is reported to be UV radiation sensitive, degrading by up to 90% in just 5 days [75]. Photodegradation could not be completely prevented in this case, despite the fact that the analysis was performed as rapidly as feasible and the samples were shielded from light in the meanwhile. Tamoxifen's high lipophilicity (measured log $K_{ow} = 6.3$) allows it to easily bind to particle detritus that settles to the bottom of sewage systems, avoiding detection [76].

Another explanation for the discrepancy between measured and expected tamoxifen concentrations could be an overestimation of PEC due to the adoption of an improperly inflated unaltered compound excretion rate [77]. After the treated wastewater passed through treatment plants, the remaining active pharmaceutical ingredients may degrade further in surface water bodies. Indeed, if a substance is sensitive to light, photodecomposition may aid the degradation in the environment. Phototransformation is straightforward in clear surface water, and the efficiency of the process is proportional to the frequency and intensity of available light [78]. Other variables, such as water hardness, pH, season, location, and latitude, may, however, influence this process [79]. Despite the fact that tetracyclines, quinolones, and sulphonamides among others are light-sensitive antibiotics, not all antibiotics are photodegradable [80]. Indeed, relevance of each antibiotics and their amount of direct and indirect photolysis in the aquatic ecosystem are different. Therefore, there is need to review the following selected organic pollutant; norfloxacin, ofloxacin, ciprofloxacin, clofibric acid and carbamazepine due to their high rate of consumption which result to their recalcitrant and persistence nature in environment most especially in hospital wastewater.

3.1. Norfloxacin (NOR)

This is one of the most widely used anti-infective drugs globally with a brand name of noroxin, among others. It belongs to the class of fluoroquinolone antibiotics which is used to treat gynecological infection, urinary tract infection, gonorrhea, inflammation of the prostate gland and bladder infection [81]. Humans and cattle only partially metabolize the drug, with a significant portion expelled in urine and feaces and released into urban wastewaters, sewage sludges and manures, posing additional environmental hazards [82]. Norfloxacin has the potential to harm aquatic ecosystems by limiting algae reproduction and survival [83], reducing *Daphnia* sp swimming capacity and predation rate [81], as well as creating functional and structural alterations in plankton systems, according to some laboratory experiments [84]. Norfloxacin can affect aquatic organisms through alteration of antioxidant enzymes, causing considerable DNA damage, and exert genotoxic and cytotoxic effects [85]. Antibiotics' effects on the soil system, on the other hand, are little known. Antibiotic concentrations of up to 10 mg/kg have been found in manures, with concentrations approaching the mg/kg level in manure-amended soils [86]. After manure amendment, most soil-dwelling organisms are expected to encounter 5–10 mg/kg of antibacterial compounds in soils [86]. Norfloxacin appears to reduce the body size of collembolans and the quantity of eggs laid in laboratory simulation experiments on Petri dishes [87]. Antibiotic use may alter the microbial balance in the intestine. The antibiotic triclosan (TCS), for example, had a considerable impact on the gut microbiota of the isopod *Balloniscus selowii*, and the changes were severe enough to obstruct nutrient absorption [88]. Norfloxacin was found to disrupt the intestinal microbiota of F. candida in a Petri dish system [89]. Variations in the amount of toxicity in various culture systems, on the other hand, contributed to the differences in the gut microbiota's reactions to

norfloxacin. In addition, the intestinal microbiota includes host-related microbiota as well as soil microbiota that is temporarily resident in the gut [90]. It is generally understood that addition of norfloxacin to soil altered the soil microbiota, particularly Gram-negative bacteria [83]. To understand the impacts of pollution on soil animals, studies that differentiate between the soil and intestinal microbiota are required, and may serve as new potential bioindicators.

3.2. Ofloxacin (OFL)

Ofloxacin is a carboxylic acid of the fluorinated quinolone-type antibiotic usually applied for the treatment of respiratory and urinary tracts infections, conjunctivitis, otitis, tuberculosis because to its widespread distribution and genotoxic effects [91]. WHO ranked OFL has one of the critically important drugs for human health due to its application [92]. OFL has poor bio-degradability which results to its accumulation into the aquatic environment for longer period of time [93]. OFL has been found in wastewater at amount ranging from 0.005 to 31.7 g/L, even after standard treatment [94]. Due to its persistency against biological degradation, OFL cannot be removed through conventional wastewater treatment plants [93], and thus subsequently escape to ground water and river surface. Furthermore, because biosolids are reused for agricultural purposes, OFL has been classified as a very dangerous substance for the aquatic environment [94]. In *Daphnia magna* F3 (third generation clone) and F4 (fourth generation clone), Ofloxacin at 200 g/L has shown to reduce the number of offsprings during initial reproduction [95]. Sometimes, the detected concentrations in aquatic environment may be lowered than the effective level on aquatic lives, however due to existence of pollutants in multiple synergetic actions of these multi-pollutants can occur on aquatic lives. Esposito et al. [96], reported that the presence of OFL in water surface with residence time of 246 h and around 13,920 h in soils. OFL is a chiral molecule and its enantiomers are optically active thus revealed its superior antibacterial power. Al-Omar [97] also reported that 90% of the dose of OFL is eliminated unaltered in the urine, with a concentration of 306.1 ng/L [98]. In an Italian hospital of 900 beds and 2000 personnel, it was found that the hospital wastewater contain OFL in at high concentration (19 μg/L) above the concentration detected for ciprofloxacin (12 μg/L) [99].

3.3. Ciprofloxacin (CIP)

Ciprofloxacin (CIP), a fluoroquinolone-family broad-spectrum antibiotic, is utilized in human and veterinary medicine all over the world [100]. CIP is partially or/and non-metabolized in animals after delivery, therefore the original compound and its metabolites usually release during excretion into the other environmental compartments, such as water bodies [101]. Furthermore, conventional wastewater treatment techniques such as activated sludge or up-flow anaerobic sludge blanket reactors have limitations on CIP removal [102], which can result in the release of active compounds into aquatic ecosystems at ng/L and g/L levels respectively [102]. Diniz et al. [103], reported up to 34 g/L of CIP in hospital wastewater, an indication that CIP is a recalcitrant molecule with great environmental stability. Furthermore, CIP concentrations of 310 g/L or higher were reported to limit bacteria growth in activated sludge aeration tanks [104].

The presence of antimicrobials in water bodies contributed to evolve resistance of bacteria genes [105]. Antimicrobial residues in the aquatic environment also have an impact on aquatic biota other than bacteria, including fish, copepods, microalgae and macrophytes [105]. CIP has been linked to change in antioxidant enzymes in exposed organisms [106], which have been linked to genotoxicity in bacteria (*Salmonella thyphimurium*) [107] and chronic toxicity in the microalgae, *Raphidocelis subcapitata, Chlamydomonas reinhardtii, Chlorella vulgaris,* and *Chlamydomonas Mexicana* [107]. Venancio et al. [108], studied the chronic toxicity of CIP in *Raphidocelis subcapitata,* and the authors reported EC_{50} (half maximal effective concentration) in the range of 5000 to 10,000 g/L after 96 h of exposure. However, none of the trials included had exposure times longer than 96 h. The present data was insufficient to cover all probable impacts of this antibiotic on the environment due to the lack of ecotoxicity testing with longer exposure periods that may cover several growth phases of these microalgae [109]. While harmful effects were evaluated for a single trophic level of species, such studies for complex combinations of organisms were relatively rare for variety of chemicals [109]. To create more realistic circumstances and give accurate information on the possible antagonistic and synergistic effects of medicines, toxicity assessments of drug combinations and long-term exposure tests should be undertaken [110]. However, there have been few published toxicity studies on the temporal development of the EC_{50}, despite the fact that it is predicted that as exposure duration increases, the EC_{50} value decreases [111]. Xiong et al. [112], found that the reverse increasing exposure duration resulted to higher EC_{50}. Nunes et al. [113], also reported that at low CIP concentrations (0.013 mg/L), there was a substantial decrease in lipid peroxidation levels, whereas at high CIP concentrations (0.078 mg/L), there was a significant rise up to 0.013 mg/L of CIP. The genotoxicity test showed a substantial rise in genetic damage index. The ecologically relevant ciprofloxacin doses examined had no significant effects on *D. magna* life-history parameters; nevertheless, oxidative stress and genotoxic damage scenarios were noticed at the same levels of ciprofloxacin.

3.4. Clofibric acid (CA)

Clofibric acid (CA) is an active metabolite of lipid regulators such as clofibrate, etofyllinoclofibrate, and etofibrate which is utilized to make anti-neoplastic, anti-lipemic, anti-cholesteremic, and even herbicides [114]. Despite its widespread usage, little research has been done on its toxicity and ecological effects. However, there have been indications that clofibric acid and its metabolites, even at low concentrations in the ecosystem, can cause environmental damage [115]. Clofibric acid is pseudo-persistent in the environment, according to experts, and. It's crucial to look at its toxicological (acute and chronic) effects on the ecosystem.

There have been several reports of acute toxicity from clofibric acid and its metabolites. For 48 h, Clofibric acid ecotoxicity EC_{50} endpoint of *Daphnid* and ceriodaphnid assays yielded >200 mg/L [116]. The authors discovered that *Daphnid* 21-day NOEC for clofibrate was 64 times lower than the ceriodaphnid 7-day NOEC value reported by Ref. [116].

Clofibric acid appears to be less harmful to the aquatic environment than clofibrate. Ferrari et al. [116], also obtained EC_{50} values of 28.2 mg/L in 24-h daphid toxicity test,. Clodacerans were shown to be unaffected by the presence of clofibric acid, which had an EC_{50} of over 200 mg/L. In a study on the acute toxicity of clofibric acid on bacteria, daphids, ciliates, and fish eggs, the authors observed a toxicity value of roughly 14 mg/L [117]. As a result, exposure to clofibric acid and its metabolites may have an immediate influence on the environment. The toxicity of clofibric acid on algae was shown to be not less than 14 mg/L in a study undertaken to determine its chronic toxicity [117,118]. Furthermore, Ferrari et al. [116], also discovered that when a chronic toxicity test was performed on rotifers, a NOEC value of 0.25 mg/L proved to be more sensitive, suggesting that Clofibric acid can have a greater impact on non-target organisms. According to Ferrari et al. [116], chronic toxicity studies showed greater toxicity than acute toxicity testing. For C. *dubia*, the acute EC_{50}/chronic NOEC ratio was calculated to be > 312 mg/L. C. *dubia* was found to be more sensitive than P. *subcapitata*, B. *calyciflorus*, and D. *rerio* in chronic concentration–effect relationship tests, with P. *subcapitata* and D. *rerio* being the least vulnerable.

A huge carp in India (*Cirrhinus mrigala*), the toxicity of Clofibric acid, one of the most regularly identified medicines in the aquatic environment was examined. Saravanan et al. [115], revealed that Indian carp fingerlings were exposed to clofibric acid at concentrations of 1 g/L, 10

g/L, and 100 g/L for 96 h and 35 days, respectively. TSH levels were observed to be lower at all doses of Clofibric Acid over the 96-h and 35-day exposure periods (except in 1 and 10 g/L at the end of the 14th day and 1 g/L at the end of the 21st day) [115]. At 1 g/L and 100 g/L of Clofibric Acid exposure, T^4 levels were shown to be lower after 96 h. During the 35-day exposure period, T^4 levels were reduced at all Clofibric Acid doses. T^3 levels in the treatments were lower in fish exposed to all doses of Clofibric Acid. These findings showed that the Clofibric Acid medication caused substantial alterations ($P < 0.01$) in C. *mrigala* thyroid hormone levels. Changes in these hormone levels might be employed as biomarkers for pharmacological medication monitoring in aquatic organisms [115].

Clofibric acid, a derivative of clofibrate, has been a major cause of concern due to its frequent occurrence in the environment [119] and high societal demand. The first findings on the existence of clofibric acid in the environment were published in 1976 [120,121]. Garrison et al. [121], discovered low concentration of clofibric acid in treated wastewater in the United States at (ng/L). Thereafter, in 1998, Quero-pastor found CA in surface water at values ranging from 0.049 to 0.066 mg/L [120] and in drinking water at maximum concentrations of 270 ng/L [122]. In tests conducted in the United States, this chemical was also discovered in lakes and rivers [120]. Further research also revealed possible presence of endocrine disrupting substances [123]. The presence of pharmaceutical compounds in the environment pose serious risk to human health and other living things in general, according to some studies, even at extremely low concentration levels [120]. Clofibric acid, in particular, has a deleterious impact on the liver, resulting in gallstones [124].

3.5. Carbamazepine (CBZ)

Carbamazepine's effectiveness has been highly commendable in the field of medicine for the treatment of many disorders such as depression, epilepsy, and arrhythmia. However, due to its extensive usage, the compound and its metabolite have been detected in water bodies in concentrations ranging from ng/L to ug/L causing various adverse effects on aquatic species [125]. Carbamazepine's ecotoxicology has been studied by a number of scholars. For instance, Carbamazepine concentrations ranged from 230 to 1110 ng/L in Shanghai's sewage treatment facility, and 1090 ng/L in the Yangtze River, according to Chen et al., [126]. Also, Liu et al. [127], reported 100% CBZ was identified in Nanjing rivers, between 0.05 and 1.6 ng/L concentration in the fish bodies and 0.2 and 6.9 ng/L concentration in the water system. Similarly, Xie et al. [128], reported 0.24–8.74 ng/L concentrations of CBZ detected in Lake Taihu, China, with 32% found in biotic samples such as crucuian carp, common carp, and yellow catfish. As a result, given the high levels of CBZ in the ecosystem, it is critical to assess its harmful effects, both acute and chronic.

Acute impact is defined as a carbamazepine side effect that develops after a single or repeated exposure within 24 h. Depending on the concentration, this might be severe or minor. Chen et al. [126], observed 3% of *Daphnia similis* died after 4 days, indicating no acute effect based on the present exposure concentration level (that is, no concentration – dependent for all concentrations when testing for Chitobiase in *Daphnia similis*). When exposed to 100 g/L, the acute effect was observed to be concentration-dependent, with EC_{50} values of 3985.24 μg/L for 48 h, 345.58 μg/L for 72 h, and 306.17 μg/L for 96 h. Chen et al. [126], revealed that CBZ concentration of 1 g/L promoted reproduction and phototactic behavior in *Daphnia magna*. Aromatic amino acids used as biomarkers for sub-lethal CBZ exposure, altered energy metabolism, according to Kovacevic et al., [129]. CBZ respiratory quotient value of 4.69 was similarly recorded by Ying et al. [130], suggesting danger of CBZ to aquatic species [131]. Other researchers, such as Ferrari et al. [116], have noted relatively little acute toxicity on bacteria, micro-crustaceans, algae, and fish, therefore not an immediate concern. Another investigation was carried out on *Cyprinus carpio* (common carp) for 24 h at a fatal dose of 59.70 mg/L, and it was found that CBZ caused changes in the activities of glutamate pyruvate transaminase, glutamate oxalocetate transaminase, and lactate dehydrogenase in numerous organs [132].

The term "chronic effect" refers to an unfavorable impact of carbamazepine that arises after a single or many exposures over a lengthy period of time. This has been proven in several investigations. For instance, Ferrari et al. [116], looked at the long-term effects of CBZ on the *Ceridaphria dubia* (micro crustacean) and found that chronic toxicity was greater than acute toxicity. Almeida et al. [133], revealed that CBZ levels in *Ruditapes philippinarum* tissues increased throughout the exposure gradient. When the exposure concentration was increased, a rise in CBZ in clam tissue was detected, reaching a peak of 6 ng/g fresh weight at 9.00 μg/L. Almeida et al. [133], reported that after 28 days of exposure, the death rate was 5% for 0.03 μg/L, and 11% for 3.00 g/L, whereas the mortality rate for 9.00 μg/L was zero. Contardo-Jara et al. [134], measured CBZ accumulation in the *Dreissena polymorpha* (Zebra mussel) after 4–7 days of exposure and found that the concentration of CBZ ranges from 0.236 to 236 g/L and that CBZ accumulation increased with exposure time at all concentrations. Long-term exposure to CBZ has been linked to a variety of disorders, including antibiotic resistance in human pathogens, carcinogenicity, genotoxicity, endocrine disruption, allergic responses, and reproductive and developmental consequences [4]. Stevens-Johnson syndrome and its related disorders have been linked to CBZ consumption in Southeast Asian nations [135]. Samantha [136], also linked the neuro-developmental abnormalities in the human embryo in the womb to CBZ exposure. Atkinson et al. [137], also reported that exposure to carbamazepine during pregnancy contributed largely to fetal death and congenital malformations [131]. Also, the CBZ detected in ground and drinking water constitute additional risk embryo and newborn through breast-feeding or intrauterine exposure. The indicator parameters for the selected emerging micropollutants are summarized in Table 2.

4. Overview of treatment methods for hospital wastewater adopted in three continents

There are different techniques used in different nations for Hospital wastewater treatment. Table 3 summarizes all of the techniques used, along with the citations. This will help the reader to understand some peculiarity based on the developmental status and regional factors of a country.

Typically, hospital wastewater is released into the municipal sewer system, where it mixes with other effluents before being treated in a sewage treatment plant. This is a common practice in countries like South Africa, Australia, Thailand, Iran, Japan, Egypt, and India. Hospital wastewater, on the other hand, can be a substantial source of hazardous materials in the aquatic environment because wastewater are released directly untreated into drainage, lakes, and rivers in countries like Taiwan, Algeria, Vietnam, Bangladesh, Nepal, Pakistan, Congo, and India,. According to Ashfaq et al. (2019), no hospital in Pakistan has established sufficient wastewater treatment facilities, regardless of its size. In Taiwan, several hospitals release their wastewaters directly into surrounding rivers (illegally or legally) without prior treatment [138]. Only 48% of the 70 state hospitals in Iran have wastewater treatment systems, while 52% did not and such hospitals dumped their wastewater into wells, 38% dumped it into the environment, and the rest dumped it into the municipal wastewater system [14]. When the indicators of wastewater treatment systems are compared to the norms of Environmental Departments, it is clear that these systems are inefficient, and in view of the recent development, Hospital wastewater treatment systems need improvement.

In Indonesia, 64% of hospitals released their wastewater directly into infiltration well or water bodies while 36% have wastewater treatment plants [139]. Wastewater Treatment Plants in Hospitals often employ a combination of chlorination and biological methods, with the discharges

Table 2
Indicator parameters for emerging micropollutants.

Indicators	Norfloxacin	Ofloxacin	Ciprofloxacin	Clofibric Acid	Carbamazepine
Concentration in water	6.8 μg/L	6.6 ng/L	>1.0 μg/L	1.0 mg/L	8.74 ng/L
Concentration in soil	9.8 μg/L	0.3 mg/L	5.0 mg/g	5.0 mg/g	6.0 ng/g
Acute Toxicity	EC_{50} of 400 mg in 12 h	–	–	EC_{50} > 28.2 mg/L in 24 h	–
Chronic toxicity	EC_{50} of 800 mg in 28 days	–	EC_{50} after 96 h	EC_{50} > 312 mg/L in 35 days	EC_{50} after 4 days
Metabolism	Biliary excretion and Renal excretion.	Renal excretion.	Renal excretion.	Renal excretion.	Renal excretion.
Biomarkers	≥0.4 mg/L after 4 and 7 days in gold fish.	0.05 mg/L after 4 or 7 days in gold fish.	–	–	–

Table 3
Treatment scenario of hospital wastewater in different countries.

Country	Treatment	References
Algeria	Direct release into the ecosystem	[143]
Australia	Co-treatment	[14]
Bangladesh	Direct release into the ecosystem	[144]
China	Specific treatment	[145]
Congo	Direct release into the ecosystem	[146]
Egypt	Co-treatment	[147]
Ethiopia	Direct release into the ecosystem	[148]
India	Co-treatment/Direct release into the ecosystem/ specific treatment	[149]
Indonesia	Direct release into the ecosystem/specific treatment	[139]
Iran	Specific treatment/co-treatment	[150]
Iraq	Specific treatment	[151]
Nepal	Direct release into the ecosystem	[152]
Republic of Korea	Specific treatment	[2]
Taiwan	Direct release into the ecosystem	[153]
Vietnam	Direct release into the ecosystem	[154]
Japan	Co-treatment	[155]
Pakistan	Direct release into the ecosystem	[156]
South Africa	Co-treatment	[157]
Thailand	Co-treatment	[158]

frequently exceeding quality standards for typical treated wastewater especially for phenol, lead, ammonia-free, free chlorine and ortho-phosphate. Low-quality discharges from hospital wastewater treatment plants, contain hazardous pollutants (lead and phenol), generated by a biological-chlorination process that are yet to be optimized [140]. In 2004, a research conducted in Kunming, a big city in China's South West revealed that 36 out of 45 hospitals have wastewater disinfection equipment. In the same year, 50 hospitals in Wuhan, China's largest city in the Central Southern area had their wastewater treatment facilities audited. It was also revealed that 46 hospitals had wastewater treatment facilities, with just around half of them fulfilling the national discharge standard [141]. Most hospitals in Iraq have treatment plant, however not up to Iraqi requirements, particularly in terms of nutrient and pathogen elimination [140]. In nations like China, the Republic of Korea, and Indonesia, where hospital wastewater is handled on-site, the situation is more strict (specific treatment). Non-governmental organizations (NGOs) are actively using this method (that is, hydrated (slaked) lime ($Ca(OH)_2$) coagulation/flocculation with aluminum sulfate and disinfection) to assist manage human excreta in various emergency contexts, such as Ebola and various infectious disease epidemics in Philippines, West Africa, and Myanmar [142]. Table 3 represents different treatment scenario of hospital wastewater in different countries. Some of these treatment approaches are co-treatment, specific treatment and direct release into the ecosystem. These are proof that there are still needs for advanced approach as regards treatment of wastewater especially hospital wastewater which require separate treatment attention. Without successful treatment of hospital wastewater, aquatic organisms and human life will continue to be under threat. The direct or indirect discharge of untreated hospital wastewater into the environment has been ascribed to different abnormalities in aquatic organisms. Some of the treatment methods used in different country are shown in Table 3.

5. Analytical techniques for determination of micro-pollutants in hospital wastewater

Several analytical techniques have been applied for detection of different concentration of emerging organic pollutants present in hospital wastewater ranging from spectrophotometry to advanced microscopic method. This will help the reader to understand the merits and demerits of one analytical technique over the other and most suitable among them all.

5.1. *Spectrophotometry*

Spectrophotometry is a branch of electromagnetic spectroscopy concerned with the quantification of radiant energy transmitted or reflected by a body as a function of wavelength [159]. The notion is straightforward, but calculating reflectance or transmittance necessitates careful consideration of the measurement's geometrical and spectral circumstances. For decades, spectrophotometric equipment have been utilized in laboratory, industrial and educational institution [160]. There are different types of spectrometry; general purpose UV–Visible, high resolution UV–Visible, Scientific Grade High Sensitivity, Fourier Transform [161]. General purpose Pre-dispersive spectrophotometer designs are also common. This implies that the source released white light split into spectra and pass via the sample with its wavelength to the detector one at a time [159]. A benefit of this design is that the sample is exposed to significantly less light energy than in post-dispersive systems. The fundamental drawback is that only one wavelength may be studied at a time, and spectra must be constructed from data points collected at various intervals [161]. Several micro-pollutants have been studied and detected using UV–Visible spectrometer namely ciprofloxacin, ofloxacin, norfloxacin moxifloxacin among others. Ciprofloxacin was analyzed as a pollutant and the concentration was found to be 0.5–25.0 μg/L [162] while ofloxacin was found to be 1.0–35.0 μg/L [98]. Norfloxacin and moxifloxacin were found to be in the range of 5–150 μg/L [163] and 2.65–230 μg/L [164] respectively. Therefore, Spectrophotometry has different merit and demerit; such as good sensitivity, simplicity in operation compared to other techniques for analyses while its detection index is single. However, the technique has a poor colour material stability and high interference [159].

5.2. *Gas chromatography*

Gas chromatography is a chromatographic technique which involves mobile phase and a suitable gas used for separation of a given sample such as crude substances [165]. In 1955, James and Martin developed a classy form of gas chromatography with solid as the stationary phase or

liquid form while the mobile is in gaseous form. In the stationary phase, when a component is more soluble, it moves slowly across the column, but when it is less soluble, it moves faster [165]. As a result, depending on their partition co-efficient between the stationary phase and the component of interest, the components in the sample mixture are divided into two groups. The nature of the stationary phase determines how gas chromatography is classified: There are two forms of chromatography: gas-liquid chromatography and gas-solid chromatography [166].

Gas–solid chromatography (GSC) refers to chromatography in which the stationary phase (adsorbent) is solid (GSC). Active carbon, silica, and alumina [166]. In GSC, the separation principle is adsorption, it has a long column life, but the main disadvantage is the possibility of changes in the component chemical composition present in the combination of sample [167]. Gas–liquid chromatography (GLC) is when liquid is the stationary phase of gas chromatography. A solid surface, such as a polymer, is used to immobilize the liquid. GLC's guiding principle is partition. Nowadays, GLC is frequently utilized in the form of a capillary column.

Gas chromatography has a number of advantages, including high separation power for most complicated mixtures. The approach is extremely sensitive, requiring only a minimal sample size for examination. It is equipped with a high-sensitivity detecting technology that is precise and accurate. The operation is accomplished in a very short amount of time and with excellent linearity [168]. The instrument cost is relatively low, easy to handle and high durability and relatively suitable for routine analysis with high precision. There are still some shortcomings such as: low Sensitivity. In most cases, the analysis often involve volatilization, and there's a danger the sample will degrade [168]. The column cannot be utilized for biological sample analysis due to its high temperature. Gas chromatography has been applied in various field of research for gaseous samples. It is used to determine how many organometallics are present in a given substance. It is also used to figure out how much estrogen is in human body. Antituberculosis pharmaceuticals, antibiotics, anti-neoplastic agents, antiviral treatments, ointments, anticonvulsants, and steroids are all routinely determined using GC [167]. Furthermore, it is also used to check the quality of dairy products. Pesticides in aquaculture products are determined using this method. It is used to diagnose some disorders, such as cancer. It is used to identify drugs and alcohols in the bloodstream [167].

5.3. Gas chromatography mass spectrometry (GC-MS)

In chromatographic methods, coupling of mass spectrometry is not only associated with gas chromatography but also with liquid chromatography [169]. GC-MS helps to determine the compounds present and to compare their concentrations. This can be achieved through these two prerequisites: i. Determination of the individual compound by their identification of the mass spectrum and ii. Calculation of the abundance peaks corresponding to those compounds in each sample [170]. These prerequisites are sometimes difficult and often resulted to waste of time due to peaks co-elution within a chromatogram and shift of retention time across samples. These two shortcomings can lead to mix of mass spectra and complicate the identity and quantification of the compound [170]. Most traditional vendor software assess compounds based on peak area or height by picking m/z values typical for the specified component from total ion count (TIC), base peak chromatogram (BPC), or extracted ion chromatogram (EIC) [170]. This technique is vulnerable to co-eluting compounds provided the contribution to the signal from other chemicals is not well managed. This can have a major impact on both quantitative and qualitative results [171]. Furthermore, the estimation of baseline contributions is difficult, and may result to errors in quantification. Majority of currently used methods rely on basic background subtraction from a local baseline or a shoulder of a specific peak of interest especially when dealing with overlapping and/or co-eluting peaks [171].

5.4. High performance liquid chromatography (HPLC)

High performance Liquid Chromatography (HPLC) is an improved form of column chromatography which is otherwise called high pressure liquid chromatography, and it is applied to separate lipid mixture via stationary phase filled column. This powerful tool is very fast, since it required solvent to be forced via high pressures of up to 400 atm. It also required very small particles size for the package of column material which results to a greater surface area for interaction between the molecule and stationary phase for a better separation of the mixture components. Kirkland and Huber were the first to suggest high-performance liquid chromatography (HPLC) [172]. In the 1970s, the HPLC technology was developed based on the concept of column chromatography under high pressure and involves pushing the mobile phase via packed column. In HPLC, the pressure mobile phase is at the top and the stationary phase is at the bottom of the column. HPLC techniques are based on four approaches: chromatography mode, separation principles, scale of operation, and analytical types [172].

There are two types of HPLC categories: reverse and normal phases, based on the chromatographic mode. In normal phase HPLC, the polar components such as silica gel are in stationary phase while the non-polar components are in mobile phase. In contrast to mixture of polar components, non-polar components of interest move swiftly and are eluted first with this approach because non-polar components have a lesser affinity for stationary phase [173]. Due to their higher affinity for the stationary phase, the polar components of interest present in the mixture are retained in the column for longer period of time and eluted later than the non-polar components [174]. In reverse phase HPLC, the stationary phase and the mobile phase are normally non-polar and polar respectively. In this mode, the non-polar molecules are retained in the column, after the polar components of the mixture are eluted. Most drugs are polar, and do not stay in the column for a longer period and thus quickly eluted [175].

Partition chromatography, adsorption chromatography, size exclusion chromatography, ion exchange chromatography, and affinity chromatography are some of the most used HPLC processes based on the separation principle [175].

On the basis of scale of operation, HPLC are classified into analytical and preparative type. The specified material is analyzed in analytical HPLC. However, sample recovery is somehow difficult. In preparative HPLC, the sample mixtures are always collected through the fraction collector while the collectors are reused [173].

HPLC can be classified into two type base on analysis-type such as; qualitative and quantitative HPLC. Qualitative HPLC is used to identify the qualities of the components of a sample combination during analysis. Quantitative analysis is used in HPLC to determine how much of each component of the sample mixture is present [176]. This analysis is carried out once the peaks have been detected and integrated [175]. The thickness of the stationary phase, particle size of the stationary phase packed in column, internal diameter of the column, flow rate of the mobile phase, length of the column, viscosity of the mobile phase, affinity of the component of interest (analyte) with mobile phase, nature of the mobile phase, and staining of the component of interest (analyte) with mobile phase are the most important components that affect the HPLC technique efficiency [176].

HPLC has been widely used in the separation of alkaloids present in plants and inorganic ions such as chloride, phosphate fluoride, bromide, nitrite, cadmium, magnesium, copper, lead, and zinc ions, detection of intoxicants, poisons in human blood, and addictive drugs such as alcohol, cocaine, morphine, heroin, and opioid drugs, and identification of illicit drugs [173]. It is also employed exclusively in forensic science for investigation, explosives analysis, lipid, steroids hormone, and bile acid identification [177]. Different techniques along with their merits and demerits are listed in Table 4 while different analytical techniques applied for the detection and quantification of pollutants in hospital wastewater is provided in Table 5.

Table 4
Analytical Techniques, their Merits and Demerits.

Techniques	Merits	Demerits	References
Spectrophotometry	Sensitivity: High and Good Operation: simple and easy	Detection index: single Colour material stability: Poor Interference: High	[159]
Gas chromatography	Powerful separation functioning chromatographic column Optional detectors of specific purpose from general purpose	Unstable heat or high boiling point substances is difficult to analyze. Malodorous sample with complex components is not suitable to detect since there is certain selectivity of substances	[167]
Gas chromatography Mass Spectrometry	Detection range: Widely Strength: Strong Sensitivity: High Anti-interference: Able	Structural recognition of similar compound: weak Professional needed for complex operation	[169]
High performance Liquid Chromatography	No limitation by sample volatility Determining organic compound with high boiling point, high relative molecular weight and poor thermal stability Analyzing at a lower temperature	Long analysis time High cost	[172]

Table 5
Different analytical techniques applied for detection and quantification of pollutants in hospital wastewater.

Analytical Techniques	Pollutants	Concentration (μg/L)	References
UV–Visible	Ciprofloxacin	0.5–25.0	[162]
	Ofloxacin	1.0–35.0	[98]
	Norfloxacin	5–150	[163]
	Moxifloxacin	2.65–230.0	[178]
Gas chromatography mass spectrometry	5-Fluorouracil	92.00	[179]
	Cyclophospamide	0.019–4.486	[180]
	Ifosfamide	0.048	[181]
	Metoprolol	17–110	[182]
	Amphetamines	0.1–0.4	[183]
High performance liquid chromatography	Carbamazepine	0.463	[163]
	Clofibric acid	0.772	[184]
	Diclofenac	0.05	[163]
	Caffeine	5.65	[163]
Ultra high performance liquid chromatography	Metformin	1.31	[185]
	Diclofenac	0.59	[185]
	Ibuprofen	0.62	[185]
	Paracetamol	137.98	[99]
	Acetaminophen	2.66	[185]
	Caffeine	35.29	[99]
	Atenolol	0.20	[185]

6. Methods of treatment of hospital wastewater

Different conventional and advanced methods mostly applied for the treatment of hospital wastewater are explained in the next section.

6.1. Physical techniques

The treatment of hospital wastewater involving combination of coagulation/flocculation/precipitation with $Al_2(SO_4)_3$ or $FeCl_3$ or appears to be a viable option for the removal of lipophilic compounds like diclofenac from the liquid phase [186]. These methods however unable to remove several hydrophilic pharmaceuticals such as iopromide, diazepam, carbamazepine, and antibiotics such as trimethoprim erythromycin, roxythromycin, among others [187]. Suspended particles, which can be detected up to three times higher quantities in hospital wastewater than in municipal sewage, can be removed effectively by flocculation/coagulation [188], thus preventing their accumulation on primary and secondary sludge. Flotation appears to remove persistent chemicals like carbamazepine (approximately 20%) [189].

6.2. Biological techniques

Due to the action of co-metabolic and metabolic mechanisms in these systems, biological treatments are one of the most effective secondary treatments barrier to most Pharmaceuticals [190]. The longer sludge retention time (>25–30 d) boost removal efficiencies, while some chemicals have thresholds beyond certain limit [191]. Membrane biological reactors and conventional activated sludge effluents have equal removal rates for basic pharmaceutical compounds like ibuprofen [192]. For several substances, membrane biological reactors performed better than traditional activated sludge, by providing a 30–50% higher removal rate in some circumstances. Furthermore, membrane biological reactors have regularly demonstrated a 40–65% improvement in the elimination of certain chemicals that are resistant to standard activated sludge treatment such as; indomethacin, diclofenac, mefenamic acid, and gemfibrozil among others [19]. There is no link between the chemical structure of pharmaceuticals and the rate of elimination. For most chemicals, however, the variation range in removal rate exhibited in membrane biological reactors is limited, whereas bigger fluctuations are recorded in traditional activated sludge [193]. The superiority of membrane biological reactor processes has also been claimed in term of pathogenic microorganisms elimination, including various viruses [5]. A biological reactor's performance can be improved by separating it into reactor cascades [194]. In wastewater treatment plants with longer sludge retention times, nitrifying bacteria play an important role of pharmaceuticals biodegradation [195].

6.3. Adsorption techniques

Adsorption technology is one of the most simple and cost effective methods of decontaminating wastewater through the removal of contaminants or pollutants in the aqueous matrix based on adsorbate-adsorbent interaction [196]. The pollutants are the absorbate while the absorbent is the catalytic surface used [42]. The most known adsorbents are agricultural wastes, activated carbon, silica gel, and cotton fibres [197], which have been used for the removal of different pollutants such as micro-pollutants, endocrine disruptors, herbicides even at low concentrations from wastewater, [198–201]. Two primary approaches, static and dynamic methods, are used in the adsorption process. Finely split adsorbents are agitated with water in the static method, and then separated by decantation or filtration. In the dynamic process, wastewater flows continuously across a fixed, mobile, or fluidized adsorbent layer [202]. The majority of chemical procedures used in hospital wastewater treatment generate a substantial amount of sludge, which must be disposed of further. When used on dilute wastewater with lower levels of micropollutants, these procedures are either inefficient or ineffective, and they necessitate a high level of skill.

6.3.1. Principles of adsorption techniques

Adsorption is the accumulation of a liquid or gas or solute (adsorbates) on the surface of a solid (adsorbent) over time while absorption

occurs when a substance diffuse into a liquid or solid [203]. The both terms encompasses the same process. While desorption is the reverse process of the both terms [204]. Surface energy, which is related to surface tension, causes adsorption. In a material, the constituent atoms' bond requirements, such as ionic, covalent, or metallic, are filled up, but bond deficiency occurs on the surface since they are completely surrounded by other atoms. As a result, the type of the bonding is determined by the nature of the participating species, and the adsorption process is divided into physisorption and chemisorption [125]. Physisorption, also known as physical adsorption, is a kind of adsorption with existence of weak forces of attraction (Van-der Waals) between the adsorbate attach to the surface of the adsorbent. It is also responsible for the non-ideal behavior of actual gases. In chemisorption, there is existence of strong force of attraction (covalent or ionic types) between the adsorbate and the adsorbent's surface [205].

6.3.2. *Adsorption mechanism of the five selected emerging micro-pollutants*

The mechanism of adsorption of the selected emerging micro-pollutants from aqueous media has been linked to several factors. Solution chemistry is the main factor upon which adsorption mechanism is

Table 6
Adsorption mechanism of five selected emerging micro-pollutants with their adsorption capacity or percentage removal by different nano-adsorbents.

Emerging micropollutant	Nano-absorbent	Experimental conditions				pHpzc	Adsorption capacity/ percentage removal	Mechanism	References
		pH	Contact Time (h)	Adsorbent dose (g/L)	Temperature (°C)				
Ciprofloxacin. pKa = 6.09	Graphene oxide/ sodium alginate	2.0	128	0.3	25	–	100.00 mg/g	π-π interaction	[208]
	Bentonite-chitosan	–	10	1.5	30	6.2	39.06 mg/g	Ion-exchange	[209]
	Biochar from tea leaves	6.0	24	1.3	30	3.1	238.1 mg/g	π-π interaction, H-bond, Electrostatic interaction	[210]
	Magnetic N-doped porous carbon	7.0	12	0.04	25	3.6	1564 mg/g	π-π interaction, H-bond, Hydrophobic interaction, Electrostatic interaction	[211]
	Fe_2O_4/graphene oxide/Biochar	6.0	72	1.0	25	6.3	283.4 mg/g	Hydrophobic interaction	[212]
	Activated carbon from hazelnut	6.0	1.5	3.0	30	6.5	73.64 mg/g	Intraparticle diffusion	[213]
	Modified hydrogel beads	8.0	12	0.25	20	8.3	154.9 mg/g	H-bond, Hydrophobic interaction	[214]
	Cationic flax noil cellulose	7.0	10	0.1	–	6.32	238.7 mg/g	Electrostatic interaction	[215]
	Activated and znO doped camphor leaves biochar	4.0	24	0.2	40	3.4	449.4 mg/g	Electrostatic interaction, π-π interaction, H-bond, Hydrophobic interaction	[216]
	Ordered carbon	6.0	24	0.03	25	8.8	233.4 mg/g	Hydrophobic interaction	[217]
	Activated carbon from bamboo	6.0	24	0.03	25	8.5	362.9 mg/g	Hydrophobic interaction	[217]
Carbamazepine	Magnetic activated carbon	8.1	24	0.03	25	6.0	68.00 mg/g	Electrostatic interaction	[218]
pKa = 13.9	Hexagonal mesoporous silicate	5.0	4	2.0	25	5.5	41.87 mg/g	Electrostatic interaction, H-bond.	[219]
	Bentonite	3.0	–	–	25	–	25.57	Electrostatic interaction	[125]
	MOF	–	24	0.1	25	9.0	–	Hydrophobic interaction	[220]
	MOF UiO-67	5.0	24	0.1	25	–	82.64 mg/g	Hydrophobic interaction, π-π interaction	[221]
	CuO/Cu_2O/Cu-biochar	–	24	2.0	25	9.5		Hydrogen-bonding, π-π interaction	[222]
	Smectite	7.00	24	5.0	23	–		π-π interaction, Hydrogen-bonding.	[223]
	Zero-valent iron/Cu nanoparticle	5.0	1.5	0.2	–	5.0	26.15 mg/g; 95%	Hydrogen-bonding, π-π interaction	[224]
	Graphene oxide nanoplatelets	2.0	2.0	1.0	25	4.87	99%	π-π interaction, Hydrogen-bonding.	[225]
	Montnorillonite Nanoclay	6.0	24	1.5	25	–	97%	Electrostatic interaction	[226]
Clofibric acid	MOF (MIL-101)	4.0	12	0.1	25	–	92.1 mg/g	Electrostatic interaction	[227]
pKa = 3.18	MOF (MIL-100-Fe)	4.0	12	1.0	25	–	88.0 mg/g	Electrostatic interaction	[227]
	Graphene oxide	11.0	2	1.0	25	3.9	994 mg/g	π-π interaction	[228]
Nofloxacin pKa 6.34	Polydopamine microsphere	6.0	1.5	0.5	35	6.3	307 mg/g	Electrostatic interaction, H-bond, π-π interaction	[229]
	MOF (UiO-66-NH_2)	8.0	6	0.1	25	6.2	222.5 mg/g	π-π interaction, Electrostatic interaction	[230]
	Microplastics	5.0	54	0.005	25	–	41.2%	Polar-polar interaction, van-der-waal interaction, π-π interaction, H-bonding.	[231]
	Modified thermal activated kaolin	–	–	0.04	25	–	88.53%	Covalent bond	[232]
Ofloxacin pKa = 5.97	MOF (ZIF-8)	9.0	–	0.2	25	–	194.9 mg/g	H-bond, Electrostatic interaction, complexation of unsaturated metal	[233]
	Modified thermal activated kaolin	–	4.2	0.04	25	–	91.46%	Covalent bond	[232]
	Calcined verdo-lodo bentonite clay	8.25	24	1.2	25	2.7	160.81 mg/g	Electrostatic	[234]

dependent [206]. Therefore, for researchers to gain more insight on the solution chemistry and how its affect adsorption mechanism, there is need for further information on solution pH, adsorbent point of zero charge (pHpzc) and the pKa of the adorbate. Considering the pKa of the selected micro-pollutants as indicated in Table 6, it can be observed that the pKa_1 of norfloxacin, ofloxacin, ciprofloxacin, clofibric acid and carbamazepine are 6.34, 5.97, 6.09, 3.18 and 13.9 respectively [90,125,184,206,207]. In combining these alongside with kinetic, isotherm, and thermodynamic models and spectroscopy analysis such as XPS, XRD and FTIR, the mechanism of adsorption of these selected emerging micro-pollutants as mentioned in Table 6 can be properly explained.

During adsorption process (Table 6), there are usually multi-mechanisms which can be identified in systematic ways. Thermodynamic modeling determines adsorption mechanism through identification of types of interactions such as; physisorption and chemisorptions which is based on the magnitude of ΔG°. When eluents (such as; organic solvent or distilled water) are effective, It usually implies the existence of a physical mechanism. Chemical adsorption is demonstrated by the efficiency of strong acids and/or bases. For further clarification, there is always a need to consider the isotherm and kinetic models based on the best-fit assumed. The spectroscopic analysis also revealed the specific functional group and location onto which the interaction occurs. This is especially crucial when it comes to the identification of the chemical bonds that cause chemical or physical interaction. The solution chemistry (pH, pKa, and pHpzc) is critical for the determination of chemical interactions between the adsorbate and adsorbent under different pH regimes. It has been reported that the adsorption pHpzc and optimum pH controls the mechanism uptake. Therefore, the adsorbent-adsorbate interactions are affected by the pH of the solution.

From Table 6, in norfloxacin, ofloxacin, carbamazepine, clofibric acid and ciprofloxacin, At pK_{a1}, the carbonyl group is deprotonated, while at pK_{a2}, the amine group is protonated [235]. These micro-pollutants can exist as a cation, anion and zwitterions. At this point, the adsorbent point of zero charge (pHzc) comes into play; when the adsorbent surface has a net negative surface charge, absorption could occur via cation exchange with the protonated amine group. Interactions with deprotonated carboxylic groups are complicated for those with a net positive surface charge [236]. It was observed that the major mechanism in these selected micro-pollutants are; electrostatic interactions, π-π (dispersive) interactions, H-bonds, hydrophobic contacts, and pore diffusion because of their low solubility, and they tend to be adsorbed in hydrophobic interactions [235]. The electrostatic interaction (acceptor-donor) attraction resulted when the adsorbate is protonated and persists in its ionic state (pH > pKa) based on the adsorbate's ionic charge and the adsorbent's net surface charge. The 5.00–9.00 pH range has limited solubility because the adsorbate is electrostatically neutral and exists as a zwitterion. The attraction or repulsion between molecules with opposing charge is known as electrostatic interaction [237]. Electrostatic interaction would promote uptake if the adsorbate-adsorbent contact is attractive. They must have an opposing charge to the adsorbent's net surface charge in order to provide an attracting force. Electrostatic interactions are most common when the adsorbent has a net negative surface charge in the pH range of 1–5.59.

6.4. Chemical techniques

Advanced oxidation processes based on ozone (O_3/UV, and O_3/H_2O_2), Fenton-type reactions, and photochemical AOPs have been found to be more efficient than ozonation and adsorption alone [238,239]. Several nanomaterials specifically metal and metal oxides [197] have been employed for wastewater treatment without high efficiency. AOPs are usually employed for the treatment of recalcitrant compounds due to increase production of radicals (that is, hydroxyl) and photon-initiated breaking of carbon-halogen bonds [240,241]. Depending on the Chemical Oxygen Demand (COD) in the wastewater, the typically used ozone dose varies from 5 to 15 mg/L, with a contact time of 15–30 min [242]. In general, > 90% of personal care and pharmaceutical products are removed under these conditions. The availability of particulate matters at monitored amounts in the secondary effluent has no effect on the removal efficiency of soluble chemicals with high ozone reaction rates [243]. Fig. 1 summarized different methods of treatment with their merits and demerits.

Of all the treatment methods of hospital wastewater, advanced oxidation processes based on free radical mechanism have been widely utilized to effectively decompose toxic recalcitrant emerging micro-pollutants into harmless species. In recent times, researchers have shown that combined treatment approach for hospital wastewater are more feasible, economical and offer greater efficacy than a single advanced oxidation processes based on the synergetic effects between the two methods [244]. The enhanced production of highly reactive molecular species in the combined system within short period of time contributed to its overall efficiency [164]. This review focused on the chemistry of photocatalytic and photo-fenton technology.

6.4.1. Photocatalytic and photo-fenton processes

The principle of photocatalytic reaction is based on excitation of a catalyst through the application of light such as visible or ultra-violet light [18]. Generation of free radicals produced during photon action would lead to oxidation or breaking down of adsorbed compounds on the catalyst surface [245]. The photocatalyst such as titanium oxide, zinc oxide, tungsten trioxide, cadmium sulphide, silicon (IV) oxide and copper oxide [205] converts chemical energy to photon energy via reduction-oxidation reaction. This causes the activation of nano-particles, leading to excitation of electrons from the valence band to conduction band and generation of electron-hole pairs. This further reacts with water and produce highly reactive hydroxyl radicals that selectively convert organic compounds into harmless species [246]. The degradation process is begun by oxidants such as OH^{o}, which are directly created by photolysis of water molecules adsorbed on the photocatalyst's active site (see Fig. 2). Furthermore, the photo-fenton reaction has multiple stages depending on their participation in free radical reactions: generation of active oxygen with the presence of species that initiates the oxidation, active oxygen containing species transformation, and transformation reaction of oxygen species with organic compound and finally intermediate reaction termination. The photo-generated ferrous ions enter Fenton reaction generate supplemental hydroxyl radicals. Consequently, the oxidation rate of photo-Fenton is accelerated compared to Fenton process [247]. In comparison to the Fenton reaction, the photo-Fenton reaction has a significantly lower total iron usage and sludge production [248]. Furthermore, photo-Fenton via solar or UV light has been shown to have a considerable impact on microorganism inactivation in polluted water bodies [249]. However, the process is dependent on the nature of microorganism present [250] and the nature of water under treatment [251]. In a study, it was found that spores of *F. solani* was more resistant to solar treatment than the vegetative cells of *E. coli* [252]. Hydroxyl radicals with 2.80 V oxidation potential degraded refractory substances such as chlorinated and phenolic compounds [253].

Fig. 2 gives the graphic illustration of photocatalytic and photo-fenton mechanisms while Table 7 summarizes pervious research finding involving application of photo-fenton and photocatalytic for the degradation of emerging micropollutants in aqueous solution. It was noted that there are few hybrid photo advanced oxidation processes (that is, photo-fenton and photocatalysis). Therefore, it is recommended that hybrid advanced oxidation processes should be acquired for efficient degradation of hospital wastewater since hospital wastewater is a multi-micro-pollutants wastewater.

Table 7 shows that most studies used simulated solution of these emerging micro-pollutants and not real environmental wastewater, where the pollutants exist as mixture. The performance of each technology was experimental conditions dependent. Again, individual

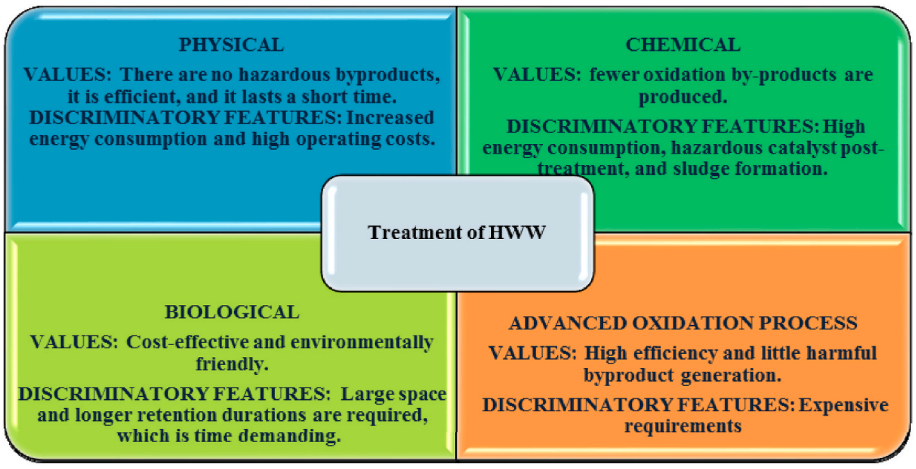

Fig. 1. Different methods of treatment of hopsital wastewater.

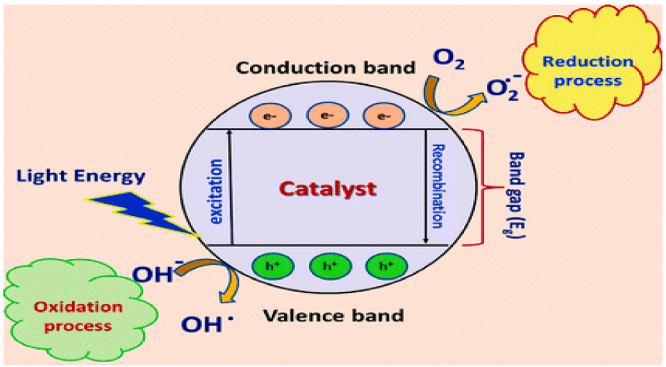

Fig. 2. Schematic representation of semiconductor photocatalytic mechanism [254].

advanced oxidation process employed produced high efficiency within short-period of time, though this should not be taken as indication of good performance because simulated solution that did not contain radical scavengers and other pollutants was used. Their inefficiencies to degrade organic pollutants in real environmental wastewater limit their full scale industrial applications.

6.4.2. Degradation mechanism of the selected emerging micro-pollutants based on photocatalytic technology

This section addressed degradation of the five selected emerging micro-pollutants (norfloxacin, ofloxacin, ciprofloxacin, clofibric acid and carbamazepine). The degradations pathways are very complex which lead to generation of several intermediates that are even more toxic and exert greater environmental impacts than the parent compound. Different analytical tools (GC-MS and HPLC-MS) were used to determine the intermediates and possible degradation pathways.

6.4.2.1. Degradation mechanism of ciprofloxacin. Fig. 3 shows the profile of six intermediates identified during the photodegradation of ciprofloxacin with the following molecular fragment ions at *m/z* of 348, 318, 274, 306, and 279 [275]. Comparing the profile of ciprofloxacin with its intermediates, it was found that A was the first intermediate to form during ciprofloxacin degradation, and the remaining four intermediates (B-E) appeared gradually based on their polarity with compound A during the photodegradation in the presence of graphitized mesoporous carbon (GMC)-TiO_2 nanocatalyst [276]. Despite the fact that the four intermediates B to E had a similar characteristics, it was observed that the retention time differ and that distinguished intermediates B, C from intermediates D, E, implying that products B, C, and D, E may be degraded in distinct ways. Furthermore, when compared to D, E, the decomposition of A to B, C occurred much faster and across a much wider range, implying that the degradation pathways of B and C should be preferred for CIP degradation over GMC-TiO_2 [276].

The intermediate A was likewise formed at first for the Degussa-P25 system, just as it was for the GMC-TiO_2 system. However, it was discovered that the amount of intermediate B-E produced, regardless of the fluctuation ranges or the time necessary to reach peak, was significantly different from that of the GMC-TiO_2 system; in particular, the amount of intermediate E produced was extremely considerable [277]. This shows that the degradation pathways of CIP in the presence of TiO_2 alone and GMC-TiO_2 nanocatalyst differ. The CIP degradation intermediate byproducts via photodegradation route are presented in Fig. 3. It was found that the mechanism of degradation of CIP followed hydroxylation, dihydroxylation, and double dihydroxylation.

6.4.2.2. Degradation mechanism of norfloxacin. The degradation of norfloxacin (NOR) degradation often occur through the following pathways Piperazine ring transformation, dehydroxylation, defluorination, and decarboxylation [278]. The molecular ions, as well as mass fragment ions, were detected by MS spectra based on the HPLC-MS analysis. Fig. 4 depicts the proposed NOR degradation routes. During the photocatalytic reaction, two main degradation pathways: hydroxylation (route 1) and piperazinyl ring cleavage (pathway 2), were predicted according to the intermediate determination (pathway 2). The F atom was hydroxylated immediately by ·OH in pathway 1, resulting in the hydrolated-NOR intermediate (m/z = 317) [279]. Following benzene ring opening of NOR2 and hydroxylation to generate NOR4 (m/z = 181) after the loss of C_4NH_6, piperazine ring clavation (NOR2; m/z = 249) [279]. NOR2 further undergo decarboxylation to yield NOR5 (m/z = 175) through continual ·OH oxidation [279]. The quinoline ring cleavage of NOR5 and the loss of functional groups –NH_2 and –CH_3 were responsible for the formation of NOR6 (m/z = 147). NOR7 (m/z = 113) was formed from NOR6 through decarboxylation and hydroxylation processes [280]. In pathway 2, ·OH oxidation gave rise to decarboxylation and piperazine ring breakage of NOR, resulting in the formation of NOR3 (m/z = 227). The prominent peaks in the MS spectra of NOR2 and NOR3 imply that the piperazine ring transition was most likely a significant factor for NOR degradation pathway [279]. Further mineralization of the intermediates usually lead to the formation of low molecular organics such as CO_2, H_2O, F^-, and NO_3^- as inorganic products [89].

6.4.2.3. Degradation mechanism of ofloxacin. The Transformation Products (TPs) of Ofloxacin (OFL) were identified and demonstrated

Table 7
Emerging micropollutants degradation by either Photocatalytic or photo-Fenton, Photocatalytic-adsorption and photo-Fenton-adsorption processes.

References	Treatment Techniques	Nanomaterial	Micro-pollutants	Research Findings
Sponza and Alicanoglu [255]	Photocatalysis	Nano-GO/M	Ofloxacin	COD (88%), TSS (82%), TKN (95%), 97% removal, at pH 7.8, after 60 min at UV power of 300 W.
Perini et al. [256],	Photo-Fenton	Fe^{2+}	Ciprofloxacin	80–95% removal, iron of 0.56 mg/L, pH 7.4, H_2O_2 of 17 mg/L, initial concentration 200 μg/L in 90 min.
	Photo-Fenton	Fe^{2+}	Amoxicillin	80–95% removal, iron of 0.56 mg/L, pH 7.4, H_2O_2 of 17 mg/L, initial concentration 200 μg/L in 90 min.
	Photo-Fenton	Fe^{3+}	Sulfathiazole	80–95% removal, iron of 0.56 mg/L, pH 7.4, H_2O_2 of 17 mg/L, initial concentration 200 μg/L in 90 min.
	Photo-Fenton	Fe^{2+}	Sulfamethazine	80–95% removal, iron of 0.56 mg/L, pH 7.4, H_2O_2 of 17 mg/L, initial concentration 200 μg/L in 90 min.
Liu et al. [257],	Adsorption-photocatalysis	TiO_2/Zeolite	Sulfadiazine (SDZ)	90% of SDZ was removed within 120 min of both adsorption and degradation by TiO_2/zeolite dosage of 1 g/L at neutral pH
Chinnaiyan et al. [258],	Photocatalysis	TiO_2	Amoxicillin trihydrate	At pH 7.6, dosage of 563 mg/L, reaction duration of 150 min, and a starting concentration of 10 mg/L, 90% elimination is achieved.
	Photocatalysis	TiO_2	Metformin HCl	At pH 7.6, dosage of 563 mg/L, reaction duration of 150 min, and a starting concentration of 10 mg/L, 90% elimination is achieved.
Tri et al. [259],	Photocatalysis	Ag-doped g-C_3N_4	Tetracycline	96.8% removal, fir 120 min, under solar light condition
Konstas et al. [260],	Photocatalysis	TiO_2CN	Venlafaxine	70% removal, in 90 min.
Ghenaatgar et al. [261],	Photocatalysis	ZrO_2/WO_3	Dexamethasone	100% removal, initial concentration of 5 mg/L, pH 3, Dose of WO_3 and ZrO_2 to be 500 and 1500 mg/L respectively.
Beheshti et al. [262],	Photocatalysis	TiO_2	Sulfamethoxazole	61.28% removal, dosage of 500 mg/L, pH 4.
	Photocatalysis	WO_3	Sulfamethoxazole	43.3% removal, dosage of 750 mg/L, pH 3.
Serna-Galvis et al. [263],	Photo-Fenton	Fe(II)	Levofloxacin	54% removal, after 90 min, 1 mg/L of Fe(II), 10 mg/L of H_2O_2, pH 6.5, 500 W/m^2
Sun et al. [264],	Photo-Fenton	α-FeOOH	Sulfadiazine	100% removal, within 60 min, initial concentration of sulfadiazine of 12 mg/L, H_2O_2 of 10 mmol/L, UV intensity of 100 μW/cm^2.
Della-Flora et al. [265],	Photo-Fenton	Fe^{2+}	Flutamide	58% removal, for 40 min, dose of 5 mg/L, 150 mg/L of H_2O_2.
Serna-Galvis et al. [263],	Photo-Fenton	Fe(II)	Oxacillin	15% removal, after 90 min, 1 mg/L of Fe(II), 10 mg/L of H_2O_2, pH 6.5, 500 W/m^2
Vieira et al. [266],	Photocatalysis	Fe°	Diclofenac	100% removal, 98% COD, dose of 0.36 g/L, for 60 min, at MW power of 780 W
	Photocatalysis	Fe°	Ibuprofen	100% removal, 98% COD, dose of 0.36 g/L, for 60 min, at MW power of 780 W
Wu et al. [267],	Adsorption-photocatalysis	La/Mg–Al with the La_2O_3	Tetracycline hydrochloride (TCH)	99.87% of TCH was removed within 110 min and reduced to 95.88% after five cycle times.
Della-Flora et al. [268],	Photo-Fenton	Fe(II)	Fluconazole	80% removal, initial concentration of 500 μg/L, H_2O_2 of 100 mg/L, time of 10 min
	Photo-Fenton	Fe(II)	Flutamide	99% removal, initial concentration of 500 μg/L, H_2O_2 of 100 mg/L, time of 10 min
	Photo-Fenton	Fe(II)	Furosemide	99% removal, initial concentration of 500 μg/L, H_2O_2 of 100 mg/L, time of 10 min
	Photo-Fenton	Fe(II)	Chloramphenicol	99% removal, initial concentration of 500 μg/L, H_2O_2 of 100 mg/L, time of 10 min
Lumbaque et al. [269],	Photo-Fenton	Fe3+-EDDS	Dipyrone	Above 77% removal, 500 μg/L of dipyrone, 230 mg/L of H_2O_2, at circumneutral pH.
	Photo-Fenton	Fe3+-EDDS	Diazepam	Above 77% removal, 500 μg/L of Diazepam, 230 mg/L of H_2O_2, at circumneutral pH
	Photo-Fenton	Fe3+-EDDS	Fluoxetine	Above 77% removal, 500 μg/L of Fluoxetine, 230 mg/L of H_2O_2, at circumneutral pH
	Photo-Fenton	Fe3+-EDDS	Paracetamol	Above 77% removal, 500 μg/L of Paracetamol, 230 mg/L of H_2O_2, at circumneutral pH
	Photo-Fenton	Fe3+-EDDS	Propranolol	Above 77% removal, 500 μg/L of Propranolol, 230 mg/L of H_2O_2, at circumneutral pH
	Photo-Fenton	Fe3+-EDDS	Progesterone	Above 77% removal, 500 μg/L of Progesterone, 230 mg/L of H_2O_2, at circumneutral pH
Wu et al. [270],	Adsorption-Photo-fenton.	L-MIL-53(Fe, Mn, Cu)	Ciprofloxacin (CIP)	15.2 and 2.49 times increase in reaction rate constant of CIP for L-MIL-53(Fe, Mn) and L-MIL-53(Fe, Cu) respectively.
Abbasi et al. [271],	Adsorption-photocatalysis	GO-CeO_2	Doxorubicin (DOX)	97% of DOX was removed within 360 min. The pH of the DOX solution widely affected the removal process; neutral and alkaline conditions of pH supported the degradation process
Chen et al. [272],	Adsorption-photocatalysis	MIL-53(Fe, Al)	Tetracycline	71.39% and 81.82% of tetracycline were removed by MIL-53(Fe) and MIL-53 (Al). within 50 min.
Xu et al. [273],	Adsorption-photocalaysis	β-Bi_2O_3/ZrO_2	Levofloxacin (LVF)	92.7% OF LVF was removed with 100 min.
	Adsorption-photocalaysis	β-Bi_2O_3/ZrO_2	Tetracycline hydrochloride (TC)	90.1% of TC was removed within 100 min.
	Adsorption-photocalaysis	β-Bi_2O_3/ZrO_2	Oxytetracycline hydrochloride (OTC).	91.2% of OTC was removed within 100 min.
Chen et al. [207],	Adsorption-photo-fenton	$LaFeO_3$/Lignin-biochar	Ofloxacin	95.6% of Ofloxacin was removed with 75 min.
Liu et al. [274],	Adsorption – Photo-Fenton.	Cu–Fe bi-metal/g-C_3N_4 Nanosheets.	Tetracycline	Tetracycline removal efficiency over a wide pH range.

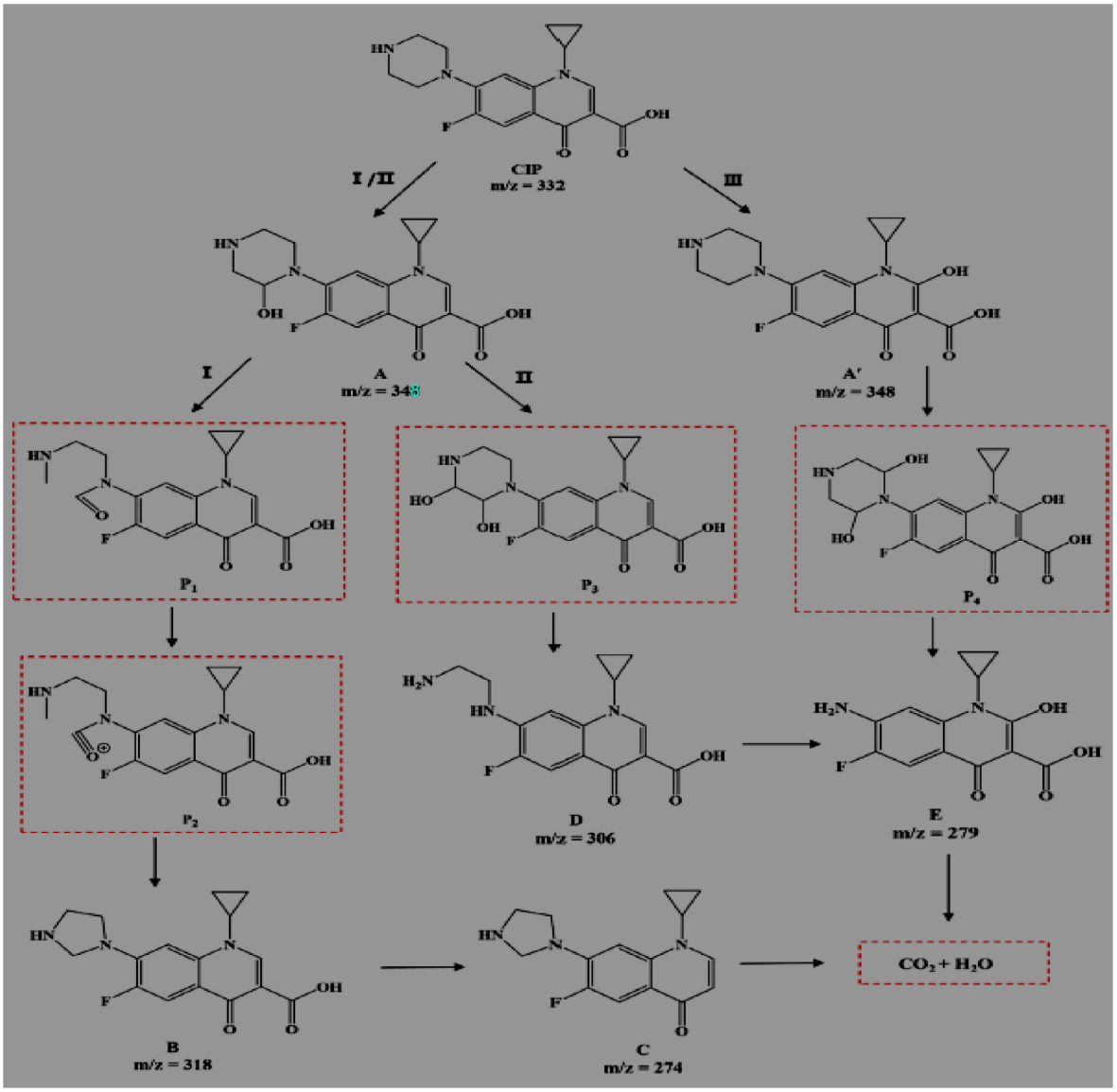

Fig. 3. The Degradation Pathway for Ciprofloxacin through photocatalysis [276].

using HPLC-ESI-Q-TOF-MS with the value of mass/charge (*m/z*) and LC/MS patterns. Fig. 5 depicts the OFL transformation route and associated TPs. The attack of oxidative species such as hydroxyl radicals on the C–C bond of OFL, resulted in the formation of acetaldehyde groups in TP1. Due to the instability of the aldehyde derivative, it was further subjected to additional oxidation, culminating in the production of TP2 [281]. Following that, the hydrogenation reaction was the most common way for TP2 to become TP3. The development of TP8 from TP2 was caused by a C–N bond rupture. The production of TP9 was caused by the decarboxylation process. TP8 could be derived directly from OFL as an essential intermediary [281]. Decarboxylation was also used to create TP4. The species that are active $\bullet O_2^-$ is included. h^+ attacked the piperazinyl substituent in OFL, resulting into complete demethylation process and formation of TP5 [207]. TP5 was then subjected to a series of tests. Due to h^+ attack, the decarboxylation step occurred, and the product was converted into TP6. After that, with a subsequent radical attack of TP6, TP7 was formed [281]. The formation was aided by demethylation and hydroxylation. The TP11 was obtained as a result of the demethylation procedure and majority of the observed intermediates were later oxidized and eventually mineralized into CO_2 and H_2O [281].

6.4.2.4. Degradation mechanism of clofibric acid (CA). The photocatalytic degradation route of CA are shown in Fig. 6 based on proposed molecular structures of the by-products. There are different pathways for photodegradation mechanism of clofibric acid [120]. Pathway 1 followed the e^- reductive mechanism, which involved dechlorination of C_3–Cl. The radical's 2-methyl-2-phenoxypropanoic acid was generated, which were then oxidized by HO· to produce P1 [282]. The reaction of 2-methyl-2-phenoxypropanoic acid radicals with diaquooxonium ions and hydrated electrons led to the formation of 2-methyl-2-phenoxypropanoic acid radicals. P3 is formed as a result of this. As a result, the aldehyde and benzene predictions were accurate [282].

The ipso-substitution reaction was responsible for Pathway 2, in which the aromatic hydrogen compound's ipso C was attacked by HO·, resulting in hydroxytative carbon-centered radicals. A series of P2 was generated during O-dealkylation processes when the chain was cleaved. The electrophilic adduct process by HO· attack, resulted in the creation of mono- and multihydroxylation byproducts, illustrated by Pathway 3. P4 was formed when HO· attacked at C2. P5 was formed after additional oxidation of P2. When HO· attacked C12 via demethylation and decarboxylation, transitory states of HO· adduct radicals were generated, resulting in the creation of HO· adduct radicals [282]. Additionally,

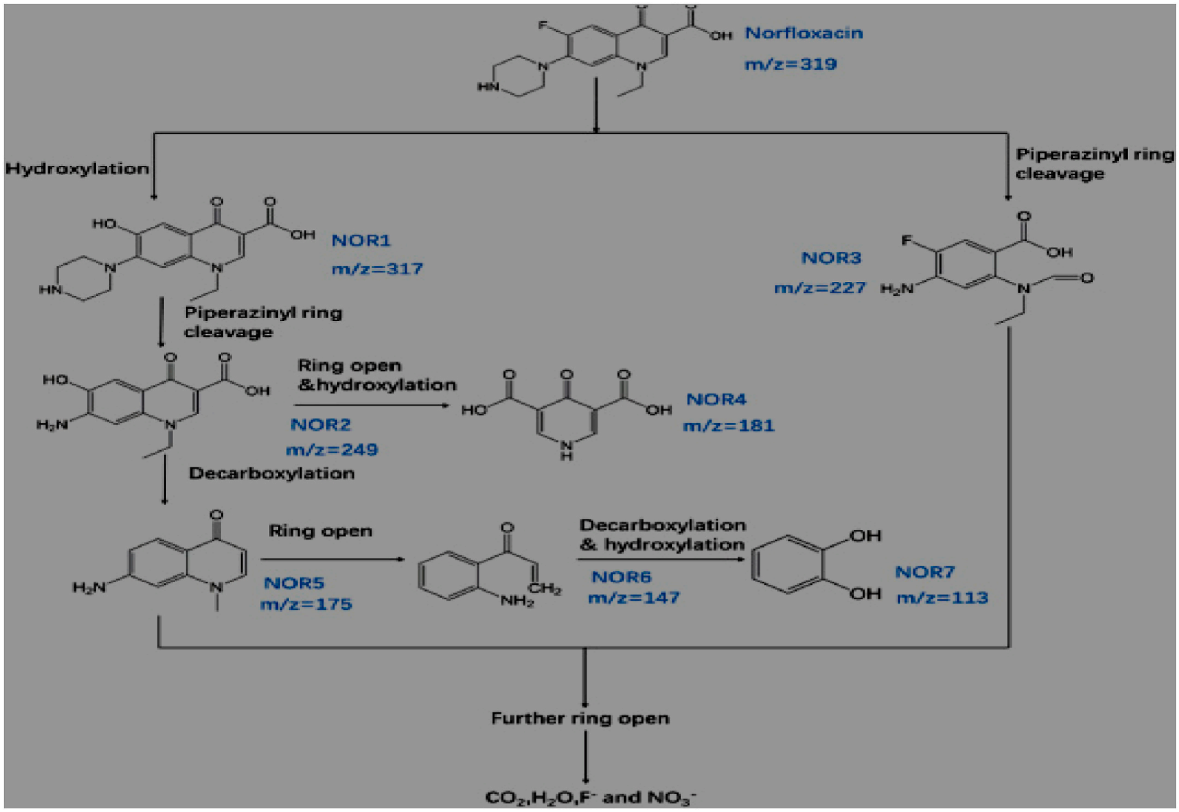

Fig. 4. Degradation pathway of Norfloxacin through photocatalysis [279].

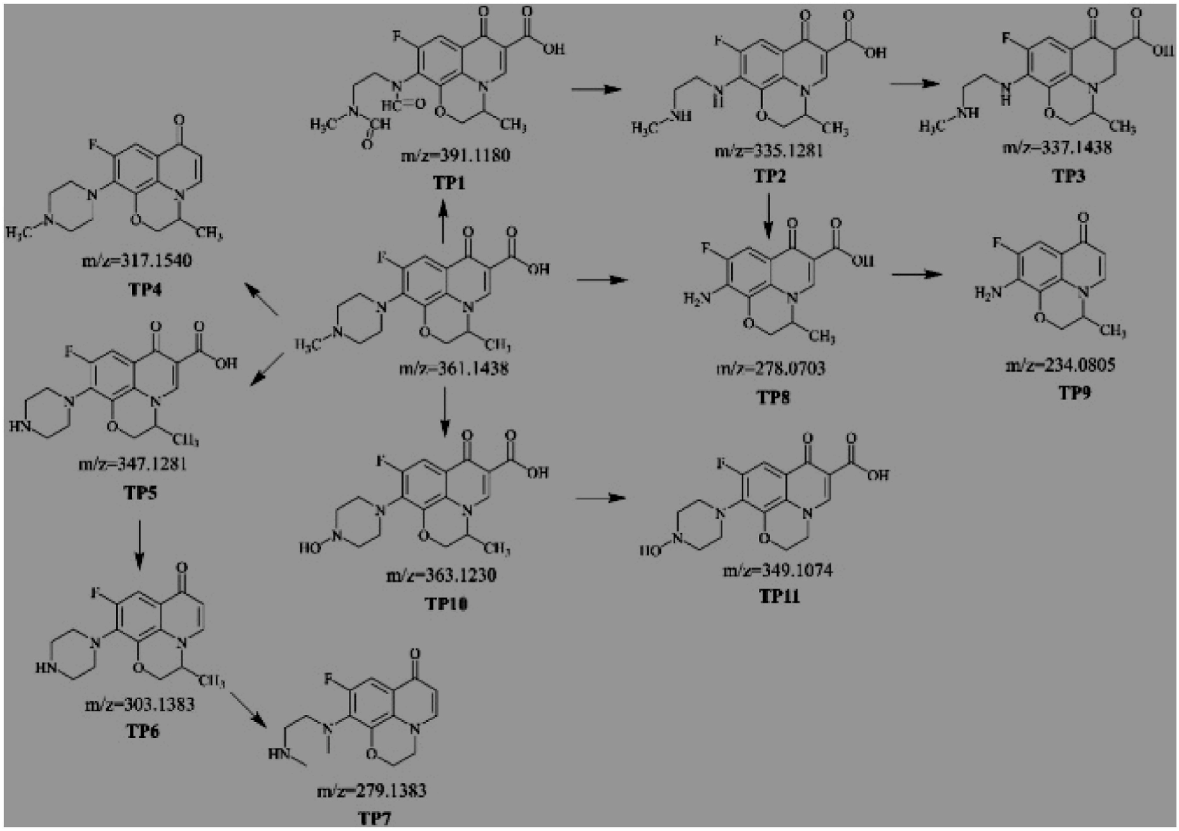

Fig. 5. Degradation pathway of Ofloxacin [281].

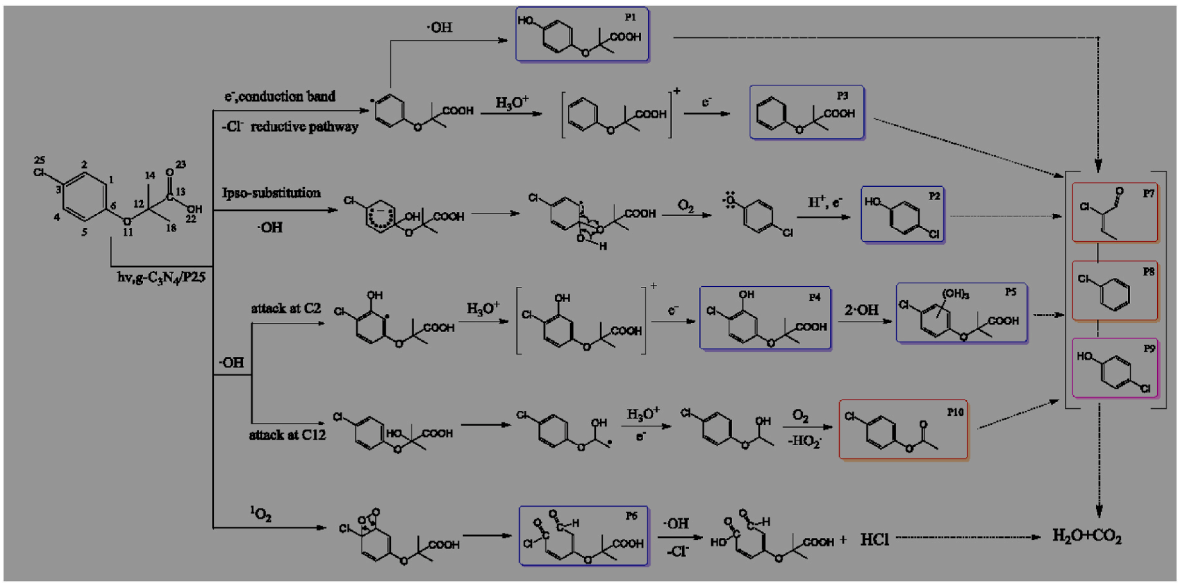

Fig. 6. Degradation pathway of Clofibric acid through photocatalysis [282].

processing of the hydroxylated by-product produced stable oxidation by-product (P10). $^1O_2$ hitting the aromatic C atom started Pathway 4 as a result of the reduced $FED^2_{HOMO} + FED^2_{LUMO}$($^1O_2$/dioxetane mechanism) value. Endoperoxides are formed when $^1O_2$ reacted with CA at C3. Aside from that, $^1O_2$ stayed on the stimulated surface longer and increased the interaction with the substrate on the surface [282]. As a result, the aldehyde and acid combined because of the endoperoxide, a chloride byproduct (P6) was then produced. Some researchers have reported similar aldehyde and carboxylic acid production mechanisms [282]. CA and its byproducts could further reduced to generate small molecule chloro-compounds such as; P7–P9.

6.4.2.5. Degradation mechanism of carbamazepine. Fig. 7 shows time course profiles of HPLC-SIR-MS spectra for carbamazepine degradation under UV light by BPO-180-72. The peak area of carbamazepine rapidly reduced as the irradiation period increased, but new distinctive peaks developed indicate conversion of carbamazepine into different transformation products [283]. For instance, ten major intermediates were with mass to charge ratio (m/z) at 253.1, 149.0, 259.1, 275.0, 253.1, 253.1, 208.2, 180.1, 301.1, and 349.2 were detected. Specific molecular

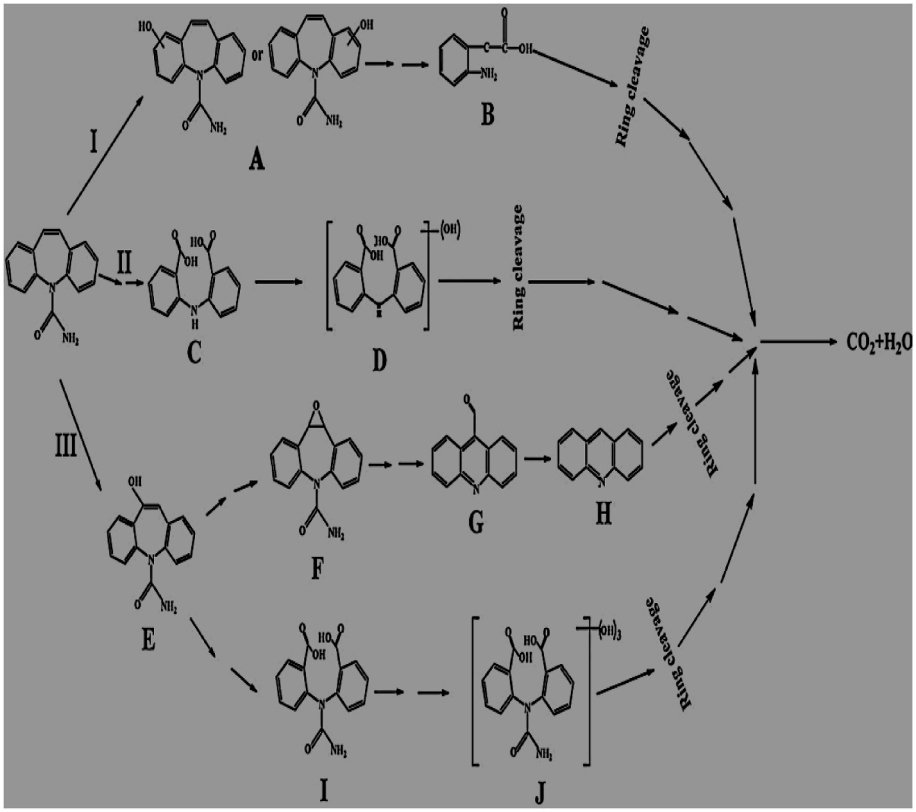

Fig. 7. Degradation pathway of Carbamazepine [284].

ions, mass fragment peaks, HPLC–MS library data, and the relevant chemical information were used to identify the products/intermediates. Hydroxylation mechanism dominated during the transformation of carbamazepine into various byproducts by photodegradation process as revealed in Fig. 5 (D and J) [284].

A preliminary degradation pathway of carbamazepine by BPO-180-72 was postulated based on the general laws of photocatalytic oxidation of organic molecules and the intermediates found by LC–MS (Fig. 5). Photogenerated holes and hydroxyl radicals were the main reactive species involved in carbamazepine degradation in aqueous $BiPO_4$ solutions [283]. The formation of $HO^{\bullet}$ radicals in aqueous solution was mostly due to the hole grabbing $HO^{\bullet}$ of water or the reduction of O_2 with electrons [284]. Bi^{III}/Bi^{V} had a lower standard redox potential (1.59 eV at pH 0) than HO·/HO for $BiPO_4$ (1.99 eV). To begin with, the produced $HO^{\bullet}$ interacted immediately with carbamazepine to produce compounds A and E. (pathways I and III) [284]. The hydroxylation of aromatic rings by $HO^{\bullet}$ radicals during the photocatalytic process has been reported to be a key reaction in the sequential ring cleavage reactions [284]. As a result, the $HO^{\bullet}$ attacked the olefinic double bond on the core heterocyclic ring, which was then oxidized by photogenerated holes in a ring-rupturing process to yield product C (pathway II). The intermediate A was further oxidized by the holes, yielding the low-molecular-weight molecule B. Meanwhile, compound E was transformed in two different ways in the reactions that followed. Product F was generated by the attack of HO· on the core heterocyclic ring's olefinic double bond and an elimination process. It was subsequently subjected to hydrogen rearrangement process, yielding compound G. The intermediate G was further oxidized by incision to form compound H. Product E was changed into compound I, which was comparable to route II, in tandem with that process. Hydroxylation played a significant role in the transformation process. The intermediates C and I probably oxidized to complex hydroxylated intermediates D and J in the presence of $HO^{\bullet}$ radicals, although no exact place for hydroxyl groups could be given from the fragmentation pattern. Finally, the ring-rupturing processes oxidized the complex hydroxylated intermediates (D and J) and low molecular molecules (B and H) to aliphatic compounds, which were mineralized to CO_2 and HO_2 [284]. In general, photogenerated holes and $HO^{\bullet}$ radical oxidation drove carbamazepine breakdown by monoclinic phase $BiPO_4$ under UV light irradiation, resulting in total mineralization of the pollutant. The presence of non-selective $HO^{\bullet}$ radicals during the degradation process was confirmed by the recently discovered complex hydroxyl compounds D and J [283].

It was noticed that the degradation of the selected emerging micro-pollutants resulted to generation of more toxic byproducts which need to be removed from wastewater prior to release into water bodies. It was also observed that single advanced oxidation process produced several intermediates and such treated water cannot support aquatic life and thus the pollutants must be sequestered. The review shows that limited information exist on the combination of two advanced oxidation processes with adsorption technology to first decompose and later remove the emerging contaminants in hospital wastewater. Thus, future research efforts should directed towards the utilization of combination of adsorption technology and advanced oxidation processes for hospital wastewater treatment.

7. Conclusion and future perspective

This review provide information on the formation, composition and properties of hospital wastewater such as: physicochemical, bacteriological, inorganic and organic properties which are ranges from microgram to nanogram. It was found that the concentrations of the selected emerging micro-pollutants (Norfloxacin, Ofloxacin, Ciprofloxacin, Carbamazepine, and Clofibric acid) are high due to their frequent application for patients and incomplete metabolism prior into the environment. Thus, continuous exposure to these contaminants could be detrimental to aquatic and human life and that hospital wastewater that harbors these compounds should be considered a major threat to ecosystem. Several treatment methods have been adopted for the treatment of hospital wastewater such as physical, biological, chemical, adsorption and advanced oxidation are not efficient due to the complexity and existence of pollutants as mixture in hospital wastewater, our findings shows that combination of advanced oxidation process with conventional method will be more suitable for successful degradation/removal of emerging contaminants in hospital wastewater. It is advisable not to treat hospital wastewater with sewer wastewaters since hospital wastewaters always have high concentration of pollutants. Therefore, there is urgent need for every hospital to have mini treatment plants comprises combination of adsorption technology and advanced oxidation processes and other conventional methods to treat their liquid wastes before release into the environment. Regulatory bodies are also expected to involve in a continuous and periodic monitoring through activation of strict enforcement and compliance to environmental safety and sustainability.

Credit author statement

OJ, Ajala: Investigation, Writing-original draft. **JO, Tijani**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing - original draft, Writing - review & editing. **RB, Salau:** Data curation, Formal analysis, Investigation. **AS, Abdulkareem:** Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing. **OS, Aremu:** Data curation, Formal analysis, Investigation.

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.

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