Removal and Recovery of Nitroimidazoles (Metronidazole and Trimethoprim) Antibiotics from a Pharmaceutical Industry Wastewater Using Reverse Osmosis

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Abstract: - In the practice of medicine, antibiotics are extremely important and are employed in the treatment of infections. A lot of antibiotics are consumed by humans and excreted via urine and feces into sewage systems and treatment plants. These are considered to be non-biodegradable, and over the years they accumulate in the aquatic environment. The presence of antibiotics in water resources causes the emergence of antibiotic-resistant bacteria, posing a serious threat to the health of human beings. Water bodies must be adequately treated before being discharged to prevent the spread of antibiotic resistance. A reverse osmosis reactor with a two membranes namely hollow fiber osmosis (HF–O) and hollow fiber composite (HF-C) modules was used in the removals and recoveries of Metronidazole (MET, C6H9N3O3) and Trimethoprim (TMP, C14H18N4O3) antibiotics at different concentrations. Nitroimidazoles (Metronidazole and Trimethoprim) were selected because they are antimicrobials with bactericidal action that present a moderately broad antibacterial spectrum. They are used in infections of the urinary tract, ears, lungs, intestines and liver. The effects of applied pressures (10, 20, 30, and 40 bar), feed concentrations (25, 50, 100, 250 and 1500 mg/l), operating temperatures (25, 35, and 45°C), and feed flow rates of 5, 7, 10, and 15 l/min on the removals and recoveries of both antibiotics were researched. Js/Jw is also increased with feed flow rate for the HF–C membranes but remains relatively constant for HF–O membranes for all tested feed flow rates. Therefore, Js/Jw is much lower for HF–O membranes (Js/Jw = 0.15 ± 0.02 g/l) than it is for HF–C membranes (Js/Jw = 0.40 ± 0.10 g/l). For the HF–C membrane, Jw was higher than for the HF–O membrane at any draw flow rate investigated, and it increased from 24.9 ± 0.6 l/m2.h permeate flux at 25 l/h feed flow rate to 31.30 l/m2.h at 100 l/h, respectively (Jw increase of 25.40%). Jw increased from 17.90 ± 0.50 l/m2.h to 19.20±0.50 l/m2.h (7.30% increase in Jw) for HF–O modules and from 24.0 ± 1.3 l/m2.h to 27.70 ± 0.20 l/m2.h (15% increase in Jw) for HF–C modules. The water permeability coefficient (Aw) and solute rejection efficiency (R) were constant at 6.73 l/m2/h/bar and 99.20%, respectively, while the solute permeability coefficients varied with pressure and correlated with Jw Antibiotic rejections varied from 94.0 to 99.80% depending on pH rejection was highest at a pH of 6.0, at 99.80%. For both membranes, the rejection rate was obtained at 295oK (22oC) for maximum antibiotic yields 60.80% and 71.60% for HF–O and, HF–C, respectively. The maximum antibiotic removal rates were 90.70% and 86.40%, respectively. The HF-C membrane was relatively more efficient at all concentrations tested than the HF-O membrane, because of its smaller pore size and its structure. 99% Metronidazole and 99% Trimethoprim removal yields were obtained in HF-C RO membrane, at 100 mg/l initial Metronidazole, at 100 mg/l initial Trimethoprim, at 180 l/h, at 4.2 l/m2.h, respectively. 99% Metronidazole and 99% Trimethoprim removal yields were observed in HF-O RO membrane, at 100 mg/l initial Metronidazole, at 100 mg/l initial Trimethoprim, at 30 bar feed pressure, at 7 l/m2.h, respectively. 99% Metronidazole and 99% Trimethoprim removal yields were observed in RO membrane, at 100 mg/l initial Metronidazole, at 100 mg/l initial Trimethoprim, at 30 bar, at 7 l/m2.h, respectively. Conventional wastewater treatment plants are not able to eliminate antibiotics deposition/resistance genes effectively and efficiently. In this regard, the adsorption method is the most effective way of removing antibiotics from wastewater from various sources.

Key-Words: - Antibiotics; External concentration polarization (ECP); Hollow fiber composite (HF-C); Hollow fiber osmosis (HF-O); Hollow fiber reverse osmosis (HFRO); Metronidazole (MET); Pharmaceutical Industry wastewater; Recovery; Thin-film composite (TFC); Trimethoprim (TMP).

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1 Introduction

Water, a renewable but limited resource available in nature, is essential to human existence as well as environmental sustainability. In certain developing nations, chemical pollution of surface waterways, mostly owing to industrial and agricultural emissions, poses a serious threat, [1]. Most developing nations respond to public health protection needs through pathogen management and water management, [2], [3], [4].

The potential negative effect of pharmaceutical compounds to aquatic and terrestrial wildlife makes interest on the study of their existence, activity and removal from waste water, [5]. As stated by the World Health Organization, [6], pharmaceuticals are natural or man-made chemicals which includes in prescription medicines, veterinary drugs and those which can be used without medical prescription. These chemicals have active ingredients which are made to have pharmacological effects when taken, [6]. They are extensively used to treat and/or prevent diseases in animals including humans. They also assist the growth of animals in aquaculture and livestock operations, [7].

Pharmaceuticals can enter the surroundings from various sources like pharmaceutical production plants, hospitals, landfills, waste water treatment plants and even graveyards, [8], as shown on Figure 1 where different interactions have been summarized. The major source is said to be the discharge from sewage treatment plants, [9]. Several pharmaceuticals which are mostly used as human medicine become excreted as either unaltered or as active metabolites, [10].

*Figure 1 can be found in the Appendix section.

Different processes take place when the pharmaceuticals are taken into the body. First, they get absorbed and distributed in the body. Then they get partly metabolized and, in the end, they get excreted either in unchanged form, as conjugates or may be excreted as biodegraded within the faces or dispersed in urine. Metabolism of pharmaceutical compounds may produce pharmacological active compounds or may detoxifies the drug molecules and converts them to the form which can be renal excreted due to polarity and hydrophilic characteristics, [9]. This makes the human excretion to be a combination of parent compound and their metabolites, consisting of transformed forms and conjugated glucuronides, [11]. All these components will enter the sewage system.

The other source is improper disposal of unwanted or expired drugs which are normally disposed of in wastewater, [12]. So, the pharmaceuticals will get to the sewage treatment plants and whether treatment is not efficient, they can be free into surface water, [10]. Their existence in aquatic system depends on their physicochemical characteristics, particularly on their hydro-solubility, stability and half-life of the molecules, [13].

Many processes can take place in compounds in the aquatic environment, like photochemical degradation, sorption onto solid matrices, dilution and transportation within the aquatic system with potential absorption in biological species, [12]. Bacteria in waste water can transform pharmaceuticals into products which are similar to metabolites from humans, but they may also produce biologically active substances by transformation of the excreted metabolites, [14]. The mixture of different compounds makes the process of removing pharmaceuticals from waste water difficult [15].

The main indicator that characterises the environmental safety of the habitat of all mankind on the Earth is the quality of natural waters, [16]. Pharmaceuticals, their metabolites, personal care products, and agrochemicals are a large group of chemicals that are classified as micropollutants, [17], [18], [19]. In addition, the main pharmaceutical environmental pollutants can be identified: medicines that do not comply with regulations (pharmaceutical waste), expired drugs, medicines that have lost their essential consumer properties, and preparations for animals. Today, there is a wide range of therapeutic drugs that are used to treat or prevent human and animal diseases. Their presence in the environment is not sufficiently assessed, which is a cause for concern, [20]. The reasons for the negative consequences are the expansion of the production of pharmaceuticals, the increase in the range of pharmaceuticals, and their active use all over the world for the treatment of long-known and new diseases. Currently, the disposal of expired pharmaceuticals is insufficiently established; often, they are simply thrown into the environment, including after the expiry date. In addition, they are excreted from the body with human physiological secretions as a result of incomplete metabolism. The result is a mixture of compounds in the wastewater. The main sources of pollution are (Figure 2) as follows: (a) Wastewater from enterprises that use insufficient purification methods; (b) Wastewater from agricultural enterprises that use medicines; (c) Domestic sewers with biological fluids of people who take medications; (d) Leaching of waste disposal sites; (e) Disposal of pharmaceutical waste by imperfect methods.

*Figure 2 can be found in the Appendix section.

Antibiotic-based pollution is being found in soil/water resources/sewage, [20], [21]. Since it is harmful to human health and ecosystems, addressing its presence has to be considered a top priority, as it causes bacterial resistance and makes treatment against any infection ineffective. These drug-resistant bacteria could enter humans/higher animals through contaminated water or through food made using that water, and impact the gut microflora within the hosts, [22], leading to several health ailments. Finding the source of contamination would help us to prevent the entry of antibiotics into humans or any living system.

The full impact remains unclear on how the presence of pharmaceuticals and their metabolites in water can affect human health and the environment. A significant pro portion of pharmaceutical waste enters the aquatic environment. Their detectable low concentrations, ranging from ng/l to g/l, can persist for long periods of time and become biologically active as they accumulate, [21]. The researchers conducted a thorough analysis, [22], on the presence of pharmaceutical preparations in various types of water, below are data on the example of different classes of drugs—sulfonamides, non-steroidal anti-inflammatory drugs, and anticonvulsant.

Inevitably, a number of issues arise, among which the quantification of pharmaceutical residues and metabolites in wastewater treatment plant effluents is of great importance. This is necessary to assess the degree of hazard to the environment, including humans.

Over the last few decades, the global water contamination problem has risen. To solve this environmental issue, many efforts have been made to minimize chemical and biological pollution of water. This requires an evaluation of water resource policy, which is of great interest to society, public authorities, and industry, [23], [24]. Water contamination is the main issue in developed and developing nations, resulting in around 14,000 fatalities and illnesses, [25]. Numerous factors, including precipitation, climate, soil type, vegetation, geology, flow conditions, groundwater level, and human activities, have impacted water quality, [26]. Pollutants from human activity, including heavy metals, radioactive contaminants, pharmaceuticals, organic dyes, etc., released in aquatic environments are significant causes of water pollution. It harms people and the environment directly, leads to secondary pollution, and damages the ecological equilibrium, [27].

Water is crucial in the production of pharmaceuticals. Still, treating wastewater from the pharmaceutical industry is significantly challenging due to the massive volume, complexity, and hazardous nature of chemicals, [28]. "Pharmaceutical wastewater" primarily refers to waste and effluents produced during the production of medications, [29]. Pharmaceutical wastewaters are typically created through chemical synthetic processes containing drug residues with high biological oxygen demand, chemical oxygen demand, pharmaceutically active compounds such as hormones, antibiotics, toxic substances, or surfactants, as well as volatile organic compounds that pose potential risks to the biosphere, [30].

Chemical and pharmaceutical chemistry uses complicated raw materials in multi-step reactions that produce pharmaceutical wastes due to poor conversion rates, [31]. There are serious pollution issues caused by the large variety of wastewater that contains toxic and dangerous chemicals, including metals, waste acids, nitro compounds, steroids, anilines, piperazine and fluorine, nitrate, phosphate, mercury, lead, chromium, and copper, [32], [33]. Organic solvents that contain ethanol, benzene, chloroform, and other organic compounds are also a significant source of trace pollution. Small- or large-scale production of traditional/ folk medicine requires various procedures, directly releasing pollutants into water, including organic acids, anthraquinones, lignin, alkaloids, tannins, proteins, carbohydrates, and starches, [34]. About half of the pharmaceutical wastewaters is thrown away without any special treatment, building up environmental pharmaceutical effluent that has resulted in the formation of antibiotic-resistant microbial strains that pose a significant threat to human health and the ecosystem, [35]. Upholding requirements for pharmaceutical quality and safety, providing clean drinking water, rehabilitating the environment, and keeping ecological balance have become complex problems and urgent tasks that need to be addressed, [36].

The effluents of pharmaceutical industries are characterized by high organic matter contents, toxicity, deep colour, and high salt contents. Among all the pharmaceutical compounds that have environmental concern, antibiotics have an important role due to their high consumption rates in both veterinary and human medicine. Development of antibiotic-resistant bacteria is the worst problem that may be created by the presence of antibiotics at low concentrations in the environment, [37]. Antibiotics are persistent and bio-accumulative contaminants and bio logically active compounds which have been developed to have an effect on organisms; hence, they have the potential to negatively affect either aquatic or tellurian ecosystems, even in low concentrations in the range of (μg–ng) per liter. In addition, antibiotics can also cause antibacterial resistance in microorganisms and be responsible for several allergenic responses, [38], [39], [40].

Massive production of antibiotics started during World War II and so far, these compounds have been widely used in order to prevent and treat infectious diseases, [40], [41], [42], [43]. Although, antibiotics have been used in large scale in the last fifty years, it was only in recent years that its occurrence in the environment became a subject of scientific and public relevance, [40], [44], [45]. Over the past few years, antibiotics have also been considered as emerging pollutants due to their continuous input and persistence in the aquatic eco systems even at low concentrations. Residues of antibiotics are present in a diversity of environmental matrices, like surface and groundwater, hospital and wastewater treatment plants effluents, soils and sediments, [40], [46], [47], [48]. Several antibiotics such as ampicillin, erythromycin, sulphamethoxazole, tetracycline and penicilloyl groups are mainly released into the environment by excretion (about 30–90%), reaching the wastewater treatment plants where they are not completely removed, and contaminating natural waterways, [45], [49], [50], [51].

Based on the very limited efficiency of conventional treatment plants such as sand filtration, chemical coagulation/flocculation and chlorination, in removing various organic micropollutants (OMPs) such as antibiotics, advanced technologies such as ozonation, advanced oxidation processes (AOPs) and activated carbon are considered to be more efficient in eliminating polar pharmaceuticals. In addition, pressure-driven membrane processes, particularly nanofiltration (NF) and reverse osmosis (RO) have also been gaining attention in the past decade and their application in drinking water treatment has been the focus of many researchers, [52], [53], [54].

Antibiotics are the most heavily used medical drugs in the European Union, with an estimated annual consumption of around 10,000 tons, [52]. It should also be noted that these consumption figures are considerably increased by the use of many of these products in veterinary medicine. High concentrations of antibiotics are now detected in drinking waters, reducing their quality. They generally have a low biodegradation and high toxicity, and some are reported to have mutagenic and carcinogenic characteristics, [54]. Conventional treatment systems, mainly based on the use of microorganisms have proven inadequate to effectively remove this type of organic compound, largely due to its complex molecular structure, [53].

Antibiotics are considered the most essential drugs in hospitals to treat/prevent diseases. The improper disposal of these antibiotics in various ways causes them to reach water bodies, [55]. Continual exposure to and sub-inhibitory concentrations of antibiotics pave way to bacterial resistance to numerous antibiotics, and form multidrug-resistant bacteria that not only cause resistance but interfere in the bio–geo–chemical cycle, [56], [57]. Besides hospital waste, municipal wastewater is considered as one of the biggest “hotspots” for antibiotics, [58]. Feces and carcasses of human and animal sources are the major sources of the introduction of antibiotics, as well as antibiotic-resistant microbes, into water ecosystems. These bacteria can transmit their genes to waterborne pathogenic microorganisms too, thus inducing resistance, [59], [60]. Thus, antibiotic resistance could become a critical issue in modern medicine, as it poses the threat of catastrophic epidemics, [61]. It becomes highly essential to ensure adequate processing before release into the environment, or else these substances can cause severe pollution and disturb the natural balance.

Nevertheless, eliminating antibiotics from wastewater is a major challenge, [62]. The most common conventional methods used in removing these antibiotics are chemical precipitation, ion exchange, biosorption, reverse osmosis, nanofiltration, etc., [63]. Each process’s characteristics, as well as biological and chemical oxygen demand, water quality conditions, and environmental factors, influence the antibiotic elimination efficiency, [64]. Irrespective of all of this, antibiotics are not entirely eliminated in wastewater treatment facilities, as they have been found in stagnant wastewater ponds, municipal sewage, hospital sewage, surface water, and groundwater, [65], [66], [67]. At present, membrane technology is considered a promising method for removing antibiotics from effluents, [62]. An efficient treatment or conservation method would have a positive impact, playing a key role in delivering noteworthy benefits in terms of economic development, either directly or indirectly, [68].

Nitroimidazole antibiotics were recently detected in waters at concentrations of 0.10–90.20 g/l, [69]. They are widely used to treat infections caused by anaerobic and protozoan bacteria (e.g., Trichomonas vaginalis and Giardia lamblia) in humans and animals and are added to chow for fish and fowl, leading to their accumulation in animals, fish-farm waters and, especially, meat industry effluents, [70]. Little is yet known about the capacity of current water treatment systems to remove nitroimidazoles, [71], but it is not expected to be very high given the complex chemical structure of these compounds. It will be necessary to develop new methods to effectively remove these contaminants from waters in a technologically feasible and economically viable manner. Nitroimidazoles (Metronidazole and Trimethoprim) were selected because they are antimicrobials with bactericidal action that present a moderately broad antibacterial spectrum. They are used in infections of the urinary tract, ears, lungs, intestines and liver.

Metronidazole (MET, $C_6H_9N_3O_3$, M_w=171.156 g/mol), sold under the brand name Flagyl and Metrogyl among others, is an antibiotic and antiprotozoal medication, [72]. The chemical structure of Metronidazole antibiotics was given in Figure 3. It is used either alone or with other antibiotics to treat pelvic inflammatory disease, endocarditis, and bacterial vaginosis, [72], It is effective for dracunculiasis, giardiasis, trichomoniasis, and amebiasis, [72]. It is an option for a first episode of mild-to-moderate Clostridioides difficile colitis if vancomycin or fidaxomicin is unavailable, [72], [73]. Metronidazole is available orally (by mouth), as a cream or gel, and by slow intravenous infusion (injection into a vein), [73], [74]. Common side effects include nausea, a metallic taste, loss of appetite, and headaches, [72]. Occasionally seizures or allergies to the medication may occur, [72]. Metronidazole began to be commercially used in 1960 in France, [75]. It is on the World Health Organization's (WHO's) List of Essential Medicines, [76]. It is available in most areas of the world, [77]. In 2023, it was the 203rd most commonly prescribed medication in the United States, with more than 2 million prescriptions, [78], [79].

*Figure 3 can be found in the Appendix section.

Metronidazole has activity against some protozoans and most anaerobic bacteria (both Gram-negative and Gram-positive classes) but not the aerobic bacteria, [80], [81]. Metronidazole is primarily used to treat: bacterial vaginosis, pelvic inflammatory disease (along with other antibacterials like ceftriaxone), pseudomembranous colitis, aspiration pneumonia, rosacea (topical), fungating wounds (topical), intra-abdominal infections, lung abscess, periodontal disease, amoebiasis, oral infections, giardiasis, trichomoniasis, and infections caused by susceptible anaerobic organisms such as Bacteroides, Fusobacterium, Clostridium, Peptostreptococcus, and Prevotella species, [82]. It is also often used along with other drugs to eradicate Helicobacter pylori and to prevent infection in people recovering from surgery, [82]. Metronidazole is bitter and so the liquid suspension contains metronidazole benzoate. This may require hydrolysis in the gastrointestinal tract and some sources speculate that it may be unsuitable in people with diarrhea or feeding-tubes in the duodenum or jejunum, [83], [84].

Metronidazole is of the nitroimidazole class. It is a prodrug that inhibits nucleic acid synthesis by forming nitroso radicals, which disrupt the DNA of microbial cells, [85], [86]. Metronidazole activates by receiving an electron from the reduced ferredoxin produced by pyruvate synthase (PFOR) in anaerobic organisms, equivalent to pyruvate dehydrogenase in aerobic organisms, thus turning into a highly reactive radical anion. After the radical loses the electron to its target, it recycles back to the un-activated form of metronidazole, ready to be activated again, [87]. This function only occurs when metronidazole is partially reduced, and, because oxygen competes with metronidazole for the electron, this reduction requires a local environment with low oxygen concentration: this usually happens only in anaerobic bacteria and protozoans. Therefore, it has relatively little effect upon human cells or aerobic bacteria, [88]. Elevation of oxygen level in the organism will decrease its rate of generating the activated metronidazole, but also increase the rate of recycling back to the un-activated metronidazole, [87].

Trimethoprim (TMP, $C_{14}H_{18}N_4O_3$, M_w=290.323 g/mol) is an antibiotic used mainly in the treatment of bladder infections, [89]. The chemical structure of Trimethoprim was determined at Figure 4. Other uses include for middle ear infections and travellers' diarrhoea, [90]. With sulfamethoxazole or dapsone it may be used for Pneumocystis pneumonia in people with HIV/AIDS, [90]. It is taken orally (swallowed by mouth), [91]. Common side effects include nausea, changes in taste, and rash, [92]. Rarely it may result in blood problems such as not enough platelets or white blood cells, [92]. Trimethoprim may cause sun sensitivity, [93]. There is evidence of potential harm during pregnancy in some animals but not humans, [94]. It works by blocking folate metabolism via dihydrofolate reductase in some bacteria, preventing creation of bacterial DNA and RNA and leading to bacterial cell death, [95]. Trimethoprim was first used in 1962, [92]. It is on the WHO's List of Essential Medicines, [96]. It is available as a generic medication, [96].

*Figure 4 can be found in the Appendix section.

Trimethoprim (TRM) is extensively utilized as an antibiotic on a global scale due to its exceptional effectiveness and accessibility, [97]. Trimethoprim belongs to a category of chemotherapeutic agents that exhibit synergistic antibacterial activity; it is used for treating infections, treating enterocolitis, and enhancing animal growth in the livestock sector, including in feed supplements, [98]. Trimethoprim can only be metabolized by approximately 20% in humans and animals and is excreted through feces and urine, with significant amounts of effluent in the sewage system, [99]. Due to its high resistance to biodegradation and widespread use and application, Trimethoprim has become ubiquitous in various water sources, including rivers, groundwater, lakes, seawater, drinking water, tap water, wastewater, and irrigation water, in concentrations between ng/L and µg/l, [100]. Research has also detected it in soil, sewage sludge, and sediment at amounts reaching up to nanograms per gram (ng/g), [101]. Multiple studies have emphasized that Trimethoprim has harmful consequences for non-target aquatic creatures, such as phytoplankton, zooplankton, and fish. These effects include increased mortality, impaired development and reproduction, as well as the emergence of antibiotic-resistant genes and infections in the environment, [102]. For this reason, it is classified as one of the fourteen pharmaceuticals that pose a high risk in hospital wastewater, [103]. As a result, there is an urgent need for approaches allowing the efficient removal of Trimethoprim from water, both for human consumption and industrial or agricultural applications.

Various methods have been used to remove antibiotics from water, including re verse osmosis, ion exchange, coagulation, co-precipitation, extraction, membrane filtration, electrochemical oxidation, and adsorption, [102]. In order to select the best approach, it is essential to take into account multiple factors, including the features of the removal technology, the optimization of the process, and its associated costs, [104]. Trimethoprim can be effectively eliminated via adsorption, and this method is preferred over others due to its simplicity, relatively low cost, eco-friendliness, and the absence of transformation during treatment, [105]. Various adsorbents, including graphene oxide, chitin/bentonite composite, and activated carbon, have been studied for their ability to absorb Trimethoprim, [106]. However, more adsorbents need to be tested to enhance the efficiency of adsorption.

It is primarily used in the treatment of urinary tract infections, although it may be used against any susceptible aerobic bacterial species, [107]. It may also be used to treat and prevent Pneumocystis jirovecii pneumonia, [108]. It is generally not recommended for the treatment of anaerobic infections such as Clostridioides difficile colitis (the leading cause of antibiotic-induced diarrhea), [109]. Trimethoprim has been used in trials to treat retinitis, [110]. Resistance to trimethoprim is increasing, but it is still a first-line antibiotic in many countries, [111]. Cultures and susceptibility tests should be done to make sure bacteria (Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae, Enterobacter species, Coagulase-negative Staphylococcus species, including S. saprophyticus, Streptococcus pneumoniae, Haemophilus influenzae) are treated by Trimethoprim, [112], [113]. The side effects of Trimethoprim are affected for nauseas, change in taste, vomiting, diarrhoea, rashes, sun sensitivity and itchiness, [114], [115].

The mechanism of action is Trimethoprim binds to dihydrofolate reductase and inhibits the reduction of dihydrofolic acid (DHF) to tetrahydrofolic acid (THF), [115]. THF is an essential precursor in the thymidine synthesis pathway and interference with this pathway inhibits bacterial Deoxyribonucleic acid (DNA) synthesis, [112]. Trimethoprim's inhibitory activity for bacterial dihydrofolate reductase is sixty thousand times greater than for human dihydrofolate reductase, [113]. Sulfamethoxazole inhibits dihydropteroate synthase, an enzyme involved further upstream in the same pathway, [114]. Trimethoprim and sulfamethoxazole are commonly used in combination due to possible synergistic effects, and reduced development of resistance, [115]. This benefit has been questioned, [115].

The presence of trimethoprim can generally be correlated to that of sulfamethoxazole since the two drugs are often administered in combination, [116]. The removal of trimethoprim has been reported as 13% and 42% by Li and Zhang, [117]. The removal of this compound was found to fluctuate within the same levels in various Urban Wastewater Treatment Plants (UWTPs) in USA (50-100%), in Germany (69%), and in Taiwan (74%), [66], [118], [119], [120]. Higher removals were obtained in five UWTPs in Australia yielding 94%, [48], and 93.3%, [121]. In contrast, the removal of trimethoprim was negligible as reported in the studies of Lindberg et al., [122], and Roberts and Thomas, [123]. Some studies have indicated that nitrifying microorganisms appear to be capable of degrading trimethoprim. This suggests an important role for aerobic conditions for the biotransformation of trimethoprim, [124], [125]. Moreover, trimethoprim elimination was found to be increased at higher SRTs, [126], [127], [128], [129].

Pharmaceutical companies and wastewater treatment plants use conventional processes including filtration, flocculation, sedimentation, etc., but they are not effective in removing antibiotics, [130]. One of the better technologies for removing antibiotics is membrane technology, which has the benefits of high productivity, ease of use, and low cost. The three primary concepts that govern the treatment using membranes are adsorption, sieving, and electrostatic phenomena. Membrane separation processes rely on hydrophobic interactions between the membrane and the analyte. The size of the pore and the size of the molecules determine the separation of materials via the membrane, [131]. The pore sizes differ from 2 nm to 100 nm depending on the type of filter chosen, [130]. Various membrane technologies, including microfiltration, ultrafiltration, nanofiltration, and reverse osmosis, which operate through electrostatic and physical forces, are used for removing antibiotics/antibiotic resistance genes from aqueous solutions such as water, [132], [133]. Thin, light-weight separation membranes with low filtering times and higher adsorption capacities are of greater use, [134]. Ceramic-based membranes are more advantageous than polymeric membranes as they can tolerate microbial degradation and high-pressure situations, [135]. Membrane filtration is more widely used in municipal and industrial water/wastewater treatment, as it provides a cost-effective solution for long-term water reuse, [136]. A variety of antibiotics, such as Chlorotetracycline, Rifampicin, Cefixime, Oxy tetracycline, sulfa drugs, Doxycycline, Tetracycline, etc., are effectively removed using reverse osmosis, [137], [138], [139]. Javad et al., [140]. Arefi-Oskoui et al., [141] and Javad et al., [140], reported that adding nanoparticles or nanocomposites to membranes does increase their potential ability to remove antibiotics. Membrane technology, however, only changes the state of the antibiotic. If direct or indirect release of concentrations in ecosystems is not prohibited, antibiotics can still recirculate and thus pose a risk of harm in specific regions, [140], [141].

Reverse osmosis (RO) is a method whereby large ions and molecules are typically removed from liquid effluents using the process of diffusion, which involves the application of pressure to the solution on one side of a semipermeable membrane. The impurities are confined on the pressured side of the membrane, while the clean effluent flows against the concentration gradient, [142]. The reverse osmosis technique can be used to remove bacteria, viruses, dissolved solid particles, and microbial agents present in wastewater. This method is mostly employed to desalinate water, [132]. The main physiochemical properties considered for the process of reverse osmosis are porosity and mechanical resistance. In this context, these membranes must be chemically and microbially resistant, as well as mechanically and structurally durable over long periods of time, and they can be eliminated by the use of polymer membranes, [142]. For amoxicillin, the removal rate via RO membranes ranges from 73.52% to 99.36%, while for ampicillin, the removal rate and permeate flux range from 75.10% to 98.80%, [143]. Further, the removal rates of antibiotics such as trimethoprim dexamethasone, febantel, ciprofloxacin and sulfamethoxazole using a hybrid of reverse and nanofiltration were observed to be 97%, according to Dolar et al., [144]. Despite the apparent benefits of utilizing an RO membrane, it is still unclear whether it can act as a complete barrier to enhance the removal of organic micropollutants. Several top scientists have identified RO as the most effective and promising method for removing organic micropollutants, [54], [145].

Next, the RO will be studied in more detail, not because it is a more suitable technique than the others, but because in locations with water scarcity where RO desalination plants abound, proving the validity of this technology for the elimination of antibiotics is very encouraging. If the analysis of membrane processes is investigated to a greater extent, it is observed that there are multiple studies that prove the efficacy of RO to eliminate antibiotic concentrations in different types of water. Following, some of the main successful studies, selected for their relevance in terms of rejection of contaminants, are explained in greater detail.

The data of the elimination percentages consulted in the international literature review establish ranges from 93% to 99.99%, repeating values higher than 99% regularly. In summary, RO presents magnificent percentages of antibiotic removal in different types of water. RO is also positioned as a candidate technology, as one of the main allies in the purpose of eliminating concentrations of antibiotics in the aquatic environment, competing with other techniques such as activated carbon adsorption, Ozonation and advanced oxidation processes, attached growth treatment processes or other membrane process.

Several approaches have been considered to eliminate Metronidazole from water and wastewater; including, oxidation processes, [146], [147], adsorption, [148], [149], [150], catalytic degradations, [151], [152], and membrane processes, [153], [154], [155]. However, membrane-based approaches are favoured over other treatment methods due to their compact, eco-friendly, easy to install and scale-up, high selectivity, and economically viable properties. There are quite a few researches conducted for Metronidazole removal via RO or nanofiltration (NF) process, [156]. In the case of the RO process, limited lifetime and membrane fouling are known as the main drawbacks of this treatment technique. Numerous attempts had been made to improve Ro technology, such as the synthesis of thin film composite (TFC) and thin film nanocomposite (TFN) membranes, as the most important inventions. Now, polyamide TFC membrane is the most widely used commercial RO membrane for water treatment owing to its appropriate separation performance, [157].

Organic pollutants such as Metronidazole may be adsorbed on the active layer owing to affinity toward polyamide (PA), [158]. This membrane contamination reduces the separation efficiency and water quality of RO membranes. Accordingly, the membrane processes require more energy demand, chemical cleaning cycles which reduce membrane lifetime and increase production cost, [158]. To overcome the mentioned challenges of RO technology, particular module designing and modifying membrane surface properties (e.g., antifouling and surface roughness) has been proposed by researchers, [158], [159].

In this study, it was aimed to removal and recovery of Nitroimidazoles (Metronidazole and Trimethoprim) Antibiotics from a pharmaceutical industry wastewater using reverse osmosis with different conditions. The effects of increasing applied pressures (10, 20, 30, and 40 bar), feed concentrations (25, 50, 100, 250 and 1500 mg/l), operating temperatures (25, 35, and 45°C), and feed flow rates of 5, 7, 10, and 15 l/min on the removals and recoveries of both antibiotics were operated. ANOVA statistical analysis was calculated for all samples.

2 Materials and Methods

2.1 Materials

All of the chemical reagents used (indigo, tert-butanol (t-BuOH), phosphoric acid, hydrochloric acid, sodium hydroxide, hydrogen peroxide, methanol, dichloromethane, para-chlorobenzoic acid (pCBA), acetonitrile, and ammonium acetate) were high-purity analytical grade reagents supplied by Sigma–Aldrich, Germany. The ultrapure water was obtained from a Milli-Q system (Millipore).

The nitroimidazoles selected for this study were as follows. (i) Metronidazole (MET), (ii) Trimethoprim (TRM), all supplied by Sigma Aldrich, Germany.

2.2 Experimental Procedures

Reverse osmosis (RO) membranes used in this study. Hollow fiber reverse osmosis (HFRO) membrane modules provided by Aquaporin, Denmark. The hollow fiber membrane modules have an active membrane area of 2.30 m^2. The HFRO membranes consist of a biomimetic Thin-film composite (TFC) selective layer supported by polysulfone fibers with an inner diameter of 195 µm.

HFRO membrane modules were exposed to 20 mg/l NaClO solution at pH=10.5. During the exposure, the solution was recirculated for 2 min at the lumen side of the fibers. After the exposure, post-treated modules were intensively flushed with deionized water for about 1 h. In this study the membranes modified HFRO modules will be referred to as chlorinated membranes and denoted HF–C.

Zeta potential measurements are the most common technique for evaluating the surface charge of the membrane. In the next Figure 5, the inner surface zeta potentials as a function of pH for both hollow fiber composite (HF–C) and hollow fiber osmosis (HF–O) membranes are shown (Figure 5).

*Figure 5 can be found in the Appendix section.

For both membrane types, zeta potential is reduced with a reduction of pH, was measured at pH=3.7 and pH=2.8 for HF–O and HF–C membranes, respectively. The isoelectric point around pH=2.0–4.0 was expected due to the nature of the polyamide and the presence of the carboxylic groups at the surface of the polyamide [160]. The shift in the isoelectric point after membrane chlorination could be explained as a side effect of the chlorination post-treatment. The chlorination promoted hydrolysis of the polyamide C–N bond and led to the cleavage of the polyamide layer. Consequently, the hydrolysis resulted in a rise of the carboxyl group number at the surface.

2.3 Reaction Kinetics

Retention factor (R) of each compound and water flux was calculated by Eq. (1) and Eq. (2), respectively:

$$R = \left[1 - \frac{C_P}{C_F}\right] x\, 100(1)$$

Where, R is the retention factor (%), C_P is the concentration in the permeate (mg/l) and C_F is the concentration in the raw solution (mg/l), [160], [161], Eq. (2):

$$J_W = \frac{Q_P}{A}(2)$$

Where, J_w is the permeate flux (l/m^2.h), Q_P is the permeate flow per hour and A is active surface area of membrane (m^2), [162], [163]. The relationship between permeate flux and operating pressure is based on Eq. (3) which was originally formulated by, [164], as:

$$J = A\,(P - \Delta\pi)(3)$$

Where, J, A, P, and p, are the permeate flux, the water permeation constant, the applied pressure and the osmotic pressure, respectively. Osmotic pressure can be predicted by using the Van't Hoff equation as follows, [165], Eq. (4):

$$\pi = V_i C_i RT (4)$$

Where, V_i, C_i, R, and T are the number of ions formed if the solute dissociates, the molar concentration of solute, the gas constant, and the absolute temperature, respectively.

2.4 Solution Diffusion Model (SDM)

The solution diffusion model is a widely recognized framework for describing the mechanism by which solutes move through membranes. This model assumes that solutes are transported through the membrane matrix by diffusion, driven by concentration gradients, [166], [167]. In this study, the SDM, which considers concentration polarization, was applied to analyse the experimental results and predict removal performance under various operating conditions. According to the SDM, the transport of solutes and solvents occurs in dependently, with solute transport being driven by the concentration difference across the membrane, [168], [169]. Furthermore, in addition to the basic removal mechanisms of the membrane, specific characteristics of Nitroimidazoles, such as hydrophobicity and ionization tendency, were used to derive L_s values from each experiment, [170]. Incorporating these L_s values aims to enhance the accuracy of the SDM in predicting Nitroimidazoles removal rates beyond simple salt rejection. This approach allows for more reliable predictions of Nitroimidazole removal performance, accommodating the unique physicochemical properties of these compounds, which affect their interaction with the membrane.

The solute flux J_s is expressed as the product of the solute permeability coefficient L_s and the difference between the feed concentration C_b and the permeate concentration C_p, [170], Eq. (5).

$$J_s = L_s (C_b - C_p)(5)$$

The solvent flux J_v is determined by the membrane water permeability L_v, the pressure difference ΔP, and the osmotic pressure difference, Δπ, Eq. (6):

$$J_v = L_v (\Delta P - \Delta\pi)(6)$$

L_v is the solvent transport parameter, L_s is the solute transport parameter, C_b is the solute concentration in the bulk solution, C_p is the solute concentration on the permeate side, Δπ is the osmotic pressure, and ΔP is the transmembrane pressure. However, as filtration progresses, concentration polarization occurs at the membrane surface, so the equations at the surface need to be modified as follows, Eq. (7):

$$J_s = L_s (C_m - C_p)(7)$$

C_m is the solute concentration at the membrane surface, and it is calculated according to the following film theory. The concentration profile at the surface is calculated using the following equation, [170], Eq. (8):

$$\frac{C_m - C_p}{C_b - C_p} = e^{\frac{Jv}{k}}(8)$$

Where, k is the mass transfer coefficient for the back diffusion of the bulk solution from the where k is the mass transfer coefficient for the back diffusion of the bulk solution from the membrane on the high-pressure side, and the growth of the concentration boundary layer is suppressed by stirring. The mass transfer coefficient k follows the equation below, Eq. (9):

$$k = 0.104\left(\frac{D_{sw}}{r}\right)\left(\frac{wr^2\rho}{\mu}\right)^{\frac{2}{3}}\left(\frac{\mu}{\rho D_{sw}}\right)^{\frac{1}{3}}(9)$$

where, D_{sw} is the solute diffusion coefficient, w is the stirring speed, r is the stirring radius, μ is the viscosity of the liquid at 25°C, and ρ represents the density of the solution.

2.5 Evaluation of Membrane RO performance

RO performance in terms of water flux and salt rejection for the neat and the modified PA(TFC) membranes dimension SCM diameter was tested employing the dead-end permeation cell manufactured by STERLITECH, USA- HP4750 Stirred Cell is a high-pressure chemical resistant stirred cell that per forms a wide variety of membrane separations. With a maximum pressure rating of 69 bar (1000 psig), the HP4750 Stirred Cell is ideally suited for reverse osmosis (RO) filtration. Using 2000 ppm (mg/l) sodium chloride (NaCl) aqueous solution at 5 bar, 25°C and pH=6.8. The samples were operated for at least 1h before any data were collected. The permeate water flux was determined by measuring the permeate volume collected over a certain period in terms of liter per square meter per hour ($l/m^2.h$) and calculated using Eq. (10):

$$J_v = \frac{Q}{Ax\Delta t}(10)$$

Where, J_v is the volumetric permeate water flux, A is the effective area of the membrane for permeation

(m^2), and Q is the volume of permeation (L) over a time interval D_t (h). The salt rejection was evaluated using Eq. (11):

$$R(\%) = C_f - C_p/C_f \; x \; 100(11)$$

In which C_p and C_f are the salt concentrations in permeate and feed, respectively. The salt concentration was determined by measuring the electrical conductivity of the salt solution using a conductance meter (DDSJ-308A, Cany Precision Instruments Co. Ltd. China) and comparing the calibration plot drawn between salt concentration and electrical conductivity. All the reported fluxes and salt rejections were averaged values from at least three samples for each membrane type.

2.6 Statistical Analysis

The analysis of variance (ANOVA) between experimental data was performed to detect F and P values. The ANOVA test was used to test the differences between dependent and independent groups, [171]. Comparison between the actual variation of the experimental data averages and standard deviation is expressed in terms of F ratio. F is equal (found variation of the date averages/expected variation of the date averages). P reports the significance level, and d.f indicates the number of degrees of freedom. Regression analysis was applied to the experimental data in order to determine the regression coefficient R^2, [172]. The aforementioned test was performed using Microsoft Excel Program.

The chi-square test was also applied to assess the association of Metronidazole and Trimethoprim clusters in both antibiotics with demographic clusters. The result was significant if the p-value was equal to or less than the alpha level (0.05). Moreover, Pearson correlation analysis was used to assess the correlation between the demographic clusters and the concentration of Metronidazole and Trimethoprim. Finally, the paired sample t-test was used to test if there was a significant difference between the averages of the Metronidazole and Trimethoprim concentrations in aquifers A and B.

2.7 Isotherm Study

The adsorption isotherms for metronidazole and Trimethoprim adsorption on HF-C RO membrane were obtained with different Metronidazole and Trimethoprim concentrations (1–30 mg/l). The Freundlich and the Langmuir adsorption isotherm models were used for evaluation experimental data. The Langmuir model (Eq. 12) and Freundlich model (Eq. 13) are given as follows:

$$Langmuir: \frac{c_f}{q_f} = \frac{1}{bqm} + \frac{c_f}{qm}(12)$$

$$Freundlich: log q_f = log K_f + \frac{1}{n} log C_f(13)$$

Where; C_f (mg/l) is the equilibrium concentration of metronidazole, q_f (mg/g) is adsorption capacity at equilibrium, qm (mg/g) is the maximum adsorption capacity, b (l/mg) is a constant related to the adsorption energy, K_f and n are Freundlich constants which characterize a particular adsorption isotherm. All the constants obtained according to the slope and intercept of the related lines and they are listed in Table 1.

*Table 1 can be found in the Appendix section.

As shown in Table 1, the Langmuir isotherm plot fits better to the experimental adsorption data with higher correlation coefficient (R^2=0.9994), which expressed that the adsorption of metronidazole ions onto HF-C RO membrane and HF-O RO membrane follows the Langmuir model. The qm and b calculated from the slope and intercept of the regression line are 215.4 mg/g and 0.52 l/mg, respectively (Table 1). Langmuir model depends on the acceptation of homogeneous distribution of metronidazole molecules on to surface of adsorbent.

2.8 Data Collection and Analysis

WHO prescribing indicators (WHO, 1993) were analysed, including number of drugs per encounter (per prescription), percentage of encounters with at least one injection or antibiotic prescribed, frequency of polypharmacy (defined as encounters with five or more drugs prescribed), percentage of drugs prescribed by generic name, percentage of drugs prescribed belonging to the 14th WHO Model List (WHO, 2005), to the Brazilian National List of Essential Medicines (RENAME), and to the local List of Essential Medicines from each city participating in the study. The list of antibiotics included in the analysis was based on the WHO antimicrobial classification for prescribing indicators (WHO, 1993).

Important items of prescriptions (such as dosage form, dose, route of administration, interval between doses, and treatment duration) and provision of additional written information, including non-pharmacological measures, were also considered.

Instructions included information on how, when and for how long the drug should be used, how the product should be stored and what to do with the unused product. Warnings corresponded to the description of precautions, drug interactions, and how to recognize adverse drug reactions and what to do about them.

Data were entered into a database developed using EpiData 3.1 and analysed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 15.0. For analysis purposes, the different levels of health care delivery were divided into two groups – centers with and without primary health care services. Data were expressed as absolute frequency and percentage, mean and standard deviation (SD). Associations between patients' age groups and number of drugs prescribed or number of antibiotics prescribed per encounter were analysed using the chi square test with adjusted standardized residuals. The student t-test was used to assess the statistical significance between means. A P-value

All experiments were carried out three times and the results are given as the means of triplicate samplings. The data relevant to the individual pollutant parameters are given as the mean with standard deviation (SD) values.

3 Results and Discussions

3.1 SEM Analysis in Both Membranes

Based on the cross-section images (Next Figure 4c and 4d), the thickness of the polyamide layer was estimated

to be 70.80 ± 9.80 nm for HF–O membranes and 49 ± 4.90 nm for the HF–C membranes. In contrast, the inner surfaces of the investigated membranes (Figure 4a and 4b) did not exhibit any significant difference between each other. Chlorine usage is a common method for disinfection in water treatment as it inhibits the growth of harmful microorganisms. However, it is widely known that polyamide membranes are highly sensitive to chlorine solutions, and shown in Figure 6.

*Figure 6 can be found in the Appendix section.

3.2 Role of Feed Flow Rate on Flux, J

For drinking water (DW), the HF–O module exhibited a J_w increase from 17.40 to 20.20 $l/m^2.h$ (about 16.20%) in comparison to HF–C module that showed J_w to increase from 20.50 to 26 $l/m^2.h$ (about 26.70%) by varying feed flow rate in the tested range (Figure 7). As shown in Figure 7, the J_w of the HF–C membranes are higher than that of the HF–O membranes at any testing conditions. J_s/J_w is also increased with feed flow rate for the HF–C membranes but remains relatively constant for HF–O membranes for all tested feed flow rates. Furthermore, J_s/J_w is much lower for HF–O membranes ($J_s/J_w = 0.15 \pm 0.02$ g/l) than it is for HF–C membranes ($J_s/J_w = 0.40 \pm 0.10$ g/l).

*Figure 7 can be found in the Appendix section.

An increase of the J_w with feed flow rate was quite surprising since we do not expect a contribution of the external concentration polarization (ECP) on the active layer side for DW water that is free of any solutes. Nevertheless, the results summarized in Figure 7 clearly indicate that J_w for both membranes increases with feed flow rate. Such behavior can only be attributed to the reduction of the ECP by reduction of the mass transfer coefficient with the flow rate. We speculate that here, by introduction of higher feed velocity, a stagnate layer of the fluid at the active layer gets disturbed, and diffused antibiotic from the pharmaceutical water can be more effectively transported to the bulk of the DW. Therefore, the net driving force—the difference in osmotic pressure between the feed side and draw side of active layer—is enhanced.

A similar rationalization can be applied to the explanation of the difference in development of J_s/J_w for the HF–C and HF–O membranes with feed flow rate. As such, the low retention HF–C membranes can transport more salt to the feed side, locally increasing its concentration at the feed side of the selective layer. As a result, we can observe an increase in J_s/J_w with feed flow rate for low retention HF–C membranes. In contrast, J_s/J_w for HF–O membranes that exhibit higher retention for antibiotic is not affected by the feed flow rate since antibiotic transport from the draw to the feed side is negligible.

3.3 Effect of Draw Flow Rate

Similar to the feed flow rate, the applied draw flow rate has also influenced the performance of HFRO modules. RO performance obtained at various draw flow rates for the two types of investigated HFRO modules is summarized in Figure 8. The feed flow rate was kept constant at 100 l/h whereas the flow rate of antibiotics was varied from 25 to 100 l/h.

*Figure 8 can be found in the Appendix section.

When DW water was applied, the HF–O modules exhibited J_w of 19.0 ± 1.0 $l/m^2.h$ at 25 l/h and J_w systematically increased with the draw flow rate to 25.40 ± 1.0 $l/m^2.\cdot h$ at 100 l/h (J_w increase of 33.50%). For the HF–C membrane, J_w was higher than for the HF–O membrane at any draw flow rate investigated, and it increased from 24.9 ± 0.6 $l/m^2.h$ at 25 l/h to 31.30 $l/m^2.h$ at 100 l/h, respectively (J_w increase of

25.40%). The rate of J_w increase with the draw flow rate does not have a linear character, as it was for the variations of the feed flow rate (Figure 8a), and reaches a plateau value (Figure 8b).

The larger impact of the draw flow rate on the change in J_w in comparison to the feed flow rate can be explained by the more severe effect of the draw flow rate on the shell side of the membrane. The cause of this is simple—dilution of the DW with permeated water contributes significantly to the reduction of the available driving force along the length of the HFRO module.

Moreover, an increase of the mass transfer coefficient makes the boundary layer at the support-bulk interface thinner, allowing accelerated diffusion of the antibiotic from the outer surface of the fiber into the support.

3.4 Configuration of RO Membrane

The configuration of Reverse osmosis (RO) membrane was shown in Figure 9.

*Figure 9 can be found in the Appendix section.

Removal of contaminants by RO is determined by complex interactions of electrostatic and other physical forces acting between specific solute, the solution and the membrane itself. Main removal mechanisms in RO membranes are steric hindrance, electrostatic interaction and hydrophobic interaction between compounds and the membrane, [173]. Taking into account that molecular weight cut off (MWCO) for the RO membrane is around 100 Da, one of the possible removal mechanisms involved may be steric hindrance (size exclusion). In addition, electrostatic attraction or repulsion forces can influence the rejection of some contaminants in RO membrane due to their charge (e.g. positive charge of macrolide antibiotics and negative of sulfamethoxazole).

3.5 Effect of Transmembrane Pressure (TMP)

In this study, the effect of elevated Transmembrane Pressure (TMP) has been analyzed using the HF–C and HF–O modules. RO performance of the investigated modules at systematically elevated TMP are summarized in Figure 10. For all the testing conditions, where TMP varied from 0.10 to 1.10 bar, the feed and draw flow rates were kept constant and were 100 l/h and 25 l/h, respectively.

*Figure 10 can be found in the Appendix section.

J_w increased from 17.90 ± 0.50 l/m^2.h to 19.20±0.50 l/m^2.h (7.30% increase in J_w) for HF–O modules and from 24.0 ± 1.3 l/m^2.h to 27.70 ± 0.20 l/m^2.h (15% increase in J_w) for HF–C modules.

The obtained results are expected since TMP does not contribute to a significant improvement of J_w for both membrane types. On the other hand, the applied pressure range is quite narrow and performance of the tested HFRO modules could be further increased by increasing TMP.

The difference in the rate of the J_w increase with the applied TMP between the HF–O and HF–C modules originate from the difference. A more permeable selective layer, like in the case of the HF–C membrane, will always be more responsive to the applied TMP than a membrane with a less permeable selective layer, like an HF–O membrane.

J_s/J_w was significantly reduced with applied TMP for HF–C membranes and negligibly for HF–O modules. We speculate that the greater increase in J_w for HF–C membranes caused a more severe dilutive role at the draw side of selective layer. As a result, the solute concentration difference between the draw side and feed side of the active layer was reduced; therefore, the driving force for solute diffusion was diminished. Consequently, we observed reduced J_s/J_w with the applied pressure.

To evaluate the effect of pressure (or flux) on the solute permeability coefficient was operated at pressures ranging from 5.20 to 19.0 bar, in Figure 11.

*Figure 11 can be found in the Appendix section.

The water permeability coefficient (A_w) and solute rejection efficiency (R) were constant at 6.73 l/m^2/h/bar and 99.20%, respectively, while the solute permeability coefficients varied with pressure and correlated with J_w (Figure 11). This implies that antibiotic solute permeability (B_s) is governed by the solvent flux (J_w). On the other hand, rejection efficiency (R) might be governed by conditions other than operational pressure or flux.

3.6 Statistical Analysis Results

3.6.1 ANOVA Statistical Analysis Results

The unique properties i.e., uniform crystals, structural robustness, facile and environmentally friendly preparation method in aqueous medium, and high-yield production, RO membrane was investigated in this study as a viable material for Metronidazole removal. The key physicochemical parameters such as contact time, adsorbent mass, pH, and Metronidazole concentration were experimented to understand their impacts on the sorption system. Box–Behnken design (BBD), a particular technique of response surface methodology (RSM) that uses a statistical approach to design the experiments in three parametric levels was used to develop a mathematical model. The model provided an in-depth view on the process, and a tool to optimize the process for the highest removal, and also to describe the interactions of operating variables on Metronidazole adsorption.

BBD design is an interesting statistical approach that conducted to fit a non-linear model on system performance as a function of study variables. In BBD, the number of experimental runs is determined by the following formula in Eq. (14):

$$N = 2^{K} + 2K + 1(14)$$

In Eq. (14), N is the number of experimental runs, and K is the number of variables.

The ANOVA statistical results of performance RO membrane for removal of selected antibiotics (Metronidazole and Trimethoprim samples are shown in Tables 2 and in Table 3, respectively. As can be seen, the variations of rejection and permeate flux are greatly influenced by parameters such as pH and operating pressure. The results were analysed through factorial analysis, based on Design Expert Software.

*Table 2 can be found in the Appendix section.

*Table 3 can be found in the Appendix section.

The experimental efficiencies were undergoing an ANOVA statistical analysis to fit a polynomial model. The result of the quadratic model fitted to the experimental data for Metronidazole and Trimethoprim are presented in Table 2 and Table 3, respectively. ANOVA for the quadratic model fitted to Metronidazole removal by RO membrane was shown in Table 2. The F-value is an important statistical value that is used to check whether the null hypothesis should be rejected or not. The Model F-value of 37.27 implies it is significant and there is only a 0.05% chance that an F-value this large could occur due to the noise for Metronidazole. If the p-value is less than 0.05, it indicates that the model terms in Table 4 are significant for Metronidazole. ANOVA for the quadratic model fitted to Trimethoprim removal by RO membrane was shown in Table 3. The Model F-value of 35.49 implies it is significant and there is only a 0.05% chance that an F-value this large could occur due to the noise for Metronidazole. If the p-value is less than 0.05, it indicates that the model terms in Table 3 are significant for Metronidazole.

In this case, A, B, C, A2, B2, C2 are significant model terms. The Lack of Fit (LOF) F-value is also a significant statistical value that reflects whether the LOF is significant relative to the pure error. For the developed model, the LOF F-value of 5.62 implies that the Lack of Fit is not significant (Table 2). The Predicted R^2 of 0.7864 is in rational agreement (within ± 0.2) with the R^2Adj of 0.9589. While R^2 measures how well a regression model fits the data, the Predicted R^2 is calculated by a subdivision of the data to predict the residual data. The Adjusted R^2 is a revised form of R^2 that used to compare different models with different numbers of predictors as the parameters adjusts for the number of predictors. Another statistical indicator, Adeq Precision, measures the ratio of signal to noise. The value of 19.6343 is above the minimum desirable value of 4 and indicates an adequate signal. A polynomial equation was developed based on quadratic model coefficients calculated for coded factors of Metronidazole in Table 4. Coefficients calculated for the quadratic model based on the coded factors for Metronidazole in Table 4.

*Table 4 can be found in the Appendix section.

In this case, A, B, C, A2, B2, C2 are significant model terms. The Lack of Fit (LOF) F-value is also a significant statistical value that reflects whether the LOF is significant relative to the pure error. For the developed model, the LOF F-value of 5.41 implies that the Lack of Fit is not significant (Table 3). The Predicted R^2 of 0.7864 is in rational agreement (within ± 0.2) with the R^2Adj of 0.9589. While R^2 measures how well a regression model fits the data, the Predicted R^2 is calculated by a subdivision of the data to predict the residual data. The Adjusted R^2 is a revised form of R^2 that used to compare different models with different numbers of predictors as the parameters adjusts for the number of predictors. Another statistical indicator, Adeq Precision, measures the ratio of signal to noise. The value of 19.6341 is above the minimum desirable value of 4 and indicates an adequate signal. A polynomial equation was developed based on quadratic model coefficients calculated for coded factors of Trimethoprim in Table 5. Coefficients calculated for the quadratic model based on the coded factors for Metronidazole in Table 5.

*Table 5 can be found in the Appendix section.

The final model equation based on code, and actual values for the variables are presented in Eqs. (15) and (16), respectively.

$$Antibiotic\ removal\ (\%) = 92.939.45A + 6.36B + 6.96C + 3.03AB + 0.9250AC - 2.90BC - 8.42A^2 - 5.04B^2 - 18.29C^2(15)$$

$$Antibiotic\ removal\ (\%) = -85.91 + 80.81 dose + 1.1 time + 31.87 pH + 0.35 dose\ x\ time + 0.82 dose\ x\ pH - 0.42 time\ x\ pH - 59.85 dose^2 - 0.009 time^2 - 2.03 pH^2 (16)$$

The Eq. (15) and Eq. (16) could be used as a tool to predict the Metronidazole and Trimethoprim removals for given levels of each factor. The coded equation (Eq. 15) provides a useful tool to identify the relative impact of each factor by comparing the factor coefficients. Accordingly, the adsorbent mass (A) has the highest coefficient in the model and hence the highest impact on the process. The equation in terms of actual factors (Eq. 16) can be used to predict the response for given levels of each factor in the original units.

Statistical analysis by ANOVA indicated that the model was statistically significant (p=0.3599) for Metronidazole in Table 6. Furthermore, internally studentized residuals were randomly scattered between -3 and +3, with no outliers detected.

*Table 6 can be found in the Appendix section.

Statistical analysis by ANOVA indicated that the model was statistically significant (p=0.3583) for Trimethoprim in Table 7. Furthermore, internally studentized residuals were randomly scattered between -3 and +3, with no outliers detected.

*Table 7 can be found in the Appendix section.

The estimated coefficients, together with their standard errors, t-statistics, and p-values, are reported for Metronidazole antibiotic in Table 8.

*Table 8 can be found in the Appendix section.

The estimated coefficients, together with their standard errors, t-statistics, and p-values, are reported for Metronidazole antibiotic in Table 9.

*Table 9 can be found in the Appendix section.

From the results in Table 2 and in Table 3, the rejection and permeate flux by RO membrane varied between 73.52% to 99.36% and 12.70 to 18.50 ($l/m^2.h$) for Metronidazole (Table 2), and 75.10% to 98.80% and 12 to 18.73 ($l/m^2.h$) for Trimethoprim (Table 3), respectively. As can be seen in Table 2 and in Table 3 the effect of transmembrane operating pressure on selected antibiotics' rejection was much more than that of pH (76% to 96% for pressure increasing from 9 to 13 bar and 80% to 90% for pH of 3.0 to 10.0). It can also be seen that the effect of concentration and temperature on the rejection was by no means noticeable. The ANOVA for rejection and permeate flux of both antibiotics are shown in Tables 2, respectively. These results indicate the significance of the main operating parameters and their interaction effects based on p-value (at $p < 0.05$ level of significance).

The permeate flux decreased slightly as concentration was increased from 10 to 500 mg/l. According to, ANOVA results for both of antibiotics (Metronidazole and Trimethoprim) permeate flux show that operating pressure and concentration have significant effect on permeate flux, based on $P < 0.0001$ for pressure and $P < 0.04$ for concentration. It can be concluded that pressure has a significant influence (more than 90%). The effect of pH and temperature on permeate flux were negligible.

The interactions among the parameters on the Metronidazole (Figure 12) and Trimethoprim (Figure 13) rejections and permeate fluxes in three-dimensional (3-D) surface plots and two-dimensional (2-D) contour plots are shown in Fig. 12 and Fig. 13.

*Figure 12 can be found in the Appendix section.

*Figure 13 can be found in the Appendix section.

Based on the results, removal efficiency increased with molecular weights of the antibiotics compounds. The best rejection was obtained for Metronidazole (99.37%) which has a higher molecular weight than Trimethoprim (365.40 g/mol). There is a consensus that nonionizable organic solutes with molecular weights between 200 and 400 g/mol are efficiently rejected by RO/NF membranes, [174], [175]. The results showed that an increase in pressure from 9 to 13 bars would lead the flux to increase as well, which was due to the solution-diffusion model. Also, the condensed membrane increases the static resistance and then more solutes are rejected, [176]. On the other hand, flux under the experimental conditions is also a function of salt retention, as the retained ions accumulate in the boundary layer of the membrane where the concentration polarization effect imposes an osmotic pressure and reduces the effective driving force across the membrane, [177]. By increasing feed pressure, the driving force will increase and the overcome membrane resistance, [178], [179], [180], [181]. In this study, increasing the pressure from 9 to 13 bar led to an increase in the permeate flux and rejection. Higher flux values were obtained at 13 bars for applied Metronidazole and Trimethoprim (18.56 $l/m^2.h$); (Figure 12 and Figure 13 for Metronidazole and Trimethoprim, respectively).

With respect to the experimental conditions used in this study, the P-value (< 0.001) showed that the pressure and pH have significant effects on the pressure and pH have significant effects on the rejection of Metronidazole and Trimethoprim individually, but all interaction effects among the operating parameters in this study were insignificant for selected antibiotic rejection. As presented in Table 2 and Table 3, P-values for all interactions were higher than 0.05.

Retention of organic pollutants in membrane separation processes depends on the characteristics of both membrane and the pollutants, [182]. In addition, most of the papers reviewed by Bellona et al., [183], have shown that the transport of uncharged organic compounds through RO membrane is controlled mainly by the sieving mechanism. However, the rejection of the uncharged organic by HF-C RO membranes is often affected by physio-chemical properties of the system, and in the case of ionized organics, the charge exclusion plays a significant role in the rejection process, [184], [185]. The sieving mechanism of solute rejection is dependent on the relation between the size of solute molecules and the size of the membrane pores. An RO membrane has a very small molecular weight cut-off (MWCO) and it can retain a large fraction of low molecular weight compounds (e.g. amino acids or sugars). As pointed out by Kimura et al., [184], negatively charged compounds would be significantly rejected by HF-C RO membranes due to the electrostatic repulsion between the compounds and membranes, even compounds with a small molecular weight (e.g. M_w=110) and a rather loose membrane (i.e. NF), [179]. Therefore, molecular weight is one of the most important factors in antibiotic removal by RO membrane.

According to, the obtained results, the degree to which the antibiotics were rejected increased as pH increased. The phenomenon can be explained through the charged membrane and the charged solute which leads to a Donnan potential. Zeta potential of the membrane had a negative charge as the absolute zeta potential value decreased towards acidic pH values. This charge variation as a function of pH is due to the dissociation of membrane functional groups such as carboxylic and amide, and adsorption of hydroxide ion. All those effects were influenced by the pH of solution, [185]. With respect to the chemical structure of antibiotics, acidic pH leads to the production of negative charged ions of antibiotics. The charged membrane attracts opposite charged ions to achieve equilibrium. At the same time, the membrane will repel the same charged ions by an electrostatic force. In addition, the opposite charged ions will also be rejected due to elector-neutrality in the solution. Because of these interactions, the water can pass through the membrane. This mechanism enhances the rejection of antibiotics due to the charges of pH, causing the membrane to be charged, [179].

Although, the increase in the feed concentration had no effect on antibiotic rejection, permeate flux decreased slightly. It is known that when concentration increases, osmosis pressure will increase as well, decreasing the effective operating pressure. At the same time, the viscosity of solution will increase, leading the flux to decrease, [186].

Based on Figure 12 and Figure 13, the distribution of contours suggested that all of the parameters were quite independent of each and that the interactions between all of the parameters (pressure, concentration, pH, and temperature) were insignificant to the antibiotics rejection and permeates flux. Since the results obtained from experiments carried out on Metronidazole were the same as those conducted on Trimethoprim, repetitive results were omitted.

3.6.2 Statistical Analysis of Metronidazole and Trimethoprim Levels in Pharmaceutical Industry Wastewater

The correlation between the demographic indexes and Metronidazole levels of pharmaceutical industry wastewater was higher than that of Trimethoprim levels of pharmaceutical industry wastewater, in general, but the two followed the same trend. In order to determine whether Metronidazole levels are higher in the pharmaceutical industry wastewater than in the Trimethoprim levels in the pharmaceutical industry wastewater, a paired sample t-test was applied. The results showed that there was a significant difference between Metronidazole levels in the pharmaceutical industry wastewater and Trimethoprim levels in the pharmaceutical industry wastewater (t=54.30; p-value < 0.0001), meaning that, on average, the concentration of Metronidazole was 16.80 ng/l higher than the Trimethoprim concentration in pharmaceutical industry wastewater (95% confidence interval ranging from 16.80 to 17.40). This result is consistent with the hypothesis that Metronidazole and Trimethoprim may originate from leakages from the sewage network, which generally lays at few meters from the ground surface.

Moreover, a chi-square test was used to test the association of Metronidazole clusters in the first pharmaceutical industry wastewater sample with the Trimethoprim clusters of the second pharmaceutical industry wastewater sample, and the association was found to be significant (X^2=21.97; p-value < 0.0001). Thus, we can reject the null hypothesis that asserts the two pharmaceutical industry wastewater samples were independent of each other in terms of Metronidazole and Trimethoprim antibiotics contamination. Finally, Pearson’s correlation analysis was applied to the Metronidazole and Trimethoprim levels in both pharmaceutical industry wastewater samples, and revealed a positive and highly significant correlation ($r=0.44$; $p < 0.00009$), suggesting the possibility of Metronidazole and Trimethoprim leaching from the upper first pharmaceutical industry wastewater sample to the lower second pharmaceutical industry wastewater.

3.8 Effect of pH on Antibiotic Rejection Efficiency

To understand the effect of feed pH on antibiotic rejection efficiency by the RO unit, we varied the pH of the feed water under a constant operating pressure (10.30 bar) (Figure 14).

*Figure 14 can be found in the Appendix section.

Antibiotic rejections varied from 94.00% to 99.80% depending on pH rejection was highest at a pH of 6.0, at 99.80% (Figure 14). At pH > 6.0, the antibiotic rejection efficiency decreased because a higher fraction of uncharged antibiotic passed through the membrane. In this study, however, antibiotic rejection efficiencies decreased at lower pH values (pH < 6.0). The rejection

efficiency at pH=5.40 was 98.40%, and an even lower rejection efficiency (96.60%) was observed at pH=3.90 (Figure 14).

3.9 Effects of Temperature on Antibiotic Rejection

For both membranes, the rejection rate was observed at 295°K (22°C) for maximum antibiotic yields 60.80% and 71.60% for HF–O and, HF–C, respectively (Figure 15). As the temperature increased from 295°C (22°C) to 310°K (37°C), the antibiotic rejection rates declined from 77.40% to 60.80% and 83.40% to 72.40%, respectively, probably because of changes in the water’s kinematic viscosity an increase in temperature causes a decrease in osmotic pressure (Figure 15).

*Figure 15 can be found in the Appendix section.

Next Fig. 16 shows nitrate removal efficiency versus applied Antibiotic concentrations for the HF–O and, HF–C membranes. The maximum antibiotic removal rates were 90.70% and 86.40%, respectively. The HF-C membrane was relatively more efficient at all concentrations tested than the HF-O membrane, because of its smaller pore size and its structure. In this study, rejection declined from 86.40% to 70.40% and 90.70% to 73.10% for HF-O and HF-C membranes, respectively, as the antibiotic feed concentrations increased from 50 to 300 mg/l (Figure 16).

*Figure 16 can be found in the Appendix section.

3.10 Metronidazole and Trimethoprim Antibiotic Yields in HF-C RO Membrane at 100 mg/l Initial Concentrations

Metronidazole and Trimethoprim antibiotic yields in HF-C RO membrane at 100 mg/l initial concentrations were determined in Table 10. 99% Metronidazole and 99% Trimethoprim antibiotics removal efficiencies were observed in HF-C RO membrane, at 100 mg/l Metronidazole initial concentration, at 100 mg/l Trimethoprim initial concentration, at 180 l/h feed flow, at 4.2 l/m^2.h permeate flux, respectively.

*Table 10 can be found in the Appendix section.

3.11 Metronidazole and Trimethoprim Antibiotic Yields in HF-O RO Membrane at 100 mg/l Initial Concentrations

Metronidazole and Trimethoprim antibiotic yields in HF-O RO membrane at 100 mg/l initial concentrations were shown in Table 11. 99% Metronidazole and 99% Trimethoprim antibiotics removal efficiencies were obtained in HF-O RO membrane, at 100 mg/l Metronidazole initial concentration, at 100 mg/l Trimethoprim initial concentration, at 30 bar feed pressure, at 7 l/m^2.h permeate flux, respectively.

*Table 11 can be found in the Appendix section.

3.12 Recoveries in Retentates for Both Antibiotics

The recoveries in retentates for Metronidazole and Trimethoprim antibiotics were given in Table 12. 99% Metronidazole and 99% Trimethoprim antibiotics removal efficiencies were obtained in RO membrane, at 100 mg/l Metronidazole initial concentration, at 100 mg/l Trimethoprim initial concentration, at 30 bar feed pressure, at 7 l/m^2.h permeate flux, respectively.

*Table 12 can be found in the Appendix section.

The era of wastewater reclamation, recycling and reuse began in the early twentieth century as a result of technological improvements in the chemical, physical, and biological processes of wastewater treatment, [186], [187]. The reuse of wastewater effluent is commonly seen in both developing and industrialized countries such as the United States of America, Japan, China, Korea and Israel, [188], [189], [190]. The majority of previous studies have focused on floatation, coagulation, and reverse osmosis or membrane bioreactor processes as potential wastewater treatment options, [191]. The use of sequencing anoxic/anaerobic membrane bioreactors, a type of Membranous Biological Reactors (MBR) method that removes nitrogen and phosphorus concurrently, has been introduced, and it outperforms the improved Luzack-Ettinger process of phosphorus removal, [192]. The percentage of activated sludge in this process was raised from 30% to 70%; Galaxolide, Tonalid, Ibuprofen, Naproxen, 17-Estradiol, and Sulfamethoxazole can be removed in wastewater treatment plants, [193]. Activated carbon filtration, with both powdered and granular activated carbon, has been used, [194].

The adsorption of micropollutant from wastewater using powdered activated carbon is an excellent method for removing micropollutants such as Sulfamethoxazole, Atenolol, Diclofenac, etc., [195]. Granulated activated carbon is the most cost-effective and frequently used material for removing organic micropollutants such as Fexofenadine, Carbamazepine, Lamotrigine, Oxazepam, Fluconazole, Cetirizine, and N,N-diethyl-meta-toluamide from contaminated drinking water, [196].

The law clarifies the governments and other stakeholders' responsibilities in the fight against antibiotic resistance, including the use and discharge of antibiotics into the environment. Recent systematic reviews laid out 17 policy measures to decrease human antibiotic usage, although, it is unclear whether or not most of the policies will have any influence on antibiotic use, [197]. Some of the recycling strategies include the construction of vertical flow wetlands, which will help in the removal of antibiotics such as sulfamethazine, ciprofloxacin and oxytetracycline with an efficiency of 68-85%. Similarly, other strategies include the construction of horizontal subsurface flow wetlands, photocatalytic degradation, Sono-catalytic irradiation, ultrafiltration, using PVC membrane, adsorption by activated carbon, carbon nanotubes, electro-coagulation, advanced oxidation processes (AOPs) in combination with UV/hydrogen peroxide, and AOPs using Fenton process.

3.13 Problems and Restrictions with Current Strategies for Antibiotics

Despite the success of these therapeutic approaches, problems and restrictions still exist. Certain antibiotics might not break down, which would leave them incompletely removed. Furthermore, it is concerning that during treatment, antibiotics can change into potentially more hazardous metabolites. Furthermore, there are financial obstacles to the widespread adoption of advanced treatment technologies because of their high energy requirements and operating costs.

The selection and optimisation of treatment strategies are further complicated by the emergence of new antibiotics and the variability in wastewater composition. In addition, questions concerning the long-term effectiveness of these methods are raised by the possible emergence of antibiotic-resistant bacteria in treated effluents. Antibiotic removal from wastewater necessitates a multimodal strategy that combines traditional and cutting-edge treatment techniques. Although biological treatment is still the mainstay, newer technologies such as membrane filtration, UV irradiation, and ozonation present promising paths for improved removal. Long-term solutions must consider the difficulties and constraints posed by these approaches to reduce the negative effects of antibiotic contamination in wastewater on the environment.

3.14 Future Perspectives and Recommendations

The future perspectives go through mitigating, preventing, and controlling antibiotic resistance, which is one of the global priorities recognized by the competent authorities. Future studies should include improvement of wastewater management practices and monitoring of environmental water contamination by antibiotics. Multiclass methods are required that allow simultaneous analysis of antibiotics and their by- products at very low concentrations. All to combat concerns with antibiotic mixtures and their effects on human health and the environment derived from chronic low-level exposure, [198].

The risk of development and proliferation of resistance to antibiotics is critical and adequate methods to assess this risk must be developed in future lines of research. The concentration of antibiotics depends on three major conditioning factors: First, economic factors, for example population density and its corresponding release of antibiotics; Second, geochemical factor, for example the texture of the sediments and the content of sedimentary organic carbon; Third, geographic and hydrological factors, for example rainfall and currents, [199]. Consequently, the locations for monitoring the concentrations of antibiotics in the aquatic environment cannot be chosen arbitrarily. A strategy is needed to determine the strategic points where monitoring should be performed.

It is important to emphasize that risk assessments of emerging contaminants (for example antibiotics) are always helpful, but your results should be treated with caution because single compound exposure scenarios are not realistic. Multiple pollutants are reproduced in combi nation with effects that are unknown and of considerable ecological concern. Therefore, prospects are to carry out more specific analyses, to define possible adverse effects on the aquatic environment and whether synergistic effects between pollutants can occur, [200].

As a summary regarding the fight against antibiotic resistance, add that there are authors who establish a series of major future lines of action: First, carry out prevention and awareness campaigns to reduce the consumption of antibiotics, as well as greater control of the elimination of expired drugs; Second, optimize the performance of existing WWTPs through the implementation of tertiary treatment techniques; Third, increase research on new and more innovative techniques for water treatment; Fourth, a strict and uniform regulation on the application of sludge from urban WWTPs and livestock manure as fertilizers in agricultural activities since they are sources of contamination of agricultural soils and, in some cases, of harvested crops; Fifth, conduct more research focused on the ecotoxicological risks associated with pharmaceutical contamination. This would allow deciding which com pounds represent a threat to the aquatic environment and therefore must be monitored and included in the lists of priority substances defined in legislative frameworks such as Directive 2013/39/EC, [201].

The global prevalence of Nitroimidazole antibiotics (Metronidazole and Trimethoprim) in WWTPs is outlined in Table 13. The concentrations and types of antibiotics are more diverse in developed countries compared to under developed countries. The Nitroimidazole antibiotics (Metronidazole and Trimethoprim) found in various regions of world was shown in Table 13.

*Table 13 can be found in the Appendix section.

Also, in the future it is necessary to globalize studies. There are knowledge gaps that must be filled through studies of the fate and transport of emerging pollutants in countries located in a wider range of climates (from tropical to arctic). Especially, there is a significant lack of information from countries such as Indonesia, India, Canada, Russia, and countries in Africa and South America, [202].

Another line of work for the future may be based on advancing and refining the methods that make it possible to determine a standardized elimination efficiency by compound types (for example, for antibiotics). These proceeds because there is scientific evidence that determines serious difficulties in comparing the efficacy of the different treatment processes because the elimination of organic micropollutants seems to be specific to each compound, [203], [204]. The comparison of removal of antibiotics from wastewater effluents through advanced treatment processes was determined at Table 14.

*Table 14 can be found in the Appendix section.

The prospects also include reducing the costs of eliminating antibiotics from the aquatic environment. For example, there are relatively recent studies on hospital effluents that establish that total costs range between 4.1 €/m^3 and 5.5 €/m^3 in the case of incorporating secondary treatment using a membrane biological reactor and advanced oxidation processes [205].

Our results dictated that the amount of micro pollutants removed during secondary treatment varied widely by com pound. While the ultrafiltration (UF) removal efficiency for the different compounds varied significantly, although, it was less than 20% for most. Excellent removal rates were achieved in the reverse osmosis treatment. They rejected more than 99% of all target compounds. Finally, electro oxidation with boron-doped diamond electrodes removed more than 95% of most of the compounds studied from the RO effluent, [206], [207].

4 Conclusion

The aim of this study was to successfully develop a removal and recovery of Nitroimidazoles (Metronidazole and Trimethoprim) antibiotics from a pharmaceutical industry wastewater using reverse osmosis.

J_s/J_w is also increased with feed flow rate for the HF–C membranes but remains relatively constant for HF–O membranes for all tested feed flow rates. Furthermore, J_s/J_w is much lower for HF–O membranes ($J_s/J_w = 0.15 \pm 0.02$ g/l) than it is for HF–C membranes ($J_s/J_w = 0.40 \pm 0.10$ g/l).

For the HF–C membrane, J_w was higher than for the HF–O membrane at any draw flow rate investigated, and it increased from 24.9 ± 0.6 l/m^2.h at 25 l/h to 31.30 l/m^2.h at 100 l/h, respectively (J_w increase of 25.40%).

J_w increased from 17.90 ± 0.50 l/m^2.h to 19.20±0.50 l/m^2.h (7.30% increase in J_w) for HF–O modules and from 24.0 ± 1.3 l/m^2.h to 27.70 ± 0.20 l/m^2.h (15% increase in J_w) for HF–C modules. The water permeability coefficient (A_w) and solute rejection efficiency (R) were constant at 6.73 l/m^2/h/bar and 99.20%, respectively, while the solute permeability coefficients varied with pressure and correlated with J_w

Antibiotic rejections varied from 94.00% to 99.80% depending on pH rejection was highest at a pH of 6.0, at 99.80%.

For both membranes, the rejection rate was observed at 295°K (22°C) for maximum antibiotic yields 60.80% and 71.60% for HF–O and, HF–C, respectively.

The maximum antibiotic removal rates were 90.70% and 86.40%, respectively. The HF-C membrane was relatively more efficient at all concentrations tested than the HF-O membrane, because of its smaller pore size and its structure.

99% Metronidazole and 99% Trimethoprim antibiotics removal efficiencies were observed in HF-C RO membrane, at 100 mg/l Metronidazole initial concentration, at 100 mg/l Trimethoprim initial concentration, at 180 l/h feed flow, at 4.2 $l/m^2.h$ permeate flux, respectively.

99% Metronidazole and 99% Trimethoprim antibiotics removal efficiencies were obtained in HF-O RO membrane, at 100 mg/l Metronidazole initial concentration, at 100 mg/l Trimethoprim initial concentration, at 30 bar feed pressure, at 7 $l/m^2.h$ permeate flux, respectively.

99% Metronidazole and 99% Trimethoprim antibiotics removal efficiencies were obtained in RO membrane, at 100 mg/l Metronidazole initial concentration, at 100 mg/l Trimethoprim initial concentration, at 30 bar feed pressure, at 7 $l/m^2.h$ permeate flux, respectively.

This study experimentally demonstrated the effectiveness of RO membranes in removing pharmaceutically Nitroimidazoles (Metronidazole and Trimethoprim) from wastewater, providing foundational insights into the optimization of membrane-based water treatment systems. The results confirmed that membrane type and structure, as well as compound-specific characteristics-such as molecular weight, hydrophobicity, and ionization state-are key factors influencing removal efficiency. RO generally outperformed HFRO due to its denser structure, which is more effective for smaller and non-ionized compounds. By incorporating these characteristics, permeability coefficients (L_s) were calculated for each compound, supporting the development of a tailored solution diffusion model that accurately reflects the behaviour of diverse Nitroimidazoles (Metronidazole and Trimethoprim) across varying conditions.

In addition to, a chi-square test was used to test the association of Metronidazole clusters in the first pharmaceutical industry wastewater sample with the Trimethoprim clusters of the second pharmaceutical industry wastewater sample, and the association was found to be significant (X^2=21.97; p-value < 0.0001). Thus, we can reject the null hypothesis that asserts the two pharmaceutical industry wastewater samples were independent of each other in terms of Metronidazole and Trimethoprim antibiotics contamination. Finally, Pearson's correlation analysis was applied to the Metronidazole and Trimethoprim levels in both pharmaceutical industry wastewater samples, and revealed a positive and highly significant correlation (r=0.44; p < 0.00009), suggesting the possibility of Metronidazole and Trimethoprim leaching from the upper first pharmaceutical industry wastewater sample to the lower second pharmaceutical industry wastewater.

The human and animal waste that is produced after the consumption of antibiotics causes the contamination of the aquatic environment. This ends up harming human health by generating resistance to antibiotics. To fight against this problem and protect the Aquatic Environment, numerous efforts are being made around the world. The problem is not easy because there are multiple routes of entry for antibiotic residues of human and animal origin into the aquatic environment and the consumption of antibiotics for medical and veterinary use has high levels in developed countries. If means for their elimination from the aquatic environment are not studied, the problem will worsen over time. Because of higher global consumption, large discharges excreted into the aquatic environment, which will be added to the existing concentrations.

The study shows the concern for the environment and human health caused by the misuse of antibiotics, which lead to the creation of antibiotic-resistant bacteria and toxic effects on aquatic life. Some treatments have been effective, though limited to biological and physical-chemical treatment. Some advanced treatment methods like membrane filtration, UV irradiation, RO membrane technologies and ozonation also exist. However, these strategies continue to be threatened with the following challenges, implying a need for more studies on the researched strategies and very flexible measures. Therefore, eradicating antibiotics in polluted wastewater could be best addressed by applying novel treatment processes, strict legal provisions, and robust monitoring mechanisms. Future research and interdisciplinary cooperation are critical to address antibiotic pollution's environmental and health consequences and to design new solutions to tackle the problem.

In summary, this research significantly contributes to advancing membrane-based water treatment solutions capable of efficiently removing

Nitroimidazoles (Metronidazole and Trimethoprim) from wastewater, offering valuable data and a predictive framework to enhance the applicability of RO technologies in managing complex environmental contaminants.

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APPENDIX

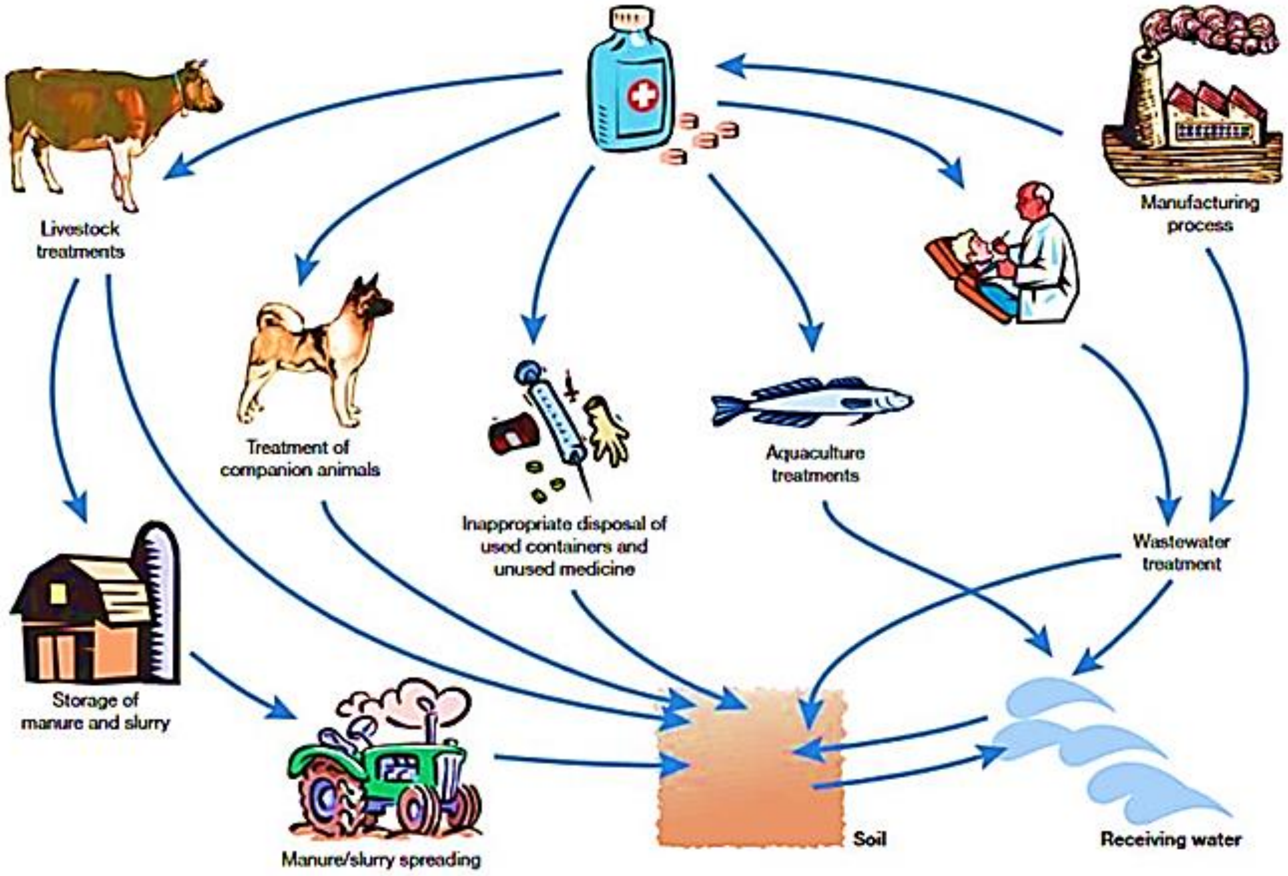


Fig. 1: The potential sources of pharmaceutical components in the surroundings

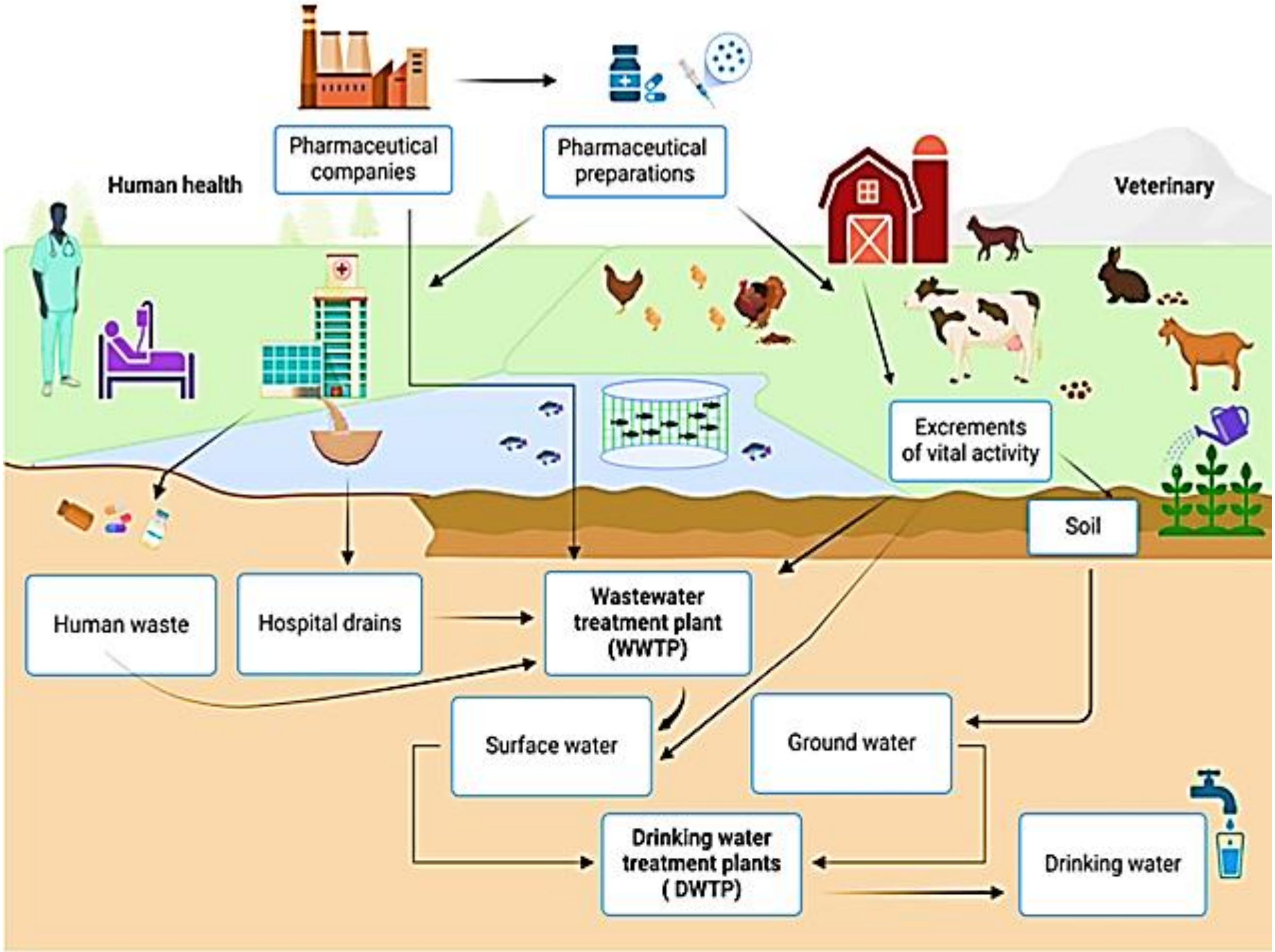


Fig. 2: Scheme of pharmaceutical products and their metabolites in the environment and water purification

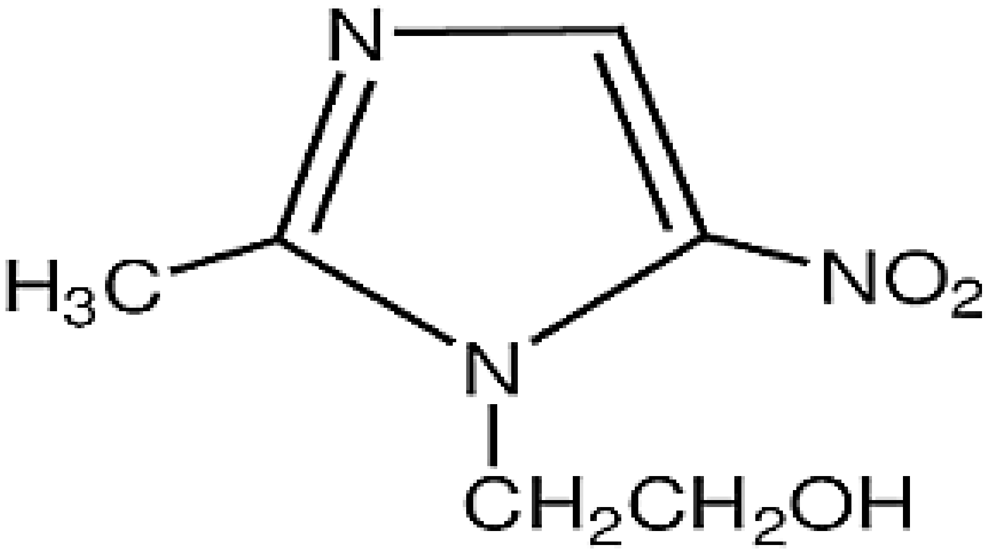


Fig. 3: Chemical structure of Metronidazole (C6H9N3O3, Mw=171.156 g/mol)

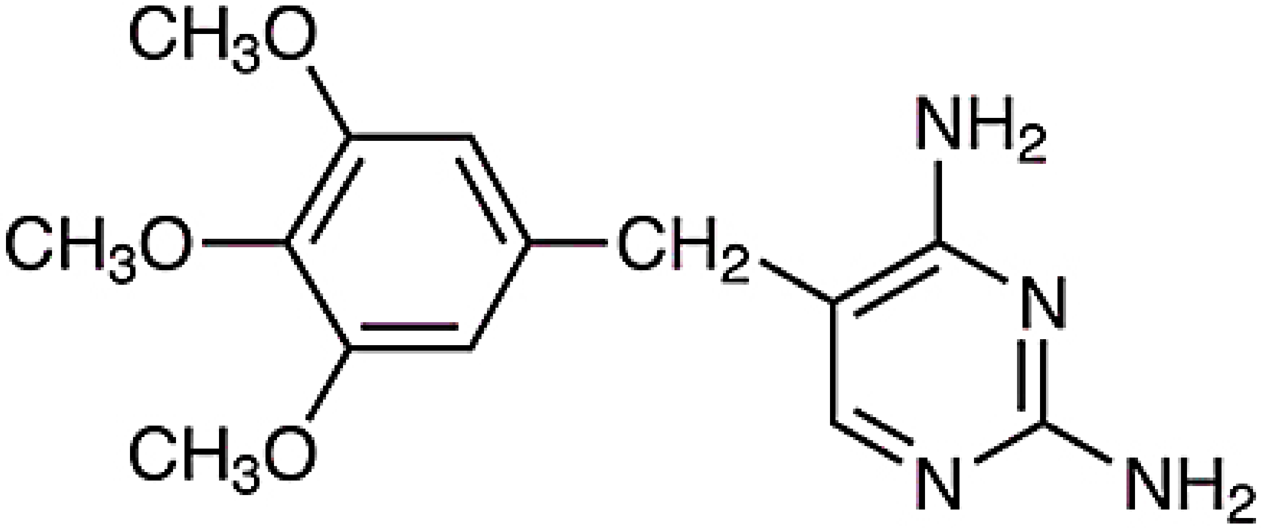


Fig. 4: Chemical structure of Trimethoprim (C14H18N4O3, Mw=290.323 g/mol)

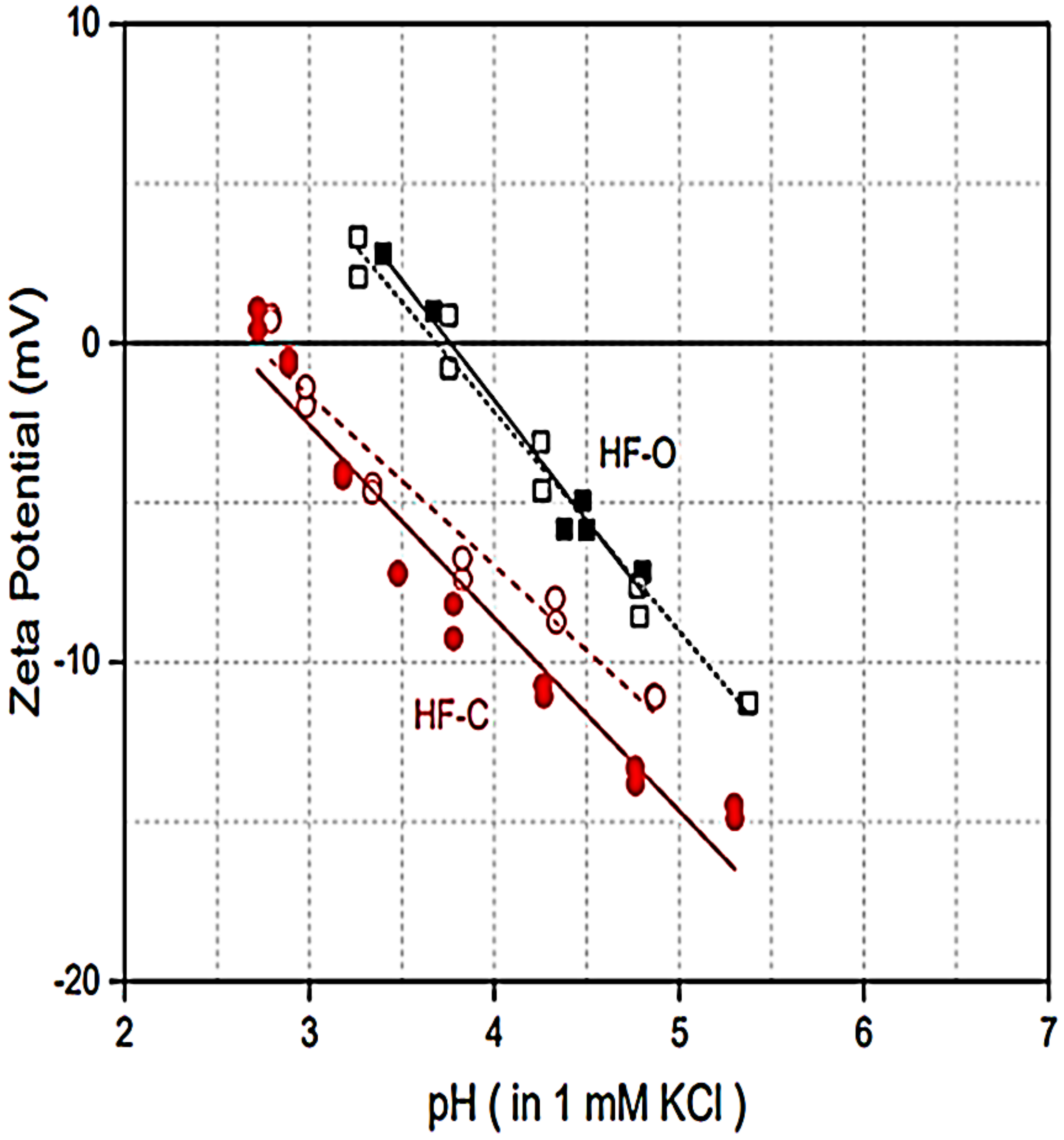
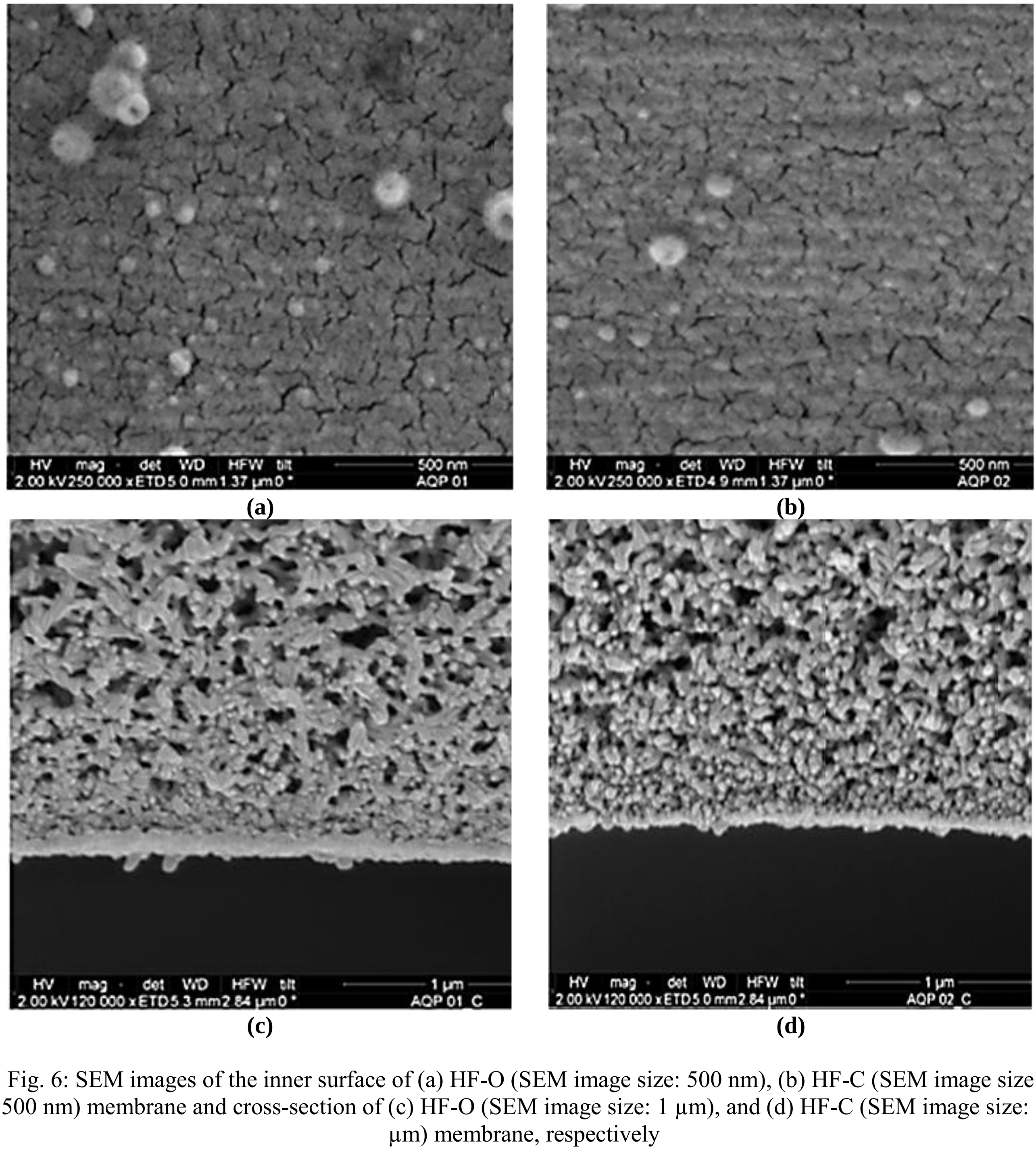


Fig. 5: Zeta potential as a function of pH at the inner surface of the HF-C and HF-O membranes

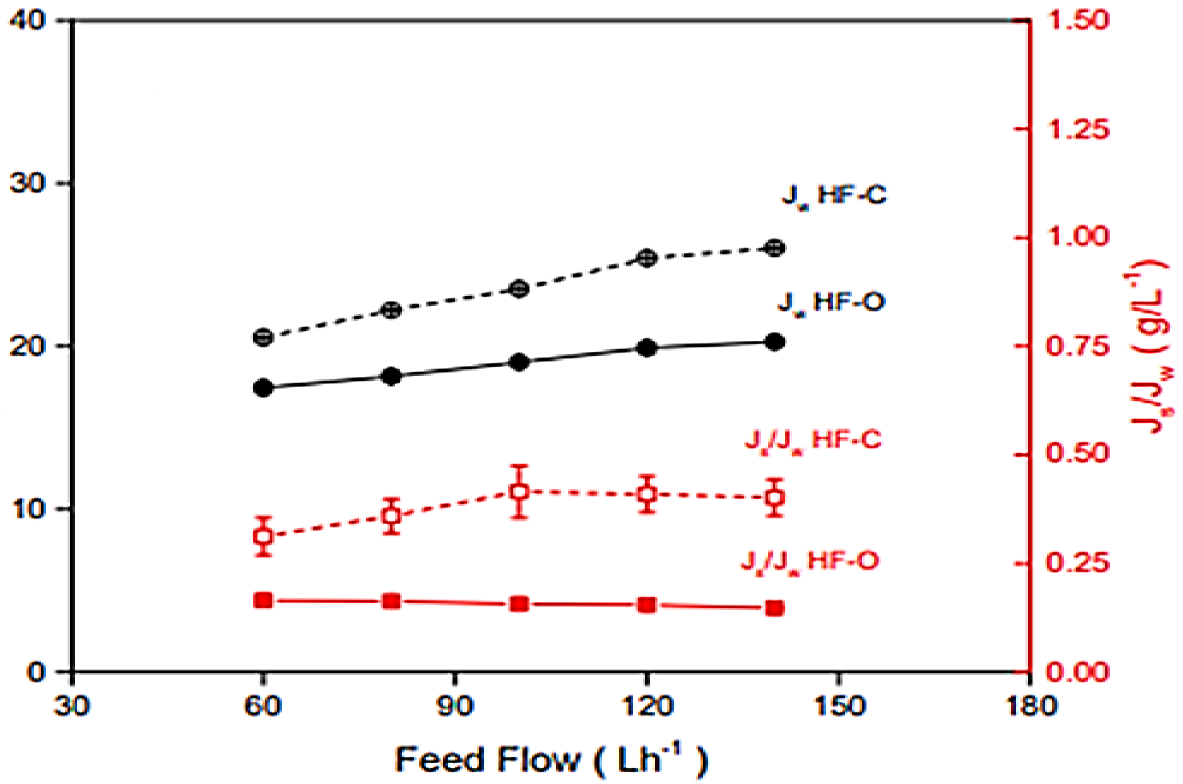
Table 1. Adsorption isotherm parameters of Langmuir and Freundlich models for adsorption of the Metronidazole and Trimethoprim antibiotics on the HF-O RO and HF-C RO membranes, respectively

Antibiotics	**Langmuir Isotherm**			**Freundlich Isotherm**		
	q_m (mg/g)	**b (l/mg)**	**R^2**	**K_f (l/g)**	**n**	**R^2**
Metronidazole with HF-C RO Membrane	215.14	0.52	0.994	65.815	2.063	0.879
Metronidazole with HF-O RO membrane	218.53	0.57	0.991	68.234	2.079	0.882
Trimethoprim with HF-C RO Membrane	221.78	0.60	0.992	67.109	2.081	0.885
Trimethoprim with HF-O RO membrane	220.09	0.51	0.990	66.257	2.006	0.883

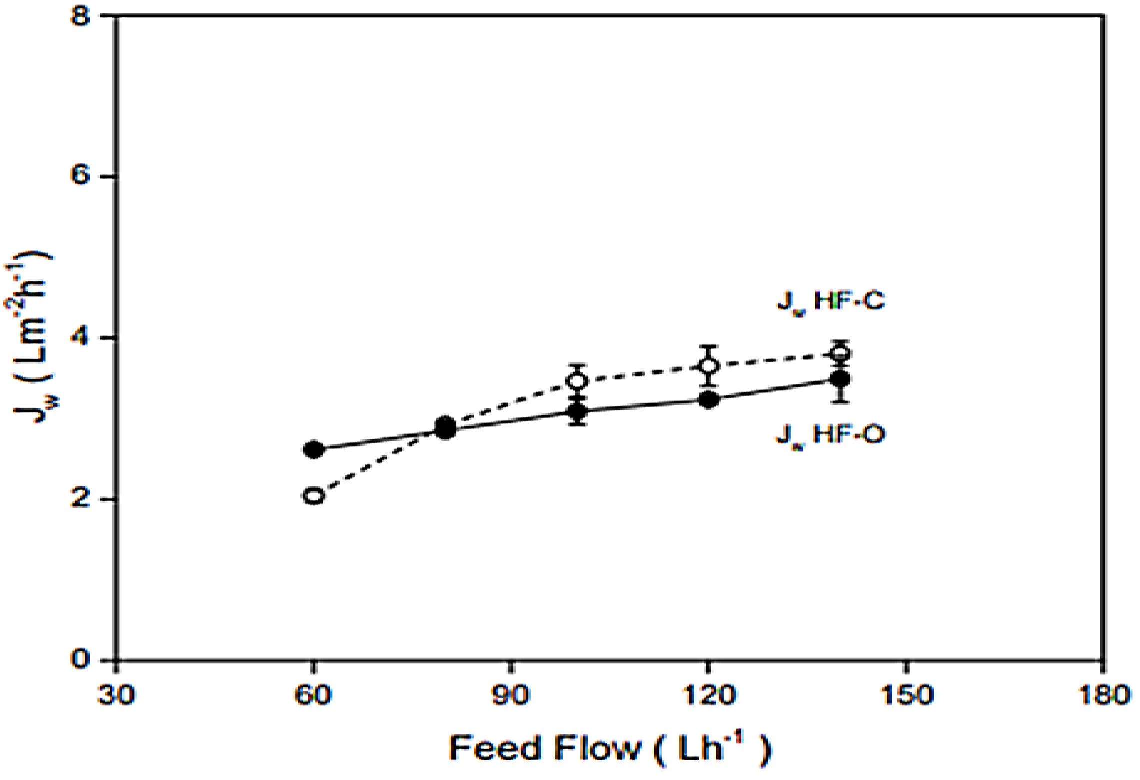


(a) (b) (c) (d)

Fig. 6: SEM images of the inner surface of (a) HF-O (SEM image size: 500 nm), (b) HF-C (SEM image size: 500 nm) membrane and cross-section of (c) HF-O (SEM image size: 1 µm), and (d) HF-C (SEM image size: 1 µm) membrane, respectively

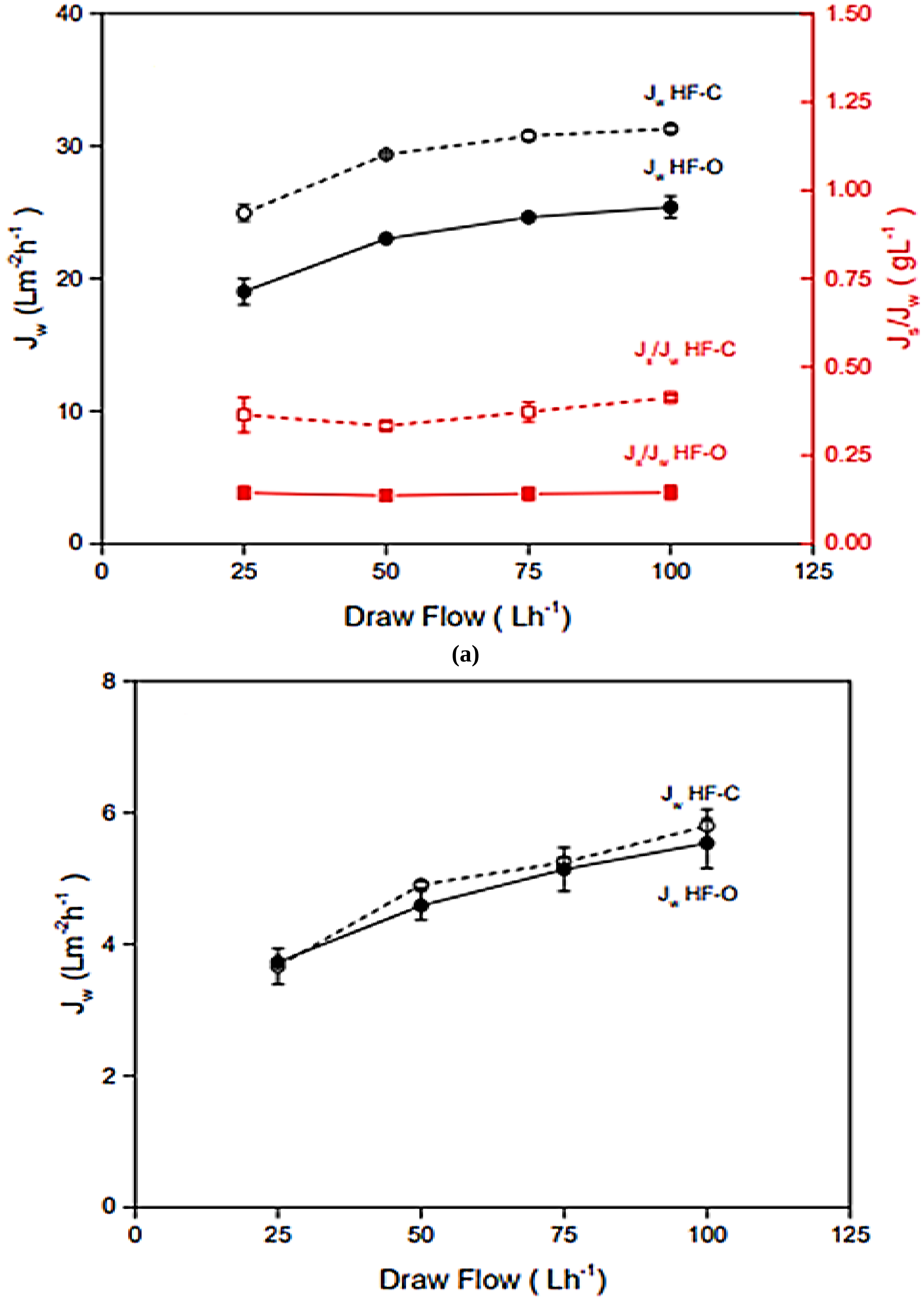


(a)



(b)

Fig. 7: (a) Jw and specific reverse solute flux (Js/Jw) for HF-C and HF-O modules as a function of feed flow rate when deionized water was used as a feed solution (FS), (b) Jw for HF-C and HF-O modules as a function of feed flow rate when deionized water was used as a FS, respectively



(a)

(b)

Fig. 8: (a) Jw and Js/Jw for HF-C and HO modules as a function of draw flow rate when deionized water was used as a draw solution (DS), (b) Jw for HF-C and HF-O modules as a function of draw flow rate when deionized water was used as a DS, respectively

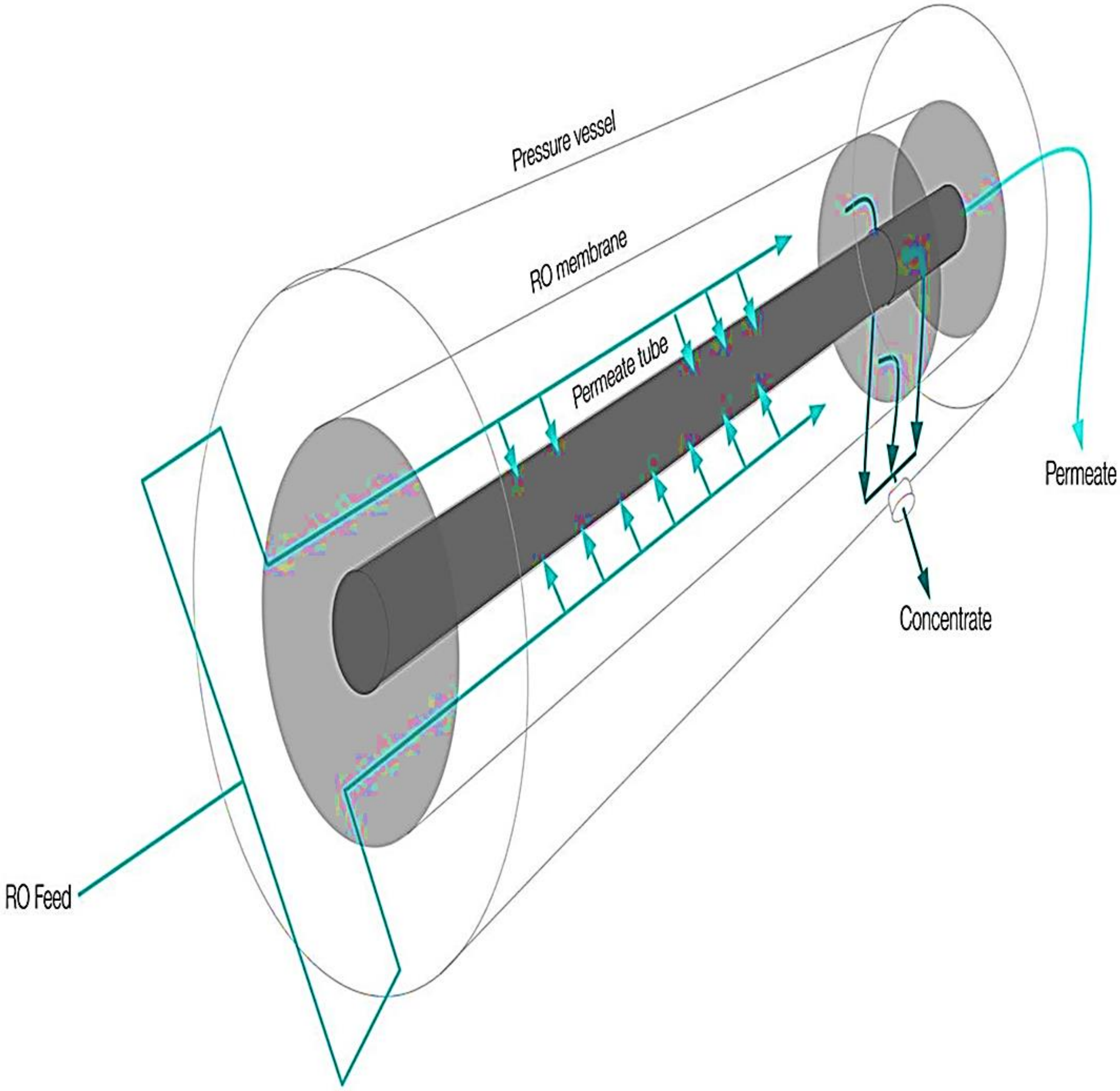
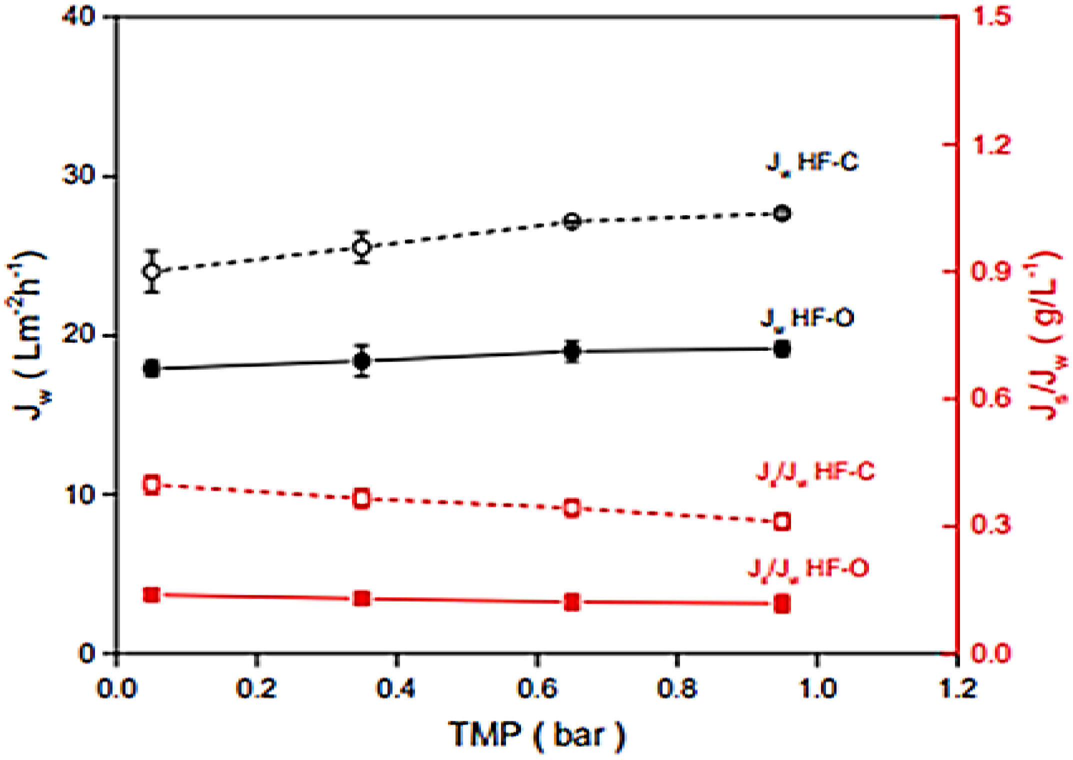
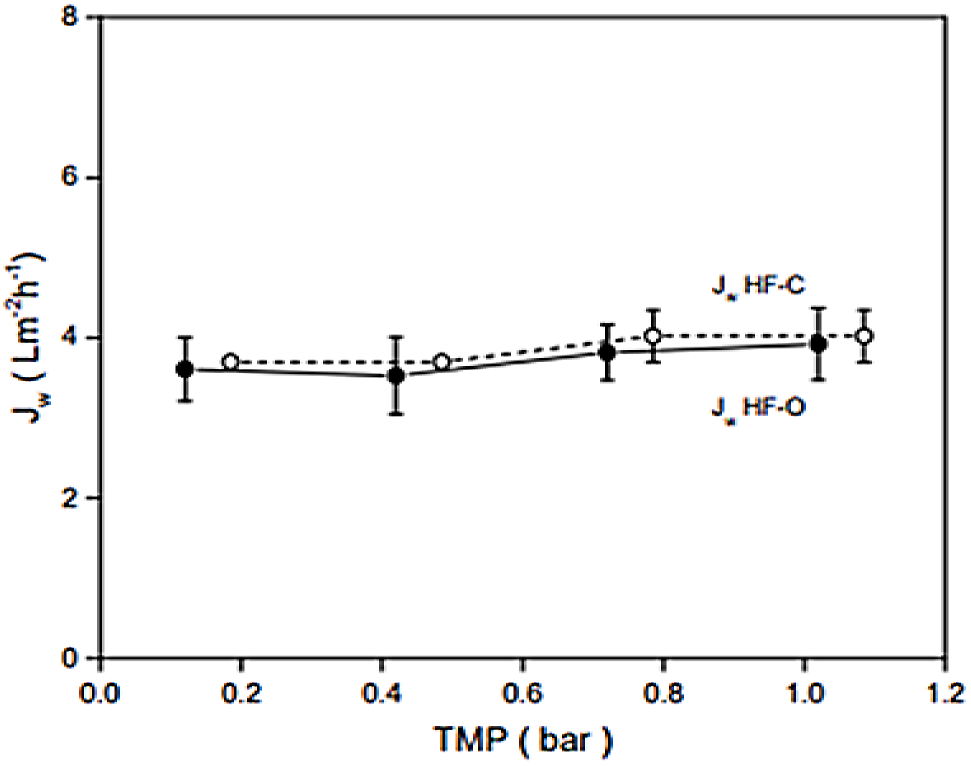


Fig. 9: Schematic diagram of reverse osmosis (RO) membrane



(a)



(b)

Fig. 10: (a) Jw and Js/Jw for HF-C and HF-O modules as a function applied TMP when deionized water was used as a TMP pressure bar, (b) Jw for HF-C and HF-O modules as a function applied when deionized water was used as a TMO pressure bar, respectively

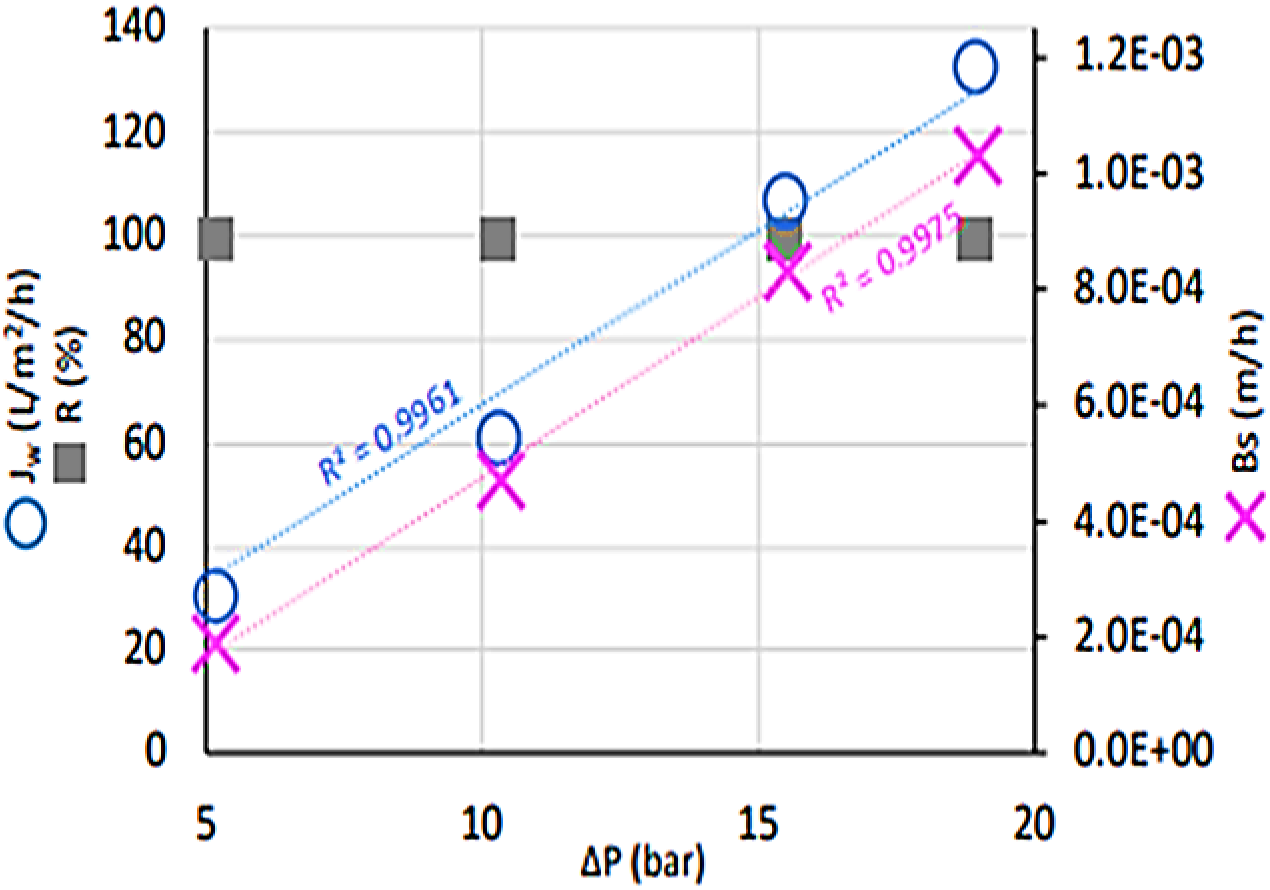


Fig. 11: To evaluate the effect of pressure (or flux) on the solute permeability coefficient was operated at pressures ranging

Table 2. ANOVA for the quadratic model fitted to Metronidazole removal by RO membrane

Source	**Sum of squares**	**DF**	**Mean square**	**F-value**	***p* value**
Model	2954.31	9	328.26	37.27	0.0005
A-dose	714.42	1	714.42	81.12	0.0003
B-time	323.85	1	323.85	36.77	0.0018
C-pH	387.81	1	387.81	44.04	0.0012
AB	36.60	1	36.60	4.16	0.0970
AC	3.42	1	3.42	0.3886	0.5604
BC	33.64	1	33.64	3.82	0.1081
A^2	261.56	1	261.56	29.70	0.0028
B^2	93.85	1	93.85	10.66	0.0223
C^2	1235.39	1	1235.39	140.28	<0.0001
Residual	44.03	5	8.81		
Lack of Fit	39.37	3	13.12	5.62	0.1547
Pure Error	4.67	2	2.33		
Cor Total	2998.34	14			
R^2	0.9853				
Adjusted R^2	0.9589				
Adeq Precision	19.6343				

Table 3. ANOVA for the quadratic model fitted to Trimethoprim removal by RO membrane.

Source	**Sum of squares**	**DF**	**Mean square**	**F-value**	***p* value**
Model	2952.53	9	328.26	35.49	0.0005
A-dose	712.64	1	712.64	79.34	0.0003
B-time	321.07	1	321.07	34.99	0.0016
C-pH	385.03	1	385.03	42.26	0.0011
AB	34.82	1	34.82	4.04	0.0968
AC	3.20	1	3.20	0.3884	0.5601
BC	31.86	1	31.86	3.61	0.1080
A^2	259.78	1	259.78	27.92	0.0025
B^2	91.07	1	91.07	10.43	0.0220
C^2	1233.50	1	1233.50	138.40	<0.0001
Residual	42.81	5	7.68		
Lack of Fit	37.59	3	12.34	5.41	0.1545
Pure Error	4.45	2	2.31		
Cor Total	2996.56	14			
R^2	0.9851				
Adjusted R^2	0.9587				
Adeq Precision	19.6341				

Table 4. Coefficients calculated for the quadratic model based on the coded factors for Metronidazole.

Factor	**Coefficient Estimate**	**df**	**Standard Error**	**95% CI Low**	**95% CI High**	**VIF**
Intercept	92.93	1	1.71	88.53	97.34	
A-dose	9.45	1	1.05	6.75	12.15	1.0000
B-time	6.36	1	1.05	3.67	9.06	1.0000
C-pH	6.96	1	1.05	4.27	9.66	1.0000
AB	3.03	1	1.48	-0.7893	6.84	1.0000
AC	0.9250	1	1.48	-2.89	4.74	1.0000
BC	-2.90	1	1.48	-6.71	0.9143	1.0000
A^2	-8.42	1	1.54	-12.39	-4.45	1.01
B^2	-5.04	1	1.54	-9.01	-1.07	1.01
C^2	-18.29	1	1.54	-22.26	-14.32	1.01

Table 5. Coefficients calculated for the quadratic model based on the coded factors for Trimethoprim.

Factor	**Coefficient Estimate**	**df**	**Standard Error**	**95% CI Low**	**95% CI High**	**VIF**
Intercept	90.05	1	1.59	88.51	97.32	
A-dose	8.67	1	1.04	6.73	12.13	1.0000
B-time	5.58	1	1.04	3.65	9.04	1.0000
C-pH	5.08	1	1.04	4.25	9.64	1.0000
AB	2.85	1	1.46	-0.7891	6.82	1.0000
AC	0.9248	1	1.46	-2.87	4.72	1.0000
BC	-2.88	1	1.46	-6.69	0.9141	1.0000
A^2	-7.64	1	1.52	-11.50	-4.43	1.01
B^2	-4.86	1	1.52	-8.80	-1.05	1.01
C^2	-16.51	1	1.52	-20.48	-12.54	1.01

Table 6. ANOVA for the reduced quadratic model for Metronidazole (DF: degrees of freedom; SS: sum of squares; MS: mean squares; F: F-value; p: p-value).

Source	**DF**	**SS**	**MS**	***F***	***p***
Regression	6	2527.71	421.29	93.32	<0.0001
Residual error	23	345.49	15.02		
Lack-of-fit	18	290.19	16.12	1.46	0.3599
Pure error	5	55.30	11.06		
Total	29	2873.20			

Table 7. ANOVA for the reduced quadratic model for Trimethoprim (DF: degrees of freedom; SS: sum of squares; MS: mean squares; F: F-value; p: p-value).

Source	DF	SS	MS	*F*	*p*
Regression	6	2525.93	420.30	93.30	<0.0001
Residual error	22	343.60	14.24		
Lack-of-fit	17	288.30	15.35	1.44	0.3583
Pure error	5	53.52	10.88		
Total	27	2869.53			

Table 8. Model coefficient estimation along with the corresponding 95% confidence intervals (CI) and standard errors (SE) for Metronidazole.

Coefficient	**Term**	**Value**	**SE**	**Low CI**	**High CI**
a_0	Intercept	67.63	1.12	65.31	69.94
a_1	C	-1.96	0.79	-3.60	-0.32
a_2	T	7.05	0.79	5.41	8.69
a_3	S	1.83	0.79	0.20	3.47
a_4	R	5.58	0.79	3.95	7.22
a_{22}	t x t	-3.36	0.73	-4.87	-1.86
a_{44}	R x R	-2.17	0.73	-3.67	-0.67

Table 9. Model coefficient estimation along with the corresponding 95% confidence intervals (CI) and standard errors (SE) for Trimethoprim.

Coefficient	**Term**	**Value**	**SE**	**Low CI**	**High CI**
a_0	Intercept	65.85	1.11	63.54	68.97
a_1	C	-1.94	0.78	-3.57	-0.31
a_2	T	7.03	0.78	5.38	8.68
a_3	S	1.81	0.78	0.19	3.45
a_4	R	5.56	0.78	3.93	7.20
a_{22}	t x t	-3.35	0.72	-4.85	-1.83
a_{44}	R x R	-2.15	0.72	-3.64	-0.65

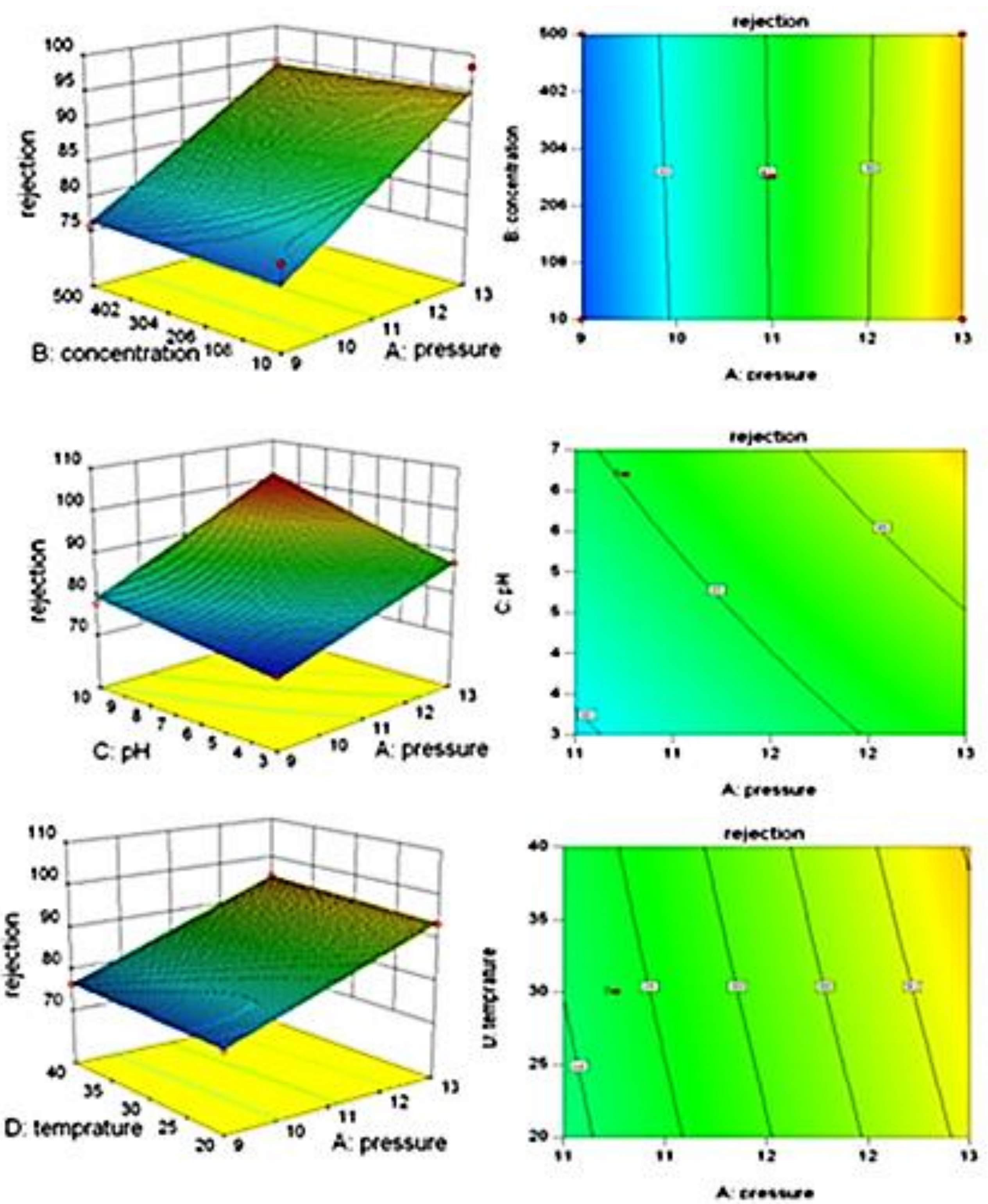


Fig. 12: Three-dimensional (3D) surface plots (left column) and two-dimensional (2D) contour plots (right column) showing the response surface function effects of the interactions between; A: pressure and concentration, B: pressure and pH, C: pressure and temperature on Metronidazole rejection

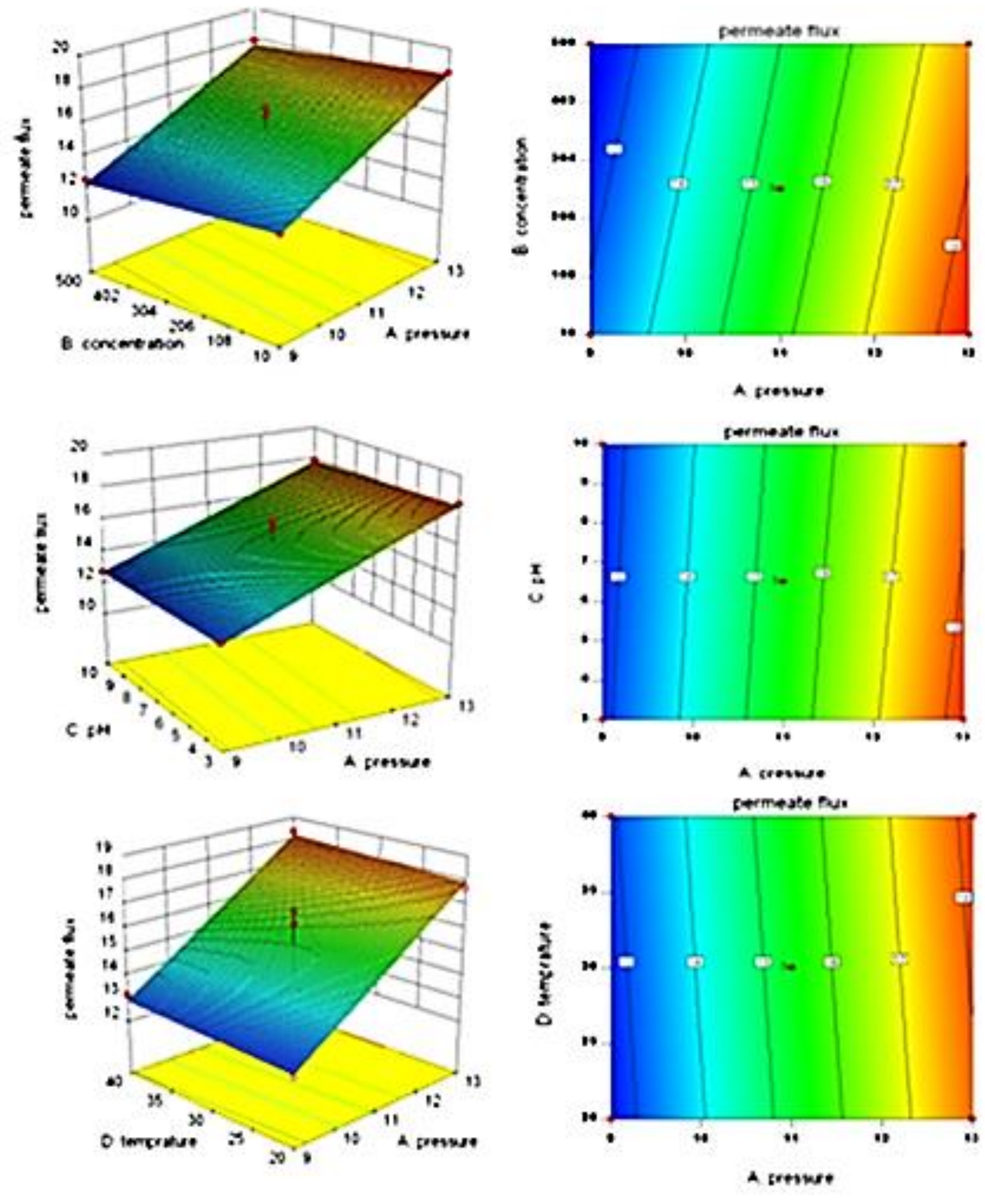


Fig. 13: Three-dimensional surface plots (left column) and two-dimensional contour plots (right column) showing the response surface function effects of the interactions between; A: pressure and concentration, B: pressure and pH, C: pressure and temperature on Trimethoprim permeate flux

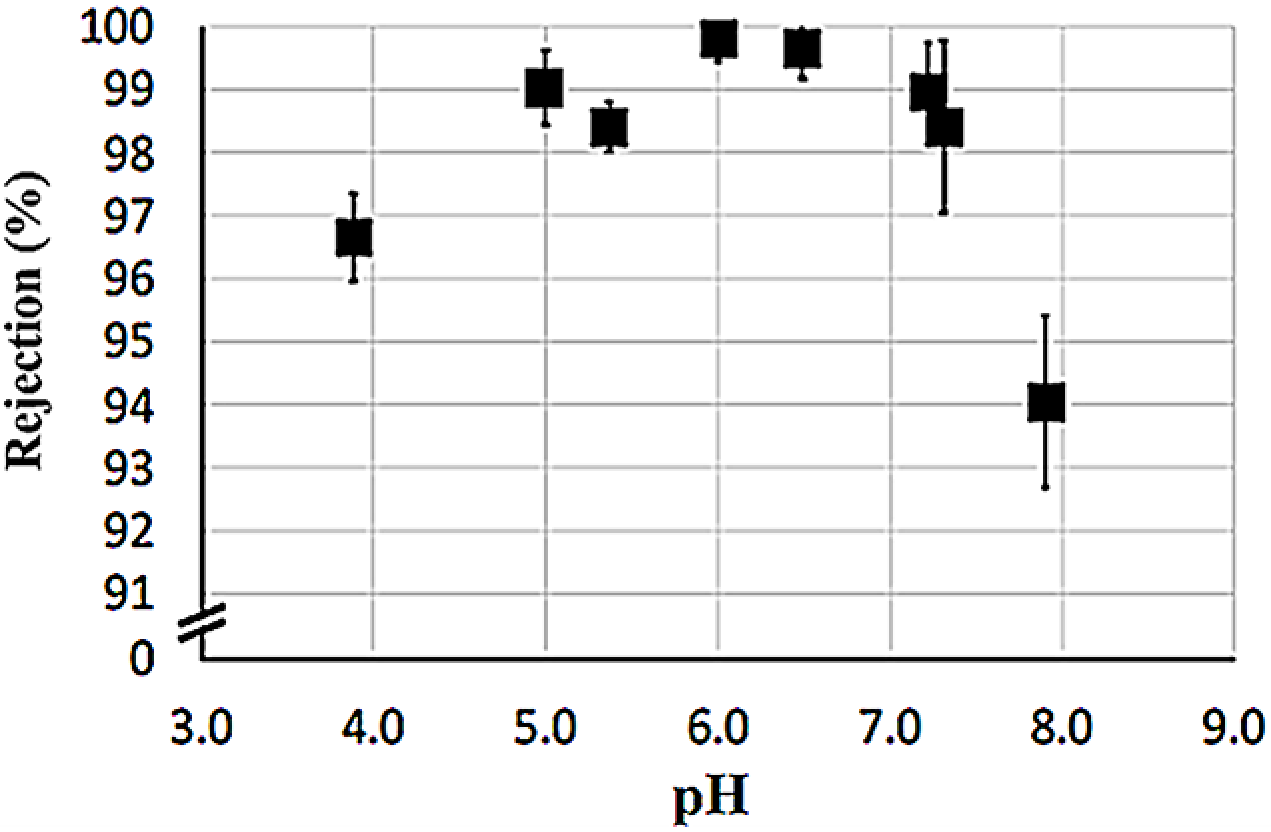


Fig. 14: pH -Rejection efficiency

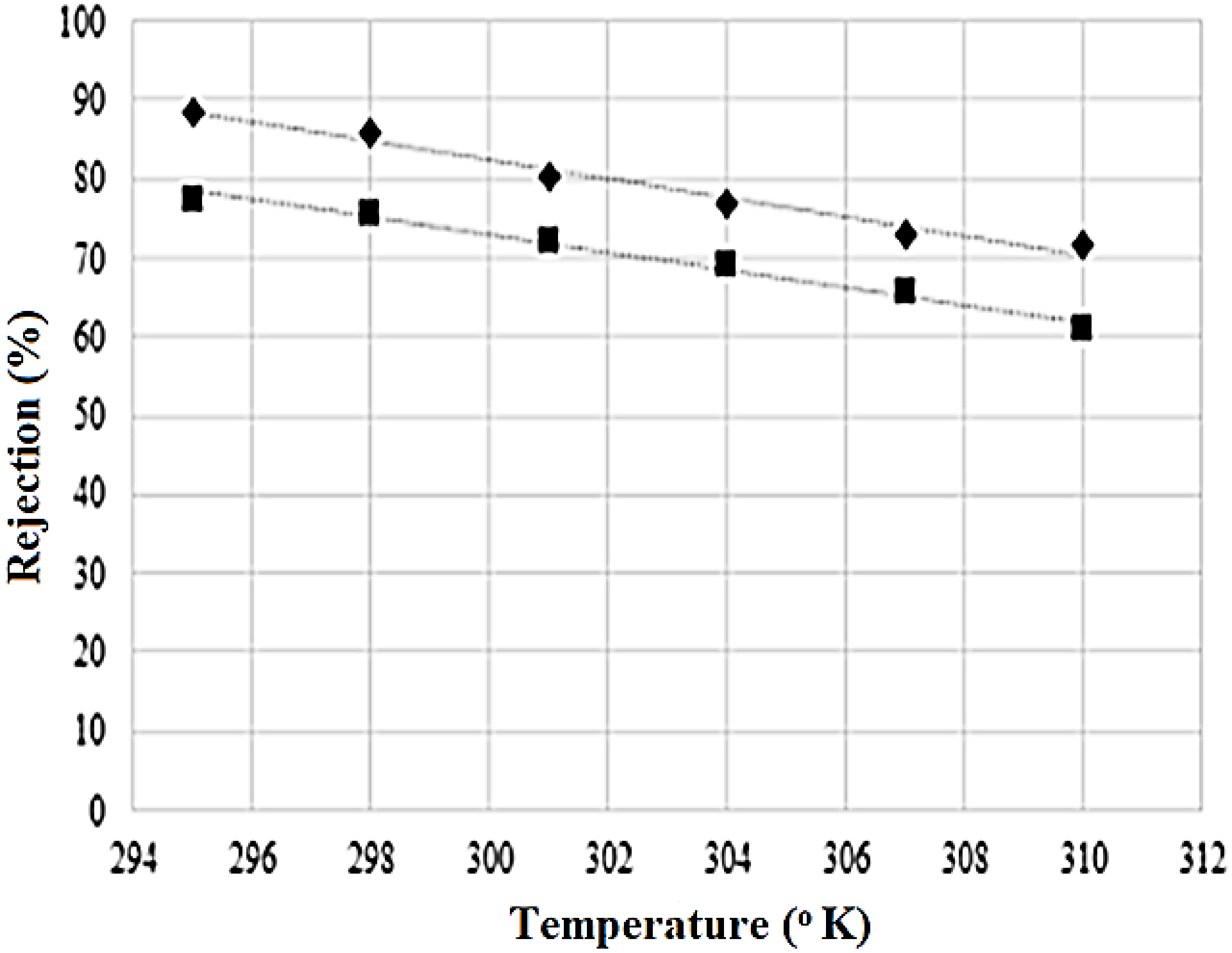


Fig. 15: Temperature - rejection efficiency

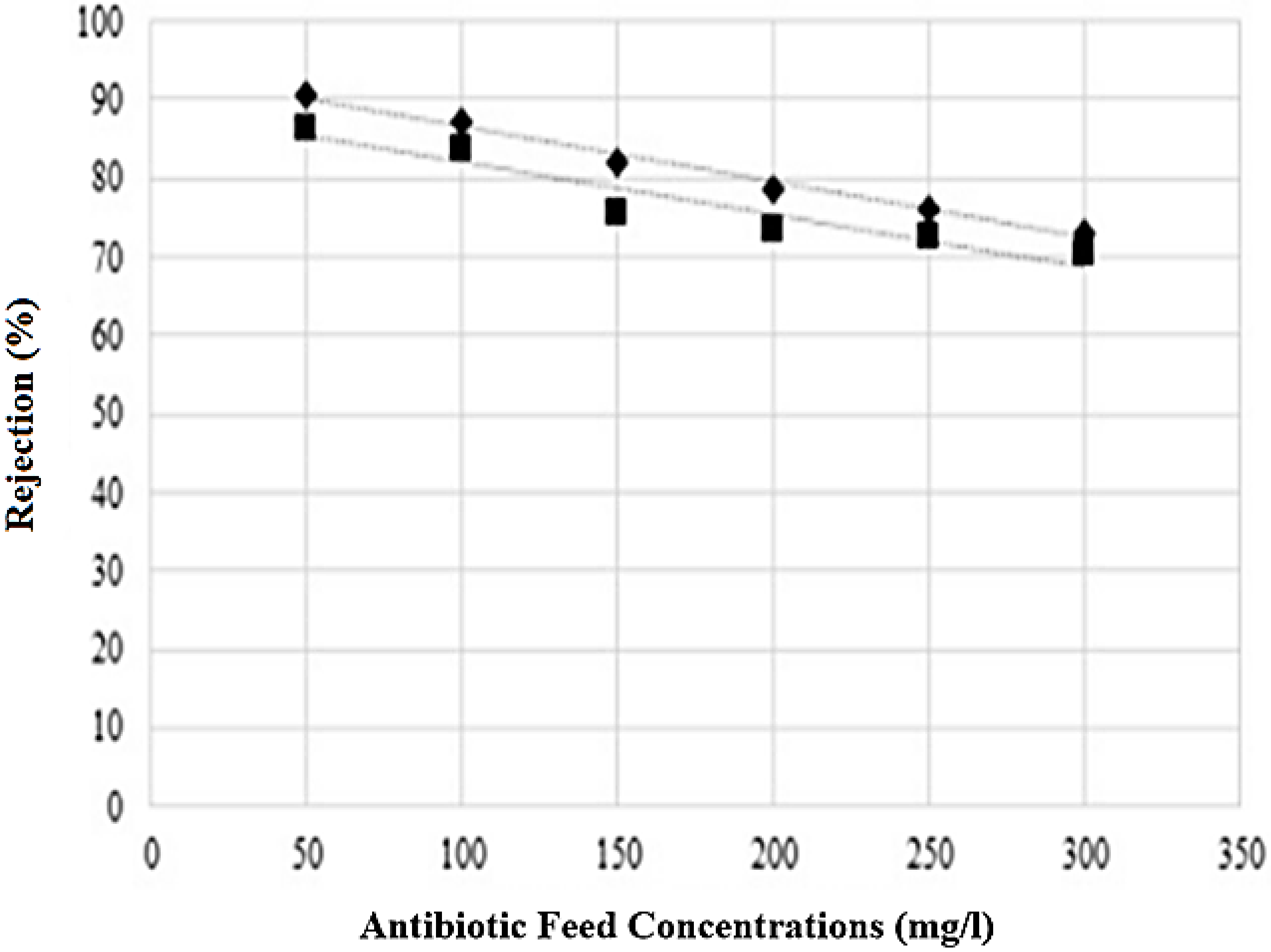


Fig. 16: antibiotic feed concentrations- rejection efficiency

Table 10. Metronidazole and Trimethoprim antibiotic yields in HF-C RO membrane at 100 mg/l initial concentrations

Feed flow (l/h)	J ($l/m^2.h$)	Metronidazole Removal Efficiency in Penetrate (%)	Trimethoprim Removal Efficiency in Penetrate (%)
30	2	88	90
60	3	89	93
90	3.5	95	97
120	3.9	98	98
180	4.2	99	99

Table 11. Metronidazole and Trimethoprim antibiotic yields in HF-O RO membrane at 100 mg/l initial concentrations

Feed Pressure (bar)	J ($l/m^2.h$)	Metronidazole Removal Efficiency in Penetrate (%)	Trimethoprim Removal Efficiency in Penetrate (%)
8	2	80	85
16	3	84	89
20	5	90	94
30	7	99	99
40	9	99	99

Table 12. Recoveries in Retentates for Metronidazole and Trimethoprim Antibiotics

Feed Pressure (bar)	J ($l/m^2.h$)	Metronidazole Recovery in Retentate (%)	Trimethoprim Recovery in Retentate (%)
8	2	84	87
16	3	85	89
20	5	89	96
30	7	99	99
40	9	99	99

Table 13. The antibiotics found in various regions of world

Antibiotics	Concentration (ng/l)	Region	References
Trimethoprim	69.10	WWTP of Portugal	[208]
Trimethoprim	120-550	Wastewater treatment Facilities Wisconsin, USA	[209]
Trimethoprim	60–450	Sewage treatment plants (STPs), Hong Kong, South China	[209], [210]
Metronidazole	2600	Rural hospital in Vietnam	[211]
Trimethoprim	7700	Rural hospital in Vietnam	[211]
Trimethoprim	300	Watersheds of Southeast Queensland, Australia	[212]
Metronidazole	0.17	WWTPs in Durban, South Africa	[213]
Trimethoprim	0.11	WWTPs in Durban, South Africa	[213]
Trimethoprim	170–490	WWTPslocatedinTurku, Tampere and Helsinki, Finland	[214]
Trimethoprim	27–89	Han River, Republic of Korea	[215]
Metronidazole	0.023	WWTPs in metropolitan Regions of Porto Alegre, Capital of Rio Grandedo Sul	[216]

		State, Brazil	
Metronidazole	42	WWTPs in the Po Valley, in Northern Italy	[217]

Table 14. The comparison of removal of antibiotics from wastewater effluents through advanced treatment processes

Antibiotics	Type of Wastewater (location)	Initial concentration	Treatment process	Results/findings (Removal efficiency)	References
Trimethoprim	Model wastewater for veterinary use (Croatia)	10 mg/l	RO membranes: XLE (Dow/FilmTec, Midland MI); HR95PP (Dow/FilmTec,Midland MI); TFC-S (KochMembrane Systems, Wilmington, MA). NF membranes: NF90 (Dow/FilmTec); HL Desal, Osmonics (GE Infrastructure Water Process Techn., Vista, CA). Surface area of membranes: 10.8 cm^2	XLE (98.60%) HR95PP (98.20%) TFC-S (100%) NF90 (99.20%) HL (88.80%)	[218]
Trimethoprim	Missouri River water (Jefferson City)	50 μg/l	Barnstead RO system: Model D2716, Cellulose acetate membrane D2731, Flow: 1.9 l/min.	(90.30%)	[219]
Trimethoprim	CAS effluent (Australia)	930 ng/l	MF/RO plant: receives ≈ 10% of CAS effluent	MF: 85 ng/l; RO:10 ng/l	[220]
Trimethoprim	Secondary effluent	400 ng/l	UF: Dead-end ultrafiltration system (Zenon	UF (0-50%) MF/RO (> 90%)	[221]

	(Beijing, China)		GE), 6 trains of Zee-Weed 1000 membrane, pore size of 0.02 mm (PVDF), flow=23 l/m^2.h, MF/RO: Spiral-wound cross flow module (Filmtec, DOW).		
Trimethoprim	Four matrices: Colorado River from Lake Mead; Ohio River near Louisville; Passaic River near Totowa; Model water.	na	Two PACs: AC800 (Acticarb, Dunnellon, FL) and WPM (Calgon Carbon Corp., Pittsburgh, PA). Contact time=4 h; AC dose=1-20 mg/l	AC800 dose=5 mg/l (93%)	[222]
Trimethoprim	Missouri River water (Jefferson City).	50 µg/l	PAC dose=0-50 mg/l; Contact time=4 h	AC dose=10 mg/l 1(55%) AC dose=20 mgL/l (65%) AC dose=50 mg/l (> 90%)	[223]
Trimethoprim	Hospital wastewater after treatment with MBR	37 ng/l	PAC Norit SAE Super, PAC retention time=2 days, dose=8-43 mg/l, contact time=3-5 days	PAC dose=23 mg/l (> 83%) PAC dose=43 mg/l (> 83%)	[223]
Metronidazole	Hospital wastewater after treatment with MBR	1860 ng/l	PAC Norit SAE Super, PAC retention time=2 days, dose=8-43 mg/l, contact time=3-5 days	PAC dose=8 mg/l (3%) PAC dose=23 mg/l (67%) PAC dose=43	[223]

				mg/l (78%)	
Metronidazole	Motril (Granada)	100-600 mg/l	Three activated carbons (0.1g): Sorbo (S); Merck(M) and carbon prepared by chemical activation of petroleum coke with KOH(C). S (BET=1225 m^2/g); M (BET=1301 m^2/g); C (BET =848 m^2/g)	Adsorption capacity S:1.92 mmol/g M:1.25 mmol/g C:1.68 mmol/g	[224]
Trimethoprim	Secondary effluent (Kloten-Opfikon, Switzerland)	1 µM	Batch experiments, O_3 dose=0.5-5.0 mg/l, DOC=5.3 mg/l	O_3 dose=3 mg/l (100%)	[225]
Trimethoprim	Secondary effluent (German)	0.34 ± 0.04 µg/l	Ozonation-UV treatment plant O_3=100 g/h, O_3 dose=5-15 mg/l, 2 diffuser/PVC bubble columns	O_3 dose: 5-15 mg/l (≥ 85%)	[226]
Trimethoprim	Secondary wastewater effluent (Spain)	na	Batch experiments, O_3 flow=35 l/h, O_3 dose=20 mg/l.	100%	[227]
Trimethoprim	Missouri River water (Jefferson City)	50 µg/l	O_3 dose=7.1 mg/l	0.3 mg/l O_3 at 1.3 min) (>95%)	[228], [229]]
Trimethoprim	CAS and sand filtration (Tokyo)	53.5 ng/l	O_3 dose=3 mg/l, Retention time=27 min	(96%)	[230]
Trimethoprim	CAS effluent (Alcala de Henares, Madrid)	73 ng/l	AirSep AS-12 PSA oxygen generation unit	O_3 dose < 90 mM (100%)	[231]
Trimethoprim	WWTPs in Beijing (China)	400 ng/l	O_3 dose=5 mg/l; Contact time=15 min, MF/RO: Spiral-wound cross flow module	(> 90%)	[232]
Trimethoprim	CAS effluent (Regensd	119 ng/l	O_3 dose=1.6-5.3 mg/l (0.36-	O_3 dose=0.40 g/g DOC	[233], [234]

	orf, Switzerland)		1.16 g/g DOC), Retention time=8-15 min, full scale 6 compartment reactor	(97%) O_3 dose=0.62 g/g DOC (95%) O_3 dose=0.79 g/g DOC (93%)	
Trimethoprim	Simulated effluent from municipal WWTP (SWW) and pre-treated real effluent from municipal WWTP (RE) (Almeria, Spain)	10 mg/l	Pilot compound parabolic collector plant (CPC), $[Fe^{2+}]$ =2 mg/l, $[H_2O_2]$=2.5 mg/l (in doses). SWW:DOC=25 mg/l RE:DOC=10 mg/l	100%	[235]
Trimethoprim	Secondary effluent (Cyprus)	100 µg/l	Pilot scale experiments $[Fe^{2+}]$=5 mg/l, $[H_2O_2]$=75 mg/l, $t_{30WT,n}$ = 20.1 min	(100%)	[232]
Trimethoprim	Missouri River water (Jefferson City).	50 µg/l	Mercury vapor lamp (254 nm), UV dose=0-10000 mJ/cm^2	UV dose:10000 mJ/cm^2 (85%	[236]
Trimethoprim	Effluent from Blue Lake WWTP; Metro WWTP and Lake Josephine (USA)	1µM	Photolysis experiments (Suntest CPS + solar simulator with a UV-Suprax optical filter, 765 W/m^2)	(18%)	[233]
Trimethoprim	Tertiary water from Las Vegas, Nevada (LVNV), Rocky Mountain Region of Colorado (RMCO) and Pinellas County,	38-760 ng/l	Bench scale UV/H_2O_2: two G15T8 germicidal lamps (General Electric, Fair field, CT, USA), UV=300-700 mJ/cm^2; $[H_2O_2]$ = 0-20 mg/l	UV dose=300 mJ/cm^2; $[H_2O_2]$= 20 mg/l (21-67%), UV dose=500 mJ/cm^2; $[H_2O_2]$= 20 mg/l (32-92%) UV	[237], [238]

	Florida (PCFL).			dose=700 mJ/cm^2; [H_2O_2]= 20 mg/l (39-92%)	
Metronidazole	HF-C RO membrane, HF-O RO Membrane and RO membrane	100 mg/l	Antibiotic rejections varied from 94.00% to 99.80% depending on pH rejection was highest at a pH of 6.0, at 99.80% at 22°C for maximum antibiotic yields 60.80% and 71.60% for HF–O and, HF–C. The maximum antibiotic removal rates were 90.70% and 86.40%. 99% Metronidazole removal yield was obtained in HF-C RO membrane, at 100 mg/l initial Metronidazole, at 180 l/h, at 4.2 l/m^2.h. 99% Metronidazole in HF-O RO membrane, at 100 mg/l initial Metronidazole, at 30 bar feed pressure, at 7 l/m^2.h. 99% Metronidazole yield was observed in RO membrane, at 100 mg/l initial Metronidazole, at 30 bar, at 7 l/m^2.h.	99% at HF-C RO membrane 99% HF-O RO membrane 99% RO membrane	In this study
Trimethoprim	HF-C RO membrane HF-O	100 mg/l	Antibiotic rejections varied from	99% at HF-C RO	In this study

	RO Membrane and RO membrane		94.00% to 99.80% depending on pH rejection was highest at a pH of 6.0, at 99.80%. For both membranes, at 22°C for maximum antibiotic yields 60.80% and 71.60% for HF–O and, HF–C. The maximum antibiotic removal rates were 90.70% and 86.40%. 99% Trimethoprim removal yields were obtained in HF-C RO membrane, at 100 mg/l initial Trimethoprim, at 180 l/h, at 4.2 l/m^2.h. 99% Trimethoprim removal yields were observed in HF-O RO membrane, at 100 mg/l initial Trimethoprim, at 30 bar feed pressure, at 7 l/m^2.h. 99% Trimethoprim removal yields were observed in RO membrane, at 100 mg/l initial Trimethoprim, at 30 bar, at 7 l/m^2.h,.	membrane 99% HF-O RO membrane 99% RO membrane	