Contemporary methods for removal of non-steroidal anti-inflammatory drugs in water reclamations

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Abstract

Global water quantity and quality are anticipated to decrease in the coming decades, as a result of both increasing global populations and the effects of climate change. Reusing and recycling water is a key part of reducing the pressure on our existing water supplies and the aquatic environment. However, the occurrence of non-steroidal anti-inflammatory drugs (NSAIDs) in secondary, and in some tertiary, treated effluents and sewage impacted water bodies is one of the major obstacles for the implementation of water reuse. For several decades, NSAIDs have been extensively used for therapeutic purposes in both humans and domestic livestock. The negative effects of NSAIDs on aquatic biota are just beginning to be realised. Currently, intensive treatments are required to remove effectively NSAIDs from recycled treated effluent in order to minimize, or eliminate risks to human health and aquatic environment. In this chapter, we focus the discussion on contemporary methods for NSAID removal including biological, physical, chemical and combined process that may provide a more effective and efficient alternative.

Key words: NSAIDs; Water Reuse; Membrane Process; Advanced Oxidation Process; Integrated Process

1. Introduction

Water reclamation refers to the treatment of used, or waste-water, to the quality suitable for either potable (e.g. drinking), or non-potable (e.g. irrigation, agricultural applications and toilet flushing) use. Water reclamation provides an alternative source of water that gives an extra level of certainty and security to water supplies in the face of a changing climate. In recent years, there has been an upward trajectory in both technology development and full-scale implementation of water reclamation. For example, NEWater, the trade name of reclaimed water produced in Singapore, now operates five full-scale NEWater plants that supply up to 40% of Singapore's water demand (i.e. water fabrication processes, non-potable applications in manufacturing processes as well as air-con cooling towers in commercial buildings). Despite recent advances, there are several barriers to acceptance of water reclamation, including capital and operation costs, presence of emerging contaminants (ECs), as well as community attitudes. Research efforts to reduce the cost, treat and remove ECs and enhance the community awareness are ongoing.

One group of EC of particular concern is the non-steroidal anti-inflammatory drugs (NSAIDs), which include aspirin, ibuprofen, naproxen, diclofenac, paracetamol. NSAIDs are commonly used in our daily life to reduce pain, decrease fever, prevent blood clots and decrease inflammation (Day and Graham 2013). As a result of this usage, the presence of NSAIDs in the environment is beginning to receive considerable attention from the scientific community, public health and ecological conservation authorities (Sutherland and Ralph 2019, Tran et al. 2018). The concerns are mainly due to their potential physicochemical toxicological properties on aquatic biota, although there are currently no environmental protection limits for NSAIDs (Sutherland & Ralph 2019). NSAIDs have been reported in both wastewater and the receiving environment at trace levels of ng/L to μg/L and while these concentrations may not always be harmful to humans, they are still considered to be undesirable with regards to the "precautionary principle" (Nguyen et al. 2018, Sutherland and Ralph 2019, Tran et al. 2018).

Currently, there are no statutory requirements for wastewater and water reclamation plants to monitor the concentrations of NSAIDs in the water and, in most instances, is not routinely monitored for. However, with increased application of water reclamation, and improved understanding on the impacts of NSAIDs in reclaimed water, technologies for the treatment and / or removal of NSAIDs will need to be developed. In this chapter, contemporary technologies for the treatment and / or removal of NSAIDs are reviewed and discussed. In

particular, integrated processes (i.e. combination of biological, physical and chemical process) for NSAID removal are delineated.

2. Contemporary methods for non-steroidal anti-inflammatory drugs removal

2.1 Biological methods

2.1.1 Bacterial based process

Microbial consortia currently play a significant role in conventional activated sludge (CAS), carrying out soluble organic matter removal, nitrification–denitrification, luxury uptake of phosphorus, and volatile fatty acid degradation. Bacteria (the major component of the microbial consortia) with such diverse metabolic capacities are employed in a series of (or single) chambers with differential redox conditions (e.g., anaerobic, anoxic, and aerobic). The potential role of wastewater treatment bacterial consortia in biodegrading NSAIDs is discussed below, and conceptualised in Figure 1.
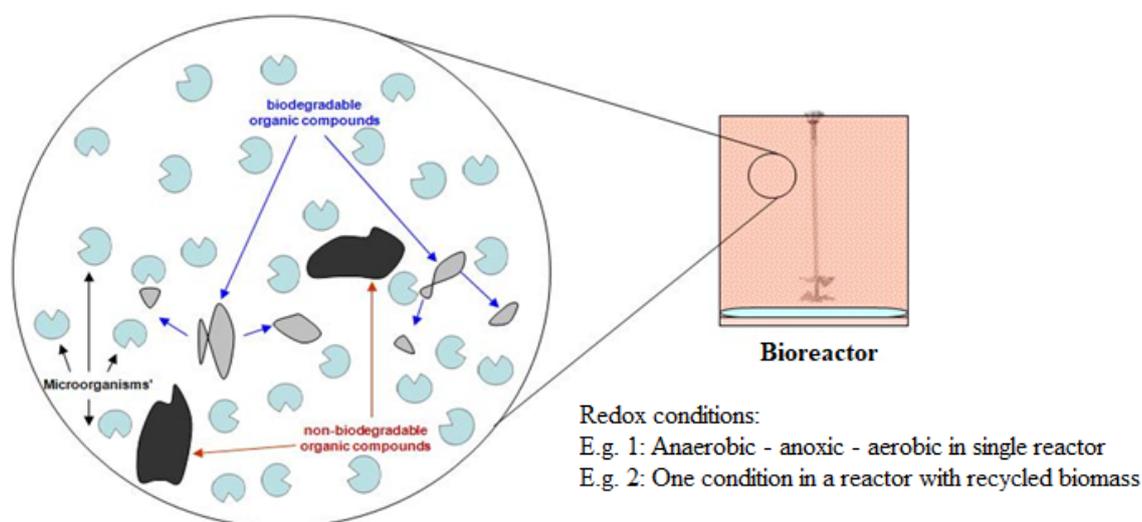

Figure 1: Biodegradation and adsorption concept of NSAIDs by bacteria in conventional activated sludge (CAS), sequencing batch reactor (SBR) and membrane bioreactor (MBR)

CAS is not designed and operated for the treatment and removal of emerging contaminants, including NSAIDs. The removal rates of NSAIDs in CAS are, therefore, often incomplete and significantly variable (Clara et al., 2005; Oppenheimer et al., 2007). For example, CAS remove 10-50% of diclofenac from influents at concentrations of 100 to 5000 µg/L (Jewell et al. 2016, Nguyen et al. 2019), while Kimura et al. (2007) found that ketoprofen and naproxen are not eliminated at all in CAS. In contrast, Tran et al (2009) found that nitrifying bacteria cultures achieved 10-30% improvement in the removal of diclofenac, ibuprofen and naproxen in comparison to CAS. Biodegradation of NSAIDs in CAS can be affected by microbial

community structure and their associated metabolic capabilities (Cui et al. 2016, Nguyen et al. 2018, Wei et al. 2016). Microbial community composition and functionality are influenced by various operating conditions, such as pH, temperature, dissolved oxygen concentration, hydraulic/solid retention time, and the type and concentration of growth substrates. For example, high removals of NSAIDs were observed in CAS systems with higher nitrifying activity (Tran et al. 2013). Higher removal efficiency of some NSAIDs could also be attributed to adsorption to sludge biomass (Radjenovic et al., 2007a). However, compounds which are relatively hydrophilic (*log D < 3.2,* acetaminophen, naproxen, ibuprofen, diclofenac) show limited sorption to sludge (Joss et al., 2006). Therefore, physicochemical properties of a compound can greatly influence its fate and removal during CAS treatment.
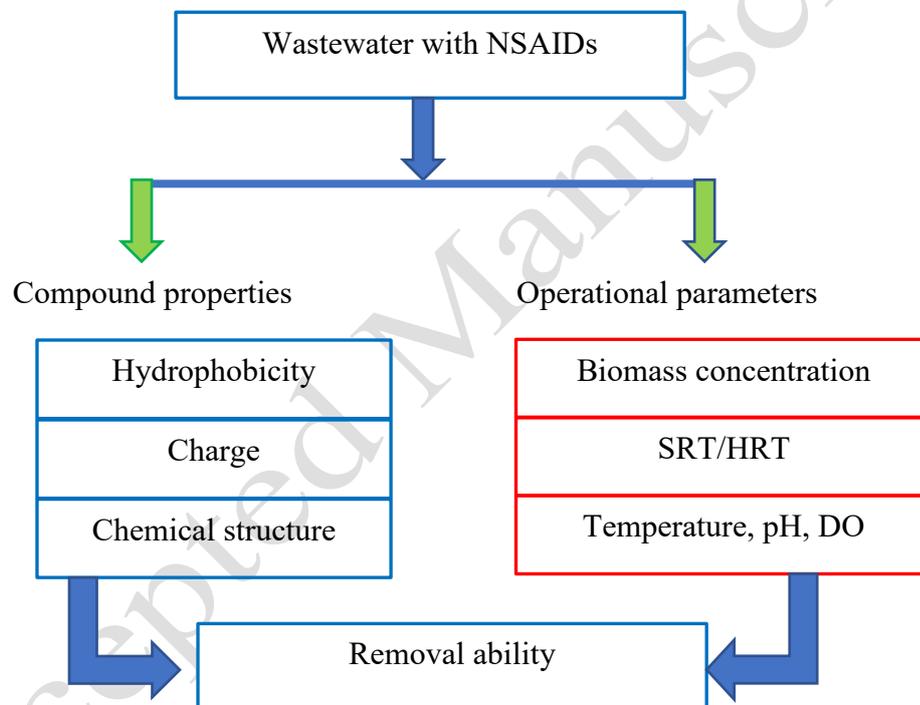
Figure 2. Factors affecting the removal of NSAIDs in the biological process. SRT/HRT stands for sludge retention time and hydraulic retention time, respectively.

Membrane bioreactor (MBR) is a combination of a membrane filtration process with a suspended growth bioreactor. MBR provides effective removal of both organic and inorganic contaminants from municipal and/or industrial wastewaters. MBR produces a more consistent effluent quality compared to that of CAS. The combination of activated sludge and membrane filtration has made MBR a reliable and popular technology for treating many types of wastewaters, particularly those that contain emerging contaminants such as NSAIDs (Bérubé et al. 2010, González et al. 2006, Petrovic et al. 2003, Snyder et al. 2007, Tadkaew et al. 2011).

However, the removal efficiency of ECs such as NSAIDs during MBR treatment depends on the physicochemical properties of the compound and the operational conditions of the wastewater treatment plant (Fig 2) (Hai et al. 2011b, Nguyen et al. 2013a, Nguyen et al. 2013e, Trinh et al. 2012). Physiochemical properties such as hydrophobicity, chemical structure, and compound polarity are likely to be important factors affecting the removal of NSAIDs in MBR systems. Understanding to what extent and how each property affects the removal of NSAIDs would help better design and operate MBR-based WWTPS for controlling NSAIDs-bearing waste streams.

Hydrophobicity is a major factor affecting the sorption of NSAIDs by MBR. Of the many NSAIDs present in wastewater, some are highly hydrophobic and can be readily removed by MBR treatment via biosorption. For example, 80% of nonylphenol was eliminated in a pilot scale MBR process treating landfill leachate (Cirja et al. 2008), largely due to the high hydrophobic nature of nonylphenol (log D = 6.19 at pH 8). In a laboratory-scale study, the removal of hydrophobic compounds (log D >3.2), such as amitriptyline 17β-estradiol, androsterone, and simvastatin, by MBR was greater than 85% at pH 8 (Tadkaew et al. 2011). However, in the same study, the authors found that less than 20% removal was achieved for hydrophilic and moderately hydrophobic compounds (Log D <3.2).

The chemical structure of the NSAIDs can be another major factor affecting their removal by MBR. Compounds with simple chemical structures (e.g., the absence of a branched alkyl chain) are likely easily degraded, whereas compounds with complex structures, or with toxic functional groups (e.g., halogens and nitro group), have a higher resistance to biodegradation, resulting in incomplete degradation (Cirja et al. 2008). In addition, simple structure (e.g., not containing multiple rings) compound with chloride groups (e.g. diclofenac) are less-removable by MBR (Hai et al. 2011a). Cirja et al. (2008) reported a decrease in the degradation rate of aromatic compounds when the number of nitro and chlorine groups increases. Therefore, MBR can represent a promising technology but further research on the removals of NASIDs in relation to MBR-based water reclamation processes is highly desired.

2.1.2 Enzyme based process

The enzymatic treatment process is at the border of traditional chemical and biological processes, where enzymes are the biological catalysts of chemical reactions. The use of enzymes purified from various plant and microbial sources for wastewater treatment has been actively studied in recent years. Enzymatic treatment processes have various advantages over conventional biological and chemical processes such as high substrate specificity, effective

degradation of recalcitrant xenobiotic compounds, high reaction rate, and biodegradability in discharged water (Hai et al. 2013, Kudanga et al. 2010, Modin et al. 2014, Yang et al. 2013). Despite all these advantages, the deployment of enzyme-based technologies in wastewater treatment is impaired by their relatively high production costs, limited scalability, sensitivity to inhibitors and low stability under harsh environmental conditions (Unuofin et al. 2019).

Among the different oxidative enzymes of interest for wastewater treatment, laccases are the most studied (Unuofin et al. 2019). Laccases are multicopper oxidases produced in fungi, bacteria and some algae, which can oxidize phenols and similar substrates and have been shown to degrade NSAID compounds (Ashe et al. 2016, Nguyen et al. 2014, Tran et al. 2010). Laccases catalyze the ring cleavage of aromatic compounds using oxygen as an electron acceptor. Kim at al. (2006) reported 71 – 100% degradation of triclosan (20 μM), while the measured laccase activity increased from 0.3 to 3 U/mL. Tran et al. (2010) reported that 2 mg/L of fungal laccase can degrade 60% of diclofenac and naproxen in the effluent after a 3 h reaction.

Enzyme washout and inactivation are the limitation of enzyme application in water treatment process (Hai et al. 2013, Hai et al. 2012). Depending on the origin of the laccase (fungal or bacterial) and the reaction conditions, the half-life of the enzyme can varies from minutes to days (Brugnari et al. 2018, Margot et al. 2013). The recovery of the enzyme and its reusability are key factors for the feasibility of continuous-mode enzymatic reactors because the high cost of the enzyme may limit their application (Lloret et al. 2012). Enzyme immobilization on a support is one of the approaches to tackle this major limitation. Different supports, namely, polyacrylonitrile, polystyrene, SiO_2 (celite), chitosan and sol-gel has been used to immobilize laccase (Yang et al. 2013). For example, Cabana et al. (2009) immobilized laccase on SiO_2 that degraded nonylphenol, bisphenol A, and triclosan in a packed bed reactor. The use of membranes with pore size smaller than the molecular weight of an enzyme is another approach to prevent enzyme washout from a continuous flow enzymatic reactor. Enzymatic membrane reactor (EMR) allow for continuous feeding and product withdrawal without loss of the enzyme. Depending on the EMR design, the enzymes may be freely circulating in the retentate or immobilized onto the membrane surface or inside its porous structure (Hai et al. 2013, Modin et al. 2014, Rios et al. 2004). An example of enzymatic membrane reactor is presented in Fig 3.
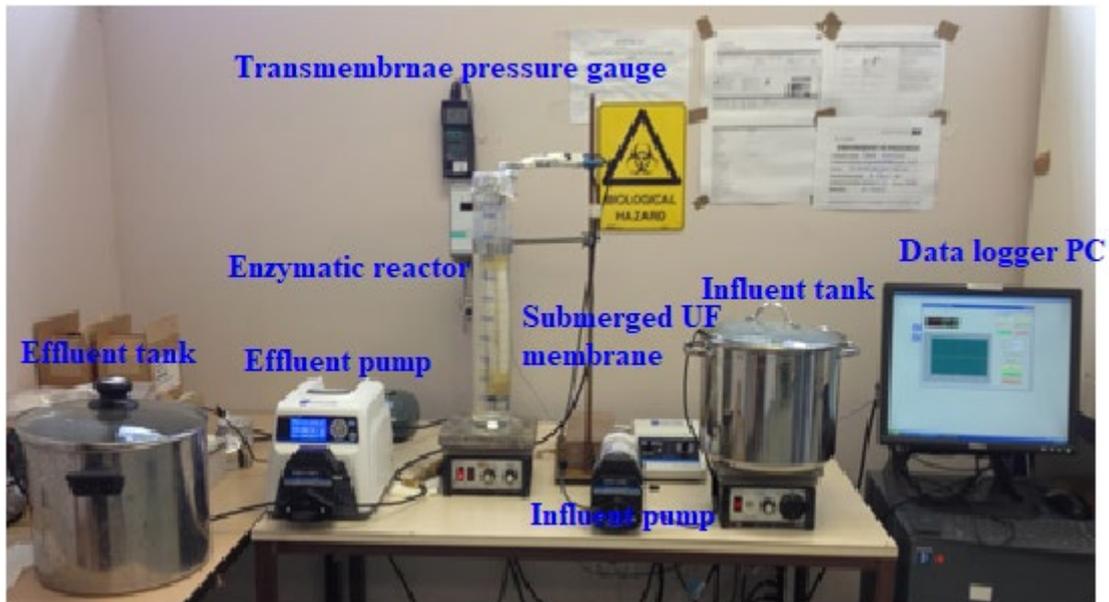
Figure 3: An example of laboratory scale enzymatic membrane reactor.

Nguyen et al (2014) reported 60% removal of diclofenac at influent concentration of 0.5 mg/L. However, enzymatic denaturation continuously occurred despite of a complete retention by the membrane initiated the periodic addition of enzyme. Indeed, the authors proposed a strategy to maintain enzymatic activity by adding 200 μL of the commercial laccase solution per L of the reactor volume every 12 h (equivalent to a laccase dose of 23 mg/L.d). Apart from enzyme reinjection, different methods have been reported to minimize the loss of enzyme during operation of an EMR. For example, ethylenediaminetetraacetic acid and polyethylene glycol, which are believed to possess a protecting role for enzymes, especially under oxidative stress, may be added to an EMR (Andersson et al. 2000, Mendoza et al. 2011). While enzymes hold a great potential, more research is needed to increase their stability before it can be implemented at industrial scale.

2.1.3 Algae based process

Microalgae have demonstrated potential for detoxifying a wide range of organic and inorganic compounds at a range of scales, from laboratory through to full-scale (Sutherland & Ralph 2019). Such detoxification typically occurs via three main pathways; bioadsorption, where the compound is adsorbed to cell wall components, or onto organic extracellular excretions, bio-uptake, where the compound is actively transported into the cell, or biodegradation, where the compound is broken down into simpler molecules through catalytic metabolic degradation (Sutherland & Ralph 2019). While coupling NSAIDs bioremediation

with technologies such as microalgal wastewater treatment could potentially be economically viable, there are several research challenges associated with microalgal NSAIDs biodegradation that need to be overcome before this is a viable option.

Detoxification via microalgal bioadsorption is dependent on the chemical structure of the compound, with hydrophobic, cationic compounds being attracted to the microalgal cell surface through electrostatic interactions, whereas hydrophilic compounds are repelled (Xiong et al. 2017). Once at the cell surface, a number of chemical interactions between the compound and the functional, charged groups on the cell surface may occur, including adsorption reactions, ion exchange reactions with functional groups on the microalgal surface, surface complexation reactions, chelation and micro-precipitation (Dönmez et al. 1999, Schmitt et al. 2001). However, NSAIDs are hydrophilic compounds, meaning that they are anionic, or negatively charged, and have low bioadsorption affinity values with microalgal cells due to the cells also being negatively charged (Sutherland & Ralph 2019). This means that the use of live microalgal cells for NSAIDs bioadsorption is not a viable option but the use of either physically or chemically modified non-living cells may potentially be a viable treatment option. Physical or chemical modifications can be made to the microalgal cell surface that permits hydrophilic interactions between the hydroxyl and carbonyl functional groups of the cell surface and the amino and carbonyl groups in the molecules (Ali et al. 2018). This can result in increased adsorption onto the cell surface for hydrophilic compounds such as NSAIDs (Ali et al. 2018).

Adsorption of a non-NSAID hydrophilic drug (Tramadol) onto non-living microalgal cells was enhanced by 70% through simple chemical treatment (0.1 N NaOH) of microalgal cell surfaces, compared to living microalgae (Ali et al. 2018). Similarly, Coimbra et al. (2018) demonstrated that physically damaged (freeze-drying and grinding) non-living microalgal cells were able to remove between 20 – 28 mg of diclofenac from water per gram of algal biomass, although no live microalgal biomass was used as a comparison.

Microalgal biodegradation involves the transformation of complex compounds into simpler breakdown molecules through either direct catalytic metabolic degradation, in which the compound serves as the carbon source or electron donor / acceptor, or by co-metabolism, in which the compound is degraded by enzymes that are catalyzing other substrates present (Tiwari et al. 2017; Sutherland & Ralph 2019). Microalgal biodegradation can occur either intracellularly, where the compound is taken up by the cell, extracellularly, where enzymes are excreted into the EPS to function as an external digestive system, or a combination of them both (Tiwari et al. 2017). The intracellular biodegradation of compounds involves a complex enzymatic process involving both Phase I and Phase II enzyme families. The main role of Phase

I enzymes in biodegradation is to make the compound more hydrophilic, while the main role of Phase II enzymes is to catalyze the degradation of the compound (Xiong et al. 2018). Microalgal-mediated biodegradation is regarded as being highly complex and the exact role of the multiple enzymes in both the Phase I and Phase II enzyme families are not fully understood (Xiong et al. 2018) and both the enzymes involved, and their respective roles is likely to differ, at least in part, between different microalgal species (Sutherland & Ralph 2019).

There are few studies that have assessed microalgal biodegradation of a limited number of NSAID compounds and despite NSAIDs being hydrophilic, the reported rates of microalgal-mediated biodegradation are low. For example, reported microalgal biodegradation rates of the NSAID diclofenac range from <7% to 22% and requiring at least 9 days exposure (Zhang et al. 2008; Garcia-Rodriguez et al. 2014; Escapa et al. 2016). However, the authors did not state whether the microalgal culture was axenic or not, or if any associated bacteria could have played a role in the reported degradation. Similarly, Ding et al. (2017) found varying rates of degradation of the NSAID, naproxen, between different microalgal species, with *Cymbella* sp. enhancing naproxen degradation by 27% above that in the control, while *Scenedesmus quadricauda* inhibited degradation by 23%, following 30 days incubation. One of the challenges to successful microalgal biodegradation of NSADs is ensuring that the microalgae can uptake the hydrophilic compounds into the cell in the first place, or that extracellular enzymes are expressed in sufficient quantity to induce extracellular degradation. Fungal biodegradation of NSADs has been attributed to extracellular ligninolytic enzymes (e.g., peroxidases, laccases), often in coordination with an internal detoxification process, involving both Phase I and Phase II enzymes, that is mediated by the cytochrome P450 family (CYP), epoxidases and transferases (Marco-Urrea et al. 2010, Olicón-Hernández et al. 2017). These enzymes have also been reported as being present, to some degree, in some microalgae but their efficacy and mode of action (redox mediator) may vary and the exact role these enzymes play in microalgal biodegradation of compounds is unknown (Domaradzka et al. 2015, Olicón-Hernández et al. 2017, Otto et al. 2015, Xiong et al. 2018). There are several strategies that may potentially improve microalgal-mediated biodegradation of NSADs. Firstly, the conditions of the growth media can be optimized to enhance the secretion, activity and stability of native laccases, for instance, Otto et al. (2010) found increased laccase production in microalgae was achieved through the simple addition of copper sulphate. Secondly, the catalytic performance of the native enzymes can be increased by random mutagenesis and/or site-directed mutagenesis (Zhang et al. 2018). Finally, exogeneous enzymes, such as fungal enzymes with high biodegradation capacity, can be recombinantly expressed in microalgae.

Microalgae have higher growth rates than fungi, minimal growth requirements (phototrophy) and therefore potentially lower bioremediation costs (Rasala and Mayfield 2015). For example, Chiaise et al. (2011) succeeded in producing the fungal laccase POX A1b in *Chlamydomonas pitschmannii*, *Chlorella emersonii*, and *Ankistrodesmus braunii* for the remediation of phenolic compounds from olive oil mill wastewaters. However, the genetic engineering of microalgae is in its infancy and numerous limitations such as low transformation efficiencies and low recombinant protein yields still need to be overcome (Rasala and Mayfield 2015). In addition to the current technology limitations, for many countries, legislation around the limited use, or the total ban of, genetically modified organisms (GMO) due to the risks and potential impact on the environment means that, at present, genetically modifying microalgae for NSAIDs biodegradation is not a viable option.

Microalgae play a role in enhancing bacterial biodegradation of NSAIDs. In microalgal-bacteria coupled treatment systems, microalgal photosynthesis provides the necessary oxygen, a key electron acceptor, for aerobic bacterial degradation of the organic compounds, while microalgal released dissolved organic matter (DOM) provides the necessary substrates for bacterial co-metabolism of compounds such as NSAIDs (Sutherland et al. 2015, Sutherland & Ralph 2019). For example, Matamoros et al. (2016) successfully demonstrated microalgal enhancement of bacterial biodegradation of the NSAID, ibuprofen. The authors found that, in the presence of microalgae, bacterial degradation of ibuprofen increased from 15 to 60%, following 3 days of incubation under laboratory conditions (Matamoros et al. 2016). However, the exact mechanism for microalgal enhancement of bacteria degradation of NSAIDs and other organic compounds is not fully understood. Investigations into the interactions between the two organisms and conditions that further enhance coupled degradation would help to enable the development of biological-mediated NSAIDs remediation.

Microalgae may also enhance the photodegradation of NSAIDs through the release of DOM, which comprises of a range of molecules such as hydrophilic organic acids, hemicellulose, humic acids and fulvic acids. This released DOM is thought to enhance photodegradation through various mechanisms, including catabolic processes, redox cycling, via production of hydroxyl radicals, or in inhibiting photo-oxidation by competitive reaction with radicals, resulting in the photosensitised transformation of NSAIDs (Van Trump et al. 2006, Norvill 2016). Photodegradation of the NSAIDs, diclofenac (Matamoros et al. 2016; Villar-Navarro et al. 2018), and ibuprofen (de Wilt et al. 2016; Matamoros et al. 2016), in the presence of microalgal derived DOMs has been successfully demonstrated in both wastewater treatment

high rate algal ponds and photobioreactors, with reported removal rates between 82 – 99% compared to 7% for biodegradation.

Options for cost-effective microalgae degradation of NSAIDs are limited due to the hydrophilic nature of the compounds and the negatively charged cell surface of the microalgae. The most promising options include coupled microalgal-bacteria degradation or enhancement of photodegradation. Further research into the mechanisms behind microalgal-assisted degradation is needed in order to optimise the treatment system.

2.1.4 Fungi based process

Considerable research has been devoted to test the performance of different white-rot fungi (WRF) for the removal of NSAID compounds. For example, Tran et al. (2010) observed the complete removal of the NSAID compounds ibuprofen, naproxen, diclofenac and ketoprofen by a white-rot fungus *Trametes versicolor* over 7 days of inoculation. Cajthaml et al. (2009) investigated the performance of eight different strains of WRF for the removal of several NSAID compounds, including diclofenac, ibuprofen and ketoprofen while almost all tested fungal strains were able to degrade the selected NSAIDs, to some degree, the strains *Irpex. lacteus* and *Pleurotus ostreatus* provided the highest removal efficiency of NSAIDs (i.e. 90% and 80%, respectively), after 7 days of incubation. Marco-Urrea et al. (2009) found that four different strains of WRF were able to completely remove the NSAID ibuprofen from culture but were ineffective at removing carbamazepine and clofibric acid. In another study by Marco-Urrea et al. (2010b), the WRF strain *T. versicolor* was capable of removing diclofenac (70%) from the culture. The authors suggested that, at least two different mechanisms were involved in the degradation of diclofenac; (i) cytochrome P450 system and (ii) laccase catalysis. However, to date the application of fungi for wastewater treatment is still at laboratory scale studies as scale-up of fungal cultures is challenging.

2.2. Advanced oxidation process

Advanced oxidation processes (AOPs) aim at chemically generating strong oxidants (e.g. hydroxyl radicals) to transform persistent organic compounds such as NSAIDs into biodegradable substances. The hydroxyl radicals ($^{\bullet}OH$) can be generated using catalysts (electrodes, metal oxides), irradiation (UV light, solar light, ultrasounds) and strong oxidising agents like hydrogen peroxide (H_2O_2) or ozone (O_3). These methods can be used separately or in combination. AOPs have been used to remove organic pollutants from reclaimed effluent

and ground water (Azbar et al. 2004). Numerous studies in the literature have demonstrated the effectiveness as well as limitation of AOPs for the removal of trace organic contaminants from wastewater (Andreozzi et al. 2004, Contreras et al. 2003, Esplugas et al. 2002, Klavarioti et al. 2009, Ternes et al. 2003). In this Chapter, we focused mostly on ozone and UV oxidation.

2.2.1. Ozonation

Ozonation process involves two reaction mechanisms i) direct reaction by ozone and ii) indirect reaction by OH radicals during ozone reactions (Rizzo et al. 2019). While ozone reacts selectively with electron-rich moieties compounds, the OH radicals can react with wide range of aromatic compounds including NSAIDs (Lee et al. 2013). Regardless of the reaction mechanisms, the required ozone treatment dose is proportional to the bulk organic content in the wastewater. Ozone (O_3) has been shown to degrade trace organic contaminants during wastewater treatment and water reuse applications (Fujioka et al. 2014, Zhang et al. 2008). Ozone reacts with TrOC through either direct reactions or through the formation of free radicals, including the hydroxyl radical ($^{\bullet}OH$) (Wert et al. 2009). Oxidation using ozone can achieve >92% removal of a number of pharmaceuticals, including NSAIDS, and pesticides such as ofloxacin, sulfamethoxazole, propranolol, carbamazepine, clofibric acid, diclofenac, atrazine and diuron (Andreozzi et al. 2004, Maldonado et al. 2006, Ternes et al. 2003). However, a number of other pharmaceuticals and personal care products (e.g. ibuprofen, naproxen, caffeine, and tonalide) could not be oxidized using the same process (Ternes et al. 2003).

2.2.2. UV oxidation

UV oxidation generates hydroxyl radicals by photolysis. Huber et al. (2003) demonstrated that UV treatment alone resulted in 75, 13, and 7% removal of diclofenac, iopromide, and sulfamethoxazole, respectively. Complete removal of several pharmaceuticals (e.g. ofloxacin, sulfamethoxazole, propranolol, carbamazepine, clofibric acid and diclofenac) was achieved using the combination of hydrogen peroxide and UV radiation (Andreozzi et al. 2004), although only 30-40% of ibuprofen, diphenhydramine, phenazone, and phenytoin could be removed using this method (Yuan et al. 2009).

The AOPs are effective at treating NSAIDs, but the operating cost of AOPs is high due to the requirements in chemicals and energy (Comninellis et al. 2008). It therefore limits their applications as a wide-spread solution of NSAIDs remediation.

2.3   Membrane separation process

High pressure membrane filtration, including nanofiltration (NF) and reverse osmosis (RO), has been widely used to remove organic pollutants including NSAIDs (Agenson et al. 2003, Hofman et al. 2007, Nghiem and Schäfer 2002, Vogel et al. 2010, Xu et al. 2006). NF/RO membranes can reject TrOCs mainly due to size exclusion, electrostatic exclusion and adsorption on the membrane (Nghiem et al. 2004a, Nguyen et al. 2013b). In a full scale study, Verliefde et al. (2008) reported a high rejection (>95%) of most investigated NSAIDs by the Triseps (X20 and ACM5) and Hydranautics (ESPA1 and ESPA4) RO membranes. In another study, an NF270 membrane achieved a high rate of rejection for charged pharmaceuticals, i.e., 96% for ibuprofen, where removal NSAIDs was enhanced by charge repulsion (Nghiem 2005). However, the rejection rate of some uncharged and small molecular weight organic contaminants by NF/RO membrane can be low (Agus and Sedlak 2010).

The low rejection of some small molecular weight and uncharged NSAIDs by NF/RO membranes, as mentioned above, has been widely reported in the literature (Agus and Sedlak 2010, Bellona et al. 2004, Kimura et al. 2003, Nghiem et al. 2004b, Steinle-Darling et al. 2010, Xu et al. 2005). For example, at extended stages of filtration there was poor rejection of chloroform and bromoform by RO (e.g., TFC-HR and XLE) and NF membranes (e.g., NF-90 and TFC-SR2) (Xu et al. 2005). Chloroform and bromoform are both neutral and have a molecular weight of 119.4 and 252.7 g/mol, respectively. The charge of the trace organic contaminants and that on the membrane can play a significant role in the rejection of TrOCs. For example, rejection of a charged compound by NF/RO membranes is usually higher than for a neutral compound with the same molecular weight or size (Xu et al. 2005). Since most pharmaceuticals are negatively charged particularly at neutral pH, a considerable number of these compounds may be completely rejected by charge repulsion between the compound and membrane charges (Nghiem 2005). Xu et al. (2005) reported that highly negative surface charge membranes such as the loose NF200 membrane, with a molecular weight cut-off (MWCO) of 300 g/mol, could reject more than 89% of low molecular weight negatively charged compounds such as ibuprofen. A high rejection of other pharmaceuticals such as dichloroacetic acid (91%) and trichloroacetic acid (94%) was also achieved using the ESNA (NF) and RO-XLE (RO) membranes (Kimura et al. 2003).

Membranes with a high degree of desalting showed the highest rejection of most NSAIDs (Bellona et al. 2004). A UTC60 aromatic polyamide membrane (an NF membrane) which has a low NaCl rejection (55%), demonstrated a poor rejection of several trace organics such as 47% for bisphenol A and 5% for chloroform (Agenson et al. 2003). Moreover, higher

membrane roughness has been highly correlated with a lower rejection of large organic contaminants (Bellona et al. 2004).

The hydrophobicity and charge of an active layer of the membrane can also affect the rejection of various NSAIDs (Xu et al. 2005). The surface hydrophobicity of a membrane can be determined by measuring the contact angle. The rejection of some organics could be improved by increasing the hydrophobicity of the membrane because it reduces the affinity between the neutral organic solute and the surface of the membrane (Ben-David et al. 2010). Furthermore, the amount of charge in the surface of the membrane affects the degree of electrostatic repulsion and rejection of negatively charged solutes that are subjected to dynamic property changes during the membrane process (Xu et al. 2005). For example, Bellona and Drewes (2005) studied the rejection of negatively charged organic acids (2-naphthalenesulfonic acid and 1,4-dinaphthalenesulfonic acid) by negatively charged NF membranes (e.g., NF-90 and NF-200). According to their findings, the rejection was larger than expected based on steric exclusion, and was mainly driven by the surface charge of the membrane and correlated with the degree of ionization of these compounds (Bellona and Drewes 2005).

Operational parameters such as feed solution pH, salinity, temperature, pressure, and cross-flow velocity can influence the rejection of NSAIDs by NF/RO membranes. The feed solution pH can govern the speciation of ionisable NSAIDs (and to a lesser extent, the membrane surface charge) and thus their rejection. For instance, Bellona et al. (2004) claimed that when using NF/RO at pH values between 3 and 9, more than 90% of trace organics such as estrone can be rejected. Sulfamethoxazole and ibuprofen are also highly soluble at high pH (in the alkaline region) where the compounds are negatively charged, but when the solution pH decreases, their solubility decreases sharply (Nghiem and Hawkes 2007). Nghiem and Hawks (2007) reported an almost complete rejection of sulfamethoxazole using the NF-270 membrane at a pH above 8.

Temperature is another parameter that can affect the water flux and rejection of NSAIDs (Steinle-Darling et al. 2010). Increasing the feed temperature can lead to a change in the structure and morphology of the polymer matrix, causing an increase in the mean pore radius and MWCO (Sharma et al. 2003). An increase in the solubility of some NSAIDs can occur due to the increase in the temperature of the surrounding solution (Wei et al. 2011).

Operating pressure and cross-flow velocity are important factors which can affect the volume and quality of a product. An increase in the operating pressure can reduce the shielding of negative charges on the surface of a membrane, which makes repulsion more effective and

enhances the rejection of negatively charged contaminants by NF/RO membranes (Binyam et al. 2009). Also, the permeate flux increases with cross-flow velocity over a range of operating conditions because increasing the cross-flow velocity increases the flux and rejection of NSAIDs due to a reduction in concentration polarization (Binyam et al. 2009, Steinle-Darling and Reinhard 2008).

The hydrophobicity of both contaminant and membrane can affect the rejection of NSAIDs by NF/RO membranes. Contaminants such as steroid hormones with a high hydrophobicity (Log D >3.2), can adsorb onto the surface of the membrane due to hydrophobic–hydrophobic interactions (Ng and Elimelech 2004, Verliefde et al. 2008). Nghiem et al. (2004b) reported that the rejection of natural hormones by the NF270 and NF90 membranes was lower than that expected based on steric hindrance. They explained this phenomenon by the adsorption of these hydrophobic compounds onto the surface of the membrane followed by diffusion through its polymeric matrix (Steinle-Darling et al. 2010). The membrane separation processes (i.e. NF/RO) has demonstrated excellent capacity in removing NSAID compounds, however their inherent operation conditions (high pressure, membrane fouling) requires pretreatment process.

2.4   Integrated process

Biological based processes are the most pragmatic approach for wastewater treatment. However, the biological treatment alone is not effective for NSAIDs compounds (Section 2.1) for water reuse purposes. Because the biological treatment processes can reduce large bulk organic content, research reports a significant synergy when it is integrated with other physical (i.e. membrane filtration and adsorption) and chemical (i.e. advanced oxidation) based processes.

2.4.1 Biological treatment coupled membrane filtration

A complementation between membrane filtration and biological degradation of NSAIDs in hybrid systems such as MBR coupled NF/RO has been successfully demonstrated (Alturki et al. 2010, Hai et al. 2016, Nguyen et al. 2013b) (Fig. 4). Alturki et al. (2010) reported that hydrophilic NSAIDs, which passed through the MBR, were effectively removed by the following NF/RO membranes. For example, the MBR-RO removed naproxen at 100% of which MBR and RO contributed 40 and 60%, respectively. The authors also reported the removal of 40 compounds to below the analytical detection limit (10 ng/L), thus the final effluent may meet the reuse water quality standard (Alturki et al. 2010). Nguyen et al. (2013b)

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reported that MBR and NF/RO removed NSAIDs based on different mechanisms. Thus, hybrid systems are very effective at removing NSAIDs. Apart from NSAIDs removal, the hybrid system also offers a stable permeate flux of NF/RO membranes over extended operating periods (Comerton et al. 2005, Dialynas and Diamadopoulos 2009, Jacob et al. 2010, Qin et al. 2006, Tam et al. 2007).
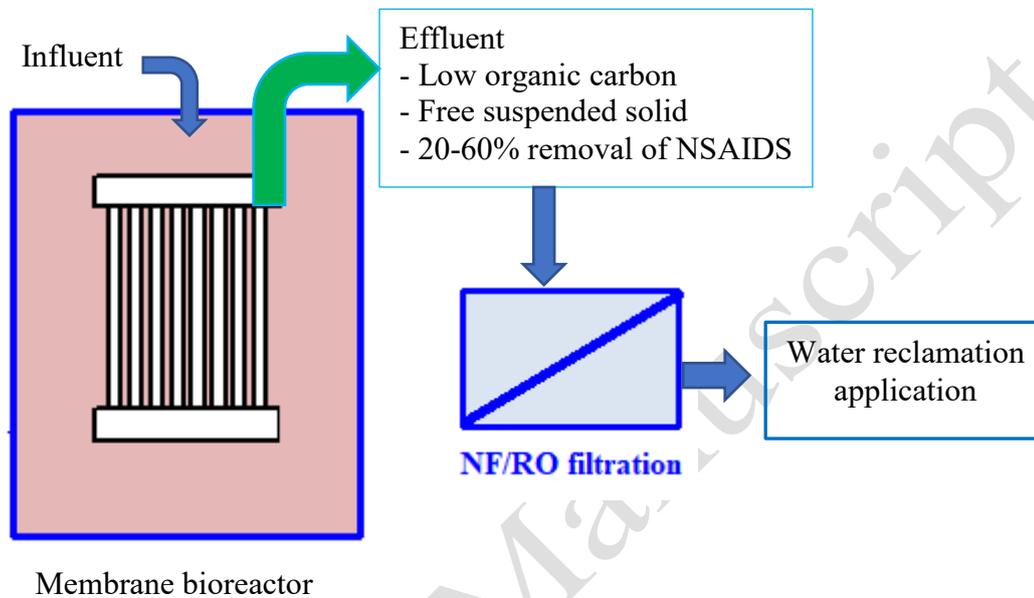

Figure 4. Schematic diagram of the combined membrane bioreactor (MBR) and nanofiltration (NF)/reverse osmosis (RO) process.

2.4.2 Biological treatment coupled activated carbon adsorption

It is well known that activated carbon is one of the most effective adsorbents for the removal of taste, color, and odor causing organic pollutants from aqueous or gaseous phases. Activated carbon is widely applied as a commercial adsorbent in the purification of water and air (Halim et al. 2010). It is also widely used for treatment of taste and odor. Treatment with activated carbon has proved to be efficient for removal of geosmin and 2-MIB (Cook et al. 2001). Zhang et al., (2011) demonstrated that granular activated carbon (GAC) is an excellent adsorbent for two algal odorants dimethyl trisulfide and β- cyclocitral. Activated carbon has been widely studied for treating landfill leachate wastewater. AC has been also investigated intensively for treatment of dye wastewater (Mall et al. 2005, Singh et al. 2003, Yeh and Thomas 1995). The

results indicated that activated carbon could be employed for efficient removal of dyes from wastewater (Gamez et al. 2007, Hai et al. 2008, Yeh and Thomas 1995).

PAC and GAC are frequently applied in drinking water treatment for removal of natural or synthetic organic compounds (SOCs) e.g., pesticides (Matsui et al. 2002). Recently several studies have evaluated adsorption of other trace organics (PhACs, EDCs) on activated carbon both under laboratory conditions and surveys at full- scale drinking water treatment plants (Kim et al. 2010, Ternes et al. 2002). For example, Hernández-Leal et al., (2011) reported complete adsorption of all studied trace organics (bisphenol-A, benzophenone-3, hexylcinnamic aldehyde, 4-methylbenzylidene-camphor (4MBC), triclosan, galaxolide, and ethylhexyl methoxycinnamate) onto PAC in batch tests with milli-Q water spiked with 100 - 1600 µg/ L of trace organics at a PAC dosage of 1.25 g/ L and contact time of 5 minutes.

GAC has a relatively larger particle size compared to PAC and, consequently, presents a relatively smaller surface area. Nevertheless, GAC has long been used in the removal of traditional organic contaminants such as pesticides (Matsui et al. 2002). GAC has been proposed as a potential treatment method to aid in the effective removal of emerging contaminants, particularly EDCs in wastewater treatment. A significant reduction in the concentration of steroidal estrogens (43-64%), mebeverine (84-99%) has been achieved in a full-scale granular activated carbon plant (Grover et al. 2010). In a study by Hernández-Leal et al., (2011) , three GAC columns were operated to treat aerobically treated grey water which was spiked with the above emerging contaminants in the range of 0.1 - 10 µg/ L at a flow rate of 0.5 bed volumes (BV)/h. They observed more than 72% removal of all compounds (bisphenol-A, hexylcinnamic aldehyde, 4-methylbenzylidene-camphor (4MBC), benzophenone-3 (BP3), triclosan, galaxolide, and ethylhexyl methoxycinnamate). Tanghe et al., (2001) reported that at least 100 mg/ g of nonyphenol adsorbed on GAC in an adsorption test. A few studies have investigated GAC adsorption as an option for tertiary treatment of conventional biologically treated wastewater (Dickenson and Drewes 2010, Grover et al. 2010), for example, Grover et al., (2010) reported that a full scale GAC plant could reduce above 60% of steroidal estrogens in sewage effluent.

Activated carbon adsorption can be coupled with a biological treatment in two different configurations i) addition of powdered activated carbon (PAC) directly in the bioreactor (Li et al. 2011, Nguyen et al. 2013d, Serrano et al. 2011, Yang et al. 2010), and ii) post-treatment of the bioreactor (e.g. MBR) permeate using either a granular activated carbon (GAC) column (Navaratna et al. 2012, Nguyen et al. 2012) or a continuously mixed reactor containing a slurry

of PAC (Lipp et al. 2012). Research results have suggested that addition of PAC enhanced NSAID removal by initial adsorption and subsequently enhance contact time with biological agents in the reactor for biodegradation. While the removal by initial adsorption has been easily demonstrated in a number of studies, the enhancement of biodegradation is an assumption. Nguyen et al. (2013a) observed an immediate improvement in naproxen, diclofenac, ketoprofen and ibuprofen removal after PAC addition to the MBR. The NSAID adsorbed onto PAC can be efficiently removed by the PAC – MBR system because of the complete retention of the sludge by the membrane (Li et al. 2011, Nguyen et al. 2013a).

In the second configuration, a GAC post-treatment can specifically target the residual NSAID compounds in the MBR permeate without significant competition or interference from the bulk organics (Nguyen et al. 2013a). Nevertheless, periodic regeneration/replenishment of the activated carbon is necessary, because over an extended operating period fouling and substrate deterioration is inevitable.

2.4.3 Biological treatment coupled with advanced oxidation process

Advanced oxidation processes (UV or ozonation) are very effective at oxidizing NSAID compounds but are mostly used as a polishing or disinfection steps. Packer et al. (2003) observed a rapid and mild photodegradation of diclofenac and ketoprofen, respectively. Nguyen et al. (2013c) reported almost 100% removal of pentachlorophenol and triclosan within 7.5 min of UV 254 nm exposure. These compounds are quite recalcitrant to biological treatment. The benefit of combining biological treatment (e.g. MBR) with UV oxidation therefore can be shown by examining the removal of these compounds. For example, diclofenac was poorly removed by the MBR (40%). By contrast, treatment by UV system following MBR attained exceptionally high removal efficiency (i.e. 98%). The MBR also provides a low background organic matter content and suspended solids free influent which is highly suitable as influent for UV oxidation process.

The efficiency of a combined MBR and ozonation process for NSAID removal has been assessed in different operational modes. de Wilt et al. (2018) reported the limitation of removing ibuprofen, naproxen and diclofenac by individual biological and ozonation process. In details, 14 and 80% removal of diclofenac was achieved by biological and ozonation process, respectively. However, their combination resulted in >99% removal, indicating the complementary impact. The combination also reduced the ozone dose due to the decrease in

organic matter of the influent (de Wilt et al. 2018). Ikehata et al. (2008) also reported that diclofenac was reactive towards ozone.

Apart from the MBR-ozonation, studies have reported the integrated MBR with ozonation (i.e. ozone is dosed directly in the reactor) (Pollice et al. 2012). Positive results include virtue of higher removal of ozonation by-products and lower ozone treatment dose requirement. A similar observation was reported by Laera et al. (2012), where the ozonation by-product was 20-fold lower in the final effluent of the integrated process than in that of MBR-post ozonation process. Mascolo et al. (2010) achieved a similar removal of an anti-viral drug (acyclovir) by both the configurations, however, the integrated process again was more beneficial in terms of removal of specific ozonation by-products.

3. Conclusions and outlooks

The necessity of water reclamation is growing, driven by a stress on water supply and increased statutory regulations with respect to wastewater effluent quality. More water reclamation schemes in regions with restricted freshwater resources for both non-potable and indirect potable purpose are on trial and full-scale operation (e.g. in Singapore). As of today, membrane filtration processes such as NF and RO continue to play a central role in propagating the success of water reclamation due to the robust performance on the removal of emerging contaminants (e.g. NSAIDs). In future, integrated processes (i.e. to combine the advantages of biological and chemical/mechanical processes) should be at the forefront of research considerations as such processes have the potential to reduce the cost and enhance the application of water reclamation.

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