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**Title:**

A Review on Removing Pharmaceutical Contaminants from Wastewater by Constructed Wetlands: Design, Performance and Mechanism

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# A Review on Removing Pharmaceutical Contaminants from Wastewater by Constructed Wetlands: Design, Performance and Mechanism

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**Abstract:** This paper presents a comprehensive review of the current state of research activities on the application of constructed wetlands for removing pharmaceutical contaminants from wastewater. The focus of the review was placed on the application of constructed wetlands as an alternative secondary wastewater treatment system or as a wastewater polishing treatment system. The design parameters of the reported constructed wetlands including the physical configuration, hydraulic mode, vegetation species, and targeting pharmaceuticals were summarized. The removal efficiencies of pharmaceuticals under different conditions in the wetlands were evaluated at the macroscopic level. In addition, the importance of the three main components of constructed wetlands (substrate, plants and microbes) for pharmaceutical removal was analyzed to elucidate the possible removal mechanisms involved. There is a general consensus among many researchers that constructed wetlands hold great potential of being used as an alternative secondary wastewater treatment system or as a wastewater polishing treatment system for the removal of pharmaceuticals, but relevant reported studies are scarce and are not conclusive in their findings. Current knowledge is limited on the removal efficiencies of pharmaceuticals in constructed wetlands, the removal mechanisms involved, the toxicity to constructed wetlands caused by pharmaceuticals, and the influences of certain important parameters (configuration design, hydraulic mode, temperature and seasonality, pH, oxygen and redox potential, etc.). This review promotes further research on these issues to provide more and better convincing evidences for the function and performance of larger laboratory-scale, pilot-scale or full-scale constructed wetlands.

**Key words:** constructed wetland; pharmaceutical; emerging pollutant; wastewater treatment

## Contents

## 1. Introduction

Pharmaceuticals of different therapeutic classes are consumed in large number annually around the world to prevent, diagnose, mitigate or cure diseases in humans as well as animals (Jones et al., 2001; Jones et al., 2007; Uslu et al., 2013; Zhang et al., 2008). In recent years, with the advancement in analytical techniques of trace pharmaceutical residues, many studies have demonstrated the widespread occurrence of pharmaceuticals in water environment (Fent et al., 2006; Jiang et al., 2013; Jones et al., 2001; Uslu et al., 2013; Verlicchi et al., 2012; Yang et al., 2011). Increasing concern has been raised on this issue to investigate the source, behavior, fate, risk, and control of such emerging pollutants (Jiang et al., 2013; Pal et al., 2010; Richardson, 2007; Zhang et al., 2013b).

The main route of pharmaceuticals brought into water environment is through the municipal wastewater. Many pharmaceuticals are not completely metabolized and ingested in the body of humans and animals, as a result, pharmaceutical metabolites, conjugates and their native forms are excreted with urine and faeces into sewage system (Carballa et al., 2004; Jones et al., 2002; Zhang et al., 2008). In households, the unused and expired pharmaceuticals are usually disposed with normal household waste or discarded into sink or toilets (Zhang et al., 2008). Those pharmaceuticals flushed down the sink or toilets are introduced to the sewage system. Besides, to a minor but relevant extent, the wastewater from hospitals or pharmaceutical manufacturers also contributes to the total loads of pharmaceuticals in municipal wastewater (Fent et al., 2006; Jones et al., 2001; Santos et al., 2013; Saussereau et al., 2013). In the municipal wastewater treatment plants (WWTPs) where the conventional treatment technologies are not specially designed for elimination of pharmaceuticals, it is found that most pharmaceuticals cannot be readily and fully

removed (Carballa et al., 2004; Jiang et al., 2013; Joss et al., 2006; Lindqvist et al., 2005; Paxéus, 2004; Petrie et al., 2013; Repice et al., 2013; Sim et al., 2010; Uslu et al., 2013; Vidal-Dorsch et al., 2012). Consequently, various kinds of pharmaceuticals and their metabolites are released into surface water, ground water, coastal water, and even drinking water via WWTPs' effluent (Jelic et al., 2011; Kim et al., 2007; Lindqvist et al., 2005; Uslu et al., 2013; Vidal-Dorsch et al., 2012; Vieno et al., 2005).

In addition to the municipal wastewater as the major pathway of pharmaceutical compounds entering fresh or marine water environments, there exist some other direct pathways including the household wastewater from small communities, the runoff or wastewater effluent from animal feedlots, and the rural wastewater (Anderson et al., 2013; Carvalho et al., 2013; Focazio et al., 2008; Matamoros et al., 2009a).

Upon entering the water environment, the pharmaceutical compounds and their metabolites became potential risks to the health of aquatic life and human beings even at trace levels in the water environment (Carlsson et al., 2006; Corcoran et al., 2010; Farré et al., 2008; Fent et al., 2006; Gagné et al., 2006; Pomati et al., 2006; Zuccato et al., 2006). The adverse effects on aquatic communities include the feminization of male fish (Corcoran et al., 2010; Fent et al., 2006), impairment of renal, gill and liver in fish (Fent et al., 2006; Gagné et al., 2006), development of pathogen resistance (Zuccato et al., 2006), and decrease in plankton diversity (Farré et al., 2008). In the case of the toxic impacts on human health, the liver of humans has been found the degenerative and inflammatory reactions induced by the exposure to diclofenac (a type of analgesic/anti-inflammatory pharmaceutical) (Fent et al., 2006). In addition, the proliferation inhibition effects were observed for the growth of human embryonic cells under the injection of a pharmaceuticals mixture (consisting of atenolol, carbamazepine, ciprofloxacin, furosemide, ibuprofen, sulfamethoxazole, etc.) (Pomati

et al., 2006). At present, the information available on the ecotoxicology of pharmaceuticals is weak and the potential risks associated with the presence of pharmaceuticals in water environment are still under debate (Jones et al., 2004). Application of the precautionary principle, therefore, is required to give rise to more stringent controls on treatment of pharmaceuticals in wastewater.

In recent years, certain advanced technologies such as advanced oxidation processes (ozonation, photolysis and heterogeneous photolysis, Fenton and photo-Fenton, sonolysis, electrochemical oxidation, etc.), activated carbon adsorption, membrane separation, and membrane bioreactor have been investigated to assess their effectiveness for the removal of pharmaceuticals from wastewater (Klamerth et al., 2010; Martínez et al., 2013; Mestre et al., 2009; Molinos-Senante et al., 2013; Naddeo et al., 2009; Rossner et al., 2009; Singh et al., 2008; Sipma et al., 2010; Trinh et al., 2012). However, these advanced treatment processes are expensive making the large-scale application cost-prohibitive. Thus, selecting low-cost alternative technologies for pharmaceutical treatment is of great significance, especially in poor regions. For this purpose, constructed wetlands which are low-cost in construction, operation and maintenance are attracting great concern on their application for the removal of pharmaceutical contaminants from wastewater.

In the past decades, constructed wetlands have been demonstrated to be efficient for treatment of conventional pollutants in a variety of wastewaters such as domestic wastewater, agricultural wastewater, industrial effluent, mine drainage, leachate, contaminated ground water, and urban runoff. (Choudhary et al., 2011; Cooper et al., 1996; Davies et al., 2008; García et al., 2010; Kadlec and Wallace, 2009; Stottmeister et al., 2003; Sundaravadivel and Vigneswaran, 2001; Vymazal, 2009; Vymazal et al., 1998). However, for the treatment of pharmaceutical contaminants in wastewater

using constructed wetlands, it is really a fresh application field. The feasibility of constructed wetlands to eliminate pharmaceuticals in wastewater is requiring comprehensive understanding on the removal efficiencies, the removal mechanisms, the influences of design and environmental factors, and the toxicity risks. Hence, much more attention is needed to pay for these issues in future research studies.

The objective of this paper is to present the state of the research activities on the application of constructed wetlands for the removal of pharmaceutical contaminants from wastewater. The review focuses on the application of constructed wetlands as an alternative secondary wastewater treatment system or as a wastewater polishing treatment system. The design parameters of constructed wetlands were summarized to provide an understanding about the target pharmaceuticals, configuration, hydraulic mode and vegetation species of the reported constructed wetlands. The removal efficiencies of pharmaceuticals in constructed wetlands were also summarized in this paper in order to evaluate the performance of constructed wetlands in a macroscopic level. In addition, the possible removal mechanisms of pharmaceuticals related to the three important components of constructed wetlands (substrate, plants and microbes) were analyzed. The overall goal of this paper aims being able to offer help for the further research in future.

## 2. Design and performance of constructed wetlands for the removal of pharmaceuticals from wastewater

### *2.1 Reported pharmaceuticals and constructed wetlands*

115 pharmaceuticals grouped to 18 categories (according to their therapeutic classes) have been reported in 38 published papers in relation to their removal using constructed wetlands (including both the applications as a secondary wastewater treatment system and a polishing wastewater treatment system). The chemical

structures and the physico-chemical properties of these pharmaceuticals can refer to the appendix form on the website of Maritime Research Center in Nanyang Technological University (http://mrc.ntu.edu.sg/RD/Pages/default.aspx). In the form on this website, the pharmaceutical compounds are presented in terms of their chemical formula, chemical structure, molecular weight (MW), dissociation constant ($pK_a$), solubility ($S_w$, 25℃), octanol-water partition coefficient as Log $K_{ow}$, and octanol-water distribution coefficient as Log $D_{ow}$ (pH=7.4). These data were collected from relevant internet databases such as ChemIDplus Advanced, ChemSpider, DrugBank, Hazardous Substances Data Bank and Wikipedia. In addition, the number and details of the literature references reviewed are also indicated in the form. As is deduced from the number of the references, the commonly investigated pharmaceuticals in constructed wetlands are diclofenac, ibuprofen, ketoprofen, naproxen, salicylic acid, sulfamethoxazole, triclosan, atenolol, clofibric acid, carbamazepine and caffeine.

The constructed wetlands used for the removal of pharmaceuticals from wastewater can be classified into surface free water constructed wetlands (SF-CWs), horizontal subsurface flow constructed wetlands (HSSF-CWs), vertical subsurface flow constructed wetlands (VSSF-CWs) and hybrid constructed wetlands (hybrid CWs). The SF-CWs are composed of shallow channels or basins planted with vegetation (including rooted and floating plants) in which free wastewater flows at relatively shallow depth over the impermeable bottom liner or the packed substrate layer (Figure 1a). In the HSSF-CW systems, wastewater is fed into the wetland at the inlet zone and flows horizontally through the substrate under the surface of wetland bed which is planted with vegetation (Figure 1b). After the treatment of wetland, the wastewater effluent is collected at the outlet zone. For the VSSF-CW systems,

wastewater is dosed onto the surface of wetland bed and then flows vertically from the planted layer down through the substrate until it reaches the outlet zone (Figure 1c). The hybrid CW systems are the combination of two or more wetlands or the combination of wetlands with other pond systems such as lagoons and facultative ponds in parallel or in series. Such hybrid systems are normally laid out in two or three stages in order to realize the improvement of treatment efficiencies.

**Figure 1**

### *2.2 Constructed wetlands as a secondary treatment for pharmaceutical removal*

Constructed wetlands working as an alternative secondary wastewater treatment system to remove pharmaceutical contaminants from wastewater is being paid increasingly concern in many countries such as Canada, China, Denmark, Italy, Portugal, Singapore, Spain and USA. The main design parameters of the constructed wetlands reported in research work are summarized in Table 1. The removal efficiencies of the investigated pharmaceuticals by the secondary treatment of constructed wetlands are listed in Table 2. The comparison between the removal efficiencies of constructed wetlands and that of conventional WWTPs is shown in Figure 2. The removal performance of pharmaceuticals in different types of constructed wetlands is compared in Figure 3.

#### *2.2.1 Design parameters of constructed wetlands*

As reported in Table 1, the size of the investigated constructed wetlands was defined in this paper as microcosm-scale (surface area < 0.5 $m^2$), mesocosm-scale (surface area in the range of 0.5 to 5 $m^2$), pilot-scale (surface area in the range of 5 to 100 $m^2$) and full-scale (surface area > 100 $m^2$), of which the mesocosm-scale attracted the most attention. Various kinds of wastewater were fed into constructed wetlands,

for example, urban wastewater from sewers or WWTPs, rural wastewater from rural communities, household wastewater from sparsely populated regions, swine wastewater from pig farms, and synthetic urban or agricultural wastewater. Except for the synthetic wastewater, most wastewater was preliminary or primary treated by screen, coarse solid tank, septic tank, homogenization tank, settling tank, aerobic reactor, or hydrolytic upflow sludge bed (HUSB). The target pharmaceutical contaminants in wastewater mainly covered analgesic/anti-inflammatory drugs, antibiotics, beta-blockers, diuretics, lipid regulators, psychiatric drugs, stimulants/psychoactive drugs and veterinary drugs. The analgesic/anti-inflammatory drugs including diclofenac, ibuprofen, ketoprofen, naproxen and salicylic acid were of great concern.

Water depth is one of the important parameters for designing constructed wetlands. As shown in Table 1, the water depth in SF-CWs was usually maintained no more than 30 cm, but larger in the gravel SF-CW beds where 10-25 cm of free water was over the gravel layer (25-60 cm deep). In HSSF-CW systems, the water depth was commonly maintained 5 cm under the surface of substrate (30-60 cm deep). However, Hussain et al. (2011) designed the water depth as 20 cm below the surface of substrate (60 cm deep), and Ranieri et al. (2011) and Reyes-Contreras et al. (2011) maintained the water depth same as the level of substrate as 60-65 cm and 50cm, respectively. For the VSSF-CW systems, the water depth was controlled just below the surface of substrate in the study of Carvalho et al. (2013), but no more data could be obtained from a very small number of other literatures.

Different constructed wetland systems reported in the literatures were designed using different hydraulic retention time (HRT): 2 to 6 days for the SF-CWs, 2 to 4 days for the HSSF-CWs, 1 to 2 days for the VSSF-CWs, and 2 to 15 days for the

hybrid CWs (Table 1). Under these different HRT conditions, both the batch and continuous operation modes were selected for research and both the planted wetland beds and the unplanted beds were investigated. In the planted wetland beds, various types of plants were applied, among which the most popular vegetations were *Typha spp.* and *Phragmites spp*. In some studies, the plant initial density was selected as 10 to 50 plants $m^{-2}$.

Regarding the substrate in constructed wetlands, gravel was the most common aggregate with design $D_{60}$ of 3 mm to 8 mm, $D_{10}$ of 0.5 mm to 4 mm, $C_u$ of 0.8 to 2, and initial porosity of 40%-45% (Table 1). In addition, other substrates including stone, lava rock, volcanic rock, zeolite, soil/red soil, sandy soil and sandy clay loam were also found to be applied in some constructed wetlands. Hussain et al. (2011 and 2012) used sandy soil or sandy clay loam soil in SF-CWs and sandy soil in HSSF-CWs. Ranieri et al. (2011) filled the HSSF-CWs with three layers including 10 cm layer of soil, 20 cm layer of stone, and 30 to 35 cm layer of gravel. Carvalho et al. (2013) built the VSSF-CW bed with three layers consisting of 10 cm layer of roots' substrate, 2 cm layer of lava rock and 4 cm layer of gravel (from upper to lower). Liu et al. (2013a) constructed the VSSF-CW bed in a different way for layer distribution (from upper to lower) as: 20 cm layer of red soil, 30 cm layer of volcanic rock or zeolite and 10 cm layer of gravel.

**Table 1**

*2.2.2 Removal performance of pharmaceuticals in constructed wetlands*

The removal efficiencies of pharmaceuticals by the secondary treatment of constructed wetlands are important criteria to evaluate the performance of constructed wetlands in a macroscopic level. In Table 2, the removal efficiencies of 36 investigated pharmaceuticals are listed for different constructed wetland systems

including SF-CW, HSSF-CW, VSSF-CW and hybrid CW system, as well as the conventional WWTPs. The other investigated pharmaceuticals whose concentrations in wastewater were frequently below the limit of detection are not included in this Table. Considering the possible influences of plant, seasonality, configuration, operation mode and flow's saturation situation, some removal efficiencies of pharmaceuticals are presented in details, for example, efficiency (plant/unplanted), efficiency (winter/summer), efficiency (low water depth/high water depth), efficiency (continuous/batch) and efficiency (saturated flow/unsaturated flow).

As shown in Table 2, the removal efficiencies of ciprofloxacin HCl, oxytetracycline HCl, nadolol, cotinine, enrofloxacin, monensin, narasin and salinomycin in conventional WWTPs have not been reported. Thus the comparison between the performance of constructed wetlands and conventional WWTPs for elimination of these pharmaceuticals are not premature at this stage. With reference to Table 2, it can be seen that the removal efficiencies of ciprofloxacin HCl, oxytetracycline HCl, nadolol, cotinine and enrofloxacin in constructed wetlands are high (mean removal efficiency > 70%), while the removal efficiencies of monensin, narasin and salinomycin in constructed wetlands are relative low in the range of 20% to 50%. For the other pharmaceuticals listed in Table 2, most of their removal efficiencies in constructed wetlands appear to be as good as or even better than that in conventional WWTPs (graphically shown in Figure 2). It can be deduced that constructed wetlands have good potential of being used as an alternative secondary wastewater treatment to remove pharmaceutical contaminants from wastewater.

According to the mean removal efficiencies of pharmaceuticals in constructed wetlands (calculated from Table 2), the pharmaceuticals can be categorized to the readily removed, moderately removed, low removed, and hardly removed. The

pharmaceuticals that are readily removed by constructed wetlands (mean removal efficiency > 70%) are acetaminophen, salicylic acid, sulfadiazine, sulfadimethoxine, sulfamethazine, sulfamethoxazole, sulfapyridine, trimethoprim, atenolol, metoprolol, furosemide, caffeine and tetracycline. The pharmaceuticals that are moderately removed by constructed wetlands (mean removal efficiency between 50% and 70%) include ibuprofen, naproxen, doxycydine and gemfibrozil. The pharmaceuticals that show low removal efficiencies in constructed wetlands (mean removal efficiency between 20% and 50%) are diclofenac, ketoprofen, amoxicillin, clarithromycin, triclosan, sotalol, clofribric acid and carbamazepine. The pharmaceuticals that are hardly removed by constructed wetlands (average removal efficiency < 20%) include ampicillin, erythromycin and lincomycin.

**Table 2**

**Figure 2**

In Figure 3, the removal efficiencies of different types of constructed wetland systems for the elimination of pharmaceuticals are compared. The VSSF-CW appears to be more efficient and reliable for the elimination of diclofenac, ibuprofen, naproxen, salicylic acid and caffeine than the CWs with other configurations. It can be attributed to their less sensitivity to overloading conditions, shorter hydraulic residence time (HRT) and better oxygenation in unsaturated flow (Matamoros et al., 2007; Matamoros et al., 2009a). However, only a very small number of studies have been conducted on VSSF-CW for the treatment of pharmaceutical contaminants. Thus the superiority of VSSF-CW for pharmaceutical removal over other types of constructed wetlands is still inconclusive.

The constructed wetland investigated most often is the HSSF-CW which has been applied separately or associated in hybrid CW system (together with lagoons, ponds,

SF-CWs or other HSSF-CWs). As shown in Figure 3, in comparison with the SF-CW, the HSSF-CW is more efficient for the removal of ketoprofen, naproxen, salicylic acid, doxycycline, sulfadimethoxine, trimethoprim, caffeine, monensin, narasin and salinomycin. Moreover, the HSSF-CW is comparable efficient for the removal of diclofenac, clarithromycin, sulfamethoxazole and carbamazepine, whereas less efficient for the removal of ibuprofen and amoxicillin. In addition, compared with the HSSF-CW for separate application, the hybrid CW system provides better removal efficiencies for acetaminophen, diclofenac, ibuprofen, naproxen and sulfamethoxazole, while lower removal efficiencies for ketoprofen, salicylic acid, carbamazepine and caffeine.

**Figure 3**

In summer, high temperature and strong sunlight irradiation were found to enhance the activities of plants and microorganisms in constructed wetlands, resulting in increased elimination of diclofenac, ibuprofen, ketoprofen, naproxen, salicylic acid, triclosan, carbamazepine and caffeine. The mean removal efficiencies of these pharmaceuticals were 23%, 53%, 30%, 61%, 82%, 48%, 25% and 90% during summer, in comparison to that of 20%, 38%, 22%, 39%, 56%, 7%, 16% and 53% correspondingly during winter (calculated from Table 2).

Hijosa-Valsero et al. (2010a) found that their most target pharmaceuticals, except for caffeine, ibuprofen and naproxen, were remarkably eliminated during the first stage regardless of the system design (a full-scale hybrid facultative pond, SF-CW and HSSF-CW system). Hussain et al. (2012) observed that the removal efficiencies of their target pharmaceuticals (monensin, salinomycin and narasin) in a mesocosm SF-CW system were significantly affected by the influent concentration levels. Matamoros and Bayona (2006) calculated the zero- or first-order areal rate constants

for caffeine, ibuprofen and naproxen in a pilot-scale HSSF-CW system. They noted that the first-order kinetics fitted well with the decay of caffeine and ibuprofen. Zhang et al. (2012a) evaluated the first-order rate constants for caffeine, carbamazepine, clofibric acid, diclofenac, ibuprofen, ketoprofen, naproxen and salicylic acid in a mesocosm HSSF-CW system. They observed that the removal of caffeine, clofibric acid and ketoprofen followed the first-order decay kinetics. As stated above, within a certain period of residence time, the removal performance of certain pharmaceuticals in constructed wetlands would be related to the influent concentrations, resulting in variable removal efficiencies under different concentration levels.

Ávila et al. (2013) and Zhang et al. (2012b) observed the significant enhancement of the elimination of pharmaceuticals when feeding in batch mode due to the higher redox status caused by the alternating cycles of saturation and unsaturation. However, Hijosa-Valsero et al. (2011b) noted very little difference when using a batch flow or a continuous flow strategy. In addition, the hydraulic loading rate (HLR) or the hydraulic retention time (HRT) was suggested as another important hydraulic parameter influencing the removal efficiencies of pharmaceuticals in constructed wetlands. Ranieri et al. (2011) observed that the removal efficiency of paracetamol in a pilot-scale HSSF-CW system decreased as the HLR was increased. Zhang et al. (2012a) found that the removal efficiencies of all the target pharmaceuticals in a mesocosm HSSF-CW system were linearly proportional to the HRT. However, the difference was not obvious when the HRT was long enough for the treatment of pharmaceutical contaminants (Zhang et al., 2011).

### *2.3 Constructed wetlands as a polishing treatment for pharmaceutical removal*

Constructed wetlands applied as a wastewater polishing treatment system to remove pharmaceutical contaminants from wastewater have been investigated in

Denmark, Korea, Portugal, Sweden, Spain, UK and USA. In comparison to the publications on the application of constructed wetlands as an alternative secondary wastewater treatment system for the removal of pharmaceuticals, the number of the research studies on this application is relatively low. The design parameters of the reported constructed wetlands are summarized in Table 3. The removal efficiencies of the investigated pharmaceuticals in different types of constructed wetland systems are listed in Table 4.

*2.3.1 Design parameters of constructed wetlands*

As reported in Table 3, the size of the investigated constructed wetlands involved microcosm-scale (surface area < 0.5 $m^2$), pilot-scale (surface area in the range of 5 to 100 $m^2$) and full-scale (surface area > 100 $m^2$), of which the full-scale constructed wetlands attracted the most attention. The wastewater fed in the constructed wetlands included the secondary or tertiary effluent water from urban or rural WWTPs and the water from the rivers which received the effluent discharge of WWTPs. The target pharmaceutical contaminants in wastewater mainly covered analgesic/ anti-inflammatory drugs, antiallergic drugs, antibiotics, antidiabetics, antidysenterics, antifungals, antihypertensives, anti-senile dementia drugs, barbiturates, beta-agonists, beta-blockers, diuretics, hormone inhibitors, lipid regulators, psychiatric drugs, receptor antagonists, stimulants/psychoactive drugs and veterinary drugs. Among these pharmaceuticals, diclofenac, ibuprofen, ketoprofen, naproxen, sulfamethoxazole, triclosan, atenolol, clofibric acid, carbamazepine and caffeine were the commonly investigated pharmaceuticals.

The constructed wetlands selected for wastewater polishing treatment (Table 3) included SF-CWs, HSSF-CWs, VSSF-CWs and hybrid CWs, of which the most popular wetlands were the SF-CWs and the hybrid SF-CWs. The SF-CWs reported by

Llorens et al. (2009); Matamoros et al. (2012a); Matamoros et al. (2008b); and Zarate Jr et al. (2012) were designed with surface area of 0.2 to 100 ha. and water depth of 0.05 to 2 m. The target wastewater was retained in these SF-CWs for 3 to 30 days and was finally discharged into the surrounding lake or river. In the hybrid SF-CWs system used by Breitholtz et al. (2012); Gross et al. (2004); Lee et al. (2011); and Park et al. (2009), two or more stages of wetland basins were laid out in parallel or in series covering a planar area of 0.36-130 ha. with water depth in the range of 0.1 to 1 m. The wastewater was typically retained in the system for 6 hours to 14 days and was finally discharged into the surrounding lake, river or sea. Moreover, SF-CWs could also include ponds to form a hybrid system for wastewater polishing treatment. Matamoros and Salvadó (2012) conducted a study on such kind of hybrid system which consisted of two parallel ponds (2 ha. area and 1 m water depth for each) followed by three parallel deep SF-CWs (0.8 ha. area and 0.5 m water depth for each) and a large shallow SF-CW (4.5 ha. area and 0.2 m water depth). The wastewater was retained in the ponds and the SF-CWs (including both the deep and shallow SF-CWs) for 4 d and 8.5 days, respectively, and was finally pumped to an 18 ha. artificial pond in order to maintain the flooding of the marshlands.

For the HSSF-CWs, Dordio et al. (2010); Dordio et al. (2009a); and Verlicchi et al. (2013) evaluated the performance of HSSF-CWs for the removal of pharmaceuticals from the secondary effluent of WWTPs. Their investigated HSSF-CWs were designed with a surface area of 0.3 $m^2$ and 28 $m^2$, respectively, and with a water depth of 0.3 m and 2.2 m, respectively. Regarding the VSSF-CW, Reif et al. (2011) studied a pilot-scale VSSF-CW in batch operating mode for purifying the wastewater effluent from a WWTP in USA. In their research work, they designed the substrate layers of the wetland from top to bottom as: 0.15 m of filter grade sand, 0.15 m of 10 mm pea

gravel, 0.05 m of 20 mm gravel and 0.6 m of 40-50 mm gravel.

In all the reported constructed wetlands, there were various types of vegetations, among which the most popular plants were *Typha spp.* and *Phragmites spp* .

**Table 3**

*2.3.2 Removal performance of pharmaceuticals in constructed wetlands*

As shown in Table 4, the data on the removal efficiencies of the investigated pharmaceuticals for each kind of constructed wetland are very limited. Thus the comparison among the different types of constructed wetlands is not feasible to date. For the commonly investigated pharmaceuticals, except for the low or inconsistent removal efficiencies obtained by Matamoros et al. (2012a); Breitholtz et al. (2012); and Verlicchi et al. (2013), the readily removed pharmaceuticals by constructed wetlands (mean removal efficiency > 70%) are diclofenac, ibuprofen, ketoprofen, triclosan and atenolol. The moderately removed pharmaceuticals by constructed wetlands (mean removal efficiency between 50% and 70%) include naproxen and caffeine; while the pharmaceuticals with low removal efficiencies in constructed wetlands (mean removal efficiency between 20% and 50%) are sulfamethoxazole, clofibric acid and carbamazepine. Breitholtz et al. (2012) investigated four full-scale hybrid SF-CWs systems with different design configurations to remove pharmaceutical compounds from four sewage treatment plants. They detected that some pharmaceuticals were at higher levels in effluent water compared to that in the influent water (shown as negative removal efficiencies in Table 4). This phenomenon could partly be attributed to the numerical variations caused by the occurrence of pharmaceuticals close to the detection limit and the daily concentration fluctuations of pharmaceuticals induced by intermittent usage. In addition, it could also possibly because that many pharmaceuticals were metabolized as glucuronides or other

conjugated metabolites and then after a period of time were converted to the parent compounds by enzymatic processes.

Dordio et al. (2009a and 2010) found that the removal kinetics of atenolol, carbamazepine, clofibric acid and ibuprofen was a fast initial step in which more than half of the initial pharmaceuticals were removed within the first 6 hours and followed by a first-order kinetics during the next period of 6-96 hours. Matamoros et al. (2008b) observed that higher removal efficiencies of their target pharmaceuticals were obtained during the first part of system compared to the latter part of system, showing a spatial trend of the removal efficiencies. This phenomenon demonstrated that the first-order removal kinetics was appropriate for the removal of carbamazepine, diclofenac, flunixin, ibuprofen and ketoprofen. As stated above, within a certain period of residence time, the removal efficiencies of certain pharmaceuticals in constructed wetlands would be related to their influent concentrations.

**Table 4**

## 3. Removal mechanisms related to the substrate, plants and microbes in constructed wetlands

### *3.1 Substrate*

Substrate (also known as support matrix) is an important component in constructed wetlands, especially in subsurface flow constructed wetlands. The substrate in constructed wetlands not only provides support for the growth of plants and microorganisms, but also interacts directly with contaminants through sorption processes. Sorption of pollutants onto the surface of substrate involves different mechanisms such as hydrophobic partitioning, van der Waals interaction, electrostatic interaction, ion exchange, and surface complexation (Dordio and Carvalho, 2013; Haberl et al., 2003; Pei et al., 2012; Reddy and DeLaune, 2008; Tolls, 2001).

Non-polar organic pollutants can be preferentially adsorbed to the substrate materials that are especially rich in organic matter such as soil, compost and agricultural wastes via hydrophobic process. Polar or ionic pollutants are dominantly adsorbed to the substrate materials (e.g. some kinds of clay) by electrostatic interactions or ionic exchange.

According to Table 1 and Table 3, the most frequently used substrate for pharmaceutical removal in constructed wetlands is gravel which did not show any negative effects on the performance of constructed wetlands. The gravel substrate was found efficient for sorption removal of the pharmaceuticals which are refractory to biodegradation but with relative high hydrophobicity, for example, carbamazepine. However, at present, very few data are available on comprehensive understanding the sorption performance of gravel and the associated mechanisms for the removal of pharmaceuticals from wastewater using constructed wetlands.

It has been reported in laboratory batch experiments that light expanded clay aggregate (LECA) is a good sorbent for the acidic pharmaceutical compounds such as clofibric acid and ibuprofen as well as the neutral pharmaceutical compounds such as carbamazepine (Dordio et al., 2009c). Dordio et al. (2007) compared three different substrate materials including LECA, expanded perlite, and sand for the removal of clofibric acid from water in laboratory. Their research results indicated that LECA exhibited a high sorption capacity for the removal of clofibric acid, while the expanded perlite only had a very limited sorption capacity and the sand did not show any sorption capacity at all. Considering the alkaline nature of LECA, electrostatic interactions in the case of the acidic pharmaceuticals have been hypothesized as being

responsible for the affinities of these compounds towards LECA's surface. For the neutral compounds, van der Waals interactions may be more relevant. Dordio et al. (2009a) found that LECA also showed strong sorption for atenolol which was alkaline and positively charged. Electrostatic interactions cannot explain this phenomenon, but perhaps ion exchange may be responsible to some extent for the removal of atenolol by LECA.

Soil is another kind of popular substrate in constructed wetlands. Hussain et al. (2012) undertook some laboratory batch experiments to investigate the removal efficiencies of three antibiotics (monensin, salinomycin, and narasin) in two SF-CWs with different soil substrates. Higher removal efficiency was observed for the sandy soil when compared with the sandy loam soil. They explained that the higher relative hydraulic conductivity of the sandy soil could facilitate water movement within the soil profile resulting in a greater opportunity of soil-to-contaminants interactions. Whereas, the sandy clay loam soil which contained higher organic matter content showed a lower infiltration rate in the soil medium. However, their experimental results didn't indicate that the sorptive capability of the sandy soil was better than that of the sandy clay loam soil. Lertpaitoonpan et al. (2009) demonstrated that higher coefficient values ($K_d$) could be found for the soils with higher organic carbon during the batch sorption process of sulfamethazine onto five soils (organic carbon content ranged from 0.1% to 3.8%).

Recently, certain biosorbents such as rice husk, pine bark, and granulated cork have been considered as interesting alternatives to the common substrate materials in

constructed wetlands due to their low cost, economical value of reuse, and easy disposal by incineration. Dordio et al. (2011c) evaluated the sorption capacity of granulated cork to remove ibuprofen, carbamazepine and clofibric acid from water. Their laboratory experiments showed that the granulated cork presented good sorption qualities and the three pharmaceutical compounds were removed in the order of efficiency as: ibuprofen > carbamazepine > clofibric acid. In comparison with LECA, granulated cork had a much larger specific sorption capacity for all the target compounds.

Sorption kinetics and isotherms have been studied to describe the sorption process of pharmaceutical compounds to certain kinds of sorbent materials. Dordio et al. (2009a; 2010; and 2011c) observed that within the initial stage of 6 hours, more than half of the initial atenolol, carbamazepine, clofibric acid and ibuprofen could be removed via adsorption. Their laboratory experiment results indicated that the Freundlich equation modeled the experimental data better than the Langmuir equation. It reflected the significant role of the heterogeneity of the sorbent material as well as the possible lateral interactions between the sorbed molecules. Xu et al. (2009) also found that the Freundlich equation could well describe the adsorption process of their target pharmaceuticals in agricultural soils. The degradation of the target pharmaceuticals followed first-order exponential decay kinetics with the adsorption affinity order as follow: triclosan > clofibric acid > naproxen > diclofenac >ibuprofen. Moreover, Yu et al. (2013) confirmed that the Freundlich equation and the first order decay kinetics fitted well the adsorption process of carbamazepine, gemfibrozil and triclosan onto three different sorbents such as Palmdale sand, Imperial Valley clay and Washington Palouse loam.

The pH of substrate materials could play an important role in the sorption capacity of substrate for pharmaceutical removal.Vasudevan et al. (2009) demonstrated that the overall sorption efficiency of ciprofloxacin could be influenced by a difference in soil pH. Hussain and Prasher (2011) observed an inverse relationship between the substrate pH and the sorption of three antibiotics (monensin, salinomycin, and narasin). Sassman and Lee (2007) also found an inverse correlation between the soil pH and the sorption coefficient of monensin and lasalocid. Lertpaitoonpan et al. (2009) explained that the pH of soil inversely influenced the sorption process of sulfamethazine due to the different ionization states of sulfamethazine under different pH conditions. At pH less than 7.4, hydrophobic partitioning was possibly responsible for the removal of the non-ionized form of sulfamethazine. At pH above 7.4, the decrease in sorption of sulfamethazine was probably due to the predominance of the anionic form of sulfamethazine. Similar trend was also found for sulfonamides that the conversion of the neutral/cationic form of sulfonamides to the anionic form of sulfonamides above pH 7.5 led to a lower sorption to soils (Kurwadkar et al., 2007).

Competitive sorption phenomenon might take place if multiple pharmaceutical compounds and other wastewater pollutants are present in the water at the same time (Conkle et al., 2010; Dordio et al., 2009c). The sorption capacity of one pharmaceutical compound may be decreased by another pharmaceutical compound or/and other contaminants due to competition for preferred binding sites on the solid matrices in constructed wetlands. Therefore, this competition effect may be of concern in constructed wetland systems which are loaded with a wide range of pharmaceutical compounds.

### *3.2 Plants*

Plants in constructed wetlands play a significant role in direct uptake of many

organic pollutants in wastewater. In the cell membranes of plant roots, there are no specific transporters for the xenobiotic organic compounds like pharmaceuticals to move into the plants tissues, but the uptake and translocation of these compounds within plants can be simply driven by diffusion (Dietz and Schnoor, 2001; Dordio et al., 2011a; Dordio and Carvalho, 2013).

The diffusion process of pharmaceuticals into plant tissues is dependent on the physico-chemical characteristics of the compounds including the hydrophobicity (as expressed by logarithm octanol/water partition coefficient $\mathrm{Log\ K_{ow}}$), water solubility and concentration (Dordio and Carvalho, 2013; Stottmeister et al., 2003). In general, the pharmaceutical compounds characterized by a $\mathrm{Log\ K_{ow}}$ in a moderate range of 0.5 to 3.5 are lipophilic enough to move through the lipid bilayer of plant cell membranes and also water soluble enough to travel into the cell fluids of plants (Dietz and Schnoor, 2001; Dordio and Carvalho, 2013; Schröder and Collins, 2002; Stottmeister et al., 2003). For instance, carbamazepine with a $\mathrm{Log\ K_{ow}}$ of 2.45 has been reported to be readily taken up by the roots of *Typha spp.* and then transported from roots to stems and leaves, ultimately showing the largest extent of accumulation in leaves (Dordio et al., 2011b). In contrast to carbamazepine, for diclofenac whose $\mathrm{Log\ K_{ow}}$ is 4.51 higher than 3.5, Zhang et al. (2012c) demonstrated the compound had limited ability to be taken up and translocated within the roots and shoots of scirpus validus.

For the nonionizable, polar, highly water soluble organic compounds, Dettenmaier et al. (2009) found that caffeine could be taken up by plant roots and translocated to shoots, which is in agreement with the findings of Matamoros et al. (2012b) and Zhang et al. (2013a). Liu et al. (2013b) also observed a similar phenomenon for three antibiotics (ciprofloxacin HCl, oxytetracycline HCl and sulfamethazine) which have

the $\mathrm{Log\ K_{ow}}$ values below 0.5. The authors suggested that such highly water soluble organic compounds were most likely to be driven by the transpiration water stream in the plant uptake and the translocation within plant tissues. Further, they also found the positive correlation between the antibiotics concentrations and the accumulation levels of antibiotics inside the plants.

After being taken up into plants tissues, the internal pharmaceutical compounds might be degraded via the metabolism processes (phytodegradation). The metabolism processes might include a series of biochemical reactions such as transformation of parent organic pollutants, conjugation of metabolites with macromolecules, and incorporation of conjugated products into plant cell walls and vacuoles (Dordio and Carvalho, 2013; Reinhold et al., 2010). Dordio et al. (2011b) detected a metabolite (10, 11-dihydro-10, 11-epoxycarbamazepine) of carbamazepine in the leaf tissues of Typha spp. indicating the occurrence of carbamazepine metabolism inside the plant tissues. Liu et al. (2013b) found the conversion of ciprofloxacin HCl and oxytetracycline HCl to their epimers such as tetracycline, chlortetracycline, enrofloxacin and ofloxacin in plants.

Plants in constructed wetlands play another important role in stimulating the development and activities of microbial populations which are supported by the rhizodeposition products (exudates, mucigels, dead cell material, etc.), causing various biological processes to occur in the rhizosphere (Calheiros et al., 2009; Cronk, 1996; Stottmeister et al., 2003). Matamoros et al. (2012b) found that the predominant removal process of ibuprofen was microbial degradation which was very possibly associated with the biofilms on the surface of plant roots. In addition to the biological processes, certain plant exudates may also function as catalytic agents for the degradation of organic compounds (Dordio and Carvalho, 2013). Most plant species

in constructed wetlands are able to release oxygen around their root tips and on young laterals (Stottmeister et al., 2003). The oxygen released in rhizosphere can also promote the oxidative chemical processes of contaminants in wastewater (Sundaravadivel and Vigneswaran, 2001) and favor the development of aerobic microorganisms in the rhizosphere inducing more efficient biodegradation processes (Cronk, 1996; Dordio and Carvalho, 2013). The continuous release of oxygen from the root zones of plants might counterbalance the chemical and biological oxygen consumption in the rhizosphere.

It has been reported that the presence of plants in constructed wetlands played a positive role in the removal of some certain pharmaceuticals such as diclofenac, ibuprofen, ketoprofen, naproxen, salicylic acid, amoxicillin, ampicillin, erythromycin, sulfadiazine, sulfamethazine, sulfamethoxazole, atenolol, clofibric acid, carbamazepine and caffeine (Dordio et al., 2010; Dordio et al., 2009a; Hijosa-Valsero et al., 2011a; Hijosa-Valsero et al., 2011b; Hijosa-Valsero et al., 2010b; Hijosa-Valsero et al., 2011c; Xian et al., 2010; Zarate Jr et al., 2012; Zhang et al., 2012a; Zhang et al., 2012b; Zhang et al., 2011). Several plant species have been reported for use in pharmaceutical wastewater treatment wetlands (Table 5) among which the most popular plants are *Phragmites australis*, *Typha spp. Typha angustifolia* and *Typha latifolia*. The experiment results of Hijosa-Valsero et al. (2010b and 2011c) indicated that *Phragmites australis* had a better performance than *Typha angustifolia.* However, Dordio et al. (2009a) observed the superiority of *Typha spp.* compared to the *Phragmites australis* due to the higher transpiration rate of *Typha spp.* Zarate Jr et al. (2012) investigated the accumulation of triclosan inside the plant tissues (roots and shoots) and their results showed the species-specific differences among different vegetations (*Pontederia cordata* and *Sagittaria graminea*),

indicating the important influences of plant species on the pharmaceutical removal.

**Table 5**

Toxicity to plants caused by pharmaceuticals is an important issue when considering the functions of plants for pharmaceutical removal. The toxicity can be evaluated through analyzing the root activity, the relative growth rate of plant (RGR) and the concentrations of photosynthetic pigments such as carotenoid and chlorophyll in plants tissues (Dordio et al., 2011a; Dordio et al., 2011b; Dordio et al., 2009b; Liu et al., 2013b). In addition, the alteration of antioxidant enzyme activities in plant tissues can also serve as an indication of the phytotoxicity caused by pharmaceutical compounds. The antioxidant enzymes like catalase (CAT), superoxide dismutase (SOD), guaiacol peroxidase (GPX) and ascorbate peroxidase (APX) have been reported for the plants which are subjected to pharmaceutical stress (Dordio et al., 2011a; Dordio et al., 2011b; Dordio et al., 2009b; Liu et al., 2013b).

### *3.3 Microbes*

Microbes in constructed wetlands usually play the main role in the processes of transformation and mineralization of nutrients and organic pollutants (Kadlec and Wallace, 2009; Sundaravadivel and Vigneswaran, 2001; Truu et al., 2009; Zhu et al., 2010; Zhu et al., 2011; Zhu et al., 2013). Biodegradation of organic compounds by microbes in constructed wetlands can occur under both the aerobic and the anaerobic conditions involving the activities of various microorganisms such as heterotrophic bacteria, autotrophic bacteria, fungi (basidiomycetes and yeasts), and specific protozoa (Kadlec and Wallace, 2009).

An important factor strongly influencing the microbial degradation process is the chemical structures of the organic compounds (Dua et al., 2002; Reddy and DeLaune, 2008). For those organic compounds with simple structures possessing high water

solubility and low adsorptivity, they could be readily degraded by microorganisms. It is attributable to the usual similarity of these organic compounds to the naturally occurring compounds which are commonly used as energy sources by microorganisms. In contrast, for those xenobiotic organic compounds (including pharmaceuticals) that have the very different structures from the naturally occurring compounds, they may be slowly degraded by microorganisms possibly due to the lack of suitable degrading genes in microorganisms. However, it does not mean that the non-specific enzymes are not able to help degrade the xenobiotic organic compounds. The degradation of such organic compounds by non-specific enzymes may still take place at a slower rate via co-metabolism reactions which do not support the microbial growth (Seffernick and Wackett, 2001). In addition, the degradation of xenobiotic organic compounds by microorganisms in constructed wetlands may also be influenced by the substrate, vegetation, oxygen and redox potential, temperature, pH, nutrient available, and presence of toxic substances (Calheiros et al., 2009; Li et al., 2010; Reddy and DeLaune, 2008; Salomo et al., 2009; Truu et al., 2009).

In the reviewed research work, aerobic biodegradation was thought to be the main contribution to the microbial degradation process of ibuprofen (Ávila et al., 2010; Ávila et al., 2013; Hijosa-Valsero et al., 2010a; Hijosa-Valsero et al., 2010b; Hijosa-Valsero et al., 2011c; Matamoros et al., 2008a; Matamoros et al., 2005; Reyes-Contreras et al., 2012), salicylic acid (Hijosa-Valsero et al., 2010b; Hijosa-Valsero et al., 2011c; Reyes-Contreras et al., 2012) and sulfamethoxazole (Hijosa-Valsero et al., 2011a), whereas anaerobic biodegradation was thought to be responsible for naproxen (Ávila et al., 2010) and caffeine (Hijosa-Valsero et al., 2010b; Hijosa-Valsero et al., 2011c; Reyes-Contreras et al., 2012). However, regarding the biodegradation of diclofenac, there exist two different points of views

and they are: 1) high redox potential could promote the removal of diclofenac (Ávila et al., 2013; Hijosa-Valsero et al., 2010b; Hijosa-Valsero et al., 2011c); 2) the removal efficiency of diclofenac could be enhanced under anaerobic conditions (Ávila et al., 2010). All the removal mechanisms stated above were inferred from the reported experiment results and do not include explicit demonstrations. Thus, it is still difficult to describe the actual removal mechanisms of pharmaceuticals to date

Certain pharmaceutical compounds (for example, ibuprofen) which contains an asymmetric carbon atom (also known as a chiral carbon atom) usually has two enantiomeric forms ( $S_{form}$ and $R_{form}$ ). The enantiomeric fraction ( $EF = S_{form}/(S_{form} + R_{form})$ ) (Hijosa-Valsero et al., 2010a; Matamoros et al., 2009b) which is compound-dependent can be used for the evaluation on the occurrence of enantioselective degradation in wastewater treatment system through investigating the change in the trend of EF. Enantioselective degradation of ibuprofen was reported by Matamoros et al. (2009b) that the $S_{form}$ ibuprofen was degraded faster than the $R_{form}$ ibuprofen under aerobic conditions (in VSSF-CW) inducing EF to decrease. This phenomenon was in agreement with the findings of Hijosa-Valsero et al. (2010a). However, EF didn't change during wastewater treatment under anaerobic conditions (in HSSF-CW) due to the similar degradation rates of $S_{form}$ ibuprofen and the $R_{form}$ ibuprofen. Owing to the different ibuprofen EF trends under aerobic and anaerobic conditions, it can be deduced which kind of metabolic pathway (aerobic biodegradation or anaerobic degradation) plays a predominant role in the removal of ibuprofen in constructed wetlands.

Evaluation of the biodegradation intermediates of pharmaceuticals in constructed wetlands is also important for elucidating the microbial degradation mechanisms, but available data are very few at present. Matamoros et al. (2008a) studied the behavior

of two biodegradation intermediates of ibuprofen including carboxy-ibuprofen (CA-IBP) and hydroxy-ibuprofen (OH-IBP) in a HSSF-CW system to assess the relative contribution of aerobic and anaerobic pathways to the ibuprofen biodegradation. Their findings indicated that the CA-IBP and OH-IBP only contributed to 5% of the degraded IBP and there was negligible accumulation of these two kinds of intermediates in the microcosms. The observation was possibly due to the similar kinetics for their consumption and formation. However, both CA-IBP and OH-IBP can be produced under aerobic conditions and only CA-IBP can be detected under anaerobic conditions (Zwiener et al., 2002). Through the analysis on the ibuprofen removal percentage attributable to the aerobic and anaerobic pathways using Equation (1) and Equation (2), the authors suggested that the aerobic metabolic pathways predominated for the removal of ibuprofen.

$$\text{Aerobic} - \text{ratio} = (C_{OH-IBP} + xC_{CA-IBP})/(C_{OH-IBP} + C_{CA-IBP}) \quad (1)$$

$$\text{Anaerobic} - \text{ratio} = yC_{CA-IBP}/(C_{OH-IBP} + C_{CA-IBP}) \quad (2)$$

Where:

$C_{CA-IBP}$ -- Concentration of CA-IBP

$C_{OH-IBP}$ -- Concentration of OH-IBP

x -- Percentage of CA-IBP obtained in the aerobic pathways, 0.4%

y -- Percentage of CA-IBP obtained in the anaerobic pathways, 1.8%

Feeding pharmaceutical contaminants to constructed wetland may affect the development and activities of microbes in constructed wetlands. Weber et al. (2011) assessed the influence of ciprofloxacin on the distribution of bacterial communities in some mesocosm-scale constructed wetlands planted with *Phragmites austrails*. Their experimental results showed that the presence of ciprofloxacin had an initial adverse effect on the bacterial communities in the constructed wetlands, thereby reducing their ability to assimilate anthropogenic carbon-based compounds. However, after a 2-5

week acclimation period, the bacterial communities could return to their normal functionality. Helt et al. (2012) investigated the effect of ciprofloxacin on the antibiotic resistance of the interstitial bacterial community (total culturable heterotrophs) and the selected faecal indicators (*Escherichia coli and Enterococcus spp.*) in the same constructed wetlands as those used by Weber et al. (2011). Helt et al. (2012) found that the antibiotic resistance level of the interstitial bacteria community peaked at 7 days following the ciprofloxacin exposure and then decreased thereafter, and also observed that the antibiotic resistance level of the faecal indicators increased.

## 4. Conclusions

Constructed wetlands are now attracting increasing attention to their application for the removal of pharmaceutical contaminants from wastewater. Based on the findings of published work on the feasibility of constructed wetlands as a means to treat pharmaceutical contaminants in wastewater, one can deduce that constructed wetlands hold great potential of being used as an alternative secondary wastewater treatment system or as a wastewater polishing treatment system. Nevertheless, it remains true that scarce data at present cannot provide very persuasive demonstrations for the performance and effectiveness of constructed wetlands in these applications. There are knowledge gap in several aspects including the removal efficiencies of pharmaceuticals in constructed wetlands, the removal mechanisms involved, the toxicity to constructed wetlands caused by pharmaceuticals, and the influences of certain important parameters (configuration design, hydraulic mode, temperature and seasonality, pH, oxygen and redox potential, etc.). Moreover, most studies were undertaken at a microcosm-scale or mesocosm-scale. Therefore, further research is required to provide more comprehensive and convincing evidences in larger laboratory-scale, pilot-scale or full-scale constructed wetlands. In addition, the current

constructed wetlands applied for the treatment of pharmaceutical pollutants in wastewater are mainly the conventional constructed wetlands including SF-CWs, HSSF-CWs, VSSF-CWs, and hybrid CW system. Some novel constructed wetlands such as the tidal flow constructed wetlands, anti-sized constructed wetlands, and the dewatered alum sludge based constructed wetlands can also be investigated.

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