Desalination and Water Treatment
www.deswater.com
doi: 10.1080/19443994.2015.1082942

57 (2016) 17023–17029
August

Taylor & Francis
Taylor & Francis Group

The competitive adsorption of pharmaceuticals on granular activated carbon in secondary effluent

Longli Bo*, Ning Gao, Jiadong Liu, Bo Gao

School of Environmental and Municipal Engineering, Xi'an University of Architecture and Technology, No. 13, Yan Ta Road, Xi'an 710055, China, Tel. +86 13630232698; email: bolongli@xauat.edu.cn (L. Bo), Tel. +86 15029083792; email: 846600164@qq.com (N. Gao), Tel. +86 15771796090; email: liujiadong@hotmail.com (J. Liu), Tel. +86 13689296473; email: gbljd1986@163.com (B. Gao)

Received 5 February 2015; Accepted 8 August 2015

ABSTRACT

The competitive adsorption characteristics of four pharmaceutical compounds, including clofibric acid (CA), carbamazepine (CBZ), naproxen (NAP), and diclofenac (DCF), were evaluated on granular activated carbon in secondary effluent. In ultrapure water (UW), the adsorption efficiencies of CA, CBZ, NAP, and DCF on coconut shell-based carbon were 63.0, 85.5, 79.1, and 68.8%, respectively, at initial concentration of 500 μg/L and carbon dosage of 133 mg/L. All the substrates could be removed completely when carbon dosage was increased to 250 mg/L. In the secondary effluent from a real wastewater treatment plant, the removal of four pharmaceuticals were decreased to 26.9, 57.9, 44.7, and 31.0%, respectively, with carbon dosage of 250 mg/L, which recovered to 39.6, 67.1, 53.4, and 48.1% after solution filtration by 0.22-μm hydrophilic membrane. The suspended solids and soluble organic compounds in wastewater were considered as the key inhibited factors for pharmaceuticals adsorption by activated carbon. The differences of adsorption efficiency between spiked UW and secondary effluent demonstrate that further purification for secondary effluent is necessary in practical wastewater treatment, when activated carbon is used as adsorbent for pharmaceuticals removal and wastewater advanced treatment.

Keywords: Pharmaceutical compounds; Granular activated carbon; Competitive adsorption; Ionic strength; Secondary effluent

1. Introduction

Over the last decade, pharmaceutical compounds, endocrine disrupting compounds, and personal care products had been frequently reported to be present in surface water, ground water, and wastewater effluent [1–3]. Those compounds present at concentration up to μg ng/L level, can be absorbed to the tissues of animals and humans (especially liver and kidney), hindering metabolic processes and occupying hormone receptors. With the development of living standards, there is an increasing consumption of pharmaceuticals, which results in great amounts of pharmaceutical residues remaining in aquatic environment [4,5]. However, most pharmaceuticals cannot be efficiently eliminated by traditional water treatment processes [6,7]. Therefore, it is necessary to adopt cost-effective treatment process for the removal of pharmaceuticals.

Previous reports had presented that high pressure membrane filtration [8,9], ozonation, advanced

*Corresponding author.

oxidation [10,11], and adsorption process could effectively eliminate these trace-level pharmaceutical compounds. However, some more toxic intermediates could be produced during ozonation and advanced oxidation processes [12]. In comparison, adsorption of granular activated carbon (GAC) is simple and relatively cost effective, which would not generate undesirable byproducts and was found to be superior to other processes in terms of simplicity of design and operation. The United States Environmental Protection Agency (USEPA) had identified GAC as the best available adsorbent for the treatment of many regulated organic pollutants [13]. To date, many researches mainly focused on the adsorption of trace pharmaceuticals under aqueous condition [14–18]. But only few studies had been reported to remove the pharmaceuticals from secondary effluent of wastewater treatment by adsorption. And most studies emphasized on individual substance [19,20]. Therefore, it is essential to study the adsorption of several pharmaceuticals in different solutions on activated carbon, which could offer theoretical basis for applying adsorption on activated carbon in wastewater purification and reclamation.

Above all, the main objective of this research is to evaluate the adsorption characteristics of pharmaceuticals on activated carbon, and identify the limiting factors from secondary effluent for practical application. Four pharmaceuticals, such as clofibric acid (CA), carbamazepine (CBZ), naproxen (NAP), and diclofenac (DCF), were detected from wastewater treatment plants in Xi'an. The tests were carried out to identify their adsorption performances on activated carbon between spiked ultrapure water (UW) and secondary effluent from a wastewater treatment plant, respectively. Meanwhile, competitive adsorption among four pharmaceuticals and background organics were compared based on the properties of the substrates and activated carbon. Finally, the mechanism of comparatively lower adsorption capacity in wastewater effluent compared to that in spiked UW was elaborated in details.

2. Materials and methods

2.1. Materials

Four target pharmaceuticals including CA, CBZ, NAP, and DCF were all purchased from Sigma-Aldrich. And the physicochemical properties and molecular structures of four pharmaceuticals are listed in Table 1. The internal standard 2,4-dichlorobenzoic acid and derivatization agent pentafluorobenzyl bromide (PFBBr) were also obtained from Sigma-Aldrich. Stock solution (1 g/L) was prepared in pure methanol for four pharmaceuticals. Working solution (500 μg/L of each pharmaceutical) was obtained by diluting the stock solution. The secondary effluent was taken from the Third Wastewater Treatment Plant in Xi'an. The main water quality parameters of the selected secondary effluent are shown in Table 2.

The adsorbent, coconut shell-based activated carbon (Red Rock Chemical Reagent, Tianjin) was selected in this research. Before use, the activated carbon was sieved to obtain the desired particle size of 0.5–0.9 mm. Then, it was mixed with 10% HCl and immersed for 24 h. Thereafter, the solution was boiled for 30 min, and then the activated carbon was thoroughly washed with UW until neutral pH. Finally, it was dried in oven at 105°C for 24 h and stored in a desiccator for subsequent tests.

2.2. Adsorption experiments

The adsorption tests were carried out at carbon dosage of 133 mg/L to preliminarily identify the adsorption capacity of four pharmaceuticals on activated carbon. The flasks were set at 25°C and shaken at 150 rpm for 24 h. The samples were filtered through a 0.45-μm membrane before analyzed by GC–MS/MS to calculate the adsorption capacity.

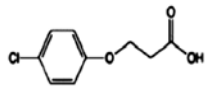
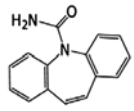
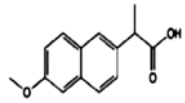
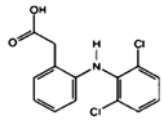
Adsorption equilibrium tests were performed in 250-mL vessels with 133 mg/L activated carbon at 25°C and were shaken at 150 rpm. Samples were taken at different time intervals and then the concentration values of the pharmaceuticals were analyzed. Initial concentration of each pharmaceutical in the solution was 500 μg/L, unless otherwise specified.

Four kinds of solution, including UW, 592 mg/L NaCl solution (prepared by UW), secondary effluent, and filtered secondary effluent via 0.22-μm filter membrane, were conducted to identify the effects of suspended solid (SS) and total dissolved solid (TDS) on adsorption of activated carbon. The experimental conditions were agreement with those applied in the comparative adsorption tests. Finally, the removal rates of target pharmaceuticals in different solutions were calculated.

2.3. Sample preparation and analysis

Samples were filtered through 0.45-μm membrane to remove particulates firstly, and then 100 mL of sample was mixed with HCl to adjust pH to 2–2.5 before adding internal standard 2,4-dichlorobenzoic acid. The water sample was extracted through a C18 cartridge, previously conditioned with 10 mL of acetone, 10 mL of methanol, and finally 10 mL of UW (pH 2–2.5).

Table 1
Physical–chemical properties of the pharmaceuticals

Compounds	Usage	Molecular formula	Chemical structure	Molecular weight	pK_a	log k_{ow}
Clofibric acid	Antiauxin	$C_{10}H_{11}ClO_3$		214.6	2.95	2.57
Carbamazepine	Antiseizure	$C_{15}H_{12}N_2O$		236.27	13.9[b]	2.45[a]
Naproxen	Analgesic	$C_{14}H_{14}O_3$		230	4.15	3.18
Diclofenac	Antiarthritic	$C_{14}H_{11}Cl_2NO_2$		298.15	4.15	4.51

[a]Ref. [27].
[b]Ref. [28].

Table 2
The wastewater quality parameters (mg/L)

COD		BOD_5		TN		TP		SS	
Influent	Effluent	Influent	Effluent	Influent	Effluent	Influent	Effluent	Influent	Effluent
317	45	106	13	44.3	15.3	4.22	0.2	168	3

Then it was eluted with 10 mL of methanol, and the eluate was concentrated by nitrogen gas at 60℃ to 1 mL. Before analysis by GC–MS/MS, 100 μL of PFBBr (8%, in methanol) was added in a vial, which was sealed and put in a drier at 100℃ for 90 min.

The concentration of four pharmaceuticals was analyzed by a GC (7890A, Agilent, USA)–MS/MS (7000B, Agilent, USA) with a 30 m × 0.25 mm × 0.25 μm HP-5MS capillary column. Carrier gas was helium with purity of 99.999% and the flow rate was at a constant velocity of 1.35 mL/min. Manual injection (1 μL) was performed in splitless mode and injector temperature was 270℃. The ion source temperature and electron energy for the filament were set at 230℃ and −70 eV, respectively. The oven temperature was held at 100℃ for 1 min following injection, then programmed to 180℃ at 20℃/min, then programmed to 220℃ at 3℃/min, which was held for 2 min, and finally programmed to 250℃. Total run time was 22.3 min. Mass spectra were obtained in full scan mode in preliminary experiments and the scan scope ranged from 50 to 450 m/z, and later in selective ion mode (SIM). The chromatogram of target pharmaceuticals is shown in Fig. 1.

The total organic carbon (TOC) of secondary effluent from wastewater treatment plant was determined by TOC analyzer (SHIMADZU, Japan). The TDSs were acquired by weighing method, the sample was

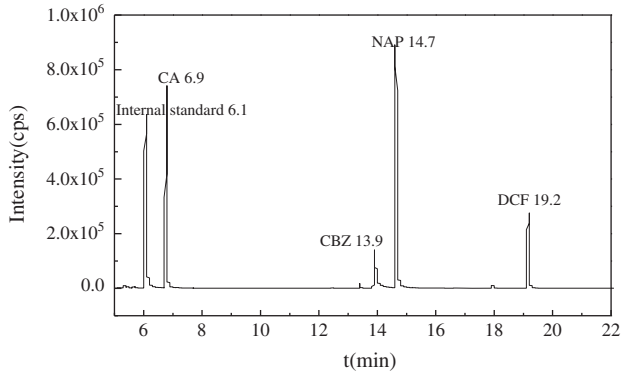


Fig. 1. SIM chromatogram of the target compounds.

filtered by 0.22-μm filter membrane and dried to constant weight before testing.

2.4. Characterization of activated carbon

Textural characteristics of the prepared activated carbon including special surface area (S_{BET}), micropore special surface area (S_{mic}), total pore volume (V_{tot}), and average pore diameter were determined basing on the adsorption/desorption curves of N_2 at 77 K using V-Sorb X800 automated adsorption apparatus, and relative data are shown in Table 3. Before determination, the samples were degassed under vacuum at 200℃ for 2 h to remove impurities from pores. The surface morphology of activated carbon was presented by scanning electron microscopy (SEM, JSM-6510LV, Japan).

3. Results and discussion

3.1. The structure of activated carbon and its performance on pharmaceuticals removal

In this study, adsorption efficiencies of the pharmaceuticals on coconut shell-based activated carbon were evaluated at carbon dosage of 133 mg/L and adsorption time of 24 h. The results indicated that the adsorption efficiency values of CA, CBZ, NAP, and DCF on activated carbon were 63.0, 85.5, 79.1, and 68.8%, respectively.

To identify the impact of structure of adsorbent on pharmaceuticals removal, the activated carbon was characterized by BET and SEM. The nitrogen adsorption/desorption curves and SEM image are shown in Fig. 2. The curves of activated carbon were characteristic of type IV isotherm, indicating multi-molecular layer adsorption played a vital role on adsorbent. There presented a typical hysteresis loop of type H4 between 0.4 and 1.0 of relative pressure, suggesting that the pores of coconut shell-based activated carbon were generated from analogous layer structure. The SEM image of activated carbon showed layer structure with mesopore feature (Fig. 2). This characterization was consistent with the BET results.

The textural parameters of activated carbon are summarized in Table 3. The specific surface area of coconut shell-based activated carbon was 916.32 m^2/g. The mesopore volume accounted for 61.3% of the total pore volume (Table 3). Its average pore diameter from Barrett–Joyner–Hanlenda (BJH) method was 4.1 nm. Thus, it was obvious that higher special surface area and well-developed pore structure of coconut shell-based activated carbon resulted in higher adsorption capacity for pharmaceuticals in this study.

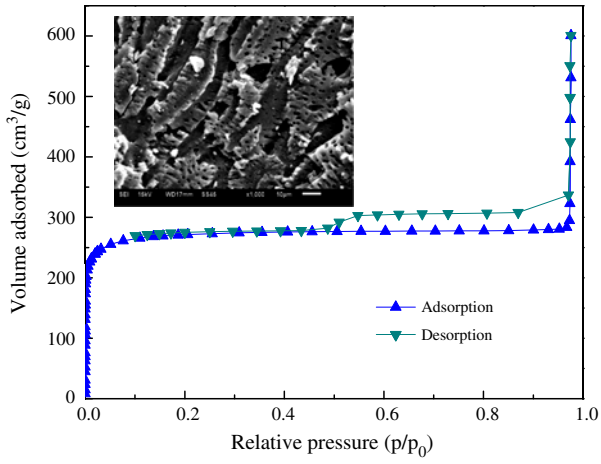


Fig. 2. The BET curves and SEM image of coconut shell-based activated carbon (adsorption/desorption curves of N_2 at 77 K using V-Sorb X800 automated adsorption apparatus).

The curves of adsorption equilibrium are shown in Fig. 3. The adsorption rate was faster at the first 8 h, and then it began to decrease until reached equilibrium at 24 h. The adsorption capacities of four pharmaceuticals (CA, CBZ, NAP, and DCF) were 2.48, 3.00, 2.74, and 2.52 mg/g, respectively.

3.2. Competitive adsorption of pharmaceuticals in different solutions

The competitive adsorption might appear on the surface of the absorbent while it was applied for the purification of wastewater. So, in this study, comparative studies were performed to analyze competitive adsorption of four pharmaceuticals on activated carbon in spiked UW and secondary effluent (SE), respectively. And the results are shown in Fig. 4.

Table 3
Textural characteristics of activated carbon

Adsorbent	S_{BET} (m^2/g)	S_{mic} (m^2/g)	V_{tot} (cm^3/g)	Micropore volume (cm^3/g)	Mesopore volume (cm^3/g)	Average pore diameter (nm)
Coconut shell-based carbon	916.32	783.56	0.93	0.36	0.57	4.1

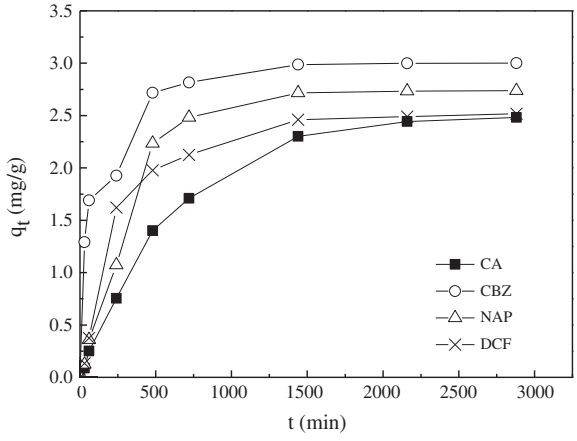


Fig. 3. The adsorption equilibrium curves of four pharmaceuticals on activated carbon (carbon dosage of 133 mg/L, shaken at 150 rpm for 24 h).

In UW, the adsorption capacity of individual pharmaceutical was obviously higher than that in mixed substrates solution, which demonstrated obviously competitive adsorption existing among the target compounds in this research. In secondary effluent, the removal rates of all compounds had been inhibited obviously, which meant some substrates in secondary effluent had affected their adsorption on activated carbon seriously.

Among the pharmaceuticals, the mechanism of competitive adsorption might be related to the pK_a and log k_{ow} of the substrates competing for the limited adsorption sites. The pK_a governed the dissociation of the substrates if it is an electrolyte [21]. The pK_a of 13.96 to CBZ indicated that it would stay at molecular state during the operation. This property resulted in strong adsorption with constant removal efficiency. Whereas the pK_a of CA was the lowest among the four target compounds, which meant the lowest adsorption affinity on activated carbon.

The log k_{ow} is another important factor for evaluation of adsorption capacity, and the pollutants with higher log k_{ow} value should have a higher adsorption affinity on activated carbon [22]. Therefore, the adsorption capacity of NAP and DCF was higher than that of CA. The log k_{ow} value of CBZ in this study was the lowest, which indicated that CBZ was the most hydrophilic compound among all the four pharmaceuticals. However, compared with log k_{ow}, pK_a of CBZ played a crucial role in controlling the adsorption capacity. At the situation in this study (pH is neutral), CBZ was existed as the state of non-polar molecule, whereas other three target compounds were dissociated into anions. The surface of the activated carbon was mainly non-polar, which made it easier to adsorb non-polar compounds. Thus, CBZ was the most absorbable compound among all the selected pharmaceuticals.

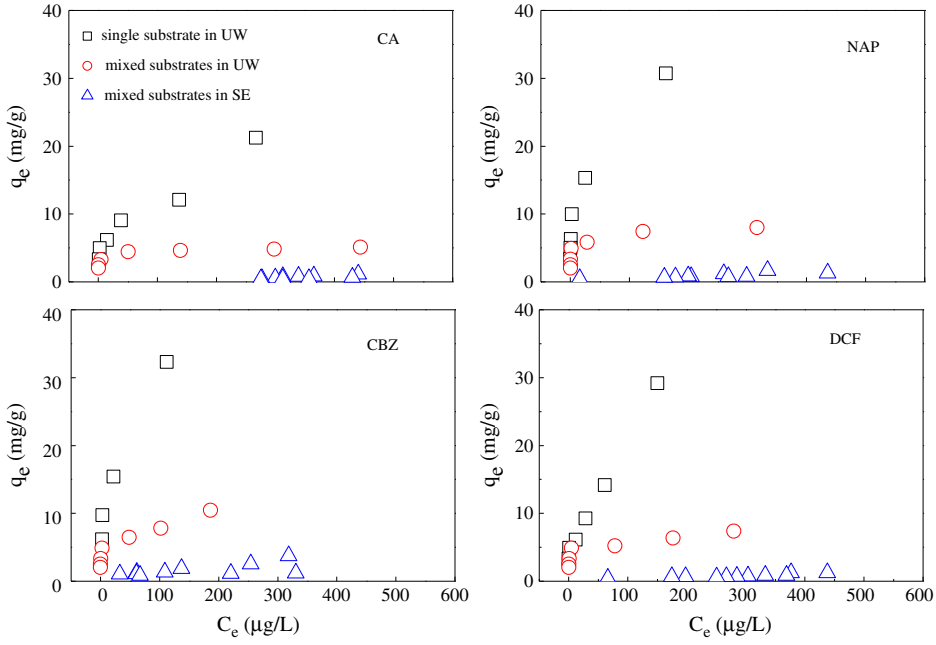


Fig. 4. The competitive adsorption of four pharmaceuticals on coconut shell-based activated carbon under different operation conditions (UW means ultrapure water, SE means secondary effluent).

To clarify the impact of the substrates in secondary effluent on competitive adsorption, the adsorption tests in UW, NaCl solution, secondary effluent, and filtrated secondary effluent were carried out and the results are shown in Fig. 5. In UW solution and 592 mg/L NaCl solution, most of the four pharmaceuticals could be removed after 24 h operation (Fig. 5). No obvious difference of removal rate had been shown in those different solutions, which indicated that the dissolved salt in wastewater would not affect the pharmaceuticals removal during active carbon adsorption process.

In secondary effluent, the removal rates of CA, CBZ, NAP, and DCF reduced to 26.9, 57.9, 44.7, and 31.0%, respectively, at carbon dosage of 250 mg/L. After filtration by 0.22-μm membrane, the SSs in secondary effluent were removed, and then the removal rates were recovered to 39.6, 67.1, 53.4, and 48.1%, respectively, but the recovering amounts were only 12.7, 9.2, 8.7, and 17.1%, respectively. Those differences indicated that the substances in secondary effluent had affected the pharmaceuticals adsorption seriously, which included SSs (organic particles), inorganic salts, and soluble organic compounds. Comparing those removal rates in four kinds of solutions, the effect of inorganic salts on adsorption efficiency was less than that of SSs. The TOC (soluble organic compounds) was 37.7 mg/L. Those comparison results revealed that the soluble organic compound was the key factor for adsorption in secondary effluent. Previous reports also indicated that organic compounds played an important role in the removal of the pharmaceuticals. This was already demonstrated by the previous reports [23,24].

Fig. 5 also demonstrated that the filtered wastewater acquired about 10% higher removal of pharmaceuticals than in the unfiltered one. This was due to SSs in the wastewater blocking part of pores of activated carbon and reducing adsorption sites, which could lead to the decrease in surface area due to pore blocking [25]. On the other side, micro-organisms' adsorption on activated carbon increased the hydrophobicity of carbon surface [26]. All these can reduce the adsorption capacity of pharmaceuticals on activated carbon.

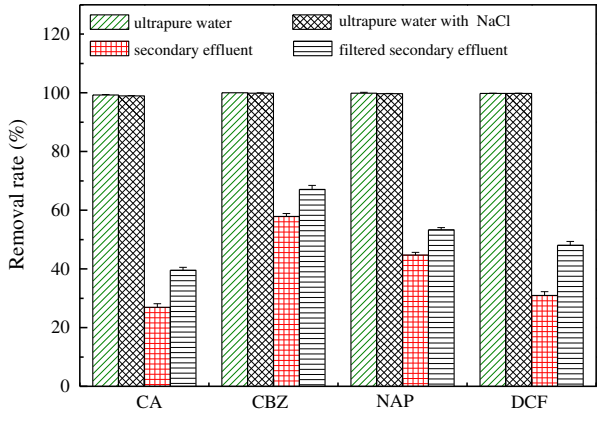


Fig. 5. The removal efficiencies of four pharmaceuticals in different solutions (UW with NaCl: 592 mg/L NaCl solution).

4. Conclusions

The adsorption processes of four pharmaceuticals, clofibric acid, carbamazepine, naproxen, and diclofenac on activated carbon were evaluated in spiked UW and secondary effluent. Coconut shell-based activated carbon can effectively remove the pharmaceuticals in the solution. While different target compounds on activated carbon had diverse adsorption capacities, which were related to the $\log k_{ow}$, pK_a value, and molecular weight. In secondary effluent, the SSs and soluble organic compounds decreased the adsorption capacity of pharmaceuticals on activated carbon dramatically. Therefore, most of the organic particles and soluble organic compounds in wastewater effluent should be removed before the activated carbon adsorption in practical application.

Acknowledgments

The study is supported by the special scientific research project from education department of Shaanxi province (Grant No. 12JK0640) and innovative research team of Xi'an University of Architecture and Technology.

References

[1] S. Jain, R.K. Vyas, P.Pandit, A.K. Dalai, Adsorption of antiviral drug, acyclovir from aqueous solution on powdered activated charcoal: Kinetics, equilibrium, and thermodynamic studies, Desalin. Water Treat. 52 (2014) 4953–4968.
[2] Q. Sui, J. Huang, S.B. Deng, G. Yu, Q. Fan, Occurrence and removal of pharmaceuticals, caffeine and DEET in wastewater treatment plants of Beijing, China, Water Res. 44 (2010) 417–426.
[3] A.Y. Lin, Y.T. Tsai, T.H. Yu, X.H. Wang, C.F. Lin, Occurrence and fate of pharmaceuticals and personal care products in Taiwan's aquatic environment, Desalin. Water Treat. 32 (2011) 57–64.
[4] J.d. Rudder, T.V.d. Wiele, W. Dhooge, F. Comhaire, W. Verstraete, Advanced water treatment with manganese oxide for the removal of 17α-ethynylestradiol (EE2), Water Res. 38 (2004) 184–192.

[5] A.M. Comerton, R.C. Andrews, D.M. Bagley, Practical overview of analytical methods for endocrine-disrupting compounds, pharmaceuticals and personal care products in water and wastewater, Philos. Trans. R. Soc. A: Math. Phys. Eng. Sci. 367 (2009) 3923–3939.
[6] M. Xie, L.D. Nghiem, W.E. Price, M. Elimelech, Comparison of the removal of hydrophobic trace organic contaminants by forward osmosis and reverse osmosis, Water Res. 46 (2012) 2683–2692.
[7] T.A. Ternes, A. Joss, H. Siegrist, Peer reviewed: Scrutinizing pharmaceuticals and personal care products in wastewater treatment, Environ. Sci. Technol. 38 (2004) 392A–399A.
[8] Y. Yoon, P. Westerhoff, S.A. Snyder, E.C. Wert, J. Yoon, Removal of endocrine disrupting compounds and pharmaceuticals by nanofiltration and ultrafiltration membranes, Desalination 202 (2007) 16–23.
[9] J. Radjenović, M. Petrović, F. Ventura, D. Barceló, Rejection of pharmaceuticals in nanofiltration and reverse osmosis membrane drinking water treatment, Water Res. 42 (2008) 3601–3610.
[10] E.J. Rosenfeldt, P.J. Chen, S. Kullman, K.G. Linden, Destruction of estrogenic activity in water using UV advanced oxidation, Sci. Total Environ. 377 (2007) 105–113.
[11] K. Ikehata, M.G. El-Din, S.A. Snyder, Ozonation and advanced oxidation treatment of emerging organic pollutants in water and wastewater, Ozone: Sci. Eng. 30 (2008) 21–26.
[12] A.D. Coelho, C. Sans, A. Agüera, M.J. Gómez, S. Esplugas, M. Dezotti, Effects of ozone pre-treatment on diclofenac: Intermediates, biodegradability and toxicity assessment, Sci. Total Environ. 407 (2009) 3572–3578.
[13] P. Westerhoff, Y. Yoon, S. Snyder, Fate of endocrine-disruptor, pharmaceutical, and personal care product chemicals during simulated drinking water treatment processes, Environ. Sci. Technol. 39 (2005) 6649–6663.
[14] P. Hongsawat, P. Prarat, C. Ngamcharussrivichai, P. Punyapalakul, Adsorption of ciprofloxacin on surface functionalized superparamagnetic porous silicas, Desalin. Water Treat. 52 (2014) 4430–4443.
[15] L. Huang, M. Wang, C. Shi, J. Huang, B. Zhang, Adsorption of tetracycline and ciprofloxacin on activated carbon prepared from lignin with H_3PO_4 activation, Desalin. Water Treat. 52 (2014) 2678–2687.
[16] Z. Yu, S. Peldszus, P.M. Huck, Adsorption characteristics of selected pharmaceuticals and an endocrine disrupting compound-Naproxen, carbamazepine and nonylphenol-on activated carbon, Water Res. 42 (2008) 2873–2882.
[17] S.H. Kim, H.K. Shon, H.H. Ngo, Adsorption characteristics of antibiotics trimethoprim on powdered and granular activated carbon, J. Ind. Eng. Chem. 16 (2010) 344–349.
[18] J.L. Sotelo, G. Ovejero, A. Rodríguez, S. álvarez, J. Galán, J. García, Competitive adsorption studies of caffeine and diclofenac aqueous solutions by activated carbon, Chem. Eng. J. 240 (2014) 443–453.
[19] J. Lü, L.Q. Zhang, L. Feng, Adsorption rules of activated carbons for trace carbamazepine in water, J. Chin. Environ. Eng. 6 (2012) 3529–3536.
[20] J. Lü, L. Feng, L.Q. Zhang, Adsorption of trace naproxen in water by different activated carbons, Chin., Acta Sci. Circumstantiae 32 (2012) 2443–2449.
[21] R. Baccar, M. Sarrà, J. Bouzid, M. Feki, P. Blánquez, Removal of pharmaceutical compounds by activated carbon prepared from agricultural by-product, Chem. Eng. J. 211–212 (2012) 310–317.
[22] E.F. Mohamed, C. Andriantsiferana, A.M. Wilhelm, H. Delmas, Competitive adsorption of phenolic compounds from aqueous solution using sludge-based activated carbon, Environ. Technol. 32 (2011) 1325–1336.
[23] K.J. Choi, S.G. Kim, S.H. Kim, Removal of tetracycline and sulfonamide classes of antibiotic compound by powdered activated carbon, Environ. Technol. 29 (2008) 333–342.
[24] S. Bekkouche, S. Baup, M. Bouhelassa, S. Molina-Boisseau, C. Petrier, Competitive adsorption of phenol and heavy metal ions onto titanium dioxide (Dugussa P25), Desalin. Water Treat. 37 (2012) 364–372.
[25] J. Rivera-Utrilla, I. Bautista-Toledo, M.A. Ferro-García, C. Moreno-Castilla, Activated carbon surface modifications by adsorption of bacteria and their effect on aqueous lead adsorption, J. Chem. Technol. Biotechnol. 76 (2001) 1209–1215.
[26] J. Rivera-Utrilla, C.V. Gómez-Pacheco, M. Sánchez-Polo, J.J. López-Peñalver, R. Ocampo-Pérez, Tetracycline removal from water by adsorption/bioadsorption on activated carbons and sludge-derived adsorbents, J. Environ. Manage. 131 (2013) 16–24.
[27] R.A. Trenholm, B.J. Vanderford, J.C. Holady, D.J. Rexing, S.A. Snyder, Broad range analysis of endocrine distuptors and pharmaceuticals using gas chromatography and liquid chromatography tandem mass spectrometry, Chemosphere 65 (2006) 1990–1998.
[28] J.E. Hoover, Carbamazepine, in: D. Troy (Ed.), Remington: The Science and Practice of Pharmacy, twenty-first ed., Lippincott Williams & Wilkins, Philadelphia, PA, 2005, p. 1503.