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Review

Fate of diclofenac in municipal wastewater treatment plant — A review

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ABSTRACT

Diclofenac (DCF) is a common anti-inflammatory pharmaceutical that is often detected in waste wasters, effluents and surface waters. Recently, DCF was included in the watch list of substances in EU that requires its environmental monitoring in the member states. DCF is also known to harmfully affect several environmental species already at concentrations of ≤1 μg/l. This review focuses on the occurrence and fate of DCF in conventional wastewater treatment processes. Research done in this area was gathered and analyzed in order to find out the possibilities to enhance DCF elimination during biological wastewater treatment. More precisely, human metabolism, concentrations in wastewater influents and effluents, elimination rates in the treatment train, roles of sorption and biotransformation mechanisms during the treatment as well as formation of transformation products are reported. Additionally, the effect of process configuration, i.e. conventional activated sludge (CAS), biological nutrient removal (BNR), membrane bioreactor (MBR) and attached-growth bioreactor, and process parameters, i.e. solids retention time (SRT) and hydraulic retention time (HRT) are presented. Generally, DCF is poorly biodegradable which often translates into low elimination rates during biological wastewater treatment. Only a minor portion is sorbed to sludge. MBR and attached-growth bioreactors may result in higher elimination of DCF over CAS or BNR. Long SRTs (>150 d) favor the DCF elimination due to sludge adaptation. Longer HRTs (>2–3 d) could significantly increase the elimination of DCF during biological wastewater treatment. Bioaugmentation could be used to enhance DCF elimination, however, this requires more research on microbial communities that are able to degrade DCF. Also, further research is needed to gain more information about the deconjugation processes and biotic and abiotic transformation and the nature of transformation products.

Contents

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1. Introduction

Diclofenac (2-(2-(2,6-dichlorophenylamino)phenyl)acetic acid) (DCF) is a common non-steroidal anti-inflammatory drug (NSAID) that is used as oral tablets or as a topical gel. It is sold under the commercial names of *Acoflam*, *Algosenac*, *Almiral*, *Ana-Flex*, *Anthraxiton*, *Antiflam*, *Arcanafenac*, *Arthrex*, *Arthrifen*, *Arthtotec*, *Diclabeta*, *Diclac*, *Dicloabac*, *Diclodoc*, *Diclofenac–Ratiopharm*, *Diclofenbeta*, *Diclomex*, *Diclowal*, *Dicuno*, *Difen*, *Diklotab*, *Dolgit–Diclo*, *Eese*, *Effekton*, *Jutafenac*, *Monoflam*, *Motifene Dual*, *Rewodina*, *Sigafenac* and *Voltaren*. Its physic-chemical properties are presented in Table 1 and molecular structure in Fig. 1.

In the point of view of environmental regulations in EU, pharmaceuticals and hormones are a highly topical group of compounds. A proposal was made during the revision of the Water Framework Directive (2000/60/EC) in European Union that would have classified DCF along with two estrogenic hormones as priority substances. In the end, in Directive 2013/39/EU, DCF and the hormones were included in the watch list of substances that will be established alongside the list of priority substances (EU, 2013). Substances in the watch list shall be monitored by the EU member states in their surface waters for a maximum of four years. However, no environmental quality standards (EQS) were assigned for the watch list substances. However, during the revision process, EQS value of 100 ng/l for inland waters and 10 ng/l for coastal water were proposed for DCF. Due to the wide interest of regulators and the public to DCF, this review focuses solely on this common anti-inflammatory drug. Its fate in the human body and during the municipal wastewater treatment is reviewed. Additionally, mechanisms of sorption and biotransformation as well as formation of transformation products are discussed. The effect of process configuration, i.e. conventional activated sludge (CAS), biological nutrient removal (BNR), membrane bioreactor (MBR) and attached-growth bioreactor as well as process parameters, i.e. solids retention time (SRT) and hydraulic retention time (HRT) are reviewed. No review has been published that would concentrate on DCF, its fate and transformation processes in conventional wastewater treatment and would have aimed to identify the possibilities to increase its elimination by enhancing the existing treatment processes. Previously published reviews have focused in reporting the concentrations of wide range of micropollutants (Ratola et al., 2012) or their removals in various biological systems (Li et al., 2014; Onesios et al., 2009; Verlicchi et al., 2012).

Table 1
Physico-chemical properties of diclofenac.

Parameter	Value	Reference
Chemical formula	$C_{14}H_{10}Cl_2NO_2$	–
CAS no	15307-86-5	–
	15307-79-6 (disodium salt)	–
Water solubility	2.37 mg/L	SRC (2013)
pK_a	4.15	SRC (2013)
$logK_{ow}$	4.51	SRC (2013)
$logK_{d,primary\ sludge}$	2.7	Ternes et al. (2004a)
	2.3	Radjenovic et al. (2009)
$logK_{d,secondary\ sludge}$	1.2	Ternes et al. (2004a)
	2.1	Radjenovic et al. (2009)
$logK_{d,\ MBR}$	2.3–2.5	Radjenovic et al. (2009)
$logK_{d,digested\ sludge}$	1.3–2.2	Carballa et al. (2008)

1.1. Human metabolism of DCF

DCF is administered topically or orally and undergoes almost complete biotransformation in the human body. Topical gel adsorption was found to be 6–7% (Davies and Anderson, 1997). The remaining part is either washed off the skin or is attached to clothing. Of the orally administered dose, between 65 and 70% is excreted in urine and 20–30% in feces as the parent drug or as metabolites (Davies and Anderson, 1997; Stierlin and Faigle, 1979). The majority of DCF is metabolized in the human body and only <1% of the orally administered dose is excreted as un-metabolized DCF. As a result of phase II metabolism involving glucuronic acid and taurine, glucuronide and sulfate conjugates of DCF are formed. These conjugates make up to 11% of the administered dose (Davies and Anderson, 1997; Stierlin and Faigle, 1979). The World Health Organization has defined a daily dose for diclofenac of 100 mg. Of this dose, less than 1 mg is eliminated from the human body as DCF and about 11 mg as DCF conjugates. The rest of the administered dose is excreted as metabolites of DCF or their conjugates.

Metabolic pathway of DCF in human body is presented in Fig. 1. Six phase I metabolites of DCF have been detected in human plasma, urine and/or feces. According to Davies and Anderson (1997), the pattern of DCF metabolites in human urine is the same after topical and oral administration. In total, the six metabolites of DCF and the conjugates of these account for 90% and 65% of the total administered DCF in urine and in feces, respectively (Blum et al., 1996; Davies and Anderson, 1997; Faigle et al., 1988; Stierlin and Faigle, 1979). The main human metabolites of DCF are 4′-OH-DCF and 5-OH-DCF. Both of them are excreted mainly in conjugated form and only less than 1% is excreted unchanged (Stierlin and Faigle, 1979). Important metabolites are also 3′-hydroxy-DCF and 4′,5-dihydroxy-DCF. The two remaining metabolites, 3′-OH-4′-OCH_3-DCF and 4′-OH-3′-OCH_3-DCF are excreted in urine only in trace amounts (Blum et al., 1996; Faigle et al., 1988).

In some animal models, 4′-OH-DCF has been shown to have 30% of the anti-inflammatory and antipyretic activity of DCF (Davies and Anderson, 1997). However, according to Wiesenberg-Boettcher et al., the anti-inflammatory activity of the main metabolites of DCF is at least 10 times lower compared to DCF activity (Wiesenberg-Boettcher et al., 1991).

1.2. Occurrence of DCF in wastewaters, effluents, environment and drinking waters

In reviewed studies, the measured maximum concentrations of DCF in municipal wastewaters vary between 0.44 and 7.1 μg/l and the mean concentrations are between 0.11 and 2.3 μg/l (Table 2). According to Sim et al. (2011), the maximum concentrations in hospital wastewater reached 6.88 μg/l and in pharmaceutical manufacturer's wastewater 203 μg/l in South Korea. The values are significantly higher than normally detected in municipal wastewater. On the other hand, Zorita et al. (2009) measured similar concentrations (around 0.2 μg/l) in both hospital and municipal wastewater in Sweden. Municipal wastewater concentrations reflect the consumption of DCF by the residents in the particular sewer system. The consumption rates vary greatly between countries and also within countries. This makes it difficult to determine typical wastewater concentrations. The yearly consumption of DCF has been reported to vary between 195 and 940 mg per inhabitant in different countries (Carballa, 2005; Clara et al., 2005b; Finnish Medicines Agency, 2013; Khan and Ongerth, 2004; Sakshaug, 2012; Ternes, 1998).

In the effluents of municipal wastewater treatment plants, DCF is among the most frequently detected pharmaceuticals (Verlicchi et al.,