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Behaviour of nonsteroidal anti-inflammatory drugs and eight of their metabolites during wastewater treatment studied by hollow fibre liquid phase microextraction and liquid chromatography mass spectrometry

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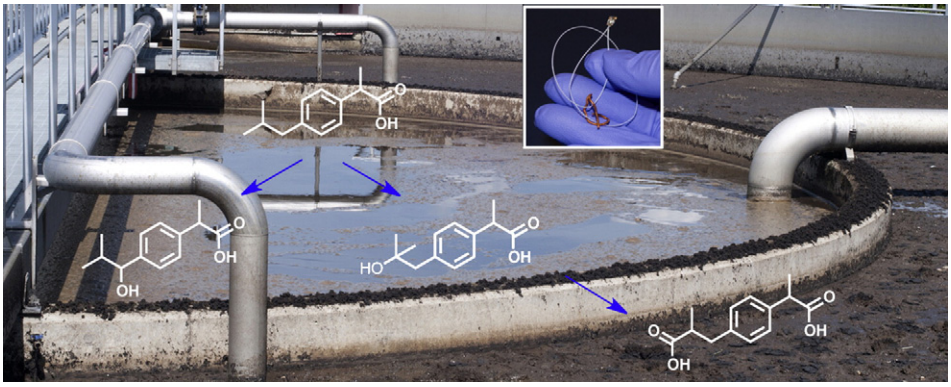
HIGHLIGHTS

- The fate of four NSAIDs and eight of their human metabolites in a WWTP was studied.
- An HF-LPME method was developed for extraction of target analytes from wastewater.
- Ibuprofen and naproxen metabolites were found in very high amounts in the influent.
- All compounds were efficiently removed during the activated sludge treatment.
- The studied metabolites are hence either not formed or quickly further degraded.

GRAPHICAL ABSTRACT



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ABSTRACT

In this work hollow fibre liquid phase microextraction combined with liquid chromatography mass spectrometry was applied for the determination of the nonsteroidal anti-inflammatory drugs (NSAIDs) ketoprofen, naproxen, diclofenac and ibuprofen as well as eight of their known human metabolites in wastewater samples. Extraction time and addition of tri-*n*-octylphosphine oxide (TOPO) to the liquid membrane were evaluated resulting in a method with an optimal extraction time of 5 h and 5% (w/V) TOPO addition to the membrane liquid (di-*n*-hexyl ether). With the optimized method, enrichment factors ranged between 778 and 4830. The method was applied for analysis of samples collected from Källby wastewater treatment plant in the city of Lund, Sweden. Samples were collected from the influent, water entering as well as exiting the conventional activated sludge treatment and the effluent to study the behaviour of these compounds during the treatment process. All twelve substances were found in the influent and for all four drugs, higher concentrations were detected of the metabolites than the parent compounds. Highest concentrations were detected of *o*-desmethylnaproxen, 2-hydroxyibuprofen and carboxyibuprofen (average influent concentrations of 45, 35 and 63 μg/L respectively). The study showed only partial removal during the primary treatment whereas both parent compounds and metabolites were efficiently removed during the activated sludge process. In the effluent all analytes were detected in concentrations below 1 μg/L thus showing that either the investigated metabolites do not belong to the NSAID transformation products formed during the activated sludge treatment or they are also quickly further transformed within the treatment.

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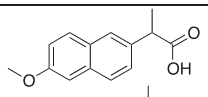
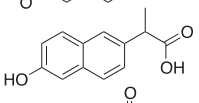
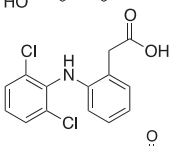
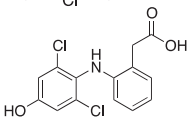
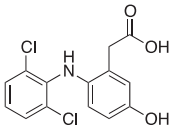
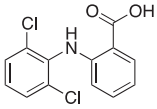
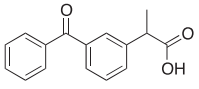
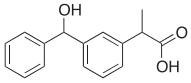
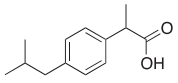
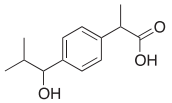
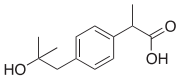
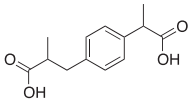
1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly applied pharmaceuticals worldwide and several studies report the presence of these substances in wastewater treatment plant (WWTP) influents due to human excretion (Dahanec et al., 2013; Migowska et al., 2012; Martín et al., 2012). However, pharmacokinetic studies reveal that these compounds undergo metabolic transformation in the human body and are to a large extent excreted as their phase I or phase II metabolites. Thus, a substantial part of the consumed NSAIDs enters WWTPs in the form of metabolites. Human metabolic pathways include phase I oxidation via insertion of a hydroxyl or carboxyl group which has been shown for both ibuprofen and diclofenac (Davies, 1998; Davies and Anderson, 1997) with 2-hydroxyibuprofen and carboxyibuprofen being the main ibuprofen metabolites (Davies, 1998) and 4′-hydroxydiclofenac being the main diclofenac metabolite (Davies and Anderson, 1997) (structures presented in Table 1). Naproxen is demethylated forming *o*-desmethylnaproxen to approx. 20% whereas about 60% of the drug remains unchanged (Vree et al., 1993). Ketoprofen can undergo hydroxylation of the aromatic ring in 3′ or 4′ position as well as reduction of the keto functionality to a hydroxyl group, forming dihydroketoprofen (Skordi et al., 2004). A major part of the parent compounds as well as their phase I metabolites undergo phase II conjugation with glucuronic acid and are mainly excreted as their corresponding acyl glucuronides (Vree et al., 1993). These do in general not possess any biological activity, but can be transformed back to the original substance in or during the transport to the WWTP (Celiz et al., 2009). Although adverse effects of NSAIDs have been shown in aquatic organisms (Parolini et al., 2011; Nishi et al., 2010; Parolini et al., 2009), data about the toxicity of their human metabolites are yet scarce and inconclusive. Neither 1-hydroxy- nor carboxyibuprofen is considered to possess any pharmacological activity (Besse and Garic, 2008) and Leinert et al.

Table 1
Analytes, structure and properties. DHK and CDI were added to the study later and were therefore not included in method optimization experiments. The diclofenac metabolites 4OH and 5OH were quantified together during method optimization since chromatographic separation of these compounds was not achieved at this stage.

Name	CAS #	Abbrev.	Structure	Log D pH 7	Log D pH 2
Naproxen	23981-80-8	NAP		0.73	2.88
o-Desmethylnaproxen	52079-10-4	ODN		0.09	2.25
Diclofenac	15307-79-6	DIC		1.77	4.55
4′-Hydroxydiclofenac	64118-84-9	4OH		1.77	4.55
5-Hydroxydiclofenac	69002-84-2	5OH		1.14	3.99
Carboxydiclofenac	13625-57-5	CDI		2.40	3.99
Ketoprofen	22071-15-4	KET		0.19	2.91
Dihydroketoprofen	59960-32-6	DHK		−1.18	1.49
Ibuprofen	15687-27-1	IBU		0.94	3.50
1-Hydroxyibuprofen	53949-53-4	1OH		−0.54	2.06
2-Hydroxyibuprofen	51146-55-5	2OH		−0.87	1.68
Carboxyibuprofen	15935-54-3	CIB		−3.63	0.86