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Research Article

Stability and Removal of Naproxen and Its Metabolite by Advanced Membrane Wastewater Treatment Plant and Micelle–Clay Complex

Naproxen, a non-steroidal anti-inflammatory drug, commonly used for fever, inflammation and for different health problems, as found for many pharmaceuticals has been recently detected in sewage effluents, surface, and ground water, and sometimes even in drinking water. An advanced wastewater treatment plant (WWTP), utilizing ultra-filtration, activated charcoal (AC), and reverse osmosis (RO) after the primary biological treatment, showed that both nano- and micro-ultrafiltration were not sufficient for removing spiked naproxen to a safe level, whereas RO membrane was quite efficient. No naproxen degradation was detected in pure water whereas it underwent biodegradation within three days in activated sludge giving *O*-desmethyl-naproxen. Adsorption performed on micelle–clay complex and AC under steady state conditions, showed that the former adsorbent is highly effective in removing naproxen with fast kinetics. Laboratory micelle–clay complex filters under continuous naproxen-spiked water flowing were found to be efficient in removing this drug, suggesting that the efficiency of existing advanced WWTP could be improved by including filtration columns filled with suitable sand/micelle–clay mixtures.

Keywords: Activated charcoal; *O*-Desmethyl-naproxen; Filtration techniques; Non-steroidal anti-inflammatory drugs

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1 Introduction

Pharmaceuticals (antibiotics, anticonvulsants, antipyretics drugs, hormones) have recently been detected in sewage effluents [1], surface and ground water [2], and sometimes even in drinking water [3, 4], suggesting that their possible environmental impact is an emerging environmental issue [5–8].

The presence of pharmaceutically active compounds (PhACs) in surface waters is well documented in the literature [9]. A major route of the PhACs into the aquatic environment is through sewage treatment plants (STPs) following excretion in feces and urine after their intended use and disposal of unused medications into the toilet [10–16]. Because effective operation of wastewater treatment plants is important for minimizing the release of the xenobiotic compounds, our study focuses on the evaluation of the performance of ultra-filtration membranes (hollow fiber and spiral wound membranes), activated charcoal, and reverse osmosis in removal of Naproxen from synthetic wastewater samples.

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Abbreviations: AC, activated charcoal; **DMN**, *O*-desmethyl-naproxen; **GAC**, granular AC; **HF**, hollow fiber; **MF**, micro-filtration; **NF**, nano-filtration; **NSAID**, non-steroidal anti-inflammatory drug; **ODTMA**, octadecyltrimethyl-ammonium; **OTC**, over-the-counter; **PhAC**, pharmaceutically active compound; **RO**, reverse osmosis; **STP**, sewage treatment plant; **SW**, spiral wound; **WWTP**, wastewater treatment plant

Naproxen (2-naphthaleneacetic acid, 6-methoxy-α-methyl-, (*S*)-(+)-(*S*)-6-methoxy-α-methyl-2-naphthaleneacetic acid) (for the chemical structure, see Fig. 1) is a non-steroidal anti-inflammatory drug (NSAID) commonly used for fever, inflammation and reducing pain and stiffness caused by different health problems (migraine, osteoarthritis, kidney stones, and also primary dysmenorrhea). Naproxen and naproxen sodium were originally marketed as prescription drugs until recently they were approved for use as over-the-counter (OTC) drugs in most countries. Naproxen belongs to propionic acid derivatives family as ibuprofen, dexibuprofen, fenoprofen, and others. All of these drugs inhibit the cyclooxygenases COX-1 and COX-2 enzymes that are responsible for the formation of important biological mediators such as prostaglandins, prostacyclin, and thromboxane. Pharmacological inhibition of COX can provide relief from the symptoms of inflammation. Most NSAID drugs are weak acids, with a pK_a ranging between 3 and 5, they are metabolized in the liver by oxidation and conjugation to inactive metabolites that typically are excreted in the urine, though some drugs can be partially excreted in bile [17, 18].

The current estimated annual consumption of these non-steroidal anti-inflammatory drugs in developed countries is several hundred tons [5].

Under extreme conditions (pH, high temperature, etc.) the naproxen degrades slowly and the formation of *O*-desmethyl-naproxen (DMN) is a result of the ether cleavage in the initial step of his microbial degradation (Fig. 1) [19]. It should be emphasized that ether compounds, such as naproxen, are quite stable at neutral and basic pH media and they are cleaved only when they are heated in concentrated acids such as sulfuric and nitric.

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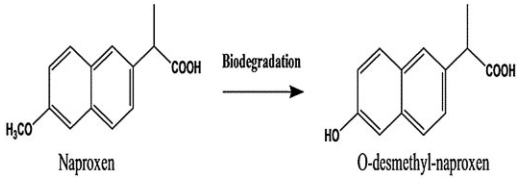

Figure 1. Biodegradation of naproxen to DMN.

Naproxen has been detected in wastewater and surface water in the ranges 0.1–2.6 [20, 21], and 0.01–0.1 $\mu g\,L^{-1}$ [22], respectively, implying that wastewater treatment plants are not currently efficient for the complete elimination of this PhAC from wastewater. In particular, sedimentation and coagulation processes were found to be ineffective for the removal of naproxen from surface water, whereas disinfection (chlorination) and adsorption could be more efficient methods [23]. However, the removal by ozonation and sorption onto granular activated charcoal (GAC) were generally found to be satisfactory [24, 25]. Moreover, water treatment by adsorption technologies using low cost adsorbents has been shown to be very effective in removing organic pollutants as well as heavy metals [26–30]. Tertiary treatments such as physical removal through micro-filtration (MF), nano-filtration (NF), reverse osmosis (RO), or chemical removal using advanced oxidation processes have been demonstrated to be effective in reducing pharmaceutical concentrations [24, 31, 32]. Reported concentration ranges of pharmaceuticals after tertiary treatment (10 $ng\,L^{-1}$ down to $pg\,L^{-1}$) are orders of magnitude lower than health-based guideline values [5], and acute toxicity data for aquatic organisms [33]. However, there is still significant uncertainty regarding the long-term risk associated with pharmaceutical mixtures present at low concentration levels for non-target wildlife organisms as well as for human health [33, 34].

The main goal of this study was to study the stability of naproxen in activated sludge and to test the performance of advance integrated membrane wastewater treatment plant in terms of naproxen removal from synthetic wastewater samples. In addition, the removal of naproxen by using filters that include micelle–clay complex and its adsorption isotherms in suspension was also studied.

2 Materials and methods

2.1 Chemicals and analytical determinations

All chemicals were of analytical grade. The clay used was Wyoming Na-montmorillonite SWY-2 (MMT) obtained from the Source Clays Registry (Clay Mineral Society, Columbia, MO). Quartz sand (grain size 0.8–1.2 mm) was purchased from Negev Industrial Minerals (Israel). Naproxen sodium was obtained as a gift from Beit Jalah (Palestine). Octadecyltrimethylammonium (ODTMA) bromide, activated charcoal (12–20 mesh), magnesium sulfate, methanol, acetonitrile, tetrahydrofuran (THF), and purified water were obtained from Sigma (USA). All solvents used were HPLC grade. High purity diethyl ether (>99%) was purchased from Biolab (Israel), orthophosphoric acid was obtained from Riedel-De Haen (Germany).

The HPLC system used was a Waters Alliance 2695 HPLC, equipped with a photodiode array detector (Waters Micromass® Masslynx™). Data acquisition and control were carried out using Empower™ software (Waters, Israel). Analytes were separated on a 4.6 × 150 mm C18 XBridge® column (5 μm particle size) used in conjunction with a 4.6 × 20 mm XBridge™ C18 guard column. Microfilters 0.45 μm (Acrodisc® GHP, Waters) were employed. The optimal conditions found for the analysis of naproxen were: mobile phase 20:80 (v/v) mixture of water/acetonitrile (pH adjusted to 3.45 using dilute *o*-phosphoric acid), flow rate 1.0 $mL\,min^{-1}$, UV detection at a wavelength of 240 nm.

A stock solution was prepared by dissolving naproxen standard in pure water at a concentration of 200 $mg\,L^{-1}$. Analytical solutions were obtained by dilution of the stock solution and injected into the liquid chromatograph. A calibration curve was acquired having a determination coefficient $R^2 = 0.9986$.

2.2 Stability study in pure water and activated sludge

Stability studies of naproxen were performed at 25°C by dissolving 100 mg of naproxen either in 1 L of pure water or in 1 L of activated sludge sampled from the wastewater treatment plant (WWTP) located in the Al-Quds University (Abu-Dies Main Campus, Palestine). Activated sludge was maintained under continuous aeration to permit the survival of microorganisms. Samples were collected time by time, filtered using 0.45-μm cellulose nitrate filters, stored at 4°C and analyzed by HPLC at the time. The degradation by-product DMN was extracted using solid phase extraction and lyophilized to have solid sample for batch experiment.

2.3 Efficiency of advanced stages in Al-Quds wastewater depuration system

The wastewater depuration system of Al-Quds University has been described previously [35, 36]. To ascertain the removal efficiency of the advanced stages of this depuration system (hollow fiber and spiral wound ultra-filtration membranes, activated carbon and reverse osmosis), 500 L of 31.1 $mg\,L^{-1}$ of naproxen were prepared and introduced into the inlet-head of the ultra-filtration stage (Fig. 2). Analytical determinations were carried out on seven water samples (labeled from No. 1 to 7 in Fig. 2) collected from different locations of the WWTP using pre-cleaned 500-mL amber glass bottles. Samples were filtered by using 0.45-μm cellulose nitrate filters, stored at 4°C and analyzed by HPLC at the time.

2.4 Micelle–clay complex preparation

The complex was prepared as described previously [37]. Briefly, 10 $g\,L^{-1}$ Na-montmorillonite SWY-2 (MMT) were added to 12 mM solution of ODTMA-bromide and stirred for 72 h. Then the suspension was centrifuged for 20 min at 15 000 rpm. The solid material (micelle–clay complex) was washed with pure water and lyophilized.

2.5 Batch adsorption studies and adsorption isotherms

2.5.1 Batch adsorption

One hundred milliliter of naproxen solutions (in the range of concentrations of 50–200 $mg\,L^{-1}$) were introduced into 250-mL Erlenmeyer flasks containing 0.5 g of either micelle–clay complex or charcoal. The obtained suspensions were shaken for 3 h at 25.0 ± 0.2°C, centrifuged for 5 min and filtered using 0.45-μm

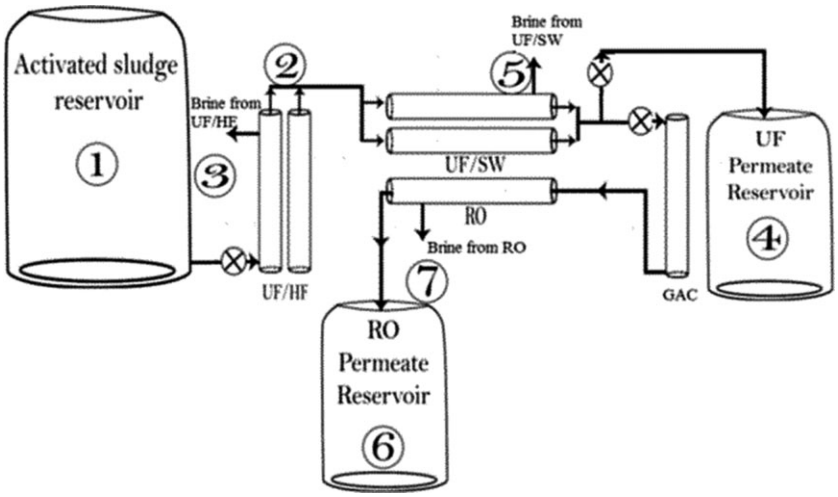

Figure 2. Scheme of a WWTP showing each section of the treatment process, including HF-UF (hollow fiber) and SW-UF (spiral wound) ultra-filtration stages, GAC and RO stages; sampling sites are indicated from 1 to 7.

Millipore filter. The liquid phases were collected and analyzed by liquid chromatography to determine the equilibrium concentrations.

A kinetic study of the extent of adsorption was further determined at 25°C by introducing 100 mL of 200 mg L^{-1} naproxen solution in 250-mL Erlenmeyer flasks containing 0.5 g of either micelle–clay complex or charcoal and determining the naproxen remaining time by time. The experiment was repeated on 50 mg L^{-1} solution of the metabolite DMN, using the same ratio solution volume/micelle–clay mass.

2.5.2 Adsorption isotherms

Equilibrium relationships between adsorbent and adsorbate were obtained by using Langmuir and Freundlich adsorption isotherms.

The linear form of the Langmuir adsorption isotherm was adopted according to Eq. (1) [18]:

$$\frac{C_e}{Q_e} = \frac{1}{KQ_{max}} + \frac{C_e}{Q_{max}} \quad (1)$$

where C_e is the equilibrium concentration of naproxen in mg L^{-1}, Q_e is the equilibrium mass of adsorbed naproxen per gram of complex or charcoal, K is the Langmuir binding constant (L mg^{-1}), and Q_{max} is the maximum mass of naproxen removed per gram of complex.

Freundlich isotherm describes the adsorption equilibrium on heterogeneous surface and its linear form is given by Eq. (2):

$$\log q_e = \log k + \frac{1}{n} \log C_e \quad (2)$$

where C_e is the equilibrium concentration of solute in mg L^{-1}, q_e is the amount of solute adsorbed per unit weight of adsorbent, k is the relative adsorption capacity of the adsorbent and n is the intensity of the adsorption.

2.6 Column experiments

Column experiments were performed using glass columns (18 × 4 cm) prepared by mixing 3 g of micelle–clay complex and 147 g sand. Sand was thoroughly washed with distilled water and dried at 105 ± 2°C for 24 h prior its use. Wool layer of 2 cm was placed at the bottom of the column to prevent clogging. 1000 mL of 252 mg L^{-1} (1 mM) naproxen sodium solution was passed through the column at a fixed flow rate of 2 mL min^{-1}. Eluted fractions of 100 mL (each) were collected time after time, and analyzed for naproxen concentration using HPLC.

All experiments described were conducted in triplicates.

3 Results and discussion

3.1 Stability of naproxen

3.1.1 Stability of naproxen in pure water

The monitoring of naproxen stability in pure water at 25°C revealed that no degradation occurred during 14 days. No traces of either chemical or biological degradation were observed during the monitoring days (data not shown). This result is in accordance with the fact that ether linkage could be cleaved only in the acidic environment and with the aid of high temperature [19, 20].

3.1.2 Biodegradation of naproxen in Al-Quds activated sludge

In the presence of activated sludge a slight decrease of naproxen concentration and appearance of a small quantity of a metabolite occurred after 24 h. After 28 days, 99% of naproxen was degraded. The degradation of the drug followed a pseudo first order kinetics with a rate constant of 7.16×10^{-3} h^{-1} and 96-h half-life at 25°C.

The presence of naproxen metabolite DMN in municipal wastewater was previously reported [10, 11].

In order to shed light on the nature of the product obtained in our experiment a more accurate biodegradation study was conducted in batch cultures using naproxen as single substrate at a concentration of 50 mg L^{-1}. LC–diode array detector, LC–MS, and ^{1}H-NMR techniques were used to identify the presence of metabolites and characterize their structure. Table 1 illustrates the progress of naproxen biodegradation as determined by LC–diode array detector: naproxen peak shows a retention time of ca. 2.3 min whereas naproxen degradation product shows a retention time of ca. 2.0 min. Naproxen biodegradation was relatively slow, showing about 80% drug disappearance in the first 15 days of incubation. Only one metabolite was detected and identified. According to molecular anions detected by MS set in negative mode (M−1 = m/z 215 and M−45 = m/z 171) we argue that the metabolite could be DMN. In

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Table 1. Progress of naproxen degradation in the sludge and increase of metabolite during 15 days of contact

	Time 0			24 h			120 h			360 h		
Compound	C	Abs	RT	C	Abs	RT	C	Abs	RT	C	Abs	RT
Naproxen	100	1.43	2.27	84.4	1.35	2.269	60.2	0.87	2.27	19.4	0.28	2.29
DMN	bld	bld	bld	5.2	0.05	1.999	40.2	0.41	1.98	80.4	1.65	2.00

C, concentration in mg L^{-1}; Abs, UV absorbance; RT, chromatographic retention time (min); bld, below the limit of detection.

addition, the singlet at 3.8 ppm belonging to the methoxy group of naproxen was not found in the ^{1}H-NMR spectrum of the isolated metabolite collected after column separation. The ether cleavage of naproxen is very well documented for mammalians [38], and fungi [39, 40] metabolism, and has been also indicated as a bacterial metabolite [19]. In some cases naproxen was found in the range 50–65% after treatment of municipal wastewater by using activated sludge [1, 10, 41]. Nevertheless, a complete removal of naproxen was reported in one study for wastewater treatments including water disinfection by chlorination after microbial degradation [42].

3.2 Efficiency of advanced stages of Al-Quds wastewater depuration system

Figure 3 summarizes the naproxen concentrations during all the wastewater treatment process by using the Al-Quds University plant (Fig. 2). The initial concentration of naproxen solution put in the main tank (emptied of the activated sludge and cleaned carefully) was 31.1 mg L^{-1}. It is clear that the RO unit gave practically a complete removal of naproxen from wastewater.

3.3 Batch adsorption studies and adsorption isotherms

The removal efficiency of naproxen by activated charcoal and micelle–clay complex was investigated using 200 mg L^{-1} naproxen solution containing 5 g L^{-1} of either micelle–clay complex or charcoal.

Kinetic parameters were calculated by means of integrated equations describing zero-, first-, and second-order reactions using mean values of triplicate data [43]. The best fit was checked by the least-square method of estimation (data not shown). The adsorption rate was best fitted by the Langmuir–Hinshelwood-type Eq. (3), which describes a second-order reaction:

$$C_0 - C_t = \frac{C_0 t}{t_{1/2} + t} \tag{3}$$

where C_t is the concentration at time t; C_0 is the initial concentration; $(C_0 - C_t)$ is the adsorbed quantity at a given time; $t_{1/2}$ is the half-time of adsorption reaction given by Eq. (4):

$$t_{1/2} = \frac{1}{KC_0} \tag{4}$$

where K is the kinetic constant of the adsorption reaction.

Figure 4 reports the kinetics of naproxen adsorption by the micelle–clay complex, revealing that this material is very effective for the drug removal from water. The adsorption half-time was 6.98 min, the kinetic constant was $7.17\,10^{-4}$ min^{-1} L mg^{-1}. In Fig. 5, we compare the removal of naproxen from water (added with three different concentrations of the drug) by the micelle–clay complex and the activated charcoal, showing that the former is more effective than activated charcoal.

Table 2 reports parameters of isotherms calculated by applying Eqs. (1) and (2) to both micelle–clay complex and activated charcoal adsorption isotherms. Comparing the correlation coefficient values

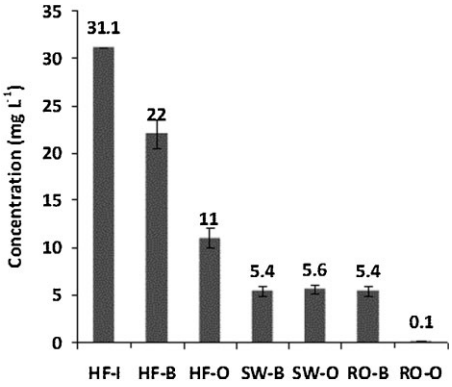

Figure 3. Concentration of naproxen after each section of the treatment process in WWTP at Al-Quds University Plant; HF-I, initial concentration at the HF-inlet (water spiked with 31.1 mg L^{-1} naproxen); HF-B, concentration in the HF-brine; HF-O, concentration at the HF-outlet; SW-B, concentration in the SW-brine; SW-O, concentration at the SW-outlet; RO-B, concentration in the RO-brine; RO-O, concentration at the RO-outlet.

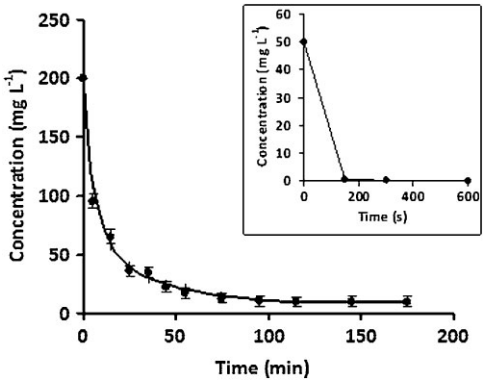

Figure 4. Adsorption of naproxen by a micelle–clay complex; initial concentration 200 mg L^{-1} (naproxen sodium); adsorbent dosage 5 g L^{-1}; temperature 25°C. The inset shows the adsorption kinetics of the metabolite DMN in the same conditions, but starting from an initial concentration of 50 mg L^{-1}, which simulates 25% extent of naproxen biodegradation occurring after eight days of contact with the activated sludge in first sector of the WWTP.

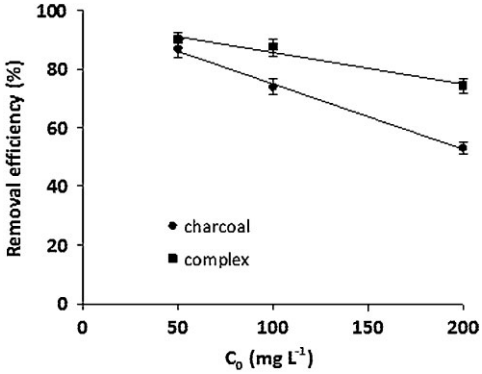

Figure 5. Removal efficiency of naproxen by charcoal (◆) and a micelle–clay complex (■); adsorbent dosage 5 g L^{-1}; contact time 3 h; temperature 25°C; initial drug concentrations 50, 100, and 200 mg L^{-1}.

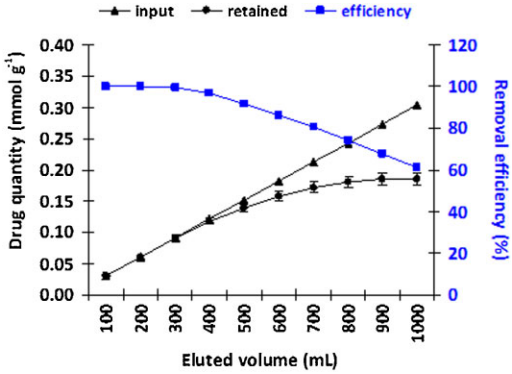

Figure 6. Efficiency of 1 mmol L^{-1} drug solution filtration by means of laboratory column (18 × 4 cm) filled with a 2% micelle–clay complex/quarts sand mixture; weight of mixture 150 g, including 3 g of micelle–clay; elution rate 2 mL min^{-1}; eluted volume 1000 mL.

obtained by Langmuir and Freundlich equations it was found that Langmuir equation gave a better fit with experimental data. When the micelle–clay complex was used for naproxen removal, the Langmuir constant Q_{max} was much higher (71.42 mg g^{-1}) compared to activated charcoal (18.87 mg g^{-1}) confirming the efficiency of the complex in removing the drug from water.

To ascertain that the micelle–clay complex can also retain the metabolite DMN, which arose from the biodegradation of naproxen in the activated sludge (the first sector of the WWTP), the adsorption experiment was repeated on this compound in the same conditions, but starting from an initial concentration of 50 mg L^{-1}. This concentration simulates 25% extent of naproxen biodegradation occurring after 8 days of contact with the activated sludge. The metabolite concentration fell down to undetectable values in few minutes (inset in Fig. 4). Also in this case the adsorption rate was best fitted by Eq. (3). The adsorption half-time of DMN was 1.5 s, the kinetic constant was 1.34 10^{-2} s^{-1} L mg^{-1}. The metabolite was quantitatively removed by the micelle–clay complex in 10 min. The rationale behind such behavior can be found in the increased negative charge on the metabolite molecule, where the methoxyl group present in the mother molecule has been substituted by a hydroxyl group. The introduction of the positively charged ODTMA micelles into the interlayer spaces of montmorillonite caused the inversion of the charge sign on the exchange sites of the modified clay, which can more easily adsorb negatively charged compounds. Increased charge of adsorbate yielded higher rate and extent of adsorption.

3.4 Column experiments

One thousand milliliter of naproxen sodium solution (252 mg L^{-1} or 1 mmol L^{-1}) were eluted in triplicate through column filters (18 × 4 cm) filled with a mixture of 2% micelle–clay complex in quartz sand. Practically, a complete removal of naproxen was observed in the first three fractions of 100 mL collected during the elution up to 300 mL (Fig. 6). The initial capacity of naproxen retention under the experimental conditions was ca. 0.1 mmol/g of micelle clay by the filter, showing a retention efficiency range of 99.9–99.8%.

Comparing results of batch adsorption kinetics reported in Fig. 4 (200 mg L^{-1} solution/5 g L^{-1} adsorbent) with those of Fig. 6, it is evident that the flow rate used (2 mL min^{-1}) can be suitable for the filtration of 300 mL of 1 mM naproxen solution, yielding a complete removal of the drug. On the other hand, the value of Q_{max} obtained by means of the Langmuir isotherm (Eq. 1) was higher than 71 mg g^{-1} (0.3 mmol g^{-1}) in the adsorption experiments performed on 100 mL of naproxen solutions (in the range of concentrations 50–200 mg L^{-1}) containing only 0.5 g of micelle–clay.

The removal efficiency was diminishing with the elution of other volumes of the naproxen solution up to 1000 mL. At the end of the experiment the column received a larger amount of naproxen (1 mmol) and was able to remove about 0.6 mmol of the input drug or 0.2 mmol g^{-1} complex.

The demonstrated capacity of naproxen removal by filtration would be increased using either a column filled with a larger percentage of the micelle–clay complex or a longer column.

It may be noted that the efficiency of filtration by activated carbon is inversely correlated with temperature. It was shown that the efficiency of filtration of two herbicides by activated carbon dropped dramatically at 35°C and was poor at 50°C [44], whereas that of the micelle–clay filter was unaffected by temperature.

The conclusion emerging is that, with a proper technology (as micelle–clay adsorbent) naproxen could be completely removed from wastewater. This high efficiency can be attributed to the strong affinity between the anionic naproxen group and the positively charged micelle–clay complex which is based on ODTMA.

Table 2. Comparison between naproxen adsorption isotherm parameters by using activated charcoal and micelle–clay complex

	Langmuir isotherm			Freundlich isotherm		
Type of adsorbents	R^2	Q_{max} (mg g^{-1})	K (L mg^{-1})	R^2	k (mg g^{-1})	n
Micelle–clay complex	0.981	71.42	0.066	0.945	4.966	0.324
Activated charcoal	0.992	18.87	0.067	0.926	0.078	0.720

4 Concluding remarks

In this study, the non-steroidal anti inflammatory drug naproxen was found to be stable in water for 14 days whereas it underwent partial degradation in activated sludge. An advanced WWTP utilizing ultra-filtration, activated charcoal and reverse osmosis showed that HF and SW ultra-filtration units were not sufficient in removing spiked naproxen to a safe level, whereas RO membrane was quite efficient. Adsorption studies on micelle (ODTMA)–clay complex and activated charcoal revealed that under steady state conditions the former adsorbent yielded a much better efficiency in removing naproxen with fast kinetics. The combined results may suggest that micelle–clay complex filters could be usefully employed for the improvement of currently used wastewater treatment systems also in the case these are furnished with advanced technology based on ultra-filtration and carbon adsorbents.

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