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Applicability of combined Fenton oxidation and nanofiltration to pharmaceutical wastewater

Ilda Vergili*, Sezin Gencdal

Faculty of Engineering, Department of Environmental Engineering, Istanbul University, 34320 Avcilar, Istanbul, Turkey, Tel. +90 212 4737070-int.17645; Fax: +90 212 4737180; email: ilda@istanbul.edu.tr (I. Vergili), Tel. +90 505 7477391; Fax: +90 212 4737180; email: sezingencdal@hotmail.com (S. Gencdal)

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ABSTRACT

The aim of this study was to investigate the applicability of combined Fenton oxidation and membrane filtration for the treatment of a real process pharmaceutical wastewater resulting from the chemical synthesis of etodolac—a pharmaceutical active compound. In single Fenton oxidation experiments, the highest process efficiencies (84% chemical oxygen demand (COD) and 95% UV_{254}) were obtained at the $H_2O_2/Fe^{2+} = 40$ ratio. However, regarding the costs of reagents, the optimum molar ratio of H_2O_2/Fe^{2+} was selected as 20 with COD removal efficiency of 82%. Although COD could not be reduced to discharge standards, etodolac removal is fixed close to 100%. Higher flux, higher rejection rates, and lower flux decline were obtained from the combined Fenton oxidation and nanofiltration (NF) of the raw wastewater from chemical synthesis process. Although effective removals of etodolac (>99.5%) were obtained for combined and single systems, single-stage NF treatment was also insufficient for the removal of organic matter. Combined Fenton oxidation and NF treatment was found to be a promising method for wastewater from chemical synthesis processes of pharmaceutical industry containing etodolac. FT-IR spectrums showed that the calcium salts could be the main foulants on the NF membrane surface.

Keywords: Pharmaceutical industry wastewater; PhAC; Etodolac; Fenton; Nanofiltration

1. Introduction

Pharmaceuticals and cosmetics, supplements, and other personal care products are used in large amounts throughout the world. The main sources of the pharmaceuticals in the environment are pharmaceutical industry, wastewater treatment plants, hospitals, and landfills [1]. The pharmaceutical manufacturing industry includes the manufacture, extraction, processing, purification, and packaging of chemicals to be used as medication for humans and animals. There are four general types of manufacturing processes used by pharmaceutical manufacturing facilities: fermentation, biological and natural extraction, chemical synthesis, and mixing,

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*Corresponding author.

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compounding, or formulating. Most of the active ingredients marketed and sold as drugs are manufactured by chemical synthesis. Wastewater from chemical synthesis plants have high biochemical oxygen demand, chemical oxygen demand (COD), and total suspended solid concentrations; large flows; and extremely variable pH values, ranging from 1.0 to 11.0 [2]. Early identification and research of pollutants resulting from the pharmaceutical industry is extremely important because of potential damage to the environment and human health [3]. Even though there is no clear evidence of public health impacts, the chronic health effects of a cocktail of biologically active substances are still unknown [4]. There are currently no regulations or directives for pharmaceutical active compounds (PhACs), and precautionary principles would suggest ensuring the removal of PhACs as far as possible through improved or existing treatment techniques. Biological treatment is the cheapest available technology to remove contaminants, but in the case of pharmaceutical wastewater, complete treatment of PhACs or ensuring the discharge standards cannot be possible. Also, most of PhACs have toxic effects on the biological treatment process. In addition, concentrations of some compounds have been found to increase during the treatment process, probably as a consequence of the transformation of conjugates back to the parent compounds [5]. Consequently, after passing through wastewater treatment, PhACs, among other compounds, are released directly into the environment [6,7]. In this context, pretreatment using advanced oxidation methods is required to ensure the discharge standards and PhACs removal.

Membrane process is becoming more attractive because of its purely physical nature of separation principle as well as the modular design of membrane processes. The main advantages of membrane processes are the quality of purified permeate, operability at ambient temperature and low energy consumption, the absence of chemicals, and the possibility to be combined with other separation processes [8,9]. Several membrane types and applications were evaluated to remove PhACs at pilot and full scale, including microfiltration (MF), nanofiltration (NF), ultrafiltration (UF), and reverse osmosis (RO), and combinations of membranes in series [1]. MF and UF are generally not fully effective in removing PhACs. The studies on the use of NF and RO treatment showed that they have potential as efficient methods for removing pharmaceuticals from the wastewater [10–14]. Additionally, NF/RO membranes provide higher removal efficiencies for organic micropollutants [12]. Also, the multivalent ions such as calcium, magnesium, and sulfate are effectively removed by NF membranes compared with UF membranes. But, the retentions of monovalent ions such as chloride, sodium, and potassium with NF membranes are lower compared with RO membranes. Fouling is the most important problem in membrane filtration, causing significant flux decline, increased operating costs, and decreased membrane lifetime. Concentrate and waste stream disposal/further treatment are also disadvantages of membrane processes [15].

The Fenton process is one of the most known advanced oxidation process (AOP). The principle of the process is the catalytic cycle of the reaction between ferrous ions (catalyst) and hydrogen peroxide (oxidant) to produce hydroxyl radicals ($^{\cdot}OH$) [16]. The hydroxyl radicals attack the organic compound leading to its partial or complete oxidation and producing carbon dioxide and water. Due to its simplicity of the technology required and the absence of mass transfer limitation, Fenton process has advantages over other types of AOPs (ozonation, UV, etc.). Other types of AOPs have high energy demands for devices such as ozonators, UV lamps, and ultrasounds: hence, they are economically disadvantageous. Studies involving degradation of the different PhACs or pharmaceutical wastewaters by Fenton oxidation have been carried out by various researchers [17–19].

In the literature, there are studies on PhACs removal from water/model waters by combined membrane separation and AOPs [16,20–23]. Only a few studies involving combined chemical oxidation and membrane filtration for real pharmaceutical wastewaters were reported in the literature [18,24]. The main objective of this study is to investigate the applicability of combined Fenton oxidation and membrane filtration for the treatment of a real process wastewater resulting from the chemical synthesis of a PhAC (etodolac). The main reason for combining the Fenton process with NF is greater pollutant removal efficiency to ensure the discharge limits (COD) and PhAC removal.

2. Materials and methods

2.1. Wastewater

The wastewater sample was obtained from the cleaning of the tanks after chemical synthesis of etodolac prior to the production of another pharmaceutical. This PhAC is a member of the pyranocarboxylic acid group of nonsteroidal anti-inflammatory drugs. Table 1 provides the structural and chemical properties of PhAC (etodolac) in the pharmaceutical wastewater. The characteristics of pharmaceutical wastewater are given in Table 2.

Table 1
The structural and chemical properties of etodolac

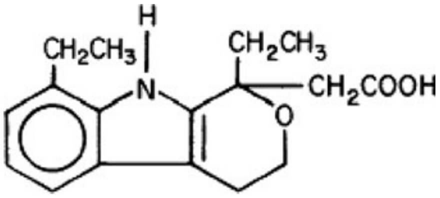
Molecular structure	
Chemical formula	$C_{17}H_{21}O_3$ N
Chemical name	1.8-Diethyl-1.3.4.9-tetrahydropyrano[3.4-b]indole-1-acetic acid
Appearance	White crystalline
Molecular weight (g/mol)	287.36
Water solubility (mg/mL)	0.0392 (20°C)
Dissociation constant (pKa)	4.65

Table 2
Characteristics of pharmaceutical wastewater

Parameter	Value
pH	8.2
Conductivity (mS/cm)	70.6
COD (mg/L)	18,000
BOD_5 (mg/L)	8,200
UV_{254} (1/cm)	0.783
TKN (mg/L)	32
$P-PO_4$ (mg/L)	2.7
Suspended solids (mg/L)	1,720
Sulfate (mg/L)	2,540
Cl^- (mg/L)	27,500
Etodolac (mg/L)	511

2.2. Fenton experiments

Fenton method is a process composed of four stages, which are as follows: pH adjustment, oxidation reaction, neutralization and coagulation, and precipitation. Organic substances are removed at two stages of the oxidation and the coagulation [25]. Batch experiments for Fenton process were performed in a three-necked glass reactor at 25 ± 1°C. The reactor was equipped with a cooling jacket. The outer surface of the reactor was covered against the light. The reaction mixture inside the reactor, consisting of 300 mL wastewater and the precise amount of $FeSO_4$ and H_2O_2, was continuously mixed by a magnetic stirrer (300 rpm). The pH of the wastewater was previously adjusted to the required value (pH 3). According to the literature, it is the optimum pH to promote the generation of hydroxyl radicals in Fenton process [16,18]. Reaction time varies depending on the load and structure of organic pollutants of the wastewater. It is difficult to determine whether the reaction was complete. According to the literature, 30 min were allowed for the completion of the reaction. The reaction time is reported to be in the range 10–30 min by several researchers [18,26,27]. Then, another 90 min were allocated for precipitation. The pH of the decanted supernatant was then adjusted to pH 8 to start coagulation, and two hours were allowed for complete precipitation of ferrous iron out as solid $Fe(OH)_3$. The coagulation step acts as a polishing step and removes the remaining after Fenton's oxidation [18]. After precipitation, the supernatant was filtered through 0.45 μm Whatman filter paper to determine the organic (COD and UV_{254}) and PhAC (etodolac) content.

The effects of H_2O_2 and Fe^{2+} dosages on treatment efficiency of Fenton oxidation were investigated at pH 3. H_2O_2 and Fe^{2+} dosages were ranged between 0.025 and 5 M, and betweeen 0.001 and 0.1 M, respectively. The Fe^{2+} dosage was kept constant at 0.05 M while studying the effect of H_2O_2 dosage. H_2O_2 concentration was kept constant at 2 M for the Fe^{2+} dosage experiments. Based on a literature review, hydrogen peroxide-to-ferrous iron molar ratios between 2.5 and 5,000 applied to pharmaceutical wastewater [18,19,28]. In this study, H_2O_2/Fe^{2+} molar ratio was tested in the range from 0.25 to 5,000.

Full mineralization of etodolac is given by Eq. (1). This equation was used to normalize the oxidant to etodolac molar ratio, that is, H_2O_2/etodolac stoichiometric molar ratio equal to 1 represents the addition of stoichiometric amounts of the reagents (1 mol of etodolac and 44 mol of H_2O_2).

$$C_{17}H_{21}O_3N + 44H_2O_2 \rightarrow 17CO_2 + 54H_2O + HNO_3 \quad (1)$$

The initial concentration etodolac of the studied pharmaceutical wastewater was 511 mg/L (1.78 M). So, with varying H_2O_2 concentration, the H_2O_2/etodolac stoichiometric molar ratio was in the range from 0.014 to 2.8.

2.3. Membrane filtration system and experiments

Membrane filtration experiments were performed in a cross-flow operation mode using a laboratory-scale membrane system equipped with a flat-sheet membrane of 80 cm^2 in size that was purchased from Osmo, Germany. The membrane module, with dimensions of 250 × 98 × 24 mm and made from stainless steel, featured a membrane channel 200 mm in length, 40 mm in width, and 1.3 mm in depth. The experimental set-up was equipped with a high-pressure pump to achieve the needed operating pressure and feed circulation. All experimental runs started with a feed volume of 3 L.

The NF membrane FM NP010 was a commercial flat-sheet membrane provided by Microdyn-Nadir, GmbH, Germany, with a molecular weight cutoff (MWCO) of 1,000 Da, according to the data provided by the manufacturer. The isoelectric point of the FM NP010 membrane was reported to be around pH 4 [29], and hence, it was negatively charged in the experiments. The membrane is made of hydrophilic polyethersulfone. The water flux of the clean membrane (at 25°C) was determined to be 137 L/m^2 h (at 12 bar). According to the pure water flux measurements as a function of transmembrane pressure (TMP) for FM NP010, the membrane permeability (pure water permeability), L_p, was found to be also 11.775 L/m^2 h bar [30]. Maximum operating pressure and temperature were given by manufacturer as 40 bar and 95°C, respectively. The detailed characteristics of the loose NF membrane FM NP010 are also given in a previous study [31]. Before first use, the membrane was pre-compacted with pure water for 5 h at a TMP of 30 bar to obtain a stable membrane structure.

The TMP was kept constant at 12 bar throughout all filtration experiments. In the experiments, a constant cross-flow rate of 3 L/min and a constant temperature of 25 ± 1°C were maintained. Two manometers on each side of the membrane module were used to measure the TMP value. A flow meter located in the concentrate stream was used to measure its volumetric flow rate. All the experiments were conducted in concentration mode of filtration. The concentrate stream thus was circulated back to the feed tank, while the permeate solution was collected in a beaker and was not returned to the feed tank. The permeate flow rate was measured using an electronic balance (Precisa 320 XB–1,200 C) and recorded by a computer.

The experiments were performed both with real process wastewater and wastewater pre-treated by Fenton oxidation. The flux was measured for 180 min. UV_{254}, COD, and etodolac removal efficiencies were evaluated at the end of the filtration.

2.3.1. Calculation of flux decline and rejections

The rejection rate was a parameter that allowed for the evaluation of the performance of the membrane rejection. It is expressed by the following equation:

$$R(\%) = \left(1 - \frac{C_p}{C_f}\right) \times 100 \tag{2}$$

where C_p and C_f represent the concentrations of a particular component in the composite permeate and feed solution, respectively.

The permeate flux is described by Darcy's law [32]:

$$J \equiv \frac{1}{A}\frac{dV}{dt} \tag{3}$$

where J is the permeate flux (L/m^2 h); A is the effective membrane filtration area (m^2); V is the total volume of the permeate (m^3); and t is the filtration time (min).

2.4. Chemicals and analytical methods

All chemicals used are of reagent grade and purchased from Merck. The chemicals used for Fenton experiments are ferrous sulfate heptahydrate ($FeSO_4{\cdot}7H_2O$) and hydrogen peroxide (H_2O_2, 35 vol. %solution). 0.1 N H_2SO_4 and 0.1 N NaOH solutions were used for pH adjustments.

The concentration of etodolac in each sample was determined by liquid chromatography–tandem mass spectrometry at the Accredited (ALS) Laboratories in Czech Republic. The limit of detection was 0.05 μg/L. The analysis was described in detail also in a previous study [33]. The analysis of the wastewater-quality parameters was conducted in accordance with standard methods [34]. The spectrophotometric measurements were recorded using a UV–vis spectrophotometer (PG Instruments T60U). The pH of the samples was monitored by a Thermo Orion 3-Star model pH meter. The conductivity measurements were conducted using a WTW InoLab Level 3 conductivity meter. Residual H_2O_2 interference has a positive error on COD measurements. Therefore, residual H_2O_2 was determined via molybdate-catalyzed iodometric titration [17]. Residual H_2O_2 measurements lower than 5 mg/L have demonstrated that during the Fenton reactions, H_2O_2 was completely used up at the end of the experiments. All experimental tests were conducted in duplicate, and the average values were used for further calculations.

Fourier transform infrared spectroscopy (FT-IR, Perkin Elmer Precisely Spectrum One, USA) was used to investigate changes in chemical bonds on membrane surfaces. All FT-IR measurements were conducted on both clean and fouled membranes. In these analyses, membranes were washed twice with pure water to remove impurities and then dried at room temperature. FT-IR spectra were recorded in the wave number range of 600–4,000 cm^{-1}.

3. Results and discussion

3.1. Fenton experiments

The required dose for H_2O_2 and Fe^{2+} is an important factor to consider as it could determine the economic feasibility of the process. Also, the H_2O_2/Fe^{2+} ratio is the key to improve the efficiency of the Fenton's treatment. The effects of H_2O_2 and Fe^{2+} dosages on treatment efficiency of Fenton oxidation were investigated at pH 3 and 25 ± 1°C to optimize the process parameters on COD removal efficiency.

3.1.1. Effect of Fe^{2+} dosage

The cost of reagents is one of the most important limiting factors for the practical use of Fenton process. Fe^{2+} dosage was ranged between 0.001 and 0.1 M to determine the optimum dose. The H_2O_2 concentration was kept constant at 2 M. As it can be seen in Fig. 1, COD removal was not obtained for 0.001 and 0.002 M Fe^{2+} dosages. The highest COD removal efficiency (84%) was obtained with 0.05 M Fe^{2+} dosage (H_2O_2/Fe^{2+} = 40). Further increasing the Fe^{2+} dosage resulted in lower COD removals (82%). This could be possibly due to the scavenging action of superfluous Fe^{2+} for the hydroxyl radical [35].

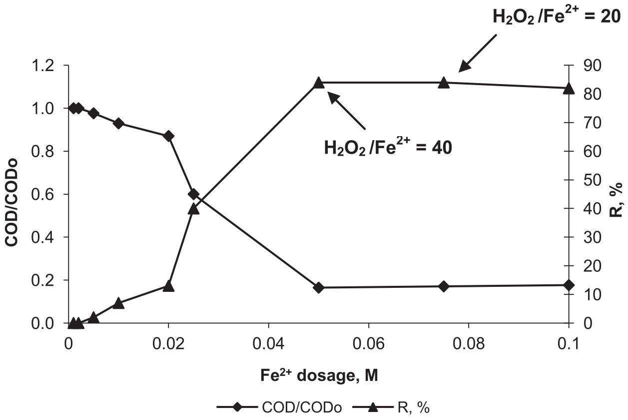


Fig. 1. COD removal efficiency with varying Fe^{2+} dosage (pH 3, 2 M H_2O_2).

3.1.2. Effect of H_2O_2 dosage

In the Fenton process, H_2O_2 is the most important parameter because it is the main cost for scale-up application. The optimization of H_2O_2 dosage is important to lower the treatment cost. H_2O_2 optimization was studied in the range of 0.025–5 M. The Fe^{2+} dosage was kept constant at 0.05 M while studying the effect of H_2O_2 dosage. As seen from Fig. 2, increase in H_2O_2 doses from 0.025 to 2 M resulted in higher COD removals and lower COD/COD_0 values. COD removal increased gradually. Further increasing the H_2O_2 dose resulted in higher COD/COD_0 values. It was found that an increase in H_2O_2 dose from 1 to 2 M improved the COD removal percentage only from 82 to 84%. Therefore, 1 M H_2O_2 was determined as optimum dosage with 82% COD removal.

Regarding the costs of reagents (H_2O_2 (35%) = 0.54 \$/kg and $FeSO_4 \cdot 7H_2O$ = 0.14 \$/kg) [36], the optimum molar ratio of H_2O_2/Fe^{2+} was selected as 20 (1 M H_2O_2/0.05 M Fe^{2+}) with 82% COD removal. For H_2O_2/Fe^{2+} = 20, UV_{254} removal was 95%, where etodolac removal was almost completely.

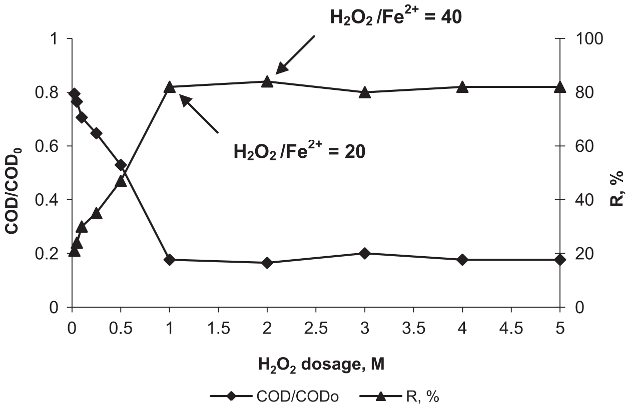


Fig. 2. COD removal efficiency with varying H_2O_2 dosage (pH 3, 0.05 M Fe^{2+}).

3.2. NF experiments

The NF experiments were performed both with real process wastewater and wastewater pretreated by Fenton oxidation. The influence of the operating conditions on the COD, UV_{254}, and etodolac removal efficiencies was studied.

3.2.1. Flux decline during experiments

Figs. 3 and 4 show the flux as a function of time for raw wastewater from chemical synthesis process and wastewater from chemical synthesis process pretreated by Fenton oxidation. Although the flux for the Fenton-pretreated wastewater (135 L/m^2 h) was found greater than the flux for the raw wastewater from chemical synthesis process (65 L/m^2 h), the flux profile of two NF experiments was similar. The percentages of flux declines were close at the end of filtration time (66 and 63%). Flux obtained from the NF of raw wastewater from chemical synthesis processes was decreased from 65 to 22 L/m^2 h, whereas a decrease from 135 to 50 L/m^2 h was determined for the NF of wastewater that pretreated with Fenton process.

For raw wastewater from chemical synthesis process, it can be said that higher organic load favors fouling and resulting in more flux decline. Similar behavior has been reported by Banerjee et al. [9] for the removal of dye from aqueous solution using a combination of Fenton oxidation process and NF. It was reported higher flux declines for NF + Fenton combination with respect to Fenton + NF combination.

3.2.2. FT-IR analysis

All FT-IR measurements were conducted on both clean and fouled NF membranes and are shown in Fig. 5. The FT-IR spectra of NF membrane fouled with raw wastewater and NF membrane fouled with pretreated wastewater NF membranes were almost same. From the FT-IR spectrum for the NF membranes fouled with raw and pretreated wastewater, it can be seen that the bands at 3,382, 1,743, and 1,653 cm^{-1} in the virgin membrane spectrum are eliminated. There is no obvious band in the range of 2,500–4,000 cm^{-1}, suggesting that the fouling layer on membrane surface of raw wastewater could consist of a large amount of inorganic matter, as organic matter always has apparent bands in this wave number range [37]. A new intense band at 1,710 cm^{-1} appears for the NF membrane fouled with raw wastewater and pretreated wastewater, as compared with the virgin membrane. The bands at 1,412 and 1,320 cm^{-1} were shifted and intensified. From the FT-IR spectrum for the membrane fouled with pharmaceutical wastewater, it can be seen that new intense band at 1,087 cm^{-1} appeared. This band is in the wave number range of 1,040–1,100 cm^{-1}, which is characteristic of SO_4^{2-} and/or CO_3^{2-} ions [38]. The calcium salts could be the main foulants on the membrane surface [37].

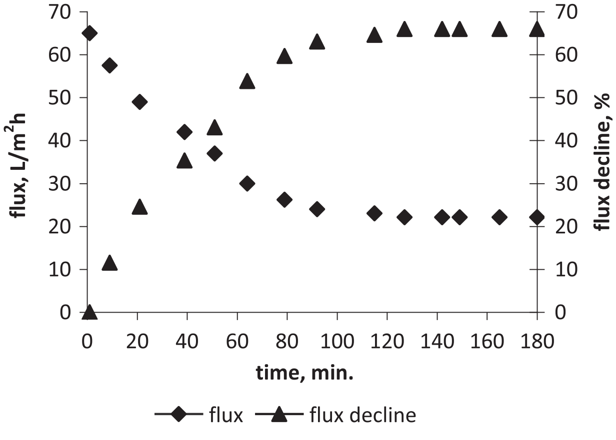


Fig. 3. Flux decline as a function of time for raw wastewater from chemical synthesis processes.

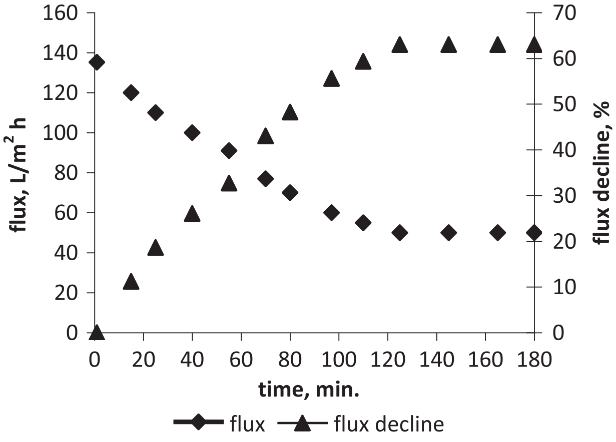


Fig. 4. Flux decline as a function of time for wastewater from chemical synthesis processes pretreated by Fenton oxidation.

3.3. Effect of Fenton and NF processes on the etodolac, UV_{254}, and COD removals

The effect of the Fenton and NF processes on the etodolac, UV_{254}, and COD is presented in Table 3. NF was insufficient for the removal of organic matter. NF improved the removal of the organic matter only 6% after Fenton process. However, removal of the aromatic compounds was high and too close for all the studied processes (93–96% UV_{254} removal). Also etodolac was removed almost completely (>99.5%).

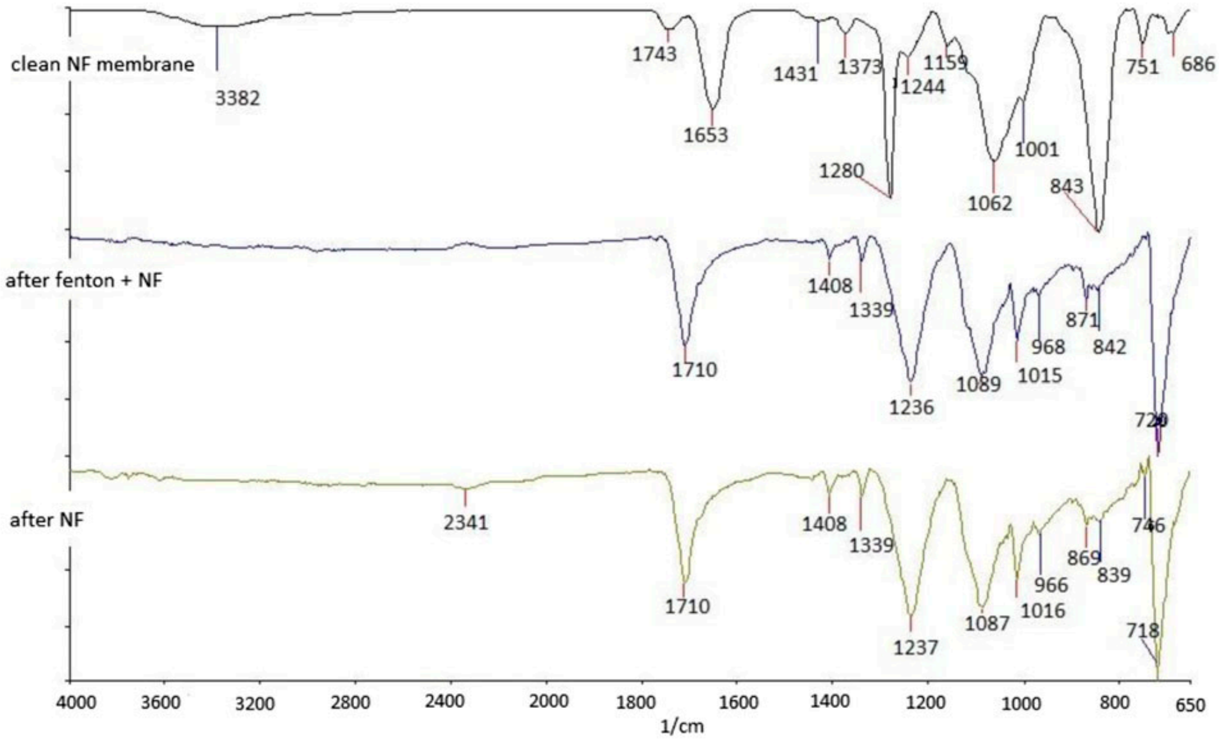


Fig. 5. FT-IR spectra of original and fouled membranes.

Table 3
Effect of Fenton and nanofiltration processes on the etodolac, UV_{254}, and COD removals

Process	Rejections (%) COD	UV_{254}	Etodolac
Fenton	82	95	99.9
NF	6	93	99.5
Fenton + NF	88	96	100

The concentration of etodolac was reduced from 511 to 0.7 mg/L using Fenton method. NF + Fenton combination resulted with 99.99% etodolac removal (etodolac concentration < 0.05 μg/L). In order to explain the differences between the removal rates of UV_{254} and COD in detail, separation behaviors of etodolac, inorganic solutes, and organics will be further analyzed in another study.

4. Conclusions

In this study, treatment of a wastewater from chemical synthesis process of a pharmaceutical factory—resulting from the production of active pharmaceutical ingredient (etodolac)–with Fenton and NF processes has been investigated. From the results of the experiments, the following conclusions can be drawn:

- The results in the use of Fenton process indicated that the overall treatment efficiency was best with removal efficiency of 84% COD removal at $H_2O_2/Fe^{2+} = 40$ ratio. However, regarding the cost of chemicals of H_2O_2, $H_2O_2/Fe^{2+} = 20$ ratio with 82% COD removal was selected as the optimum condition for the Fenton process.
- Single-stage NF treatment was insufficient for the removal of organic matter. COD removal was too low (6%).
- Although effective removals of etodolac (>99.5%) were obtained for combined and single systems, COD could not be reduced to discharge standards. Also, NF and Fenton process can be suggested for the removal of PhACs.
- The flux obtained for the Fenton-pretreated wastewater was found greater than the flux obtained for the raw wastewater from chemical synthesis processes. This result may be attributed to higher organic load of raw water. The decreased flux can be mainly related with

membrane fouling. Higher organic load favors fouling and resulting in more flux decline.

- FT-IR spectrums showed that the calcium salts could be the main foulants on the NF membrane surface.
- Fenton process and NF combination was found as an effective treatment method to ensure PhAC removal. Also, Fenton process was found as an effective pretreatment method to ensure higher flux for NF process.
- In order to explain the differences between the removal rates of UV_{254} and COD in detail, separation behaviors of etodolac, inorganic solutes, and organics will be further analyzed in another study.

Acknowledgements

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Nomenclature

A — effective membrane filtration area (m^2)
AOP — advanced oxidation processes
BOD — biochemical oxygen demand (mg/L)
C_f — component concentration in feed (mg/L)
CMF — concentration mode of filtration
COD — chemical oxygen demand (mg/L)
C_p — component concentration in permeate (mg/L)
FT-IR — fourier transform infrared spectroscopy
J — permeate flux (L/m^2 h)
L_p — permeability (L/m^2 h bar)
MF — microfiltration
MWCO — molecular weight cut-off (Dalton)
NF — nanofiltration
PES — polyethersulfone
PhACs — pharmaceutical active compound(s) (mg/L)
pKa — dissociation constant
R — rejection rate (%)
RO — reverse osmosis
t — filtration time (min)
TKN — Total Kjeldahl Nitrogen (mg/L)
TMP — transmembrane pressure (bar)
UF — ultrafiltration
UV_{254} — ultraviolet absorption at 254 nm (1/cm)
V — total volume of the permeate (m^3)

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