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STUDIES REGARDING THE DEGRADATION OF SOME NONSTEROIDAL ANTI-INFLAMMATORY DRUGS UNDER FENTON AND PHOTO-FENTON OXIDATION PROCESS

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ABSTRACT: In this study the assessment of the degradation efficiency of four nonsteroidal anti-inflammatory drugs namely Ketoprofen, Naproxen, Diclofenac and Ibuprofen, under the Fenton and Photo-Fenton oxidation process was performed. It was observed that the main parameters that influence the Fenton and Photo-Fenton oxidative processes of the selected NSAIDs were the concentration of the catalyst (Fe^{+2}), the concentration of the oxidizing agent (H_2O_2), the pH value, the reaction time and also the quantity of light radiation. For the Fenton process the following yields of degradation were obtained: 86.02% Ketoprofen, 90.09% Naproxen, 81.92% Diclofenac, and 85.98% Ibuprofen. In the case of the Photo-Fenton process a slight improvement in the rate of degradation was observed but insignificant compared to the Fenton process. The degradation was performed using 500 µl of Fe^{+2} solution (1000 mg/L) and 400 µl of H_2O_2 (30%), at a pH value of 3, with a total reaction time of 30 minutes.

Keywords: Nonsteroidal anti-inflammatory drugs, Fenton oxidation process, Photo-Fenton oxidation process, high performance liquid chromatography, advanced oxidation process.

INTRODUCTION:

Diclofenac (DIC), Ibuprofen (IBU), Ketoprofen (KET), Naproxen (NAP) are non-steroidal anti-inflammatory drugs (NSAIDs) widely used in the treatment of humans but also of animals, due to their analgesic, antipyretic, anti-inflammatory properties.

These are among the most commonly used drugs in pain therapy. NSAIDs are sometimes referred to as non-narcotic analgesics, which do not cause euphoria and their use does not lead to addiction (Wieszczycka et al., 2017).

Due to the increased consumption of the NSAIDs because of their properties and the easy way to obtain, without prescription, they are found in high concentrations in the environment, especially in surface waters, with potentially harmful effects both on aquatic ecosystems and on human health. (Kermia et al., 2016; Sousa et al., 2018).

The presence of NSAIDs in the environment has led to the decimation of the number of eagles (*Gyps vultures*) in Asia due to renal insufficiency and gout caused by the ingestion of meat from cattle treated with Diclofenac. Ibuprofen is considered toxic to the microalgae (*Selenastrum capricornium*), also Ketoprofen is guilty of the disappearance of male eider ducks (*Somateria mollissima)* (Madikizela et al., 2017; Cuklev et al., 2012).

Experiments with chronic and acute exposure using nonsteroidal anti-inflammatory drugs were performed on Zebra fish (*Danio rerio*). A small dose of Ibruprofen has been found to significantly reduce the number of eggs produced by an adult fish and also have estrogenic effects on them and, together with Diclofenac, delay the development of embryos. Ketoprofen likewise has these endocrine disturbances on fish (Xia et al., 2017; Wang et al., 2018).

On human, gastrointestinal disturbances and also an increase in body resistance at administration have been observed (Madikizela et al., 2017; Cuklev et al., 2012).

Recently, the European Comission has introduced Diclofenac on the Watch List of Substances (Directive 2013/39/EU) and along with various pharmaceuticals and hormones (Sousa et al., 2018), it is the most studied compound in the follow-up campaigns for substances included on the list.

For example, Baena-Nogueras and her colleagues (2017) note in their study that the concentrations of Ibruprofen found in the coastal waters of Taiwan and the Baltic Sea (Germany) ranged between 57.1-109 ng/L, while Gong and his colleagues (2017) found in drinking water in the UK and Wales concentrations between 25.000-475.000 ng/L (Baena-Nogueras et al., 2017; Gong et al., 2017).

Wastewater treatment plants constitute the point of transfer of these NSAIDs into the environment. It is highlighted that most of these substances are partially eliminated by treating wastewater and therefore are detected in secondary effluents (Koumaki et al., 2017).

Due to the chemical stability of the compounds, they are partially disposed of by wastewater treatment plants and require advanced oxidative processes to remove them from the circuit (Beldean-Galea et al., 2014).

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Mirzaei and collegues (2017) assert in their article that 64% of emerging contaminants are less than 50 % removed and 9% do not undergo any change after conventional treatment processes (Mirzaei et al., 2017).

Advanced oxidation processes (AOPs) are the missing links between physicochemical and biological processes commonly used in sewage treatment and the ever more stringent limits imposed by legislation to obtain high quality water. AOPs do not generate waste and can be applied as a pretreatment process before the biological step, which increases the biodegradability of refractory compounds (Dewil et al., 2017; Mirzaei et al., 2017).

The Fenton degradation is part of the advanced degradation processes (O_3/UV, O_3/ultrasonic (O_3/US), O_3/H_2O_2, O_3/UV/US, O_3/US/$FeSO_4$, H_2O_2/UV, heterocatalytic/H_2O_2, Fe^{+2}/H_2O_2 (Fenton), Fe^{+2}/H_2O_2/UV (Photo-Fenton), it uses a mixture of hydrogen peroxide (oxidizing agent - H_2O_2) and ferrous ion (catalyst - Fe^{+2}) that mineralizes organic substances up to CO_2 and H_2O. It is a very useful method because the reagents are cheap, easy to use and environmentally friendly (Beldean-Galea et al., 2015).

The aim of this study was to find a feasible method (Fenton or Photo-Fenton) for the mineralization of four NSAIDs (Ketoprofen, Naproxen Diclofenac and Ibuprofen) and the influence of various parameters from the process (amount of catalyst, amount of oxidant, pH, light radiation, time) to understand the underlying mechanisms of advanced oxidation processes.

MATERIALS AND METHODS:

Materials

Iron (II) sulfate heptahydrate, hydrogen peroxide (30% w/w), potassium dihydrogen phosphate, acetonitrile, sodium hydroxide, distilled water.

A mixture of KET, NAP, DIC, IBU in purity of >98% were purchased from Sigma-Aldrich (Paris, France). A stock solution in concentration of 1000 mg/L of each compound was prepared in a mixture of distilled water: acetonitrile (1:1 *v/v*).

Experimental

The oxidation experiments were performed in a 50 mL brown beaker to prevent the interference of sun radiation, equipped with a magnetic stirrer, to ensure the homogeneity in the reactor. All the experiments were carried out at room temperature (25˚C). The experimental mixture consisting in 10 mL of distilled water, spiked with 100 µL of anti-inflammatory mixture (100 mg/L), different quantities of H_2O_2 (30%), $FeSO_4$ x $7H_2O$ solution (1000 mg/L), NaOH solution (0,1M) to alkalinize the experimental mixture was added into the built-in reactor. In order to study the degradation rate of the selected NSAID, at different times (10, 20, 30 minutes), an aliquot of the mixtures from the reactor were taken and injected directly in the high performance liquid chromatography (HPLC).

Analytical method:

The analyses of the NSAIDs were performed using a HPLC system, model Shimadzu, equipped with a UV-Vis detector and a Reodine manual injection valve equipped with a loop of 5 µL. The separation of the compounds was performed on a reverse phase column type Phenomenex C12 (120 mm x 4.6 mm, particle size 5 µm). An isocratic elution mode using a mobile phase containing a mixture of acetonitrile: potassium dihydrogen phosphate (15mM) (55:45 *v/v*) at a flow rate of 1 mL/min was used for HPLC analysis. The detection of the compounds was carried out at 210 nm wavelength.

The NSAIDs concentration in the water samples were calculated using the calibration curve method. For this purpose, five standard solutions in concentration of 6.25, 12.5, 25, 50, 100 mg/L for each compounds were prepared.

The limit of detection (LOD) and limit of quantification (LOQ) were determined taking into consideration the standard deviation of the response factor of the detector (σ) for each compound and the slope (S) of each calibration curve. These parameters have been calculated according to the following equations: LOD = 3.3σ/S and LOQ = 10σ/S. The performances of the analytical method are presented in table 1.

Tab. 1.
The regression equations, correlation coefficients (R^2), LODs, LOQs of the tested

Compound	Concentration (mg/L)	Regression equations	R^2	Average	Standard deviation (σ)	Relative standard deviation (%)	LOD (mg/L)	LOQ (mg/L)
Ketoprofen	1-100	y=37133x+125954	0.9976	281920.7	12221.7	4.34	1.09	3.29
Naproxen		y=38195x+91249	0.9985	292140.7	10136.9	3.47	0.88	2.65
Diclofenac		y=43429x+114016	0.9978	328217.3	11437	3.48	0.87	2.63
Ibuprofen		y=17351x+48580	0.9979	128343	4757.6	3.71	0.9	2.74

Studia Universitatis "Vasile Goldiş", Seria Ştiinţele Vieţii
Vol. 28 issue 1, 2018, pp 43-50

The method has a good linearity, a relative standard deviation under 7%, and low LODs and LOQs. The developed method has been successfully applied in the analysis of selected compounds in water samples.

In terms of extraction, in order to avoid errors in the recovery of compounds of interest in the aqueous matrix, the Fenton and Photo-Fenton degradation processes of the compounds were studied by direct injection of the sample into the system. On this line, synthetic samples were prepared at detectable concentration levels (over LOQ).

RESULTS AND DISCUSSIONS:

Optimization of process parameters

In the Fenton systems the pH, dosing the oxidant, the catalyst, the reaction temperature, UV radiation and total reaction time, should be studied because of their significant effect on the oxidation capacity of the Fenton reagent. Thus, systematic introduction and analysis of these parameters is required.

Effect of hydrogen peroxide

In order to determine the quantity of H_2O_2 for optimum NSAIDs degradation efficiency, different amount of H_2O_2 between 300 µL and 800 µL were used. At different time intervals (10, 20, 30 minutes) aliquots of the reaction mixtures were sampled and analyzed by HPLC in order to monitor the anti-inflammatory degradation rate. Fe^{+2} concentration was maintained at 1000 mg/L.

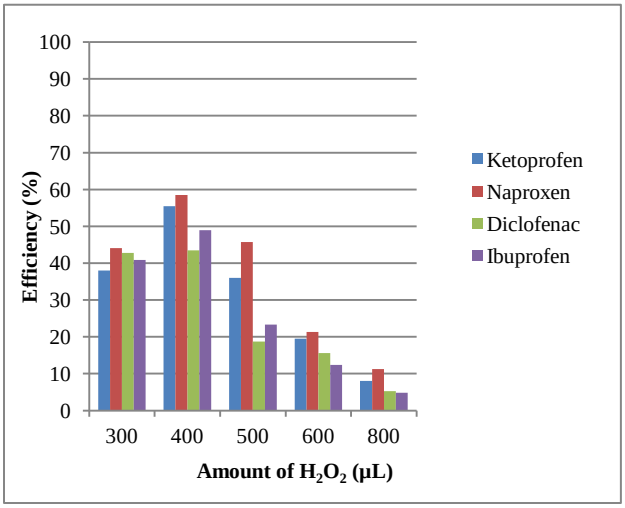

Fig. 1. The influence of H_2O_2 on degradation

Hydrogen peroxide is the main source of hydroxyl radicals in Fenton systems and it depends on the concentration of Fe^{+2} ions (Mirzaei et al., 2017).

A high concentration of hydrogen peroxide can lead to the cleansing effect due to the excess of •OH radicals and a low concentration of it will not be able to produce the required amount of •OH radicals in order to degrade the compounds.

As can be seen, the efficiency of the degradation varies with the amount of H_2O_2 used, the maximum efficiency was obtained using 400 µL H_2O_2 (Fig. 1).

Effect of Fe^{+2}

To find the optimal amount of catalyst at which degradation reaches the maximum point, different amounts of $FeSO_4$ x $7H_2O$ solution (1000 mg/L) between 200 µL and 1000 µL were tested. The amount of H_2O_2 was maintained at 400 µL.

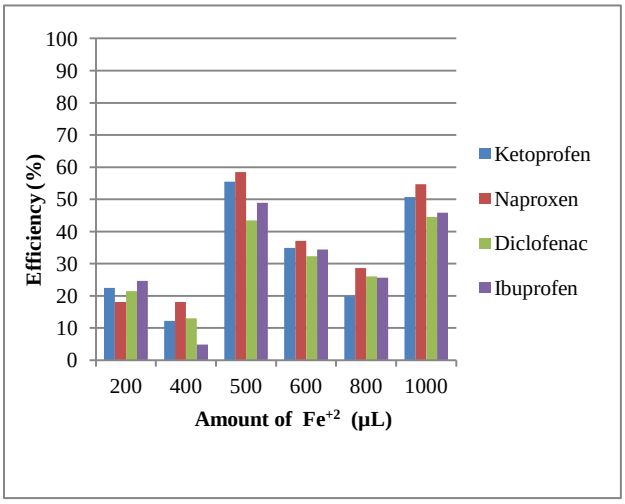

Fig. 2. The influence of Fe^{+2} on degradation

Although the large amount of Fe^{+2} ions increases the production of •OH radicals, the degradation rate decreases due to the cleansing effect of the radicals (Fig. 2). Also, the large amount of Fe^{+2} ions will ultimately generate sludge with a high concentration of Fe^{+3} ions.

Increasing the amount of $FeSO_4$ x $7H_2O$ increases the turbidity of the analyzed mixture, the yellow-red color specific to iron appears.

Effect of pH

To determine the influence of pH on Fenton degradation of the analyzed compounds, different pH ranges between 3 and 7 were tested using 500 µL of Fe^{+2} solution (1000 mg/L), 400 µL of H_2O_2 (30%), 100 µL mix NSAIDs solution (100 mg/L). The alkalization of the experimental mixture was made using NaOH solution (0.1M).

The obtained results showed that, the maximum degradation of NAIDs takes place at a pH equal to 3 (Figure 3). To remember, the acidity constants of the analytes are in the range of 3-5. The compounds are in molecular form when the pH is lower than the acidic constant, and when the pH is higher than the acidic constants, it loses a proton becoming more easily cleaved in front of the hydroxyl radicals.

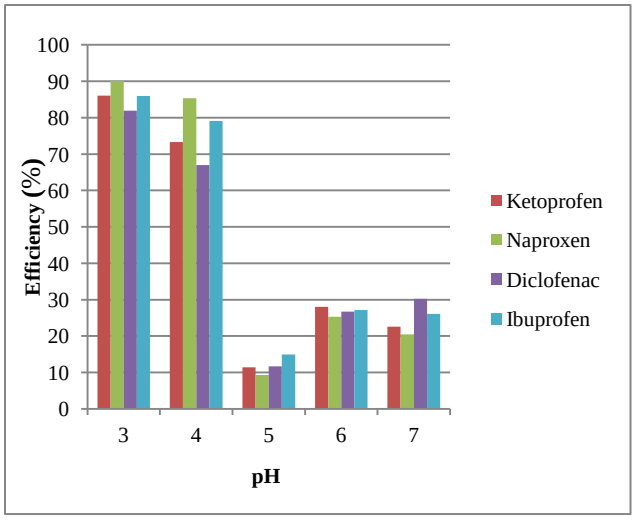

Fig. 3. The influence of pH on degradation

Effect of time

The rate of degradation of the NSAIDs depends on the presence and the abundance of hydroxyl radicals. As can be seen in Figure 4, they are consumed in the first 20 minutes of the reaction. With the evolution of the reaction, the degradation rate decreases due to the consumption of hydroxyl radicals and the reduction of the contaminant concentration.

Studia Universitatis "Vasile Goldiş", Seria Ştiinţele Vieţii
Vol. 28 issue 1, 2018, pp 43-50

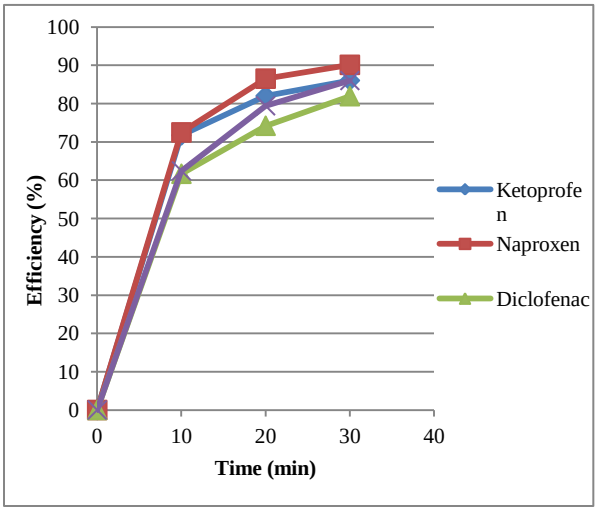

Fig. 4. The influence of time on degradation

Taking into consideration the results presented above it can be conclude that, the best degradation rate (86.02% Ketoprofen, 90.09% Naproxen, 81.92% Diclofenac, and 85.98% Ibuprofen) were obtained using 500 µL Fe^{+2} solution (1000 mg/L) and 400 µL H_2O_2 (30%) at pH 3, and a reaction time of 30 minutes.

Moreover, it can be observed that, the Fenton process can not completely mineralize these compounds, and the process require further optimization.

Photo-Fenton

Following the results of Fenton's experiments, the Photo-Fenton process was studied with the goal of the degradation efficiency improvement. For this purpose, a 50 watt deuterium arc lamp with a range of 180 nm to 370 nm was used. The conditions of the experimental mixture were kept as the same as for Fenton degradation (10 mL distilled water spiked with 100 µL anti-inflammatory mixture (100 mg/L), 500 µL $FeSO_4$ x $7H_2O$ solution (1000 mg/L), 400 µL H_2O_2 (30%), at pH 3).

The mixture was analyzed after 10, 20, 30 minutes to observe the effectiveness over time.

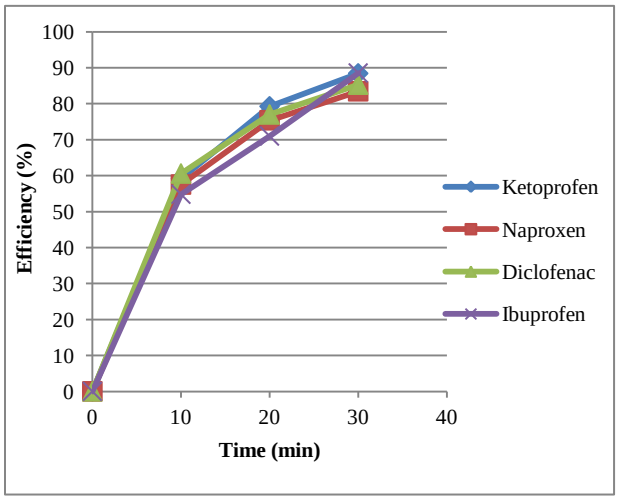

Fig. 5. Influence of UV radiation on degradation

As can be seen in figure 5, ultraviolet radiation (180-370 nm) accelerates the Fenton process by photo-reduction of Fe^{+3}, but the yield of the reaction is still relatively low. The following degradation rates were obtained: 88.40% Ketoprofen, 83.43% Naproxen, 85.27% Diclofenac and 88.52% Ibuprofen.

Fenton optimization

Since the catalyst (Fe^{+2}) and oxidant (H_2O_2) are rapidly consumed and the degradation efficiency does not reach to 100%, optimization of the Fenton process is still necessary. In this order, the Fenton mixture (catalyst and oxidant) was refreshed every 10 minutes and the degradation rate was evaluated during a period of 30 minutes.

As can be observed in figure 6, the degradation rates of the studied compounds are closed to 100% (94.76%, Diclofenac, 97.09%, Ibuprofen, 100%, Naproxen) but a total mineralization of the compounds to CO_2 and water does not occur under the described Fenton condition. Moreover, the Fenton degradation leads to different degradation by-products. This conclusion can be justified by the increasing of the pick area corresponding to Ketoprofen which in the first stage of Fenton degradation process decrease and after 20 minutes the Ketoprofen peak area increase proportional with the degradation rate of other three compounds (Figure 7). This means that, the optimization of a more specific HPLC method able to separate the Ketoprofen peak to all other corresponding to the degradation by-products is mandatory.

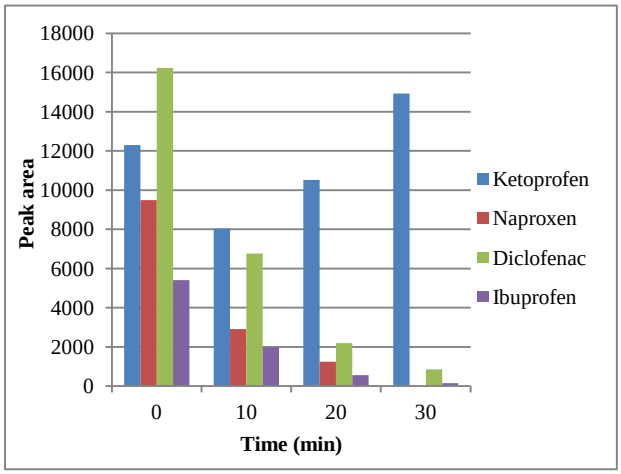

Fig. 6. The influence of Fenton`s excess

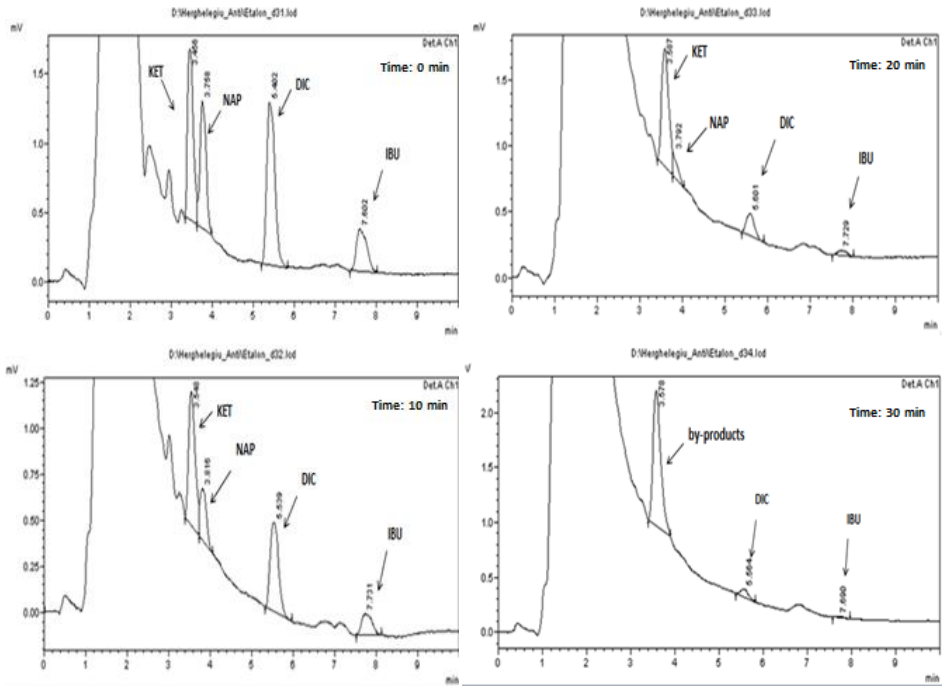

Fig. 7. The chromatograms of the NSAIDs mixture subjected to Fenton degradation process.

Studia Universitatis "Vasile Goldiş", Seria Ştiinţele Vieţii
Vol. 28 issue 1, 2018, pp 43-50

CONCLUSIONS:

Development of the alternative method for removal of the recalcitrant organic pollutants from wastewater is mandatory due to their persistence and toxic effect against to the aquatic life.

Fenton oxidative process is an attractive method because the price of the reagent is low, it is easy to use and friendly for environment.

For the Fenton process the amount of catalyst (Fe^{+2}), oxidant (H_2O_2), the pH and the reaction time are the most important parameters which influence the degradation rate of the organic compounds.

In the case of selected NSAID the optimum conditions for their Fenton degradation, were pH 3, a reaction time of 30 minutes and a catalyst:oxidant volume ration of 1.25 *v/v*.

The degradation rates of the selected NSAIDs are closely to 100% and even by the refreshment of the Fenton mixture a complete mineralization of the compounds cannot be obtained.

By use of the UV radiation in combination with the Fenton process a slowly increase of the degradation rate of NSAIDs occur but not to 100%.

In this way consideration should be given to the use of solar radiation coupled with Fenton's reagent to degrade recalcitrant compounds.

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