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ADVANCED OXIDATION TREATMENT OF PENTOXIFYLLINE IN AQUEOUS SOLUTIONS

The degradation of pentoxifylline (PTX) using H₂O₂, UV, H₂O₂/UV, Fenton and photo-Fenton processes has been examined in aqueous solutions. The influence of oxidation agent and initial PTX concentration, on H₂O₂, H₂O₂/UV, Fenton and photo-Fenton reactions was investigated. The addition of inorganic ions (Cl⁻, NO₃⁻, SO₄²⁻ and CO₃²⁻) on the degradation efficiency of PTX was tested for H₂O₂/UV, Fenton and photo-Fenton processes. The results indicate that the photo-Fenton reaction is the most sufficient for PTX removal. The complete pharmaceuticals decomposition is achieved after 5 min under optimized concentration of FeSO₄·7H₂O and H₂O₂. The degradation of PTX is inhibited in the presence of inorganic matter in H₂O₂/UV and Fenton reaction. In the photo-Fenton process addition of above compounds does not affect the reaction rate. Structures of ten products of photo-Fenton reaction have been proposed.

1. INTRODUCTION

The pharmaceutical industry is one of the fastest growing areas of the economy. A lot of pharmaceutical compounds are only partially metabolized and excreted by humans or animals, and spilled into wastewaters. Pharmaceuticals and their metabolized products are characterized by a complex structure of molecules which limits their distribution through traditional biological methods applied in municipal wastewater treatment plants. Thus, they are reported in the environment worldwide [1, 2]. In order to improve the quality of wastewater entering to the large bodies of water, multi-stage

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waste treatment may be applied. Recently more attention has been paid to advanced oxidation processes (AOPs) which have demonstrated to be efficient to remove non-biodegradable pollutants [3]. AOPs are based on reaction between organic molecules and hydroxyl radicals ($\cdot\text{OH}$) generated in water systems and characterized by high oxidation potential ($E^\circ = 2.8$ V vs. standard hydrogen electrode (SHE)), high reactivity and non-selectivity. Among these techniques, $\text{H}_2\text{O}_2/\text{UV}$, ozonation, Fenton, photo-Fenton, Fenton-like and photo-Fenton-like reactions are the most popular. Ozone treatment is effective in degrading enrofloxacin in synthetic wastewater [4]. Reaction with O_3 and $\text{H}_2\text{O}_2/\text{UV}$ provide decontamination of aqueous pharmaceutical mixtures containing ofloxacin, as well as five other drugs, namely carbamazepine, propranolol, clofibric acid, diclofenac, and sulfamethoxazole [5]. Undoubtedly, among various AOP variants, the Fenton process is the most attractive option because of its low cost, lack of toxicity of its reagents (Fe(II) and H_2O_2) and relative simplicity of the technology. Therefore, increasing number of studies employing this process for degradation of pharmaceuticals in pure water as well as in sewage has been carried out. In some cases, the efficiency of Fenton treatment of wastewater can be enhanced by UV or solar irradiation [6].

The aim of this work was to compare various oxidation processes for the effectiveness of degrading pentoxifylline (3,7-dimethyl-1-(5-oxohexyl)-3,7-dihydro-1H-purine-2,6-dione) (Fig. 1). This derivative of xanthine is used in treatment peripheral arterial disease, it is known for decreasing blood viscosity and inhibiting aggregation of platelets. Further investigations showed the influence of PTX on sperm motility and potential use in breast cancer treatment.

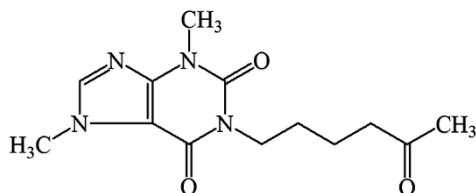


Fig. 1. Chemical structure of pentoxifylline

Pentoxifylline was treated with chloride dioxide [7], ozone and $\text{O}_3/\text{H}_2\text{O}_2$ [8], alkaline permanganate [9], electrochemical oxidation [10], diperiodatocuprate(III) with and without osmium(VIII) catalyst in aqueous alkaline medium [11], by non-thermal plasma [12] and diperiodatocuprate(III) with ruthenium(III) catalyst [13]. However, comparison of degradation efficiencies of PTX with H_2O_2 , $\text{H}_2\text{O}_2/\text{UV}$, UV irradiation alone, Fenton's reagent and photo-Fenton processes has not been taken into account. In this work, optimal parameters for decomposition of PTX in the above mentioned AOPs have been established. Structures of products obtained in photo-Fenton reaction have been proposed.

2. MATERIALS AND METHODS

Chemicals. Pentoxifylline (PTX) (99% purity) and ferrous sulfate heptahydrate (99%) were purchased from Sigma Aldrich. Hydrogen peroxide (30%), potassium dihydrogen phosphate, sodium hydroxide, sulfuric acid, sodium chloride, sodium nitrate, sodium carbonate were purchased from P.P.H. Gliwice (Poland), methanol (HPLC-grade) from Chempur (Poland). For preparing standard solutions including pentoxifylline deionized water was used.

Experimental setup and analytical methods. For irradiation experiments, a cylindrical quartz reactor 16 cm high, 5 cm in diameter under magnetic stirring was used. UV irradiation sources were four low-pressure mercury discharge lamps (Philips, TUV PL-L 35W 4P HO) with maximum emission at 253.7 nm. The light intensities (at 254 nm) were 63.7 W/m². The distance between the reactor and the light source was 4 cm. The irradiance was measured by a UV radiometer (Radiometer RR-20 OPTEL, Poland). The whole system was surrounded externally by reflective aluminum foil. The pH was measured with a pH meter CP-505 ELMETRON. Degradation reaction progress was monitored by HPLC (Agilent 1200 Series LC chromatographic system equipped with a vacuum degasser (G1322A), an autosampler (G1311A), a thermostated column compartment (G1316A) and a diode array detector (G1315B)). Analyses were performed on Zorbax Eclipse XDB-C18 column, 250×4.6 mm, 5 μm particle size (Agilent, USA). The mobile phase consisted of a mixture of potassium dihydrogen phosphate (5.44 g/dm³) (P) and methanol (M): phase 1 – 70/30 vol. % P/M and phase 2 – 30/70 vol. % P/M. Samples were analysed using 10 min linear gradient, and the content of phase 2 was progressively increased from 15 to 85% (1.0 cm³/min). The detector was set at 272 nm for pentoxifylline. The column temperature was set at 30 °C, the injection volume was 10 μl with a draw speed of 200 μl/min. For identification purposes, standard addition was used by comparing the relative retention time and peak purity with UV-VIS spectral reference data. The experiments were carried out thrice under identical conditions and the relative error between the consecutive experiments was in the range of approximately 1.6%.

Isolation and identification of intermediate products were performed by UPLC-MS (4000 Q-TRAP used ionization method ESI (electrospray ionization)). UPLC chromatographic analysis Acquity BEH-C18 column 50×2.1 mm, 1.7 μm particle size. The mobile phase consisted of a mixture of water and acetonitrile. Samples were analysed using linear gradient, and the content of acetonitrile was increased from 10 to 30% during 5 min and then decreased progressively from 30 to 10% in 3 min (0.3 cm³/min, λ = 272 nm).

Experimental procedure. Six aqueous solutions of PTX were applied: solution A (0.1 mM), solution B (0.25 mM), solution C (0.5 mM), solution D (0.75 mM), solution E

(1 mM) and solution F (10 mM). All processes were carried out at room temperature (24 ± 3 °C). To examine the kinetic reaction, samples were collected after 5, 10, 15, 20, 25 and 30 min.

Oxidation with hydrogen peroxide was conducted by introducing 200 cm³ of solution A and various amounts of hydrogen peroxide (from 0.24 to 4.88 mM) into glass beaker located on the magnetic stirrer.

In a direct photolysis reaction, 200 cm³ of solution A was introduced into quartz reactor and UV irradiated for 30 min. In reaction with hydrogen peroxide/UV system hydrogen peroxide (from 0.24 to 4.88 mM) was added to the reactor.

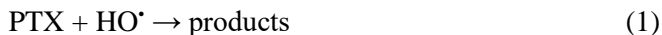
In the Fenton and photo-Fenton reaction, pH of the solution A was adjusted to 3.5 with H₂SO₄ to prevent the formation of iron hydroxides. Then required amounts of ferrous sulfate heptahydrate (from 0.09 to 1.80 mM) and hydrogen peroxide (from 0.24 to 4.88 mM) were added to 200 cm³ of solution. In each withdrawn sample, reaction was stopped by increasing the pH to 9 by adding sodium hydroxide. The procedure for photo-Fenton reaction was similar, however a beaker was converted into a batch photoreactor. To examine the initial PTX concentration on PTX decomposition, to 200 cm³ of solution A–F, appropriate amount of ferrous sulfate heptahydrate (from 0.18 to 1.80 mM) and hydrogen peroxide (from 1.22 to 122 mM) were added. The reactions were carried out for 30 min.

To examine the effect of inorganic salts, 10 mM of appropriate inorganic salt (sodium chloride, nitrate, sulfate or carbonate) was added to 200 cm³ of solution A. Then, reactions (1.22 mM H₂O₂/UV, Fenton (1.22 mM H₂O₂/0.18 mM FeSO₄·7H₂O) or photo-Fenton (1.22 mM H₂O₂/0.18 mM FeSO₄·7H₂O /UV) were performed for 30 min.

3. RESULTS AND DISCUSSION

3.1. REMOVAL OF PTX BY DIRECT PHOTOLYSIS, OR USING HYDROGEN PEROXIDE AND HYDROGEN PEROXIDE/UV SYSTEM

Pentoxifylline was not efficiently oxidized with hydrogen peroxide even after 30 min of the reaction when 0.24 mM to 4.88 mM of oxidant agent was used. The direct photolysis provided only 12 and 24% removal of PTX after 15 and 30 min of irradiation, respectively, while a combined system UV/H₂O₂ gave full decomposition of PTX after 15 min. The process is based on PTX reaction with hydroxyl radicals (Eq. (1)), which are formed by hydrogen peroxide photolysis (Eq. (2))



In order to find the optimal amount of oxidant, a series of experiments with various hydrogen peroxide dosages (from 0.24 mM to 4.88 mM) were conducted. After 5 min of the reaction (PTX/H₂O₂/UV), 4%, 94%, 87% and 85% decomposition of active pharmaceutical ingredient (API) was obtained using 0.24 mM, 1.22 mM, 2.44 mM and 4.88 mM of H₂O₂, respectively.

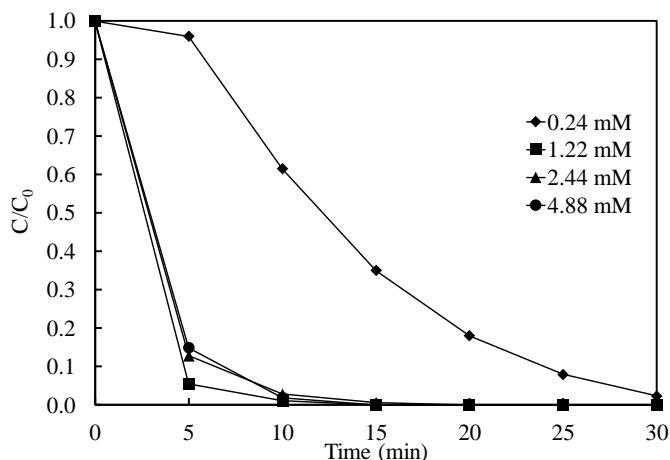


Fig. 2. Effect of various hydrogen peroxide dosages on the PTX degradation by UV/H₂O₂ system. PTX 0.1 mM, H₂O₂ (0.24–4.88 mM); C – the concentration of PTX, C₀ – the initial concentration of PTX

Table 1

Pseudo-first order rate constants (*k*) of PTX degradation by direct photolysis, H₂O₂ and H₂O₂/UV system

Objective	Pseudo-first order kinetics fitting $k \times 10^{-2} [\text{min}^{-1}]$	R^2
UV	0.92	0.99
4.88 mM H ₂ O ₂	0.04	0.98
0.24 mM H ₂ O ₂ /UV	12.50	0.93
1.22 mM H ₂ O ₂ /UV	44.70	0.97
2.44 mM H ₂ O ₂ /UV	33.70	0.99
4.88 mM H ₂ O ₂ /UV	39.40	0.99

As seen in Fig. 2, the complete PTX removal was achieved after 15 min of the reaction when 1.22 mM of H₂O₂ was added. At the same time 64%, 99% and 99% decrease of PTX concentration for 0.24 mM, 2.44 mM and 4.88 mM of H₂O₂, respectively, were observed. These experiments have shown that addition of larger doses of hydrogen peroxide did not cause more efficient degradation of PTX, probably due to effective quenching of hydroxyl radicals. Overdosing of oxidation agent may lead to generating

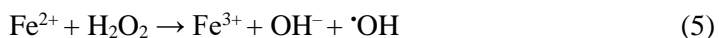
hydroperoxyl radicals (HOO^\bullet) (Eq. (3)) [14] less reactive than HO^\bullet and able to further consume valuable hydroxyl radicals (Eq. (4)) [15]



Obviously, the highest value of the pseudo-first order degradation rate constants for photo-oxidation process was noticed when 1.22 mM of hydrogen peroxide was applied (Table 1).

3.2. FENTON REACTION. EFFECT OF Fe^{2+} AND H_2O_2 DOSAGE ON PENTOXIFYLLINE DEGRADATION

The Fenton process has become a subject of much attention due to its satisfying results in wastewater purification. During the process, degradation occurs thanks to rapidly generated hydroxyl radicals. The radicals, produced by decomposition of H_2O_2 in the presence of ferrous ion (Eq. (5)), react with organic matter R causing its chemical destruction (Eq. (6)).



Certainly, the degradation efficiency of Fenton reaction is dependent on the concentration of hydroxyl radicals [16]. Therefore a study was conducted to determine appropriate amounts of hydrogen peroxide and ferrous sulfate to obtain the best operating conditions for degradation of PTX.

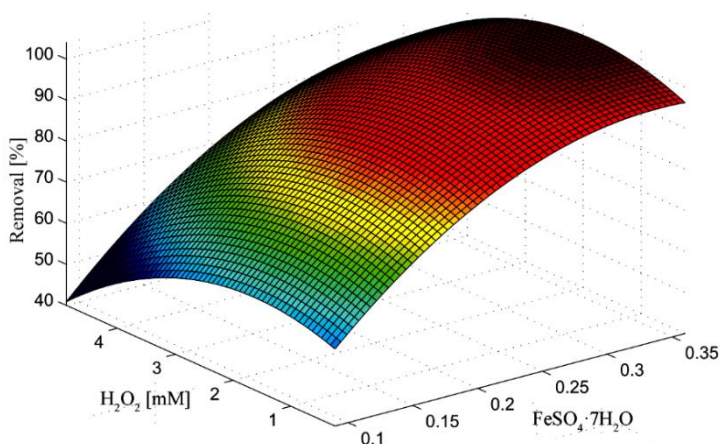


Fig. 3. Removal of PTX with Fenton reaction under various $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ dosages (0.09–0.36 mM); H_2O_2 dose 0.24–4.88 mM, PTX 0.1 mM

The analysis of Fig. 3. suggests that for each series of experiments (assuming that the amount of hydrogen peroxide is constant, and the amount of ferrous sulfate is variable), the increasing amounts of salt, improve the removal of PTX. According to Eq. (5), we can deduce that higher concentration of ferrous sulfate causes faster generation of hydroxyl radicals (responsible for the destruction of organic matter). The maximum efficiency was obtained when 2.44 mM H₂O₂ and 0.36 mM FeSO₄·7H₂O were used. After 5 min of the reaction a 100% decomposition of API was observed. However, application of such amount of oxidant agent generates high costs in industrial scale. Moreover, high concentration of hydrogen peroxide is not desirable in environment. The minimum efficiency was observed when 4.88 mM H₂O₂ and 0.09 mM FeSO₄·7H₂O were applied. It can be a consequence of parallel reaction between hydrogen peroxide with ferrous ions when one of them is present in excess [17]:



3.3. PHOTO-FENTON REACTION

Effect of [H₂O₂] on pentoxifylline degradation. Taking under consideration previously studied Fenton reaction, 0.18 mM FeSO₄·7H₂O as an average content of catalyst has been chosen. For this amount of salt, the total degradation of drug has not been achieved for any ratios of FeSO₄·7H₂O to H₂O₂. Nevertheless, this amount can be reasonable for use in industrial environments. Based on literature review, ultraviolet radiation seemed to be a factor improving efficiency of the process. For example, the complete Ampicillin removal was reached after 10 min and 3 min for Fenton and photo-Fenton reactions, respectively, when optimized values of pH, FeSO₄·7H₂O and H₂O₂ concentrations were used [18]. 44% and 56% COD removal were obtained after 30 min of Fenton-like and photo-Fenton-like reactions, respectively, when Procaine Penicillin G was degraded. Moreover, products formed during the photo-Fenton-like reactions were more effective in biodegradability improvement than the dark oxidation reaction [19].

The photo-Fenton involves irradiation with UV light, which results in significantly higher degradation than Fenton reaction, as the Fe(III) is photoreduced to Fe(II) (Eq. (8)) [20]. During this step more hydroxyl radicals are produced, ferric ions are regenerated and further reaction with H₂O₂ becomes possible.



In our study, the effect of hydrogen peroxide concentration on the PTX degradation was investigated using 0.24 mM, 1.22 mM, 2.44 mM and 4.88 mM H₂O₂, with the initial API concentration of 0.1 mM and 0.18 mM of FeSO₄·7H₂O. The PTX concentration decreased very rapidly in the first few minutes (Fig. 4). For 1.22 mM and 2.44 mM of

hydrogen peroxide, after 5 min of the reaction PTX was not observed in the system. For 0.24 mM, 97% removal was obtained. The results confirm that photo-Fenton reaction is a valuable method in degradation of PTX. Comparing Fenton and photo-Fenton reaction (0.18 mM $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$, 1.22 mM H_2O_2 , 5 min), 83% and 100% degradation was achieved, respectively.

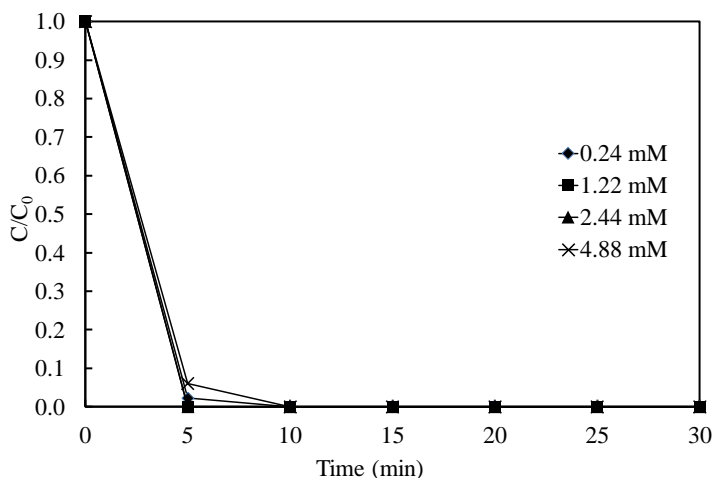


Fig. 4. Effect of different hydrogen peroxide dosages on the PTX degradation by photo-Fenton reaction; PTX 0.1 mM, $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ 0.18 mM, H_2O_2 (from 0.24 to 4.88 mM)

However, it should be noted that degradation rate of PTX does not increase with increasing hydrogen peroxide dose. The higher H_2O_2 concentration (4.88 mM) inhibited decay of PTX. This result is similar to that obtained by Trovó et al. [21] during decomposition of diclofenac. Undesirable effect can be caused by self-decomposition (Eq. (9)) and scavenging of hydroxyl radicals by an excess of oxidant (Eq. (4)).



Effect of initial pentoxifylline concentration on its degradation. The influence of the initial PTX concentration (from 0.1 to 10 mM) on the photo-Fenton degradation is shown in Fig. 5. The degradation was monitored under standardized conditions: 200 cm³ of appropriate solution (A, B, C, D, E or F), 0.18 mM $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$, 1.22 mM H_2O_2 under UV irradiation. The higher PTX concentration used, the slower decomposition rate was. Only between 0.1 mM and 0.25 mM PTX insignificant differences in the degradation course were noticed. After 5 min, 100% and 96% of 0.1 mM and 0.25 mM PTX was degraded, respectively. When 0.5 and 0.75 mM PTX solutions were oxidized under similar conditions, 72% and 42% of the examined API was decomposed, respectively. For those concentrations, the total decomposition was not achieved even after 1 h.

When 10 mM PTX solution was used, after 1 h of the reaction only 10% removal was noticed. The increase in the initial PTX concentration inhibits its removal. Increased PTX concentration might also induce an increase of the internal optical density that limited UV light propagation in solution. Therefore generation of active radicals could be restricted. All these factors cause a decrease in the rate of PTX degradation. The kinetics of concentration removal for PTX in photo-Fenton system followed pseudo-first order reaction with the reaction rate constants: 0.099 min^{-1} (R^2 0.91); 0.054 min^{-1} (R^2 0.96); 0.053 min^{-1} (R^2 0.96), 0.0028 min^{-1} (R^2 0.90) for 0.5, 0.75, 1 and 10 mM PTX, respectively.

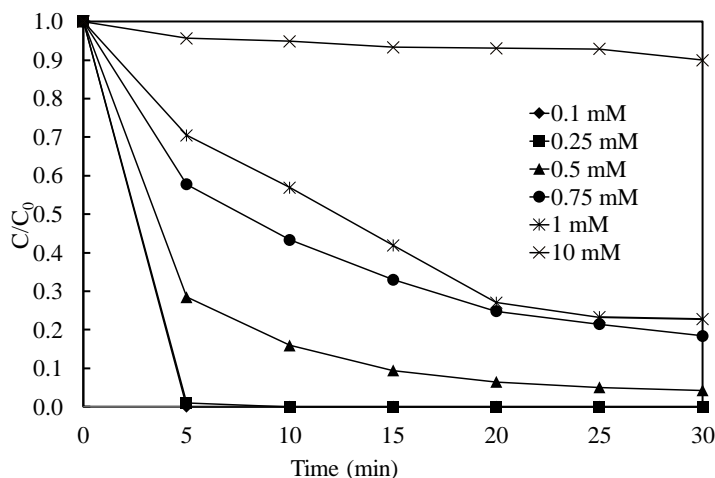


Fig. 5. Effect of initial PTX concentrations on degradation in photo-Fenton reaction: PTX (0.1–10 mM), $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ 0.18 mM, H_2O_2 1.22 mM

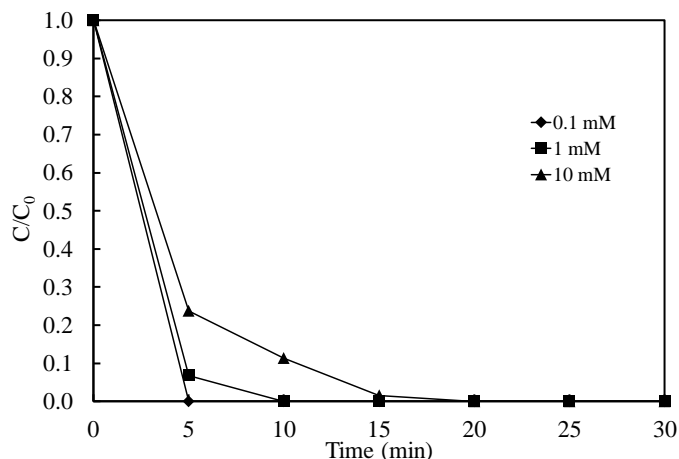


Fig. 6. Effect of initial PTX and oxidant agents concentrations on degradation processes in the photo-Fenton reaction: $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ 18 mM, H_2O_2 122 mM

In the following experiments, to 200 cm³ of solution A, 0.18 of mM ferrous sulfate and 1.22 mM of hydrogen peroxide and into 200 cm³ of solution E, 1.80 mM of ferrous sulfate and 12.20 mM of hydrogen peroxide were added. For reaction of 200 cm³ of 10 mM PTX 18 mM ferrous sulfate and 122 mM hydrogen peroxide were applied. As is seen in Fig. 6, the amount of oxidant agent was proportionally increased with respect to the concentration of PTX (Fig. 6). The increased concentration of PTX required longer time of the reaction. 100% decomposition of PTX was achieved after 5, 10 and 20 minutes for 0.1 mM, 1 mM and 10 mM PTX solutions, respectively.

3.4. EFFECT OF INORGANIC SALTS ON PENTOXIFYLLINE DEGRADATION

The effect of four different inorganic anions commonly occurring in natural water (chloride, nitrate, sulphate and carbonate) on PTX degradation is presented in Table 2. In each experiment, salts were added to the solution A (200 cm³) as a solid in an amount to provide their concentration 10 mM. The kinetic experiments were carried out for 1.22 mM H₂O₂ in H₂O₂/UV system and 1.22 mM H₂O₂/0.18 mM FeSO₄·7H₂O in the Fenton and photo-Fenton reaction).

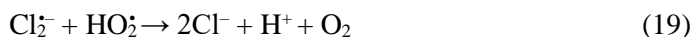
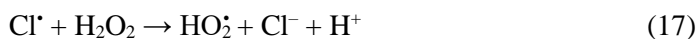
Table 2

Removal of PTX [%] after 5 min of the reaction.
Effect of various anions: PTX 0.1 mM, inorganic salt 10 mM

Salt	1.22 mM H ₂ O ₂ /UV	Fenton reaction 1.22 mM H ₂ O ₂ /0.18 mM FeSO ₄ ·7H ₂ O	Photo-Fenton reaction 1.22 mM H ₂ O ₂ / 0.18 mM FeSO ₄ ·7H ₂ O/UV
Without salt	94.67	87.31	100
10 mM NaCl	90.47	79.06	100
10 mM NaNO ₃	87.00	73.50	100
10 mM Na ₂ SO ₄	82.30	80.60	100
10 mM Na ₂ CO ₃	57.77	20.67	43.97

In the case of H₂O₂/UV reaction, sodium chloride, nitrate, sulphate and carbonate revealed inhibiting effect on PTX degradation followed the order: NaCl < NaNO₃ < Na₂SO₄ < Na₂CO₃. The most important role in the degradation of PTX played hydroxyl radicals obtained from the photolysis of hydrogen peroxide (Eq. (2)). Chloride or nitrate ions in the tested system partially quench hydroxyl radicals (Eqs. (10)–(21)). Inhibiting effect of inorganic salts in sequence NaCl < NaNO₃ on the degradation rate in H₂O₂/UV system was also observed [22] during oxidation of nitrosamines.





In our experiments, chloride, nitrate and sulfate ions only slightly slow down the degradation process of PTX. Higher inhibiting effect is observed when sodium carbonate is used. Carbonates are well-known scavengers of hydroxyl radicals. They react with HO^\bullet generating carbonate radicals which are less reactive than hydroxyl radicals [23].



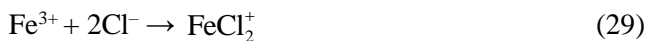
Introduction of sodium carbonate into PTX solution caused enhancement of the degradation rate. However, this might be also a consequence of increased pH values from 6.4 to 7.5 after addition of Na_2CO_3 .

It has been reported that not only $\text{H}_2\text{O}_2/\text{UV}$ but also the Fenton process efficiency can be lower due to additional substances in the reaction system. It can be caused by quenching effect of hydroxyl radicals. Due to the formation of less reactive Fe(II) complexes, the concentration of free iron ions is insufficient in the Fenton process. Moreover, new radicals (e.g. Cl^\bullet , Cl_2^-) are formed, which are less reactive than HO^\bullet . The effects of inorganic compounds on the rate of degradation in the Fenton process is

shown in Table 2. All tested salts revealed inhibiting effect on PTX degradation followed the order: $\text{Na}_2\text{SO}_4 < \text{NaCl}^- < \text{NaNO}_3 < \text{CaCO}_3$. It has been reported that nitrate ions do not tend to form complex with iron ions [24]. They can only scavenge HO^\bullet radicals according to equation



Degradation of PTX was slightly inhibited by chloride ions. After 5 min of the reaction, 87% of PTX was removed when only the Fenton process was applied. At the same time, 79% of PTX was decomposed in the Fenton reaction combined with sodium chloride. This can be caused by scavenging of hydroxyl radicals by direct reaction of chloride ions with HO^\bullet , consumption of necessary (for generation of hydroxyl radicals) iron active species by chloride ions (Eqs. (25)–(31)) or reagent consumption during the chloride radicals and hydrogen peroxide reaction (Eqs. (17), (18))



Sodium bicarbonate was not reported to generate complex with iron ions in acidic conditions. It can inhibit degradation by scavenging hydroxyl radicals):



Nevertheless, the decrease of the reaction rate was significant. The degradation rate of PTX was reduced approximately by 76% when carbonate ions were introduced into solution.

As far as the photo-Fenton process is concerned, sodium chloride, nitrate as well as carbonate were not found to delay the PTX degradation (Table 2). The complete decomposition of PTX in absence as well as in the presence of appropriate inorganic salts was noticed after 5 min. However, the delay effect in the photo-Fenton process is insignificant in comparison with H₂O₂/UV and Fenton reactions. This confirms the efficacy of the photo-Fenton reaction.

3.5. DEGRADATION PRODUCTS OF PTX OXIDATION

To identify the intermediate products UPLC-MS (4000 Q-TRAP) analysis was employed. 4000 Q-TRAP is a triple quadrupole-type instrument with a linear ion trap in place of the third quadrupole. Proposed structures of compounds formed during PTX decomposition by the photo-Fenton process are presented in Table 3.

Table 3

Proposed structures of PTX by-products received during oxidation of PTX by photo-Fenton reaction detected by UPLC-MS

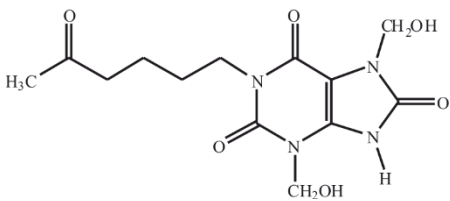
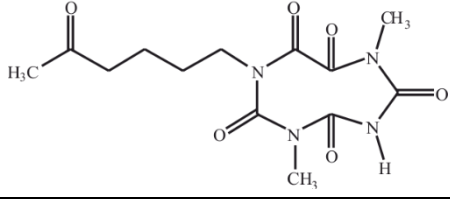
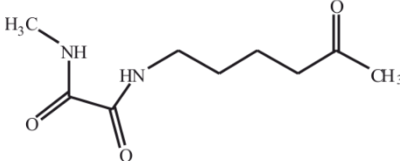
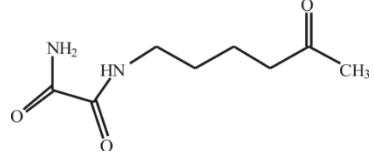
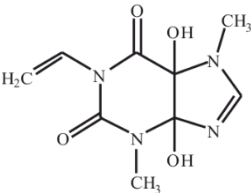
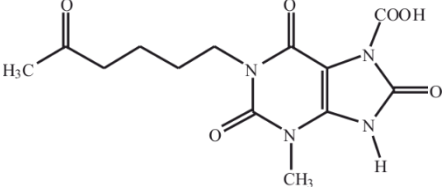
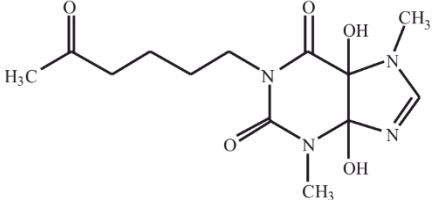
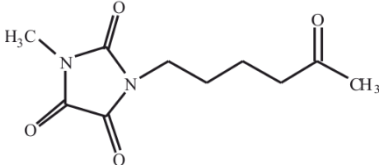
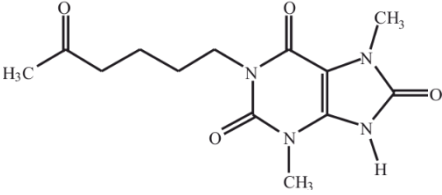
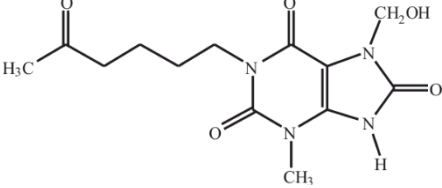
RT [min]	No.	Product structure	m/z [ESI]
0.43	P1		349 [M + Na]
0.43	P2		349 [M + Na]
1.22	P3		223 [M + Na]
1.22	P4		209 [M + Na]

Table 3

Proposed structures of PTX by-products received during oxidation of PTX by photo-Fenton reaction detected by UPLC-MS

<i>RT</i> [min]	No.	Product structure	<i>m/z</i> [ESI]
1.76	P5		263 [M + H]
2.22	P6		347 [M + Na]
2.69	P7		335 [M + Na]
2.69	P8		249 [M + Na]
3.15	P9		317 [M + Na]
3.95	P10		333 [M + Na]

As it was mentioned previously, hydroxyl radicals are characterized by high reactivity and non-selectivity. They can attack many structural parts of a PTX molecule. Product (P9) is obtained by hydroxyl radical addition in 8 position and further molecule stabilization by keton formation. At the same time, the competitive reaction takes place in which two hydroxyl radicals are substituted in position 4 and 5 to form the product (P7). (P7) can be further transformed into (P2) or (P5). Aliphatic substituents are also good reagents in radical reactions. As a result of hydroxyl radical substitution to the methyl group in 7 position, the product (P10) is formed. Further oxidation of (P10) leads to carboxylic compound (P6) or competitive product (P1). The cyclic product (P2), formed in destructive oxidation of axanthine ring, is also converted into 1-methyl-3-(5-oxohexyl)-imidazolidin-2,4,5-trione (P8) as a result of subsequent rearrangements and oxidation reactions. Decarboxylation of (P8) occurring at position 1 gives a linear product (P3). The last reaction belonging to this path of degradation is (P3) demethylation leading directly to the product (P4).

4. CONCLUSION

The reaction of PTX with H_2O_2 , H_2O_2/UV , UV irradiation alone, Fenton and photo-Fenton processes have been tested. In H_2O_2/UV system, 100% of parent compound was removed after 20 min, compared to 16% in the absence of UV light. Oxidation with the usage of hydrogen peroxide without irradiation is ineffective. In the case of H_2O_2/UV system, the optimum concentration of hydrogen peroxide is 1.22 mM when 0.1 mM PTX is used. Higher concentrations of H_2O_2 decrease the yield of the PTX degradation. The most significant degradation rate was observed in the case of photo-Fenton reaction. The complete PTX removal was reached after 5 min of the reaction, when optimized concentrations of $FeSO_4 \cdot 7H_2O$ and H_2O_2 were used. The degradation of PTX was inhibited in the presence of inorganic salts and H_2O_2/UV , and Fenton reaction. In the photo-Fenton process, addition of the above compounds does not affect the reaction rate. The increase of PTX concentration inhibits the removal of API. Chemical structure of products obtained in photo-Fenton reaction have been proposed.

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