Advanced Oxidation Processes: Ozonation and Fenton Processes Applied to the Removal of Pharmaceuticals

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Abstract   This chapter aims to present the fundamentals, important variables, and pharmaceuticals removed by ozonation and Fenton, which are only two of the current existing advanced oxidation processes. Some toxicological information regarding pharmaceuticals oxidized by ozonation is also included. Some strategies to improve such processes, like adding a catalyst, light, or electrical current, are also analyzed. Thus, this chapter intends to present general but fundamental aspects of the aforementioned processes.

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1 Introduction

For centuries, the scientific and technological efforts of human being were mainly dedicated to provide comfort and make life "easier." In the last decades, however, it has been demonstrated that such a good intention while benefiting many has also had a detrimental effect on global environment, thus affecting the whole planet. This awareness of unsustainability has urged the development of processes not only for cleaner good production but also to clean the already contaminated industrial effluents and water bodies. In this context, pharmaceutical compounds have been identified as an important group of water pollutants, and therefore their removal by any means is imperative. To achieve so, advanced oxidation processes (AOPs) have emerged as an important alternative to eliminate them. Therefore, herein the fundamentals, advantages, and drawbacks of two important AOPs, ozonation and Fenton, are summarized. General aspects of variants of ozonation, like catalyzed ozonation and peroxonation, are revised too. The results of applying such processes to some pharmaceutical removal can also be found. The included pharmaceuticals were the most referenced ones in the last 5 years.

2 Ozonation

2.1 Fundamentals

The ozone molecule (O_3) possesses a high oxidant power ($E° = 2.07$ V); it is highly reactive and finds a diversity of applications, mainly in the oxidation of organic/inorganic compounds, disinfection, wastewater, and potable water treatment. Due to its reactivity, ozone tends to form oxygen. However, at some atmospheric conditions (like pressure, temperature, humidity, velocity) and pH, the ozone half-life can be increased from seconds until days.

A limitation of ozonation is its inherent high cost to produce ozone at the point of use. Ozone production is mainly conducted by electrical discharge or electrolysis at industrial or laboratory scale [1].

Compound oxidation by ozone can be either through direct or indirect mechanisms. Although in practice both ways may take place simultaneously, it is necessary to specify the difference between the two routes as follows.

2.1.1 Indirect Reaction

In this mechanism ozone is not the oxidant specie but helps to the generation of species that have an unpaired electron. This is possible under alkaline conditions, and under this condition is when ozonation can be considered an advanced oxidation process since it is based on the production of hydroxyl radicals. For a better explanation of this reaction path, it is necessary to consider three steps: initiation, chain propagation, and termination. The main reactions involved in these steps are summarized in Table 1. In summary, the main oxidant specie is the hydroxyl radical and not the ozone molecule.

In the first step, ozone reacts with hydroxide ions to generate superoxide anion ($O_2^{\bullet-}$) and hydroperoxyl radical ($HO_2^{\bullet}$). Some species from the first stage react once more with ozone to obtain new anions and radicals like the following: ozonide anion ($O_3^{\bullet-}$), hydrogen trioxide ($HO_3^{\bullet}$), and hydroxyl radical ($OH^{\bullet}$) which is the most powerful oxidant. The second stage is denominated chain reaction because of the regeneration of hydroperoxyl radicals on reaction (7), which also participates in reaction (2), so this promotes the chain reaction.

Moreover, hydroxyl radical can also react with some organic molecules (R), and this is exemplified in reactions (8)–(11). In this route new species are formed like organic radicals ($R^{\bullet}$), and when there is the presence of oxygen, peroxy radicals $ROO^{\bullet}$ can also be formed.

Unfortunately not all reactions allow to increase the amount of strong oxidants like in the stage of chain reaction. As a consequence of the reactivity of hydroxyl radicals with some organic/inorganic compounds, other anions that act as scavengers are generated. In this case, in reactions (12) and (13), carbonate/bicarbonate

Table 1 Ozone decomposition reactions [2]

Step	Reaction	
Initiation	$O_3 + OH^- \rightarrow O_2^{\bullet-} + HO_2^{\bullet}$	(1)
	$HO_2^{\bullet} \leftrightarrow O_2^{\bullet-} + H^+$	(2)
Chain propagation	$O_3 + O_2^{\bullet-} \rightarrow O_3^{\bullet-} + O_2$	(3)
	$HO_3^{\bullet} \leftrightarrow O_3^{\bullet-} + H^+$	(4)
	$HO_3^{\bullet} \rightarrow OH^{\bullet} + O_2$	(5)
	$OH^{\bullet} + O_3 \rightarrow HO_4^{\bullet}$	(6)
	$HO_4^{\bullet} \rightarrow O_2 + HO_2^{\bullet}$	(7)
	In presence of organic molecules (R):	
	$H_2R + OH^{\bullet} \rightarrow HR^{\bullet} + H_2O$	(8)
	$HR^{\bullet} + O_2 \rightarrow HRO_2^{\bullet}$	(9)
	$HRO_2^{\bullet} \rightarrow R + HO_2^{\bullet}$	(10)
	$HRO_2^{\bullet} \rightarrow RO + OH^{\bullet}$	(11)
Termination	$OH^{\bullet} + CO_3^{2-} \rightarrow OH^- + CO_3^{\bullet-}$	(12)
	$OH^{\bullet} + HCO_3^- \rightarrow OH^- + HCO_3^{\bullet}$	(13)
	$OH^{\bullet} + HO_2^{\bullet} \rightarrow O_2 + H_2O$	(14)
Overall reaction	$3O_3 + OH^- + H^+ \rightarrow 2OH^{\bullet} + 4O_2$	(15)

appears to quench the chain reaction; these ions are produced initially from CO_2 dissolved into the water, which tends to form carbonic acid; as a consequence this acid is partially dissociated to carbonate, and a second dissociation forms ion bicarbonate. Reaction (15) is the result of combining the first reactions (1)–(7).

2.1.2 Direct Oxidation Reaction

Another path for the ozone decomposition is the direct reaction or also so-called Criegee mechanism, which consists of selective reactions between the ozone molecules with an unsaturated bond. In this mechanism the degree of nucleophilicity is determinant; for that reason, the reactivity of ozone molecule increases when there is the presence of saturate aliphatic or aromatic compounds. The oxidation is slower in the presence of unsaturated aliphatic, non-dissociated, and dissociated organic compounds.

On the other hand, with respect to the inorganic compounds, sometimes these can react much faster than organic compounds. More or less in the same way this happens with its degree of nucleophilicity. On the contrary, ionized or dissociated inorganic compounds can react faster with ozone [2]. This type of oxidation is favored under acidic reaction conditions.

2.2 Technologies for Ozonation Applied to the Removal of Pharmaceutical Compounds and Other Organic Molecules

The removal of pollutants in solution by ozonation implies the use of multiphase reactors in order to efficiently contact gas and liquid and even solid if the use of a heterogeneous catalyst is on demand. Thus, at this point, it is worth highlighting the importance of the reactors in ozonation process and also pointing out the most significant factors to be taken into account in their operation and design.

According to existing literature [3–5], semi-batch upflow bubble column is the preferred reactor to carry out the ozonation of pharmaceutical compounds. This reactor mainly consists of a cylindrical bubble column with a gas diffusor at the bottom where the ozone stream is fed. Ozone is produced from the decomposition of oxygen or air by an ozone generator; thus, the reactor feed stream is usually a mixture of ozone and air or oxygen since the effectiveness of ozone generation is not 100%. This reactor is batch regarding the liquid phase and semi-batch regarding the gas phase, and this is to be considered in the transport balances used for design. Since O_3 can be highly toxic, a common characteristic among ozonation reactors is that the outlet gas line of the reactor is connected to a trap with KI solution, in order to destroy the unconsumed ozone. To enhance the gas-liquid mass transfer, the
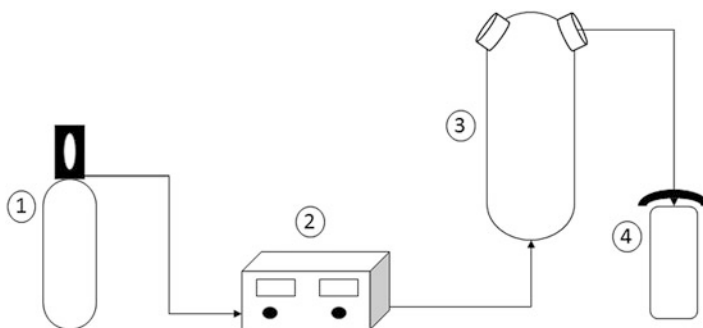
Fig. 1 Semi-batch ozonation system. Description: (1) oxygen, (2) ozonator, (3) upflow bubble column reactor, (4) KI trap

reactor is coupled to a magnetic stirring apparatus [6]. Figure 1 depicts a typical setup of an upflow bubble column reactor [7].

A variant of the reactor depicted in Fig. 1 is the semicontinuous reactor that has also been utilized to conduct the catalyzed ozonation of industrial effluents [8–10]. The main difference with a typical semi-batch reactor is the recirculation of liquid phase by a pump; the other elements are basically the same. An advantage of this kind of systems is the increase of volume, which allows working at pilot scale. In this context, a rather novel proposal was made by Crousier et al., who tested the TOCCATA® catalyst in the treatment on urban wastewater [9]. In this work the reactor consisted of two bubble columns, one column was packed with the catalyst (TOCCATA®) and the other remained empty. This arrangement allowed the wastewater to be treated in both columns.

In any type of upflow bubble columns, special care should be taken with the particle size and density of the catalyst and gas flow rate. If the adequate values of these variables are not used, the catalyst will not be properly fluidized, and thus mass transfer would be the limiting step, and catalyst would be subdued.

Although the destruction of ozone is carried out in the trap of KI of the semi-batch and semicontinuous reactors, it still has the disadvantage of wasting ozone, because this gas is continuously supplied to the reactor and its generation can be costly. Furthermore, in the aforementioned systems, the ozone destruction is not complete, and this is another disadvantage because of ozone undesirable effects [11]. This has motivated the design of new ozonation reactors like the one proposed by Lucas et al. [12]. Such a reaction system was called multi-orifice oscillatory baffled column (MOBC). Its design of several orifices in each baffle allows a reduction in the volume reactor and intensifies the ozonation process. To test the efficiency of this reactor, the degradation of p-hydroxybenzoic (p-HBA) acid was carried out [12] and was also benchmarked against a conventional bubble column. The reaction conditions were a total volume reaction of 9.6 L, liquid flow rate of 4 L/min, pH 10 ± 0.1, gas flow rate of 2.1–4.7 L/min with ozone concentration of 23 gO_3/m^3, and 50 mg/L of p-HBA. Main results reported of this investigation were an increase of 20% of p-HBA degradation, 75% in the rate of mineralization per

mole of ozone consumed, and the increase from 4.5 to 5 times of rate of mineralization per mole of ozone supplied. All these results are compared with those obtained in a conventional bubble column. It is well known that one baffle may increase dissolved oxygen concentration in water up to six times [13]. Additionally, the use of several baffles along the column allows a better distribution of the bubbles and the complete ozone consumption.

In this sense, another promising technology is the cocurrent downflow bubble column (CDBC) that has been successfully applied to conduct heterogeneous catalyzed hydrogenation and UV photo-catalyzed processes [14–16]. The main difference with the aforementioned reactors is that both phases, gas and liquid, are fed at the column top.

2.3 Pharmaceutical Compound Removal by Ozonation

O_3 molecule high oxidant power and also the oxidant radicals produced during its decomposition have been applied for the removal of several compounds. Although there are many other pharmaceutical compounds that have been attempted to be degraded by ozone, Table 2 summarizes the ones that have been mostly reported.

It is worth noticing that the initial concentrations of the pharmaceutical compounds are rather low and this is because many of them have been shown [18, 20–25] to represent a biological hazard even at very low concentrations. It can also be observed that a complete mineralization is not reached in some cases. This may be due to the low ozone dosage, but also one should not forget the effect of the alkalinity produced by carbonated and bicarbonates, which tend to be scavengers of the hydroxyl radical. On the other hand, despite that mineralization is not

Table 2 Ozonation applied to removal of pharmaceutical compound

Pharmaceutical	Reaction conditions	Removal (%)	References
Carbamazepine (CBZ) Diclofenac (DCF) Sulfamethoxazole (SMX) Trimethoprim (TMP)	Ozone dosage: 1.6 mg/L 2.3 mg/L 2.8 mg/L 4.5 mg/L $C_0 = 5$ mg/L, for each compound	LC-MS: 100 LC-MS: 100 LC-MS: 100 LC-MS: 100	[17]
Indomethacin (IM)	$[O_3]$: 35 mg/L Flow rate: 250 mL/min pH: 7 C_0: 25 μM Time: 30 min	TOC ~50	[18]
Mixture: Atenolol (ATL) Hydrochlorothiazide (HCT) Ofloxacin (OFX) Trimethoprim (TMP)	$[O_3]$: 2.5 mg/L Flow rate: 36 L/h pH: 7 C_0: 2.5 mg/L Time: 120 min	TOC ~35	[19]

complete, in several cases like mentioned earlier, by-products are less harmful, with respect to parent compounds. Thus, in those cases where mineralization is not complete, it is desirable to establish the toxicology of the treated solution in order to elucidate weather or not the ozone treatment is effective in oxidizing the organic compounds into less toxic ones. Ozone concentration can be low either because of inherent limitations of the system or mainly because ozonation may become rather expensive due to the high consumption of energy and type of technology to generate it. Thus, to reduce the cost of treatment, the most of ozone applications tend to employ low concentrations of this oxidant.

Regarding pH, during ozonation this parameter is usually adjusted to a neutral value in order to promote the two mechanisms of ozone attack.

In order to increase removal efficiency and reduce the amount of ozone usage, there are reported some successfully assessed approaches. One is the addition of catalysts and the other one is the addition of hydrogen peroxide (peroxonation). The following two sections deal with such processes.

2.4 Pharmaceutical Compound Removal by Catalyzed Ozonation

The ozonation process can be enhanced by the addition of a catalyst, which can be homogeneous or heterogeneous. In the former case, this material must be a transition metal that can be oxidized and reduced back to initial state, but this kind of catalyst is not used in several applications because its recovery is rather difficult. For that reason, the most employed catalyst is the heterogeneous [26, 27]. Considering this, it is easy to identify when the ozonation is heterogeneously catalyzed, because chemisorption reactions between ozone – catalytic surface – organic molecule occur simultaneously [28].

In this process, there are several variables that affect the efficiency of the process. These are pH, ozone dosage, stirring, temperature, type, concentration, and size of the catalyst. Stirring and particle size are particularly important when the efficiency of two catalysts are to be compared since in order to have a reflection of the catalytic surface, the whole process should be free of transport phenomena resistances. These variables are also important in order to avoid catalyst sub-utilization. Stirring is the first variable to be assessed since will not affect only the mass transfer from the solution to the catalyst but also from the ozone to the bulk solution and therefore to the catalyst. Particle size effect should also be discriminated since the very beginning. A particle size lower than 60 μm usually guarantees the elimination of intra-particle transport resistances. Regarding pH, when its value increases, the ozone is decomposed into hydroxyl radicals which are more reactive than ozone and less selective [7]; it also affects the surface of catalyst and the dissociation of organic pollutants in water [29]. If the pH value is low, ozone exists in water in a molecular state [30]. In acid medium, the oxidation of

contaminants is by molecular ozone oxidation and not by hydroxyl radicals. Optimal values of pH have been obtained in neutral or alkaline medium [27, 31]. Based on reactions (12) and (13), it is clear that carbonate ions are scavengers much stronger than bicarbonate ions. The increase of these ions is by addition of Na_2CO_3; this is common in dyes containing effluents [32]. If the HO$^{\bullet}$ scavengers are present in the process, the molecular ozonation might prevail. Other HO$^{\bullet}$ scavengers are phosphate and tert-butanol, the former blocks the Lewis site of catalyst [27], the latter reacts in bulk solution with HO$^{\bullet}$ [33]. The presence of tert-butanol reduces the percentage of mineralization even more than 20%.

The addition of catalyst increases the number of active sites, but not always higher dosages of catalysts increase the removal of pollutant. This is why this process is not always an alternative to not catalyzed ozonation, despite reducing ozone flow rate and its concentration.
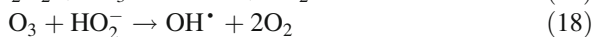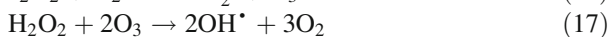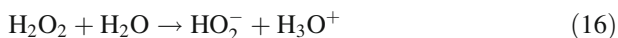
Table 3 shows typical assessed variables and their values applied to the pharmaceutical removal by catalyzed ozonation. The shown pharmaceuticals were selected because they represent an important portion of the existing literature.

Table 3 Catalyzed ozonation applied to the removal of pharmaceutical compounds

| Pharmaceutical	Reaction conditions	Removal (%)	References
Sulfamethoxazole (SMX)	Catalyst: Fe_3O_4 Catalyst dosage: 0.3 g/L [O_3]: 2 g/h pH: 7 C_0: 50 mg/L Time: 5 min	100	[34]
Phenacetin (PNT)	Catalyst: $CuFe_2O_4$ Catalyst dosage: 2.0 g/L [O_3]: 0.36 mg/min pH: 7.72 C_0: 0.2 mM Time: 5 min Time: 3 h (mineralization)	100 TOC: 90	[35]
Sulfamethazine	Catalyst: $Cu_{0.1}Fe_{0.9}OOH$ Catalyst dosage: 0.2 g/L [O_3]: 15 mg/min pH: 7 C_0: 20 mg/L Time: 10 min Time: 120 min (mineralization)	100 TOC: 44	[36]
Ibuprofen	Catalyst: Fe_2O_3/Al_2O_3@SBA-15 Catalyst dosage: 1.5 g/L [O_3]: 30 mg/L Flow rate: 0.2 L/min pH: 7 C_0: 10 mg/L Time: 60 min	90 TOC: 26	[37]

2.5 Pharmaceutical Compound Removal by Peroxonation

In order to enhance ozonation action, H_2O_2 instead of a catalyst can be added to the reacting system, and this process is known as peroxonation. The added reactions of this process are presented below. In summary, these reactions imply that the interaction H_2O_2/O_3 can be affected by other species like water, as can be seen in reaction (16) where water is partially dissociated into hydroxide anions. This ion can also react with ozone (reaction 18), obtaining a hydroxyl radical, which is also produced by reaction (17).

$$H_2O_2 + H_2O \rightarrow HO_2^- + H_3O^+ \tag{16}$$
$$H_2O_2 + 2O_3 \rightarrow 2OH^\bullet + 3O_2 \tag{17}$$
$$O_3 + HO_2^- \rightarrow OH^\bullet + 2O_2 \tag{18}$$

Some pharmaceutical compounds that have been removed by peroxonation are in Table 4. Reaction conditions and removal efficiency are also included.

Gomes and collaborators [18, 21, 39] have reported that when more than 10 mM of hydrogen peroxide is used, this reagent and ozone can act as radical scavengers, and their addition may be detrimental rather than helpful. This phenomenon occurs by the following reactions (19) and (20):

$$OH^\bullet + H_2O_2 \rightarrow HO_2^\bullet + H_2O \tag{19}$$
$$OH^\bullet + O_3 \rightarrow HO_2^\bullet + O_2 \tag{20}$$
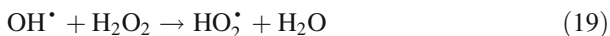
The products of these reactions are radicals with lower oxidant power than hydroxyl radicals. Thus H_2O_2 concentration must be kept at low values to prevent its action as scavenger. Regarding pH values, these are preferred neutral.

Table 4 Peroxonation applied to removal of pharmaceutical compounds

Pharmaceutical	Reaction conditions	Removal (%)	References
Fluoxetine	[O_3]: 30 mg/L [H_2O_2]: 0.02 mM C_0: 50 mg/L Time: 20 min	86.14	[38]
Sulfamethoxazole (SMX) and Diclofenac (DCF)	[O_3]: 20 mg/L [H_2O_2]: 5 mM pH: 7 C_0: 88.5 mg/L Time: 120 min	100 COD: 91	[21]

2.6 Kinetics of Pharmaceuticals Removed by Ozonation

Based on bench-scale studies, in general it is necessary to consider the kinetic study with the purpose of understanding the behavior of reactors at full scale [40]. All cases presented in this chapter used the following method to establish the reaction rate and kinetic constant, considering the data obtained from the profile degradation of the main pollutant and is known as integral method. The following equation can be integrated, assuming an nth pseudo-order reaction,

$$r_1 = -\frac{dC}{dt} = k_{obs}C^n \tag{21}$$

In most of the cases, this order has been found to be 1 or 2 for most of pharmaceuticals [21, 41]. When Eq. (21) is integrated assuming either order 1 or order 2, the resulting equations are (22) and (23), respectively.

$$\frac{\ln C_0}{\ln C_t} = k_{obs}t \tag{22}$$

$$\frac{1}{C_t} - \frac{1}{C_0} = k_{obs}t \tag{23}$$

Sometimes in the aforementioned equations, mineralization data from analysis of COD or TOC can also be employed. In the ozonation process, the kinetic study is focused on the determination of reactivity of ozone in direct and indirect form. To achieve so, the kinetic constants respect to ozone (k_{O3}) and hydroxyl radical ($k_{HO\bullet}$) are calculated. Generally speaking, in the degradation of pharmaceuticals like trimethoprim, valsartan, furosemide, lidocaine, tramadol, and fluconazole between others, the reported kinetic constants are in the order of 1–10^7 M^{-1} s^{-1} with respect to the ozone and for hydroxyl radical in the order of 1×10^8–10^{10} M^{-1} s^{-1} [18, 21, 31]. Despite several studies employing distilled water, this behavior can be extrapolated to other water matrix. The nature of nonselective oxidant of hydroxyl radical allows that their kinetic constants are higher than ozone. The study of [42] determined that pharmaceutical compounds with aromatic ring show high reactivity (~10^4–10^7 M^{-1} s^{-1}), while saturated aliphatic compounds present a very low reactivity (<5 M^{-1} s^{-1}).

2.7 Toxicity of Effluents Treated by Ozonation

In all water treatments, the aim is to remove contaminants either by chemical reduction or oxidation. In the latter, near complete mineralization is usually taken as an indicative of the treated effluent that can be safely discharged. This, however, is not always a guarantee [43]. This is due to the generation of species more harmful than the parent compound and to the addition of chemicals for changing pH, for example. In this section a variety of tests that have been applied to the effluents treated by ozonation is presented.

Within literature, it can be observed that toxicity removal directly depends on ozone dosage. For instance, working at high ozone dosages, toxicity can be eliminated at 100%, this was demonstrated with the indomethacin ozonation where several ozone concentrations were assessed and toxicity was estimated by means of essays with a luminescent bacterium called *Photobacterium phosphoreum*. Authors report that 35 mg/L of ozone concentration is enough to eliminate the toxicity after 60 min [18]. According to this investigation, it is not necessary to mineralize all organic matter; in fact the TOC removal is almost 50%. Some by-products that remain are essentially chloride and organic acids (acetic, formic, and oxalic). Oxalic acid, however, has been demonstrated to be highly toxic when biological hazard is established by means of other essays, with *Lactuca sativa*, for example.

Ecotoxicity tests can also be simultaneously conducted by some microbiological tests and can be corroborated with a software. In fact ECOSAR program (version 1.11), developed by USEPA, has been applied in the study of ofloxacin (OFX) ozonation, specifically on the determination of its hazard indices on *green algae*, *daphnia*, and fish [5]. Based on the proposed mechanism for the OFX degradation, 14 by-products were identified, which most of them after the treatment are not harmful, but when is exposed until 96 h, some by-products like OFX 336A and OFX 364 present a high chronic toxicity. In such study, ozone concentration was 15 mg/L in the flow rate.

As can be seen from the results presented above, the increase of ozone concentration increases the efficiency of toxicity removal. Such concentration, however, may be so high than the process cost that significantly increases too. In this case, adding a catalyst might be practical. Specifically, the group of Fei Qi and Zhonglin Chen, has tested the molecule of bezafibrate (BZF) with two different catalysts [39, 44]. In one study, these investigators employed 50 mg/L of a catalyst-denominated cobalt-doped red mud (Co/RM), with 0.5 mg/L of ozone concentration to remove 2.76 µM of BZF. Toxicity assessment was evaluated by *Chlorella vulgaris*, which presented a 96h-EC_{50} of 63%. In a second study, the reaction conditions, toxicity tests, and pollutant of the first study were kept constant; the only difference was the catalyst, where instead of cobalt cerium (IV), (Ce (IV)/RM-p) was employed and more than 50% of detoxification in 96h-EC_{50} test was attained. Still, toxicity was not fully eliminated when using the catalyst. A similar problem is observed during the peroxonation process. This can be ascribed to the addition of hydrogen peroxide whose excess must be quenched with catalase solution.

Sulfamethoxazole and diclofenac were studied by Rui Martins' group [21]; from this investigation, they assessed the removal of both pollutants in a synthetic solution and also from a secondary effluent by peroxonation. The toxicity was evaluated by a procedure described in ISO/DIS11348/3, which employs marine bacteria called *Vibrio fischeri* and measures the percentage on inhibition of light emission. Using this method, the samples of these water matrices (synthetic and secondary effluent) were analyzed; after 2 h of peroxonation, results are the following: the inhibition was 29% and 38%, for secondary effluent and synthetic solution, respectively.
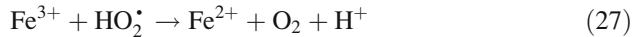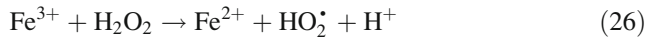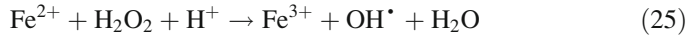
3 Fenton Process Applied to the Removal of Pharmaceutical Compounds
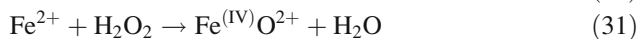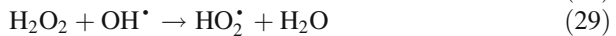
3.1 Fenton Process Fundamentals

Fenton reaction (24) is named after H.J.H. Fenton who added Fe^{2+} ions to catalyze the decomposition of H_2O_2 into hydroxyl radicals, hydroxyl ions, and Fe^{3+} ions and to intensify, in this way, tartaric acid oxidation.

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\bullet} + OH^{-} \tag{24}$$
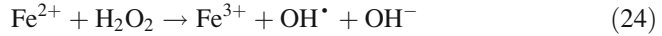
This reaction depends strongly on pH values, specifically on the ratio Fe^{2+}/Fe^{3+} ($E^{\circ} = 0.77$ V/SHE). The best results to dissociate hydrogen peroxide toward hydroxyl radicals have been reported in the range of 2.8–3 of pH [45, 46]. Taking into account that in acidic media Fenton's reaction presents better results, similar reactions occur simultaneously (25). When Fe^{3+}, decompose hydrogen peroxide is so-called Fenton reaction (26) and tends to form hydroperoxyl radicals, and by means of this reaction, the catalytic ion Fe^{2+} (27) is regenerated.
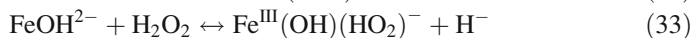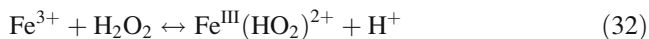
$$Fe^{2+} + H_2O_2 + H^{+} \rightarrow Fe^{3+} + OH^{\bullet} + H_2O \tag{25}$$
$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + HO_2^{\bullet} + H^{+} \tag{26}$$
$$Fe^{3+} + HO_2^{\bullet} \rightarrow Fe^{2+} + O_2 + H^{+} \tag{27}$$

The excess of Fenton's reagent (Fe^{2+}/H_2O_2) has been reported to inhibit the oxidant power of hydroxyl radical generating undesirable reactions (28)–(31) [47], through which scavenging species or oxidants with lower oxidant power are obtained. Additionally, working under neutral media, the reaction (30) takes place at this condition, and selective oxidants like high-valent ferryl-oxo species $Fe^{(IV)}$ might be produced [48].

$$Fe^{2+} + OH^{\bullet} \rightarrow Fe^{3+} + OH^{-} \tag{28}$$
$$H_2O_2 + OH^{\bullet} \rightarrow HO_2^{\bullet} + H_2O \tag{29}$$
$$OH^{\bullet} + OH^{\bullet} \rightarrow H_2O_2 \tag{30}$$
$$Fe^{2+} + H_2O_2 \rightarrow Fe^{(IV)}O^{2+} + H_2O \tag{31}$$

The main disadvantages of Fenton reaction are the storage and the risks of hydrogen peroxide; also the catalytic ion Fe^{2+} tends to oxidize toward Fe^{3+}, which forms sludge or metal hydroxides (reactions 32 and 33) and Fe(III) carboxylic acids complexes [46, 49] and the acid pH [50]. Nevertheless, some variants of this process are focused on generating hydrogen peroxide in situ, to minimize the process costs, disadvantages, and undesirable reactions abovementioned. Also, other than Fe salts have been used as source of catalyst. In this sense, iron-pillared clays have been successfully used and have considerably reduced the difficulty of recovering the catalyst [51]. Also, other metals, like cupper, have been successfully

applied as catalysts of H_2O_2 dissociation [52]. In such a case, the process is called Fenton-like.

$$Fe^{3+} + H_2O_2 \leftrightarrow Fe^{III}(HO_2)^{2+} + H^+ \tag{32}$$
$$FeOH^{2-} + H_2O_2 \leftrightarrow Fe^{III}(OH)(HO_2)^- + H^- \tag{33}$$

3.2 Hydrogen Peroxide In Situ Production (Electrochemical and Photochemical Methods)

The oxidant power of hydrogen peroxide not only finds application in wastewater treatment; it can also be applied to organic synthesis and paper industry, like disinfectant [53]; in addition it is used as rocket fuel [54]. One of the main advantages that make of H_2O_2 an environmentally safe oxidant is the by-products (oxygen and water). To diminish the risk in the handling of this oxidant, some methods, like anthraquinone process [53], electrochemical process [55], and photocatalytic process [56], have been developed in the generation of hydrogen peroxide. Specifically the last two mentioned processes are preferred because of the low energetic costs and because it allows the H_2O_2 production at mild conditions and most of them are green technologies.

According to the electrochemical process, the hydrogen peroxide is produced mainly by oxygen reduction at the cathode in acidic/neutral media by the following reaction [55]:

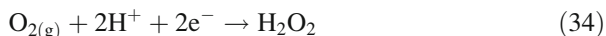$$O_{2(g)} + 2H^+ + 2e^- \rightarrow H_2O_2 \tag{34}$$

Table 5 summarizes the results of some investigations about this topic in which it can be observed that the carbonaceous materials are the most studied ones with respect to this process by the low cost and high concentrations electro-generated in electrochemical cells; it also requires an acidic media (pH 2–4) and an electrolyte-like sodium sulfate. On the other hand, in this kind of carbonaceous materials is not possible to employ high current intensities ($i > 300$ mA), due to the material structure. However a variant of carbonaceous materials called gas diffusion [63] electrode (GDE) is also applied with success at undivided cells, even at pilot-scale (reactors type filter press) applications [64, 65] in the pharmaceutical removal (ranitidine and metronidazole). In such investigations the amount of H_2O_2 is not reported, but the mineralization is almost complete in volumes of 2.5 L and 10 L, respectively. The main advantage of GDE is that it can simultaneously be applied to current intensity and flow rate of air/oxygen. GDE also is doped with other materials like CeO_2 with the purpose of increasing the production of H_2O_2 [61]. Another material reported with a high concentration of hydrogen peroxide is the boron-doped diamond [57, 63], which has the advantage of support high current densities and overpotential oxygen.

Table 5 H_2O_2 generated by electrolysis

Electro-generated H_2O_2 (mg/L)	Reaction conditions	Observations	References
82	Anode: boron-doped diamond Cathode: boron-doped diamond j: 31 mA/cm^2 $V = 3$ L Recirculation: 12 L/min Electrolyte: 0.05 M Na$_2$SO$_4$ pH 3 Time: 180 min	Reactor type filter press	[57]
116	Cathode: graphite felt Anode: Pt Rotating speed: 10 rpm j: 50 mA/cm^2 $V = 0.1$ L Electrolyte: 0.05 M Na$_2$SO$_4$ pH 3 Time: 60 min	Rotating reactor with rotating disk anodes Without oxygen aeration	[58]
472.9	Cathode: carbon black/PTFE Anode: Pt j: 5 mA/cm^2 $V = 0.1$ L Electrolyte: 0.05 M Na$_2$SO$_4$ pH 3 Time: 60 min	Without oxygen aeration	[59]
960	Cathode: modified carbon felt j: 50 mA/cm^3 $V = 1$ L Electrolyte: 0.05 M Na$_2$SO$_4$ Time: 180 min	Jet aerator Does not require oxygen supply	[60]
871	Working electrode: gas diffusion electrode (GDE) with 4% of CeO$_2$/C Counter electrode: Pt Reference electrode: Ag/AgCl (KCl sat) E: -2.3 V $V = 250$ mL Electrolyte: NaOH 1M Time: 120 min	Divided cell	[61]
240	Working electrode: modified (with iron (II) phthalocyanine) GDE (gas diffusion electrode) Counter electrode: Pt Reference electrode: Ag/AgCl E: -1.0 (vs Ag/AgCl $V = 400$ mL Electrolyte: 0.1 M H$_2$SO$_4$ and 0.1 M K$_2$SO$_4$ Time: 90 min	Divided cell The presence of a modifier induces an increase in ring current	[62]

Table 5 (continued)

Electro-generated H₂O₂ (mg/L)	Reaction conditions	Observations	References
9,371	Cathode: carbon black/PTFE j: 60 mA/cm^2 $V = 20$ mL (cathodic cell) and 40 mL (anodic cell) Flow rate (air): 40 mL/min Electrolyte: 0.2 M Na$_2$SO$_4$ pH 4 Time: 120 min	Divided cell (nafion 117) Phenol (C_0: 100 mg/L), remotion 100% (40 min) TOC removal 85% (120 min)	[20]
180.27	Anode: stainless steel Cathode: reticulated vitreous carbon (RVC) i: 170 mA $V = 1$ L each compartment Catholyte: 0.05 M Na$_2$SO$_4$, 0.01 M H$_2$SO$_4$ Anolyte: 0.8 M H$_2$SO$_4$ ΔE_{Cell}: 2–3 V pH ~2 Time: 180 min	Divided cell 0.001 M FeSO$_4 \cdot$7H$_2$O in the catholyte, for electro-Fenton process 90% of discoloration for blue basic 9 (C_0: 0.08 mM) at 14 min Reactive black 5 (C_0: 0.063 mM) at 90 min Acid orange 7 (C_0: 0.14 mM) at 70 min	[21]

More recently the investigation of undivided cells has focused on not feeding oxygen to the cell. This can be functional by the modification of the reaction system, at this respect a reactor with rotating disk anodes [58] and other possibility is with a jet aerator system [60] which can be produced until 960 mg/L.

In order to increase by ten times the concentration of hydrogen peroxide by an electrochemical method, the cell can be improved coupling three electrodes separated by a membrane [66, 67], each compartment is called catholyte (or cathodic cell) and anolyte (or anodic cell). It is noted that in this variant, the hydrogen peroxide concentration is almost 10,000 mg/L (see Table 5).

H₂O₂ can also be produced in situ by photocatalysis. Considering this, essentially there are two ways to generate hydrogen peroxide by photocatalysis. Both are based on the use of a semiconductor photocatalyst to generate hydrogen peroxide by two-electron reduction of O₂ [68]. The most employed method is using an organic reducer like ethanol, methanol, oxalate, or other similar organic compounds, which is required as a sacrificial electron source; in contrast there are undesirable reactions [68–70]. In this case, alcohols are employed to reduce the probability of electron-hole recombination [71]. In order to decrease the concentration of by-products and eliminate the use of organic reducers, recently some studies report the use of catalysts that can produce hydrogen peroxide only by water oxidation [56, 71]. Table 6 shows the concentrations obtained by several catalysts, taking into account the two methods mentioned above. It can be observed that the employed volume is rather low when comparing with the electrochemical method.

Table 6 H_2O_2 generated by photochemical methods

H_2O_2 photo-catalyzed (mg/L)	Reaction conditions	Observations	References
115.64	Photoirradation: $\lambda > 280$ nm Catalyst: $Au_{0.1}Ag_{0.4}/TiO_2$ Catalyst dosage: 5 mg System: ethanol/water [4/96] v/v $V = 5$ mL Time: 12 h	266 μmol of CH_3CHO 13.8 nm, metal particle size	[22]
2.14	Photoirradation: 100 mW/cm^2 Catalyst: composite MMO@C$_3$N$_4$ Catalyst dosage: 1 g/L pH 3 Time: 90 min	Production only from water and oxygen	[71]
3,741	Photoirradation: $\lambda < 420$ nm, Xe lamp 300 W Catalyst: $Cd_3(C_3N_3S_3)_2$ Catalyst dosage: 80 mg/L $V = 20$ mL System: methanol/water [1/19] v/v pH 2.8 Time: 4 h	Visible light illumination	[70]
204	Photoirradiation: $\lambda > 420$ nm Xe lamp 2 kW Catalyst: graphite carbon nitride g-C$_3$N$_4$ Catalyst dosage: 20 mg $V = 5$ mL System: methanol/water [9/1] v/v Time: 12 h	The catalyst can also be activated by sunlight. Inexpensive metal-free photocatalyst	[72]
54.42	Photoirradiation: 0.56 W/cm^2 λ: 420 nm Xe lamp 300 W Catalyst: graphite carbon nitride g-C$_3$N$_4$ Catalyst dosage: 50 mg $V = 50$ mL Time: 120 min	Production only from water and oxygen	[56]

Moreover, the catalyst dosage is too high, so in most of the cases, the catalyst can be activated by sunlight. In fact, working volumes at pilot scale are not reported, and this suggests this method requires further improvement in order to be applied at larger scale.

3.3 Pharmaceuticals Removed by Fenton

Despite the drawbacks implicit in this process, this has been successfully applied to the removal of pharmaceutical compounds. Table 7 summarizes some applications in real and synthetic effluents. In this process the catalyst can be homogeneous or heterogeneous. In the former case, the typical source of Fe^{2+} is the commercial salt $FeSO_4$ or $FeSO_4 \cdot 7H_2O$ [73–76]. One of the major problems related to homogeneous Fenton is the high concentrations of Fe^{n+} ions (in order of 20–80 mg/L) that need the process for an efficient removal of pollutant. The acceptable discharge to the environment is only of 2 mg/L [81]. In homogeneous systems, the separation of the catalyst is rather difficult. Nevertheless, $FeSO_4$ has also been applied at industrial scale (250 L) in the removal of berberine employing real wastewater, obtaining good results and mineralization almost complete at low concentrations and only partial for a high pollutant load [75]. Considering this and meanly the recovery of catalyst, a significant amount of research has focused on the use of heterogeneous catalysts like iron oxides, iron doped with other metals, supported iron, and other approaches. The aim of this method is to facilitate the separation of iron ions after the treatment [82]. In both catalytic systems, the key parameter is the molar ratio H_2O_2/Fe^{2+}. When this ratio is higher than 10, the removal efficiency decays by the scavenging effect of hydroxyl radical [83]. Some catalysts, like nanostructured, provide more surface area and active sites which decompose hydrogen peroxide [84]. Other important parameter in heterogeneous catalysis is the decrease of the catalyst activity after a long time of use. This loss of activity can be mainly due to the catalyst leaching. This, however, promotes homogeneous fenton. Nevertheless, heterogenous fenton allows the re-use of the catalyst. Moreover, unlike homogeneous Fenton, the heterogeneous one can be conducted under near neutral pH [78]. The main limitation for heterogeneous Fenton is the catalyst synthesis, since in the most cases this is only a few grams. In the investigations shown in Table 7, there is only one investigation at pilot scale employing a catalyst-denominated modified polyacrylonitrile obtaining a poor removal of initial concentration.

As can be observed in most of the cases, the pollutant mineralization is only partial, and the treatment time sometimes is rather large. This has motivated the combination of this process with others like photochemical and electrochemical. These so modified processes are called photo-Fenton and electro-Fenton [46].

Table 7 Examples of pharmaceutical compounds removed by Fenton

Pharmaceutical compound	Reaction conditions	Removal (%)	Observations	References
Acetaminophen, atenolol, atrazine, carbamazepine, metoprolol, Dilantin, DEE, diclofenac, pentoxifylline, oxybenzone, caffeine, fluoxetine, gemfibrozil, ibuprofen, iopromide, naproxen, propranolol, sulfamethoxazole, and trimethoprim	Catalyst: Fe^{2+} Catalyst dosage: 20 mg/L $[H_2O_2/Fe^{2+}]$: 2.5 M ratio pH: 3 C_0: 9.6 mg/L [C_0: 1 µg/L for each compound] Time: 30 min	100 HPLC/LC-MS and GC TOC ~30	Not eliminated, atrazine and iopromide	[73]
Sulfamethoxazole/ acetaminophen	Catalyst: Fe^{2+} $[H_2O_2]$: 1.3×10^{-4} mol/L V: 1 L $[H_2O_2/Fe^{2+}]$: 5 M ratio C_0: 11.88 mg/L Time: 120 min	TOC: 11.3	In situ generation of H_2O_2 by previous ozonation process	[74]
Berberine	Catalyst: $FeSO_4$ V: 250 L $[Fe^{2+}/H_2O_2]$: 0.1 M ratio pH: 3 C_0: 4,061 mg/L high concentration C_0: 709 mg/L low concentration Volumetric flow rate: 100 L/h Time: 60 min (hydraulic retention time)	COD: 35.6 for high concentration COD: 91.4% for low concentration	Industrial scale BOD_5/COD: 0.3, increased biodegradability Real wastewater with pH extremely low 0.06–0.09	[75]
Carbamazepine (CBZ)	Catalyst: $FeSO_4.7H_2O$ V: 100 mL $[H_2O_2]$: 8.5 g/L $[Fe^{2+}/H_2O_2]$: 1 M ratio pH: 3.5 C_0: 442 mg/L Time ~25 min	HPLC: 49.49	Industrial wastewater Treatment followed by GAC obtaining 99.51% of removal	[76]

Table 7 (continued)

Pharmaceutical compound	Reaction conditions	Removal (%)	Observations	References
Steroid hormones, personal care products, and pharmaceuticals	Catalyst: PAN (modified polyacrylonitrile) V: 31.34 L [H_2O_2]: 200 mg/L Volumetric flow rate: 10.6 L/h pH natural of wastewater C_0: 6–11.08 mg/L Time ~180 min	LC-MS/MS: >90 (hormones) LC-MS/MS: >40 (pharmaceuticals) TOC: 30–40	Pilot plant. Municipal wastewater The catalyst not needs ranges of pH 2–4 Reported leaching is less than 4% BOD reduce to less than 1 mg/L	[77]
Diclofenac	Catalyst: Fe-doped CeO_2 Catalyst dosage: 0.5 g/L V: 150 mL [H_2O_2]: 10 mM pH 5 C_0: 20 mg/L Time: 40 min	HPLC: 85.25	Removal of 2.2% only with H_2O_2 after 40 min	[78]
Paracetamol	Catalyst: MGN1 (Fe_3O_4 powder <50 nm) MGN2 (Fe_3O_4 powder <5 nm) MGM (Fe_3O_4 powder <50 nm) Catalyst dosage: 6 g/L V: 650 mL [H_2O_2]: 153 mM pH 2.6 C_0: 100 mg/L Time: 5 h	TOC: 43 (MGN1) TOC: 34 (MGN2) TOC: 39 (MGM)	With three catalysts, the total removal of paracetamol was obtained Without catalyst there is no removal	[79]
Ofloxacin	Catalyst: alginate iron (4%) Catalyst dosage: 400 mg/L V: 100 mL [H_2O_2]: 4.067 mM pH 3 C_0: 30 mg/L Time: 180 min	UV: 98	After three successive runs, activity decreases only around 10%	[80]

4 Conclusions

Ozonation and Fenton are processes that are capable to remove 100% of a wide variety of pharmaceutical compounds from wastewater. These processes fail, however, on achieving full mineralization, and this may lead to worsen the problem from a toxicological point of view. Therefore such processes should be combined with toxicological analysis, either theoretical or experimental, of the treated effluents. The main reaction variables affecting the efficiency of such processes are pH, ozone, and H_2O_2 concentration, reactor design, and the presence of catalysts, light, or electrolysis.

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