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Comparison of metoprolol degradation by Fe^{III}-NTA modified Fenton-like reaction in the absence and presence of manganese: Efficiency and intermediates

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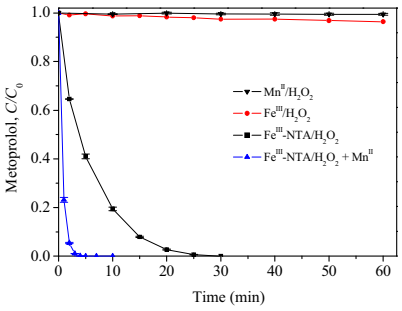
HIGHLIGHTS

- Metoprolol degradation by Fe^{III}-NTA/H_2O_2 was enhanced in the presence of Mn^{II}.
- Rapid degradation of metoprolol was obtained by Fe^{III}-NTA/H_2O_2-Mn at pH 4.0–8.0.
- Fe^{III}-NTA/H_2O_2-Mn led to more efficient degradation of metoprolol and intermediates.
- Degradation pathways of metoprolol were proposed.

GRAPHICAL ABSTRACT



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ABSTRACT

The degradation of metoprolol in aqueous solutions by traditional Fenton-like reaction (Fe^{III}/H_2O_2), and Fe^{III}-NTA modified Fenton-like reaction (Fe^{III}-NTA/H_2O_2) in the absence and presence of Mn^{II} (Fe^{III}-NTA/H_2O_2-Mn) have been investigated. The results show that Fe^{III}-NTA/H_2O_2 is able to degrade metoprolol at initial neutral pH. In particular, the presence of Mn^{II} greatly improved the degradation rate of metoprolol by Fe^{III}-NTA/H_2O_2 over a wide pH range of 4.0–8.0. Under the same conditions, the degradation rate constants of metoprolol (k) obtained in Fe^{III}-NTA/H_2O_2-Mn system were typically 7–9-fold larger than those obtained in Fe^{III}-NTA/H_2O_2 system. The involved reactions in Fe^{III}-NTA/H_2O_2-Mn system were proposed on the basis of important parameters analysis including ferrous ion concentration, dissolved oxygen (DO) concentration, and the quenching experiments for hydroxyl radial ($HO^{\cdot}$) and superoxide anion radical ($O_2^{\cdot-}$). Several intermediates have been identified by mass spectrometry. Our results suggest that the degradation of metoprolol in both Fe^{III}-NTA/H_2O_2 and Fe^{III}-NTA/H_2O_2-Mn systems were caused by $HO^{\cdot}$ attack. The degradation pathways of metoprolol were proposed on the basis of the identified intermediates. Fe^{III}-NTA/H_2O_2-Mn system led to more efficient degradation of metoprolol and its intermediates.

1. Introduction

Metoprolol, a selective β1 receptor blocking drug, is widely used in the therapy of hypertension and angina. In the past decade, metoprolol and its metabolites have been detected in sewage treatment plant effluents, surface water, groundwater, and even

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in drinking water, which pose a potential risk to human health [1,2]. The degradation rate of metoprolol in water by the direct photolysis is small, e.g., the extrapolated half-lives of metoprolol in central Europe and the U.S. were reported at 28–95 d in summer and 190–449 d in winter [3]. Thus, metoprolol is most likely to be pseudo-persistent in natural waters if do not consider the indirect photolysis effects. In addition, the efficiency of metoprolol removal is lower than 30% in traditional sewage treatment plant [4]. There is an urgent need to improve the removal efficiencies of pharmaceuticals in water.

A far more effective method is the so-called advanced oxidation processes (AOPs), involving the generation of hydroxyl radical ($HO^{\cdot}$) [5–7], have been widely applied in water treatment for harmful organic compounds removal. Efficient degradation of metoprolol has been obtained by photocatalysis, UV/H_2O_2 and Fenton-related processes [8–10]. Two decades ago, research by Sun and Pignatello [11] showed the successful degradation of 2,4-dichlorophen-oxyacetic acid at pH 6.0 by chelates modified Fenton-like reaction. Chelating agents modified Fenton-like reaction has been receiving increasing attention because it can work at neutral pH conditions, which overcomes the limitation of acidic pH (e.g., optimal pH 2.8–3.0) by using traditional Fenton and/or Fenton-like reaction. S,S-ethylenediamine-N,N′-disuccinic acid (EDDS) modified Fenton reaction (i.e., Fe^{II}-EDDS/H_2O_2) and Fenton-like reaction (i.e., Fe^{III}-EDDS/H_2O_2) are capable of degrading 4-chlorophenol, bisphenol A, naphthenic acid, and 4-tert-butylphenol at near neutral or basic pH conditions [12–15]. The use of Fe^{III}-EDDS for photo-Fenton reaction at neutral pH is also successful in degrading micro-pollutants in wastewater treatment plant effluents [16–18]. In addition, nitrilotriacetic acid (NTA) and ethylenediaminetetraacetic acid (EDTA) modified Fenton-like reactions (i.e., Fe^{III}-NTA/H_2O_2 and Fe^{III}-EDTA/H_2O_2) have also been proved to be highly effective in degrading atrazine, carbamazepine, fenuron, naphthenic acid, parachlorobenzoic acid and sulfamethoxazole at neutral or slightly basic pH conditions [19–22]. In particular, our recent finding suggested that the presence of manganese (Mn^{II}) could greatly enhance the Fenton-like catalytic activity of Fe^{III}-NTA/H_2O_2 [23]. The potential mechanism may involve an enhanced generation of superoxide anion radical ($O_2^{\cdot-}$) by the Mn^{II}, which can accelerate the reduction of Fe^{III}-NTA to Fe^{II}-NTA and indirectly improve the generation of $HO^{\cdot}$ [23]. The Mn^{II}/Fe^{III}-NTA catalytic system would be very promising since Fe^{III} and Mn^{II} are quite ubiquitous in the environment and can be used as natural Fenton-like catalyst in the presence of NTA (or natural Fe^{III} complexing agents) and H_2O_2. However, little research on this system has been reported.

The purpose of this study is to demonstrate the potential effectiveness of Fe^{III}-NTA/H_2O_2-Mn for water treatment. In the present study, we choose metoprolol as a target compound, to evaluate the efficiency and intermediates generated from metoprolol degradation by Fe^{III}-NTA/H_2O_2 in the absence and presence of Mn^{II}. The degradation kinetics of metoprolol in both systems were compared under various conditions. The involved reactions in Fe^{III}-NTA/H_2O_2-Mn system were proposed on the basis of certain important parameters analysis such as ferrous ion concentration, dissolved oxygen (DO) concentration, and the quenching experiments for $HO^{\cdot}$ and $O_2^{\cdot-}$. The intermediates were identified by liquid chromatography/mass spectrometry.

2. Materials and methods

2.1. Chemicals

Ferric chloride hexahydrate, hydrogen peroxide (30% H_2O_2, w/w), sodium hydroxide and sulfuric acid were purchased from Sinopharm Chemical Reagent Co., Ltd. Metoprolol tartrate (purity ⩾ 98%) was purchased from LKT Laboratories, Inc. NTA was purchased from Acros Organics. Formic acid and manganese nitrate tetrahydrate were purchased from Sigma-Aldrich. HPLC-grade methanol, 2-propanol and water were purchased from Fisher Scientific. Chloroform was purchased from Chinasun Specialty Products Co., Ltd. All chemicals were of reagent grade or better, and used as received without further purification. Milli-Q water was used to prepare solutions.

2.2. Experimental procedures

All experiments were performed in 125 ml glass Erlenmeyer flasks. Briefly, 100 ml of metoprolol aqueous solution and an appropriate amount of freshly prepared Fe^{III}-NTA solution were added into the flask. The flask was then placed in a water-jacketed glass vessel water bath (25 ± 1 °C) under a magnetic stirring condition. After that, an appropriate amount of Mn^{II} was added to the solution. The pH of the solution was then adjusted to the desired value using 1.0/0.1 M NaOH or 1.0/0.1 M H_2SO_4. Finally, Fenton-like reaction was started by the addition of an appropriate amount of H_2O_2. It is worth noting that the water-jacketed glass vessel was covered with aluminum foil to prevent the effect of light on the Fenton-like reaction. Samples (1 ml) were withdrawn at different time intervals and mixed with 0.1 ml of methanol immediately to quench the reaction.

2.3. Analytical methods

The concentration of metoprolol was determined by a high performance liquid chromatography (HPLC, Agilent 1100) with fluorescence detection. An Ultra C-18 column (5 μm, 250 × 4.6 mm) was used for the chromatographic separation. The mobile phase consisted of methanol and 0.1% formic acid aqueous solution (35:65, v/v) at a flow rate of 0.9 ml min^{-1}. The column temperature was 30 °C. The injection volume was 20 μl, and the fluorescence detection was performed at 275 nm of excitation and 298 nm of emission.

The degradation intermediates were identified by an Agilent 1200 HPLC system coupled to a 6130 quadrupole mass spectrometer. The MS detector was performed for a full scan range of m/z 30–600 under an ESI + APCI positive mode. The MS operating conditions were as follows: Fragmentor 90, drying gas flow rate 6 L min^{-1}, nebulizer pressure 45 psi, dry gas temperature 300 °C, vaporizer temperature 250 °C, capillary voltage 3500 V, corona current 4.0 μA and charging voltage 2000 V.

The concentration of ferrous ion in the aqueous solutions was determined by using the 1,10-phenathroline method. The concentration of H_2O_2 was determined by the iodide method [24]. The dissolved oxygen (DO) concentration in the aqueous solutions during the reaction time was monitored by a dO_2 sensor (Model Z010023525, AppliSens).

3. Results and discussion

3.1. Comparison of metoprolol degradation by Fe^{III}/H_2O_2, Fe^{III}-NTA/H_2O_2 and Fe^{III}-NTA/H_2O_2-Mn

Fig. 1 shows a comparison of metoprolol degradation by Fe^{III}/H_2O_2, Fe^{III}-NTA/H_2O_2 and Fe^{III}-NTA/H_2O_2-Mn systems at initial neutral pH. A minimum degradation of metoprolol was observed in Fe^{III}/H_2O_2 system, with 3.61% degradation efficiency of metoprolol after 60 min of the reaction time. This result was expected because of the precipitation of ferric ion at pH 7.0 in the absence of chelator. In contrast, Fe^{III}-NTA complex is able to catalyze

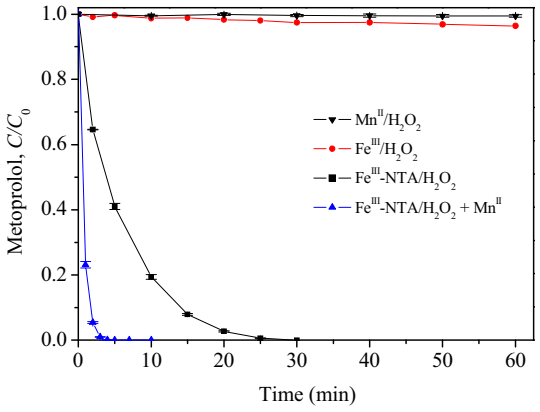


Fig. 1. Comparison of metoprolol degradation by Fe^{III}/H_2O_2, Fe^{III}-NTA/H_2O_2 and Fe^{III}-NTA/H_2O_2-Mn systems. Experimental conditions: 29.2 μM of metoprolol, 0.1 mM of Fe^{III}, NTA/Fe^{III} molar ratio of 2:1, H_2O_2/Fe^{III} molar ratio of 100:1, Mn^{II}/Fe^{III} molar ratio of 1:1, and initial pH of 7.0.

Fenton-like reaction at pH 7.0, resulted in 100% degradation efficiency of metoprolol after 30 min of the reaction time in Fe^{III}-NTA/H_2O_2 system. In particular, Fe^{III}-NTA/H_2O_2-Mn system led to a very fast degradation of metoprolol, with 100% degradation efficiency of metoprolol after 7 min of the reaction time. The result is consistent with our recent finding that the presence of Mn^{II} could enhance Fe^{III}-NTA-catalyzed Fenton-like reaction [23].

The effects of Mn^{II} concentration on the degradation kinetics of metoprolol in Fe^{III}-NTA/H_2O_2-Mn system were shown in Fig. 2. An increase in Mn^{II} concentration from 0.01 to 0.1 mM, corresponding to Mn:Fe molar ratios of 0.1:1 to 1:1, had a positive effect on metoprolol degradation. The apparent degradation rate constant of metoprolol (k) increased from 0.7547 to 1.6048 min^{-1}. However, further increasing Mn^{II} concentration from 0.2 to 1.0 mM led to a slight inhibitory effect on the degradation rate of metoprolol, e.g., the k value of metoprolol decreased from 1.6289 to 1.1103 min^{-1}. This is because when Mn^{II} concentration was larger than 0.2 mM, hydrous manganese dioxide could form from free Mn^{II} in excess under the given conditions, which is capable of catalyzing the decomposition of H_2O_2 to O_2 and H_2O [25]. It is worth noting that even at a high concentration of 1.0 mM of Mn^{II}, corresponding to Mn:Fe molar ratio of 10:1, the k value of metoprolol was still larger (6-fold) than that in the absence of Mn^{II}.

Quenching tests showed that the degradation of metoprolol in Fe^{III}-NTA/H_2O_2-Mn system was significantly inhibited by the addition of 2-propanol, but not by chloroform (Fig. S1, in Supplementary data), which suggests that the degradation of metoprolol was probably caused by $HO^{\cdot}$ attack. The presence of Mn^{II} is unable to directly catalyze Fenton-like reaction to generate $HO^{\cdot}$, this is because no degradation of metoprolol was observed in the absence of Fe^{III} (e.g., Mn^{II}-NTA/H_2O_2 in Fig. 1). Thus, the very fast degradation of metoprolol in Fe^{III}-NTA/H_2O_2-Mn system could be attributed to an indirect enhancement of Fe^{III}-NTA-catalyzed Fenton-like reaction by Mn^{II}. One hypothesis is that the presence of Mn^{II} favors the production of $O_2^{\cdot-}$, which enhances the reduction of Fe^{III}-NTA to Fe^{II}-NTA, and in turn increases the production of $HO^{\cdot}$ from the reaction of Fe^{II}-NTA with H_2O_2. In order to prove this, the concentration of ferrous ion in the aqueous solutions was monitored during the reaction time, and the results were shown in Fig. 3. It can be seen that the concentration of ferrous ion in Fe^{III}-NTA/H_2O_2-Mn system increased rapidly from 0 to 0.40 mg L^{-1} within 5 min of reaction time, and then gradually decreased to 0.11 mg L^{-1} within 30 min of reaction time. On the contrary, the concentration of ferrous ion in Fe^{III}-NTA/H_2O_2 system was always below 0.02 mg L^{-1}, which was much smaller than that in Fe^{III}-NTA/H_2O_2-Mn system. In addition, changes in DO concentrations in both systems with the reaction time were also monitored. It can be observed from Fig. 3 that the DO concentration in Fe^{III}-NTA/H_2O_2-Mn system increased significantly from 100% (i.e., 100% air saturation) to 275% within 7 min of reaction time, and then gradually decreased to 211% within 30 min of reaction time, which was much higher than that in Fe^{III}-NTA/H_2O_2 system. The results suggested that more oxygen was produced in Fe^{III}-NTA/H_2O_2-Mn system. Moreover, Fig. 3 provides further evidence that the decomposition rate of H_2O_2 in Fe^{III}-NTA/H_2O_2-Mn system was faster than that in Fe^{III}-NTA/H_2O_2 system.

On the basis of Haber-Weiss reactions, the involved main reactions in Fe^{III}-NTA/H_2O_2-Mn system were proposed by R1-R8. As shown in reactions R1-R3, it was $O_2^{\cdot-}$ and not free $HO^{\cdot}$ which was generated from the reaction of Mn^{II}-NTA with H_2O_2. One the basis of reactions R4 and R5, $O_2^{\cdot-}$ should rapidly reduce Fe^{III}-NTA (and Mn^{III}-NTA) to Fe^{II}-NTA (and Mn^{II}-NTA), leading to the production of oxygen. Thus, R1-R5 also explain the rapid decomposition of H_2O_2 and the significant increase of DO concentration in Fe^{III}-NTA/H_2O_2-Mn system. Most importantly, $HO^{\cdot}$ is generated from the reaction of Fe^{II}-NTA with H_2O_2, which lead to metoprolol destruction (as shown in R6 and R8). Because Fe^{II}-NTA is mainly generated

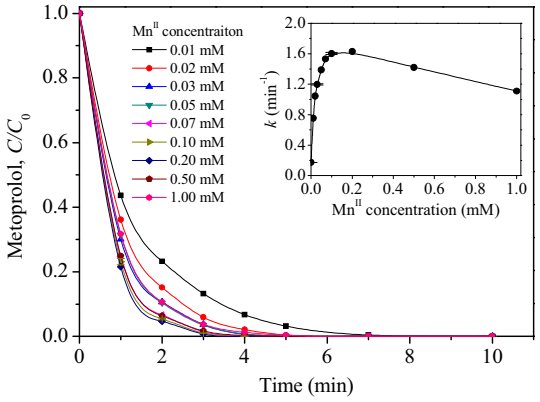


Fig. 2. Effects of Mn^{II} concentration on the degradation kinetics of metoprolol in Fe^{III}-NTA/H_2O_2-Mn system. Experimental conditions: 29.2 μM of metoprolol, 0.1 mM of Fe^{III}, NTA/Fe^{III} molar ratio of 2:1, H_2O_2/Fe^{III} molar ratio of 100:1, Mn^{II}/Fe^{III} molar ratio of 0.1:1–10:1, and initial pH of 7.0.

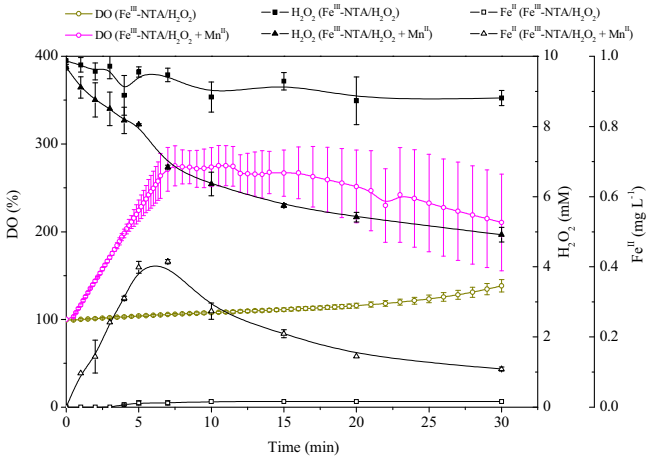


Fig. 3. Changes in DO concentration, H_2O_2 concentration and ferrous ion concentration with the reaction time in Fe^{III}-NTA/H_2O_2 and Fe^{III}-NTA/H_2O_2-Mn systems. Experimental conditions: 29.2 μM of metoprolol, 0.1 mM of Fe^{III}, NTA/Fe^{III} molar ratio of 2:1, H_2O_2/Fe^{III} molar ratio of 100:1, Mn^{II}/Fe^{III} molar ratio of 1:1, and initial pH of 7.0.

from the reaction of Fe^{III}-NTA with H_2O_2 in Fe^{III}-NTA/H_2O_2 system (i.e., R7), thus the generation rate of Fe^{II}-NTA in Fe^{III}-NTA/H_2O_2 system is much slower than that in Fe^{III}-NTA/H_2O_2-Mn system.

$$Mn^{II}\text{-NTA} + 2H_2O_2 \leftrightarrow Mn^{II}\text{-NTA-}2H_2O_2 \quad (R1)$$

$$Mn^{II}\text{-NTA-}2H_2O_2 \rightarrow Mn^{III}\text{-NTA-}H_2O_2\text{-}HO^{\cdot} + OH^- \quad (R2)$$

$$Mn^{III}\text{-NTA-}H_2O_2\text{-}HO^{\cdot} \rightarrow Mn^{III}\text{-NTA} + O_2^{\cdot-} + H_2O + H^+ \quad (R3)$$

$$Mn^{III}\text{-NTA} + O_2^{\cdot-} \rightarrow Mn^{II}\text{-NTA} + O_2 \quad (R4)$$

$$Fe^{III}\text{-NTA} + O_2^{\cdot-} \xrightarrow{Fast} Fe^{II}\text{-NTA} + O_2 \quad (R5)$$

$$Fe^{II}\text{-NTA} + H_2O_2 \rightarrow Fe^{III}\text{-NTA} + HO^{\cdot} + OH^- \quad (R6)$$

$$Fe^{III}\text{-NTA} + H_2O_2 \xrightarrow{Slow} Fe^{II}\text{-NTA} + 2H^+ + O_2^{\cdot-} \quad (R7)$$

$$\text{Metoprolol} + HO^{\cdot} \rightarrow \text{Degradation products} \quad (R8)$$

3.2. Effects of initial pH

The effects of initial pH on the degradation kinetics of metoprolol by Fe^{III}/H_2O_2, Fe^{III}-NTA/H_2O_2 and Fe^{III}-NTA/H_2O_2-Mn systems were investigated over the range of pH 3.0–9.0 (Fig. 4). In Fe^{III}/H_2O_2 system, a k value of 0.0976 min^{-1} was obtained at an initial pH 3.0. When the initial pH value was higher than 5.0, the degradation of metoprolol was significantly inhibited in Fe^{III}/H_2O_2 system due to the precipitation of ferric ion. In Fe^{III}-NTA/H_2O_2 system, an increase in the initial pH value from 3.0 to 9.0 had a positive effect on the degradation rate of metoprolol, resulted in increasing the k value of metoprolol from 0.0033 to 0.7190 min^{-1}. The small degradation rates of metoprolol under acidic pH conditions (e.g., pH 3.0–4.0) can be explained either by relatively low regeneration rate of Fe^{II}-NTA, or by low catalytic activity of Fe^{III}-NTA species toward H_2O_2 at acidic pH. First of all, $O_2^{\cdot-}$ was believed to play an important role in reducing Fe^{III}-NTA to Fe^{II}-NTA which then react with H_2O_2 to generate $HO^{\cdot}$. Since more $O_2^{\cdot-}$ changes to perhydroxyl radical ($HOO^{\cdot}$) at pH 3.0–4.0 (Eq. (1)) [26], the regeneration rate of Fe^{II}-NTA can be limited due to the weak reduction capability of $HOO^{\cdot}$.

$$HOO^{\cdot} \leftrightarrow O_2^{\cdot-} + H^+ \quad pKa = 4.8 \quad (1)$$

On the other hand, Fe^{III}-NTA species and free NTA also react with $HO^{\cdot}$. The reaction between $HO^{\cdot}$ and Fe^{III}-NTA species/free NTA would have an inhibiting effect on the degradation rate of metoprolol since the reactions are competing. A larger reaction rate between $HO^{\cdot}$ and Fe^{III}-NTA species/free NTA would lead to a smaller degradation rate of metoprolol. According to the literature [21,27], Fe^{III}-NTA species and free NTA are strongly pH-dependent. Although the reaction rate constant of Fe^{III}-NTA species with $HO^{\cdot}$ is rarely reported (e.g., 1.6×10^8 M^{-1} s^{-1} was reported at pH 2.0 [28]), the reaction rate constants of $HO^{\cdot}$ with free NTA have been reported at 6.1×10^7, 7.5×10^8, 5.5×10^8, 4.77×10^8, 2.5×10^9 and 4.2×10^9 M^{-1} s^{-1} at pH 2.0, 4.0, 6.0, 8.0, 9.0 and 10 [21,27], respectively. It can be seen that the reaction rate of $HO^{\cdot}$ with free NTA was increased with the increase of pH from 2.0 to 10. Thus, the decrease of pH should favor the degradation of metoprolol. However, the present and previous studies have shown that the fast degradation of model contaminants and the decomposition of H_2O_2 occurred at neutral or slight basic pH in Fe^{III}-NTA/H_2O_2 system [20,27], which rules out the effect of free NTA. Therefore, it is logically possible that Fe^{III}-NTA species at acidic pH (i.e., $Fe^{III}(NTA)(H_2O)_2$ [29]) might be inefficient for the activation of H_2O_2 to induce Fenton-like reaction, or the reaction of $Fe^{III}(NTA)(H_2O)_2$ with $HO^{\cdot}$ might act as an inhibitory reaction.

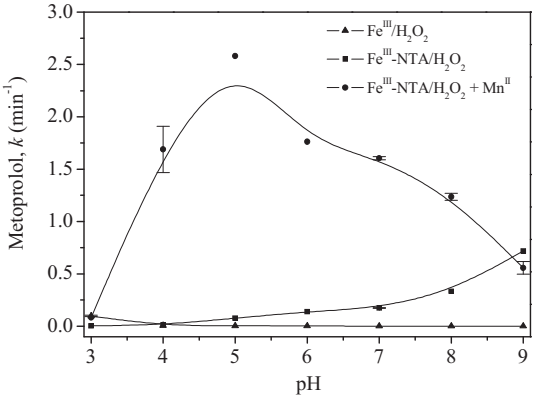


Fig. 4. Effects of initial pH on the degradation kinetics of metoprolol by Fe^{III}/H_2O_2, Fe^{III}-NTA/H_2O_2 and Fe^{III}-NTA/H_2O_2-Mn systems. Experimental conditions: 29.2 μM of metoprolol, 0.1 mM of Fe^{III}, NTA/Fe^{III} molar ratio of 2:1, H_2O_2/Fe^{III} molar ratio of 100:1, Mn^{II}/Fe^{III} molar ratio of 1:1, and initial pH of 3.0–9.0.

Maximum degradation rates of metoprolol were obtained in Fe^{III}-NTA/H_2O_2-Mn system. It can be seen that the k values of metoprolol were much larger than those in Fe^{III}-NTA/H_2O_2 system over the initial pH range of 4.0–8.0. At initial pH 3.0, the k value of metoprolol was 0.0819 min^{-1} in Fe^{III}-NTA/H_2O_2-Mn system, which was close to that in Fe^{III}/H_2O_2 system (0.0976 min^{-1}). With increasing the initial pH from 3.0 to 5.0, the k values of metoprolol increased greatly from 0.0819 to 2.5809 min^{-1} in Fe^{III}-NTA/H_2O_2-Mn system. On the basis of the pKa value of $HOO^{\cdot}/O_2^{\cdot-}$ (pKa = 4.8) [26], the fraction of $O_2^{\cdot-}$ was calculated at 1.56%, 13.68% and 61.31% (of the total amount of $HOO^{\cdot}$ and $O_2^{\cdot-}$) at pH 3.0, 4.0 and 5.0, respectively. It can be seen that the increase of the k values of metoprolol was consistent with the increase of the fraction of $O_2^{\cdot-}$ at pH 3.0–5.0. Thus, the results support our hypothesis that $O_2^{\cdot-}$ plays an important role in reducing Fe^{III}-NTA to Fe^{II}-NTA, which in turn improves the generation of $HO^{\cdot}$ and leads to a rapid degradation of metoprolol. It is worth noting that the fraction of $HOO^{\cdot}$ is 38.69% at pH 5.0. $HOO^{\cdot}$ is also an oxidant with an oxidation potential of 1.78 V [30], weaker than $HO^{\cdot}$, thus the fastest degradation of metoprolol at pH 5.0 can be explained by $HOO^{\cdot}$ along with $HO^{\cdot}$ attack. At neutral pH, the fraction of $O_2^{\cdot-}$ would increase to >99% and the fraction of $HOO^{\cdot}$ would decrease to <1%. Therefore, the degradation of metoprolol at neutral pH would be mainly caused by $HO^{\cdot}$ attack. The large fraction of $O_2^{\cdot-}$ at neural pH or slight basic pH could favor the generation of Fe^{II}-NTA. Unlike Fe^{III}-NTA/H_2O_2 system, however, the k values of metoprolol in Fe^{III}-NTA/H_2O_2-Mn system gradually decreased with the increasing initial pH from 5.0 to 9.0. In particular, at initial pH 9.0, the k value of metoprolol in Fe^{III}-NTA/H_2O_2-Mn system was smaller than that in Fe^{III}-NTA/H_2O_2 system. This can be explained by the fact that the complexation constants of NTA with Fe^{III}/Fe^{II}(-log k = 15.9 and 9.8) are much larger than that with Mn^{II} (log k = 7.46) [31], thus Mn^{II} would firstly leach due to the degradation of NTA by $HO^{\cdot}$ attack. The leached Mn^{II} could form hydrous manganese dioxide when the solution pH value is >5.0, which can directly catalyze the decomposition of H_2O_2 to O_2 and H_2O [25]. Additionally, the decrease of Mn^{II} concentration in aqueous phase would lead to the rate of $O_2^{\cdot-}$ production decreasing, which in turn decrease the generation rates of Fe^{II}-NTA and $HO^{\cdot}$.

3.3. Effects of NTA:Fe molar ratios

The effects of NTA/Fe molar ratios on the degradation kinetics of metoprolol by Fe^{III}-NTA/H_2O_2 and Fe^{III}-NTA/H_2O_2-Mn systems at initial neutral pH were investigated (Fig. 5). It can be seen that over

the range of NTA:Fe molar ratios tested, the *k* values of metoprolol in Fe^{III}-NTA/H_2O_2-Mn system were 7–17-fold larger than those in Fe^{III}-NTA/H_2O_2 system. An increase in NTA/Fe molar ratio from 0.5:1 to 2:1 had positive effects on the degradation rates of metoprolol in both Fe^{III}-NTA/H_2O_2 and Fe^{III}-NTA/H_2O_2-Mn systems. The *k* values of metoprolol increased from 0.0311 to 0.1754 min^{-1} in Fe^{III}-NTA/H_2O_2 system and increased from 0.3450 to 1.6048 min^{-1} in Fe^{III}-NTA/H_2O_2-Mn system, respectively. When NTA/Fe molar ratio was larger than 2:1, however, a slight decrease in the *k* values of metoprolol was observed in either Fe^{III}-NTA/H_2O_2 or Fe^{III}-NTA/H_2O_2-Mn system. This can be explained by the fact that the free NTA in excess scavenges HO·. Although the reaction rate constant of metoprolol with HO· ($5.2–8.4 \times 10^9$ M^{-1} s^{-1}) [32,33] is larger than that of Fe^{III}-NTA/free NTA with HO·, it is believed that the competitive consumption of HO· by the free NTA in excess can slightly limit the degradation of metoprolol.

3.4. Effects of H_2O_2:Fe^{III} molar ratios

Fig. 6 shows the effects of H_2O_2/Fe^{III} molar ratios on the degradation kinetics of metoprolol by Fe^{III}-NTA/H_2O_2 and Fe^{III}-NTA/H_2O_2-Mn systems at initial neutral pH. Without the addition of H_2O_2, no degradation of metoprolol was observed in both systems. Over the range of H_2O_2/Fe^{III} molar ratios tested, the *k* values of metoprolol in Fe^{III}-NTA/H_2O_2-Mn system were 5–9-fold larger than those in Fe^{III}-NTA/H_2O_2 system. With increasing H_2O_2/Fe^{III} molar ratio from 10:1 to 200:1, the *k* values of metoprolol continuously increased from 0.0598 to 0.2276 min^{-1} in Fe^{III}-NTA/H_2O_2 system. In Fe^{III}-NTA/H_2O_2-Mn system, the *k* values of metoprolol increased greatly from 0.3384 to 1.6048 min^{-1} and reached a plateau with increasing H_2O_2/Fe^{III} molar ratio from 10:1 to 100:1. It is expected that the use of higher molar ratio of H_2O_2/Fe^{III} led to higher rate of HO· generation, by which faster degradation of metoprolol could be obtained. No inhibitory effect of H_2O_2 on the degradation kinetics of metoprolol was observed even at H_2O_2/Fe^{III} molar ratio of 200:1. This is because the reaction rate constant of H_2O_2 with HO· ($(1.2–4.5) \times 10^7$ M^{-1} s^{-1}) [34] is much smaller than those of metoprolol, Fe^{III}-NTA and free NTA with HO·.

3.5. Effect of Fe^{III} dosage

Fe^{III} acts as the catalyst to initiate Fenton-like reaction, a high rate of HO· generation might be obtained at high concentration of Fe^{III}-NTA. The effects of Fe^{III} dosages on the degradation kinetics of metoprolol by Fe^{III}-NTA/H_2O_2 and Fe^{III}-NTA/H_2O_2-Mn systems at initial neutral pH were shown in Fig. 7. No degradation of metoprolol was observed in the absence of Fe^{III}, which suggests that HO· is generated from the Fenton-like reaction of $Fe^{III/II}$-NTA/H_2O_2. Over

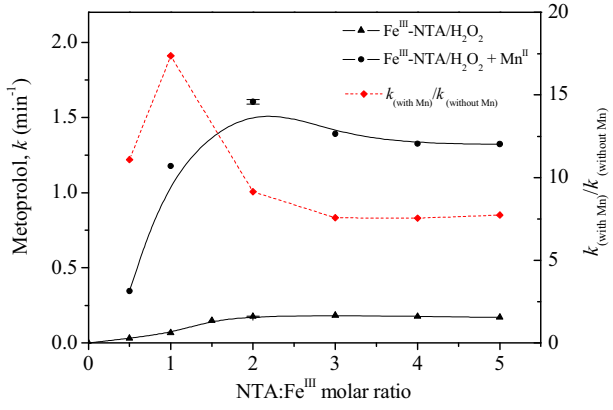


Fig. 5. Effects of NTA/Fe^{III} molar ratios on the degradation kinetics of metoprolol by Fe^{III}-NTA/H_2O_2 and Fe^{III}-NTA/H_2O_2-Mn systems. Experimental conditions: 29.2 μM of metoprolol, 0.1 mM of Fe^{III}, NTA/Fe^{III} molar ratio of 0.5:1–5:1, H_2O_2/Fe^{III} molar ratio of 100:1, Mn^{II}/Fe^{III} molar ratio of 1:1, and initial pH of 7.0.

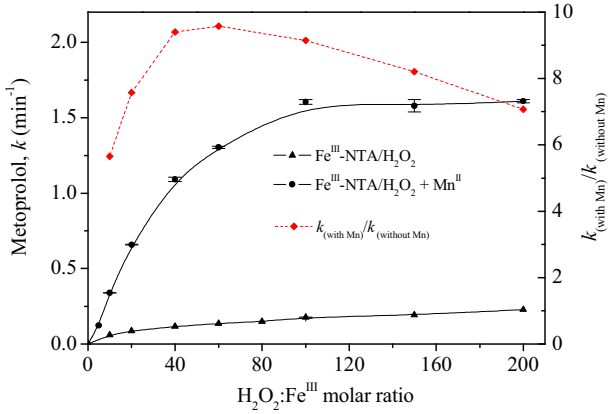


Fig. 6. Effects of H_2O_2/Fe^{III} molar ratios on the degradation kinetics of metoprolol by Fe^{III}-NTA/H_2O_2 and Fe^{III}-NTA/H_2O_2-Mn systems. Experimental conditions: 29.2 μM of metoprolol, 0.1 mM of Fe^{III}, NTA/Fe^{III} molar ratio of 2:1, H_2O_2/Fe^{III} molar ratio of 5:1–200:1, Mn^{II}/Fe^{III} molar ratio of 1:1, and initial pH of 7.0.

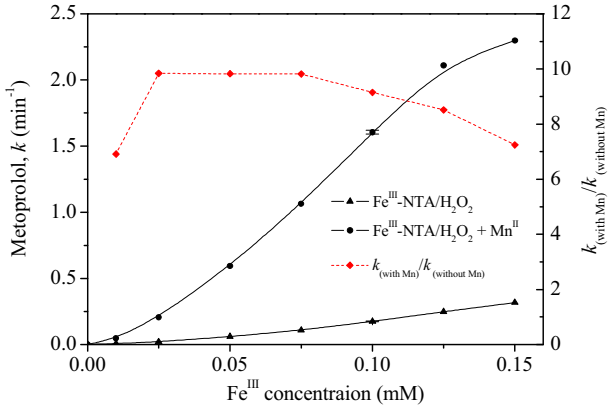


Fig. 7. Effects of Fe^{III} dosages on the degradation kinetics of metoprolol by Fe^{III}-NTA/H_2O_2 and Fe^{III}-NTA/H_2O_2-Mn systems. Experimental conditions: 29.2 μM of metoprolol, 0.01–0.15 mM of Fe^{III}, NTA/Fe^{III} molar ratio of 2:1, H_2O_2/Fe^{III} molar ratio of 100:1, Mn^{II}/Fe^{III} molar ratio of 1:1, and initial pH of 7.0.

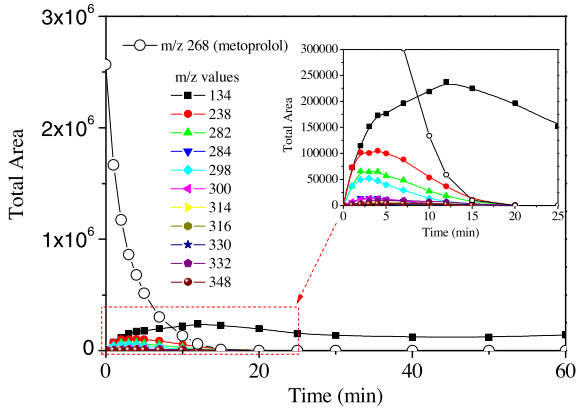
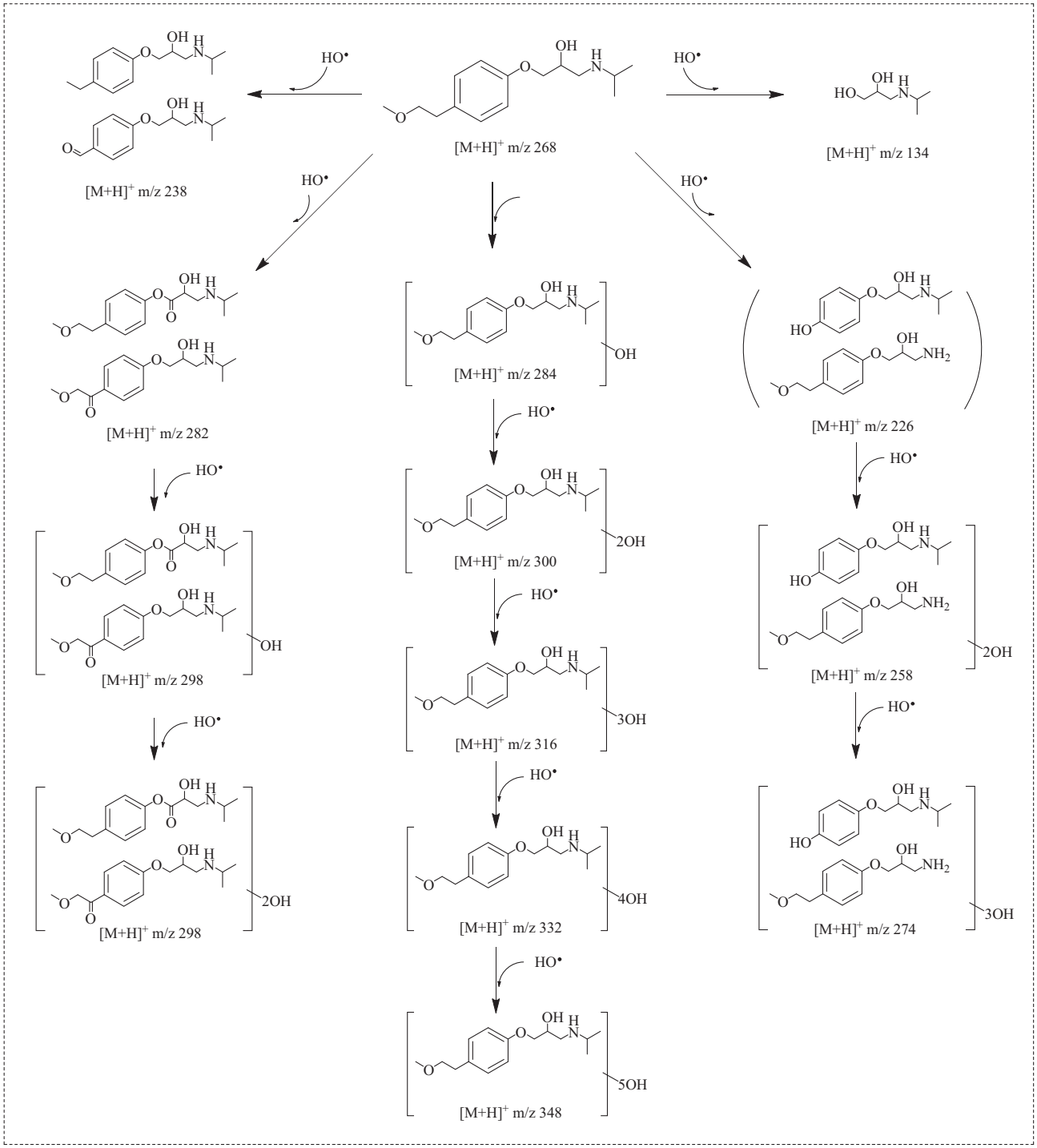


Fig. 8. Changes in the total molecular ion chromatogram area of metoprolol and its intermediates with the reaction time. Experimental conditions: 292 μM of metoprolol, 0.1 mM of Fe^{III}, NTA/Fe^{III} molar ratio of 2:1, H_2O_2/Fe^{III} molar ratio of 100:1, Mn^{II}/Fe^{III} molar ratio of 1:1, and initial pH of 7.0.



Scheme 1. Intermediates and degradation pathways of metoprolol.

the range of Fe^{III} concentrations tested, the *k* values of metoprolol in Fe^{III}-NTA/H_2O_2-Mn system were 7–9-fold larger than that in Fe^{III}-NTA/H_2O_2 system. An increase in Fe^{III} concentrations from 0 to 0.15 mM has positive effects on the degradation rate of metoprolol in both systems. The *k* values of metoprolol increased from 0 to 0.3174 min^{-1} in Fe^{III}-NTA/H_2O_2 system and to 2.2988 min^{-1} in Fe^{III}-NTA/H_2O_2-Mn system, respectively. The results indicate that the rate of $HO^{\cdot}$ generation is greatly enhanced by increasing Fe^{III}-NTA concentration, especially in Fe^{III}-NTA/H_2O_2-Mn system. This can be explained by the fact that high concentration of

Fe^{III}-NTA would increase the generation rate of Fe^{II}-NTA (R5) and (R7), which in turn reacts with H_2O_2 to produce more HO·.

3.6. Intermediates and degradation pathways

It was worth noting that a high initial concentration of metoprolol (292 μM, ten times higher than that in typical experiments) was used in order to capture more intermediates. The typical full-scan total molecular ion chromatograms of samples at different reaction time (RT) can be found in the Supplementary data. Two major peaks with molecular ion ($[M+H]^+$) at mass-to-charge (m/z) ratios of 268 and 192 were observed in samples before the treatment, corresponding to metoprolol and NTA, respectively. Several intermediates were detected in samples after the reaction by mass spectrometry, their molecular ion were identified at m/z 134, 238, 258, 274, 282, 284, 298, 300, 314, 316, 330, 332 and 348. A major degradation product is 3-(isopropylamino)propane-1,2-diol (m/z 134), which formed by the cleavage of aromatic ether bond of metoprolol due to the attack of HO·. A same intermediate has been detected in the degradation of metoprolol by photocatalysis, γ-irradiation, Fenton and photo-Fenton processes [8,10,33,35]. In addition, the attack of HO· on the ether bond and/or the β-C in methoxyethyl side chain of metoprolol gave intermediates with molecular ion at m/z 238, corresponding to 4-(2-hydroxy-3-(isopropylamino)propoxy)benzaldehyde and 1-(4-ethylphenoxy)-3-(isopropylamino)propan-2-ol, consistent with previous studies [8,10].

The hydroxylation of benzene ring (and/or side chain) of metoprolol led to the formation of hydroxyl-metoprolol isomers (m/z 284). The intermediates with molecular ion at m/z 282 could be 4-(2-methoxyethyl)phenyl 2-hydroxy-3-(isopropylamino)propanoate and 1-(4-(2-hydroxy-3-(isopropylamino)propoxy)phenyl)-2-methoxyethanone, which were formed by the oxidation of hydroxyl group to keto group in hydroxyl-metoprolol (i.e., 3-(isopropylamino)-1-(4-(2-methoxyethyl)phenoxy)propane-1,2-diol and 1-(4-(1-hydroxy-2-methoxyethyl)phenoxy)-3-(isopropylamino)propan-2-ol). Moreover, the addition of 1 HO·, 2 HO·, 3 HO· and 4 HO· on hydroxyl-metoprolol gave intermediates with molecular ion at m/z 300, 316, 332 and 348, corresponding to di-, tri-, tetra-, and penta-hydroxyl-metoprolol, respectively. The intermediates with molecular ion at m/z 298 and 314 could be formed by the addition of 1 HO· and 2 HO· on the detected intermediates (m/z 282). The intermediates with molecular ion at m/z 258 and 274 were probably formed by the addition of 2 HO· and 3 HO· on two undetected intermediates (m/z 226), i.e., 1-amino-3-(4-(2-methoxyethyl)phenoxy)propan-2-ol and 4-(2-hydroxy-3-(isopropylamino)propoxy)phenol [33,36].

A comparison of Figs. S2 and S3 demonstrates that Fe^{III}-NTA/H_2O_2-Mn system led to more efficient degradation of metoprolol and its intermediates. In addition, Fig. 8 shows the changes in the total molecular ion chromatogram area of metoprolol and its intermediates with the reaction time. It can be seen that the total areas of major intermediates (i.e., m/z 238, 282, 284, 298, 300, etc.) increased rapidly to reach their maximum values within the first 3–5 min of the reaction time, and then decreased to undetectable levels at 20 min of the reaction time. In particular, the major intermediate (m/z 134) increased continuously until almost complete degradation of metoprolol took place (12–15 min of the reaction time), and then began to decrease slowly over time. The degradation pathways of metoprolol were proposed on the basis of these identified intermediates, which were presented in Scheme 1. Our results clearly suggested that the degradation of metoprolol and its intermediates were mainly caused by HO· attack.

4. Conclusion

The results of this study indicate that Fe^{III}-NTA/H_2O_2 is able to degrade metoprolol at initial neutral pH, and the degradation rate of metoprolol can be greatly improved with the presence of Mn^{II}. The k values of metoprolol in Fe^{III}-NTA/H_2O_2-Mn system were typically 7–9-fold larger than those in Fe^{III}-NTA/H_2O_2 system. It can be concluded that the presence of Mn^{II} does not directly catalyze Fenton-like reaction, but indirectly enhance Fe^{III}-NTA-catalyzed Fenton-like reaction over a wide pH range of 4.0–8.0. The main intermediates during the degradation of metoprolol have been identified by mass spectrometry, which suggested that the degradation of metoprolol and its intermediates were mainly caused by HO· attack. Fe^{III}-NTA/H_2O_2-Mn system led to more efficient degradation of metoprolol and its intermediates.

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Appendix A. Supplementary data

Quenching tests with 2-propanol and chloroform on the degradation of metoprolol in Fe^{III}-NTA/H_2O_2-Mn system (Fig. S1). Total molecular ion chromatogram of metoprolol and its intermediates in Fe^{III}-NTA/H_2O_2 and Fe^{III}-NTA/H_2O_2-Mn systems (Fig. S2 and Fig. S3). Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cej.2016.12.098.

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