Degradation of metformin in water using electro-Fenton process

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Abstract. Metformin has become an emerging contaminant in water compartments like many other pharmaceutical drugs. Moreover, conventional treatment methods are not enough to remove metformin in water. The use of advanced oxidation processes (AOPs) may be a solution to this problem. Electro-Fenton is an AOP that combines electrolysis and Fenton process to form reactive specie used to treat contaminants in water. The effects and optimum values of parameters for metformin degradation with electro-Fenton namely Fe²⁺ concentration, applied current, and pH were observed and gathered in this study, as well as rate constants of the degradation. The experimental solutions were contained in a continuously stirred vessel with boron-doped diamond as anode and carbon felt for the cathode. It was observed that the optimal values for each parameter are 0.1 mM for Fe²⁺ concentration, 300 mA for current, and pH=3. At these optimum conditions, a percent removal of 99.57 % was observed after 27 min of electrolysis. The value of the absolute rate constant (kₘₐₓ) was found out to be $(5.2658 \pm 0.0656) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, which was calculated based on the competition kinetics and Vierordt’s methods.

1. Introduction
Diabetes is one of the largest diseases worldwide. It is characterized by high blood glucose level due to impaired insulin production or impaired interaction with insulin [1]. Over the past decades, the number of cases of diabetes has increased significantly and is expected to increase in the coming years. In 2014, 422 million adults were living with diabetes according to World Health Organization (WHO) [2]. With this tremendous amount of diabetes cases comes a huge demand on diabetes-treating medicines. Diabetes has two types but type 2 is the more prevalent one [2,3]. Biguanides are used in the treatment of type 2 diabetes. These include phenformin, buformin and metformin. Metformin (figure 1) is the most prescribed pharmaceutical for the treatment of type 2 diabetes [4]. With this number of prescriptions involving metformin, it poses an environmental concern since it is not metabolized by the human body and is transported to different environmental compartments [5]. Metformin was detected in different bodies of water across the world [6]. When metformin undergoes biological treatment, a fraction of it is converted into guanylurea but most of it remains as metformin. This raises a need for studies regarding possible treatment methods to remove it from water [7,8]. Advanced oxidation process (AOP) has been studied for the treatment of pharmaceuticals in water. In AOPs, hydroxyl radical (•OH) is commonly used [8]. Hydroxyl radical is also the second strongest known oxidant, next to fluorine.
Previous studies have shown that conventional treatment methods alone are not enough to degrade contaminants including metformin [9-11]. Additional usage of AOP to conventional treatment methods increased the removal of numerous contaminants many-fold [11]. Possible AOPs for the degradation of metformin include UV/H$_2$O$_2$, Fenton, electro/photo/sonolysis and their combinations, as well as microwave, gamma radiation, electron beam and non-thermal plasma [8]. UV [10-13], Fenton [10,11] and photocatalysis [7,14] have been studied recently for metformin treatment. One AOP that has just started getting attention in the past few years is electro-Fenton (e-Fenton) [15]. The process itself is eco-friendly and the products and reagents are environmentally benign, though AOPs in general produce relatively safe products compared to other chemical oxidative processes since partial oxidation of a target compound by other chemical oxidative processes can lead to the formation of more hazardous compounds [8]. E-Fenton is also one of the more economical AOPs as it operates at a relatively lower cost [16]. It combines the principle of electrolysis and Fenton reaction whereby the reduction of oxygen (O$_2$) at the cathode continuously generates hydrogen peroxide (H$_2$O$_2$) in an acidic solution (equation (1)). Additionally, H$_2$O$_2$ may also be supplied externally. With the formation and/or addition of H$_2$O$_2$, Fenton reaction (equation (2)) takes place to form the reactive species 'OH, which is the key component for AOPs to degrade the contaminant [17-19].

\[
O_2 + 2H^+ + 2e^- \rightarrow H_2O_2 \quad (1)
\]

\[
Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + OH^* \quad (2)
\]

Metformin is now considered an emerging contaminant due to its increase in usage and prescription, its persistence on different environmental compartments, and its endocrine disrupting potential [4,9,20,21]. AOPs have been observed to be a good solution for the treatment of many pharmaceuticals. However, the high percentages of removal observed in other pharmaceuticals were not seen in metformin [11]. Only few AOPs have been tested to treat metformin in water: UV/H$_2$O$_2$ [10-13], dark Fenton and photo-Fenton [10,11], and photocatalysis [7,14]. Metformin was shown to be persistent even under the AOPs afore mentioned, which usually completely remove other pharmaceuticals. Therefore, a study must be made to find the most cost-effective and efficient AOP to remove metformin from the environment. To the best of our knowledge, e-Fenton has not been tested for the treatment of metformin in water. Thus, the objective of this study was to investigate the degradation of metformin using e-Fenton. The effects and optimal values of the concentration of ferrous ion (Fe$^{2+}$), applied current and pH were observed and determined. The apparent rate constant ($k_{app}$) and ultimately the absolute rate constants ($k_{abs}$) at the optimal conditions using competition reaction kinetics method were determined.

2. Methods

2.1. Chemicals and reagents

Metformin hydrochloride (metformin HCl) from Sigma-Aldrich was used as the target compound for the e-Fenton process. Distilled water was used as the solvent. Sodium sulfate (Na$_2$SO$_4$) from Alysons’ Chemical Enterprises was used as supporting electrolyte with a concentration of 16 g/L. 1 mL of 1 M sulfuric acid diluted with 15 mL of water was used for the adjustment of pH. 30% w/v (weight by volume) H$_2$O$_2$ (Perhydrol at 30%) was used with ferrous sulfate (FeSO$_4$7H$_2$O; TM Media, AR grade, 99.5%) to facilitate the Fenton reaction. Finally, benzoic acid (BA; Sigma Aldrich, AR grade, 99.5%)
was used as the standard substrate for the competition kinetics reaction.

2.2. Apparatus and analytical methods

For the electrolytic system, figure 2 shows the diagram of the e-Fenton experimental setup. The experiment was carried out in a 600-mL beaker. The solution was homogenized using a magnetic stirrer. The cell was equipped with two electrodes type namely boron-doped diamond (BDD) (20×50×1 mm³) from NeoCoat as anode and carbon felt from MonotaRO (30×60×5 mm³) as cathode. Both were mounted parallel to one another, 4-cm apart and perpendicular to the base. Tektronix PS280 DC power supply was used in DC configuration to act as a battery in a closed circuit. The electrolytic solution contained distilled water, metformin, Na₂SO₄, FeSO₄, H₂O₂ each with varying quantities.

For the analytical methods, samples for the calibration curve were analyzed in PerkinElmer® Lambda™ 35 UV-Vis spectrophotometer with UV WinLab software. The pH of the electrolytic solutions was measured using Mettler Toledo FiveEasy™ F520 pH meter. The concentration of metformin at specific times during its degradation was also analyzed using the UV-vis spectrophotometer.

![Figure 2. Experimental setup: (1) electrodes (BDD anode, carbon felt cathode), (2) magnetic stirrer, (3) power supply and (4) solution [16].](image)

2.3. Calibration curve

Metformin HCl and BA were dissolved separately each in 25 mL of distilled water to attain 1.25 mM metformin and 2 mM BA solutions. From the stock solutions, 7 samples (0.005, 0.01, 0.03, 0.05, 0.1, 0.15 and 0.2 mM) of metformin and BA of varying volumes were taken and diluted individually to 10 mL to attain varying concentrations. Each solution was analyzed using the UV-vis spectrophotometer. The absorbance versus concentration of both were then plotted.

2.4. Apparent rate constant

The degradation of metformin (equation (3)) follows a pseudo-first order reaction kinetics since the amount of •OH in the system does not accumulate (equation (4)). Optimum values for the parameters were determined in this part. Such parameters are the concentration of Fe²⁺ ions, applied current, and the pH of the solution. Linearizing equation (4) yields equation (5) where M is metformin, t is time, and [M]₀ and [M] corresponds to the concentration of metformin at initial time and at time t, respectively.

\[
M + OH^* \rightarrow \text{products} \tag{3}
\]

\[-\frac{d[M]}{dt} = k_{app}[M] \tag{4}\]

\[\ln[M] = -k_{app}t + \ln[M]_0 \tag{5}\]

For all trials, 16.56 g of metformin was dissolved in enough distilled water and was transferred to
a volumetric flask. 10-g Na₂SO₄ was added to facilitate electrical conductivity and FeSO₄ was added as the Fenton reagent. The solution was then diluted to 500 mL mark. Next, the pH was adjusted using prepared sulfuric acid solution. Finally, 0.27 mL of 30% w/v H₂O₂ was added to the solution prior to applying the current. This amount of H₂O₂ corresponds to a concentration of 600 mg L⁻¹.

2.5. Effect of Fe²⁺ concentration
For the determination of the optimum Fe²⁺ concentration, concentrations of 0.1, 0.2, and 0.3 mM of Fe²⁺ were tested by dissolving 7.5954, 15.1908 and 22.7862 mg of FeSO₄ in water. To start the e-Fenton reaction, the DC power supply was set to supply 300 mA at the same time the H₂O₂ was added. Samples of the metformin-water solution at 3-min intervals were collected and were immediately analyzed in the UV-vis spectrophotometer. Plots of absorbance versus wavelength were outputted by the UV-vis spectrophotometer. With these values and the calibration curve of metformin at 233 nm wavelength, the concentrations of metformin at each time were obtained and a graph of this was plotted. The apparent rate constants of each case were obtained using equation (5). The highest apparent rate constant signifies the optimum Fe²⁺ concentration. The optimum Fe²⁺ that was determined in this part was used for the determination of other optimum parameter values.

2.6. Effect of applied current
For the optimum applied current, currents of 100, 200, 300, and 400 mA were tested. Concentration of Fe²⁺ in this part was the optimum concentration that was determined in the previous part. Everything else was similar with the first procedure for the preparations, as well as the analytical methods and calculations. The k_app and the optimum value of current applied were determined.

2.7. Effect of pH
Finally, for the determination of optimum pH of solution, pH at 2, 3 and 4 were tested with the optimum values determined in the previous two optimum parameters. After doing the same procedure for the determination of optimum values, the optimum pH was determined. All the values of optimum parameters in this part of the experiments were used for the determination of the absolute rate constant.

2.8. Absolute rate constant
The actual degradation reaction of metformin follows the second-order kinetics model (equation (6)). In the determination of second order reaction constant (absolute rate constant (k_abs)), the same setup was used from the previous parts. Other necessary reagents were added also to proceed with the electrolysis and Fenton reaction. Method of competition kinetics was used in computing the k_abs. The simultaneous degradation of the contaminant metformin (equation (3)) and BA (the standard compound/competitor) (equation (7)) was observed. Equal amounts of metformin and BA (0.2 mM) were used. The literature k_abs value of BA is 4.3 × 10⁹ M⁻¹ s⁻¹ [22]. The samples were analyzed using UV-vis spectrophotometer, which were taken after every 3 minutes of the reaction from the start and from the previous measurement. The absorbance versus wavelength graph of the solutions was gathered and the concentration of each compound was computed by Vierordt’s method [23], as shown in equations (10) and (11) where ε is the molar absorptivity of compound x and y at wavelengths λ₁ and λ₂ and b as the path length (1 cm). The k_app of BA was determined following a pseudo-first-order kinetics model (equation (8)). Ratio and proportion with the literature k_abs of BA and the obtained k_app of both compounds was used to determine the k_abs for metformin (equation (9)).

\[
- \frac{d[M]}{dt} = k_{abs}[M][OH^+] \quad (6)
\]

\[
BA + OH^* \rightarrow \text{products} \quad (7)
\]
\[
\frac{d[BA]}{dt} = k_{app}[BA]
\]  
(8)

\[
\frac{k_{app,BA}}{k_{app,met}} = \frac{k_{abs,BA}}{k_{abs,met}}
\]
(9)

\[
A_1 = \varepsilon_{x1} b C_x + \varepsilon_{y1} b C_y
\]
(10)

\[
A_2 = \varepsilon_{x2} b C_x + \varepsilon_{y2} b C_y
\]
(11)

3. Results and discussion

3.1. Calibration curve

To measure the unknown concentration of metformin HCl and BA in the sample runs, calibration curve was constructed for metformin, and Vierordt’s method [23] was used for BA. Metformin HCl and BA showed a peak around 233 and 220 nm, respectively, which follows the findings of different articles involving the determination of concentration of metformin HCl and BA using UV spectrophotometric methods [24-26]. With this, all proceeding analyses with regard to metformin were evaluated at \(\lambda_{\text{max,metformin}} = 233\) nm.

3.2. Effect of Fe\(^{2+}\) concentration

Fe\(^{2+}\) concentration is directly proportional with the efficiency [15]. As shown in equation (2), Fe\(^{2+}\) ion is consumed to form •OH. Shown in Table 1 are the removal time and the corresponding % removal wherein all the runs reached >99% degradation. The time course of the degradation is shown in figure 3. It is evident in figure 3 that the degradation of metformin is faster at higher concentrations. With this, an increase in \(-k_{app}\) was observed (table 2). On the other hand, too much Fe\(^{2+}\) can lead to lesser efficiency since it can react with •OH to form Fe\(^{3+}\) and OH\(^-\) ions (equation (12)). There is an increase in efficiency at 1.0-1.5 mM but at higher concentrations, there is no significant increase. In an industrial standpoint, it is more beneficial to use lower concentration of Fe\(^{2+}\) since the increase in the degradation at higher Fe\(^{2+}\) concentration is not that significant [27].

\[
\text{Fe}^{2+} + \text{HO}^* \rightarrow \text{Fe}^{3+} + \text{OH}^-
\]
(12)

Table 1. Metformin removal time and percentage at different Fe\(^{2+}\) concentrations.

| Fe\(^{2+}\) concentration (mM) | Percentage of removal (%) | Time at highest removal, t (min) |
|-------------------------------|---------------------------|---------------------------------|
| 0.1                           | 99.43                     | 21                              |
| 0.2                           | 99.27                     | 21                              |
| 0.3                           | 99.10                     | 21                              |

Figure 3. Degradation of metformin at different Fe\(^{2+}\) concentrations.
Table 2. Apparent rate constant (-$k_{app}$) at different Fe$^{2+}$ concentration.

| Concentration of Fe$^{2+}$ (mM) | -$k_{app}$ (min$^{-1}$) |
|---------------------------------|------------------------|
| 0.1                             | 0.242                  |
| 0.2                             | 0.237                  |
| 0.3                             | 0.268                  |

3.3. Effect of applied current

Current is the driving force in e-Fenton process. It enables the production of H$_2$O$_2$, hence making the production of •OH possible (equation (2)). With this, an increase in current should increase the production of •OH [28] and the regeneration of Fe$^{3+}$ [29]. But, the applied current must be balance since applying too much can decrease the efficiency of the e-Fenton process due to undesirable reactions as shown in (equations (13) and (14)) [30,31].

$$2H_2O \rightarrow 4H^+ + O_2 + 4e^-$$  \hspace{1cm} (13)

$$4H^+ + O_2 + 4e^- \rightarrow 2H_2O$$  \hspace{1cm} (14)

Figure 4 shows the degradation of metformin at different applied current. Table 3 lists the corresponding % removal and the time at highest removal. Table 4 shows the different values of $k_{app}$ at different applied current. It was observed that 300 mA was the optimal current since the efficiency was decreased at 300 to 400 mA. The increase in the concentration beyond 24 minutes might have been an error in the analysis. This finding also followed the general trends in the degradation of pharmaceutical products using e-Fenton such as those studies conducted by [30,31].

Table 3. Metformin removal time and percentage at different applied current.

| Applied current (mA) | Percentage of removal (%) | Time at highest removal, t (min) |
|----------------------|---------------------------|---------------------------------|
| 100                  | 76.76                     | 30                              |
| 200                  | 90.73                     | 30                              |
| 300                  | 98.93                     | 27                              |
| 400                  | 84.87                     | 24                              |

Table 4. Apparent rate constant (-$k_{app}$) at different applied currents.

| Applied Current (mA) | -$k_{app}$ (min$^{-1}$) |
|----------------------|------------------------|
| 100                  | 0.041                  |
| 200                  | 0.046                  |
| 300                  | 0.132                  |
| 400                  | 0.069                  |
3.4. Effect of pH

pH is one of the most important factors in e-Fenton process. Most of studies with e-Fenton process were done at acidic conditions and have reported an optimum pH of 3 [27,32-34]. In this part of the study, same $\lambda_{\text{max}}$ were used for the determination of metformin HCl concentration. It was observed that there was no precipitate at pH = 2, but darker precipitate was evident at pH = 4. This is due to side reactions that decreases the efficiency of the e-Fenton process [15]. Acidic condition is favorable in e-Fenton process since it promotes the evolution of $\text{H}_2\text{O}_2$ (equation (15)). But, at much lower or higher pH, side reaction can occur (formation of oxonium ion equation (16) at lower pH [34] and the instability of $\text{H}_2\text{O}_2$ at higher pH shown by equation (17)) [15].

$$\text{H}_2\text{O}_2 + 2\text{H}^+ + 2e^- \rightarrow 2\text{H}_2\text{O} \quad (15)$$
$$\text{H}_2\text{O}_2 + \text{H}^+ \rightarrow \text{H}_3\text{O}_2^+ \quad (16)$$
$$2\text{H}_2\text{O}_2 \rightarrow 2\text{H}_2\text{O} + \text{O}_2 \quad (17)$$

This increase and decrease on the degradation of organics was observed in the determination of optimum pH. Figure 5 shows the degradation of metformin at different values of pH. At all trials involving pH, a pH = 3 showed a higher -$k_{\text{app}}$ value which states that at pH = 3, the degradation of metformin proceeds the fastest. The $k_{\text{app}}$ values at different pH are shown in table 5. The pH, % removal, and time at highest removal are shown in table 6. The concentration versus time graph at different pH is shown in figure 5.

| pH | $k_{\text{app}}$ (min$^{-1}$) |
|----|------------------------------|
| 2  | 0.055                        |
| 3  | 0.142                        |
| 4  | 0.048                        |

![Figure 5. Degradation of metformin at different pH.](image)

Table 5. Apparent rate constant (-$k_{\text{app}}$) at pH.

| pH | Percentage of removal (%) | Time at highest removal, t (min) |
|----|---------------------------|---------------------------------|
| 2  | 91.41                     | 30                              |
| 3  | 99.57                     | 27                              |
| 4  | 78.05                     | 30                              |

Table 6. Degradation of metformin at different pH.

An average of 99.57% removal was observed at the optimum parameter (0.3 mM Fe$^{2+}$ conc, I = 300 mA, pH = 3) at $t = 27$ minutes (table 6). This proves that e-Fenton is an effective way of removing metformin in water. Different studies involving metformin and AOPs also showed the same trend of having a >90% removal for 30 minutes of treatment [11,13]. Even though HCl is present in the target
compound, its mineralization yields only Cl\(^-\) ions, water and CO\(_2\) [7]. As for the generation of active chlorine species, it is produced more extensively on dimensionally stable anodes (DSA) than BDD [35].

3.5. Absolute rate constant

The determination of the absolute rate constant (\(-k\text{abs}\)) of metformin HCl (220 nm) and BA (233 nm) used the simultaneous equation method (Vierordt’s method) [23]. Additionally, their molar absorptivity was computed from the equation of the line at both wavelengths. Since the cuvette’s path length is 1 cm, the slope is equivalent to the molar absorptivity of each compound at different wavelength. Shown in table 7 is the molar absorptivity of each compound.

**Table 7.** Molar absorptivity of metformin and BA at wavelengths \(\lambda_1 = 220\) nm and \(\lambda_2 = 233\) nm.

| Molar absorptivity of metformin at \(\lambda_1\), \(\varepsilon_{x1}\) | 14.22373591 |
|-------------------|-----------------|
| Molar absorptivity of metformin at \(\lambda_2\), \(\varepsilon_{x2}\) | 17.66750797 |
| Molar absorptivity of BA at \(\lambda_1\), \(\varepsilon_{y1}\) | 11.94645545 |
| Molar absorptivity of BA at \(\lambda_2\), \(\varepsilon_{y2}\) | 4.581817989 |

After the determination of molar absorptivities, competition kinetics was done and absorbance at 220 and 233 nm was recorded and was substituted to equations (10) and (11), alongside with the molar absorptivities. The concentration of metformin and BA was then calculated and was plotted at different times, as shown in figure 6. Assuming pseudo first-order kinetics, for the average of two trials, the apparent rate constants were calculated as follows: \(-k\text{app,met}\) values of 0.06041 s\(^{-1}\) and \(-k\text{app,BA}\) values of 0.04935 s\(^{-1}\). Finally, \(k\text{abs}\) was calculated using equation (9) an average value of \(5.2658 \times 10^9\) M\(^{-1}\) s\(^{-1}\). No absolute rate constant was found on literature for comparison.

![Figure 6. Concentration of metformin and BA at different times.](image)

4. Conclusion

This does not happen in the setup since, this study has shown that e-Fenton is capable of degrading metformin in water like many other pharmaceutical drugs. The degradation of metformin followed a pseudo-first order reaction and therefore \(k\text{app}\) was obtained. The effects of adjusting the parameters were examined in this study. The optimal value for Fe\(^{2+}\) concentration was 0.3 mM based on it having the highest \(-k\text{app}\) which was 0.2680 min\(^{-1}\). From this, increasing the Fe\(^{2+}\) concentrations also increase the rate of degradation Likewise, effect of adjusting the applied current was tested at 100, 200, 300 and 400 mA. The optimal current was 300 mA with \(-k\text{app}\) of 0.1324 min\(^{-1}\). From this, increasing the applied current allowed a faster degradation up until 300 mA. Beyond that, the rate of degradation decreased. The optimal pH was 3 with \(-k\text{app}\) of 0.1416 min\(^{-1}\). Similar with applied current, the rate only increased up to pH 3 and decreased beyond pH 3 up to pH 4. The value of \(k\text{abs}\) was obtained with the optimal values obtained previously using method of competition kinetics. The value for \(k\text{abs}\) (mean ±
std. deviation) was $(5.2658 \pm 0.0656) \times 10^9$ M$^{-1}$ s$^{-1}$.

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