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Electrochemical Degradation of Metoprolol Using Graphite-PVC Composite as Anode: Elucidation and Characterization of New by-products Using LC-TOF/MS

Zainab Haider Mussa[1,2], Fouad Fadhil Al-Qaim[1,3*], Ali Yuzir[1], Kamyar Shameli[1]

[1]Malaysia-Japan International Institute of Technology (MJIIT), Universiti Teknologi Malaysia, Jalan Sultan Yahya Petra,54100 Kuala Lumpur.
[2]College of Pharmacy, University of Al-Ameed, Karbala PO Box 198, Iraq.
[3]Department of Chemistry, Faculty of Science for Women, University of Babylon, PO Box 4, Hilla, Iraq.

***Corresponding author:** Fouad Fadhil Al-Qaim, email: fouadalkaim@yahoo.com; Tel.: +60173394821

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Abstract. Metoprolol (MTP) is one of pharmaceuticals used for treatment of heart failure and hypertension. It was frequently detected in wastewater samples either influent or effluent. The application of graphite-PVC composite as anode was investigated for the degradation of metoprolol in the presence of strong electrolyte such as sodium chloride (NaCl). The degradation rate was strongly influenced by initial concentrations of metoprolol, NaCl concentration and applied voltage. An initial concentration of 2 mg/L was eliminated more than 95% after 30 min under optimum conditions; 5000 mg/L NaCl and 5 V. The consumption energy of the electrochemical reaction was 0.665 Wh/mg for metoprolol after 30 min. The kinetic rate constant of metoprolol could be ranged between 0.0016 and 0.0801 min^{-1}. The electrochemical degradation efficiency of metoprolol and its by-products has been achieved. The degradation of metoprolol produced four transformated products as investigated and elucidated using liquid chromatography-time of flight/mass spectrometry. The proposed degradation pathway of metoprolol was schemed on the base of the identified intermediates.
Keywords: Metoprolol; electrochemical degradation; by-products; solid phase extraction; LC-TOF/MS.

Resumen. El metoprolol (MTP) es uno de los fármacos utilizados para el tratamiento de la insuficiencia cardíaca y la hipertensión. Se detecta frecuentemente en muestras de aguas residuales, ya sea de afluentes o efluentes. Se investigó la aplicación del compuesto de grafito-PVC como ánodo para la degradación del metoprolol en presencia de un electrolito fuerte como el cloruro de sodio (NaCl). La velocidad de degradación depende de las concentraciones iniciales de metoprolol, la concentración de NaCl y el voltaje aplicado. Una concentración inicial de 2 mg/L de MTP fue eliminada con más del 95% después de 30 minutos en condiciones óptimas; 5000 mg/L de NaCl y 5 V. La energía de consumo de la reacción electroquímica fue de 0,665 Wh/mg para el metoprolol después de 30 min. La constante cinética de degradación metoprolol oscila entre 0.0016 y 0.0801 min^{-1}. Se logró la eficiente degradación electroquímica del metoprolol y sus subproductos, ya que se detectaron cuatro subproductos electrogenerados según los resultados de cromatografía líquida - tiempo de vuelo/espectrometría de masas. La vía de degradación propuesta del metoprolol se esquematizó sobre la base de los productos intermedios identificados.
Palabras clave: Metoprolol; degradación electroquímica; subproductos; extracción en fase sólida; LC-TOF/MS.

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Introduction

Over the last 20 years, pharmaceuticals have been receiving an increasing attention as potential bioactive organic compounds in the aquatic environment. They are considered as emerging pollutants in water bodies because they still remain unregulated or are currently undergoing a regularization process.

The occurrence of these compounds was observed in influent, effluent of sewage treatment plants and hospital, and surface water in Malaysia with concentration of metoprolol ranged from 25 to 364 ng/L [1-3]. Some studies have reported the abundance of drugs in groundwater, urban wastewater plants, rivers, hospital wastewater and lakes around the world, however, the median of metoprolol in river was 52 ng/L [4-7]. Although, the concentration of these pollutants is low in the environment, these pharmaceuticals may pose adverse effects on the organisms and humans due to long-term exposure [8-10]**.** This frequent detection may be attributed to the fact that the conventional wastewater treatment plants are not sufficient to achieve this purpose [11].

Metoprolol is a selective beta-1 blocker commonly employed as the succinate and tartrate derivatives. Metoprolol is indicated for the treatment of angina, heart failure, myocardial infarction, atrial fibrillation, atrial flutter and hypertension [12]**.**

Various strategies were reported on the treatment of wastewater effluent including biological methods (enzymes and microorganisms), physical methods (filtration, flocculation, and adsorption), and oxidation methods (advanced oxidation and chemical oxidation) [13,14]. However, today the use of electrochemical oxidation technique in wastewater treatment is getting more attention as this method does not involve the use of additional chemicals [15,16]. Previous studies have shown that this technique provided high efficiency in the removal of organic and inorganic pollutants from the effluents [17-20]. According to Liu et al. (2019), this technique requires simple equipment, easy implementation, and on-site treatment in less space [21]. Furthermore, it is well reviewed that a very common chlorinated compounds such as chloroflourocarbons have been removed using direct electrochemical reduction process and catalytic degradation with electrogenerated mediators process from wastewater. However, removal of these compounds is important due to its participation for depleting the stratospheric ozone layer [22].

Electrochemical process is called anodic oxidation, where the direct and indirect oxidation process could be occurred on the surface of anode and/or at the bulk solution realising $\mathrm{ClO^-/HOCl}$ as an oxidizing agent [23]. Anodic oxidation with conductive graphite-PVC composite anode has presented many advantages as compared to other known chemical and photochemical processes in which it was used for treatment of leachate and wastewater contaminated with drugs [24]. Few electrochemical methods have been used for treatment of metoprolol. De Vidales et al. (2015) used BDD as anode and Na_2SO_4 as an electrolyte for the electrochemical treatment of metoprolol. He observed that the by-products which are formed after electrochemical treatment stayed and gathered in solution [25]. However, in our present study, all by-products were eliminated completely using graphite-PVC electrode and NaCl electrolyte.

Removal of pollutants depends on the active chlorine$\mathrm{Cl_2/ClO^-}$ which is strongly depending on the presence of NaCl as supporting electrolyte. This event can be explained by the primary transformation of $\mathrm{Cl^-}$ into $\mathrm{Cl_2}$ then into $\mathrm{ClO^-/HOCl}$ [26].

$$\mathrm{2Cl^-} \rightarrow \mathrm{Cl_2} + \mathrm{2e^-} \tag{1}$$

$$\mathrm{Cl_2} + \mathrm{H_2O} \rightarrow \mathrm{H^+} + \mathrm{Cl^-} + \mathrm{HOCl} \tag{2}$$

$$\mathrm{HOCl} \leftrightarrow \mathrm{H^+} + \mathrm{ClO^-} \tag{3}$$

$$\mathrm{ClO^-} + \text{organic pollutant} \rightarrow \mathrm{CO_2} + \mathrm{H_2O} + \mathrm{Cl^-} \tag{4}$$

In any degradation process, the most common question is “what is the fate of treated compound and how to identify the by-products after degradation?”. In this report, the electrochemical treatment process for metoprolol was investigated using graphite-PVC as anode. Some of the aims of the study are as follow: (1) to investigate the efficiency of the electrochemical process for removal of metoprolol and its by-products under different experimental parameters, (2) to evaluate the consumption energy and kinetics during the electrochemical treatment profile, (3) to identify the by-products formed during the electrochemical treatment process.

Experimental

Reagents

Metoprolol was supplied by Sigma-Aldrich (≥98%). Organic solvents such as methanol, acetonitrile and formic acid, and other chemicals used were HPLC-grade from Aldrich and J-baker. Graphite powder was obtaind from University Kebangsaan Malaysia, Malaysia. All aqueous solutions were prepared with de-ionized water (DIW) with conductivity ≤18 S/cm at ambient temperature. NaCl was purchased from Merck with high purity ≥99.5%. Metoprolol (0.01 g) dissolve in 10 mL of methanol to prepare a stock solution of 1000 mg/L. Subsequent concentrations 2, 5 and 10 mg/L were prepared after diluting in de-ionized water.

Preparation of a Graphite-polyvinyl Chloride Composite Electrode

The graphite–PVC composite electrode was prepared by mixing together a weighed portion of graphite powder (100 mesh in size and 99.9% purity, Aldrich chemical Company) and polyvinyl chloride (PVC) in 8 mL tetrahydrofuran (THF) solvent and swirled flatly to homogeneous followed by drying in an oven at 50 ℃ for 3 h. The mixture was then placed in 2 cm diameter stainless steel mould and pressed at 10 ton/cm^2 using hydraulic machine (ATLAS auto touch HYDRAULIC). A typical pellet contained approximately 95% of graphite powder, and approximately 5% of PVC. The total weighed of pellet obtained is approximately 2g. Graphite-PVC pellet connected to a silver wire with silver conducting paint and sealed to a glass rode. Subsequently, epoxy gum was applied to cover the silver wire connected surface as show in Fig. 1.

A 100 mL of metoprolol solution was electrochemically treated at different interval times (0, 10, 20, 30, 40, 50, 60, 70 and 80 min). However, consumption energy was investigated at different values of applied voltages and sodium chloride during the electrochemical oxidation process to ensure that the present study is preferred for this purpose. Metoprolol was tested without switching on power as a control test to confirm that the removal of metoprolol is not due to the adsorption to the electrodes.

A solution of 2 mg/L of metoprolol was subjected to non-electrochemical process (i.e. switch off direct current (DC) power supply) for 60 min at a fixed concentration of 5000 mg/L NaCl. All samples were analysed and compared to the origin solution using LC-TOF/MS.

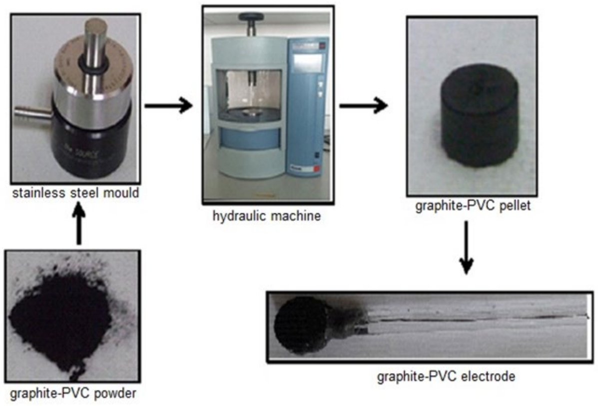

Fig.1. Steps of preparation of graphite-PVC electrode

Set up of Electrochemical Process

The schematic experimental setup is as shown in Fig. 2. The reaction was carried out using 100 mL pyrex glass. The glass pyrex electrochemical cell (reactor) was placed on magnetic stirring block in order to keep its contents well mixed during the experiment. Graphite-PVC pellet and Pt plate were used paralleled as anode and cathode, respectively. The distance between the electrodes was 4 cm. The electrodes were then connected to a direct current (DC) power supply (CPX200 DUAL, 35V 10A PSU).

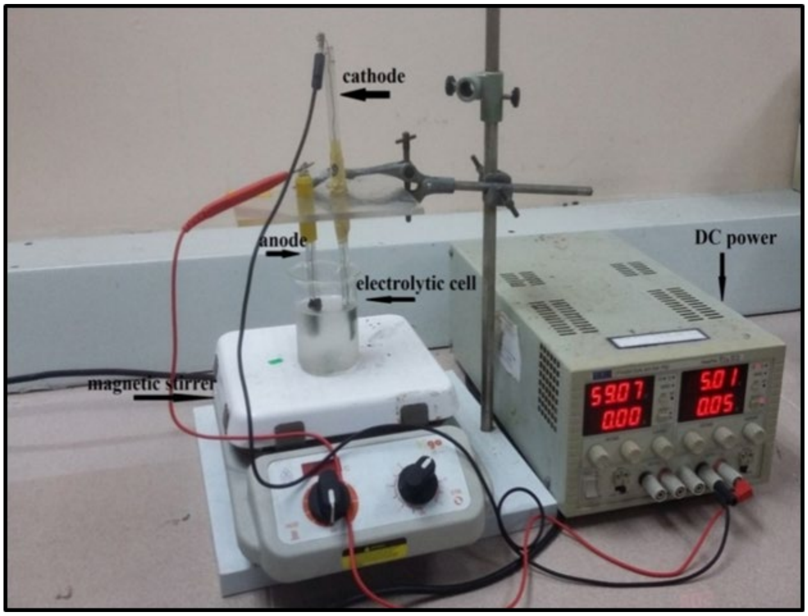

Fig.2. The schematic diagram of the electrochemical process use

Solid Phase Extraction (SPE) Method

All samples after electrochemical treatment were filtered through 0.45 µm GF/F glass fiber filter before SPE experiments. The SPE cartridges were preconditioned with, 2 mL of MeOH and 2 mL of deionized water at a flow rate of 3 mL/min. After the preconditioning step, aliquots of 100 mL of sample were loaded into the cartridge. Samples were passed through the cartridges at a flow rate of 3 mL/min. The cartridges were later dried under vacuum for approximately 5 min at a flow rate of 15 mL/min to remove excess of water.

The pharmaceutical compounds were subsequently eluted to a 12 mL glass tubes by sequentially passing 5 mL of methanol, then evaporated to dryness under a gentle stream of N_2 gas. Dry extracts were then reconstituted with 1.0 mL of MeOH–DIW (10:90, v/v) and then transferred to 250 µL deactivated glass insert with polymer feet inserted in amber glass vials from Agilent Technologies (USA). The extract (30 µL) was automatically injected into LC–ESI–TOF/MS system for analysis. All SPE steps have been presented in Fig. 3.

Each by-product was identified based on mass value (*m/z*) and retention times. Quantification was carried out using the TOF mode by extracting the narrow window extracted ion chromatogram (nwXIC) of the molecular ion for each compound (typically extracted using a 20 mDa window) compared with previous studies that used 20 and 50 mDa windows [27,28]**.**

Positive identification of the target compounds was based on (a) accurate mass measurement of the base ion with an error of ≤ ± 3.5 ppm for most compounds; and (b) LC retention time of the analyte compared with that of a standard with an error of ≤ ± 0.3% for most of compounds.

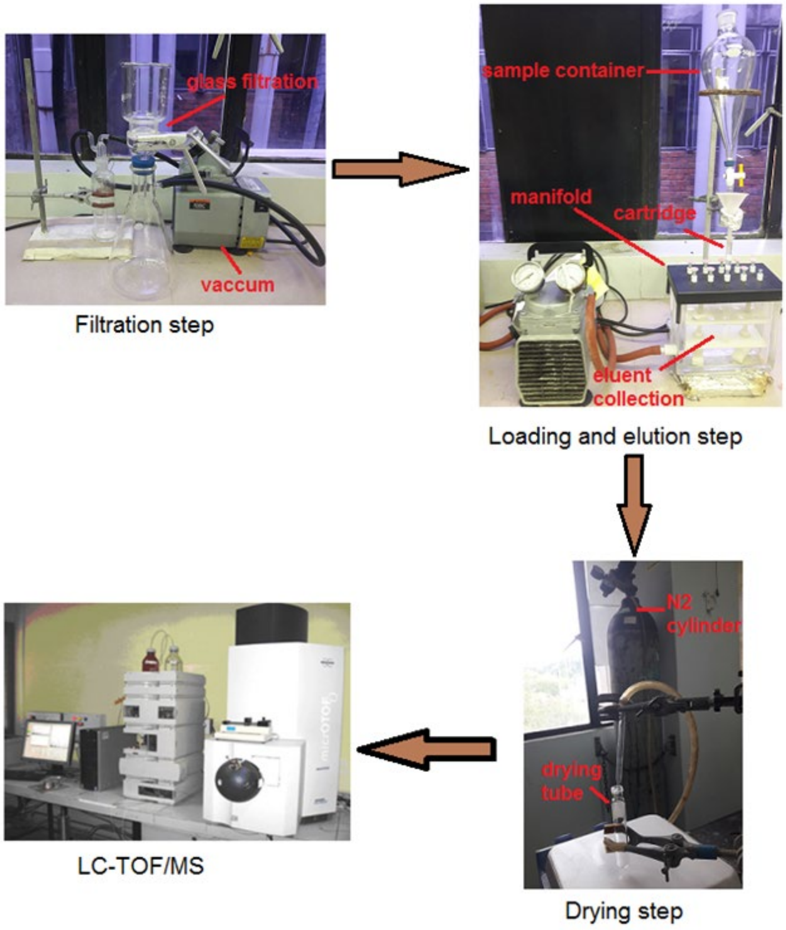

Fig. 3. Solid phase extraction setup.

Liquid Chromatography-time of flight/Mass Spectrometry

Separation of the studied pharmaceuticals was performed on the dionex Ultimate 3000/LC 09115047 (USA) system equipped with a vacuum degasser, a quaternary pump, and an auto-sampler. Sample aliquots of 30 µL were injected to Gemini 5 µm NX 110A C18 column (2 mm x 150 mm, Phenomenex). Electrospray ionization (ESI) source was utilized as ionization source.

Metoprolol and one of its by-products were analysed in positive ionization mode ESI (+). The elution off the column was achieved with a mobile phase consisting of (A) 0.1% FA in DIW and (B) ACN-MeOH (3:1, v/v) at 0.3 mL/min. the gradient elution is as follow:

5% B (0 min) → 60% B (linear increased in 3 min) → 97% B (linear increased in 3 min) → 97% B (hold 5 min) → 5% B (linear decreased in 0.1 min) → 5% B (hold 5 min)

Three by-products were analysed in negative ionization mode (ESI –) and they eluted off the column with a mobile phase consisting of a mixture of ACN-MeOH (2:3, v/v) as mobile phase (B) and 0.1% FA in DIW as mobile phase (A) at 0.3 mL/min. the gradient elution is as follow:

5% B (0 min) → 95% B (linear increased in 5 min) → 95% B (hold 5 min) → 5% B (linear decreased in 0.1 min) → 5% (hold 5 min)

Mass spectrometry was performed on ESI-TOF instrument (Bruker/Germany). The results were obtained with the following settings: MS capillary voltages, 4000/3500 [ESI (+)/ESI (−)]; drying gas flow rate, 8.0 L/min; drying gas temperature, 190 ℃; and nebulizer pressure, 4.0 bar. Two molecular ions, $[M+H]^+$ and $[M-H]^-$, were observed for ESI (+) and ESI (−) analysis, respectively. All analytes were acquired using an independent reference spray via the LockSpray interference to ensure accuracy and reproducibility. A mixture of sodium hydroxide and formic acid (FA) was used as the lock mass m/z 90.9766 to 974.8132. The accurate mass was calculated using Daltonics Data Analysis software incorporated in the instrument.

Results and discussion

Electrochemical Evaluations

Removal of metoprolol was investigated using electrochemical treatment process under different conditions such as initial concentration, applied voltage and sodium chloride. It was observed that the efficiency of electrochemical process was impacted by rate of generation the oxidizing agent ClO^- which is the most effective oxidizing agent for the removal of pollutants such as metoprolol.

Effect of Initial Concentration

Fig. 4 shows the removal% of metoprolol for each initial concentration (2, 5 and 10 mg/L). Experimental results showed that all trends of removal% have different profile which means decreased as the initial concentration increased. By comparing initial concentration of 10, 5 and 2 mg/L, their removal% are > 95% after 60 min. This phenomenon has been reported previously by Mussa et al. (2016) [29]. It was observed that low removal% was accompanied with high initial concentration (10 mg/L), at the beginning of the treatment, whilst high removal% was found with low initial concentration (2 mg/L). The reason may be attributed to the fact that the number of moles of MTP at high initial concentration is more than its number at low initial concentration.

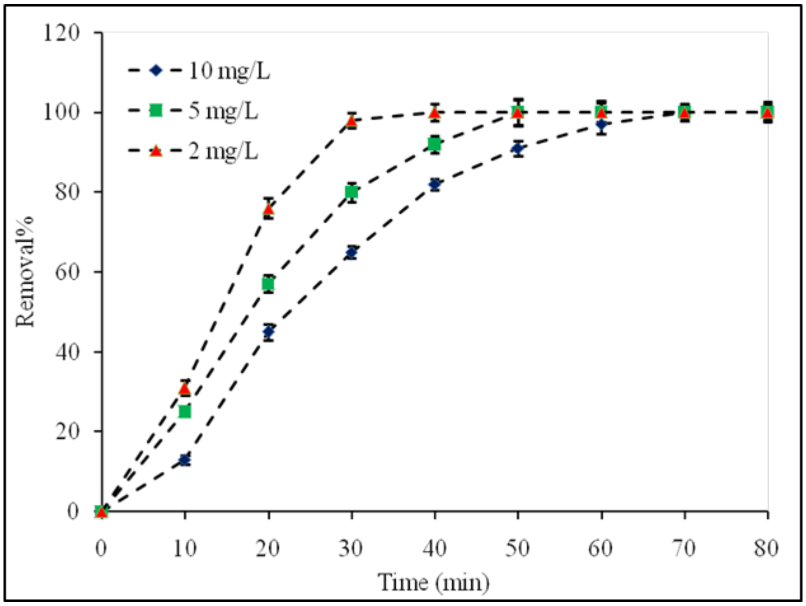

Fig. 4. Impact of initial concentration of metoprolol on the removal% (5V, 5000 mg/L NaCl, 100 mL solution).

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Effect of NaCl

Several experiments were conducted to study the removal behavior under various concentrations of NaCl (1000, 3000 and 5000 mg/L). Experimental results showed that most MTP was eliminated very effectively using graphite-PVC anode using 5000 mg/L NaCl, the removal of MTP reduced sharply at low concentration of NaCl (1000 mg/L and 3000 mg/L) as shown in Fig. 5. Almost no removal was found for the lowest concentration of 1000 mg/L of NaCl. The effect of NaCl concentration on the removal of MTP from aqueous solution by electrochemical treatment process using graphite-PVC anode can be discussed as presented in equations 1-4, by the considering the formation of active oxidizing agent (ClO^-).

In electrochemical treatment process, low consumption energy is preferred for this type of treatment unless the removal% is high. From Table 1, it was observed that the highest consumption energy of 2.804 Wh/mg and low removal% of < 10% were determined using 1000 mg/L NaCl after 70 min of electrochemical treatment process. Average energy consumption values of the electrochemical process measured are mostly similar between 3000 and 5000 mg/L NaCl.

The lowest consumption energy (0.548 Wh/mg) was determined using 5000 mg/L NaCl while 0.595 Wh/mg was determined using 3000 mg/L NaCl after 10 and 20 min, respectively. From the results, 5000 mg/L NaCl was the best choice for further experiments.

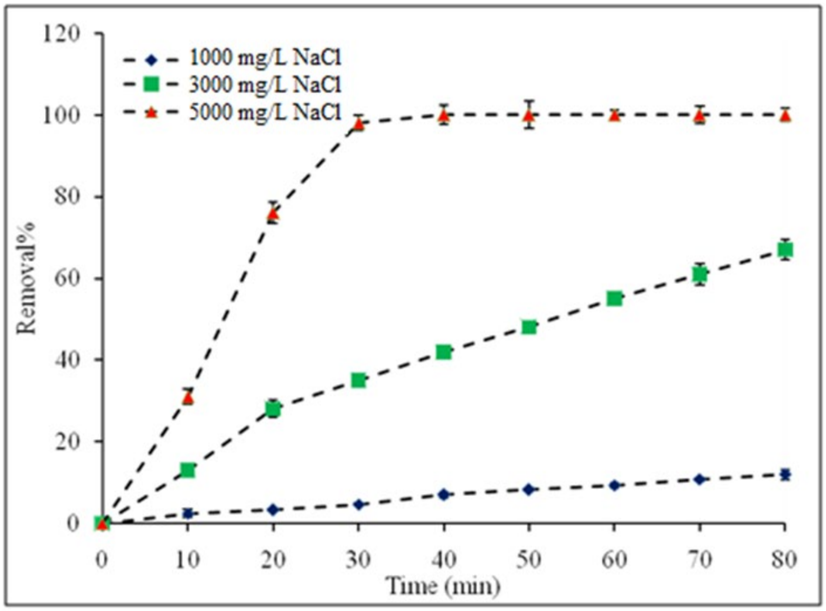

Fig. 5. Impact of NaCl concentration on the removal% (2 mg/L of MTP, 5V, 100 mL solution).

Effect of Applied Voltage

The effect of applied voltage on the electrochemical treatment of MTP was also investigated through the determination of removal% and consumption energy. Fig. 6 shows that the removal% are in range of 9.8 to 60%, 31 to 100% and 22 to 93% at 3, 5 and 7 V, respectively. Normally, a greater removal of MTP is associated with a greater value of applied voltage. Comparing the removal% of 3, 5 and 7V, it is obvious that the efficiency of electrochemical treatment at 7 V was greater than that of 3 V.

It is well known that high applied voltage may mean high consumption of energy, so this concept was considered in this study. From Table 1 consumption energy was very high at 7 V comparing to 5 V. On the other hand, removal% was almost same between 7 and 5 V under same conditions. It could be concluded that the removal% at 5 V is more preferred compared to 7 V since the consumption energy is much lower 0.666

Wh/mg compared to 7V of 1.117 Wh/mg. Although energy consumption at 5 and 3 V is almost similar, 5 V was selected due to high removal% was gained 98% compared to 3 V (31.2%) after 30 min.

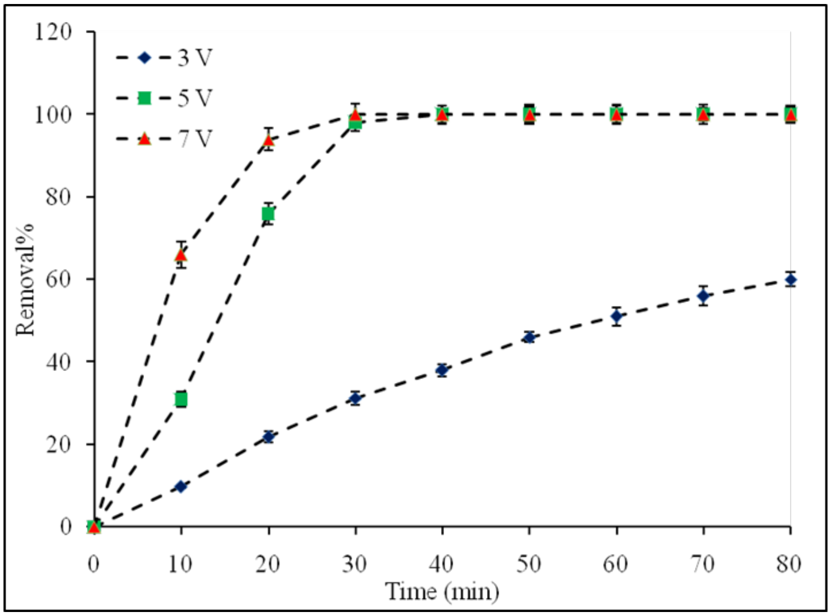

Fig. 6. Impact of applied voltage on the removal% (2 mg/L of MTP, 5000 mg/L NaCl, 100 mL solution).

Table 1. Energy consumption of metoprolol.

Time	**Applied voltage**			**NaCl concentration**		
	3V	**5V**	**7V**	**1000 mg/L**	**3000 mg/L**	**5000 mg/L**
10	0.510	0.548	0.795	1.812	0.641	0.548
20	0.459	0.595	1.117	2.525	0.595	0.595
30	0.481	0.665	-	2.717	0.714	0.665
40	0.526	-	-	2.451	0.794	-
50	0.543	-	-	2.541	0.868	-
60	0.588	-	-	2.660	0.909	-
70	0.625	-	-	2.804	0.956	-
80	0.667	-	-	2.778	0.995	-

Electro-reaction Kinetics

The kinetic studies of the degradation metoprolol were investigated under different conditions: NaCl concentration, applied voltage and initial concentration as presented in Table 2. It is well known that most of catalytic reactions could follow a second-order reaction, as described by the equation 5 [30,31].

$$\frac{\mathrm{d[MTP]_t}}{\mathrm{dt}} = -\mathrm{k_{obs}[ClO]_t^-[MTP]_t} \quad (5)$$

where, k_{app} is the apparent second-order rate coefficient; $[\mathrm{ClO}^-]_t$ is the total concentration of ClO^- species at the reaction time of t; $[\mathrm{MTP}]_t$ is the total concentration of the MTP at the reaction time of t.

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In the presence of a high excess of ClO^-, the concentration remains always constant throughout the reaction (i.e. $[ClO^-]_t = [ClO^-]_o$). Hence, k_{app} . $[ClO^-]_t$ could be regarded as a constant so the pseudo-first-order kinetic constant k_{obs} is introduced as obtained in equation 6.

$$\frac{d[MTP]_t}{dt} = -k_{obs}[MTP]_t \tag{6}$$

After integration equation 6 then rearranged it, we get equation 7 as presented here:

$$\ln([MTP]_t/[MTP]_0) = -k_{obs}t \tag{7}$$

According to this equation, ln $([MTP]_t/[MTP]_0)$ was plotted versus time to generate straight line, correlation coefficient (R^2) ≥0.9334, with a slope of $-k_{obs}$. Electrocatalytic-kinetics rate constants were presented in Table 2. It was observed that in the presence of NaCl and high applied voltage, the rate constant value becomes more enhanced. The reason may due to the generation of ClO^-which is contributed strongly for the elimination purpose.

However, the value of k_{obs} of 0.0801 min^{-1} was the greatest at 5000 mg/L NaCl compared to 0.1 g and 0.3 g NaCl which was 0.0016 and 0.0136 min^{-1}, respectively. In case of applied voltage, high k_{obs} of 0.0801 min^{-1} was observed at 5 V which is (8) times greater than k_{obs} at 3 V. For further investigation, electro-reaction kinetics was tested at different initial concentration of MTP. It was observed that the greatest rate constant was at initial concentration of 2 mg/L whilst the smallest rate constant was recorded at initial concentration of 10 mg/L. k_{obs} values were arranged as follow: 0.0801, 0.0564 and 0.0427 min^{-1} for 2, 5 and 10 mg/L, respectively. These results are quite good compared to the previous work which is provided on electrochemical fenton on metoprol [32,33]. The reason why low k_{obs} was obtained with high initial concentration at fixed volume (100 mL) may due to the fact that the number of molecules of MTP at 10 mg/L are more than its number of molecules at 2 mg/L hence only few molecules could be removed at high concentration compared to the low concentration under same conditions.

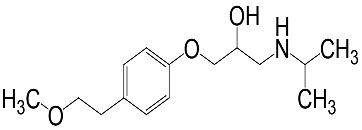
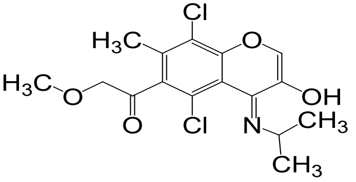
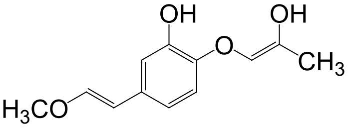
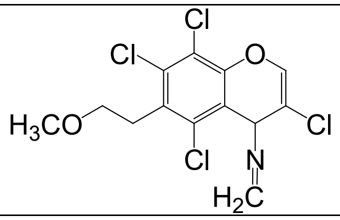
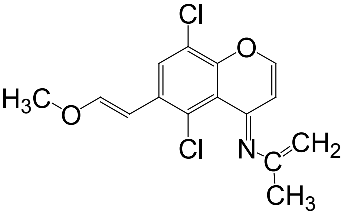
Table 2. Pseudo first order rate constants for metoprolol under different conditions such as initial concentration, sodium chloride concentration and applied voltage.

Parameters	Quantity	No. points	Rate constant (min^{-1})	Correlation coefficient (R^2)
Initial concentration (mg/L)	2	6	0.0801	0.9169
	5	8	0.0564	0.9442
	10	9	0.0427	0.9388
Sodium chloride (mg/L)	1000	9	0.0016	0.9917
	3000	9	0.0136	0.9951
	5000	6	0.0801	0.9169
Applied voltage (V)	3	9	0.0118	0.9972
	5	6	0.0801	0.9169

Identification of the by-products

So far, few studies have been reported about the electrochemical degradation of metoporlol and its by-products. In order to accomplish this objective, the samples were analyzed by LC-TOF/MS after electrochemical degradation process. Table 3 presents the retention times, elemental composition, chemical structure, signal to noise ratio and ring double bond for the by-products of metoporlol as obtained by LC-ToF/MS instrument. The error was ranged between 2 and 2.9 ppm.

Table 3. Accurate mass measurements obtained by LC-TOF/MS for the by-products after electrochemical oxidation treatment of metoprolol.

No.	**t_R (min)**	**Composition molecular ion**	**Chemical structure**	**Error ppm**	***m/z***	***RDB***
MTP	5.101	C15H26NO3 $[M+H]^+$		192	268.1009	3.5
PI-P1	9.200	$C_{16}H_{18}Cl_2NO_4$ $[M+H]^+$		1892	358.0716	7.5
NI-P1	8.197	$C_{12}H_{13}O_4$ $[M-H]^-$		177	221.0773	6.5
NI-P2	9.067	$C_{13}H_{10}Cl_4NO_2$ $[M-H]^-$		44	351.9329	7.5
NI-P3	11.275	$C_{15}H_{12}Cl_2NO_2$ $[M-H]^-$		30	308.0200	9.5

One by-product PI-P1 was detected in positive ion mode and it is corresponded to compound with molecular formula $C_{16}H_{18}Cl_2NO_4$ (*m/z*358.0716). Three by-products were detected in negative ionisation mode; NI-P1, NI-P2 and NI-P3 could correspond to $C_{12}H_{13}O_4$ (*m/z*221.0773), $C_{13}H_{10}Cl_4NO_2$ (*m/z*351.9329) and $C_{15}H_{12}Cl_2NO_2$ (*m/z*308.0200), respectively. All LC chromatograms of by-products were presented in Fig. 7 combined with the mass spectra for each product.

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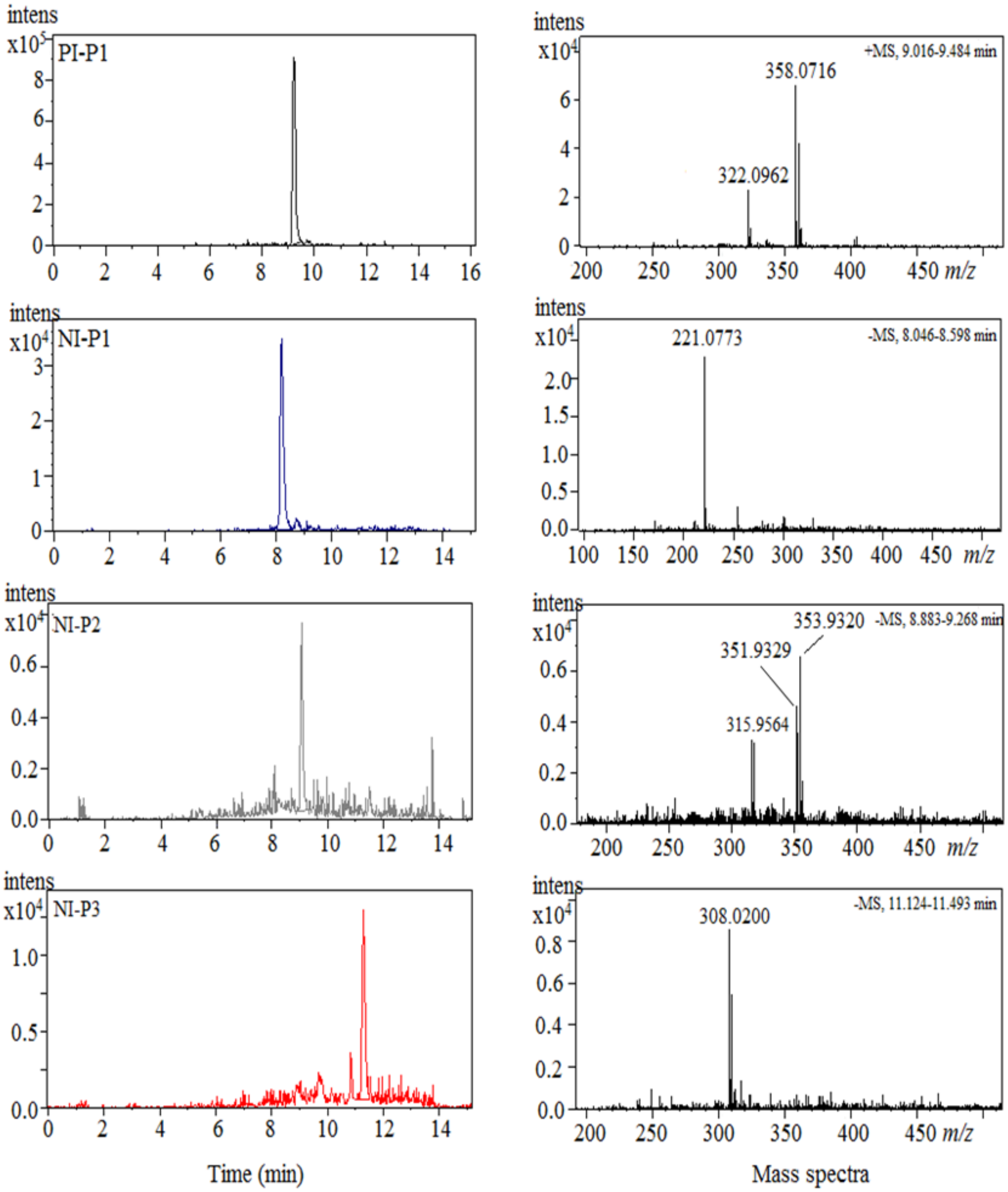

Fig. 7. Extracted ion chromatogram vs mass spectrometry profile for one by-products detected in PI mode (PI-P1) and three by-products detected in NI mode (NI-P1 to NI-P3) of metoprolol after electrochemical treatment under 5V, 5000 mg/L NaCl, 20 min and 200 µg/L.

Elucidation of the by-products

This study reports to elucidate clearly the formation of chlorinated by-products of metoprolol in two ionization modes positive ionization (PI) and negative ionization (NI). It is important that most of by-products had at least two chlorine atoms in their structure molecule, thus indicating that chlorination reactions can occur

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during the electrochemical oxidation process treatment when solution contains chlorine. Two different chlorinated by-products can be elucidated ($C_{16}H_{18}Cl_2NO_4$, PI-P1 and $C_{13}H_{10}Cl_4NO_2$, NI-P2). Fig. 8a shows the spectra of by-product with two chlorine atoms (358.0716). The most striking aspects of these spectra are the clusters of intense peaks that are each separated by 2 *m/z* units. However, the peaks at *m/z* 358, 360 and 362 in the spectrum of [$C_{16}H_{18}Cl_2NO_4$] has isotopic patterns that refers to M, M+2, and M+4, respectively. Careful examination of this compound shows that the peaks at *m/z*358, 360 and 362 in compound PI-P1 spectrum has approximate intensities 100.0%, 67% and 11%, respectively relative to each other, which confirms the presence of two Cl atoms. On the other hand, product NI-P3 ($C_{15}H_{12}Cl_2NO_2$, *m/z* 308.0200) in negative ionization mode shows that this compound has same profile of PI-P1 product. The tetra-chlorine adduct was presented in product NI-P2 ($C_{13}H_{10}Cl_4NO_2$, *m/z* 351.9329) resulting five peaks M, M+2, M+4, M+6 and M+8 which are represented *m/z* 351.9, 353.9, 355.9, 358.0 and 360.0, respectively with probability percentages 75%, 100%, 50%, 11% and 1%, respectively (Fig. 8b).

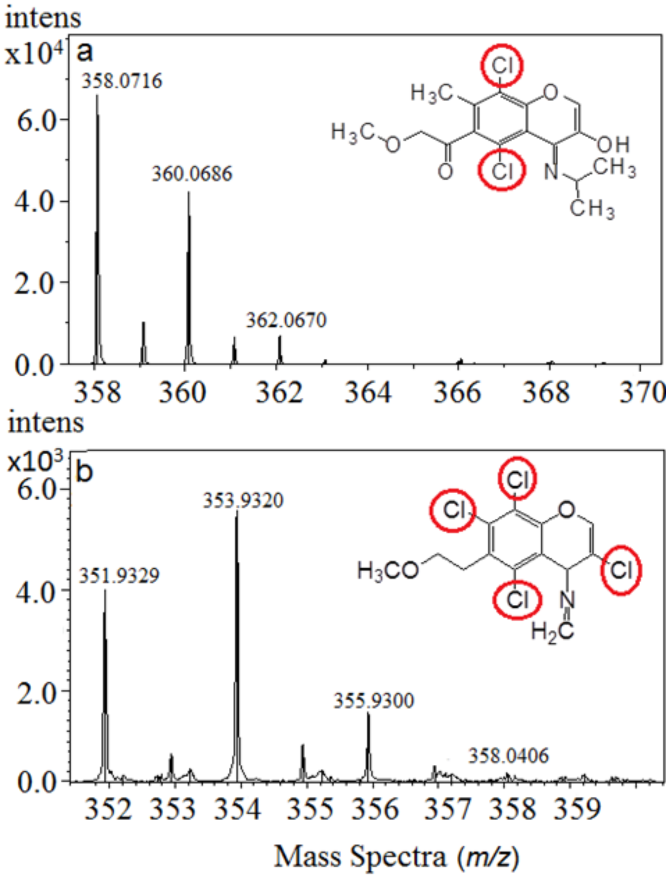

Fig. 8. Elucidation profile of the chlorinated by-products during electrochemical oxidation process of metoprolol; (**a**) di-chlorine atoms; (**b**) tetra-chlorine atoms.

The oxidation pathway shown in Scheme 1 involves cycling the open chain of metoprolol as the ring double bond increased. However, product NI-P1 (*m/z* 221) has eluted at tR8.197 min. The mass spectrum of NI-P1 did not indicate the presence of halogens. Furthermore, the product [M-C_3H_8N-4H+O] loss 47 Da due to losing the terminal chain (C_3H_7N).Loss of water, hydrogen abstraction and forming cycle in the ESI− product ion mass spectra of (NI-P3, m/z 308) indicated that the increasing of ring double bond from four to nine as

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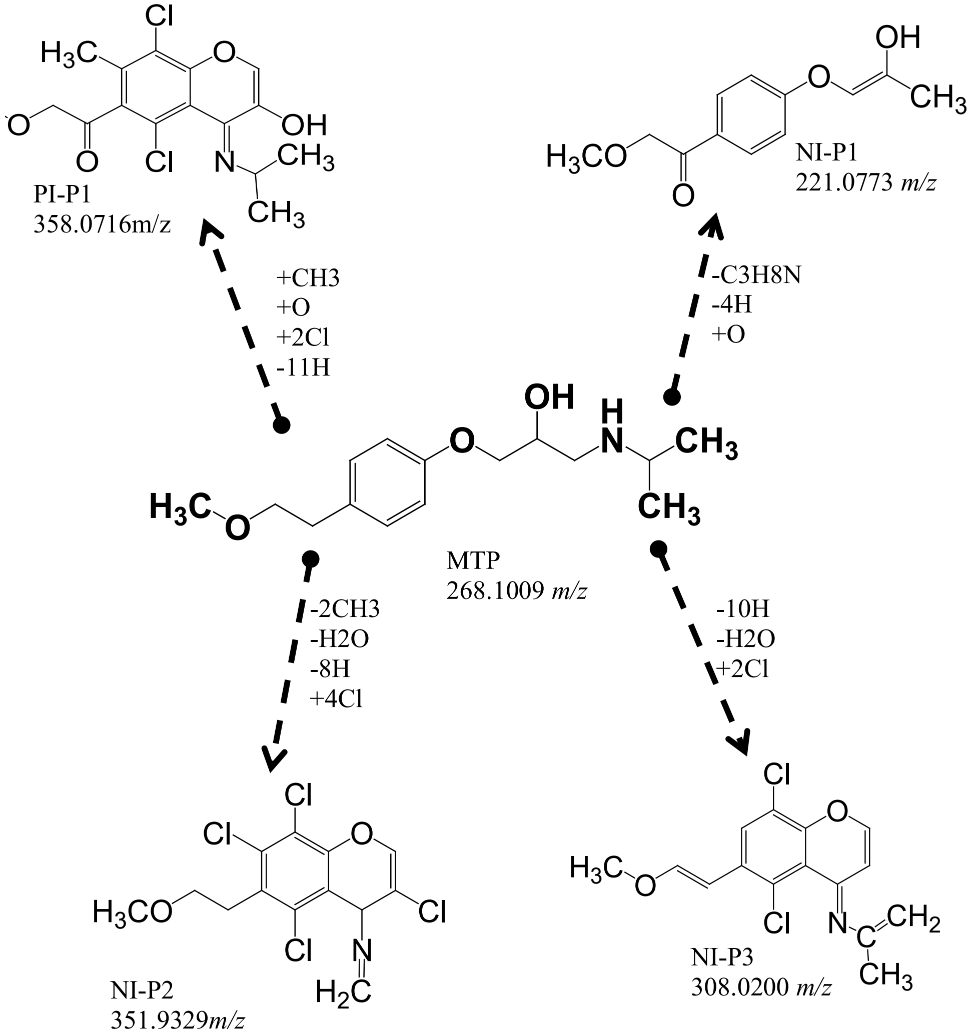
shown in Table 3. The mass value of the product was increased by 40 Da due to two chlorine atoms have been added. In the same manner to NI-P3, two by-products PI-P1 and NI-P2 were formed by the addition of 90 and 84 Da, respectively. For the PI-P1, two chlorine atoms and one methyl group have been substituted on the benzene ring producing $C_{16}H_{18}Cl_2NO_4$ while NI-P2 loss two methyl groups and water molecule but four chlorine atoms have been substituted on the benzene ring forming product of $C_{13}H_{10}Cl_4NO_2$.



Scheme 1. Proposed pathway degradation after electrochemical degradation process of metoprolol under these conditions: 5000 mg/L NaCl, 5V, 200µg/L, 100 mL of solution.

Monitoring of By-products After Electrochemical Oxidation Process

The monitoring of the chromatographic areas of the by-products of metoprolol during the electrochemical process is necessary to evaluate the efficiency of electrochemical process. 100 ml of metoprolol solutions were treated electrochemically using graphite-PVC electrode under 5V, 5000 mg/L NaCl and 200 µg/L. The evolution of the chromatographic areas with electrochemical oxidation time for the by-products was shown in Fig. 9. It was observed that the degradation of metoprolol is simultaneously accompanied by the

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appearance of the oxidation by-products, which are already formed in the first 20 minutes of the treatment. As observed in the degradation curves for PI and NI modes, the most of by-products increased steadily at 20 min of electrochemical oxidation treatment then decreased with the time of electrolysis. PI-P1 by-product was increased until 20 min then reduced with time, it was completely removed after 80 min. The by-product NI-P1 has the highest peak area compared to others while NI-P2 has the lowest peak area in NI mode. In the light of the above results, it was observed that all chlorinated and non-chlorinated by-products were completely removed after 120 min indicating that the efficiency of electrochemical process to degrade the by-products after they formed.

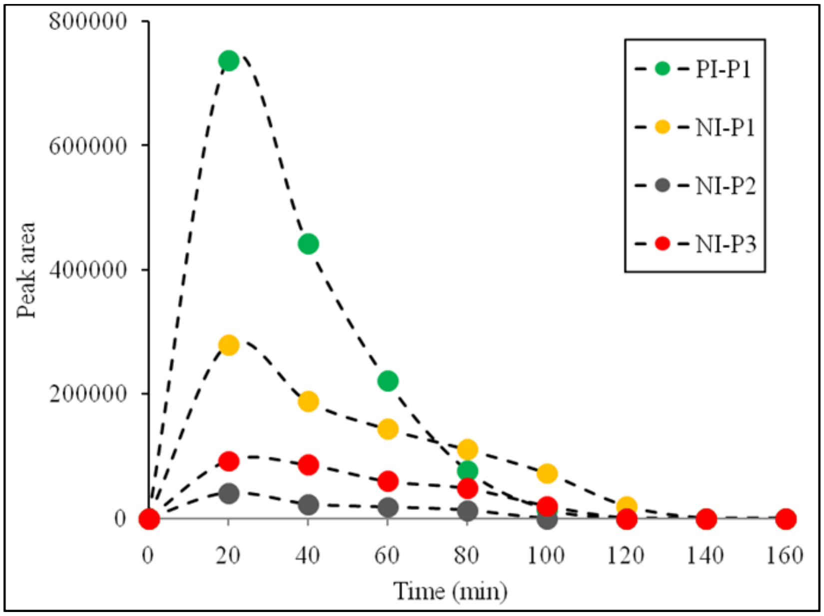

Fig. 9 Monitoring the by-products after electrochemical degradation of metoprolol: 100 mL of solution,5 V, 5000 mg/L NaCl, and 200μg/L metoprolol.

Conclusion

In this research work, metoprolol was treated using electrochemical oxidation process. The electrochemical process showed that MTP and its by-products were eliminated within 140-160 min using graphite-PVC composite electrode. This present study was reported for the first time explaining the elucidation of the formation chlorinated by-products. Electrochemical treatment for MTP was investigated in the presence of NaCl as supporting electrolyte under different applied voltage. Pseudo first-order kinetics was the dominant during the treatment process in which the rate constant was ranged between 0.0016 and 0.0801 min^{-1}. The formation of chlorinated products was enhanced strongly at the first 20 min then most of by-products were eliminated after 80 min. Four by-products were formed and analysed using LC-TOF/MS.

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