Impact of gamma-irradiation on the degradation and mineralization of hydroxychloroquine aqueous solutions

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Abstract
In this work, the effect of gamma irradiation emitted by Cobalt 60 source has been investigated for the degradation of hydroxychloroquine (HCQ). The monitoring of the gamma irradiation treatment of HCQ aqueous solutions was followed by UV–visible, chemical oxygen demand, total organic carbon (TOC) and LC/MS analyses. Effects of several important parameters such as concentration, dose rate and pH on the degradation efficiency were studied then evaluated. Achieved results showed that % TOC removal efficiency of 98.5 was obtained after 8 kGy absorbed dose which warrants HCQ mineralization. The process was found to be more efficient when the initial pollutant concentration was low, with higher dose rate and at neutral pH. Furthermore, HCQ degradation kinetic study revealed a pseudo-first-order kinetic. Additionally, based on by-products identified by LC/MS, a degradation mechanistic schema mediated through hydroxyl radicals generated by water radiolysis has been proposed. Finally, in order to check the potential industrial application viability the energy consuming was evaluated.

Keywords Gamma irradiation · Hydroxychloroquine removal · Advanced oxidation process · LC/MS · Energy consumption

Introduction
Hydroxychloroquine also named 2-[[4-[(7-chloroquinolin-4-yl) amino] pentyl] (ethyl) amino] ethanol is widely used in drugs for treatment of several rheumatology and dermatology diseases (Bensalah et al. 2020; Fox et al. 1993). HCQ is particularly indicated to prevent malaria and to treat systemic lupus erythematosus, rheumatoid arthritis and polymorphic eruption (Ben-Zvi et al. 2012; Schrezenmeier et al. 2020). Recently, during the COVID 19 pandemic, national and international organisations permitted the therapeutic option for hospitalized patients suffering with coronavirus by chloroquine and hydroxychloroquine (Gao et al. 2020; Mahase 2020) but the prescription of HCQ to treat COVID-19 is only an unproven hypothesis still being evaluated (Axfors et al. 2021).

Thus, enormous quantities of HCQ are needed to treat different diseases over the world (Zhanel et al. 2021) leading consequently the discharge of domestic wastewaters contaminated with HCQ into the environment. HCQ belongs to aminooquinolone class, so it is, high potential to persist, bioaccumulate, and exhibit toxicity (Pal et al. 2020; Wani et al. 2015). The high contamination risks of natural water due to the large-scale production and use of HCQ need greater attention to mitigate its harmful impacts on human/animal health and the environment.

It is therefore essential to develop new and promoted methods for identifying, quantifying and treating drug wastes and residues in order to reduce and/or treat the contaminated sites. In this context, many research studies were performed to treat drugs residues in water (Ighalo et al. 2021; Satyanarayana et al. 2020). Part of them, conventional methods (flocculation, coagulation…) which results showed that these techniques are insufficient, unable to reach degradation of organic pollutants and present several limitations for wastewater treatment (Liu et al. 2013; Liu et al. 2012; Merzouk et al. 2011). Nevertheless, promising alternatives...
based on Advanced Oxidation Processes (AOP’s) have appeared for wastewater treatment due to their capability to mineralize or to transform organic compounds into substances easily biodegrade (Ghime et al. 2019; Ma et al. 2021; Mohajerani et al. 2009; Oturan et al. 2014; Wang et al. 2012). It is well established that all AOP (Photo-Fenton, electro-Fenton, photocatalysis, ozonation, sonolysis, anodic oxidation and ionizing radiation) have a common denominator due to radical species production, especially hydroxyl radical which has a powerful oxidizing agents with a high ability to react with organic substance leading to their total mineralization into carbon dioxide and water (Askri et al. 2020; Chen et al. 2020; Dabić et al. 2019; Ennouri et al. 2021; Ismail et al. 2021; Zaouak et al. 2013, 2014, 2015, 2018, 2021a, b; Wein et al. 2020).

To our knowledge, there are few studies devoted to HCQ degradation in water. Recently, Dabić et al. (2019) demonstrated the effectiveness sunlight photolysis degradation of HCQ using both nuclear magnetic resonance spectroscopy and high performance liquid chromatography-mass spectrometry. In the same vein, Bensalah et al (2020) reported the complete degradation of HCQ in aqueous solutions by association of electrochemical oxidation on BDD anode with UV irradiation and sonication. It was found that combination enhance the removal efficiency regardless initial pH value and current density. Despite these few studies, it is important to point out that from a degradation point of view of HCQ, particularly information about degradation mechanism schema remains scanty and not yet understood. In this context, this work was designed to investigate the degradation of HCQ using gamma irradiation, as it was advised by international agencies (IAEA, FAO and WHO) to accomplish favourable goals in removal of hazardous wastes (He et al. 2014) and reduce climate change effects. HCQ samples were irradiated with doses of 1 to 8 kGy and treatment monitoring has been carried out using UV−visible, COD, TOC and LC/MS analyses. Also, effects of concentration, dose rate and pH on the degradation efficiency were evaluated. Stimulatingly, the HCQ kinetic and the energy consumption throughout treatment were determined to check viability of the process for future industrial application. Finally, a degradation mechanism scheme of HCQ mediated by hydroxyl radical was illustrated.

**Materials and methods**

**Chemical**

HCQ is deriving from the 4-aminoquinolines class, chemically named 2-[(4-[(7-chloroquinolin-4-yl) amino] pentyl] (ethyl) amino] ethanol was supplied by Sanofi (Tunisia). Its empirical formula is C_{19}H_{28}ClN_{3} with molecular weight of 333.89 g mol⁻¹ (Lee et al. 2011; Zaouak et al. 2019). The structural formula is shown in Fig. 1.

**Experiments**

**Irradiation methodology**

All HCQ samples were irradiated by gamma rays emitted by the Tunisian Cobalt 60 facility. For an accurate control of the irradiation time, a specific determination of the dose rate is compulsory. Dose rates of 26.31 and 6.81 Gy min⁻¹ were determined with Red Perspex dosimeters (Getoff. 1996; M’Garrech et al. 2012). Appropriate doses ranging from 1 to 8 kGy, with 1 kGy interval between two consecutives experiments, were adopted to irradiate HCQ aqueous solutions. It is important to mention that when gamma rays interact with water, unstable and stable oxidizing and reducing species are formed following Eq. 1 (Buxton et al. 1988; Guo et al. 2012; Midassi et al. 2020).

\[
\text{H}_2\text{O} \xrightarrow{\gamma} e_{\text{aq}}^- + \cdot OH, \text{H}_3\text{O}^+, \text{H}_2, \text{H}_2\text{O}_2, \text{OH}^- \quad (1)
\]

**Analyses**

**Spectroscopic analysis**

UV−visible spectrophotometer type Shimadzu UV-1700 was used for quantitative analysis of HCQ solutions. Irradiated aqueous solutions were also followed by COD and TOC measurements. COD measurements were carried out using a HI 83,212 type analyser. COD analysis is referred to standard methods for the examination of water and wastewater in a strong acid medium using as an oxidizer the dichromate solution. However, TOC measurements have been recorded using TOC Shimatzu type analyser, initially calibrated by means of organic compounds solutions.

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![Fig. 1 Structural chemical formula of HCQ](image-url)
**HPLC/MS analysis**

HPLC (Agilent 1100), with a diode array detector was used for LC analysis. The separation was made under gradient elution mode with C18 column (150 x 2.1 mm, 5 μm). The mobile phase was a mixture of eluent A (buffered water phosphate salt pH = 3.5) and eluent B (acetonitrile, CH₃CN) at a fixed flow rate of 1 mL/min at 30 °C column temperature. A volume of 10 μL of each sample was injected. The gradient elution begun with 80% of eluent A during 5 min, then eluent A decreased to 40% within 15 min, and after that the elution gradient remains constant (40% A + 60% B) until the end of analysis. The UV detector was set at 340 nm wavelength. MS analysis was operated in the positive electrospray ionization mode over the mass range m/z 50 to 450. Nebulizing and drying gas was nitrogen.

**Results and discussion**

**Evolution of absorption spectra of hydroxychloroquine**

Figure 2 illustrates the evolution in absorption spectra of HCQ aqueous solutions after the application of different gamma absorbed doses varying from 1 to 8 kGy. UV–visible spectrum of non-irradiated HCQ solution shows four absorption peaks located at $\lambda = 222, 237, 332$ and 345 nm. The two first peaks are possibly due to $\pi \rightarrow \pi^*$ transition in aromatic/conjugated systems. Both peaks located at 332 and 345 nm are owing to $n \rightarrow \pi^*$ transition and could be referred to the conjugation of quinoline with N-ethyl group.

As presented in Fig. 2, the intensity of all bands decreases as a function of absorbed doses and disappear totally beyond 8 kGy. This decreasing behaviour demonstrates that the cleavage of the starting molecule leads to the opening of the aromatic rings in favour of aliphatic compounds. The same behaviour was amply described in the literature and could be explained by the important role of the hydroxyl radicals, issuing by water radiolysis, which react rapidly and with non-selectively with organic matter leading to low molecular weight products like carboxylic acids which ultimately transformed into carbon dioxide and water after successive hydroxyl radical’s attacks (LaVerne. 2000; Ponomarev et al. 2020; Sánchez-Polo et al. 2009; Zaouak et al. 2020, 2021a, b).

By exploiting the proportionality relationship between the absorbance and the concentration, it is possible to demonstrate that the HCQ degradation reaction follows a pseudo-first-order kinetic since \( \ln [\text{HCQ}] / [\text{HCQ}]_0 \) varies linear with time (Fig. 3). Under this condition, the kinetic equation to be considered is:

\[
\frac{d[\text{HCQ}]}{dt} = -k_{\text{HCQ}} [\text{HCQ}]^1 [\text{OH}^*]^n \tag{2}
\]

Applying a quasi-steady state approximation for hydroxyl radical entities, by arguing that these chemical species are as transient ones as their concentration, the previous equation can be written more simply:

\[
\frac{d[\text{HCQ}]}{dt} = -k_{\text{app}, \text{HCQ}} [\text{HCQ}] \tag{3}
\]

and the integrated kinetic equation has for expression:
The corresponding apparent rate constant value obtained is approximately \( k_{\text{app}} = (0.0093 \pm 0.0025 \text{ min}^{-1}) \). An adj-\( R^2 = 0.997 \) has been found proving an excellent fitting procedure.

Concentration effect on the degradation of hydroxychloroquine

When aqueous solution of HCQ is subjected to gamma irradiation field, degradation of HCQ takes place as a result of its reaction with \( \text{OH} \cdot \), \( \text{e}^-_{\text{aq}} \) and \( \text{H} \cdot \) (the main reactive species of water radiolysis (reaction (1))). The simplified radiolytic degradation mechanism of HCQ could be explained by the following reactions:

\[
\text{HCQ} + \text{OH} \cdot / e^-_{\text{aq}} / \text{H} \longrightarrow \text{Intermediates} \quad (5)
\]

\[
\text{Intermediates} + \text{OH} \cdot / e^-_{\text{aq}} / \text{H} \longrightarrow \text{By – products} \quad (6)
\]

The effect of initial substrate concentration (100, 150 and 200 ppm) on radiolytic degradation efficiency of HCQ was studied. It can be obviously seen from Fig. 4 that the degradation efficiency decreases with the increase in the concentration. This result indicates that the increase in pollutant concentration has a negative influence on degradation efficiency. Indeed, the radiolytic degradation efficiency under the concentration of 100 ppm is much higher than that under the concentration of 150 and 200 ppm. Only 65% removal efficiency was obtained for 200 ppm initial concentration while 97% for 100 ppm. This result is in agreement with published findings for the radiolytic decomposition of some other organic pollutants (Khan et al. (2014, 2015), Sayed et al. (2016). It may be explained by the fact that at higher concentration, excess by-products could be produced, which may possibly scavenge the reactive radicals and thereby decreasing the effective concentration of these radicals. As a first observation, low removal efficiency was obtained when high initial HCQ concentration was used.

Dose rate effect on hydroxychloroquine degradation

Two different dose rates (26.31 and 6.18 Gy/min) have been applied in the degradation of HCQ study. Figure 5 shows that at higher dose rate, the % of HCQ degradation reaches 98% while 85% when the dose rate is lower. These results were expected due to self-combinations of reactive species issuing from water radiolysis (Eqs. 7, 8, 9) able to degrade HCQ and leading to reduce the effective concentration of these radicals which subsequently decreased the efficiency of HCQ at low dose rates (Drzewicz et al. 1999; LaVerne. 2000).

\[
\text{OH} \cdot + \text{OH} \cdot \longrightarrow \text{H}_2 \text{O}_2 \quad (7)
\]

\[
\text{OH} \cdot + \text{H} \longrightarrow \text{H}_2 \text{O} \quad (8)
\]

\[
\text{OH} \cdot + e^-_{\text{aq}} \longrightarrow \text{OH}^- \quad (9)
\]
Effect of pH on hydroxychloroquine degradation

pH is an important parameter in the gamma irradiation degradation studies. Consequently, three pH values were applied (pH = 10, pH = 6.2 and pH = 3) in order to monitor the progress of the removal efficiency of HCQ. Graphs of Fig. 6 show that the HCQ elimination percentage as a function of the irradiation dose is higher at pH 6.2 and pH 10 than at acidic pH. In fact, this achieved result could be explained that in acidic medium, the concentration of oxidizing and reducing entities which are responsible for degradation, decreases due to their implications in reactions with hydrogen ions (Eqs. 10 and 11).

\[ \text{H}^+ + \text{OH}^- \rightarrow \text{H}_2\text{O} \]  
(10)

\[ \text{e}^-_{\text{aq}} + \text{H}^+ \rightarrow \text{H}^- \]  
(11)

At alkaline medium, a better percentage of elimination was obtained, reflecting the presence of a higher number of reactive species in the solution due to the reaction of hydrogen radicals with hydroxide ions to form solvated electrons (Eq. 12) (Brillas et al. 2009).

\[ \text{H}^+ + \text{OH}^- \rightarrow \text{e}^-_{\text{aq}} + \text{H}_2\text{O} \]  
(12)

However, increasing the concentration of solvated electrons at high pH leads to a decrease in the concentration of hydroxyl radicals so that the redox reaction is extremely rapid (Brillas et al. 2009; Zaouak et al. 2020). For all these reasons, the best efficiency is obtained at pH = 6.2 when all reactive species are free and are not involved in others reactions.

Influence of irradiation on the degree of mineralization

The progress of mineralization has been investigated by using both COD and TOC analyses. Their respective amounts have been calculated using the following equations:

\[ \% \text{COD} = \frac{\text{COD}_0 - \text{COD}_t}{\text{COD}_0} \times 100 \]  
(13)

\[ \% \text{TOC} = \frac{\text{TOC}_0 - \text{TOC}_t}{\text{TOC}_0} \times 100 \]  
(14)

where COD_0, TOC_0 and TOC_t, TOC_t are COD and TOC quantities at initial time t = 0 and at a given time t, respectively.

Figure 7 illustrates the variation of TOC and COD removal efficiencies as a function as the absorbed dose. Both percentages elimination of COD and TOC increase with increasing applied dose. It can be also noted a rapid COD elimination at the beginning of the treatment followed by slowing down towards the end. This presents an evidence that aromatic rings degradation occurs upon application of low doses. While the slowing down obtained later is due to a slower carboxylic acids degradation, which are more refractory to treatment (Drzewicz et al. 1999; La Verne et al. 2000; Mhemdi et al. 2013).

The same findings were observed for the %TOC variation. A rapid increase in TOC at the beginning of treatment is owing to high degradation kinetics of cyclic intermediates.
The slowing down phase obtained later is in favour of much slower degradation of formed aliphatic intermediates by cleavage of the long chains into carbon dioxide and water. Similar results have been obtained in previous studies (LaVerne et al. 2000; Ponomarev et al. 2020; Sánchez-Polo et al. 2009; Zaouak et al. 2020, 2021a, b).

**Identification of degradation products**

The radiation-induced degradation of HCQ leads to several by-products, among them 7-chloro-4-quinolinamine, 4-Amino-7-hydroxy-benzopyridine and 1-(N-ethyl-N-hydroxy-methylen-amino)-4-aminopentane. Table 1 illustrates LC/MS identified intermediates with their respective chemical structure, formula and m/z values.

On the basis of the obtained results and according to similar studies on the HCQ treatment (Bensalah et al. 2020; Midassi et al. 2020), HCQ degradation schema is proposed in Fig. 8. The process was probably initiated by OH attack leading to dealkylation the aromatic part through breaking up of C-N bond in the aliphatic tertiary amine chain (attached to the nitrogen atom substituting the aromatic pyridine ring) to form 7-chloro-4-quinolinamine and 1-(N-ethyl-N-hydroxy-methylenamino)-4-aminopentane as main by-products. Immediately 4-Amino-7-hydroxy-benzopyridine was formed after hydroxyl radical attack onto 7-hydroxy-4-quinolinamine breaking the C–Cl bond and releasing chloride ions. It has been reported that the chlorine group is responsible for the toxicity of organic compounds. Therefore, the de-chlorination achieved in HCQ treatment attest the decrease in overall toxicity of aqueous solution. All by-products undergo oxidative decomposition through hydroxyl radical attack opening aromatic rings to carboxylic acids (among them oxamic and oxalic acids) and release inorganic nitrogen species predominantly in the form of NO₃⁻ and NH₄⁺ (Bensalah et al. 2020). The carboxylic acids are slowly oxidized, and require the consumption of high irradiation dose to be slowly mineralized into carbon dioxide and water.

**Evaluation of the energy consumption**

To determine the viability of the process into industrial applications, it is important to consider the cost of such treatment. For this reason, we have tried to estimate the energy consumed per mass of TOC removed during the treatment by ionizing radiation. Equation 15 gives the equation that

| Table 1 The intermediate degradation products of HCQ |
| --- |
| **Number** | **Compound Name** | **Chemical Structure** | **Formula** | **m/z value** |
| 1 | Hydroxychloroquine | ![Chemical Structure](image) | C₁₈H₂₅ClNO₃ | 336 |
| 2 | 7-chloro-4-quinolinamine | ![Chemical Structure](image) | C₃H₇ClN₂ | 179 |
| 3 | 1-(N-ethyl-N-hydroxy-methylen-amino)-4-aminopentane | ![Chemical Structure](image) | C₁₉H₂₁NO₂ | 176 |
| 4 | 4-Amino-7-hydroxy-benzopyridine | ![Chemical Structure](image) | C₆H₇N₂O | 161 |
has been used to determine the energy consumption (Brillas et al. 2009, Zaouak et al. 2021a, b).

Energy consumption \( (\text{kWh} (\text{g TOC})^{-1}) = \frac{P \times t}{\Delta (\text{TOC})_{\text{exp}}} \times V_S \) \hspace{1cm} (15)
where \( P \) (in kW) is the electrical power of the gamma irradiator facility, \( t \) (in hours) is the irradiation time, \( V_S \) is the solution volume (L), and \( \Delta (\text{TOC})_{\text{exp}} \) is the experimental TOC decay (mg/L).

Figure 9 shows that the energy consumed increases significantly for high TOC removal efficiency. This behaviour is probably due to the formation of intermediates which are more refractory and hardly oxidizable such as carboxylic acids. It can be noted that, under the best operating conditions, the mineralization of HCQ, needs 4.35 kWh (g TOC)\(^{-1}\). Therefore, in practice, an amount of 50 to 60% of TOC removals are generally sufficient to eliminate organic matter which are responsible for the toxicity by formation of short aliphatic chain such carboxylic acids known to be non-toxic and biodegradable. Thus, being satisfied with 60% mineralization of the initial value of TOC in our case, the energy cost will be approximately of 0.68 kWh per g of TOC removed. This will be achieved only with 4 kGy irradiation dose.

Our findings appear very satisfactory compared with already published results on HCQ degradation using others advanced oxidation process such as electrochemical oxidation using BDD only and combined with both sonication and UV-irradiation (Table 2). These results show that different % of TOC removals of HCQ are comparable. However, regarding time and consequently cost of treatment, the method applied in this work was found to be more suitable for HCQ degradation. In addition, using gamma irradiated treatment method we can irradiate and treat synchronously or continuously large volumes of HCQ contaminated wastewaters. With such procedure, we can also combine qualitative and quantitative performances of irradiation process.

**Conclusion**

This work confirmed that gamma irradiation was an effective advanced oxidation process to completely deplete HCQ in aqueous solutions at different operating conditions (initial pH, HCQ concentration and dose rate). Low concentration with higher dose rate gives better efficiency due to several competitive reactions between HCQ, by-products and radical species issuing from water radiolysis. Neutral pH improves significantly the removal efficiencies of HCQ and TOC removal. Best result was achieved after 8 kGy at 6.2 initial
pH value under 26.31 Gy.min⁻¹ dose rate. In addition, the performed kinetic study showed that HCQ degradation follow a pseudo-first-order kinetic with an apparent rate constant equal to \( k_{\text{app}} = (0.0093 \pm 0.0025) \text{ min}^{-1} \). Based on LC/MS identified by-products, the degradation mechanism of HCQ was proposed. Finally, the evaluation of the energy consumption was performed in order to predict the viability of gamma irradiation process on an industrial scale.

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Author contributions ZA contributed to conceptualization, original draft preparation; JS contributed to methodology; HC contributed to visualization, investigation. JH contributed to reviewing and editing.

Declarations

Conflict of interest The authors declared that they have no conflicts of interest to disclose.

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**Table 2** Comparative study of % TOC removal degradation of HCQ achieved with different AOP’s

| Method treatment                                      | % TOC removal | Time of treatment (min) | References                  |
|-------------------------------------------------------|---------------|-------------------------|-----------------------------|
| UV irradiation combined with electrochemical oxidation | 98%           | 300                     | (Bensalah et al. 2020)      |
| Anodic oxidation on BDD                                | 75%           | 300                     | (Bensalah et al. 2020)      |
| Sono assistant Electrochemical oxidation              | 87%           | 300                     | (Bensalah et al. 2020)      |
| Gamma Irradiation                                     | 96%           | 304                     | This work                   |
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