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ORIGINAL PAPER

Decomposition mechanism of hydroxychloroquine in aqueous solution by gamma irradiation

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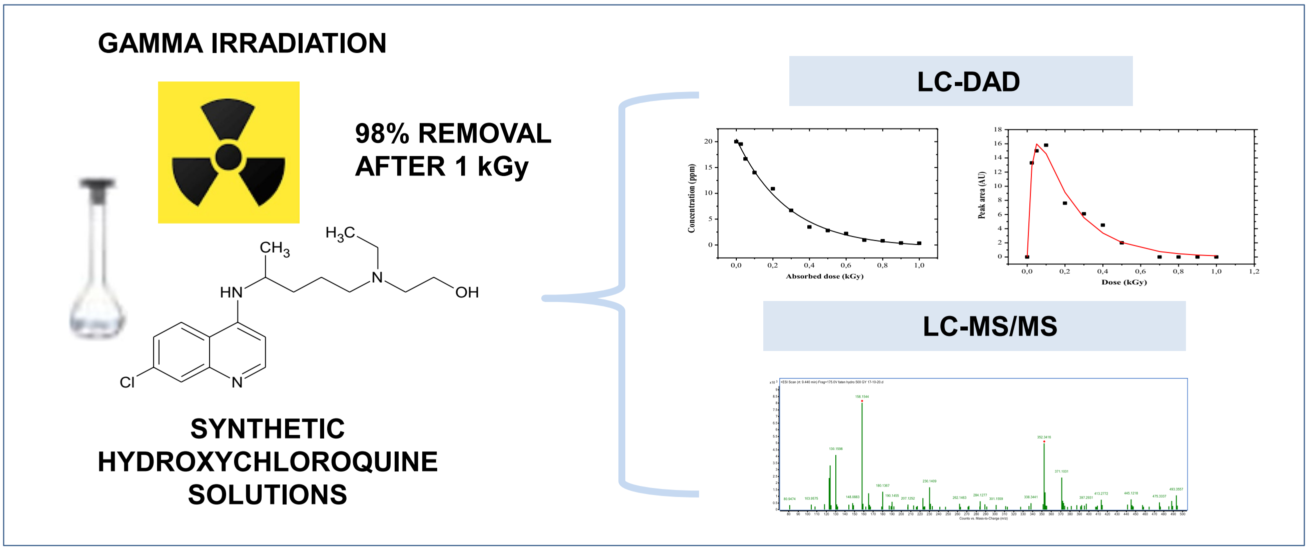
Abstract

One of the advanced oxidative processes is gamma irradiation, an efficient technique for removing pesticides and pharmaceutical products. Radiolytic degradation leads to free radical's formation, which facilitates molecular lesion and breaks the chemical bonds. The use of pharmaceutical compounds, such as hydroxychloroquine (HCQ), is increasing nowadays due to the Covid 19 pandemic situation. This study focused on gamma radiation-induced degradation of HCQ in aqueous solution. The degradation was monitored by High-Performance Liquid Chromatography (HPLC) using an Eclipse XDB-C18 column (150 × 3.0 mm, 3.5 µm) and a mobile phase composed of 94% water (phosphate buffer at pH = 3.6) and 6% acetonitrile, with a DAD detection at $\lambda = 343$ nm. The effect of different gamma radiation doses (from 0.05 to 3 kGy) was investigated. Chromatographic analysis shows that 1 kGy dose is effective to degrade completely HCQ at 20 ppm and following a first-pseudo-kinetic order with a dose constant corresponding to 4.2 kGy^{-1}. A comparison was done between gamma degradation and other methods. LC-QToF-MS/MS identified the intermediate products, and their kinetic constants were determined. A mechanism pathway was proposed for HCQ degradation under gamma irradiation.

Graphical abstract



Keywords Hydroxychloroquine · Advanced oxidation process · γ-irradiation · Kinetic rate · LC–MS/MS · Mechanism pathway

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Introduction

Most pharmaceuticals introduced into our environment invade surface water (watercourses, lakes and streams), groundwater and drinking water (Beek et al. 2016). Domestic, urban, hospital and industrial wastewater added to aquaculture and livestock farming constitute the main sources of pharmaceutical introduction into water sources (Bottoni et al. 2010). Due to the increasing concern about their negative impacts on aquatic organisms and their potential adverse health impacts on humans, pharmaceutical residues are classified as environmental micropollutants and they are catching the attention of researchers worldwide (World Health Organization 2012). Hence, achieving the degradation of pharmaceuticals in aqueous solutions with efficient technologies and low cost is an emerging challenge for the scientific community. Research proved that conventional water treatment processes such as coagulation-flocculation, filtration and adsorption cannot completely remove pharmaceuticals (Verlicchi et al. 2013). For this reason, studies are now being focused on advanced oxidation processes (AOPs) application. AOPs, using highly reactive species, proved to achieve high elimination rates of different pharmaceuticals (Liu et al. 2020; Wang and Zhuan 2020). Extensive research investigated pharmaceuticals degradation in aqueous medium using AOPs such as photo-Fenton oxidation (Perini et al. 2017), ultrasound (Rayaroth et al. 2016), ozone (Almomani et al. 2016) and UV radiation (Kawabata et al. 2013; Hora et al. 2019). In particular, gamma irradiation has appeared as an effective alternative for degrading various contaminants, including pharmaceuticals in water (Dan et al. 2019; Wang and Chu 2016). Gamma rays excite the irradiated solution and induce, consequently, water radiolysis. The generated radicals are highly reactive, mainly hydroxyl radicals, solvated electrons and hydrogen radicals (Wang et al. 2019). These species are capable of decomposing the target pollutant into carbon dioxide and water. Radiolysis treatment has recently gained much attention since the reactive species can be formed without the addition of chemicals or electric supply and the produced compounds are biodegradable (Alsager et al. 2018a).

Hydroxychloroquine (HCQ), chemically the 2-[N-4-{(7-chloroquinolin-4-yl)amino}pentyl-N ethyl] aminoethanol, belongs to the family of 4-aminoquinolines. It is commonly classified as an antimalarial drug after its long history in treating malaria (Zvi et al. 2012). HCQ is also prescribed for treatment in inflammatory rheumatic diseases, especially systemic lupus erythematosus and rheumatoid arthritis (Bothwell and Furst 2005; Floris et al. 2018). Thanks to its anti-inflammatory and antiviral effects, HCQ has been recently proposed as a possible treatment for Coronavirus (Covid-19) (Sinha and Balayla 2020; Gautret et al. 2020) and the interest in its potential therapeutic use continues to grow. HCQ is classified among the pharmaceutical contaminants of emerging concern due to its persistence, bioaccumulation and possible transfer to living organisms (Howard and Muir 2011; Gosu et al. 2016). This emphasizes the need for efficient degradation technologies able to eliminate HCQ from water. Currently, few studies have been dealt with the removal of HCQ from water. Bensalah et al. (Bensalah et al. 2020) investigated the degradation of HCQ in an aqueous solution by electrochemical oxidation with boron-doped diamond and its combination with UV irradiation and sonication. The authors confirmed that the combination of different AOPs enhanced degradation efficiency and kinetics. Another study by Dabic (Dabić et al. 2019) focused on the photolytic degradation of HCQ in pure water under simulated solar radiation and this technology might play an essential role in preventing the accumulation of HCQ in the aquatic environment. The use of wastewater, not treated appropriately, can lead to emerging pollutants' dispersion on soil and water (Medrano-Rodríguez et al. 2020). Bandala et al. (Bandala et al. 2021) reported that the consumption of HCQ has increased due to the sanitary situation of the corona virus and an important quantity of contaminated water was rejected to the environment. This emphasizes the need for effective technologies and methodologies for HCQ degradation in wastewater effluent.

Nevertheless, to the better of our knowledge, no papers were published exploring the effect of gamma irradiation as an innovative advanced oxidation process for the elimination of HCQ from water. This work's objective was to study the efficiency of gamma rays to remove HCQ from aqueous media. LC/MS/MS analysis was undertaken to identify the degradation intermediates as well as their kinetics, and a plausible removal pathway of HCQ radiolysis was proposed.

Materials and methods

Chemicals

Hydroxychloroquine (purity ≥ 99%) was supplied by Medis (Tunisia). For HPLC analysis, solvents (acetonitrile and methanol) were purchased from Sigma Aldrich. Ultrapure water was obtained from a Milli-Q water purification system (Millipore). Figure 1 presents the chemical structure of HCQ.

All sample solutions were prepared with ultrapure water. The studied samples at 20 ppm, as selected target concentration, were obtained by dissolving the analytical standard in water. The solution pH was adjusted using HCl and NaOH

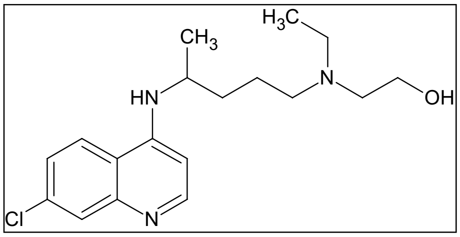


Fig. 1 Chemical structure of HCQ

at 0.1 M. No scavenger was added to the samples to study the fundamental approach.

Analytical system

The analysis of HCQ was carried out by LC-DAD (Agilent 1200 Infinity series) with an automatic injector. The chromatographic column was Eclipse XDB-C18 (150 × 3.0 mm, 3.5 µm). The mobile phase used to separate HCQ and its by-products was a buffered solution (phosphate at pH = 3.6) 96% with 6% acetonitrile in an isocratic mode at 1 mL min^{-1} flow rate. The oven temperature was maintained at 30 °C. The injected volume was 20 µL, and the wavelength was fixed at 343 nm. This wavelength is commonly used by researchers for HCQ analysis with HPLC (Xiong et al. 2021; Singh et al. 2015), corresponding to the maximum of the absorbance of HCQ in UV. Each sample was analyzed three times to verify the stability of the system.

For structural identification of the main by-products generated by the chemical reaction between radicals formed by water radiolysis (Eq. 1) and HCQ, a chromatographic system coupled to a quadrupole Time-of-Flight spectrometry mass (QTOF) was used.

$$H_2O \rightarrow e^-_{aq} + H^{\bullet} + {}^{\bullet}OH \qquad (1)$$

The Agilent system 6530 QTOF MS/MS, composed of an ESI source, was used to collect the mass data of the compounds. The mobile phase was a mixture of acetonitrile and buffered water (phosphate salt, pH = 3.6) with a gradient mobile phase program. The gradient elution started with 60% acetonitrile to 95% in 4 min and was maintained for 2 min. The injected volume was 5 µL with a flow rate of 0.7 mL min $^{-1}$. All the mass spectra were acquired at positive mode over the mass range m/z 50–450. Nitrogen was used as a sheath gas at a flow rate of 10 L min^{-1}, and the spray voltage was fixed at 3500 V. The collision energy was optimized at 20 V.

The Brüker 700 MHz NMR system was employed to analyze the solutions of HCQ dissolved into deuterated water, before and after treatment by gamma irradiation.

Irradiation apparatus

A cobalt-60 source, installed in the National Center for Nuclear Science and technology in Sidi Thabet, Tunisia, was employed as a gamma radiation source at 28 Gy min^{-1} (Dridi et al. 2020). All the studied samples were irradiated at room temperature in glass vials. The irradiated doses were conducted from 0.05 to 3 kGy.

Chemical yield values and kinetic constant

The chemical yield, commonly named G-value, is calculated on the basis of the following equation:

$$G = \frac{\Delta C \times 6.02310^{23}}{D \times 6.2410^{16}} \qquad (2)$$

G is G-value (µmol J^{-1}), D is the absorbed dose (Gy), ΔC is the pollutant concentration (mol L^{-1}) at D, 6.023 10^{23} is the Avogadro's number and 6.24 10^{16} the conversion factor from Gy to 100 eV L^{-1}.

G-value is defined as the number of reactive molecules per 100 eV absorbed energy (Spinks and Woods 1990; Woods and Pikaev 1994).

The dose constant was calculated based on a pseudo-first-order kinetic, which describe the degradation rate of HCQ, as the following equation:

$$Ln\left(C_0\right) - \ln\left(C\right) = k \times D \qquad (3)$$

D is the absorbed dose (kGy); C is the concentration (ppm); C_0 is the initial concentration (20 ppm); and k is the dose constant (kGy^{-1}).

The doses were calculated for 0.5 and 0.9, which represent the removal of 50% and 90% of the studied compound, by using the following equations, respectively:

$$D_{0.5} = \frac{\ln 2}{k} \qquad (4)$$

$$D_{0.9} = \frac{\ln 10}{k} \qquad (5)$$

Results and discussion

Radiolytic degradation of HCQ in aqueous solution

It is well reported that gamma-induced degradation of pollutant aqueous solutions is initiated by the reactive species of the water radiolysis such as hydroxyl radicals $^{\bullet}OH$, hydrated electrons e_{aq}^- and hydrogen radicals $H^{\bullet}$ (Boujelbane et al.

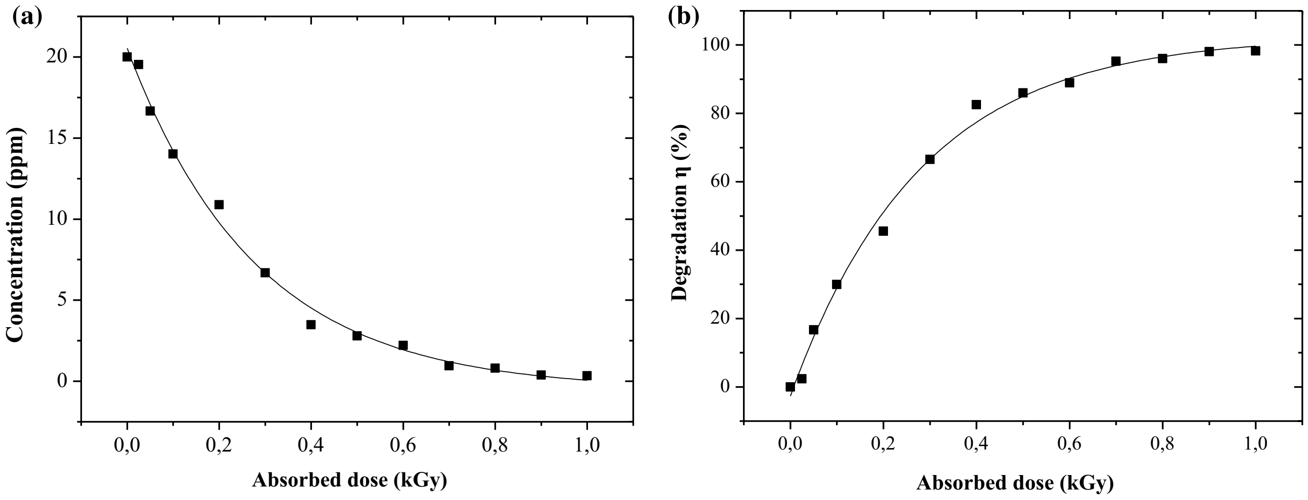


Fig. 2 Variation of concentration (**a**) and removal efficiency (**b**) of HCQ at 20 ppm in function of absorbed doses

2021; Yu et al. 2010). These powerful oxidants are able to decompose the target organic compound into water and carbon dioxide.

The HCQ, with an initial concentration of 20 ppm, was irradiated under several doses varying from 0.05 to 3 kGy. The samples were analyzed by the liquid chromatographic system before and after irradiation. Figure 2 shows the variation of HCQ concentration and the removal efficiency with the different absorbed doses. It was observed that there is a rapid decrease in HCQ concentration with higher radiation absorbed dose and the studied compound was effectively removed after 1 kGy reaching 98.3% of degradation extent. Hence, gamma rays seem to be an efficient technology for HCQ removal from aqueous solution. Indeed, Zheng et al. (2011) reported that ibuprofen, at 28.3 ppm, was 100% removed at 1.1 kGy and Changotra et al. (2018) found that ofloxacin (0.05 mM) was 99.6% degraded after 3 kGy of exposure; these two studies highlighted the efficiency of gamma irradiation for pharmaceutical pollutant removal in aqueous media (Zheng et al. 2011; Changotra et al. 2018a).

On the other hand, it appeared that HCQ concentration decreased exponentially with increased absorbed dose and a pseudo-first-order kinetic degradation (Eq. 3) could be noticed as depicted by Fig. 3. The good *R*-squared value of 0.992 confirms the pseudo-first model order. The dose constant *k* is the apparent pseudo-first-order kinetic constant used to describe the degradation rate (Jia-Tong et al. 2017), and it could be determined from the slope of the plot (Fig. 3). For a solution of HCQ (20 ppm), the observed dose constant corresponds to 4.24 kGy^{-1}.

The chemical yields G of HCQ were calculated and plotted with the degradation efficiency (%) against the absorbed doses (Fig. 4). Results revealed that the chemical yield was decreasing as the removal efficiency was increasing with

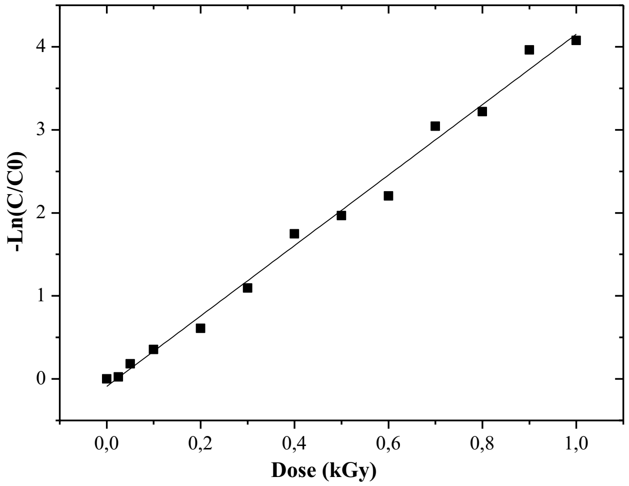


Fig. 3 Kinetic degradation of HCQ at 20 ppm with absorbed doses

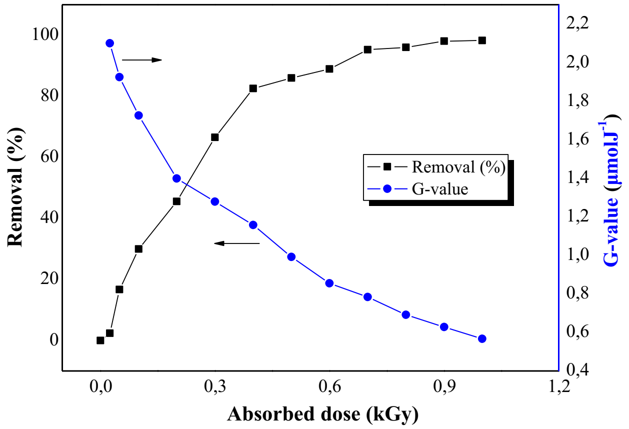


Fig. 4 G-values and percentage of removal of HCQ at 20 ppm in function of the absorbed dose using gamma treatment

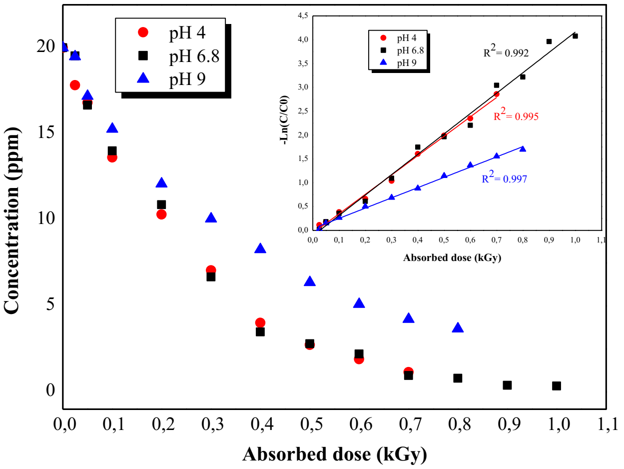


Fig. 5 Variation of the HCQ concentration with the absorbed doses at pH 4, 6.8 and 9

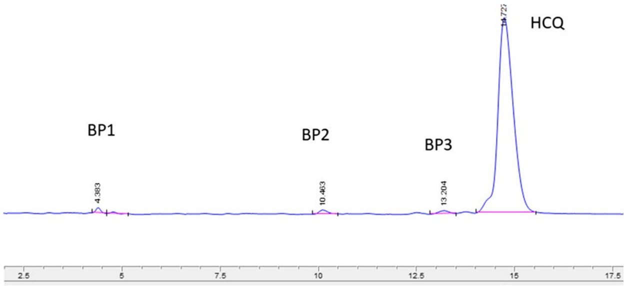


Fig. 6 Chromatogram of HCQ and its three main by-products BP1, BP2 and BP3 after gamma irradiation of 0.3 kGy

increasing radiation doses. This confirmed the competition occurring between the by-products and the target molecule to react with the radicals generated by water radiolysis (Boujelbane et al. 2021; Changotra et al. 2018b).

For degradation of 50% and 90% of 20 ppm HCQ, on the basis of Eqs. (4) and (5), 0.16 kGy and 0.54 kGy, respectively, were needed. The results showed that HCQ followed a pseudo-first-order with a half-life of 0.16 kGy corresponding to 5.7 min of radiation exposure; this time depends on the compound structure, its concentration, the solvent and the chemicals added into the solution (Liu et al. 2014). In our case, HCQ was studied in the fundamental approach.

Effect of pH on HCQ removal by gamma irradiation

In order to investigate the effect of solution pH on the degradation efficiency of HCQ using gamma rays, we irradiated 20 ppm solutions at pH of 4, 6.8 and 9. Figure 5 shows the concentration variation with the absorbed doses for the different tested pH. It appeared that the HCQ concentration decreased exponentially with the doses, for all pH values (Fig. 5). In acidic and neutral conditions, a complete overlap of the degradation efficiencies was noted and this result was in concordance with what reported in the literature (Alsager et al. 2018b). On the other hand, the efficiency for HCQ removal decreased in a basic medium. For an absorbed dose of 0.5 kGy, an efficiency degradation of 86% was achieved both for neutral and acidic solutions, whereas the degradation efficiency equaled only to 68% at pH 9. The decrease in degradation efficiency in basic solutions is in agreement with publications reported for different pharmaceuticals such as ofloxacin (Changotra et al. 2018a) and sulfamethoxazole (Zhuan and Wang 2020). The variation of the degradation efficiency with pH value could be explained by the decrease in the effective radical concentration. In fact, the pH of the solvent influences the percentage of the different radicals generated during the radiolysis of the water. Under alkaline conditions, $^{\bullet}$OH readily reacts with OH^- to generate O^- according to Eq. (6), reducing the concentration of $^{\bullet}$OH and the degradation efficiency hence decreased (Changotra et al. 2018a). In acidic media, the hydrated electrons e_{aq}^- reacts with H^+ to produce $^{\bullet}$H (Eq. 7). Thus, the reaction of e_{aq}^- with $^{\bullet}$OH is inhibited, thereby decreasing the available concentration of reactive radicals $^{\bullet}$OH and enhancing the degradation process (Guo et al. 2012). Neutral or acidic media are more preferable than an alkaline solution for the degradation of HCQ under gamma irradiation.

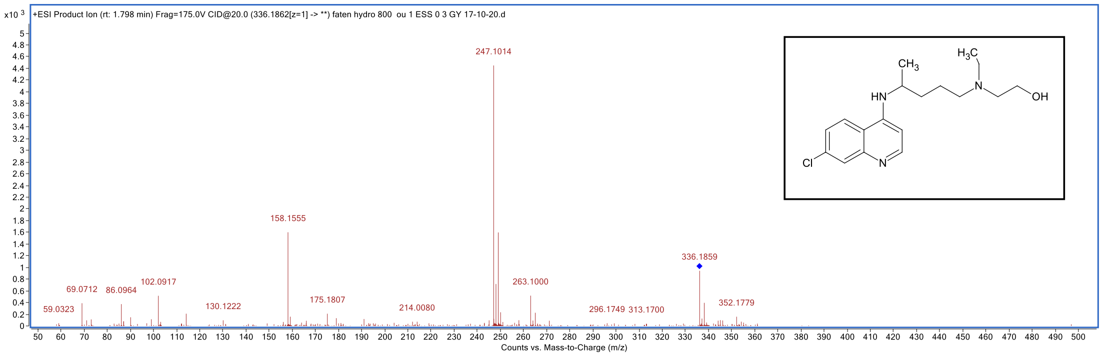
$$^{\bullet}OH + OH^- \rightarrow O^- + H_2O \tag{6}$$

$$e_{aq}^- + H^+ \rightarrow {}^{\bullet}H \tag{7}$$

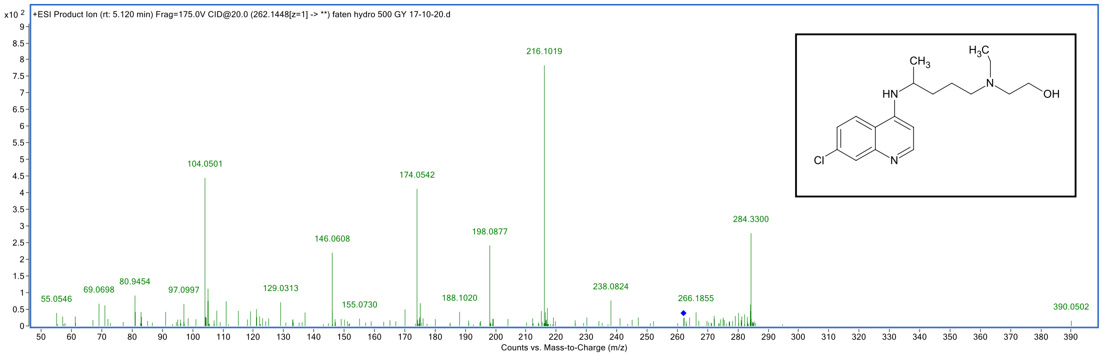
As depicted by Fig. 5, the data obtained from the pH values of 4, 6.8 and 9 fitted well to Eq. (3). The dose constant k was determined for each media pH, and the corresponding values were 4.07 kGy^{-1}, 4,24 kGy^{-1} and 2.21 kGy^{-1}, respectively, for pH 4, 6.8 and 9. It appeared that the

Table 1 Comparison of the different methods for HCQ degradation

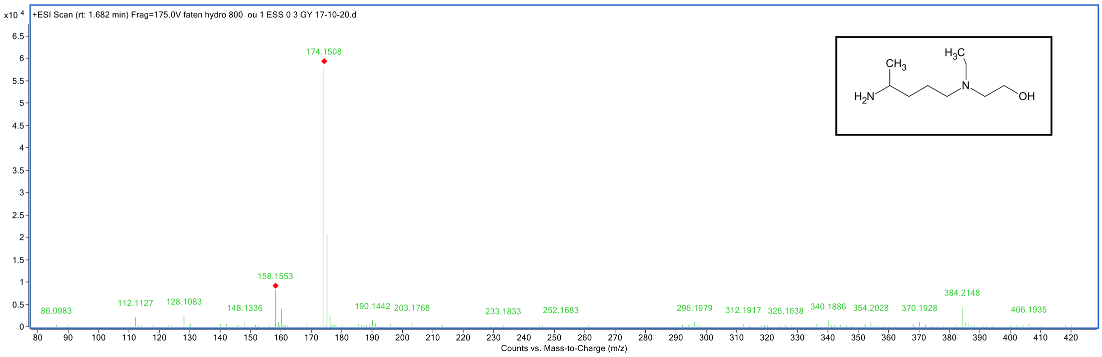
Hydrolysis (Babić et al. 2017)	Photolysis (Dabić et al. 2019)	Photo-assisted electrochemical oxidation (Bensalah et al. 2020)	Radiolysis (this study)
At 25 °C $T_{1/2}$ = 365 days	k = 0.001 min^{-1} $T_{1/2}$ = 11.6 h	Completely degraded after 40 min at pH = 9	98.3% removal after 1 kGy (35 min) at pH 6.8 $T_{1/2}$ = 5.7 min



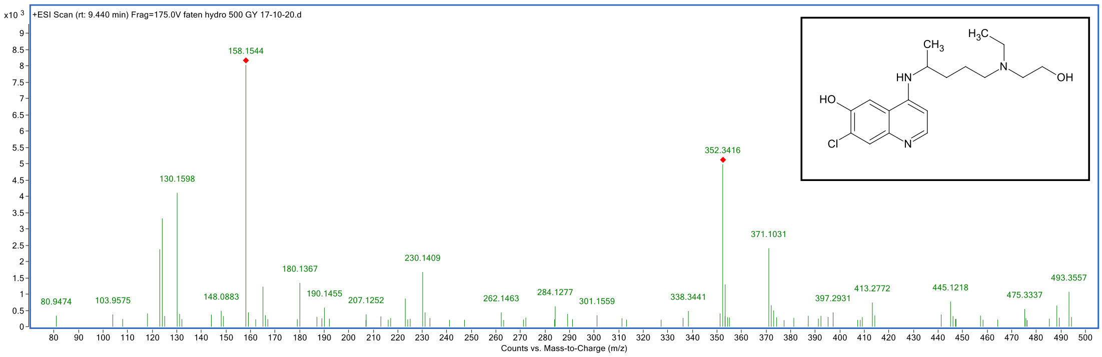
(a) Spectrum of the HCQ (m/z= $[M+H]^+ = 336$) and its fragments by LC-MS/MS.



(b) Spectrum of BP1 (m/z= $[M+H]^+ = 262$) and its fragments by LC-MS/MS.



(c) Spectrum of BP2 (m/z= $[M+H]^+ = 174$) and its fragments by LC-MS/MS.



(d) Spectrum of BP3 (m/z= $[M+H]^+ = 352$) and its fragments by LC-MS/MS.

◂**Fig. 7** **a**: Spectrum of the HCQ (m/z = $[M+H]^+$ = 336) and its fragments by LC–MS/MS. **b**: Spectrum of BP1 (m/z = $[M+H]^+$ = 262) and its fragments by LC–MS/MS. **c**: Spectrum of BP2 (m/z = $[M+H]^+$ = 174) and its fragments by LC–MS/MS. **d**: Spectrum of BP3 (m/z = $[M+H]^+$ = 352) and its fragments by LC–MS/MS.

alkaline solution is characterized by lower k value than those obtained for acidic and neutral media, confirming the decrease of degradation efficiency.

Comparative study of HCQ degradation by different processes

Exploring the literature, we summarized in Table 1 the results of different processes used to degrade HCQ in aqueous solution. It appeared that hydrolysis of HCQ (Babıć et al. 2017), at 25 °C, expiring one year and is too slow compared to the other reported technologies. Photo-assisted electrochemical degradation is more efficient than the photolytic one for HCQ removal (Bensalah et al. 2020; Dabić et al. 2019). In our study, the elimination of HCQ under gamma irradiation is faster and taking only 35 min for a total efficiency of 98.3% at neutral pH. It can be noted that gamma technology is a cost-effective (once the irradiator is installed) and ecofriendly treatment (Gar Alalm et al. 2015; Kim et al. 2015).

By-products and degradation mechanism

Figure 6 shows the chromatographic profile of HCQ at gamma dose of 300 Gy. The peak characterizing HCQ appeared at a retention time of 14.2 min. Three other peaks are present corresponding to the by-products BP1, BP2 and BP3 with retention times equaled to 5, 10.5 and 13.2 min, respectively.

Furthermore, the by-products were analyzed by LC coupled to QToF MS/MS. For each product, an extracted mass spectrum was analyzed to identify its chemical structure. Figure 7 a–d gathers the mass spectra of HCQ and its intermediate products. Table 2 presents the $[M+H]^+$ and the main fragments of HCQ, by-products and the respective structures deducted after fragmentation by MS/MS. After identifying of the different intermediate irradiation products, a possible pathway for HCQ degradation was proposed in Fig. 8.

Kinetics of the intermediate products

The kinetics of the appearance or disappearance of BP1, BP2 and BP3 was followed by LC-DAD. Figure 9 summarizes the variation of the peak areas of the three main products.

In terms of reaction mechanisms, the decomposition of a substance by chemical reactions will go through many reaction stages. From the initial precursor, a reaction occurs to decompose it into intermediate products. If continued to react with oxidizing or reducing agents, these intermediate products will gradually be lost with the reaction time. According to the classification of chemical reaction kinetics, such reactions are called series reactions of the form A → B → C, where B is the intermediate product of the decomposition of substance A. For a first-order serial reaction, the concentration of the intermediate B overtime is calculated using the following formula (Himmelblau et al. 1967):

$$C_B = \frac{k_1 C_A^0}{k_2 - k_1}\left(e^{-k_1 D} - e^{-k_2 D}\right) \quad (8)$$

In Eq. 8, there are three unknown variables, k_1, k_2, and $C_A{}^0$. To solve the above system of equations with the experimental data set for the concentration of substance BP by absorbed dose, Microsoft Excel was used to find the most suitable regression equation. In the degradation reaction of HCQ, the concentrations of three relatively stable intermediates (BP1, BP2, and BP3) over time were investigated. Their reaction kinetics were in good agreement with the first-order serial reaction as shown in Table 3.

Mineralization study

To evaluate the total degradation of the treated solutions, ^{1}H NMR technique was used (Boujelbane et al. 2021; Liu et al. 2014; Saadaoui et al. 2021). Figure 10 presents the NMR spectrum of HCQ after treatment at 3 kGy. In the irradiated spectrum, there is only the peak corresponding to the deuterated water. This result confirms the complete mineralization of HCQ by gamma irradiation treatment and no by-product exists and can be detected after this dose.

Table 2 MS/MS data of HCQ with their fragments

Molecule	m/z = $[M+H]^+$	m/z main fragments	structure
HCQ	336	247 158	$C_{18}H_{26}ClN_3O$
BP1	352	267 73	$C_{18}H_{26}ClN_3O_2$
BP2	262	216 174	$C_{13}H_{18}N_2O_2$
BP3	174	85 69	$C_7H_{18}N_2O$

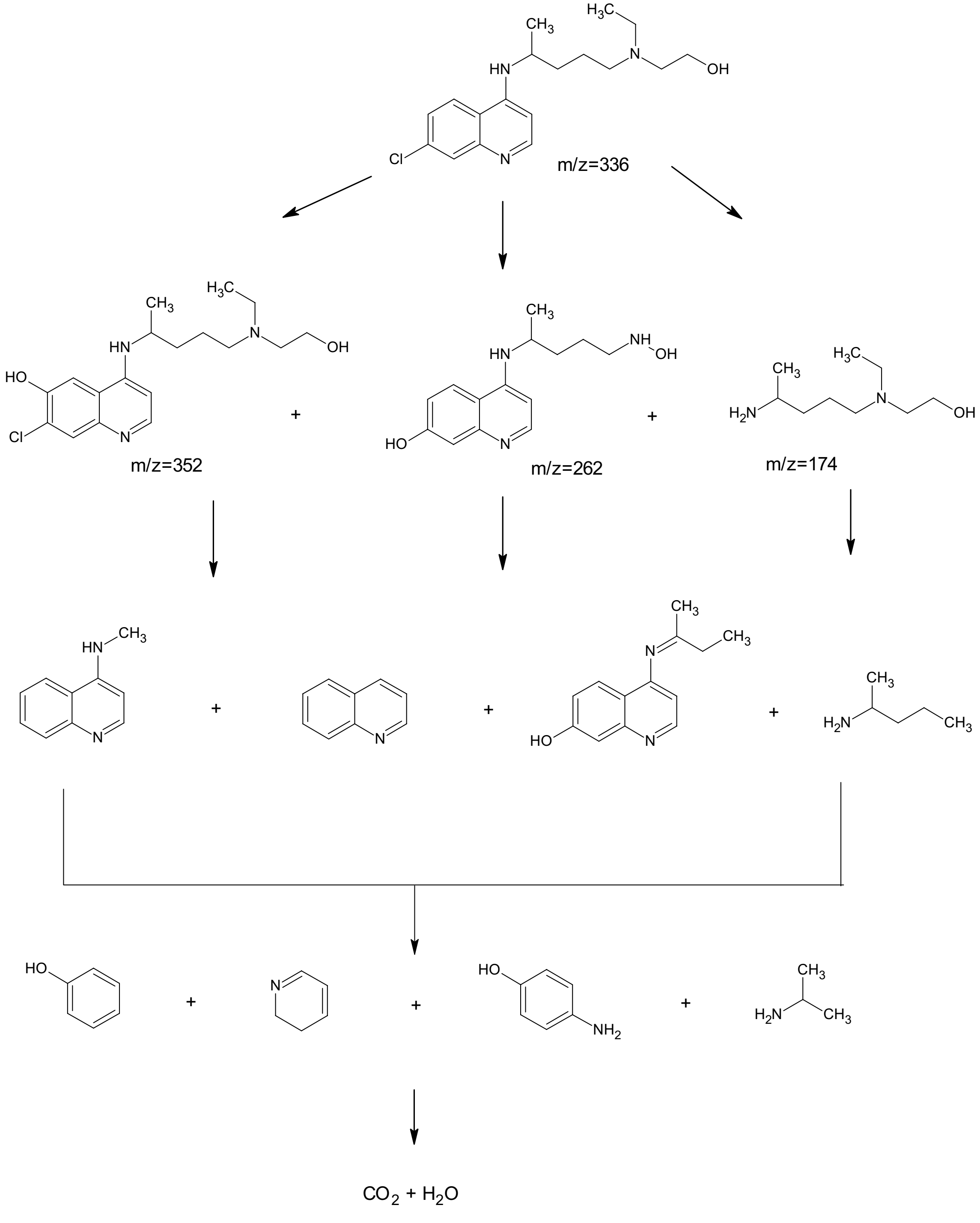


Fig. 8 Proposed mechanism pathway of HCQ degradation under gamma irradiation

Conclusion

The AOPs technologies as gamma irradiation are an excellent alternative for pharmaceutical's degradation. The study of gamma irradiation effect on HCQ shows that 1 kGy is enough to destroy this compound at 20 ppm and its intermediates. The degradation of HCQ followed a pseudo-first-order kinetic, with a dose constant of 4.24 kGy^{-1}, in accordance with the reported studies for the majority of organic compounds. The pH value appeared to affect the HCQ degradation efficiency, and higher removal yield was achieved in neutral or acidic conditions. LC–MS/MS allowed to identify three by-products, and a plausible degradation pathway of HCQ was proposed. Furthermore,

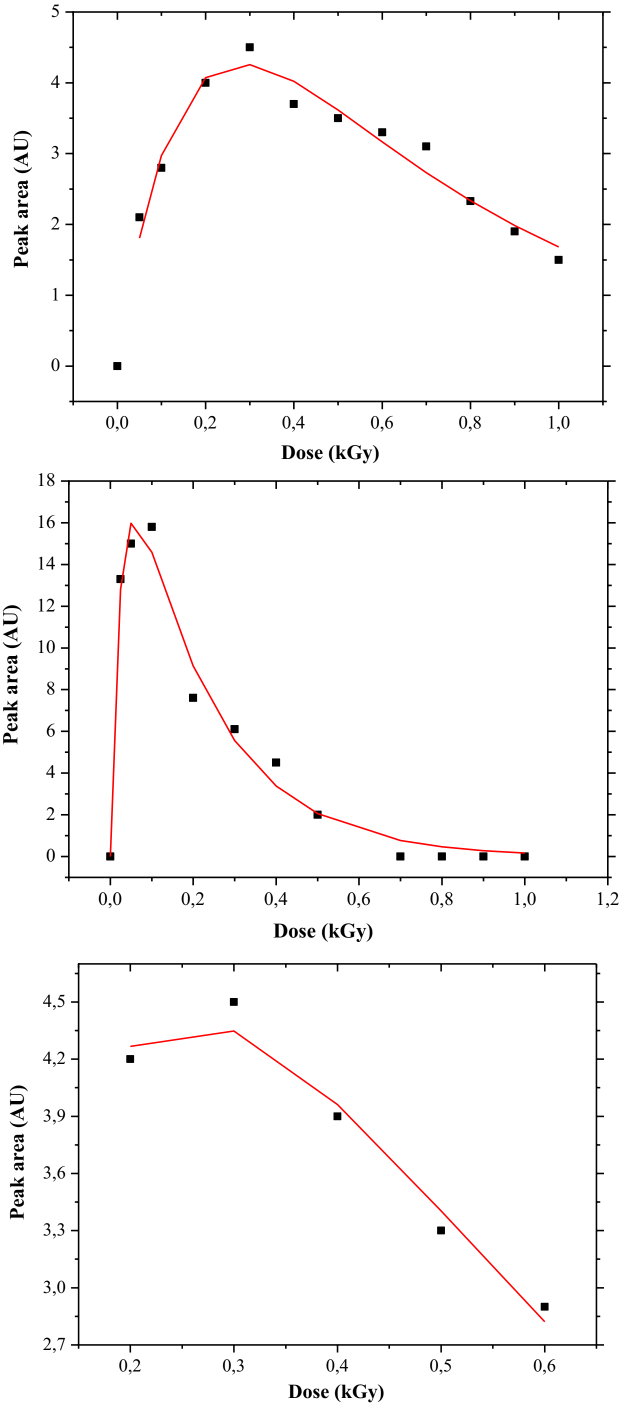


Fig. 9 Experimental and model concentration profiles of BP1, BP2 and BP3, respectively, without self-recombination of reactive species

Table 3 Reaction kinetic parameters of three main by-products

No	Abbreviation of BP	Regressed equation	R^2	D_{opt}(kGy)
1	BP1	$C_{BP1} = \frac{5.35C_A^0}{2.68-5.35}\left(e^{-5.35D} - e^{-2.68D}\right)$	0.9645	0.2589
2	BP2	$C_{BP2} = \frac{1.72C_A^0}{6.40-1.72}\left(e^{-1.72D} - e^{-6.40D}\right)$	0.9992	0.2808
3	BP3	$C_{BP3} = \frac{4.97C_A^0}{40.38-4.97}\left(e^{-4.97D} - e^{-40.38D}\right)$	0.9598	0.0592

*D_{opt} is the absorbed dose at which concentrations of BP reached maximum values

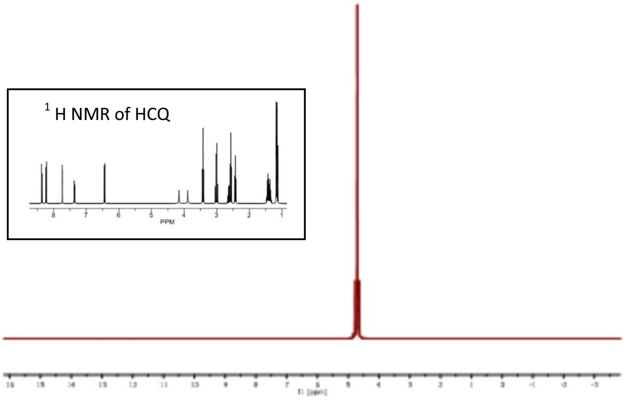


Fig. 10 ^{1}H NMR spectrum after 3 kGy of gamma irradiation of HCQ at 20 ppm

the kinetic reactions of the intermediate products were simulated and were in accordance with the results. ^{1}H NMR demonstrated total mineralization of 20 ppm HCQ when irradiated at 3 kGy. These encouraging results confirmed the importance of radiation technology for water treatment before rejection to the environment or reused in the agriculture field.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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