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THE INFLUENCE OF THE AQUEOUS COMPOSITION OVER DEGRADATION OF HYDROXYCHLOROQUINE

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The present study explored the HCQ behavior in aqueous fluids and how the chemical composition of the aqueous matrix might influence the HCQ in different media. The HCQ degradation was investigated in five chemically different natural waters. It was correlated with the pH values, rapid degradation appearing at higher pH values. The increase of NO_3^- *and* Fe^{3+} *concentrations generated the degradation increase. Another effect was observed by enhancing the* HCO_3^- *concentration. Thus the use of natural waters with slightly acidic pH, low* NO_3^-*,* Fe^{3+} *and high* HCO_3^- *will preserve the therapeutic effects of HCQ over humans and animals.*

Keywords: hydroxychloroquine, natural water, degradation

1. Introduction

Hydroxychloroquine (HCQ), 2-[N-4-{(7-chloroquinolin-4-yl)amino}pentyl-N ethyl] aminoethanol, belongs to the class of 4-aminoquinolines, used in antimalarial drugs and in the treatment of rheumatologic and dermatologic diseases [1,2]. Due to its logKow = 3.03 and solubility S=86 g/L, the HCQ is considered a highly soluble pharmaceutical in aqueous media [3] whose effects might contribute to the complex processes in which HCQ is involved [4]. Hydroxychloroquine sulphate (HCQ) was obtained by the addition of the hydroxy group to chloroquine (CQ), in order to reduce its toxicity (Fig. 1), CQ being considered several times more toxic than HCQ. The nitrogen atom from the ring of HCQ increases its hydrophilicity and also its impact on aqueous systems. HCQ is a basic substance having pKa values of 7.28 and 9.76.

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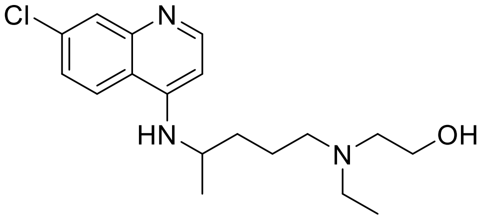


Fig. 1 Structure of hydroxychloroquine ($C_{18}H_{26}ClN_3O$).

Kinetics allow to predict how the reaction rate will change under different reaction conditions. HCQ can be degraded in different ways in the environment [5], chemically or photochemically [6]. In aqueous samples the hydrolytic degradation plays an important role, the mineral composition of natural water and some of its natural constituents, such as nitrate (NO_3^-), iron(III) (Fe^{3+}), bicarbonate (HCO_3^-) and pH influencing the HCQ fate in aqueus solutions during time. The natural constituents mentioned above can produce reactive substances, or can consume them and pH can influence the composition of the matrix. The NO_3^- ions are among the collectors of organic radical and light filters in natural aqueous media [7]. The presence of different forms in solutions of HCO_3^- is influenced by the pH, in aqueous solutions. The photodegradation by which the organic molecules from drugs or excipients are degraded at room or day light must also be taken into account. The kinetics of degradation is influenced by all the factors mentioned above.

This study contributes to an understanding of HCQ behavior in aqueous fluids and how the chemical composition of the aqueous matrix might influence the HCQ tranformations, kinetics and stability in these media, taking into account its high solubility. It is important to assess the rate of hydrolysis of pH influenced reactions and HCQ stability in aqueous matrices, the correlations of degradation rates being studied as a function of pH and ionic strength, based on the chemical composition.

2. Materials and methods

2.1. Chemical reagents and instrumentation

All reagents used in determination were of analytical grade. Pure HCQ samples were obtained from Romanian Agency of Drugs. All the other salts were from Sigma Aldrich. Ultrapure water was obtained by using a Millipore Direct - Q 3V instrument from Merck.

A chromatographic RP-HPLC method was performed by using a Waters HPLC instrument, equipped with an UV-DAD detector, a quaternary pump, a degasser, an autosampler, and Chemstation software for data acquisition and analysis [8]. The signal was detected with a UV detector at λ = 343 nm an integration and system parameters were controlled by Chrompack compact, software 3.0.1 system. Chromatographic analysis was carried out at 25° C, using a C-18 ODS-3 (250×6 mm, 5 µm) column. The separation was achieved by isocratic elution with a flow rate of 1.5 ml/min. The mobile phase was made by water, and organic (acetonitrile:methanol: 50:50, v/v) with ratio of 75:25, v/v. The pH 5.0 of inorganic phase was adjusted with dilute orthophosphoric acid and with sodium hydroxide solution. The pH was measured on a 10% solution with a pH-meter Consort P 901. The conductivity of aqueous samples was measured on a 10% solution with an Electrochemical Analyzer Consort K 912. Specific electrical conductivity, the inorganic matrices of the samples and the pH were measured before each experiment based on (EN 27888:1993-11) and (DIN 38404-5:1984-01, C5).

2.2. Sample collection and preparation for physical-chemical characterization.

Natural waters were collected from different aqueous sources of natural mineral water. The collected samples were filtered on 0.45 µm cellulose membrane filters and analyzed by ion chromatography standardized methods, developed in our group [9]. Synthetic aqueous solutions were prepared with different concentrations of NO_3^-, Fe^{3+}, HCO_3^- and different values of pH [10, 11].

2.3. Pseudo first-order constants, half-lives and Arrhenius equation

The hydrolysis reactions are of second order overall and pseudo first-order for the compound of interest. There were developed plots of $\ln(C_t/C_0)$ vs. time for the studied conditions, equation 1 (pH, ionic strength) [12]. Confidence intervals were calculated at 95%.

$$ln(C_t/C_0) = -k' \cdot t \tag{1}$$

where C_0 is the concentration of HCQ at t = 0, C_t is the concentration of HCQ at the time t when the measurement was done, k' is the pseudo first-order rate constant (1/t) and t is time.

Half life ($t_{1/2}$) represents the necessary time for a compound to degrade to 1/2 of its initial concentration (equation 2).

$$t_{1/2} = ln2/k' \tag{2}$$

$t_{1/2}$ were calculated for each rate constant and then all individual half-lives were averaged together for the given conditions.

The effect of temperature on degradation rate was obtained from Arrhenius equation, linearized form, equation 3:

$$-lnk' = lnA + \left(\frac{E_a}{R}\right) \cdot \left(\frac{1}{T}\right) \tag{3}$$

where A its the pre-exponential factor or collision factor, E_a is the experimental activation energy (kJ/mol), R is the universal gas constant with a value of 8.3141 kJ/K·mol and T is the absolute temperature (K).

Linear regression was conducted using ANOVA, in order to assess the relationship between k', pH and ionic strength. Confidence intervals at 95% were calculated for degradation rates in duplicate.

3. Results and discussions

The HCQ hydrolytic stability was examined based on OECD guideline [13] and on other experiments presented in the literature [14]. All the experiments were repeated three times, all having errors below 5%. Synthetic aqueous solutions were prepared and used for the influences of the aqueous matrix over the HCQ stability, with different concentrations of NO_3^-, Fe^{3+}, HCO_3^- and different values of pH. Then the HCQ stability in time was checked in natural aqueous samples, whose matrices were completely characterized, immediately after collection. The chemical characterization of the studied environmental aqueous systems is presented in Table 1.

Table 1

Chemical composition of the studied natural waters: electrical conductivityaverage values of the main inorganic ions, standard deviation is calculated for the samples monthly prelevated during 30 months [15]

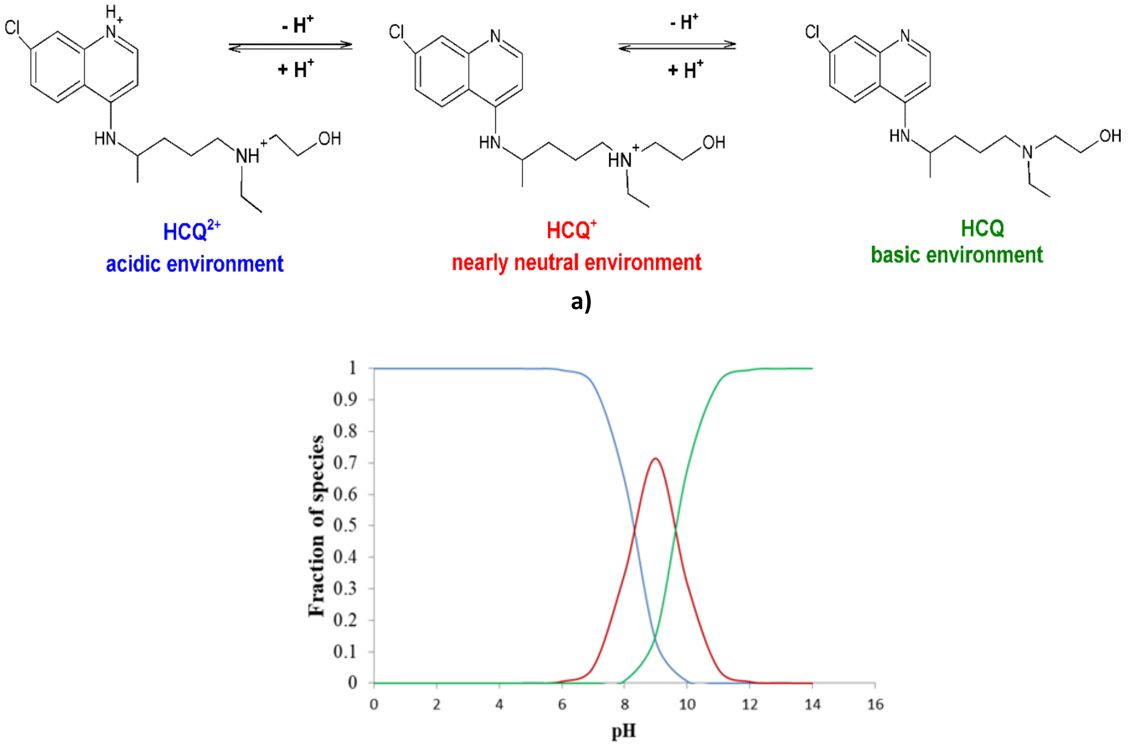
Natural water	C.E. (µS/cm)	pH	Na^+ (mg/L)	K^+ (mg/L)	Ca^{2+} (mg/L)	HCO_3^- (mg/L)	Mg^{2+} (mg/L)	Fe^{3+} (mg/L)	NO_3^- (mg/L)
1	319	7.5	3.46±0.28	1.55±0.09	40±0.29	209±18.2	13.9±0.11	2.0±0.019	2.64
2	300	8	2.68±0.25	1.79±0.14	46.1±0.35	212±20.5	11.5±0.09	3.5±0.03	3.20
3	1756	6.4	6.86±0.55	3.93±0.25	287±20.5	1305±100.45	89.0±0.07	6.03±0.05	0.04
4	1200	6.0	59.3±5.0	3.46±0.20	192±15.2	914±80.7	32.7±0.02	8.16±0.07	0.02
5	1210	5.8	180±9.2	8.22±0.74	130±9.7	1044±101.6	29.7±0.025	7.37±0.07	0.01

C.E = electrical conductivity.

The kinetics of HCQ degradation in aqueous samples was studied, by plotting $\ln(C_t/C_0)$ vs. reaction time t and it was observed that the HCQ degradation follows a pseudo-first order kinetics, the rate constant, k being calculated from the slope of the regression line, where C_t represents the concentration of HCQ at time, t (min) and C_0 its initial concentration (mg/L).

Influence of the chemical matrix of the aqueous samples over HCQ stability

The HCQ hydrophilic nature and its high solubility predict its behavior in natural aqueous systems, by a multitude of interactions. The HCQ solubility is influenced by the environmental conditions such as the chemical composition of the natural water, the temperature and by room light. The HCQ stability in aqueous solutions was evaluated based on its kinetics, being influenced by the ionic strength of the aqueous solution, its pH, and HCQ initial concentration. For example, the distribution of HCQ chemical species by pH can be observed in Fig. 2.



a)

b)

Fig. 2. a) The effect of pH on HCQ chemical species, completely protonated form = HCQ^{2+}, slightly protonated form = HCQ^{+} and deprotonated form = HCQ. b) Distribution chart of HCQ chemical species function of pH

The pH aqueous solutions also influence the degradation products (DP). Fig. 8 shows the HCQ degradation products at different pH-s and in the presence of light.

Among the inorganic ions that mainly influences its stability, NO_3^-, Fe^{3+} and HCO_3^- were studied in synthetic solutions.

Based on the obtained results, the study continued in natural aqueous matrices, presented in Table 1.

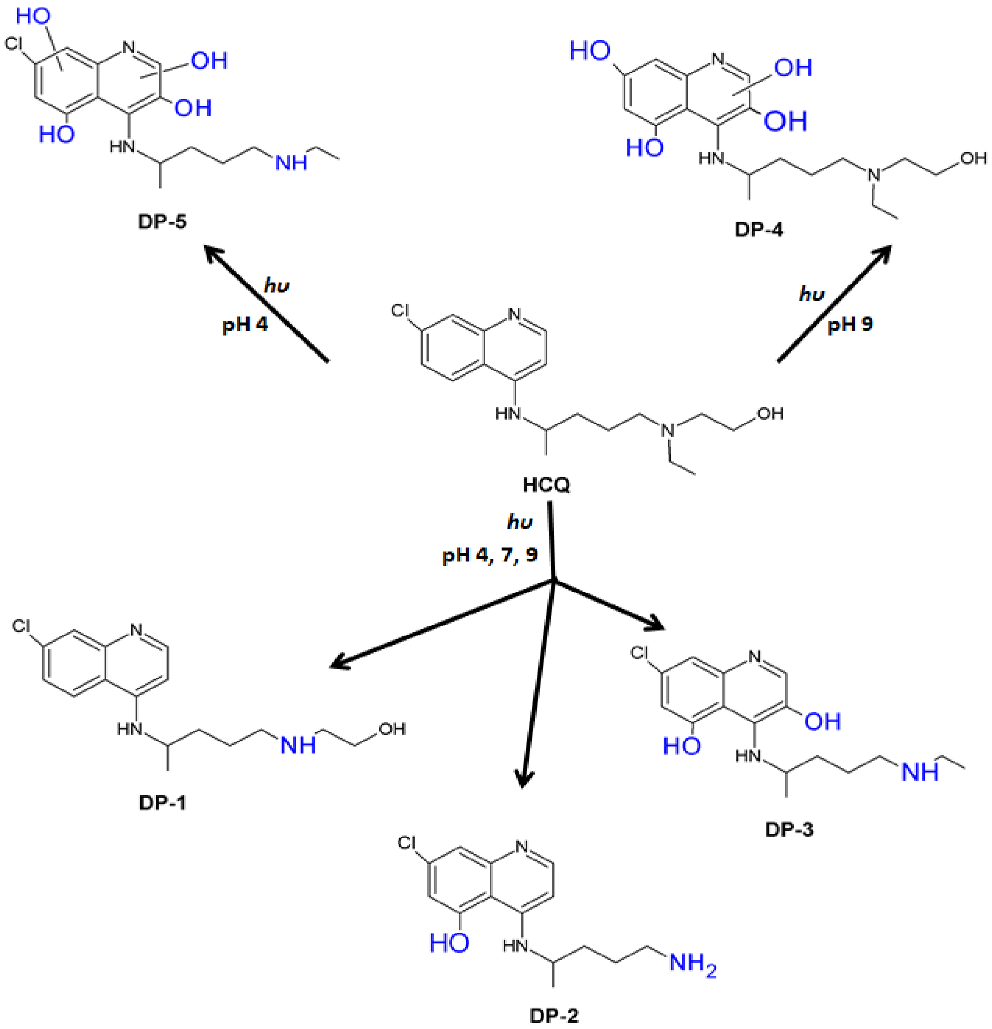


Fig. 3. Degradation steps of HCQ in aqueous samples at pH 4, 7 and 9 [7]. (DP 1-5 = degradation products)

3.1. Influence of pH

The pH influence on the sunlight degradation was studied in the range of pH values between 5 and 9, at HCQ concentration of 10 mg/L, taking into account that this is the concentration of HCQ in a medium 75 kilogram human body, by ingesting a 200 mg containing HCQ pill per day. The influence of pH on the HCQ degradation in aqueous solutions is presented in Fig. 4.

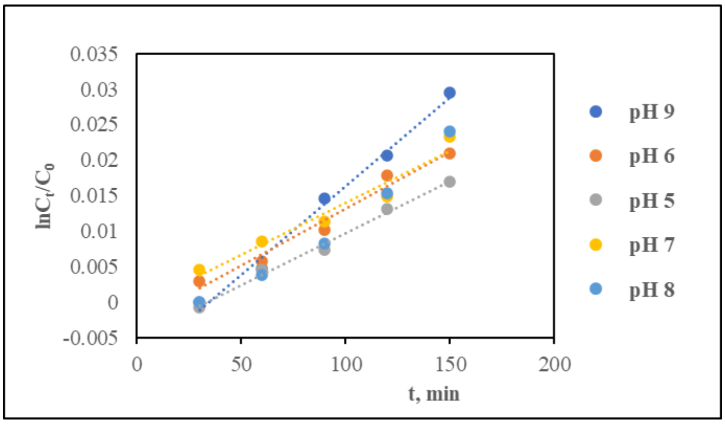


Fig. 4. Influence of pH of the synthetic samples over HCQ behavior

In the pH range 5-9, the plot of ln C_t/C_0 vs. time yielded straight lines, indicating a slow degradation of HCQ which followed a pseudo-first order kinetics. During the first four hours of exposure at room light, degradation rate constants k'_1 of HCQ were between $2.3x10^{-4}$ and $4.6x10^{-4}$ h^{-1} and the correlation coefficients values (R^2) were between 0.9891 and 0.9964 (Tabel 2).

Table 2

The influence of pH over the degradation of HCQ in synthetic aqueous solutions

pH	k'_1	R^2	$t_{1/2}$ (days)
5	0.000461	0.9926	62.70328
6	0.000345	0.9891	83.60438
7	0.000299	0.9964	96.46659
8	0.000311	0.9954	92.89375
9	0.000415	0.9911	69.67032

The HCQ degradation was correlated with the pH values, faster degradation appearing at higher pH values. HCQ is a basic substance, completely protonated at acidic pH values, as H_2HCQ^{2+}. At neutral values of pH, two protonated forms of HCQ are formed: H_2HCQ^{2+} and $HHCQ^+$. In alkaline media, the ratio between the protonated form $HHCQ^+$: HCQ is 1 to 6, meaning that the HCQ is mostly deprotonated.

Regarding the half-life times ($t_{1/2}$), the values increase from slightly acid pH to neutral one and then decrease once again. The favorable range for pH values is from slightly acid to neutral.

3.2. Influence of NO_3^- concentration

The presence of NO_3^- ions in the aqueous matrix influences the fate of organic compounds in environmental, based on its concentrations. At higher NO_3^- concentrations the organic compounds' degradation processes is faster, but it depends on the presence of other species from the solution, too. To determine the influence of NO_3^- concentration over HCQ stability in aqueous solutions, its concentration ranged at lower concentrations than those admitted by legislation, where the maximum concentration level in drinking water is 50 mg/L NO_3^-.

The HCQ degradation kinetics in the presence of NO_3^- ions at different concentrations, between 1 and 25 mg/L is showed in Fig. 5.

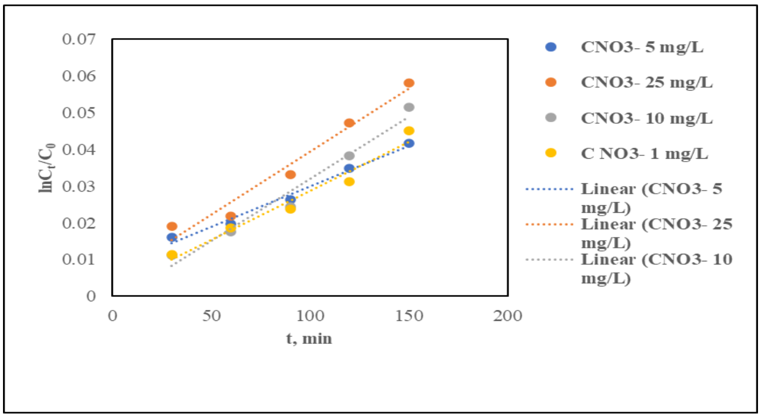


Fig. 5. Influence of NO_3^- concentration of the synthetic samples over HCQ behavior

The increase of NO_3^- concentration led to faster HCQ degradation, which could be attributed to the hydroxyl radical formation in the presence of NO_3^- ions in the aqueous solution. The concentration of HCQ was 10 mg/L, at a pH value of 7.5. Usually the presence of NO_3^- in aqueous matrices enhances the kinetic of degradation of organic compounds, based on the formation of $^{\cdot}OH$ radical in the presence of light, but there are also results which proved the contrary. In our study, the degradation rates were between 4.6×10^{-4} and 18.6×10^{-4} h^{-1} for concentrations between 1 and 25 mg/L NO_3^- and the R^2 between 0.9895 and 0.9962 (Table 3).

Table 3

The influence of NO_3^- concentration over the degradation of HCQ in synthetic aqueous solutions

NO_3^- (mg/L)	k_1'	R^2	$t_{1/2}$ (days)
1	0.000461	0.9925	62.70328
5	0.001382	0.9895	20.90109
10	0.001612	0.9962	17.91522
25	0.001842	0.9933	15.67582

Our study showed that by increasing NO_3^- anions concentration in the aqueous solutions, the HCQ degradation rate increased. It can be observed that the $t_{1/2}$ decreases by increasing the NO_3^- concentrations in the aqueous solution. The HCQ molecule slowly modifies in low NO_3^- aqueous solutions.

3.3. Influence of iron concentration

Iron(III) can exists in natural waters in different forms depending on pH conditions [16]. There are two principal types of ferrous waters: sulphate-ferrous/ferric and bicarbonate-ferrous/ferric ones. The bicarbonate ferrous/ferric water is arsenic poor, has below 6 pH values and has important haemopoietic properties with beneficial effects on specific respiratory diseases.

Fig. 6 presents the effect of water Fe(III) on the HCQ degradation. It was tested in a range of Fe(III) concentrations between 5 and 20 mg/L, resulting in a degradation rates between $14.7x10^{-3}$ and $30.3x10^{-3}$ h^{-1} and R^2 between 0.9841 and 0.9988.

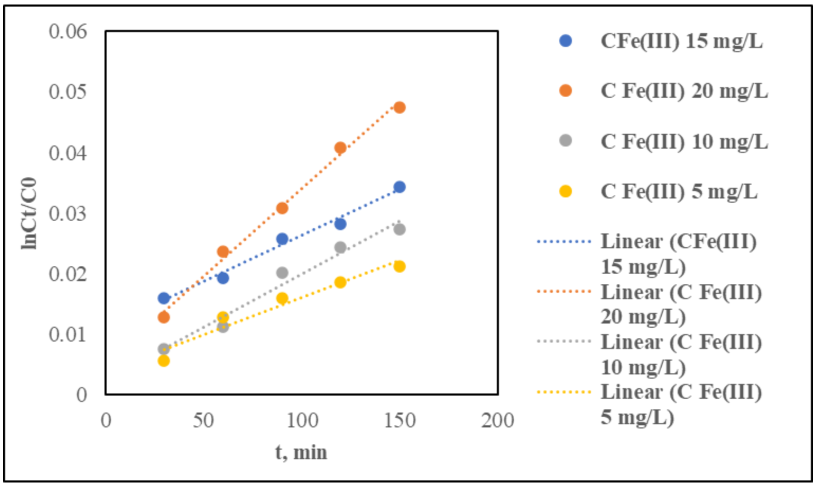


Fig. 6. The influence of Fe^{3+} concentration of the synthetic samples over HCQ behavior

A faster HCQ degradation at higher Fe^{3+} concentration values could be attributed to hydroxyl radicals in correlation with the solutions' pH.

3.4. Influence of bicarbonate concentration

Many studies showed the positive effects of bicarbonate mineral waters in prevention of cardiovascular diseases. Studies also showed that bicarbonate played an important role in determining the effect of organic pollutants [17] since it is present at important levels of concentration in natural waters.

From this study, it was observed that by increasing the HCO_3^- concentration, the HCQ degradation process decreases. It was carried out in a solution containing 10 mg/L HCQ in a range of HCO_3^- concentrations between 50 and 1000 mg/L (Fig. 7).

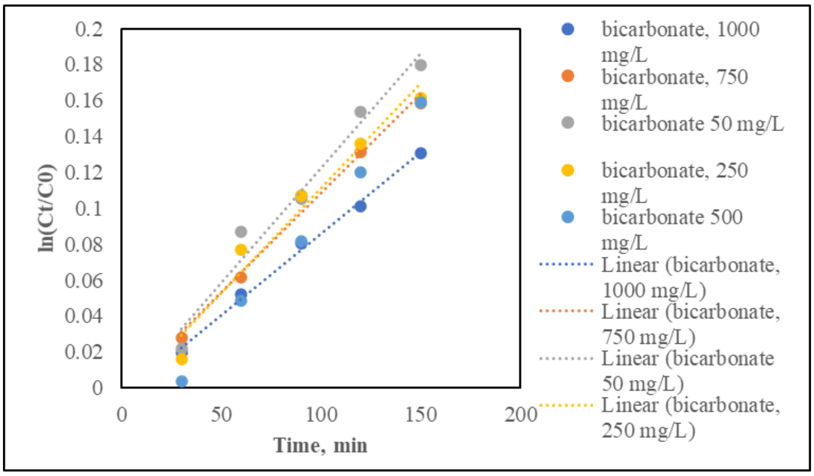


Fig. 7. The influence of HCO_3^- concentration of the synthetic samples over HCQ behavior

The results showed that the degradation rate constants of HCQ were between 2.76×10^{-3} h^{-1} and 1.84×10^{-3} h^{-1} for HCO_3^- concentrations of 50 and 1000 mg/L and the R^2 were between 0.9876 and 0.9932 (Table 4). This was explained by the consequently modified pH values and by the mixing effect. The inhibition of degradation at higher HCO_3^- concentrations might be also explained by the slow increase of pH of the aqueous solution. By increasing HCO_3^- concentration, at a 1000 mg/L concentration the value of pH is around 8 and at a 50 mg/L HCO_3^- concentration, the value of pH is around 6.

Table 4

The influence of HCO_3^- concentration over the degradation of HCQ in synthetic aqueous solutions

HCO_3^- (mg/L)	k_1'	R^2	$t_{1/2}$ (days)
50	0.002994	0.9915	9.646659
250	0.002879	0.9915	10.03253
500	0.002764	0.9923	10.45055
750	0.002533	0.9876	11.4006
1000	0.001842	0.9932	15.67582

The values of $t_{1/2}$ vary between 9 and almost 16 days in the studied range of HCO_3^- concentrations, showing that HCQ degrades slowly at higher HCO_3^- concentrations. This might be useful when ingesting the pills with natural mineral water. There are complex physicochemical interactions taking place in HCQ molecule because of a chlorine atom and a hydroxyl group structure. These groups can be substituted and these substitutions can change the acidity or the basicity of the reactive sites in the molecule. The changes of pH due to the changes of HCO_3^- concentration might cause changes of the HCQ structure that give birth to steric modifications [18], which might be responsible for different reaction pathways depending on the HCO_3^- concentration and of the pH.

3.5. Influence of initial HCQ concentration

The degradation kinetics, both chemical degradation and light degradation at different intial HCQ concentrations, between 5 and 20 mg/L is presented in Fig. 8. The degradation rate constants were in the range of 0.0020 and 0.0025 h^{-1} for the initial concentrations values mentioned above, with R^2 ranging between 0.9861 and 0.9984.

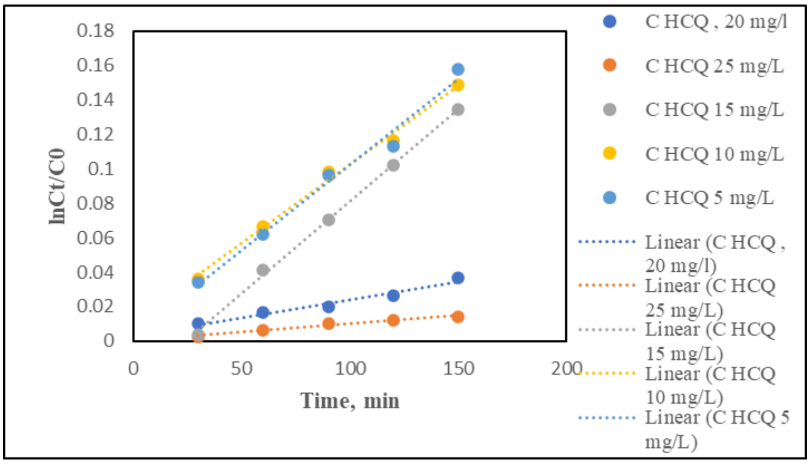


Fig. 8. The influence of initial HCQ concentration of the synthetic samples

The degradation rate constant decreased by increasing the initial HCQ concentration. It is possible that this effect appeared because the process took place at room light and more HCQ was present in solution, at pH 7. The same amount degraded due to light, by absorbing photons, because the number of available photons did not change.

3.6. Degradation of HCQ in natural waters

In the aquatic environment, pH values can vary from slightly acid to slightly basic ones, because of the presence of several inorganic species in aqueous matrix. The distribution of carbonate species is connected to the pH variation, such as hydroxyl ions from the solution. The initial concentration of HCQ can also influence its degradation, but taking into account all the mentioned variations, the hydrolytic stability of HCQ is not higher than 10% in aqueous media with average chemical compositions. For the medical tablets containing 200 mg HCQ (one tablet per day), this means a loss of approx. 20 mg and consequently less therapeutic effect in medical treatments. In Fig. 8 is presented the degradation steps of HCQ in aqueous samples.

Our hypothesis presumes that the chemical compostion of the water used to dissolve the HCQ tablet influences its fate in the organism and there are chemical aqueous matrices which can better preserve the quality of the HCQ pills.

The influence chart of the chemical composition of natural water over HCQ degradation is presented in Fig. 9.

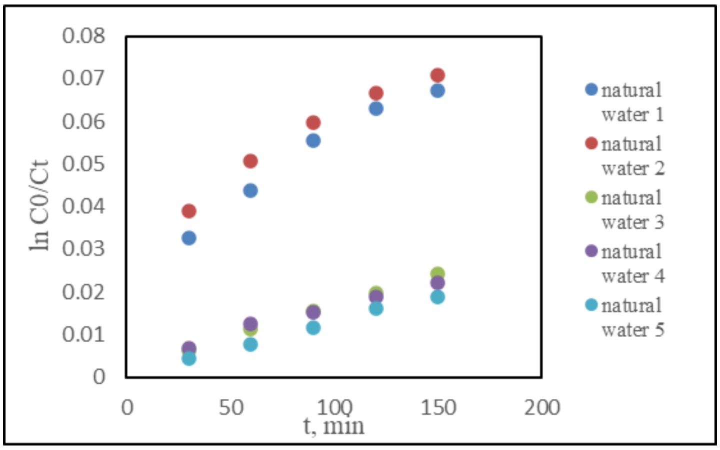


Fig. 9. The influence of the chemical composition of natural water over HCQ degradation (natural water 1 -5 from Tabel 1)

In Tabel 5 can be observed the influence of the ionic species from natural water over the HCQ degradation. The positive role of HCO_3^- over the HCQ degradation is maintained and it diminishes the effects of the other species in solution. The increasing total concentration of inorganic species in solution creates also a light attenuation, compensating the diminishing effect of Fe^{3+} and furthermore the rate of the HCQ degradation.

Table 5

The influence of the chemical composition of natural waters over the degradation of HCQ in aqueous solutions

Natural water	k'_1	$t_{1/2}$	R^2	HCO_3^- (mg/L)	pH	Fe^{3+} (mg/L)
2	6.91×10^{-4}	1003.25	0.9680	212±20.5	8	3.5±0.03
3	2.3×10^{-4}	3009.75	0.9992	1305±100.45	6.4	6.03±0.059

The combined effect of all the species is a more important suppression of HCQ degradation at lower HCO_3^- concentrations and a slighter one at higher HCO_3^- concentrations. These observations are sustained by comparing the results obtained in two of the five natural waters studied, natural waters 2 and 3 (from Table 1), which significantly differ considering their chemical composition.

4. Conclusions

This study's preliminary information results provide interesting insights into the aqueous fate of HCQ that are important for environmental and medical purposes. Results of the present analysis may be applicable for the conservation of HCQ in aqueous solutions for medical purposes. It was found that the pH of the solutions, the inorganic anions such as HCO_3^- and NO_3^- and cations such as Fe^{3+} and Mn^{2+} , (for whom results will be presented in a further study) play a major role on the HCQ behavior. By increasing the pH, the kinetics of HCQ degradation also increase, the same process taking place by increasing the NO_3^- concentration. An opposite effect was observed by increasing the HCO_3^- concentration, when the degradation of HCQ was inhibited. Taking into account all these, it might be a better solution to use natural mineral waters with slightly acidic pH, low amounts of NO_3^- and high concentrations of HCO_3^- in order to preserve the therapeutic effects of HCQ over humans and animals. The study will be continued, with focus on finding better results for preserving the HCQ qualities in aqueous solutions.

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