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Abstract

Kinetics of photodegradation of novel oral anticoagulants dabigatran, rivaroxaban, and apixaban were studied under simulated solar light irradiation in purified, mineral, and river waters. Dabigatran and rivaroxaban underwent direct photolysis with polychromatic quantum yields of 2.2×10^{-4} and 4.4×10^{-2}, respectively. The direct photodegradation of apixaban was not observed after 19 hours of irradiation. Kinetics of degradation of rivaroxaban was not impacted by the nature of the aqueous matrix while photosensitization from nitrate ions was observed for dabigatran and apixaban dissolved in a mineral water. The photosensitized reactions were limited in the tested river water (Isle River, Périgueux, France) certainly due to the hydroxyl radical scavenging effect of the dissolved organic matter. The study of photoproduct structures allowed to identify two compounds for dabigatran. One of them is the 4-aminobenzamidine while the second one is a cyclisation product. In the case of rivaroxaban, as studied by very high field NMR, only one photoproduct was observed *i.e.* a photoisomer. Finally, seven photoproducts were clearly identified from the degradation of apixaban under simulated solar light.

Keywords: photolysis; solar light irradiation; surface water; apixaban; dabigatran; rivaroxaban

1. Introduction

Until recently, oral anticoagulants were synonyms of vitamin K antagonists (VKAs) such as warfarin. These medicines are used for venous thromboembolism, stroke, atrial fibrillation treatment, and most generally in medicinal conditions that require chronic anticoagulation (Hanslik et al., 2004). VKAs may not be appropriate for many patients especially due to the necessity of dietary precautions and frequent laboratory monitoring (El-Helou et al., 2013). In fact, if warfarin concentration is too low the anticoagulation effect does not act efficiently; a too high concentration causes excessive bleeding. In this context, novel oral anticoagulants (NOACs) were developed (Spyropoulos, 2008; Beyer-Westendorf et al., 2014). The U.S. Food and Drug Administration (F.D.A.) recently approved the use of three new active ingredients, namely dabigatran etexilate (2010), rivaroxaban (2011), and apixaban (2012) (Wanat, 2013). Dabigatran etexilate is a prodrug that is converted to dabigatran and acts as a direct thrombin inhibitor (Khoo et al., 2010). Rivaroxaban and apixaban are direct factor Xa inhibitors that do not require cofactors for activity (Gulseth et al., 2008; Frost et al., 2013). These three compounds are also increasingly used in Europe. In particular, these NOACs currently represent 30% of ingested anticoagulants in France with an increase in their consumption by a factor of 10 between the second trimester 2012 and the third trimester 2013 (ANSM, 2013). The main limitation for their use was the absence of antidote. In 2015, the F.D.A. approved the idarucizumab as dabigatran antidote while rivaroxaban and apixaban antidote (andexanet alpha) is about to be validated (Pollack et al., 2015; Siegal et al., 2015). Thus, their prescriptions are expected to continue to rise in the near future.

To our knowledge, information reported in the literature about the occurrence of NOACs in the aquatic compartment, their fates, and their toxicity, as well as their degradation products are very scarce (Kasad, 2013; Ramisetti et al., 2014; Secrétan et al.; 2015; Swain et al., 2016; Tantawy et al., 2016; Wingert et al., 2016). This is especially worring since human

metabolism studies have shown that NOACs are eliminated in urines as unchanged forms at levels between 27 and 85% of the delivered dose (eVidal, 2017). In fact, organic pollutants are known to undergo degradation processes in environmental waters which must be taken into consideration. Photolysis can be one of the major ways of degradation for pharmaceutical compounds absorbing solar light as well as for those degraded by photosensitization (Szabo et al., 2011; Zuo et al., 2013; Carlson et al., 2015; Zhang et al., 2016; Chen et al., 2017).

This study has for objective to bring information on the environmental fate of NOACs. In particular, direct and indirect photolysis of NOACs was studied in different aqueous matrices. Results on molar absorption coefficients, rate constants and polychromatic quantum yields of photodegradation are discussed. Rate constants were obtained from simulated solar light irradiation in purified, mineral, and river waters to evaluate the effect of ions and dissolved organic matter naturally present in surface waters. Finally, the elucidation of structures of photoproducts was performed using LC-HRMS, and 700 and 800 MHz NMR spectrometers.

2. Materials and methods

2.1. Chemicals. The novel oral anticoagulants (NOACs) dabigatran (APIChem Technology, CAS 211914-51-1, 99%), rivaroxaban (AKSci, CAS 366789-02-8, 98%), and apixaban (APIChem Technology, CAS 503612-47-3, 99%), as well as 4-aminobenzamidine dihydrochloride (≥ 99.0%), methanol (CHROMASOLV®, ≥ 99.9%), and sodium bicarbonate salt (≥ 99.5%) were purchased from Sigma-Aldrich (Saint-Quentin Fallavier, France). Sodium nitrate salt (analytical reagent grade) was provided by Fisher Chemical. All chemicals were used as received. Purified water was produced using a Milli-Q® Direct-Q® 5 system (Millipore, resistivity 18.2 MΩ.cm). Mineral water (Volvic) contains 7.2 and 74.0 $mg.L^{-1}$ of nitrate and hydrogen carbonate ions, respectively. River water was collected from the Isle River (Périgueux, France). This surface water contained 7.7 and 140-200 $mg.L^{-1}$ of nitrate and hydrogen carbonate ions, respectively. Before use, the river water was filtered on a 0.45 µm hydrophilic PVDF Durapore® membrane (Millipore). Stock solutions of NOACs were prepared in purified water at concentrations of $5.0x10^{-5}$, $1.0x10^{-5}$, and $3.0x10^{-6}$ $mol.L^{-1}$ for dabigatran, rivaroxaban, and apixaban, respectively. During the preparation, volumetric flasks were covered with aluminum foils and solutions were left under magnetic stirring during one week. Then, stock solutions were stored in amber glass bottles at room temperature until use to prevent photodegradation and solubility problems, respectively. The stability of the three compounds was checked.

2.2. UV-Visible spectroscopy. UV-Visible absorption spectra were recorded on a UV-1800 spectrophotometer (Shimadzu, Japan). A 1-nm resolution and a “medium” scan rate were used to record the reference spectrum and spectra in the range 200-400 nm (NOACs do not absorb visible light) using either 1 or 5 cm quartz cells (QS, Hellma Analytics).

Molar absorption coefficients of dabigatran and rivaroxaban in purified water were calculated from the absorbance of five solutions with concentrations included in the range 10^{-6} - 10^{-5} mol.L^{-1}. Due to the particularly low solubility of apixaban in water, a stock solution was prepared in methanol at a concentration of $9.6x10^{-6}$ mol.L^{-1}. Then, this stock solution was used to prepare five solutions at concentrations between $1.0x10^{-6}$ and $4.8x10^{-6}$ mol.L^{-1} by adding purified water (*i.e.* the maximal proportion of methanol was of 50%).

The solar light emission spectrum at the Earth surface was recorded using a USB2000+ radiometer coupled to an optical fiber (Ocean Optics, Florida, USA).

2.3. Irradiation experiments. Solar radiations at the Earth surface were simulated using a SUNTEST CPS apparatus from Atlas Material Testing Solutions (Illinois, USA). The irradiance was set to 250 W.m^{-2}. In the case of kinetic studies, purified, mineral, and river waters were spiked with the stock solutions prepared in purified water to obtain final concentrations of $3.5x10^{-7}$, $3.5x10^{-7}$, and $4.5x10^{-7}$ mol.L^{-1} for dabigatran, rivaroxaban, and apixaban, respectively. For the elucidation of photoproduct structures, non-irradiated and irradiated stock solutions were analyzed without pre-treatment.

Before irradiation, samples were placed into 12 mL transparent glass tubes (optical pathlength: 1.5 cm) and were sealed to avoid water evaporation. NOACs were irradiated in purified water alone and doped with nitrate and bicarbonate ions (same concentrations as in mineral water), in mineral water, and in river water. For each aqueous matrix, two tubes were filled with 10 mL of solution and one of them was wrapped in an aluminum foil for dark control. To obtain kinetic data, aliquots of each sample were collected before irradiation and after scheduled irradiation time. For each kinetics, at least five samplings were performed and the analysis was repeated in triplicate. The maximum irradiation time was of 10 hours for dabigatran, 4 hours for rivaroxaban, and 19 hours for apixaban. To calculate the

polychromatic quantum yields of photodegradation, photon fluence rates were measured with a one nanometer interval in the range 290-350 nm using a USB2000+ radiometer coupled to an optical fiber (Ocean Optics, Florida, USA).

2.4. HPLC and LC-QToF-MS analyses. For kinetics studies, HPLC analyses were carried out using an Agilent 1100 series chromatograph (Agilent Technologies) equipped with a variable wavelength detector (Zuo, 2014). For dabigatran and rivaroxaban, the column was a Nucleosil® C_{18} Nautilus, 250 mm x 4.6 mm, with a particle size of 5 µm (Macherey-Nagel) while for apixaban the column was a Nucleodur® 100-5 C_{18} ec, 250 mm x 4.6 mm, with a particle size of 5 µm (Macherey-Nagel). Solvent A was methanol and solvent B purified water. Analyses were carried out in isocratic mode with a ratio of 60:40 (A:B, v/v) for rivaroxaban and apixaban, and a ratio of 30:70 (A:B, v/v) for dabigatran. The UV detection was performed at 303, 248, and 277 nm for dabigatran, rivaroxaban, and apixaban, respectively.

UV absorption spectra of photoproducts were recorded with an HPLC Spectra System P1000 coupled with a diode array detector model UV6000LP (Thermo Separation® Products). For each NOAC, elution conditions described above were used. With the goal to check the elution of all the products formed after irradiation, other analyses were performed in gradient mode. The gradient elution started with 10% of A and reached 100% in 25 minutes linearly. Then, it was kept stable during 5 minutes. No new photoproducts were observed compared to isocratic mode analyses.

LC-HRMS analyses were carried out using an Agilent 1290 HPLC system coupled to an Agilent 6540 QToF mass spectrometer (Agilent Technologies, Inc., Santa Clara, CA, USA) equipped with an Agilent Jet Stream electrospray ionization source (ESI). The chromatographic separation of the parent compound and of its photoproducts was performed

on a Kinetex C_{18} column (100 x 2.1 mm, 1.7 µm; Phenomenex®, Agilent Technologies, Les Ulis, France) regulated at 40°C. Gradient LC elution was performed at a flow rate of 0.3 $mL.min^{-1}$ using 0.1% formic acid in purified water as mobile phase A and 0.1% formic acid in acetonitrile as mobile phase B. The gradient started with 10% of B and was linearly increased to 35% in 13 minutes. The fraction B was then immediately increased and held at 100% for 1 min, before returning to the starting conditions for 3 min. Sample injection volume was set at 5 µL. Non-irradiated and irradiated stock solutions in purified water were analyzed without pre-treatment.

After elution, the analytes were detected using the QToF operating in positive ion mode (ESI+) with the following parameters: capillary voltage, 3000 V; nebulizer pressure, 40 psig; drying gas, 8 L/min; gas temperature, 300 °C; sheath gas flow, 11 L/min; sheath gas temperature, 400 C; nozzle voltage, 0 V; fragmentor voltage, 190 V. LC-MS accurate mass spectra were recorded across the range m/z 70 − 1000 at 2 GHz. The data recorded were processed with MassHunter Qualitative software (version B.06.00, Agilent Technologies, Santa Clara, CA, USA). Accurate mass measurements of each peak from the extracted ion chromatograms were obtained by means of a calibrant solution delivered by an external quaternary pump, allowing system to continuously correct for any mass drift by using the reference mass ion HP-921 [hexakis-(1H,1H,3H-tetrafluoropropoxy)-phosphazine] at m/z 922.0098. Stability of mass accuracy was checked before, and if values went above 0.2 ppm error, then the instrument was recalibrated. The instrument was operated in single MS with full spectra (1 spectrum/s) and in MS/MS (2 spectra/s) using an isolation width set at medium (m/z ~ 4), and collision energies of 10, 20, and 40 eV. A standard solution containing 36 compounds was injected before the samples to check the retention time of compounds and the instrumental sensitivity.

2.5. Rate constants and polychromatic quantum yields. Following the absorption of a photon, an organic contaminant (C) can be degraded and one or several photoproducts (P) are formed. The equation of the reaction is:

$$C \xrightarrow{h\nu} P$$

Under specific experimental conditions (*i.e.* low absorbance), this reaction generally follows an apparent first-order kinetics modeled by equation 1:

$$\ln\left(\frac{[C]_0}{[C]_t}\right) = k_{poly} \cdot t \quad \text{eq. (1)}$$

where $[C]_0$ and $[C]_t$ are the organic contaminant concentrations (mol.L^{-1}) respectively before irradiation and at the instant t, k_{poly} is the apparent first-order rate constant under polychromatic irradiation (s^{-1}), and t is the irradiation time (s).

In this framework, the rate of photolysis of C is given by equation 2:

$$v(C) = k_{poly} \cdot [C]_t = \sum_{\lambda_1}^{\lambda_n} I_{0,\lambda_i} \cdot (1 - e^{-2.303 \cdot A_{\lambda_i}}) \cdot \phi_{\lambda_i} \quad \text{eq. (2)}$$

where I_{0,λ_i} is the photon fluence rate of the irradiation source (E.L^{-1}.s^{-1}), A_{λ_i} is the absorbance of C and ϕ_{λ_i} is the quantum yield of photolysis of C (mol.E^{-1}) at the λ_i wavelength. λ_1-λ_n is the overlapping wavelength range between the UV-Vis absorptions of the organic contaminant and the emission spectrum of the radiation source.

In environmental conditions, the absorbance of C is generally low (A < 0.02, hyper dilute medium). Based on this hypothesis, the expression of polychromatic quantum yield of photolysis (ϕ_{poly}, mol.E^{-1}) of C is given by equation 3:

$$\phi_{poly} = \frac{k_{poly}}{2.303 \cdot l \cdot} \cdot \sum_{\lambda_1}^{\lambda_n} \frac{1}{\varepsilon_{\lambda_i} \cdot I_{0,\lambda_i}} \quad \text{eq. (3)}$$

where l is the sample's optical pathlength (cm) and ε_{λ_i} is the molar absorption coefficient (L.mol^{-1}.cm^{-1}) at the λ_i wavelength.

2.6. Nuclear magnetic resonance spectroscopy. LC-QToF-MS analyses were not enough to identify the structure of the rivaroxaban photoproduct due to the same fragmentation pattern (see supplementary materials). The main limitation for NMR analyses was the low solubility of rivaroxaban in water and thus the low concentration of its degradation product. In order to concentrate both compounds, a solution of rivaroxaban was prepared in methanol at an initial concentration of 52.9 $mg.L^{-1}$ and was irradiated with a SUNTEST CPS+ (250 $W.m^{-2}$) during 8 hours. A volume of 8 mL of this solution was evaporated and the residue dissolved in 500 µL of methanol-d_3 (Eurisotop, France) for NMR experiments. The photochemical reactivity of rivaroxaban was the same in purified water and in methanol. A second sample of pure rivaroxaban (few mg of powder were dissolved in methanol-d_3) was prepared.

1D and 2D NMR spectra of non-irradiated and irradiated rivaroxaban were recorded at room temperature on Bruker Avance III HD SB 700 MHz and 800 MHz spectrometers. The 700 MHz spectrometer was equipped with a 5 mm 1H-13C/15N/D TXI probe with Z-gradients operating at 176.07 MHz and 700.15 MHz for ^{13}C and ^{1}H, respectively. The 800 MHz spectrometer was equipped with a 5 mm 1H-13C/15N/D TCI cryoprobe with Z-gradients operating at 81,08 MHz, 201.21 MHz and 800.23 MHz for ^{15}N, ^{13}C and ^{1}H, respectively. In order to assign the 2 structures, the following experiments were performed: 1D-^{1}H and 1D-^{13}C experiments and, HSQC ^{1}H-^{13}C, HMBC ^{1}H-^{13}C, COSY, TOCSY, NOESY, and SOFAST-HMQC ^{1}H-^{15}N, two-dimensional experiments. Data treatment was accomplished using the TopSpin Bruker software.

3. Results and discussion

3.1. Ultraviolet absorption spectra. UV absorption spectra of dabigatran, rivaroxaban, and apixaban, are presented in Fig. 1. Dabigatran dissolved in deionized water displays two maxima located at 302 nm (ε_{302} = 24 180 L.mol^{-1}.cm^{-1}) and 220 nm (ε_{220} = 40 940 L.mol^{-1}.cm^{-1}). In the case of rivaroxaban, the spectrum recorded in the aqueous medium shows a maximum at 248 nm (ε = 23 820 L.mol^{-1}.cm^{-1}). Moreover, a shoulder was observed at 273 nm (ε = 14 930 L.mol^{-1}.cm^{-1}). UV absorptions of apixaban have been studied in a mixture of methanol and water due to the very low solubility of the drug into the aqueous solvent. A maximum of absorption is observed at 278 nm (ε = 14 320 L.mol^{-1}.cm^{-1}). This maximum was found at the same wavelength in pure methanol (9.6x10^{-6} mol.L^{-1}) and in pure water (3.0x10^{-6} mol.L^{-1}). The calculated molar absorption coefficient in pure methanol was of 14 700 L.mol^{-1}.cm^{-1}.

Please insert Fig. 1.

The three novel oral anticoagulants (NOACs) absorb photons above 300 nm. Therefore, they absorb the solar light reaching the Earth surface and they can undergo direct photolysis (Fig. 1). The study of this abiotic degradation pathway is of main concern from the environmental point of view. Moreover, the role of ions and dissolved organic matter (DOM) naturally present in surface waters is also discussed further.

3.2. Rate constants and quantum yields of photolysis. Dabigatran, rivaroxaban, and apixaban were irradiated under simulated solar light in unspiked and spiked purified water with nitrate (NO_3^-) and hydrogen carbonate (HCO_3^-) ions, in mineral and in river waters. Calculated rate constants, coefficients of determination, half-lives ($t_{1/2}$), and polychromatic

quantum yields of photolysis are compiled in Table 1. In each case, NOACs photolysis followed apparent first-order kinetics. From dark control samples no thermal degradation and no hydrolysis were observed at the same time as the irradiation experiments.

Kinetics of photodegradation of dabigatran was dependent on the nature of the aqueous matrix. The calculated half-life was of 19.9 hours in deionized water and decreased by a factor of 2.7 to reach 7.4 hours in the mineral water. Afterwards, dabigatran was irradiated in purified water spiked with nitrate ions at a concentration of 7.2 $mg.L^{-1}$ *i.e.*, the same concentration occurring in mineral water. The obtained half-life was of 6.8 hours, which is almost the same value as that obtained in mineral water. In river water (nitrate ions concentration: 7.7 $mg.L^{-1}$), 50% of dabigatran was degraded in 24.1 hours; therefore, in this aqueous medium the degradation induced by light is less efficient by a factor 3.3 compared to the mineral water.

For rivaroxaban, kinetics of photodegradation were not significantly dependent on the nature of the aqueous matrix. In fact, half-lives of 2.3, 2.1, and 2.2 hours were obtained in purified, mineral, and river waters, respectively. Photolysis of rivaroxaban in purified water spiked with nitrate ions led to a half-life of 2.0 hours.

The behavior of apixaban under simulated solar light irradiation is a function of the aqueous medium. In purified water no degradation of the drug was observed after 19 hours of irradiation. At the opposite, in mineral water, a degradation was observed with a calculated half-life of 23.6 hours. This half-life decreased by a factor of 2.3 (10.4 hours) when apixaban was irradiated in purified water in the presence of nitrate ions. When both nitrate and hydrogen carbonate (74.0 $mg.L^{-1}$) ions were present in the medium, the half-life increased to 26.9 hours. In the river water, 50% of degradation would be reached after 96.3 hours, clearly showing a lowering of the photodegradation efficiency.

Please insert Table 1.

From these results, we can state that among the three NOACs, dabigatran and rivaroxaban are subject to direct photolysis under simulated sunlight irradiation, *i.e.*, degradation occurs in purified water. At the opposite, direct photodegradation of apixaban is not significant. In addition to direct photolysis, photosensitized reactions are clearly observed for dabigatran and apixaban. Ions naturally present in the mineral water can be at the origin of this processes. The photosensitizing potential of nitrate ions was particularly reviewed by Mack and Bolton (1999). These ions absorb solar light and then react with water to produce highly reactive hydroxyl radicals (Zuo et al., 2006; Chen et al., 2013). The photodegradation kinetics of dabigatran is accelerated in mineral water and in purified water spiked with nitrate ions. Both aqueous media led to a half-life close to 7.0 hours. We can thus conclude that the ion mainly responsible for the acceleration of dabigatran photodegradation was NO_3^-. In the case of apixaban, circumstances are slightly different. Nitrate ions are also proved to accelerate the drug photolysis but this result is not sufficient to explain the obtained half-life in mineral water. In fact, 50% of degradation would be reached after 23.6 and 10.4 hours in mineral water and deionized water spiked with NO_3^-, respectively. Addition of hydrogen carbonate ions to water spiked with nitrate ions induced an increase of the half-life by a factor of 2.6 ($t_{1/2}$ = 26.9 h). Hydrogen carbonate ions are among the most widespread anions in environmental waters and they are known to act as scavengers of hydroxyl radicals (Nakatani et al., 2007; Tercero Espinoza et al., 2007). Therefore, in our case the increase of apixaban half-life is mainly due to the reaction of HCO_3^- ions with hydroxyl radicals produced by nitrate ions under simulated sunlight irradiation. Finally, rivaroxaban photolysis seems not to be significantly impacted by ions present in the mineral water. This result can be explained by the very fast direct phototransformation of rivaroxaban. As a consequence, indirect photochemistry is unable to affect the phototransformation rate significantly.

In the river water, the concentration of nitrate ions (7.7 $mg.L^{-1}$) is close to that measured in mineral water (7.2 $mg.L^{-1}$). The concentration of hydrogen carbonate ions is included between 200 and 140 $mg.L^{-1}$, *i.e.*, at least twice as high as in mineral water. Thus, the HCO_3^- ions scavenging effect is expected to be more efficient in river water than in mineral water. In surface waters, the ions effects are added to those of DOM that can act as photosensitizer, as screen through competitive light absorption, as inhibitor of triplet-sensitized transformation by reducing partially oxidized intermediates to the starting compounds, and as radical scavenger (Walse et al., 2004; Wenk et al., 2011, Chen et al., 2013; Liang et al., 2015; Zhang et al., 2016). In the case of dabigatran, the half-life in river water increases by a factor of 3.3 in comparison with the mineral water. This increase cannot be assigned only to the scavenging effect of HCO_3^- ions. In fact, the comparison of results in mineral water and in purified water spiked with NO_3^- ions shows no clear effect of HCO_3^- ions on the rate constants for photolysis of dabigatran (Table 1). In the same way, apixaban half-life increases by a factor of 4.1. Thus, the increase of half-lives of dabigatran and apixaban cannot be explained only by the concentration increase of HCO_3^- ions in the river water but by the effect of DOM. Results obtained with rivaroxaban help to understand its role. In fact, rivaroxaban phototransformation is apparently not impacted by the presence of DOM. Thus, no significant screen effect is observed from DOM (see SF1 of supplementary materials). This result leads to the conclusion that the observed slowing down of the degradation of dabigatran and apixaban in river water is mainly due to a scavenging of hydroxyl radicals. The effect of DOM is emphasized with apixaban, for which the degradation occurs only by means of photosensitization.

Finally, the efficiency of NOACs direct photolysis was evaluated from polychromatic quantum yields of photodegradation. Values of $2.2x10^{-4}$ and $4.4x10^{-2}$ $mol.E^{-1}$ were calculated for dabigatran and rivaroxaban, respectively. Dabigatran absorbs sunlight to a higher extent

than rivaroxaban (Fig. 1), which partially offset the strong difference in the photolysis quantum yields. In the case of apixaban, no quantum yield for photolysis was determined due to the absence of degradation after 19 hours of simulated sunlight irradiation.

3.3. Structures of NOACs photoproducts. For each NOAC, non-irradiated and irradiated solutions were analyzed by means of LC-QToF-MS. Three products (D1, D2, and D3) were observed for dabigatran and one product (R1) for rivaroxaban, both irradiated in purified water. For apixaban, seven products (A1 to A7) were observed in mineral water. Results are gathered in Table 2.

In the case of dabigatran, among the three photoproducts observed two of them were associated to the drug photodegradation (Fig. 2). These compounds have m/z of 136.0874 (D1, $C_7H_{10}N_3$) and 323.1145 (D2, $C_{17}H_{15}N_4O_3$). D1 fragmentation spectrum displays m/z at 119 (-17) associated to the loss of a NH_3 group located on the amidine part, and at 92 (-27) associated to the loss of the C=NH fragment (see SF4 of supplementary materials).

Please insert Table 2.

D1 was identified as the 4-aminobenzamidine (4-AB). This hypothesis was confirmed from LC-UV (Fig. 3a) and LC-QToF (see SF4 of supplementary materials) analyses of the standard. 4-AB is known to act as inhibitor of trypsin, an enzyme involved in the digestion of proteins (Safarik et al., 2002). D2 structure is formed from the other moiety of dabigatran for which an intramolecular cyclization and a demethylation occurred (Fig. 2). Only one fragment (m/z = 251) is clearly observed for D2. This fragment is associated to a decarboxylation and a CO elimination. The UV spectrum of D2 is displayed in Fig. 3a.

Please insert Fig. 2.

Finally, a last photoproduct (D3) with a m/z of 279.1248 ($C_{16}H_{15}N_4O$) was observed. This compound is not directly formed from dabigatran but from D2. In fact, D2 and D3 have a m/z difference of 44 (CO_2 group) and produce the same fragment at m/z = 251. Therefore, we can assume that D3 is formed from the photo-decarboxylation of D2.

Please insert Fig. 3.

Rivaroxaban degradation induced by simulated solar light irradiation in purified water produces only one main photoproduct with molecular ion at m/z 436.0732 (named R1) in ESI+ mode (Table 2). R1 has the same m/z as rivaroxaban, *i.e.* a photoisomerization occurred. The UV absorption spectrum of R1 displays one band at 245 nm while that of rivaroxaban presents a maximum at 248 nm with a shoulder at 273 nm (Fig. 3b). The substituted thiophene moiety is responsible for the maximum of absorption around 245 nm (Boig et al., 1953); this part of the parent compound is unchanged in R1. This result is supported by the presence of a fragment at m/z 145 assigned to the substituted thiophene ring and observed on both spectra of isomers (see SF8 of supplementary materials).

Please insert Fig. 4.

Processes of photoisomerization involving an intramolecular cyclisation as photo-Fries (Sandner et al., 1968) and Norrish type II reaction (Norrish et al., 1937) were considered. The two processes lead to structures in which the substituted thiophene ring is unchanged as validated using high field NMR. Indeed, ^{1}H and ^{13}C NMR spectra show the same splitting patterns for both compounds (see SF9 and SF10 of supplementary materials). The SOFAST-HMQC ^{1}H-^{15}N 2D map undoubtedly shows the presence of a NH group in the R1 structure

(Fig. 4a) and the TOCSY sequence clearly exhibits two correlation pathways between NH proton (8.93 and 8.75 for R and R1 structures, respectively) and protons at 3.74 (J3), 4.92 (J4), and 4.24/3.95 (J5) ppm for R, 4.24/3.95 (J5) ppm for R and 3.74/3.84 ppm (J3), 4.96 (J4), and 4.00/4.26 (J5) ppm for R1 (Fig. 4b). On this basis, the proposed structure for R1 is presented in Fig. 5.

Please insert Fig. 5.

The simulated sunlight irradiation of apixaban in mineral water results in the clear observation of seven photoproducts (Table 2). Assuming that LC-MS/MS structure responses are the same for each compound, four degradation products can be considered as major (A3, A5, A6, and A7). Their structures are presented in Fig. 6. Structures of minor photoproducts have also been determined (A1, A2, and A4; see SS2, SS3, and SS5 of supplementary materials).

Please insert Fig. 6.

A1 (m/z = 191.1186) and A2 (m/z = 287.1146) are assigned to $C_{11}H_{15}N_2O$ and $C_{14}H_{15}N_4O_3$, chemical formula, respectively. Concerning the main photoproducts, A3 (354.1581, $C_{18}H_{20}N_5O_3$) is formed from the release of methoxybenzene, A4 and A5 (476.1939, $C_{25}H_{26}N_5O_5$) are obtained by hydroxylation of the phenyl group, A6 (446.1818, $C_{24}H_{24}N_5O_4$) is formed from the substitution of the methoxy group by a hydroxy group, and A7 (458.1820, $C_{25}H_{24}N_5O_4$) is obtained from the formation of an unsaturation into the 2-oxo-1-piperidinyl ring linked to the pyrazole ring. This latter structure is in agreement with a polarity lowering and thus a retention time increase. The fragmentation pattern of each photoproduct is described in SS4, SS6, SS7, and SS8 of supplementary materials.

4. Conclusion

Kinetics of photodegradation show that photolysis can be one of the main ways of degradation for NOACs present in surface waters. Rivaroxaban degradation is not significantly impacted by the nature of the aqueous matrix. This compound seems only to undergo direct photolysis leading to a photoisomerization. The structure of the photoisomer has been clearly identified from NMR spectra. Dabigatran is photolyzed by direct and indirect routes. Nitrate ions are mainly responsible for the acceleration of dabigatran degradation. Results in river water show that dissolved organic matter slows down the degradation of dabigatran probably related to its action as a scavenger of hydroxyl radicals. Two photoproducts are formed, *i.e.* the 4-aminobenzamidine and a cyclization product. Apixaban is degraded only by photosensitization which is induced by nitrate ions. At the opposite, hydrogen carbonate ions partially block the degradation of apixaban. This effect is also observed in the presence of dissolved organic matter. Seven photoproducts were clearly identified under simulated solar light irradiation of apixaban.

Following these results, it will be important to evaluate the ecotoxicological impact of NOACs photoproducts. Compounds of potential concern are especially the isomer of rivaroxaban and the 4-aminobenzamidine, which is a known inhibitor of trypsin and could be at the origin of toxic effects.

ACKNOWLEDGEMENTS

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431

432 SUPPLEMENTARY MATERIALS

433 Supplementary information related to this article can be found at

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Photodegradation of novel oral anticoagulants under sunlight irradiation in aqueous matrices

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Tables

Table 1

Apparent first-order rate constants (k, min^{-1}), coefficients of determination (R^2), half-lives ($t_{1/2}$, h), and polychromatic quantum yields of photolysis (ϕ, $mol.E^{-1}$) obtained from Suntest irradiation of NOACs in aqueous matrices. ND: not degraded. Error bar on first-order rate constants: ±10%.

NOAC	Aqueous matrix	k x 10^4	R^2	$t_{1/2}$	ϕ
Dabigatran	purified water	6.0	0.9944	19.9	$2.2x10^{-4}$
	mineral water	14.1	0.9778	7.4	-
	purified water + NO_3^-	17.1	0.9953	6.8	-
	river water	4.7	0.9633	24.1	-
Rivaroxaban	purified water	49.4	0.9975	2.3	$4.4x10^{-2}$
	mineral water	55.9	0.9943	2.1	-
	purified water + NO_3^-	57.5	0.9808	2.0	-
	river water	51.6	0.9960	2.2	-
Apixaban	purified water	ND	-	-	ND
	mineral water	4.9	0.9924	23.6	-
	purified water + NO_3^-	11.1	0.9892	10.4	-
	purified water + NO_3^- + HCO_3^-	4.3	0.9823	26.9	-
	river water	1.2	0.9875	96.3	-

38

39 **Table 2**

40 LC-MS/MS (ESI+) analyses of NOACs and of their photoproducts. RT: retention time.

NOAC	Name	m/z (RT in min)	Proposed chemical formula	Δ(m/z) (ppm)	Fragments (relative intensity in %)
Dabigatran	D	472.2116 (2.2)	$C_{25}H_{26}N_7O_3$	-4.02	-
	D1	136.0874 (1.0)	$C_7H_{10}N_3$	0.73	119 (100), 92 (17)
	D2	323.1145 (2.3)	$C_{17}H_{15}N_4O_3$	-0.31	251 (100)
	D3	279.1248 (3.2)	$C_{16}H_{15}N_4O$	-0.72	251 (100)
Rivaroxaban	R	436.0739 (11.3)	$C_{19}H_{19}ClN_3O_5S$	-1.15	-
	R1	436.0732 (8.2)	$C_{19}H_{19}ClN_3O_5S$	0.46	436 (73), 231 (63), 145 (100)
Apixaban	A	460.2012 (11.7)	$C_{25}H_{26}N_5O_4$	-5.87	-
	A1	191.1186 (1.5)	$C_{11}H_{15}N_2O$	-1.05	191 (100), 147 (16), 107 (13)
	A2	287.1146 (5.3)	$C_{14}H_{15}N_4O_3$	-0.70	270 (100), 242 (9)
	A3	354.1581 (5.5)	$C_{18}H_{20}N_5O_3$	-4.24	337 (100)
	A4	476.1939 (8.0)	$C_{25}H_{26}N_5O_5$	-1.05	459 (100), 241 (13), 199 (74)
	A5	476.1939 (8.5)	$C_{25}H_{26}N_5O_5$	-1.05	459 (100), 361 (11), 241 (18), 200 (13), 199 (70)
	A6	446.1818 (8.8)	$C_{24}H_{24}N_5O_4$	2.24	430 (23), 429 (83), 282 (13), 227 (15), 186 (13), 185 (100), 171 (12), 93 (11)
	A7	458.1820 (12.3)	$C_{25}H_{24}N_5O_4$	1.75	458 (42), 441 (100), 385 (64), 342 (10), 277 (15), 199 (36)

41

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Figures

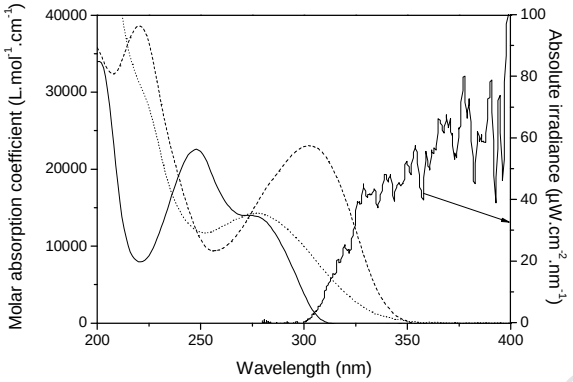
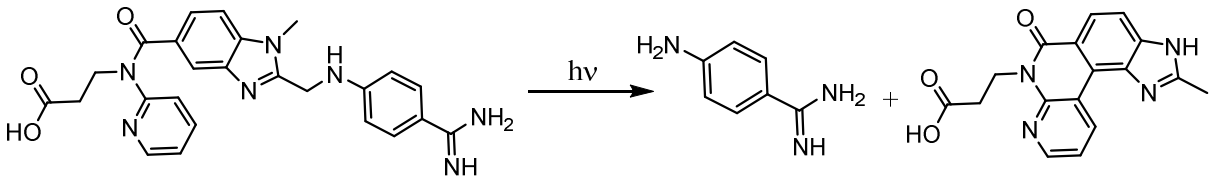


Fig. 1. UV absorption spectra of dabigatran (dashed line) and rivaroxaban (solid line) dissolved in purified water, and of apixaban (dotted line) dissolved in a methanol-water mixture. Solar light emission spectrum at the Earth surface on May 5, 2016 at coordinates (45.195510, 0.718811).

37



D D1 (4-aminobenzamidine) D2

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39

40 **Fig. 2.** Photodegradation of dabigatran under simulated solar light irradiation in purified

41 water.

42

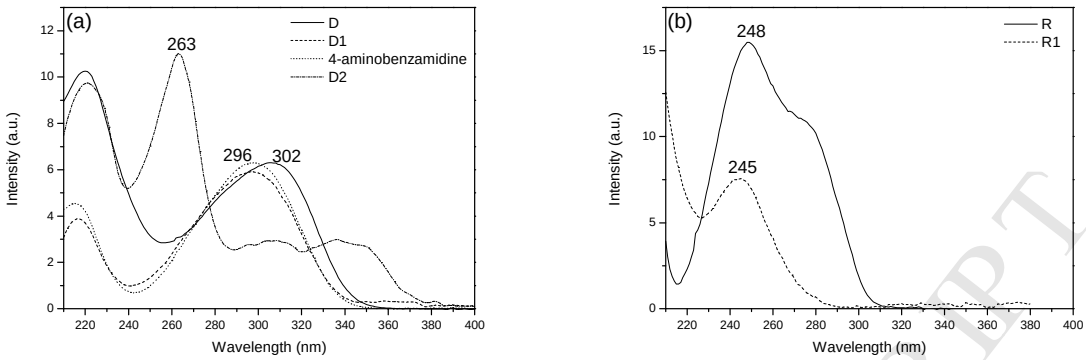

Fig. 3. UV absorption spectra of (a) dabigatran (solid line), D1 (dashed line), 4-aminobenzamidine (dotted line), and D2 (dashed-dotted line); (b) rivaroxaban (solid line) and of its photoisomer (R1, dashed line).

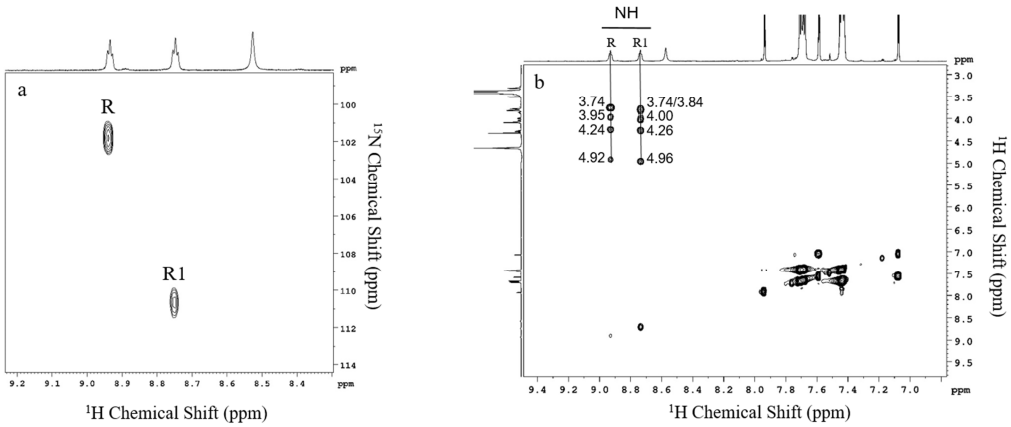

Fig. 4. Selected expansions of 2D NMR spectra of rivaroxaban (R) and of its photoisomer (R1) in MeOH-d_3: (a) SOFAST-HMQC ^{1}H-^{15}N and (b) TOCSY NMR spectra.

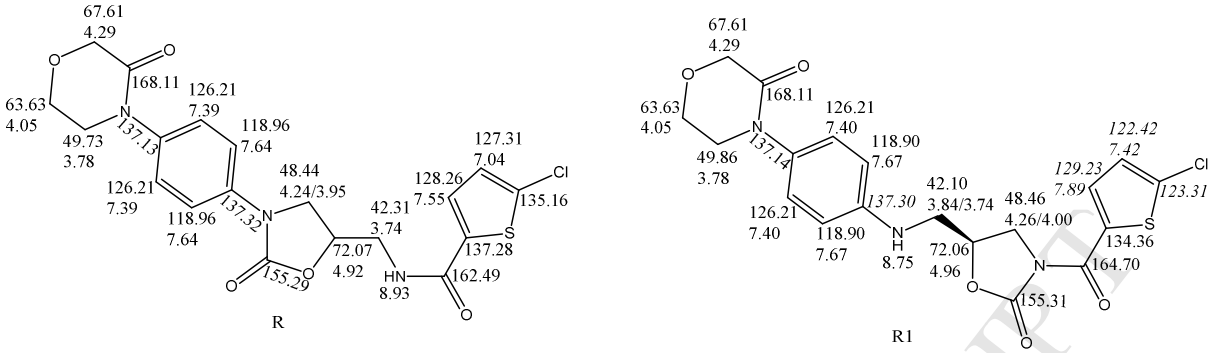

Fig. 5. ^{13}C and ^{1}H chemical shifts (ppm) of rivaroxaban (R) and its photoisomer (R1). Chemical shifts in italics: the similarity of the two structures (R and R1) as well as the low concentration of the samples did not allow, despite the use of a very high magnetic field, to remove the ambiguity on the assignment of chemical shifts.

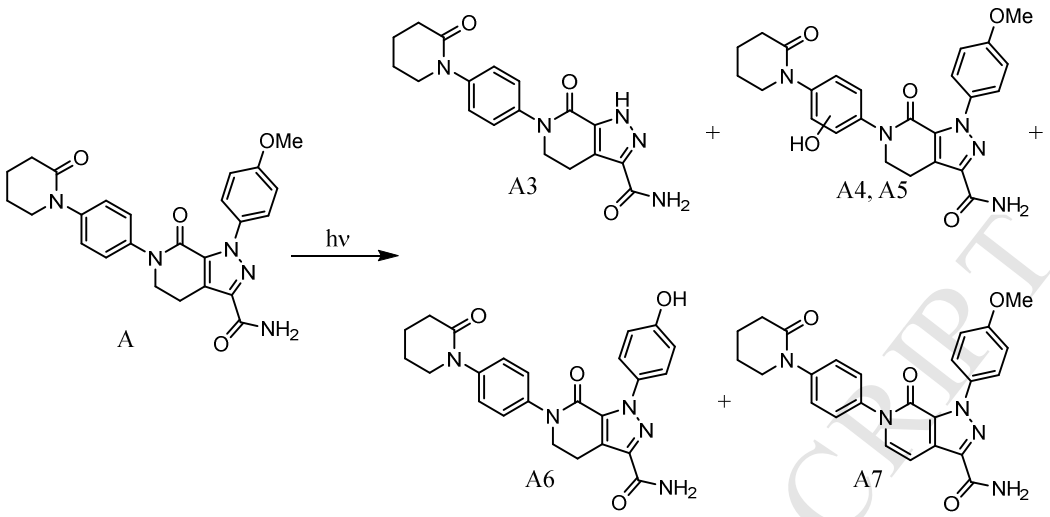

Fig. 6. Major photoproducts of apixaban formed under simulated solar light irradiation in mineral water.

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Highlights

- Dabigatran undergoes direct and indirect photolysis, $t_{1/2}$ is of 24h in river water.
- Direct photolysis is predominant for rivaroxaban, $t_{1/2}$ is of 2.2h in river water.
- Argatroban is mainly photodegraded by photosensitization.
- Structures of main photoproducts have been identified.