

INVESTIGATION OF THE TRANSFORMATION OF 5-FLUOROURACIL CYTOSTATICS BY UV AND VUV PHOTOLYSIS

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Abstract

In this work, UV (254 nm), UV/VUV_{185 nm}, and VUV_{172 nm} photolysis of 5-fluorouracil (5-FLU), a cytostatic drug were investigated. For the water treatments three type of lightsources were applied: a low-pressure mercury vapour lamps emitting only 254 nm UV light, an other low-pressure mercury vapour lamps emitting both 254 nm UV and 185 nm VUV light, and a Xe excimer light source emitting 172 nm VUV photons. In parallel, with the transformation of 5-FLU, H₂O₂ formation was detected and measured. During UV/VUV_{185 nm} photolysis, the formation of H₂O₂ follows a maximum curve, while in the case of UV photolysis, it shows a saturation curve. Its concentration reached higher value in the case of UV/VUV_{185 nm} than in UV radiation. To enhance the efficiency of the reactors, we used air, O₂ and N₂ gases and assessed their effect to the photolysis of 5-FLU to see wich parameters are the most suitable for transforming it.

Introduction

5 Fluorouracil (5-FLU) is an antineoplastic drug that is being used in a wide variety of cancer treatments such as breast cancer, colon cancer, stomach cancer and some types of skin cancer. 5-FLU is a genotoxic compound, it builds into the DNA and by alkalinizing it, it also inhibits the thimidilate sinthase enzyme resulting in fatal DNA errors [1]. In some countries (depending on the size of the population and the incidence of cancer), several kilogram of 5-FLU is used each year, which can result in up to 100 µg in hospital effluents [2]. 5-FLU is a potential contaminant of natural waters through hospital wastewater and its metabolites selected by the human body can pose an environmental risk in the sewer system. Due to its low absorbance above 290 nm, it does not or slowly transform with direct photolysis under the influence of sunlight, so it is likely accumulate in surface waters. On the other hand, 5-FLU has low Henry's law constant (1.66×10^{-10} atm L mol⁻¹ [3]), and it has low logK_{ow} (-0.89 [4]), and neither hydrolysis nor volatilization is typical. Consequently 5-FLU can be disposed primarily by photolysis, so it is very important to investigate the efficacy of AOPs in the conversion of 5-FLU and its degradation products.

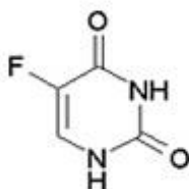


Figure 1. Chemical structure of 5-fluorouracil

One of the most efficient technologies for persistant water pollutant are the advanced oxidation processes wich use electromagnetic radiation (like gamma-, UV-and/or VUV radiation) in some instances alongside oxidating agents such as H₂O₂ and ferrous ions to create highly reactive species (H• and OH• radicals) to transform organic molecules.

UV photolysis is widely used in water treatment for disinfection due to its germicidal effect. In most cases, for UV photolysis low-pressure mercury vapour lamp is used, emitting at 254 nm, both on a laboratory and industrial scale. The efficiency of the method is mainly determined by the molar absorbance of the target compound and the quantum efficiency for its transformation. During its discharge the majority of the emitted photons (approximately 90%) have a wavelength of 254 nm, the rest of them has a wavelength of 185 nm, which is absorbed on the lamp made of traditional quartz. In the case of lamp made of synthetic quartz, it able to emit both 254 nm UV and 185 nm VUV photons.

There are two main sources of VUV_{172 nm} radiation. The low pressure mercury vapour lamp (mentioned above) and the excimer lamps. The excimer lamps contain noble gases, which form dimers in response to an electric impulse with the sufficient energy. These dimers dissociate afterwards emitting VUV photons that can be taken as quasi monochromatic light. Excimer lamps have a number of advantages such as no warmup time, quasi monochromatic light emission, high spectral power density, low heating ('cold lamps').

Experimental

Two types of low-pressure mercury vapour lamps was used as light sources: a LightTech GCL307T5L light source for UV (254 nm) photolysis, a GCL307T5VH type light source for UV/VUV (254/185 nm) photolysis, and a Radium Xeradex™ lamp for VUV (172 nm) photolysis. The envelope of the UV lamp emitting at 254 nm was made of commercial quartz, while the UV/VUV (254/185 nm) lamp's envelope was made of synthetic quartz to be able to transmit the 185 nm VUV photons. The intensity of 185 nm VUV light radiation is about 6-8% of UV light radiation.

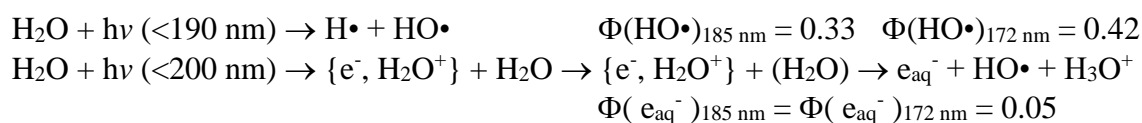
5-FLU (Sigma-Aldrich, ≥99%) solutions (500 mL) with 1.0×10^{-4} mol L⁻¹ initial concentration was made in ultrapure MILLI-Q water (MILLIPORE Milli-Q Direct 8/16).

Separation of the organic substances of the treated samples and determination of 5-FLU concentration was performed by liquid chromatography using Agilent 1100 type HPLC (High Performance Liquid Chromatography) equipped with a diode array UV (DAD) detector. The column (Aminex HPX-87H, 300×7.5 mm) was thermostated at 30 °C, the flow rate of eluent was 0.9 mL min⁻¹, and 20 μL sample was injected.

Total organic carbon (TOC) measurements were performed using an Analytik Jena N/C 3100 analyzer. The concentration of H₂O₂ was measured with a cuvette test by Merck, with a 0.015 - 6.00 mg L⁻¹ measuring range.

Results and discussion

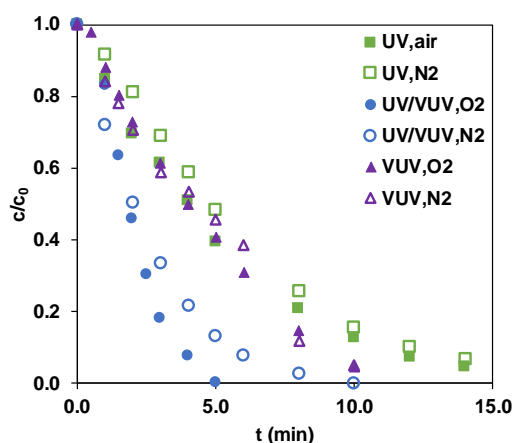
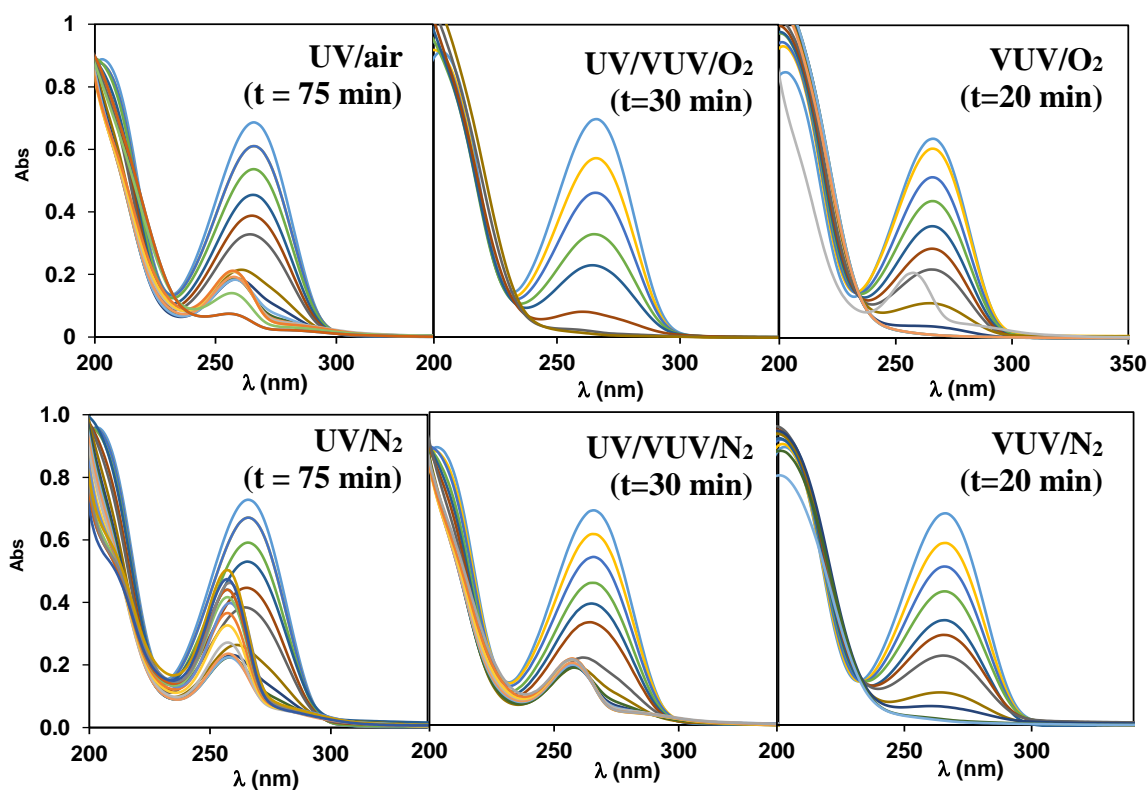
At first, transformation rates of 5-FLU were compared in the cases of UV, UV/VUV_{185 nm}, and VUV_{172 nm} irradiated solutions (table 1). Direct photolysis was effective in the transformation of 5-FLU, which is supported by several literatures [4, 5], but using UV/VUV_{185 nm} photolysis it increases the transformation rate at least one and a half times (Fig 2.). In the case of 254 nm UV radiated solution, UV photons are absorbed by the organic substances, direct photolysis of 5-FLU takes place, which efficiency depends on the molar absorbance of the target substance ($\epsilon_{254 \text{ nm}}=5296.6 \text{ M}^{-1} \text{ cm}^{-1}$) at 254 nm and the quantum yield of its transformation. In the case of VUV photons, it is absorbed by water to form radicals,



so the transformation of 5-FLU is initiated by H• and/or HO•.

Table 1. Initial transformation rates of 5-FU at 1.0×10^{-4} M initial concentration

	UV air	UV N ₂	UV/VUV _{185nm} O ₂	UV/VUV _{185nm} N ₂	VUV _{172nm} O ₂	VUV _{172nm} N ₂
r_0 ($\times 10^{-7}$ M s ⁻¹)	1.99	1.81	2.73	4.47	1.45	1.55
Φ	0.054	0.049	0.23	0.82	0.014	0.014

**Fig 2.** Relative concentration of 5-FLU versus time of irradiation in the case of UV UV/VUV_{185 nm} and VUV_{172 nm} photolysis**Fig 3.** The change of absorbance of the treated 5-FLU solutions

In most cases, the dissolved O₂ has a positive effect on the transformation rate as during 5-FLU UV photolysis (Fig 2). In the case of UV/VUV_{185 nm} photolysis, dissolved O₂ reduced the transformation of 5-FLU (Fig 2), while it had no significant effect on VUV_{172 nm} photolysis

(Fig 2). During UV/VUV_{185 nm} and VUV_{172 nm} photolysis, dissolved O₂ reacts with H•, reducing the concentration of one of the primary radicals formed during water photolysis, but opens a new way for the transformation of organic substances through the formation of peroxy radical. The importance of O₂ is demonstrated by the change of the spectra of the treated solutions, which is affected by the O₂ concentration in the case of UV and VUV photolysis too.

In the case of toxic or biologically active compounds, it is important to achieve not only to transformation of the parent compound, or if it is, to mineralize it. During UV photolysis, the TOC value of the treated solution slowly decreased (Fig. 4a), while in the case of UV/VUV_{185 nm} photolysis, the degree of mineralization is significant, the TOC value decreased by approx. 70% (Fig. 4a). Although 172 nm VUV photons did not increase the transformation rate compared to UV photolysis (Table 1.), the mineralization was much more efficient, TOC decreased by approx. 85%. During the oxidative transformation of 5-FLU and its degradation products, through the formation and transformation of organic peroxy radicals, quite a lot of HO₂•/O₂• is formed. These low reactivity radicals or radical ions do not play a significant role in the direct conversion of organic matter. Radicals are mainly recombining to form H₂O₂. Thus, a change in the concentration of H₂O₂ formed indicates the intensity of the transformation of organic substances.

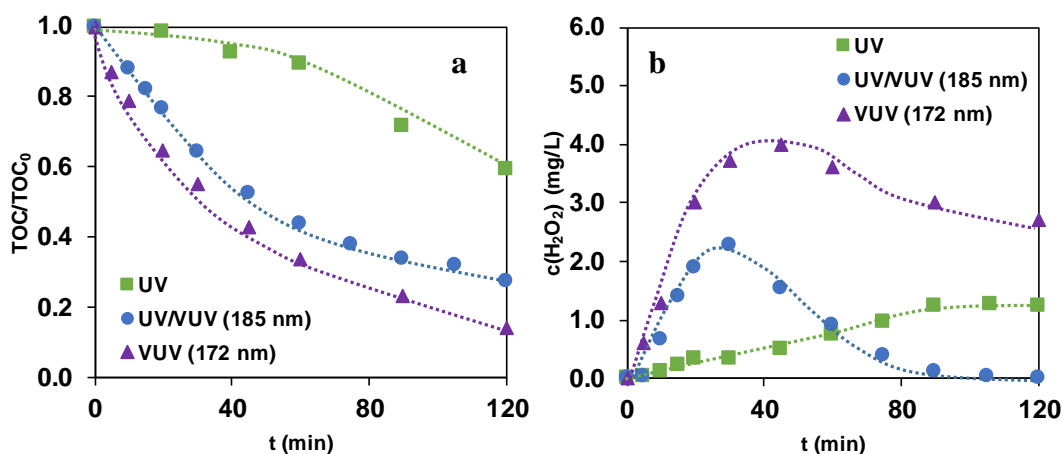


Fig 4. The relative concentration of TOC (a) and the concentration of H₂O₂ (b) versus time of irradiation in the case of UV UV/VUV_{185 nm} and VUV_{172 nm} photolysis of 5-FLU

During UV photolysis, a small decrease in TOC and, accordingly, a slow accumulation of H₂O₂ were observed. (Fig. 4). In the case of UV/VUV_{185 nm} photolysis, the H₂O₂ concentration varies according to a maximum curve, which indicates a more intensive transformation of organic compounds. The H₂O₂ concentration reaches the highest value in the case of VUV_{172 nm} photolysis, which suggests, as does the TOC, that the intermediates can be transformed most efficiently in this case.

Conclusion

The UV, UV/VUV_{185 nm}, and VUV_{172 nm} photolysis are effective for the elimination of 5-FLU from aqueous solutions, the highest transformation rate was measured in the case of UV/VUV_{185 nm} photolysis. Dissolved O₂ has no significant effect on the transformation rate even in the case of VUV_{172 nm} photolysis. The highest mineralization rate was observed in the case of VUV_{172 nm} photolysis. Although the photon flux of 172 nm light is much higher than of 185 nm light, the transformation is slower, partly because of the contribution of 254 nm in the case of UV/VUV_{185 nm} photolysis, and partly because of the extreme inhomogeneity of 172 nm radiated aqueous solution.

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