UDC 544.45/.454, 542.943-92

DOI: 10.15372/KhUR2021277

UV Photolysis of Several Conventional Pharmaceuticals: Degradability and Products

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(Received May 24, 2020; revised August 25, 2020)

Abstract

Direct UV photolysis of the aqueous solutions of seven well-known pharmaceuticals was accomplished using a high-pressure mercury lamp. Within 30 min of irradiation, active substances of ranitidine and phthalylsulphathiazole were almost completely destructed, whereas paracetamol and novocaine were destroyed to a lesser extent. Stable organic products are not formed during the destruction of paracetamol, while the photolysis of sulphaguanidine leads to the formation of acetic acid, which was confirmed by means of ^{1}H NMR spectroscopy. It is concluded that UV photolysis may be used for initial wastewater treatment to remove the studied micropollutants.

Keywords: micropollutants, pharmaceuticals, UV photolysis, high-pressure mercury lamp, wastewater treatment, NMR spectroscopy

INTRODUCTION

About twenty years ago, it obvious that pharmaceuticals moved into the category of widespread and potentially dangerous pollutants by their content in the environment and by the nature of their impact on ecosystems. Nowadays, pharmaceuticals along with cosmetic-hygienic substances, as well as compounds causing endocrine disorders, are found to be the main organic micropollutants. The term "micropollutant" generally encompasses organic and inorganic pollutants present in water in the concentration range from nanograms to grams per litre [1–3]. The sources of sewage pollution by the pharmaceuticals are medications unsuitable for use, as well as pharmaceuticals, which were not subjected to metabolism in the patients' bodies and, therefore, were excreted in the domestic wastewater [1].

In this connection, the development of methods of pharmaceuticals removal from sewage becomes urgent. During the last decade, the processes of organic micropollutant destruction by means of UV radiation are intensively studied. Some of these studies are devoted either to solar irradiation in aqueous environment or to combined oxidation methods. However, there is a great deal of publications focused on a direct UV photolysis, *e.g.* [4–7].

Currently, this area is at the stage of data accumulation about photolysis of certain substances; therefore, systematic investigation of the degradation of significant samples of micropollutants under comparable conditions is of great value. It

is worth to note that the significant number of published studies on the direct photolysis of pharmaceuticals have been carried out using low- and medium-pressure mercury lamps. For instance, Kim and Tanaka [6] determined the rates of photolysis for 30 medical and hygienic substances in model aqueous solutions under irradiation with low-pressure mercury lamps. The effectiveness of destruction changed from 3 % (for theophylline) to 100 % (for diclofenac). Photolysis by the low- and medium-pressure mercury lamps of 15 micropollutants, including such well-known pharmaceuticals as triclosan and ibuprofen, was studied in [7]. Some authors executed their experiments with the UV sources emitting only radiation of selected wavelength. For example, Dantas *et al.* examined direct photolysis of propranolol and metronidazole by UV-254 and UV-365 (black light) lamp [8]. Only Matafonova and Batoev [9] performed the photolysis of micropollutants with the aid of excilamps used as a quite specific source of high-energy UV radiation.

The aim of the present study is to investigate the efficiency of the direct photolysis of pharmaceuticals irradiated with high-pressure mercury lamp. The intensity of spectral lines of mercury-vapour lamps is known to depend on mercury pressure. In low-pressure lamps only the lines at 185 and 254 nm are of detectable intensity. Medium and high-pressure mercury lamps also emit lines of different intensity in visible range [10]. These bright lines are superimposed on the background of continuous radiation. It was of interest to obtain the information concerning the combined influence of the irradiation of the wider spectrum on the degradation of pharmaceuticals. For this purpose, both previously characterized pharmaceuticals and the samples of medication, for which there are no data on photolysis, were selected for the study. No data were found on the photolysis of novocaine and phthalylsulphathiazole.

EXPERIMENTAL

The following human pharmaceuticals further referred to as their trade names were selected for study (IUPAC names of active substances are given in parentheses):

1) tablets of paracetamol (N-(4-hydroxyphenyl)acetamide);

2) tablets of metronidazole (2-(2-methyl-5-nitroimidazol-1-yl)ethanol);

3) tablets of phthalylsulphathiazole (2-[[4-(1,3-thiazol-2-ylsulphamoyl)phenyl]carbamoyl] benzoic acid);

4) tablets of ranitidine ((*E*)-1-N-[2-[[5-[(dimethylamino)methyl]furan-2-yl]methylsulphanyl]ethyl]-1-N-methyl-2-nitroethene-1,1-diamine);

5) tablets of sulphaguanidine (2-(4-aminophenyl)sulphonylguanidine);

6) injectable solution of novocaine (2-(diethylamino)ethyl-4-aminobenzoate);

7) injectable solution of spasmalgon (a combined pharmaceutical consisting of three substances, namely:

– sodium metamizole ((1,5-dimethyl-3-oxo-2-phenylpyrazol-4-yl)-methylamino]methanesulphonate);

– fenpiverinium ((4-(1-methylpiperidin-1-ium-1-yl)-2,2-diphenylbutanamide) bromide);

– pitofenone ((methyl 2-[4-(2-piperidin-1-ylethoxy)benzoyl]benzoate) hydrochloride).

During the experiments, we tracked only the change of active substance concentration, whereas excipients included in tablet forms were not considered as far as they are not harmful.

Every experiment ran as follows. The aqueous solutions of tablet forms were filtered through paper filters. The initial concentrations of all the compounds were set to 0.25 mM. Each sample solution (25 mL) in a special quartz vial was placed into photolysis chamber FK-12M (Volta, Russia) equipped with 1 kW mercury quartz lamp DRT-1000 (Lisma, Russia), radiating light in the range of 240–320 nm. The sample was irradiated for 10 min. It was equilibrated after exposure, and its concentration was monitored relying on the absorption spectrum recorded by means of Specord 50 instrument (Analytik Jena, Germany). Then the sample was returned to the solution, which was irradiated again for 10 min followed by absorbance measurement. Photolysis of each sample was performed as long as its absorbance either stopped changing or reached the value of less than 0.01.

The same procedures were performed in heavy water (isotopic purity 99.95 %) in order to identify UV photolysis products by means of NMR spectroscopy. One-dimensional ^{1}H NMR spectra were recorded at 400 MHz using 400-MR instrument (Agilent, USA). Chemical shifts of non-exchangeable protons were measured relative to sodium 2,2-dimethyl-2-silapentane-5-sulphonate (DSS). Measurements were made in standard 5 mm

NMR tubes using a minimum volume of 0.5 mL of solution at $T = 298$ K. All NMR measurements were made in the fast-exchange condition for the interacting molecules on the NMR timescale. Thus obtained NMR data were processed with the aid of VNMRj 3.1 and MestReNova 12.0 software.

The method of permanganate oxidizability was used to estimate the residual organic matter content in the samples after irradiation. Determination of permanganate index is based on the oxidation of substances present in water by potassium permanganate in sulphuric acid medium [11]. Unutilized potassium permanganate further reacted with an excess of potassium iodide; released iodine was titrated with sodium thiosulphate.

Quantum yields of phototransformation (Φ) were calculated as follows:

$$\Phi = \frac{\Delta C}{(1 - 10^{-A_\lambda})tI_0}$$

where ΔC is the change of molar concentration for t seconds, A_λ is absorbance at wavelength λ, $I_0 = 0.5115 \cdot 10^{-7}$ E/s is light intensity estimated by means of chemical actinometry. Ferrioxalate actinometer was applied, in which ammonium salt was used instead of conventional potassium ferrioxalate [12].

RESULTS AND DISCUSSION

All the studied pharmaceuticals absorb in the UV spectral region emitted by the mercury lamp (Table 1). Three pharmaceuticals (sulphaguanidine, paracetamole, spasmalgon) absorb in the vicinity of the main mercury lamp line of 254 nm, which is common for all types of the lamps. Three substances (novocaine, metronidazole, ranitidine) have additional absorbance near the line 350 nm, manifesting itself in the case of using high-pressure lamps.

All pharmaceuticals were expected to be subjected to phototransformation after exposure to high-pressure lamp irradiation owing to their absorbance spectra. Indeed, the changes in UV spectra of the substrates allow concluding that the studied substances undergo photodegradation. In several cases the characteristic absorption bands readily disappeared in the spectra, whereas no new peaks appeared. The results for phthalylsulphathiazole are demonstrated in Figure 1, *a* as an example of such behaviour. Figure 1, *b* shows the results for metronidazole, which demonstrate the intensity of the line with wavelength of 320 nm to decrease gradually. The spectra of paracetamol and novocaine underwent only minor changes during the experimental time.

All the studied solutions remained transparent and colourless during the photolysis except spasmalgon solution, which became brownish after UV irradiation. The same occurred during UV photolysis of diclofenac as described in [13], and the authors concluded that it was the consequence of covalent dimerization of diclofenac. However, a complete photodegradation of metamizole was reported, with its fraction in spasmalgon tablet being over 90 %, after 45 min of UV exposure [14]. Thus, the observed colouration of spasmalgon solution is rather due to irradiated pitofenone hydrochloride and fenpiverinium bromide. Presumably, the brownish tint is caused by bromine release. The absence of colour for most original and intermediate solutions under study signifies that the contribution of the visible lines in high-pressure lamp irradiation should be negligible in phototransformation of the substances.

TABLE 1

Analytical characteristics and results of the photolysis of pharmaceutical solutions

Pharmaceutical	Wavelength of maximum absorption, λ, nm	Degree of phototransformation* after 30 min of irradiation, %	Value of permanganate oxidizability after photolysis is finished, mg O/L	Phototransformation quantum yield, Φ
Novocaine	292	4	48	0.1
Paracetamol	244	7	51	0.2
Spasmalgon	228	22	62	0.7
Metronidazole	320	66	46	1.2
Sulphaguanidine	260	71	29	2.0
Ranitidine	313	96	57	4.5
Phthalylsulphathiazole	285	99	32	4.8

* The value was calculated as $((C_0 - C)/C_0) \cdot 100$, where C_0 is initial concentration and C is concentration after 30 min phototransformation.

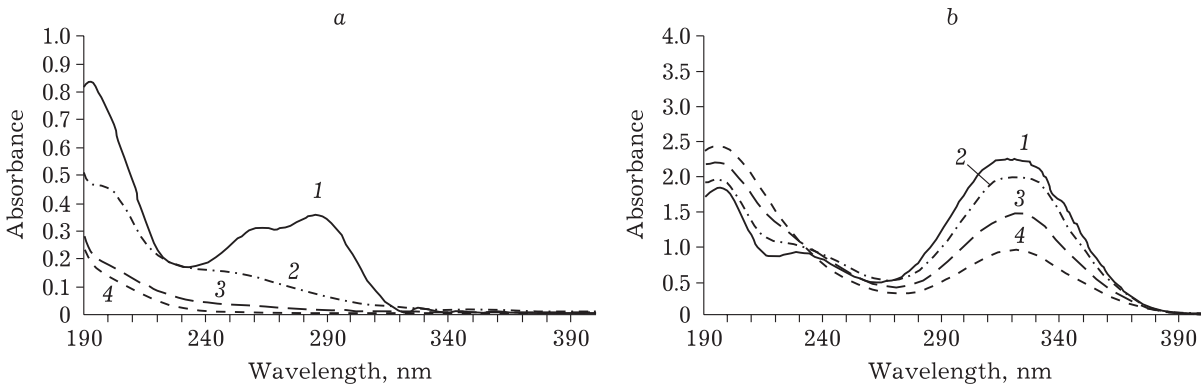

Fig. 1. UV spectra of phthalylsulphathiazole (*a*) and metronidazole (*b*) at different times of UV irradiation: *1* – before UV irradiation, *2,3,4* – after UV irradiation for 10, 20, 30 min, respectively.

The pharmaceuticals selected for the study have different structures; therefore, they are expected to have different photodegradability. Indeed, the substrates have been transformed with different rates. The degrees of the transformation of the studied pharmaceuticals for the same period are shown in Table 1. All the kinetic curves descend though the decrease of the concentrations of novocaine and paracetamol is insignificant (Fig. 2). The concentrations of other substrates under photolysis changed gradually, in particular ranitidine and phthalylsulphathiazole showed significantly high degradation rate. The similar behaviour of ranitidine, *i.e.* its almost total photodegradation, was reported both spectrophotometrically [14, 15] and by quantum yield ($\Phi = 5.3$ in [16]). Quite similar kinetic curves were also shown for metronidazole in [14, 17].

The quantum yields for the degradation of all pharmaceuticals degradation are given in Table 1 as well. All the pharmaceuticals can be obviously divided into three groups. Part of them has quantum yields close to 1, several others possess quite small quantum yields, whereas the third group possesses higher quantum yields exceeding 2. The smaller the value of quantum yield is, the lower degree of transformation can be expected.

The authors of [18] reported a much lower value of quantum yield for paracetamol (acetaminophen) photodegradation ($1.4 \cdot 10^{-3}$) than the value found in the present study. The difference of the data obtained could result from the application of different sources of UV radiation. Photolysis was carried out in [18] at a selected wavelength of 254 nm using low-pressure Hg lamp. The contribution of the high-energy line at 185 nm in the spectrum of high-pressure mercury lamp used in the present work can be considered as a reason of higher quantum yield of the degradation process. This is consistent, for instance, with the opinion of the authors of [19] considering that UV emitted at wavelengths less than 200 nm (such as 185 nm) photolyzes water. Hydroxyl radicals formed as a result of the photolysis contribute to the oxidation of organic substances [19].

The principal issue is about the depth of photolysis and possible products of phototransformation. The nature and intensity of UV spectra recorded after irradiation suggest that the majority of pharmaceuticals were subjected to photodegradation to a significant degree. Anyway, the systems of conjugated π-bonds providing the absorbance of the initial compounds have been destruct-

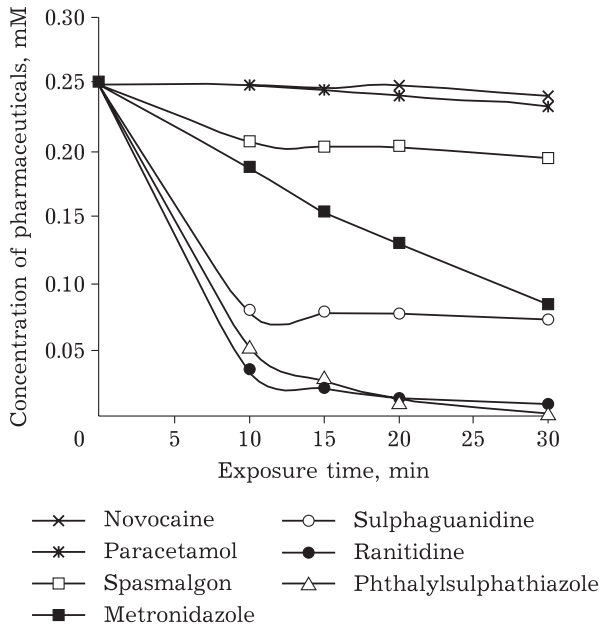

Fig. 2. Kinetic curves of photodegradation of studied pharmaceuticals in aqueous solution.

ed. However non-absorbing derivatives could remain in the solutions.

To assess the presence of organic compounds in solutions after photolysis, we determined permanganate oxidizability (see Table 1). The resulting values show that all the solutions contain a certain amount of organic compounds after photolysis. The highest value of permanganate index was detected for spasmalgon, which correlates with colouration of solution (either free bromine or dimers of active substances might interfere with the detection), as well as with the peculiarity of the corresponding kinetic curve (see Fig. 2): from a certain moment, the pharmaceutical concentration stops decreasing.

However, the value of oxidizability gives only restricted information about possible by-products of photolysis. The more detailed study of the products of degradation was performed by means of ^{1}H NMR spectroscopy for sulphaguanidine and paracetamol having medium and low degradability, respectively.

The relatively simple structure of paracetamol does not require additional measurements for signal assignment (Fig. 3, *a*). Hydroxyl and amide protons were exchanged with deuterons of solvent; therefore, their signals were absent in the spectrum. The narrow intensive singlet (2.01 ppm) corresponds to the signal of methyl group. The doublets at 7.12 and 6.77 ppm relate to the protons of aromatic ring, which has two substituents in *para*-position. There is a broadened peak in the range of 4.50–4.75 ppm corresponding to water protons. Small amounts of water are present in all the solutions, and the corresponding signals were recorded even after implementation of a special procedure for water peaks suppression.

Figures 3, *b* and *c* contain NMR spectra of paracetamol before and after UV exposure, respectively. UV irradiation did not affect the structure of paracetamol as there are neither new peaks in the spectrum nor significant changes in the existing peaks. Low-intensity peaks near 2 ppm are the signals of impurities.

Analysis of relative integral intensities of NMR peaks is the main criterion that allows one to reveal a decrease of initial paracetamol concentration. The values of relative integral intensities of the three peaks relating to paracetamol and the residual water peak are shown in Table 2. Obviously, on increasing irradiation time, the water fraction increases, while the paracetamol fraction decreases.

The absence of signals relating to the products of paracetamol photolysis along with a decrease of the integral intensities of signals at increasing photolysis time is likely to point to complete oxidation of paracetamol up to water, carbon dioxide, ammonium salts and nitrates. It could also signify that the amounts of intermediates and possible oxidation products are quite small. This is probable since the degradation rate is relatively low; therefore, NMR spectrum of paracetamol is readable even after 100 min of irradiation while new signals are not observed. This result agrees with the reports on the photolytic degradation of paracetamol. The authors of [8, 20, 21] have shown the destruction of aromatic ring of the molecule in similar oxidative systems. At the same time, there is an evidence of a preservation of aromatic ring during photolysis [18]. This could be ascribed to milder conditions maintained in the study. The experiment was obviously carried out using UV source with excluded 185 nm line. It is the radiation that causes major transformation as it was mentioned above.

Figure 4, *a* shows ^{1}H NMR spectrum of the stock solution of sulphaguanidine. Protons of the three amino groups exchanged with deuterons of solvent, and there are no corresponding signals in the spectrum. Similarly to the NMR spectrum of paracetamol, the doublets at 7.53 and 6.74 ppm relate to the protons of aromatic ring which has two substituents in *para*-position.

^{1}H NMR spectra recorded after photolysis of sulphaguanidine are presented in Fig. 4, *b* and *c*. Analysis of the spectra shows that sulphaguanidine molecule almost completely degraded during photolysis time. The spectrum (see Fig. 4, *b*) demonstrates that against the backdrop of the obvious decrease of intensity of signals in "aromatic" region (which is indirectly confirmed by a decrease of signal-to-noise ratio) there appears a quite intensive singlet at 2.28 ppm, which apparently relates to methyl group of acetic acid formed in the reaction.

After 100 min of irradiation, the signals of sulphaguanidine aromatic ring virtually disappear from the spectrum (see Fig. 4, *c*), which clearly indicates its destruction, whereas the signal relating to acetic acid residue is still present. The disappearance of the signals of sulphaguanidine aromatic ring, along with the appearance of a singlet signal in the "aliphatic" region of the spectrum (2.28 ppm) during the photolysis, indicates a complete degradation of the molecule with the formation of a stable product, which is apparently acetic acid.

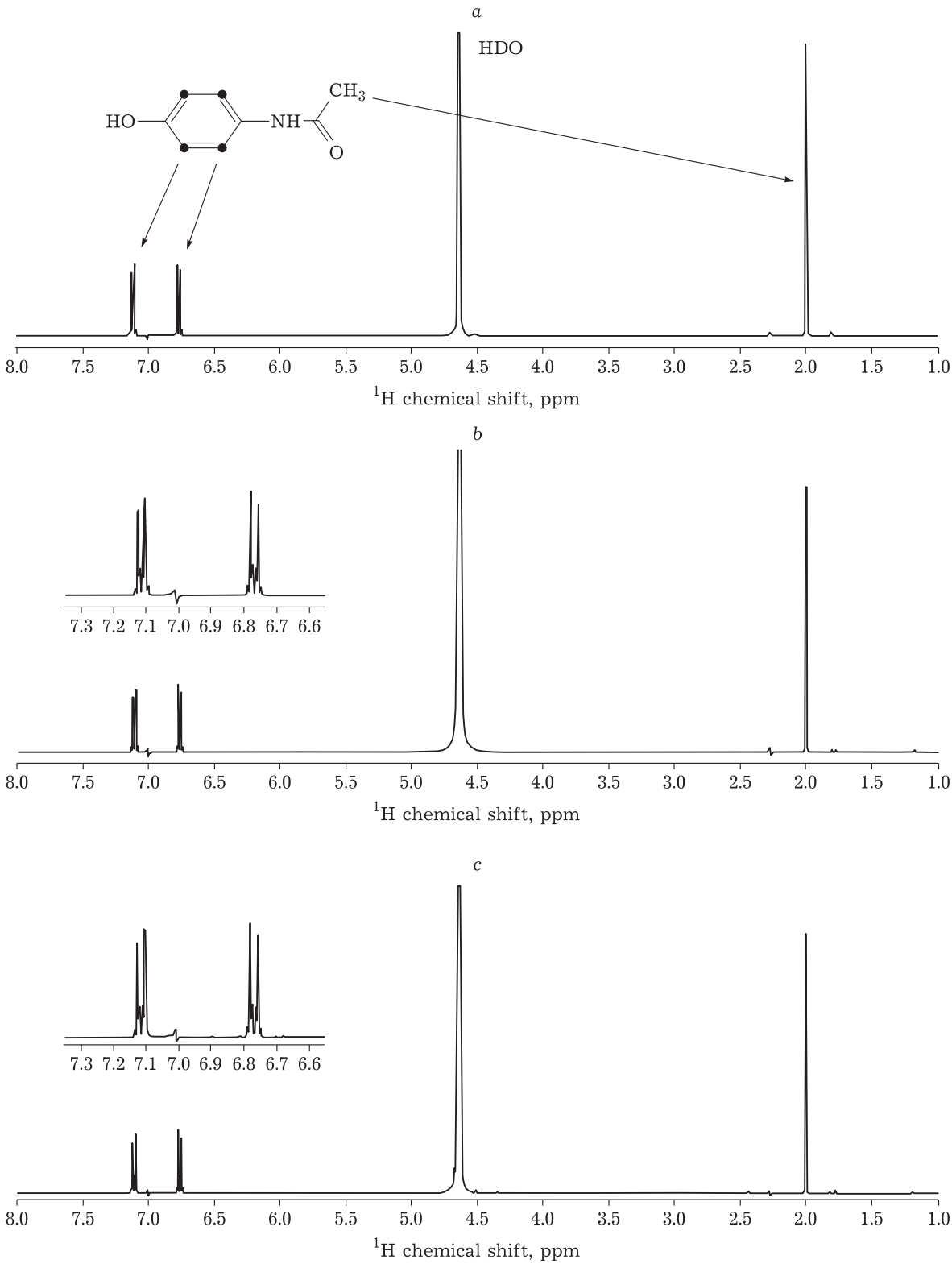

Fig. 3. ^{1}H NMR spectra of paracetamol solution: *a* – before UV irradiation, *b* – after UV irradiation for 50 min, *c* – after UV irradiation for 100 min.

CONCLUSION

Summarizing the above-reported study, we conclude that:

1. The direct photolysis of all studied pharmaceuticals by means of UV irradiation from high-pressure mercury lamp leads to the initial degradation of these pharmaceuticals. Under the same

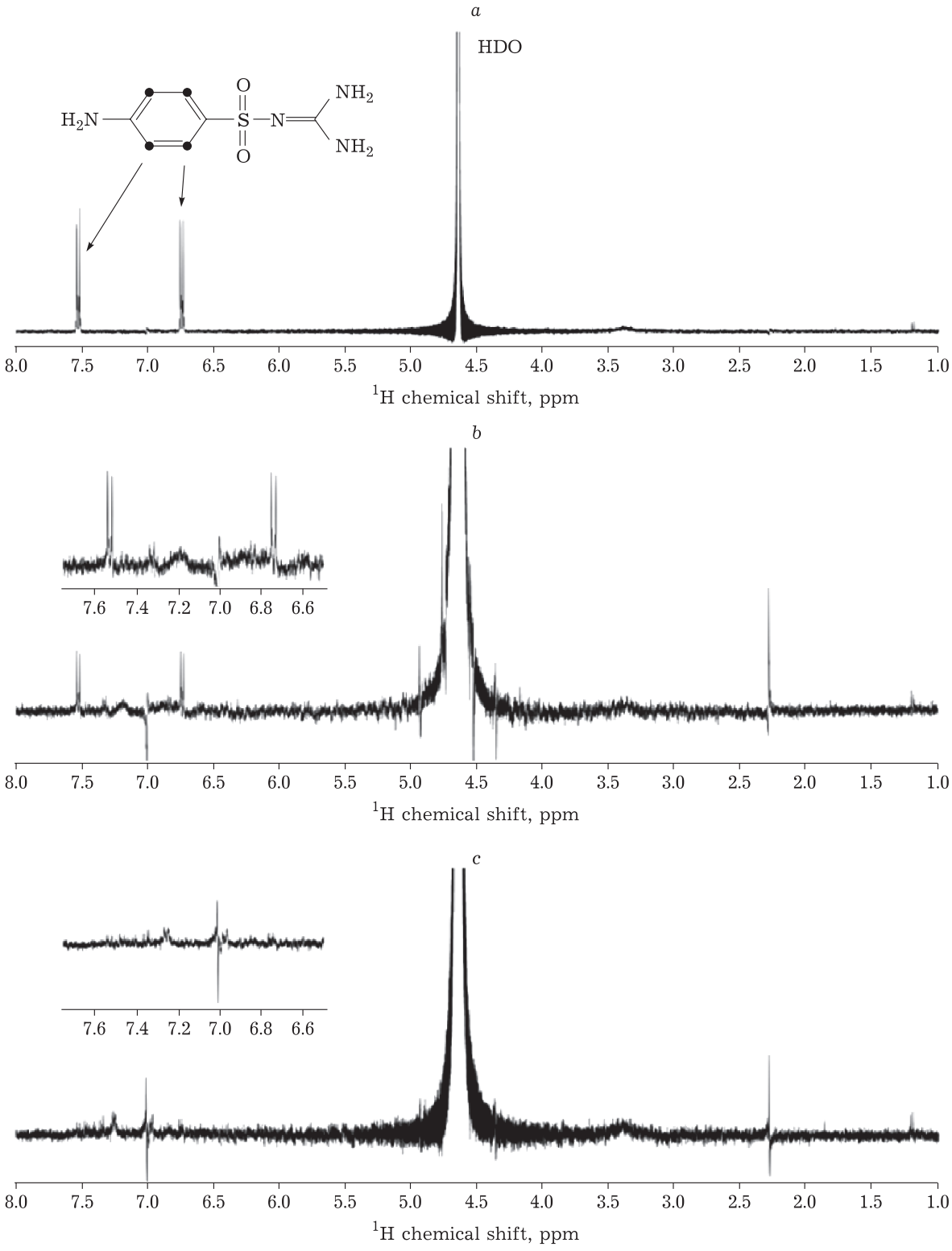

Fig. 4. ^{1}H NMR spectra of sulphaguanidine solution: *a* – before UV irradiation, *b* – after UV irradiation for 50 min, *c* – after UV irradiation for 100 min.

conditions, photodegradation of ranitidine and phthalylsulphathiazole occurs more easily than photodegardation of paracetamol and novocaine. Degradability of the studied micropollutants during 30 min can be arranged in the following sequence: phthalylsulphathiazole ≈ ranitidine > sulphaguanidine > metronidazole > spasmalgon > novocaine ≈ paracetamol.

TABLE 2

Values of the integral intensities of the main signals in the ^{1}H NMR spectrum of paracetamol solution

Sample	Boundaries of integral, ppm		Integral intensity value, %
	from	to	
Stock solution	7.35	6.94	1.69
	6.94	6.53	1.80
	4.89	4.38	93.95
	2.24	1.78	2.56
After UV irradiation for 50 min	7.35	6.94	0.63
	6.94	6.53	0.62
	4.90	4.29	97.84
	2.24	1.78	0.91
After UV irradiation for 100 min	7.35	6.94	0.41
	6.94	6.53	0.41
	4.91	4.29	98.60
	2.24	1.78	0.58

2. Stable intermediates are not formed under the photolysis of paracetamol; it is completely degraded. Sulphaguanidine undergoes a more rapid phototransformation, but acetic acid is maintained among the stable degradation products. To the best of our knowledge, it is the first report on sulphaguanidine photodegradability.

3. In the processes of water purification, balancing an appropriate degradability and the absence of stable toxic products is important. The obtained results show that direct photolysis may be used for the initial treatment of wastewater containing micropollutants. The results have a potential for application to local sewage treatment prior to discharge of wastewater into a centralized water circulation system.

As a minor issue, further comprehensive studies are needed to elucidate the reason of colouration of spasmalgon solution during UV photolysis.

REFERENCES

1 Ternes T. A., Joss A. Human Pharmaceuticals, Hormones and Fragrances: The Challenge of Micropollutants in Urban Water Management. UK, London: IWA Publishing, 2006.

2 Joss A., Siegrist H., Ternes T. A. Are we about to upgrade wastewater treatment for removing organic micropollutants? // Water Sci. Technol. 2008. Vol. 57. P. 251–255.

3 Schwarzenbach R. P., Escher B. I., Fenner K., Hofstetter T. B., Johnson C. A., von Gunten U., Wehrli B. The challenge of micropollutants in aquatic systems // Science. 2006. Vol. 313. P. 1072–1077.

4 Wols B. A., Hofman-Caris C. H. M. Review of photochemical reaction constants of organic micropollutants required for UV advanced oxidation processes in water // Water Res. 2012. Vol. 46. P. 2815–2827.

5 Wu B., Zhang T., Li J., Ye Y., Chen H. The photodegradation of metronidazole in the presence of coexisting pharmaceuticals // Water Sci. Technol. 2012 Vol. 66 P. 735–740.

6 Kim I., Tanaka H. Photodegradation characteristics of PPCPs in water with UV treatment // Environ. Int. 2009. Vol. 35. P. 793–802.

7 Carlson J. C., Stefan M. I., Parnis J. M., Metcalfe C. D. Direct UV photolysis of selected pharmaceuticals, personal care products and endocrine disruptors in aqueous solution // Water Res. 2015. Vol. 84. P. 350–361.

8 Dantas R. F., Rossiter O., Ribeiro Teixeira A. K., Simões A. S. M., da Silva V. L. Direct UV photolysis of propranolol and metronidazole in aqueous solution // Chem. Eng. J. 2010. Vol. 158. P. 143–147.

9 Matafonova G., Batoev V. Comparison of energy requirements for removal of organic micropollutants from lake water and wastewater effluents by direct UV and UV/H_2O_2 using excilamp // Desalin. Water Treat. 2017. Vol. 85. P. 92–102.

10 Ewing G. W. Instrumental Methods of Chemical Analysis. Fifth edition, NY, 1985.

11 ISO 8467:1993. Water quality – Determination of permanganate index. Moscow, 2014. (in Russ.).

12 Hatchard C. G., Parker C. A. A new sensitive chemical actinometer. II. Potassium ferrioxalate as a standard chemical actinometer // Proc. Roy. Soc. A. 1956, Vol. 235, P. 518–536.

13 Keen O. S., Thurman E. M., Ferrer I., Dotson A. D., Linden R. G. Dimer formation during UV photolysis of diclofenac // Chemosphere. 2013. Vol. 93. P. 1948–1956.

14 Afonso-Olivares C., Fernández-Rodríguez C., Ojeda-González R. J., Sosa-Ferrera Z., Santana-Rodríguez J. J., Doña Rodríguez J. M. Estimation of kinetic parameters and UV doses necessary to remove twenty-three pharmaceuticals from pretreated urban wastewater by UV/H_2O_2 // J. Photochem. Photobiol. A, Chem. 2016. Vol. 329. P. 130–138.

15 Bergheim M., Gieré R., Kümmerer K. Biodegradability and ecotoxicitiy of tramadol, ranitidine, and their photoderivatives in the aquatic environment // Environ. Sci. Pollut. Res. 2012. Vol. 19. P. 72–85.

16 Latch D. E., Stender B. L., Packer J. L., Arnold W. A., McNeill K. Photochemical fate of pharmaceuticals in the environment: cimetidine and ranitidine // Environ. Sci. Technol. 2003. Vol. 37. P. 3342–3350.

17 Andreozzi R., Caprio V., Marotta R., Vogna D. Paracetamol oxidation from aqueous solutions by means of ozonation and H_2O_2/UV system // Water Res. 2003. Vol. 37. P. 993–1004.
18 Pozdnyakov I. P., Zhang X., Maksimova T. A., Yanshole V. V., Wu F., Grivin V. P., Plyusnin V. F. Wavelength-dependent photochemistry of acetaminophen in aqueous solutions [in Russian] // J. Photochem. and Photobiol. A: Chemistry. 2014. Vol. 274. P. 117–123.
19 Han W., Zhang P., Zhu W., Yin J., Li L. Photocatalysis of *p*-chlorobenzoic acid in aqueous solution under irradiation of 254 nm and 185 nm UV light // Water Research. 2004. Vol. 38, No. 19. P. 4197–4203.
20 Moctezuma E., Leyva E., Aguilar C. A., Luna R. A., Montalvo C. Photocatalytic degradation of paracetamol: Intermediates and total reaction mechanism // J. Hazard. Mater. 2012. Vol. 243. P. 130–138.
21 Neamţu M., Bobu M., Kettrup A., Siminiceanu I. Ozone photolysis of paracetamol in aqueous solution // J. Environ. Sci. Health. 2013. Vol. 48. P. 1264–1271.