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Investigation of the photolysis and TiO_2, $SrTiO_3$, H_2O_2-mediated photocatalysis of an antipsychotic drug loxapine – Evaluation of kinetics, identification of photoproducts, and *in silico* estimation of properties

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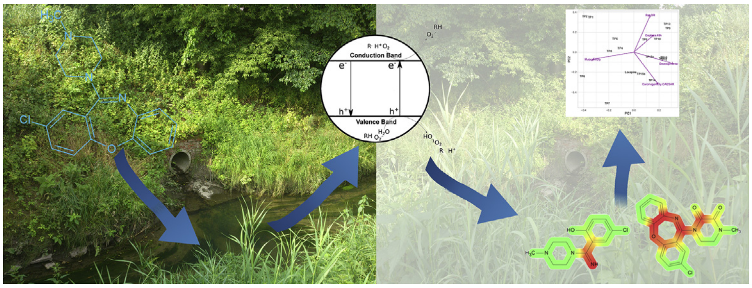
HIGHLIGHTS

- Direct photolysis and photocatalysis with the use of TiO_2, $SrTiO_3$ and H_2O_2 of loxapine were studied.
- Influence of catalyst concentration on removal of the drug substance was evaluated.
- Kinetics parameters of reactions were compared.
- Sixteen photoproducts were detected, and their structures were elucidated.
- Properties of phototransformation products was assessed with the use of computational methods, and compared by PCA.

GRAPHICAL ABSTRACT



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ABSTRACT

The photolytic and photocatalytic transformation of loxapine with the use of H_2O_2, TiO_2 and $SrTiO_3$ under the simulated solar radiation was studied. A micro-scale method for simultaneous irradiation of multiple samples in photostability chamber was applied. RP-UHPLC-DAD coupled with ESI-Q-TOF mass spectrometer was used for the quantitative and qualitative analysis of the processes. Influence of catalysts concentration on kinetic parameters of loxapine photodecomposition was evaluated, and TiO_2 at medium concentration ($100\,mg\,L^{-1}$) turned out to be the most effective. Sixteen transformation products were detected and their structures were elucidated. On the basis of the elucidated structures, computational evaluation of toxicity, bioconcentration and bioaccumulation factors as well as biodegradability of transformation products were conducted. The multivariate chemometric method (principal component analysis) was used to compare the calculated properties as well as the applied methods. Most of the transformation products were generally less toxic and more biodegradable than the parent compound.

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1. Introduction

The interaction between pharmaceutical molecules and ultraviolet–visible radiation (UV–Vis) may be considered from different points of view such as drug stability, environmental fate and wastewater treatment, or lastly, *in vitro* simulation of metabolism. Therefore, the study of consequences arising from this process should be considered as an indispensable part of investigation of active pharmaceutical substances (Ruokolainen et al., 2016; Trawiński and Skibiński, 2017a,b).

Since the fate of pharmaceuticals in the environment is not constantly monitored, they are still classified as the contaminants of an emerging concern. Additionally, concentrations of pharmaceuticals detected in the environment could be harmful to aquatic organisms (Kellner et al., 2015; Oaks et al., 2004). Currently applied water treatment methods, including adsorption, flocculation, sludge stabilization, sludge anaerobic treatment, nitrification, oxidation with the use of O_3, Cl_2, ClO_2 and Fenton reagent or UV irradiation, have often low removal efficiency of psychiatric pharmaceuticals (below 10% in some cases) (Calisto and Esteves, 2009). Therefore, the methods for their effective removal are widely investigated (Metcalfe et al., 2010; Peysson and Vulliet, 2013; Subedi and Kannan, 2015; Trawiński and Skibiński, 2017a,b). In the case of phototransformation, the susceptibility of a molecule to the direct photolysis clearly depends on the absorption of energy corresponding with the wavelength range of solar spectrum ($\lambda = 290–800$ nm), and on the absorption competition of light between the pollutants and the other light-absorbing components of water, such as colored dissolved organic matter (CDOM). The compounds absorbing radiation only below the lower border of this range (such as ibuprofen) cannot undergo the direct photolysis and, theoretically, should not be affected by radiation which increases their environmental persistence. Nevertheless such compounds could be marked by high values of the second-order kinetics constants with the photo-produced reactive species, which considerably reduces their decomposition half-life. On the other hand, the drug molecules intensively absorbing radiation of $\lambda > 290$ nm may undergo the rapid photolysis which is connected with their effective elimination but also with the formation of the potentially toxic products (Tonnesen, 2004). The unsatisfactory efficiency of direct photolysis in the case of some compounds led to the research on indirect photodegradation. This process mainly based on formation of the reactive oxygen species (ROS), primarily hydroxyl radical, is utilized in recently extensively investigated and developed advanced oxidation methods (AOPs). Such approach is usually based on the use of homogeneous or heterogeneous photocatalysis, in this particular case assisted by the radiation of UV–Vis range (Trawiński and Skibiński, 2017a,b). Amongst the homogeneous photocatalysis one of the most studied is the photo-Fenton method, yielding creation of hydroxyl radicals, and also other reactive species, such as hydroperoxyl radicals or ferryl ions, which could react with the pollutants molecules (Klamerth et al., 2013, 2010; Lee and von Guten, 2010). The principle of the heterogeneous photocatalysis arises from an interaction of the semiconductors (catalysts) and photons which, if possess sufficient energy, promote electrons from the valence to conduction band. Formed that way the electron – hole pair is able to generate ROS, as well as to interact with the molecules themselves. Despite a very large number of investigated photocatalysts (such as zinc, tungsten, molybdenum, copper or bismuth compounds), the most frequently applied is TiO_2, especially a composition of 75% anatase and 25% rutile, hence it often showed the best photocatalytic activity toward organic and inorganic molecules (Di Paola et al., 2012; Kanakaraju et al., 2014). Bare TiO_2 as well as photocatalysts based on this semiconductor are widely studied for the removal of various contaminants (Marinho et al., 2017; Sivagami et al., 2016; Trawiński and Skibiński, 2017a,b; West and Rowland, 2012; Yu et al., 2015) $SrTiO_3$, a ternary oxide, possessing a perovskite crystal structure, is marked by similar photochemical properties, for instance bandgap width (approximately 3.2 eV) or high photostability (Di Paola et al., 2012). Several studies proved high photocatalytic activity of this semiconductor for degradation of organic as well as inorganic pollutants, even better than TiO_2 in some cases (Chen et al., 2009; He, 2009; Zheng et al., 2011).

The investigation of the mentioned processes concerning drug-radiation interactions is particularly important in the case of widely used classes of pharmaceuticals, such as the psychotropic medications. Taking into account that the treatment of the mental conditions usually demands a chronic therapy, the quality and stability of the applied drugs is crucial. Moreover, an obvious consequence of a large consumption of this group of drugs is their significant release to the environment. Thus, in this case, the assessment of environmental fate and study on potential wastewater treatment methods is the key issue (Trawiński and Skibiński, 2017a,b). Loxapine, a dibenz[b,f][1,4]oxazepine derivative, is a typical antipsychotic agent, however possessing some properties representative for the atypical class (such as ratio of binding to D_2 and 5-HT_2 receptors). One of its main metabolites amoxapine (product of *N*-desmethylation) is approved as an antidepressant drug (Luo et al., 2011).

The aim of this study was to assess the influence of the UV–Vis radiation on the stability of loxapine, its direct, H_2O_2-assisted photolytic and photocatalytic transformation with the use of TiO_2 and $SrTiO_3$, evaluation of influence of the applied catalyst concentration, identification of intermediates, reaction pathways and *in silico* assessment of the formed transformation products (TPs) toxicity at various endpoints, bioconcentration and bioaccumulation factors as well as biodegradability including the obtained data exploration with the use of the principal component analysis (PCA).

2. Materials and methods

2.1. Materials

Loxapine succinate, formic acid for LC-MS, water for LC-MS and titanium (IV) oxide, nanopowder 21 nm particle size (Aeroxide® 25) and *p*-benzoquinone were purchased from Sigma-Aldrich Co. (St. Louis, USA). Strontium titanate, nanoparticles (100 nm, cubic phase) was purchased form US Research Nanomaterials, Inc. (Houston, USA). Hypergrade acetonitrile for LC-MS, acetonitrile gradient grade for liquid chromatography, and propan-2-ol for gradient chromatography were purchased from Merck (Darmstadt, Germany). Hydrogen peroxide 30% pure p. a. was purchased from Chempur, (Piekary Śląskie, Poland). Ultrapure water was obtained using SolPure 7 deionizer (POL-LAB, Poland).

2.2. Sample preparation

Stock solution of loxapine succinate was prepared in acetonitrile at concentration 13.6 mg mL^{-1}, which corresponded to 10 mg mL^{-1} concentration of loxapine as a base, and was refrigerated at 7 °C. Working solutions were prepared by diluting the stock solution in water and H_2O_2 to obtain 10 mg L^{-1} concentration of loxapine and 1, 5 or 10 mM of H_2O_2. Concentration of acetonitrile did not exceed 1%, as it was recommended in the OECD Guidelines for the Testing of Chemicals (OECD, 2008).

In order to reach the adsorption-desorption equilibrium, TiO_2 and $SrTiO_3$ loadings (50 100 and 200 mg L^{-1}) were added to the working solution, and stirred in the dark for 30 min before