Jakub Trawiński

Studies on the photochemical degradation of the selected psychotropic drugs

Introduction

Psychotropic drugs are widely used group of pharmaceuticals these days. Moreover the therapy with the use of them is often long-lasting. As a consequence, safety of the therapy utilizing psychotropic medications is crucial. One of the aspects of the therapy safety is stability of the pharmaceutical substance, that is its susceptibility to degradation under the storage conditions, including humidity, high temperature or natural and artificial UV-Vis radiation. The degradation process leads not only to decrease of the active pharmaceutical ingredient concentration, but may also result in formation of the toxic transformation products. Taking into account commonness of drugs photolability, studies devoted to the interaction between pharmaceutical substances and radiation are indispensable, and should include both quantitative and qualitative aspect. On the other hand high consumption of the psychotropic drugs, combined with poor efficiency of the commonly applied wastewater treatment methods against this group of pollutants, results in the presence of them in the environment, and, as a consequence, negative influence on the aquatic organisms. From this point of view photodegradation may be seen as a positive phenomenon, which can result in removal of pharmaceutical substances from the environment. Nevertheless, similarly as in the case of pharmaceutical aspect of photodegradation, this process may lead to formation of potentially toxic and poorly biodegradable compounds. Besides, the processes of photolytic and photocatalytic degradation of drugs may be used as a complimentary method during the process of wastewater treatment. For these reasons studies on the processes of photodegradation of psychotropic drugs, as well as on the properties of their phototransformation products are necessary.

Objectives

The aim of this research was quantitative (determination of kinetics of the photochemical reactions) and qualitative (identification of the transformation products) evaluation of the photodegradation processes of the selected psychotropic drugs under the

simulated solar radiation, on the basis of the available literature. The next goal was to perform a comparative study on the photodegradation products ionization efficiency by ESI and APCI LC-MS ion sources. The third aim was study on the efficiency of homogeneous and heterogeneous photocatalysis used as the treatment methods of water contaminated with psychotropic pharmaceuticals. The next aim was an *in silico* analysis of the formed phototransformation products toxicity and other parameters such as biodegradability, bioconcentration and bioaccumulation, as well as a comparative analysis of the applied mathematical models. The next objective of this research was a comparison of the photocatalytic efficiency of thirteen metal oxides, used in the foregoing studies on application of the heterogeneous photocatalysis for water purification, with the use of model mixture containing psychotropic pharmaceuticals. The last objective of this research was an evaluation of influence of three metal oxides, used as the excipients in the pharmaceutical formulations, on the photostability of sertindole.

Materials and methods

The studies were conducted using substances that belong to three pharmacological groups: antipsychotic, antidepressant and anxiolytic drugs. All the experiments were conducted using the aqueous solutions of these substances, which contained maximally 2% of the organic solvent. The photodegradation experiments were conducted in the photostability chamber equipped with a xenon burner and D65 filter, which ensured simulation of the solar radiation in the wavelength range of 290 – 800 nm. In the case of the photocatalytic experiments overall thirteen nanostructured substances, previously described in the literature as possessing photocatalytic properties, were used. For the sake of even distribution of the catalysts in the irradiated suspensions, vigorous stirring was applied. The samples obtained during the experiments were submitted to the quantitative and qualitative analysis with the use of system consisting of the hybrid high resolution Q-TOF mass spectrometer coupled with ultra high performance liquid chromatograph with DAD detection (Agilent). After the preliminary study, ESI in the positive mode was applied as the ion source. All the chromatographic experiments were conducted in the reverse phase (RP) mode, with the use of C-18 column (Merck). Water containing 0.1% of formic acid and acetonitrile or methanol were used as a mobile phase. Isolation procedure of one of the loxapine photodegradation products were performed using ultrafast liquid chromatography (UFLC) system (Shimadzu) and semi-preparative (C-18) chromatographic column (Agilent). The collected fractions

containing the compound of interest were evaporated under the stream of nitrogen, and then submitted to the FT-IR (Thermo) and ^{1}H NMR (Bruker) analyses. Computational evaluation of the photodegradation products toxicity, as well as the other properties, was performed using the following software: ACD/Percepta (ACD/Labs), Vega, T.E.S.T., Ecosar, BCFBAF and BioWin. The obtained results were submitted to the multivariate chemometric analysis with the use of R software (GNU Project).

Results and discussion

The experimental part of this research was preceded by the extensive analysis of the available literature concerning studies on the processes of photodegradation of psychotropic drugs, which revealed that the studied issue is widespread and extremely important. Then, in order to optimize the method of quantitative and qualitative analysis of the photodegradation processes, comparison between ESI and APCI ion sources was conducted. The study showed that ESI ensures better effects than APCI both from quantitative and qualitative point of view.

The main part of the research was a comprehensive analysis of the photodegradation processes of seven psychotropic drugs: agomelatine, tiapride, tandospirone, asenapine, loxapine, clozapine and sertindole. In the case of agomelatine photostability of this pharmaceutical under the simulated solar radiation was studied. The experiment revealed that this drug is a photolabile compound, and its degradation results in formation of six phototransformation products, mainly formed as a consequence of aromatic and aliphatic hydroxylation and dihydroxylation. The identified phototransformation products were submitted to the computational analysis of toxicity.

The remaining pharmaceuticals were submitted to the degradation with the use of photolysis as well as homogeneous and heterogeneous photocatalysis (or as in the case of clozapine – only heterogeneous). The obtained results showed that the studied compounds are characterized by different susceptibility to the simulated solar radiation. Clozapine, loxapine and, especially, tiapride are substances relatively resistant to action of the UV-Vis radiation, nevertheless they undergo the photodegradation. On the other hand tandospirone is highly photolabile substance, while asenapine possess intermediate properties. In all of the studied cases photocatalysis significantly increased the degradation rate, however better results were observed in the case of heterogeneous catalysis. Evaluation of the influence of the catalyst loading on the degradation rate was conducted in the cases of loxapine (TiO_2 and $SrTiO_3$ were used) and clozapine (only TiO_2 was used). In the first case the best results were achieved after

application of the intermediate loadings, while in the second experiment the highest loading was the most effective. In the experiments concerning clozapine the influence of an organic matrix present in the river water was also studied. As was expected, the dissolved organic matter caused increase of the photolytic degradation rate, as a consequence of the indirect photolysis. What is more, the photocatalytic process was also accelerated by the organic matrix. The qualitative analysis of the photolytic and photocatalytic degradation processes confirmed that numerous transformation products were formed during all the experiments. Although, obviously, they are specific to every parent compound, generally majority of them were formed as a consequence of hydroxylation, oxidation and cleavage of the molecules.

Computational analysis of toxicity, performed in all the described experiments, revealed that the products of phototransformation are often more toxic to rodents that the parent compounds. Opposite trend was observed in the case of aquatic toxicity, however the differences between the compounds are significantly lower. Assessment of mutagenicity, carcinogenicity and developmental toxicity showed that among the photodegradation products are compound possessing very high toxicity. *In silico* evaluation of biodegradability, bioconcentration and bioaccumulation showed that, generally, the products of photodegradation possess more favorable properties (from the environmental point of view) than the parent compounds.

During the studies on the photodegradation processes of tandospirone, asenapine, loxapine and clozapine, influence of the reactive oxygen species (ROS) on the photocatalytic degradation was performed. The obtained results showed that hydroxyl radicals are the major species involved in the process. The superoxide anion radicals are also important during the photocatalysis, however their role is less significant. Influence of singlet oxygen on the photocatalytic degradation of clozapine showed that this ROS does not influence the studied process.

The next part of the research was a comparison of photocatalytic properties of the thirteen metal oxides. The performed experiments, with the use of solution containing twenty-six psychotropic pharmaceuticals as a model mixture, showed that the highest efficiency possess TiO_2 and ZnO. Among the remaining catalysts $SrTiO_3$, WO_3 and Bi_2O_3 possess relatively high photocatalytic efficiency.

The last part of the research was an evaluation of influence of metal oxides, used as the excipients in the pharmaceutical formulations, on the photostability of the pharmaceutical substances. For this reason photodegradation of sertindole, and influence of presence of TiO_2, Fe_2O_3, FeOOH and mixtures of TiO_2 and aforementioned iron oxides on this process was

studied. Additionally photodegradation experiments were also conducted with the use of pharmaceutical formulations, containing sertindole accompanied with TiO_2, Fe_2O_3 and FeOOH. The study revealed that both TiO_2 and Fe_2O_3 accelerate photodegradation of sertindole, while presence of FeOOH decreases the photolysis rate.

Conclusions

The performed experiments on the photodegradation processes of the selected psychotropic drugs showed that, in terms of photolability the studied compounds differ from each other to a large extent. Substances such as tiapride, loxapine and clozapine turned out to be relatively photostable. On the other hand tandospirone undergoes fast photodegradation, while asenapine possesses intermediate properties. On the contrary to the foregoing studies, agomelatine was found as a substance susceptible to the action of simulated solar radiation. In all the experiments application of photocatalysis caused significant increase of the degradation rate, however better results were obtained in the case of heterogeneous catalysis. Increase of the catalyst loading generally results in the increase of degradation rate, however in the case of heterogeneous photocatalysis retardation of the reaction, caused by the shielding effect, may be also observed. Majority of the photodegradation products were formed as a consequence of hydroxylation and oxidation. Among the ROS the hydroxyl radicals played the major role, while activity of the superoxide anion radicals was significantly less important. *In silico* evaluation of toxicity revealed that the products of photodegradation often possess higher toxicity to rodents than the parent compounds. In terms of aquatic toxicity differences between compounds are less significant, however transformation products are sometimes less toxic than the parent compounds. In the case of mutagenicity, carcinogenicity and developmental toxicity such trends were not observed. Nevertheless some of the photodegradation products may possess significant toxic properties. The parent compounds are usually less biodegradable and possess higher bioconcentration and bioaccumulation factors than the products of photodegradation. The applied computational toxicity assessment methods often give differing results, however they can be used during the preliminary assessment of the compounds properties. Evaluation of the photocatalytic properties of thirteen metal oxides showed that TiO_2 and ZnO possess the highest efficiency. The remaining catalysts are significantly less effective, however among them $SrTiO_3$, WO_3 and Bi_2O_3 possess relatively high efficiency, which suggests that structural modifications of these substances may result in obtaining of the novel, high-performance photocatalysts. Evaluation

of influence of the metal oxides on sertindole photostability showed that the presence of TiO_2, Fe_2O_3 and FeOOH in the pharmaceutical formulations can increase the photodegradation rate of the active pharmaceutical ingredients. Therefore studies on the novel excipients, which do not possess photocatalytic properties is desirable. Studies on the ionization efficiency in the LC-MS analysis of the photodegradation processes of psychotropic drugs showed that ESI outperforms APCI, both from the quantitative and qualitative point of view.