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Toxicity Removal of Pharmaceuticals Mixtures through Electron Beam Irradiation

Boiani, N.F.[1]; Tominaga, F.K.[1]; Borrely, S.I.[1]

[1]*nathboiani@gmail.com*,
Instituto de Pesquisas Energética e Nucleares (IPEN/CNEN - SP)
Av. Professor Lineu Prestes 2242
05508-000 São Paulo, SP, Brazil

1. Introduction

Contamination of the aquatic environment by pharmaceuticals is becoming a global phenomenon of growing concern due to the significant risks it can bring to [1,2,3]. Pharmaceuticals can be only partially metabolized during therapeutic use, resulting in the excretion and release of residual fractions into sewage, unaltered or in the form of metabolites, and may remain active in sewage treatment facilities for a long time [4,5,6]. Many studies have shown that wastewater treatment plants are not designed to eliminate these compounds, as such the main source of drug residues in the aquatic environment [4,5,7].

Due to the frequency of its detection in the environment, its persistence and toxicity, the most studied pharmaceutical groups are antibiotics, psychiatric drugs, hormones, analgesics and anti-inflammatory, β-blockers, and antidiabetic drugs [7,8].

Advanced Oxidative Processes (AOPs) have been applied as an alternative or complement to conventional sewage treatment processes, aiming the degradation and removal of toxicity pollutants. Electron beam irradiation (EBI) is considered a clean process that offers an environmentally friendly alternative to degrade pollutants in the aquatic environment. This technology has been demonstrated effective for removal of multiclass pharmaceutical residues present in wastewater by using low doses (0.5 – 5.0 kGy) [9,10]. The degradation of the mechanism is based on chemical transformations induced by ionizing radiation through reactions with highly reactive species, such as the hydrated electron, • OH and H • radicals, formed by radiolysis of water [9].

In this study, we focused on toxicity removal of: fluoxetine, propranolol, diclofenac, acetylsalicylic acid, metformin and sulfadiazine, combined in three different tertiary mixtures (PRP+FLX+SDZ; PRP+FLX+DIC; ASA+FLX+MET).

2. Methodology

Reagents

Fluoxetine hydrochloride [$C_{17}H_{18}F_3NO$. HCl; MM = 309.33 g/mol; methyl[(3S)-3-phenyl-3-[4-(trifluoromethyl) phenoxy] propyl] amine]; CAS 54910-89-3]; Propranolol [$C_{16}H_{21}NO_2$; MM = 259.34 g/mol; (*RS*)-1-(isopropylamino)-3-(naphthalen-1-yloxy)propan-2-ol; CAS 525-66-6] and Diclofenac [$C_{14}H_{11}Cl_2NO_2$; MM = 296.148 g/mol; 2-[2-(2,6-dichloroanilino)phenyl]acetic acid; CAS: 15307-86-5] were purchased from Divis Pharmaceuticals Pvt. Ltd. (98.8% of purity). Sulfadiazine [$C_{10}H_{10}N_4O_2S$; MM = 250.270 g mol-1; 4-amino-N-pirimidina-2-il-benzenosulfonamida; CAS 68-35-9, 99.9% of purity] and Metformin [$C_4H_{11}N_5$; MM = 129.164 g/mol; 1,1-dimethylbiguanide; CAS 657-24-9, 97% of purity] were obtained from Sigma-Aldrich. Acetylsalicylic acid [$C_9H_8O_4$; MM = 180.16 g mol^{-1}; 2-acetoxybenzoic acid; CAS 50-78-2] was purchased from Labsynth (99.5% of purity).

All aqueous solution prepared for irradiations experiments were diluted using ultra-pure water (Millipore Milli-Q) and prepared at concentrations of 10-20mg/L (FLX), 80mg/L (PRP), 50 mg/L (DIC), 50mg/L (SDZ), 10 mg/L (ASA) and 10 mg/L(MET). These compounds were combined into three different tertiary mixtures, following the proportions 1:1:1.

Irradiation process

A Dynamitron Electron Beam Accelerator was applied for the irradiations. The beam energy was fixed at 1.4 MeV during all the experiments. Liquid samples were irradiated using a batch system in borosilicate containers (Pyrex) a volume of 246 mL was used in order to ensure a suitable beam penetration, 4mm thickness for aqueous samples. The recipient's speed was 6.72 m min^{-1} for samples passing under the electron beam. Absorbed doses were confirmed using a Perspex Harwell Red dosimeter, batch KZ-4034, with less than 5% variation.

Toxicity assays using *Daphnia similis*

The acute toxicity tests with *D. similis* were performed according to Brazilian standard methods (NBR 12713/2016). The effect observed was the immobility to organisms after 48 hours of exposure to the samples. The results of the toxicity tests were obtained based on the mean value of solutions concentration, which affects the exposed organism (EC50%), as well as the 95% confidence intervals, calculated from the estimated endpoint by the Trimmed Spearman-Karber method [11].

The tests were performed in duplicate, three different tertiary mixtures of pharmaceuticals were analysed.

3. Results and Discussion

The obtained results herein demonstrate that EBI was effective in degrading both compounds at low doses. Figure 1 presents the PRP +FLX + SDZ mixture detoxification results for 2.5 and 5.0 kGy. The mixture toxicities decreased from 10.6 to 2.5 and 2.3 TU at 2.5 and 5 kGy, respectively, corresponding to toxicity removal efficiencies of 76.4% and 78.1%. Figure 2(a) presents the PRP + FLX + DIC mixture detoxification results for 5 kGy, with toxicities decreased from 17.9 to 6.4 TU, corresponding to toxicity removal efficiencies of 64.3%. Figure 2(b) presents the ASA + FLX + MET mixture detoxification results for 2.5 kGy, when toxicities decreased from 3.3 to 2.3 TU, resulting to toxicity removal efficiencies of 30.7%.

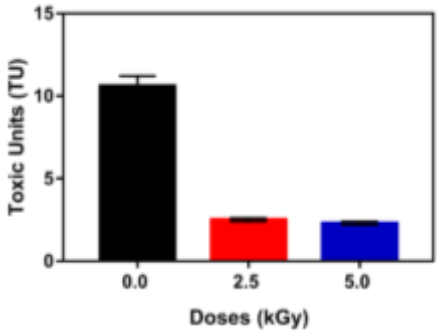

Figure 1: Acute toxicity (in toxic units, TU = 100/EC50%) of tertiary mixture of PRP + FLX + SDZ treated by electron beam irradiation assessed using *D. similis.*

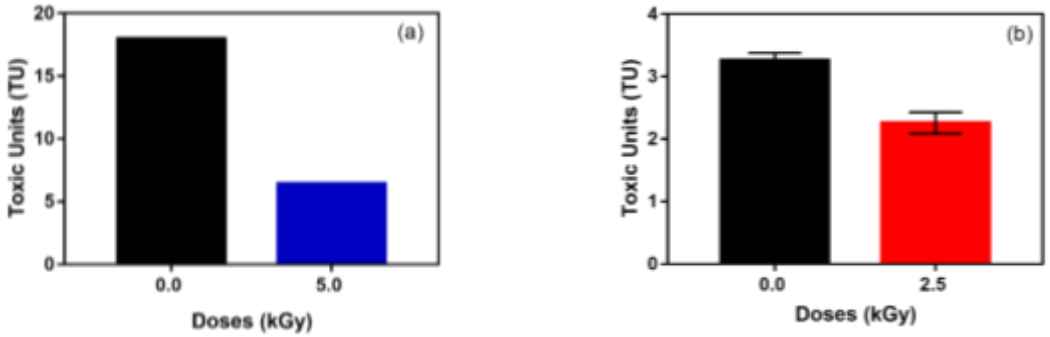

Figure 2 : Acute toxicity (in toxic units, TU = 100/EC50%) of tertiary mixture of (a) PRP + FLX + DIC and (b) ASA + FLX + MET treated by electron beam irradiation assessed using *D. similis*.

The results obtained reinforce that low doses can be suitable for the detoxification of pharmaceutical samples, highlighting the importance of evaluating mixtures [9]. In real effluents, pharmaceuticals are present in combination with dozens of compounds, in a complex mixture of contaminants, which can lead to unwanted effects. The ubiquity of a number of potentially toxic emerging contaminants in the environment leads to the need to better understand their occurrence, fate and ecological impact [12].

According to the literature, EBI is a viable technology for the removal of toxicity from pharmaceuticals mixtures using low doses. In a binary mixture of acetylsalicylic acid with fluoxetine, toxicity reduction values of 60% were obtained for *D. similis* at doses of 1.0 and 2.5 kGy [13]. One study reported approximately 80% toxicity removal efficiency for *D. similis* exposed to binary mixture of fluoxetine and propranolol irradiated at 5.0 kGy [14]. The effects of radiation in a pharmaceutical mixture were also evaluated, where a 50% reduction in toxicity was evidenced for a binary mixture containing fluoxetine and diclofenac, irradiated at 5.0 kGy [9]. A toxicity reduction of 80% for *D. similis* was demonstrated in samples of fluoxetine diluted in raw domestic sewage irradiated at 5.0 kGy [15].

4. Conclusions

The obtained results demonstrate the potential of electron beam irradiation as an effective alternative in reducing the toxicity of pharmaceutical products of different classes. This technology proved to be efficient in removing the toxicity of the three different tertiary mixtures of pharmaceutical. These data and the literature indicate the need for further studies on mixtures, and that EBI can be an interesting alternative process applied as a pre-treatment technology capable of degrading and detoxifying pharmaceutical products found in environmental matrices.

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