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Manual or automated measuring of antipsychotics' chemical oxygen demand

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ABSTRACT

Antipsychotic (AP) drugs are becoming accumulated in terrestrial and aqueous resources due to their actual consumption. Thus, the search of methods for assessing the contamination load of these drugs is mandatory. The COD is a key parameter used for monitoring water quality upon the assessment of the effect of polluting agents on the oxygen level.

Thus, the present work aims to assess the chemical oxygen demand (COD) levels of several typical and atypical antipsychotic drugs in order to obtain structure-activity relationships. It was implemented the titrimetric method with potassium dichromate as oxidant and a digestion step of 2 h, followed by the measurement of remained unreduced dichromate by titration. After that, an automated sequential injection analysis (SIA) method was, also, used aiming to overcome some drawbacks of the titrimetric method.

The results obtained showed a relationship between the chemical structures of antipsychotic drugs and their COD values, where the presence of aromatic rings and oxidable groups give higher COD values.

It was obtained a good compliance between the results of the reference batch procedure and the SIA system, and the APs were clustered in two groups, with the values ratio between the methodologies, of 2 or 4, in the case of lower or higher COD values, respectively. The SIA methodology is capable of operating as a screening method, in any stage of a synthetic process, being also more environmentally friendly, and cost-effective.

Besides, the studies presented open promising perspectives for the improvement of the effectiveness of pharmaceutical removal from the waste effluents, by assessing COD values.

1. Introduction

Surface and groundwater pollution by pharmaceuticals is considered a concern worldwide (Khetan and Collins, 2007).

Although human pharmaceuticals are found at ng L^{-1} levels, there are already numerous pharmaceutical compounds at low concentrations in the aquatic environment, (Kostich and Lazorchak, 2008) that due to their persistence exhibit an accumulative pollutant effect and their environmental impact is of concern due to the ecotoxicological effects that these low concentrations can promote in the aquatic environment (Pereira et al., 2017). Additionally, there is an increased use of newly manufactured compounds, for example antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) that associated with the lack of efficient technologies for wastewater treatment, are causing an increment of the pharmaceutical concentrations in water streams becoming a serious problem in the near future (Yu et al., 2009). So, the presence and the behavior of these compounds in the aquatic environment need to be addressed in order to improve the quality of environmental health (Fent et al., 2006; Santos et al., 2010). Depaolini et al. evaluated the salbutamol residues in wastewaters and they concluded that the residues values were highly constant over a relatively long time (three months). The authors justify this results maybe because the microbial population and weathering status of samples were stable for the investigation period but also because of the short time spent in the environment (estimated in 7 h) (Depaolini et al., 2016).

The consumption level of the AP drugs has seen a huge increase (171%) during the last years (INFARMED, 2000–2012), but little attention has been given to their environmental fate in comparison to other pharmaceuticals micropollutants (Wilde et al., 2016).

For this reason, the search of methods for assessing the contamination load of these drugs is mandatory.

AP drugs are used in psychiatric patients for treatment of acute

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psychotic episodes such as anxiety or in the prevention of relapses in patients with schizophrenia. They may also be administered in patients with other psychotic disorders such as mania, bipolar disorder, and delusional disorders, even when they don't present symptoms of psychosis (Grundmann et al., 2014; Zhang et al., 2007, 2008).

There are two classes of AP drugs: typical or first generation and atypical or second-generation APs. The second generation APs are most effective against both negatives and positives symptoms of psychiatric patients, as in other symptoms like aggressiveness and depressive symptoms. Moreover, second-generation APs can produce less extrapyramidal side effects, tardive dyskinesia, and neuroleptic malignant syndrome when compared to the first generation APs (El-Didamony et al., 2015; Zhang et al., 2007).

All APs have some antagonistic effect on the dopamine D_2 receptors. Regarding the second-generation APs, they also have antagonist activity at some serotonin receptors, especially the receptor 2A (Divac et al., 2014). The differences in the chemical structures of AP drugs play a crucial role in their interactions with neurotransmitter receptors, resulting in their respective neuropharmacological properties (Jafari et al., 2012).

The chemical structures of AP drugs may also present different behavior at the environmental level since all APs have aromatic rings in their chemical structures and the diversity regarding the number, type, and position of substituent groups, determines not only their particular chemical properties but also their environmental fate and behavior (Cvetnic et al., 2017). When industrial, hospital or wastewater treatment plants effluents are analyzed it is difficult to relate observed effects to specific pollutants present in these effluents (Deshpande and Satyanarayan, 2011). However, it was possible to identify the pollutant present in the wastewater using, for example, gas-chromatography-mass spectrometry (GC-MS) and high-performed liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) (Ghoshdastidar et al., 2015).

So, it is important to understand how each pollutant contributes to the environmental fate evaluating each specific pollutant degradability. There is no literature about COD values for these drugs, so it is extremely important to develop a methodology to evaluate the action/disposal capacity of these drugs in the environment.

Chemical oxygen demand (COD), is one of the methods used to determine the quality of water and a key parameter used in environmental pollution monitoring (Zhang et al., 2010). COD is defined as the amount of a specified oxidant that reacts with the sample under controlled conditions. The amount of oxidant consumed is expressed in terms of its oxygen equivalent. The extent of sample oxidation can be affected by digestion time, reagent strength, and sample COD concentration (Eaton et al., 2017). This is also a measure widely used to evaluate the effectiveness of wastewater treatment plants (Aquino et al., 2006)

There are currently technologies that have been studied for the determination of COD and that allow monitoring of the behavior and presence of pharmaceutical compounds in the environment such as: photooxidation (irradiation with ultraviolet (UV) light) (Limones-Herrero et al., 2014); advanced oxidation processes (oxidation processes which emphasize treating contaminants in water, soil and air, on the presence and reactivity of hydroxyl radicals (OH·) generated in atmosphere and also in water environment or under supercritical conditions of temperature and pressure with or without catalyst, and/or reactive power) (Mendez-Arriaga et al., 2011); electrochemical oxidation or electrodegradation (degradation of pharmaceutical compounds with use of electrodes of different materials) (Santos et al., 2013); ionization (oxidation of pharmaceutical compounds either by a direct reaction with ozone or indirectly with highly reactive radicals (Wilde et al., 2016), among others. However, there are two methods that are most used for determining this parameter: colorimetric and titrimetric (Eaton et al., 2017). The titrimetric method presents some disadvantages such as: incomplete oxidation and mineralization, low sensitivity and precision, uses large sample volumes, and reagents such as Ag_2SO_4, concentrated H_2SO_4 and toxic $HgSO_4$, chemicals not environmentally friendly and causing secondary pollution (Hassan et al., in press; Zhang et al., 2011). Besides that, it involves a time consumption reflux process of 2–4 h which makes it non-applicable for high-throughput screening (Hassan et al., in press). However, this method has advantages compared with the colorimetric. The titrimetric method can be used in samples with high turbidity and residual color while in the colorimetric method this is not possible, especially with a maximum absorption at around 600 nm (Aquino et al., 2006).

Since in the wastewater or in water environment the concentration level of pharmaceuticals are far below the sensitivity of the methods used, there are the possibility to use a pre concentration method, being the solid-phase extraction (SPE) the most frequently used technique for enrichment of trace organic compounds in aqueous samples, as reported by Zgola-Grzeskowiak and Grzeskowiak (2013).

So, in the present work, it was decided to perform the titrimetric method and a new proposed methodology based on sequential injection analysis (SIA), for the determination of a group of drugs that have never been studied before, the antipsychotic (AP) drugs.

It is very important to have data to implement structure-activity relationship (SAR) studies to evaluate their degradability before they enter the environment, as a part of a sustainable development of chemicals in order to clarify the impact of particular structural elements and to guide their modification to reduce their hazardous potential.

It is aimed the evaluation of the COD levels for the chemical oxidation of several AP drugs, both typical and atypical types by performing the reference titrimetric method, and by applying a sequential injection analysis (SIA) the results will be compared and the advantages pointed out.

2. Material and methods

2.1. Reagents

All solutions were prepared using chemicals of analytical grade with no further purification and water from a MilliQ plus system with specific conductivity of less than 0.1 mS cm^{-1}.

All antipsychotic drugs solutions with a concentration of 100 ppm were prepared by using pharmaceutical formulations such as tablets and injectable solutions.

The solutions of chlorpromazine (Largactil IV® 50 mg/2 ml injectable solution), levomepromazine (Nozinan® 25 mg/ml injection solution) zuclopenthixol (Cisordinol Acutard® 50 mg/ml solution for injection), flupenthixol (Fluanxol Retard® 100 mg/ml solution for injection), tiapride (Tiapridal® 100 mg/2 ml solution for injection), risperidone (Risperidone Sandoz® 1 mg/ml oral solution) and haloperidol (Haldol decanoato® 50 mg/ml injection solution) were prepared by dilution in water of the commercially available formulations. The solutions of chlorpromazine (powder (P), Sigma-Aldrich), olanzapine (Bluepharma Olanzapine® 2.5 mg film-coated tablets), clozapine (Clozapine Generis® 25 mg tablets) and cyamemazine (Tercian® 100 mg film-coated tablets) were prepared by dissolving the powders in water.

The reagents for performing the COD test using the titrimetric method were: potassium hydrogen phthalate solution equivalent 5000 mg L^{-1} O_2; potassium dichromate digestion solution 0.01667 mol L^{-1}; sulfuric acid reagent; ferroin indicator solution and the titrant ferrous ammonium sulfate (FAS) 0.10 mol L^{-1}, as described in Standard Methods for the Examination of Water and Wastewater (Eaton et al., 2017).

In SIA system, the carrier solution was ultrapure water. A solution of Ce (IV) 2 mol L^{-1} was prepared daily through dissolution of cerium (IV) sulfate in concentrated sulfuric acid to obtain a final concentration of 3.19 mol L^{-1}. Glutamic acid/glucose and potassium hydrogen phthalate solutions were used as standard solutions. A stock solution of glutamic acid/ glucose (150 mg L^{-1}) and intermediate solutions (10;