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Biological and photochemical degradation of cytostatic drugs under laboratory conditions

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HIGHLIGHTS

- Cytostatic drugs with reactive chemical groups are rapidly hydrolyzed.
- Biodegradation is not capable to eliminate all cytostatic drugs.
- UV-C and photolysis are not effective for the elimination of cytostatics.
- UV-H_2O_2 eliminates all compounds and no traces are present after 4 min.
- Unless AOP is used, WWTP effluents are a main source of cytostatics to rivers.

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ABSTRACT

Cytostatic drugs, used in chemotherapy, have emerged as new environmental contaminants due to their recurrent presence in surface waters and genotoxic effects. Yet, their degradability and environmental fate is largely unknown. The aim of this study was to determine the degradation kinetics of 16 cytostatic drugs, prioritized according to their usage and occurrence in hospital and wastewater treatment plants (WWTP) effluents, through the following laboratory scale processes: hydrolysis, aerobic biodegradation, UV-C photolysis, UV-C/H_2O_2 and simulated solar radiation. Some drugs were unstable in milli-Q water (vincristine, vinblastine, daunorubicin, doxorubicin and irinotecan); others were photodegraded under UV-C light (melphalan and etoposide) but some others were found to be recalcitrant to biodegradation and/or UV-C, making necessary the use of advanced oxidation processes (AOPs) such as UV-C/H_2O_2 for complete elimination (cytarabine, ifosfamide and cyclophosphamide). Finally, radiation in a solar box was used to simulate the fate of cytostatic drugs in surface waters under natural radiation and complete removal was not observed for any drug. The degradation process was monitored using liquid chromatography coupled to high resolution mass spectrometry and pseudo-first order kinetic degradation constants were calculated. This study provides new data on the degradability of cytostatic compounds in water, thus contributing to the existing knowledge on their fate and risk in the environment.

1. Introduction

In the last years, cancer incidence in the global population is gradually increasing. In 2012, an estimated 14.1 million new cases of cancer occurred worldwide and caused 8.2 million deaths [1]. The incidence of cancer leads to the production and consumption of a large number and quantities of cytostatic drugs. On a country-wide basis, consumption of the most commonly used anticancer drugs (~10–20 drugs) is in the order of tonnes yr^{-1} [2,3] which warrants research on their fate and behaviour in the environment.

Once administered, cytostatic compounds are directly discharged into the sewer system by urinary and/or faecal excretions [4,5] and $\mu g\,L^{-1}$ concentrations have been detected in hospital effluents [6,7], in wastewater treatment plant (WWTPs) effluents [8] and in river waters [9]. Thus, sewage waters from urban areas and hospitals are the main source of cytostatic compounds towards WWTPs, although hospitals account for 5.5% [10] to 17% of the total discharged [11]. Cytostatics have been reported to have low biodegradability [12]. Indeed, some cytostatic compounds such as cyclophosphamide, ifosfamide and tamoxifen have been fre-

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Table 1
Physicochemical parameters of the primary treatment effluent and the activated sludge used in the biodegradation experiments.

Primary effluent		Bioreactor		
			t0	48h
pH	7.6	pH	7.4 ± 0.1	7.7 ± 0.2
DOC (mg C L^{-1})	51.8	TOC (mg/l) (1:1)	176 ± 34	9.4 ± 0.9
IC (mg C L^{-1})	80.2	TSS (mg/L)	1153 ± 67	1167 ± 72
TN (mg L^{-1})	37.3	TVSS (mg/L)	887 ± 146	990 ± 85
COD (mg O_2 L^{-1})	253			
BOD5 (mg L^{-1})	76.88			
BOD5/COD	0.30			
SS (mg L^{-1})	110			
UV_{254} (m^{-1})	36.2			
Turbidity (NTU)	70			
Alcalinity ($MgCaCO_3$ L^{-1})	369			
Conductivity (μS)	1945			
DOC; disolved organic carbon		TOC; total organic carbon		
IC; inorganic carbon		TSS; total suspended solids		
TN; total nitrogen		TVSS; total volatile suspended solids		
COD; chemical oxigen demand				
BOD5; biochemical oxigen demand				
UV; adsorbance at 254 nm				

quently reported in WWTP effluents indicating partial removal [5] attributed to their high stability [13].

Studies focused on the degradation of pharmaceuticals only include few cytostatic drugs. The elimination using activated sludge and membrane-bio-reactors was studied for cyclophosphamide [14] and ifosfamide [8,15], 5-fluorouracil, doxorubicin, epirubicin and daunorubicin [16]. No degradation was observed in some cases [8] and some compounds affected sludge viability [14]. Advanced Oxidation Process (AOP) techniques with UV-H_2O_2 or ozone have been proven to eliminate cyclophosphamide and ifosfamide at laboratory and pilot plant scale [17–19]. However, degradation constants have only been calculated for a few cytostatic compounds.

This paper aims to study the degradation kinetics of 16 widely used cytostatic drugs under laboratory conditions using hydrolysis, biodegradation, UV-C and simulated solar radiation. Because of the urgent need to eliminate these compounds from hospital and WWTP effluents to reduce their impact in the environment, AOP with UV-C/H_2O_2 was also tested to reach complete removal. The degradability herein studied includes a systematic and comprehensive approach that covers the most relevant natural and chemical degradation processes. Degradability in batch experiments were monitored using liquid chromatography coupled to Orbitrap mass spectrometry (LC-HRMS) due to its high sensitivity and selectivity [20].

2. Materials and methods

2.1. Chemicals and reagents

In this study sixteen cytostatic drugs were studied, prioritized according to major medical prescriptions, those usually detected in hospital and wastewater treatment plants effluents and those affecting DNA [6,8,16,21–23]. Compounds studied, their classification and physico-chemical properties are indicated in Table SI1. Stock solutions were prepared at 2000 mg L^{-1} and working solution at 100 mg L^{-1} in methanol (MeOH from Merck, Germany). Milli-Q water was produced from an Integral Water Purification System from Millipore (Billerica, MA, USA). Metavanadate, sodium hydrogen sulfite (40% w/v) and hydrogen peroxide solution (30% w/w) were supplied by Panreac Quimica Inc. (Spain).

Effluent from primary treatment and activated sludge collected from Calafell WWTP (Catalonia, Spain) were used to study the biodegradation of cytostatic drugs and their characteristics are shown in Table 1.

2.2. Experimental devices and conditions

To determine the simultaneous degradability of 16 cytostatic drugs under various controlled conditions, bench scale experiments were conducted at a concentration of 50 μg L^{-1} each, which is a concentration where cytostatics are often detected in wastewater [5]. Hydrolysis, UV-C, UV-C/H_2O_2 and photolysis experiments were carried out in spiked milli-Q water (pH of 6.3). Hydrolysis was used as control condition to evaluate the water stability of cytostatic drugs in water. For biodegradation experiments, cytostatic drugs were spiked in real wastewater (pH of 7.6) to simulate an activated sludge treatment and to test the effect of cytostatic drugs on bacteria adaptation and degradation potential.

To determine the losses due to adsorption in the reactors and other material used in the laboratory, we compared the spiked concentration and the measured concentration at t = 0 min. For the 5 conditions tested, the recovery of non-hydrolyzed compounds was of between 72 ± 4 and 98 ± 15%, indicating high efficiency of the experimental setup. The specific conditions for each experiment and the time aliquots analysed are detailed below.

2.2.1. Hydrolysis

Hydrolysis has been selected as the first step in the evaluation of the stability of cytostatic compounds in water. Cytostatic drugs have a solubility ranging from 0.0446 and 1.76E5 mg L^{-1}, and have reactive groups, which favour hydrolytic reactions. 1 L of milli-Q water was placed in a flask (covered with aluminium foil) and spiked with the mixture of the drugs and kept at room temperature (22 °C). 1 mL aliquots were taken at 0, 2, 5, 7, 10, 15, 30, 60 min, 2, 4, 24 and 48 h.

2.2.2. Biodegradation

A sequential batch reactor (SBR) to simulate activated sludge treatment was used. Two 1 L aerated reactors magnetically stirred and covered with aluminium foil to avoid light interference were inoculated with activated sludge to obtain an initial Total Suspended Solids (TSS) concentration of 1–1.2 g L^{-1}. Reactors were filled with WWTP primary effluent and one was spiked with cytostatics (B1) and the other was kept as control. A constant saturation level of O_2 was obtained by means of an air bubbling system with ceramic submerged diffusers. Aliquots were taken at 0, 15, 30, 45, 60 min, 2, 4, 8, 24 and 48 h. For this experiment, time zero corresponds to the moment just before starting the aeration of the bioreactor, with the spiked water already in contact with the

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