

# Use of physical pretreatment and biodegradation for the removal of antidepressants and psychiatrically active substances from wastewater

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**Abstract.** The occurrence of pharmaceutically active compounds in wastewater is very problematic, especially due to the high persistence of some substances in relation to standard treatment technologies. These substances can further contaminate the environment through receiving water or sewage sludge. The occurrence of antidepressants and psychiatrically active substances in wastewater has increased significantly in recent years. This study focuses on the possibility of removing selected antidepressants and psychiatrically active substances from wastewater. Specifically, citalopram, venlafaxine, lamotrigine, carbamazepine and its metabolite carbamazepine 10,11-epoxide using physical-biological methods. Samples were collected from three wastewater treatment plants in the Moravian-Silesian Region. The patented equipment EP2388068 at the T.G. Masaryk water research institute in Ostrava was used for physical pretreatment. The samples were exposed to an electrostatic field and a mixed bacterial culture of the genus *Rhodococcus*, namely *Rhodococcus erythropolis*, *Rhodococcus rhodochrous* and *Rhodococcus degradans*, was used for subsequent biodegradation. The presence of drugs and their quantity was verified by HPLC/MS/MS analysis.

## 1 Introduction

Antidepressants and psychiatrically active substances belong to the group of pharmaceutically active compounds (PhACs), which is one of the biggest contributors to environmental pollution [1]. PhACs are often distributed into the environment through the pharmaceutical industry or through patients. According to the OECD, 30-90% of the dose of an administered pharmaceutical is excreted by the patient in the urine or faeces into wastewater [2], either as metabolites or unchanged [3]. The presence of pharmaceutically active compounds in wastewater is of great concern, particularly because drugs themselves are designed to interact with living organisms and elicit a response even at low doses [4].

Antidepressants and psychiatrically active substances are used to treat mental disorders such as depression, anxiety, schizophrenia, neurodevelopmental disorders, eating disorders,

etc. According to WHO, 970 million people worldwide suffered from mental health disorders in 2019. As a result of the COVID-19 pandemic, WHO estimates a 25.6% increase in mental health disorders and a 27.6% increase in anxiety and major depressive disorders [5]. Monthly consumption of antidepressants and anti-anxiety drugs in Poland increased from over 40 million doses (DDD) in January 2018 to approximately 60 million doses in October 2021. SSRI and SNRI class antidepressants were the most commonly prescribed drugs, accounting for 64% and 14.5% of the total volume, respectively. All other classes of antidepressants combined accounted for 21% of the total volume of drugs consumed [2,6]. Between January and December 2020, a total of 78 million prescriptions for antidepressants were dispensed in England, almost 4 million more than in 2019 [7]. In the Czech Republic, according to a study by the National Institute of Mental Health, as a result of the COVID-19 pandemic, the prevalence of mental illness increased by about 10%, the prevalence of depression increased three times, and the prevalence of anxiety disorders increased twice as much [6]. At the same time, the number of cases of young people receiving disability pensions due to mental illness is increasing. In 2014, 1081 people under the age of 19 received a pension, rising to almost 1600 by 2023. According to CSSA data from 31 December 2023, mental and behavioural disorders are the second most common reason for disability pensions, with 107,973 people receiving such pensions last year. Musculoskeletal and connective tissue disorders came first, with 112,058 people receiving this pension [8]. This information suggests that the concentration of the aforementioned antidepressants and psychiatrically active substances may be increasing in wastewater.

**Citalopram (CIT)** belongs to the class of selective serotonin reuptake inhibitors (SSRIs). It is used to treat depression, obsessive-compulsive disorders, or anxiety disorders [9]. There are many studies that have detected this drug in wastewater and surface water usually in the order of ng/L, for example Germany 160-180 ng/L in influent to WWTPs and 120-180 ng/L in effluent and <0.3-96 ng/L in surface water [1]. Other European countries where citalopram has been detected are Slovakia 86 ng/L influent and 84 ng/L effluent [10] Spain 163-319 ng/L influent and 21-288 ng/L effluent, Portugal 99.2-213.6 ng/L inflow and 82.8-95.6 ng/L outflow [11], Norway 62.9-303.6 ng/L inflow and 21.9-238.4 ng/L outflow [12], Greece 109.7-540.6 ng/L inflow and 19.9-766.2 ng/L outflow [13]. But there are only few studies on appropriate removal mechanisms [14].

Other drugs that are often prescribed to patients are serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants, which include **venlafaxine (VEN)**, which is used to treat depression or to prevent the recurrence of depressive episodes. Its main metabolite, O-demethylvenlafaxine, is as effective as venlafaxine and is beginning to be administered as a standalone drug [15]. The highest concentrations in wastewater measured by Schlusener et al. [16] were  $260 \pm 6$  ng/L for venlafaxine and up to  $640 \pm 14$  ng/L for its main metabolite O-desmethylvenlafaxine. Similar concentrations of venlafaxine in wastewater were found by Schultz et al. [17] 873-930 ng/L, Lajeunesse et al. 176-215 ng/L [18] and Loos et al. [19] averaged 119 ng/L and the maximum measured concentration was 548 ng/L. A German study determined the occurrence of drugs in various German rivers and streams. Venlafaxine was measured at concentrations ranging from <18 to 122 ng/L [20].

**Carbamazepine (CBZ)** is classified as an antiepileptic drug. It is widely used in medical practice to treat epilepsy, pain symptoms, trigeminal neuralgia, anxiety disorders and depression. **Carbamazepine-10,11-epoxide (CBZ-EP)** is an epoxide and metabolite of carbamazepine [21]. Information on the occurrence of this drug in various environmental compartments shows a wide range of concentrations. For example, values ranging from 0.001 to 16.5 µg/L are reported for wastewater [22, 23, 24]. In rivers, carbamazepine concentrations range from 0.013 to 84 µg/L [25, 26]. In surface water, carbamazepine concentrations have been found to range from a minimum of 0.002 to a maximum of 10 µg/L [24, 27, 28].

**Lamotrigine** (LMT), like carbamazepine, is used to treat epilepsy and bipolar disorder. It is a relatively new drug that was first detected in the aquatic environment in 2010 [29,30]. In the case of lamotrigine, concentrations of up to 1.1 µg/L were detected in the influent to the WWTP and 1.7 µg/L in the effluent, with generally higher concentrations in treated waters. Lamotrigine was detected at concentrations up to 0.73 µg/L in all rivers and streams investigated in central Germany [31].

Antidepressants and antiepileptics have been proposed for listing as priority substances under the Water Policy Directive 2013/39/EU [32] due to their frequent use and their high occurrence in wastewater [33]. Citalopram, venlafaxine and carbamazepine are also included among the priority substances under the Proposal for a Directive of the European Parliament and of the Council on urban wastewater treatment [34].

### 1.1 Ecotoxicity

One of the main problems with the occurrence of the aforementioned pharmaceuticals in wastewater is their resistance to treatment technologies, which can cause the accumulation of these substances in aquatic organisms. The action of antidepressants, either in unchanged form or through metabolites, on these non-target organisms may cause changes in their social behaviour, development, or may affect other physiological functions [7, 35].

The WWTP is a significant source of antidepressant release into the aquatic ecosystem. Since most antidepressants are poorly degraded in current wastewater treatment processes, e.g., in activated sludge systems, drug residues, metabolites, or their conjugates enter receiving waters via wastewater or sludge [36]. In addition, wastewater treatment processes such as activated sludge treatment and chlorination process for disinfection can induce chemical transformation of antidepressants. For example, venlafaxine is mainly converted to O-desmethylvenlafaxine (ODV), which may have greater biological activity in aquatic biota than venlafaxine itself [37]. In most cases, the measured levels of individual antidepressants in WWTP effluents are lower than the concentrations that elicit physiological or behavioural responses in aquatic biota. However, similar mechanisms of action of antidepressants can induce additive or synergistic effects [37, 38]. Tissue-specific bioaccumulation of citalopram, sertraline and venlafaxine was recorded in rainbow trout (*Oncorhynchus mykiss*) exposed to effluent from a Swedish municipal wastewater treatment plant. These antidepressants were found in the liver and brain of most of the fish [39]. Antidepressants, along with other PhACs, have been discovered in the bodies of wild fish in urban rivers that receive wastewater from sewage treatment plants in the US. The most detected compound in filleted fish samples was venlafaxine (22.9 ng/L) [40]. Venlafaxine and citalopram were found in fish (*Platichthys flesus*) collected from the Clyde estuary in Scotland. The concentrations of the above drugs found in the muscle and tissue of the fish ranged from 0.11-0.31 ng/g and 0.33-2.71 ng/g fish weight, respectively [41]. In a study conducted by Melvin [42], male greater mosquitofish (*Gambusia holbrooki*) exhibited disturbed circadian rhythmicity when exposed to 100 µg/l venlafaxine. Large horned snails (*Planorbis corneus*) exposed to 1 000 µg/l citalopram for 29 days showed weight loss and tissue reactions in the hepatopancreas [7, 43]. Exposure to carbamazepine negatively affects the ability to move in *Daphnia magna* and also stops the growth of the aquatic alga *Chlorella vulgaris* [44].

In addition, aquatic organisms in the wild are constantly exposed to several types of antidepressants simultaneously, which may pose a higher risk [45]. Therefore, efficient and sensitive methods for determining the presence and quantifying environmental levels of antidepressants are needed to assess and prevent their potential effects in the environment [39].

## 1.2 Pollutant removal options

There is a large number of research papers and literature on the possibilities to remove the above-mentioned pharmaceuticals from wastewater. However, some methods cannot be applied to several types of pharmaceutical pollutants at the same time. For example, chlorination appears to be a highly effective method for the removal of citalopram, achieving removal efficiencies of 95-98% [46]. However, in the case of venlafaxine, chlorination of wastewater has been shown to produce the carcinogenic N - nitrosodimethylamide (NDMA) [15]. The use of biodegradation also faces problems, with carbamazepine and lamotrigine, for example, being almost persistent towards the use of biodegradation [31]. The use of advanced oxidation methods (AOPs) appears to be very effective methods that can remove a wide range of organic pollutants from wastewater and sewage sludge. These methods rely on the formation of hydroxyl radicals (OH<sup>-</sup>), which are highly reactive and thus affect organic pollutants that can be completely mineralized or converted to less complex forms [47]. AOPs include a large variety of methods such as the use of UV or solar photocatalysis, electrolysis, ozonization or ultrasound. Less common methods include, for example, the use of ionizing radiation, microwaves or pulsed plasma [47].

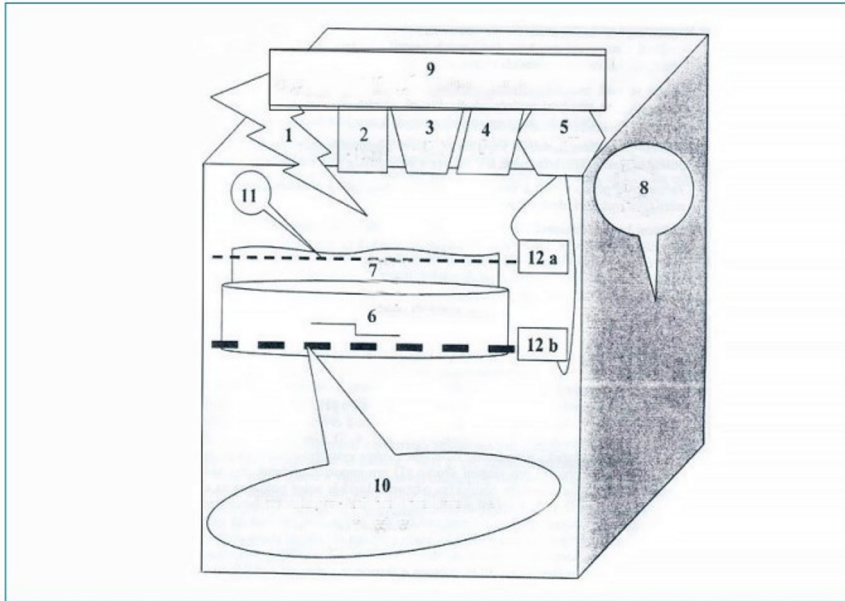
This study focused on the potential for removal of multiple pollutant species through biodegradation with physical pretreatment. Physical pretreatment uses the aforementioned AOP and consists of exposing the sample to an electrostatic field, assuming disintegration of the individual matrices, which can make the subsequent biodegradation more efficient.

## 2 Materials and methods

Wastewater samples were taken from the Central Wastewater Treatment Plant in Ostrava-Privoz (ÚČOV), from the WWTP in Havířov and from the WWTP in Frýdek-Místek. After sampling, the samples were sent for initial HPLC/MS/MS analysis to the laboratory of ALS Czech Republic, s.r.o. in Ostrava.

The central wastewater treatment plant in Ostrava-Privoz has a capacity of 638,850 equivalent inhabitants. The treatment concept is based on mechanical-biological treatment of sewage and industrial wastewater on the principle of low-load activation with nitrification and pre-supervised denitrification with an automated control system for all technological processes. After treatment, the wastewater flows into the Černý potok. The Frýdek-Místek wastewater treatment plant has a capacity of 164,466 equivalent inhabitants. It is a mechanical-biological wastewater treatment plant with cascade activation and chemical phosphorus removal. The Havířov WWTP has a capacity of 103,000 equivalent inhabitants and provides municipal wastewater treatment for the city of Havířov and the adjacent municipalities of Horní Suchá and Šenov.

Part of the samples was subjected to physical pre-treatment on the patented equipment EP 2388068, which is currently conceived as a laboratory - testing, prospectively as an industrial one at the VÚV TGM in Ostrava. The device can be used for combined or uniform pretreatment by spark discharge, ultrasound, focused microwave field, electrostatic field or UV radiation. In this project, samples were exposed to electrostatic fields. The technical design of the equipment is shown in Figure 1.



**Fig. 1.** 1, 2, 3, 4, 5 - generators of force fields (spark discharge - high thermal plasma, microwave field, ultrasound, UV radiation, electrostatic field - cold plasma), 6 - plastic tub (sample container), 7 - sample to be tested, 8 - Faraday cage, 9 - sliding bridge, 10, 11 - conductive metal grid, 12 a, b - HV supply cables [48].

## 2.1 Laboratory measurements

The water samples were sent for initial HPLC/MS/MS analysis to the laboratory of ALS Czech Republic, s.r.o. in Ostrava. Subsequently, a part of the samples was sent for physical pre-treatment to the VÚV TGM in Ostrava, where the samples were subjected to physical pre-treatment on EP 2388068 equipment, under the influence of an electrostatic field at a voltage of 15 kV, current 0.1 mA for 8 hours.

After physical pre-treatment and transfer of the samples to the laboratory of the Department of Environmental Engineering Technical University of Ostrava, water samples of 1 l volume were transferred to 2 l biodegradation beakers with the following protocol:

### *Samples "bacteria"*

1 l of wastewater (not subjected to physical pre-treatment), 200 ml of M011 Soyabean Casein Digest Medium (Tryptone Soya Broth) and 200 ml of a mixed culture of *Rhodococcus degradans* (4446 CCM) *Rhodococcus erythropolis* (277 CCM) and *Rhodococcus rhodochrous* (2751 CCM).

### *Samples "bacteria physics"*

1 l of wastewater after physical pretreatment, 200 ml of culture medium M011 Soyabean Casein Digest Medium (Tryptone Soya Broth) and 200 ml of mixed culture of *Rhodococcus degradans* (4446 CCM) *Rhodococcus erythropolis* (277 CCM) and *Rhodococcus rhodochrous* (2751 CCM).

### *Samples "control"*

1 l of wastewater (not subjected to physical pre-treatment) and 400 ml of distilled water.

### *Samples "physics control"*

1 l of wastewater after physical pre-treatment and 400 ml of distilled water.

All measurements were carried out at 23 °C, pH 8.1 under continuous oxygenation provided by the JK-AP7500 360 l/h aquarium aerators (see Figure 2). The samples collected were subjected to biodegradation for 20 days. Distilled water was regularly refilled during the measurements to eliminate evaporation of the liquid phase.



**Fig. 2.** Biodegradation beakers with individual samples.

## 2.2 Sample analysis

Each of the carried out measurements was completed after 20 days. Subsequently, the samples were transferred into purified glass bottles and transferred in refrigerated boxes for HPLC/MS/MS analysis to the laboratory of ALS Czech Republic, s.r.o. in Ostrava.

### 3 Results and discussion

In this section, the results obtained in this study are presented and discussed with data from other studies. The table 1 shows the final concentrations of the drugs measured.

**Table 1.** Drug concentrations in individual WWTPs.

Drug	WWTP	Input	Input physics	Bacteria	Bacteria physics	Control	Physics control
		µg/l					
CBZ*	Ostrava	0.564	0.471	0.500	0.471	0.464	0.429
	F-M	0.386	0.379	0.371	0.343	0.364	0.336
	Havířov	0.443	0.357	0.364	0.350	0.336	0.293
CBZ-EP	Ostrava	0.350	0.350	0.429	0.386	0.414	0.357
	F-M	0.400	0.371	0.386	0.379	0.421	0.371
	Havířov	0.393	0.314	0.379	0.350	0.343	0.314
CIT	Ostrava	0.157	0.121	LOQ	LOQ	0.121	0.100
	F-M	0.150	0.121	0.114	LOQ	0.129	0.136
	Havířov	0.164	0.136	0.114	LOQ	0.143	0.100
LMT	Ostrava	0.664	0.614	0.686	0.614	0.586	0.521
	F-M	0.543	0.600	0.536	0.521	0.493	0.529
	Havířov	0.871	0.843	0.821	0.743	0.800	0.729
VEN	Ostrava	0.286	0.243	0.264	0.200	0.243	0.200
	F-M	0.264	0.264	0.236	0.200	0.214	0.214
	Havířov	0.393	0.386	0.314	0.314	0.329	0.271

\*Explanation of used abbreviations: carbamazepine (CBZ), carbamazepine-10,11,epoxide (CBZ-EP), citalopram (CIT), lamotrigine (LMT) and venlafaxine (VEN).

Our measured drug concentrations for the input water samples are consistent with values reported in other studies, except for carbamazepine-10,11-epoxide. Information on the occurrence of carbamazepine in different environmental compartments shows a wide range of concentrations. For example, values ranging from 0.001 to 16.5 µg/L are reported for WWTP [22, 23, 24], which is consistent with our results (0.357 to 0.564 µg/L).

Carbamazepine-10,11-epoxide was measured in this experiment at concentrations of 0.314 - 0.400 µg/L. While in the study [49], CBZ-EP was detected at a concentration of 7.6 ng/L. Similarly, in study [50], CBZ-EP was detected at concentrations lower than 30 ng/L.

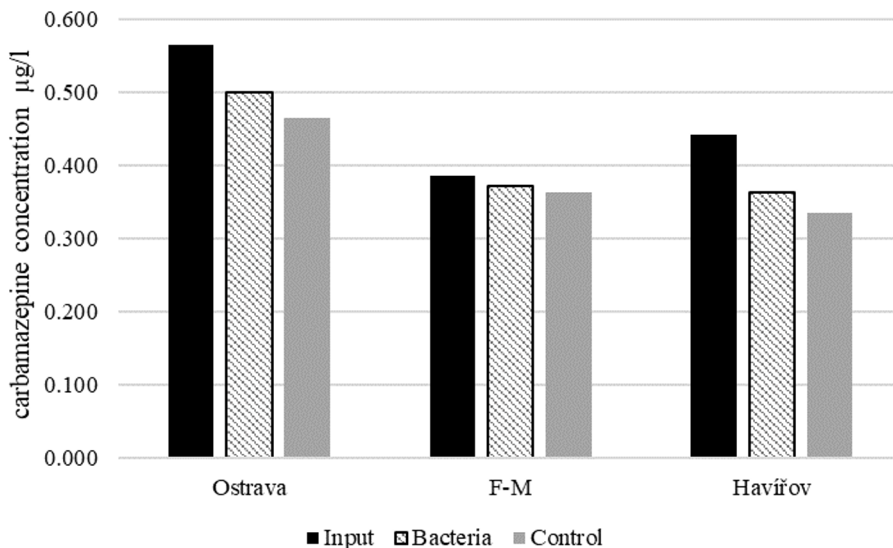
In this study, citalopram was detected at concentrations of 0.136 - 0.157 µg/L. In the Czech Republic, Golovko et al. [1] detected citalopram at concentrations of 27-180 ng/L in WWTP influent and 30-120 ng/L in effluent.

Lamotrigine measured in the investigated wastewater ranged from 0.543 µg/L to 0.843 µg/L. In a study by Bollmann et al. [31], lamotrigine concentrations of up to 1.1 µg/L were determined in the influent to the WWTP and 1.7 µg/L in the effluent, with generally higher concentrations in the treated water. Ferrer and Thurman [51] showed that lamotrigine was present in 94% of wastewater samples with an average concentration of 488 ng/L.

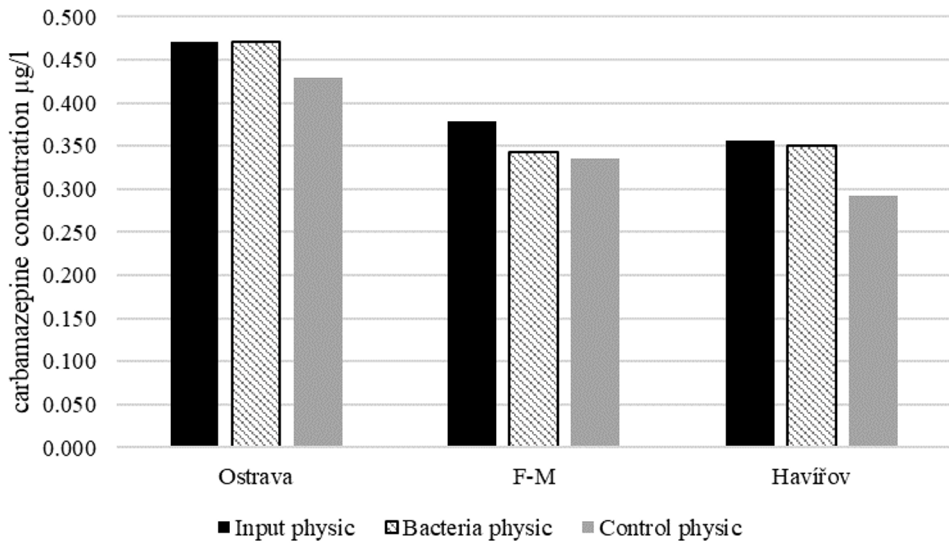
Concentrations of venlafaxine ranged from 176 to 215 ng/L in the effluents of WWTPs in Canada and reached concentrations of up to 211 ng/L in effluents from Spain [18]. Schlüsener et al. [16] measured venlafaxine concentrations of  $260 \pm 6$  ng/L. Similar concentrations of venlafaxine in wastewater were found by Lajeunesse et al. 176-215 ng/L [18] and Loos et al. [19] average of 119 ng/l and maximum measured concentration of 548 ng/l. Our measured values were 0.264-0.386  $\mu\text{g/L}$  and are rather among the higher measured concentrations.

For the two selected drugs carbamazepine and citalopram, the results are shown graphically for better clarity (Figure 3-6) and interesting phenomena within the experiment are highlighted.

Using carbamazepine as an example (see Figures 3 and 4), it can be observed that the use of physical pretreatment slightly reduced the initial concentration of the drug in the sample. Subsequent biodegradation in both cases (without and with pretreatment) negligibly reduced the drug concentration in the sample. Interestingly, the carbamazepine concentrations in the controls are lower than after biodegradation.

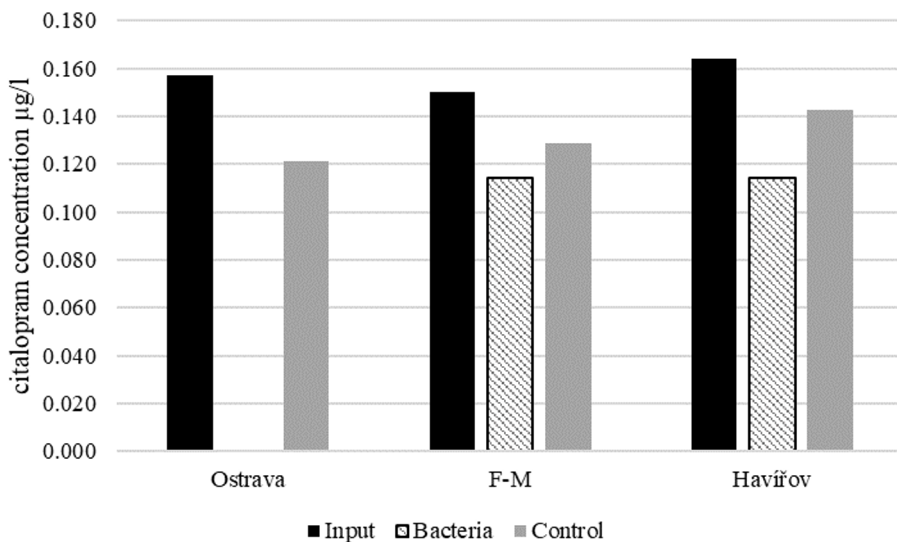


**Fig. 3.** Comparison of carbamazepine concentrations in samples without physical pretreatment.

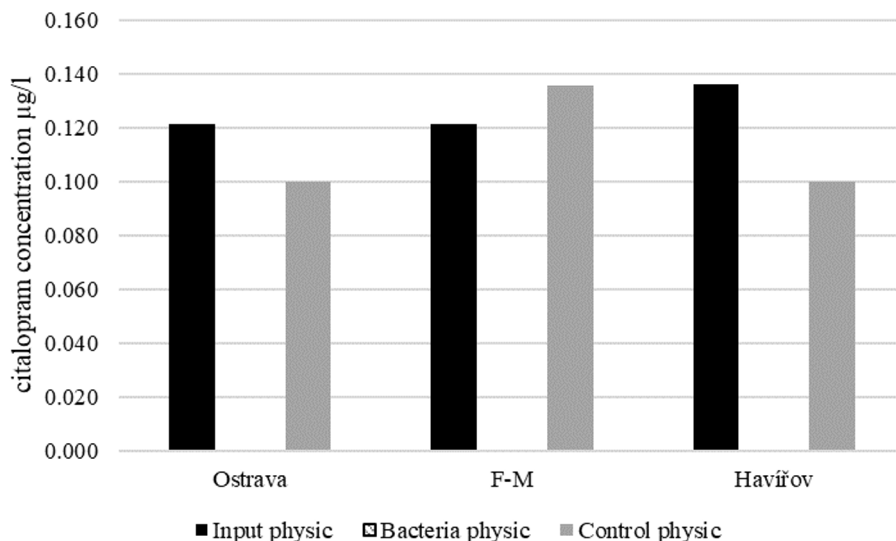


**Fig. 4.** Comparison of carbamazepine concentrations in samples with physical pretreatment.

For citalopram, again, there was a slight decrease in the concentration of the drug in the samples after the use of physical pretreatment. For samples without physical pretreatment (Figure 5), biodegradation resulted in a more significant reduction in the concentration of citalopram compared to the carbamazepine biodegradation results. The concentration of citalopram in the Ostrava WWTP was below the detection limit of the method. Citalopram in the samples after physical pretreatment was completely biodegraded (below the method detection limit) (Figure 6). At the same time, the controls for all samples did not contain a lower concentration of the drug than the samples after biodegradation, as is the case for carbamazepine



**Fig. 5.** Comparison of citalopram concentrations in samples without physical pretreatment.



**Fig. 6.** Comparison of citalopram concentrations in samples with physical pretreatment.

## 4 Conclusions

The results obtained show that the use of physical pretreatment did not have a significantly demonstrable effect on the degradation of carbamazepine, carbamazepine-10,11-epoxide, citalopram, lamotrigine and venlafaxine. In further experiments, it is necessary to focus on the variation of individual measurement parameters (time, voltage), the combination of physical phenomena acting on the samples, and possibly also on biodegradation parameters.

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