

Impact of ultrasound treatment on the reduction of wastewater toxicity and synergistic effect of ketoprofen and diclofenac

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ABSTRACT

The aim of the study was to evaluate acute toxicity of wastewater containing pharmaceuticals exposed to the treatment. The active action of the ultrasonic field (power 750 W, frequency 20 kHz, the amplitude of vibrations 12 μm) was used as a factor degrading the structure of pharmaceuticals. Tests were carried out using three species of organisms, known indicators in environmental tests. *Daphnia magna* (DAPHTOXKIT FTM) was used for the tests. Second, in order to evaluate the reproducibility of the toxic effect decrease for another group of organisms, *Thamnocephalus platyurus* crustacean larvae (THAMNOTOXKIT FTM) were selected in the next stage. Because these tests require 24 or 48 h to perform, we decided to conduct research using the bioluminescent bacteria *Aliivibrio fischeri* and MICROTOX apparatus, which provided results in 3 h. The effectiveness of the tested method of degradation of pharmaceuticals was estimated based on the degree of toxic effect reduction of ketoprofen and diclofenac, as well as their mixture and expressed in half-maximal effective concentration. Reduction of toxicity for *Daphnia magna* was 35%, 22%, and 33% and for *Thamnocephalus* 28%, 24%, and 30% for ketoprofen, diclofenac and a mixture of both drugs respectively. The reduction of toxicity in the ultrasonic field for *Aliivibrio* was 60%, 54%, and 37.91% for ketoprofen, diclofenac, and a mixture of pharmaceuticals respectively. On the basis of toxicity tests, it was also found that there is a synergistic effect between selected pharmaceuticals. Our tests have shown that sample sonication may effectively reduce the concentration and ecotoxicity of pharmaceutical pollutants in wastewater.

Keywords: Wastewater; Toxicity; Ketoprofen; Diclofenac; Ultrasonic field

1. Introduction

In recent years, significant interest has been shown in the application of ultrasound as an advanced oxidation process for the treatment of chemical and hazardous contaminants in wastewater and the natural environment [1,2]. Sonochemistry has been demonstrated as a promising method for the destruction of pharmaceutical aqueous pollutants [3,4]. Degradation of pharmaceuticals and other chemical pollutants may lead to a reduction of toxicity of these substances in the water and sewage environment.

It is important that many chemicals and pharmaceuticals have synergistic properties, which significantly increase their toxicity and impact on aquatic plants, animals and human health. Since the reduction of pharmaceutical toxicity is not proportional to the reduction of the concentration of a pollutant, tests on living organisms and luminescent bacteria have been carried out.

The major objectives of ultrasound research in water treatment are the destruction/transformation of contaminants (pharmaceuticals) and disinfection [5]. Degradation of

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pharmaceutical impurities is possible through the acoustic cavitation created by ultrasound. Sound passes through a liquid as a wave consisting of compression and decompression cycles. As a result of compression and rarefaction, the molecules are torn apart, pushed from each other and tiny microbubbles are formed [3]. These microbubbles gradually grow during in alternating cycles, until they reach a critical size. Subsequent compression causes these cavities to collapse almost instantaneously, with a concomitant release of a significant amount of energy [6]. The reaction rate of this process is a function of the physicochemical properties of the chosen compounds. Volatile and hydrophobic pollutants are degraded by thermal reactions in the “hot spots” of the cavitation bubble. In sewage sludge treatment, ultrasounds are applied as a preliminary conditioner to enhance anaerobic sludge stabilization [7,8]. More hydrophilic compounds are decomposed in the bulk liquid by hydroxyl radicals. Shear forces created in the cavitation process can be used to improve efficiency in sludge dewatering and to obtain sludge disintegration. The ultrasonic disruption of sludge putrescible biomass influences its further microbial degradation, which occurs up to four times faster compared with the conventional treatment [6,7].

Therefore, ultrasonic destruction of pharmaceuticals in aqueous phase generally occurs as the result of imploding cavitation bubbles and involves several reaction pathways and zones such as pyrolysis inside the bubble and/or at the bubble-liquid interface and hydroxyl radical-mediated reactions at the bubble-liquid interface and/or in the liquid bulk [6,7,9].

Due to insufficient purifying of wastewater from chemical and pharmaceutical substances, they can be detected in effluents from treatment plants. This may cause toxicity to living organisms and cause a potential hazard to human health.

The paper aimed to determine the ultrasonic field influence on wastewater toxicity reduction and the synergistic effect of ketoprofen and diclofenac.

2. Materials and methods

2.1. Ultrasounds

During the tests on the acute toxicity of pharmaceuticals subjected to conditioning, the active action of the ultrasonic field was used as a factor degrading the structure of pharmaceuticals. Samples with constant volume and concentration of pharmaceuticals (in accordance with the scheme below) were subjected to the ultrasonic field. The Sonic Vibracell VC750 generator by Sonics and Materials Inc., Newtown, USA. The sonication times chosen based on previous studies and literature review were: 0, 30, 60, 120, and 240 s. Process parameters were: power 750 W, frequency 20 kHz, the amplitude of vibration 12 μm , energy 750 J, ultrasonic wave intensity 176.84 W/m^2 , time 0–240 s, cross-section of the vessel 0.0176 m^2 , initial liquid temperature 21°C.

Concentrations of samples exposed to sonication:

- Toxicology for *Daphnia magna*: 200 mg/L for ketoprofen and mixture, 250 mg/L for diclofenac;
- Toxicology for *Thamnocephalus platyurus*: 100 mg/L for ketoprofen, diclofenac, and mixture;

- Toxicology for *Aliivibrio fischeri*: 1 mg/L for ketoprofen, diclofenac, and mixture.

2.2. Tested substances

The model solution of wastewater containing pharmaceutical (determined on the basis of previous tests) was used for the research. From the entire group of nonsteroidal anti-inflammatory drugs (NSAID), two pharmaceuticals were selected for testing: ketoprofen (CAS 22071-15-4) and diclofenac (CAS 15307-79-6). Pharmaceuticals were selected on the basis of contrast: good and hardly removed from wastewater [10,11]. Ketoprofen is one of the propionic acid class of NSAID with analgesic and antipyretic effects. It acts by inhibiting the body's production of prostaglandin. It was approved for medical use in 1980. Ketoprofen is a widely-used analgesic and is frequently prescribed for arthritis-related inflammatory pains [12,13]. Diclofenac is an NSAID used to treat pain and inflammatory diseases were patented in 1965 and approved for medical use in the United States in 1988. It is available as both sodium or potassium salt. In the toxicity test, sodium salt was used [12,13]. A mixture of selected pharmaceuticals was made by mixing 1 g ketoprofen with 1 g diclofenac, and an aqueous solution was prepared.

2.3. Indicative organisms

Two kinds of aqueous organisms (*Daphnia magna* and *Thamnocephalus platyurus*) and one type of luminescent bacteria (*Aliivibrio fischeri*) were used for the toxicity tests. In the first stage of the research, including *Daphnia magna* tests, the DAPHTOXKIT F™ test kit was used [14]. In order to evaluate the reproducibility of toxic effect decrease for another group of organisms, *Thamnocephalus platyurus* larvae (THAMNOTOXKIT F™) were selected as the indicator of toxicity in the second stage. The larvae were smaller and more sensitive to pollution than *Daphnia magna*, which resulted in different drug concentration causing immobilization of organisms. [14,15].

These two tests require 24 or 48 h to obtain the result, next used test involving bioluminescent bacteria *Aliivibrio fischeri* and Microtox equipment, give results in 3 h. Because living organisms exhibit different characteristic features and resistance regardless of its mass, toxicity cannot be assessed proportionally or mathematically, to investigate its determination, it was decided to examine organisms at various levels in the trophic chain. An additional advantage of the MICROTOX test is its mobility and speed of its implementation and receipt of results. This allows examining various samples online, practically at the place of possible contamination, or on-site production line, which facilitates the use of such tests on an industrial or technical scale [16,17].

Since impurities and toxic substances accumulate in each trophic chain, the determination of acute toxicity for three species gave a more complete picture of the reduction of toxicity in samples conditioned by the ultrasonic field.

Hatching, breeding, and testing of all indicative organisms (and bacteria) were carried out in accordance with the test instructions [14,15]. The tests were carried out in

static laboratory conditions, using two trays with test wells (for *Daphnia magna* and *Thamnocephalus*) and in a glass measuring cuvettes (for *Aliivibrio fischeri* bacteria). Each research series was repeated 10 times for *Daphnia magna* and *Thamnocephalus platyurus* and 4 times for bacteria.

3. Results

So far, it has not been constructed the apparatus, by means of which it would be possible to conduct toxicity tests of chemical impurities. Only living organisms at a different level of organization, allow assessing the biological activity and toxicity of tested pharmaceuticals. Earlier studies on effluent tests using different species showed that micro-invertebrates could be used as a sensitive indicator for effluent toxicity study.

The results are presented as the half maximal effective concentration (EC₅₀) value value (for *Daphnia magna* and *Thamnocephalus platyurus*) and as a percentage of the toxic effect reduction (for *Aliivibrio fischeri*, percent of bacteria's luminescence inhibition converted to toxic effect reduction). Due to the relatively low concentration of pharmaceuticals used for the test, forced by the small size and lower level of bacteria in the trophic chain, the overall toxicity value calculated by the software of the MICROTOX apparatus did not allow for the presentation of toxicity in the form of EC₅₀. Therefore, attention was focused on the inhibition of the toxic effect observed due to inhibition of bacterial luminescence. The results of the tests carried out are shown in Tables 1 and 2.

For both pharmaceuticals (and their mixture) the most favorable exposure time was 240 s and decrease in the toxic effect was obtained for all samples:

- *Ketoprofen* – the mean value of the EC₅₀ for *Daphnia magna* raised from 76.3 mg/L for samples not modified to 107.8 mg/L for samples subjected to 240 s sonication, which indicates a decrease in the toxic effect by approximately 35%. For *Thamnocephalus platyurus* EC₅₀ value grow from 25.1 to 35.0 mg/L respectively, which proves a decrease in toxicity by 28%.
- *Diclofenac* – the mean value of the EC₅₀ for *Daphnia magna* changed from 103.4 mg/L for samples not modified to

133.7 mg/L for samples subjected to 240 s sonication, which indicates a decrease in the toxic effect by approx. 22%. For *Thamnocephalus platyurus* EC₅₀ value grow from 40.8 to 54.0 mg/L respectively, which proves a toxicity decrease by 24%.

- *Mixture* – the mean value of the EC₅₀ for *Daphnia magna* raised from 58.0 mg/L for samples not modified to 86.9 mg/L for samples subjected to 240 s sonication, which indicates a decrease in the toxic effect by approximately 33%. *Thamnocephalus platyurus* EC₅₀ value grow from 19.5 to 28.2 mg/L respectively, which proves a decrease in toxicity by 30%.
- *Ketoprofen* – the most favorable exposure time was 240 s, the mean value of the toxic effect decreased from 96.2% for samples not modified to 38.8% for samples subjected to 240 s sonication, which indicates a decrease in the toxic effect by approximately 60%.
- *Diclofenac* – the best exposure time was 240 s, the mean value of the toxic effect changed from 92.9% for samples not modified to 43% for samples subjected to 240 s sonication, which indicates a drop in the toxic effect by about 54%.
- *Mixture* – the best exposure time was 240 s, the mean value of the toxic effect decreased from 83.4% for samples not modified to 51.8% for samples subjected to 240 s sonication, which indicates a decrease in the toxic effect by approximately 38%.

4. Discussion

Organisms and humans depend on each other to get by, because of that fact ecotoxicity impact studies have great relevance. Research presented in this article seeks to define, highlight and find a way of ecotoxicity reduction. The results of our study indicate that the treatment of wastewater containing pharmaceuticals with an ultrasonic field leads to changes in the level of toxicity. We also report the association between sample sonication time and a greater reduction of toxicity.

In the first stage of the research *Daphnia magna* as the toxicity indicator was used. Among the NSAID tested, ketoprofen showed higher toxicity with an average EC₅₀ value of 76.3 mg/L (mean of 10 test series), whereas the EC₅₀ of diclofenac was 103.4 mg/L. The highest toxicity was demonstrated by the sample containing a mixture

Table 1
Changes in the EC₅₀ concentration (av. 10 series) of nonsteroidal anti-inflammatory drugs for the *Daphnia magna* (D) and *Thamnocephalus platyurus* (T) in relation to the time of ultrasound exposure

t, s	EC ₅₀ , mg/L					
	Ketoprofen		Diclofenac		Mixture 1:1	
	D	T	D	T	D	T
0	76.3	25.1	103.4	40.8	58.0	19.5
30	73.5	23.7	100.9	39.0	56.0	18.9
60	78.1	26.8	105.5	43.0	59.7	21.0
120	86.0	28.7	110.7	45.9	67.2	23.4
240	107.8	35.0	133.7	54.0	86.9	28.2

Table 2
Changes in the value of the toxic effect (av. 4 series) of nonsteroidal anti-inflammatory drugs for bacteria *Aliivibrio fischeri* in relation to the time of ultrasound exposure

t, s	Toxic effect, %		
	Ketoprofen	Diclofenac	Mixture 1:1
0	96.2	92.9	83.4
30	92.7	87.0	83.5
60	83.2	77.3	70.0
120	70.7	53.5	62.7
240	38.8	43.0	51.8

of both pharmaceuticals (1:1) and it was about 58 mg/L. There is relatively little data in the literature on the effects of diclofenac and ketoprofen on the aquatic fauna and flora. *Daphnia magna* Cleuvers [18] reported an EC₅₀ for diclofenac of approximately 68 mg/L. Also, Haap et al. [19] demonstrated similar toxicity of diclofenac (70 mg/L). On the other hand, Czech et al. [20] obtained a much lower EC₅₀ value of 3.2 mg/L, indicating significantly higher toxicity.

In the second stage of research, we used *Thamnocephalus platyurus* larvae. In the tested NSAID samples, ketoprofen was characterized by higher toxicity, with an average EC₅₀ of 25.1 mg/L (mean of 10 test series), while the EC₅₀ of diclofenac was 40.8 mg/L. Similar to *Daphnia magna*, the highest toxicity was demonstrated by a solution containing a mixture of both pharmaceuticals (1:1), the average EC₅₀ value was 19.5 mg/L. This is in line with a study by Nałęcz-Jawecki and Persoone [21], who evaluated the toxic effect of several pharmaceuticals against *Thamnocephalus platyurus* and received EC₅₀ of 41 and 46 mg/L for diclofenac.

In the third stage of research, we used bioluminescent bacteria *Aliivibrio fischeri*. In the tested NSAID samples, ketoprofen was characterized by higher toxicity, with an average toxic effect of 96.2% (more than 96% reduction in luminescence), while diclofenac toxic effect was 92.9%. Unlike in the case of studies using *Daphnia magna* and *Thamnocephalus platyurus*, the lowest toxicity was found in a solution containing a mixture of both pharmaceuticals (1:1). The average value of the toxic effect was 83.4%.

Overall, the toxicity value for the mixture was higher than the predicted value being the sum of toxicity of pharmaceuticals included in the mixture, which may indicate a synergistic effect. The synergistic effect can be described as the interaction of various factors, the effect of which is greater than the sum of individual separate activities. The synergistic effect observed in our study may result from the interaction of active substances of individual

pharmaceuticals at the biochemical level, as well as the synergistic response of the body to the toxin (at the physiological level).

For example in other studies the combination of ultrasound, Fenton and ozonation indicated that effects of ultrasonic watt and reaction temperatures in sono-Fenton systems were significant in degradation efficiency of tetracycline, which is an antibiotic widely used in humans and animals [22]. The paper focuses on assessing the support for removing pharmaceuticals from wastewater using parameters describing changes in the toxicity of pharmaceuticals in relation to selected aquatic organisms. The efficiency of the tested sonication process may be lower than absorption, membrane technique or oxidation process, but create a wider possibility during transfer to technological scale.

In Table 3 it was presented the comparison of the efficiency of different diclofenac degradation methods [2,23–30].

5. Conclusions

The main results of our study are as follows:

- During the toxicity reduction tests in the ultrasonic field, using *Daphnia magna*, the most favorable results were obtained for 240 s sonication (35% for ketoprofen, 22% for diclofenac and 33% for a mixture of both pharmaceuticals);
- While determining the toxicity reduction in the ultrasonic field, using *Thamnocephalus platyurus*, the most favorable reduction values were obtained for 240 s sonication (28% for ketoprofen, 24% for diclofenac and 30% for a mixture of these pharmaceuticals);
- Reduction of toxicity in the ultrasonic field (240 s sonication) for *Aliivibrio fischeri* bacteria was 60% for ketoprofen, 54% for diclofenac and 38% for a pharmaceutical mixture.

Table 3
Comparison of different diclofenac degradation methods

No.	Method	Exposition time, min	Initial concentration, $\mu\text{mol/L}$	Reactor volume, L	Chemical addition		Degradation, %	Source
					Substance	Dose, mmol/L		
1	Sonocatalysis	30	157	0,30	TiO ₂	1,25	84	2
2	EC* (on Nb)	30	157	0,10	Na ₂ SO ₄	100	84	23
3	AC/EC**	5	0,157	0,50	Na ₂ SO ₄	30	93	24
4	Sonication	4	31,060	1,00	–	–	94	Research
5	Ozonation	20	629	1,00	O ₃	9,06	95	25
6	Photocatalysis	120	63	5,00	TiO ₂	2,5	95	26
7	Fenton	2	17	0,10	H ₂ O ₂	5,88	>99	27
					H ₂ O ₂	1		
					Fe ³⁺	0,5		
8	Photo-Fenton	<0,5	120	1,40	H ₂ O ₂	10	>99	28
					H ₂ O ₂	10		
					Fe ³⁺	0,25		
9	Sonolysis	90	15,72	0,25	–	–	>99	39
10	EC* (on Si)	200	550	0,10	Na ₂ SO ₄	50	>99	30

*EC – electrochemical oxidation

**AC/EC – sonolysis, acoustic cavitation/electrochemical degradation

- With the extension of the exposure time in the ultrasonic field for over 240 s (not presented in the article), no significant improvement in the efficiency of the sonication process was observed, while the energy consumption increased.
- Based on toxicity tests, we found a synergistic toxic effect of diclofenac and ketoprofen;
- Extension of the sonication time increased the EC₅₀ thus indicating a decrease in acute toxicity of pharmaceuticals and possibly a reduction of their concentration in wastewater.

Overall, we have shown that sample sonication may effectively reduce the concentration and ecotoxicity of pharmaceutical pollutants in wastewater, thus creating the basis for the potential future transfer of the presented method to industry.

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