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Degradation of benzodiazepines using water falling film dielectric barrier discharge reactor

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Abstract: Classical methods of wastewater treatment are often not suitable for the treatment of pharmaceutical waste. The previous studies have shown that the use of the advanced oxidation procedures (AOP) can lead to a more efficient degradation of various biologically active compounds, which are active pharmaceutical ingredients of applied drugs. The aim of this paper is the application of the plasma technology on the degradation of a two active pharmaceutical ingredients (APIs, diazepam and alprazolam) and the finished products (Bensedin® and Ksalol®) using the dielectric barrier discharge (DBD) reactor for AOP. We studied the degradation rate of these pharmaceuticals, depending on the number of passes through the reactor. This degradation method was efficient 61 % for diazepam and 95 % alprazolam. We also examined the influence of the pH adjustment between the passes of APIs through the DBD reactor. The degradation rate of APIs and the finished products was monitored by the high performance liquid chromatography (HPLC) technique, using a photodiode array detector. The concentration of the dissolved ozone was determined using the iodometric procedure.

Keywords: alprazolam; diazepam; oxidation; pollutants.

INTRODUCTION

Modern society faces the increasing use of pharmaceutical products and, consequently, the increasing amounts of these products end up in the natural environment.[1–10] What is difficult to control is the generation of pharmaceutical waste made by the users of pharmaceutical products.

Unlike other pollutants whose amounts in the environment have been reduced by the introducing of stricter laws, it is very difficult to apply equivalent standards when medicinal products are considered, taking into account all the benefits they brought to human and animal populations. In the light of the facts

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above, the amounts of pharmaceutical waste may also be expected to increase in the future.

Pharmaceutical waste is generated either during the process of an active pharmaceutical ingredient (API)/finished product manufacturing, or from the APIs/finished products that are past their expiry dates.

The finished products containing diazepam and alprazolam or any other benzodiazepine as their active ingredients, belong to a group of the most commonly used pharmaceutical products. In nearly all developing countries these are among the top twenty most commonly used pharmaceutical products.[11]

By their nature, the pharmaceutical products are the biologically active compounds. The parameters used to monitor the effect of the biologically active compounds on the living organisms are biodegradation and bioaccumulation. Pharmaceutical waste belongs to the group of primary pollutants, being toxic for both humans and animals; it is poorly degradable[12] and is not readily removed. A number of investigations shown the standard wastewater treatment methods as unreliable in the treatment of the pharmaceutical waste. Such methods are generally non-destructive to diazepam and to the structurally similar substances.[8,13–15] The application of advanced oxidation processes (AOP) may result in a more effective degradation of such substances.[16,17] These processes involve the creation of radicals (*e.g.*, hydroxyl radicals) and their reaction with the sample.

One of the most recent AOP technologies is the plasma-based technology, which finds the increasing application in the water treatment for the purpose of removing a variety of different pollutants.[18–23]

One of the methods to generate plasma is the dielectric barrier discharge (DBD). DBD reactor, as a system for ozone generating, was recently developed and described.[24] This reactor has been proved to be applicable and very effective in a variety of fields, such as the removal of phenol and chlorophenols from water,[25] the degradation of phenol solutions,[26] decolorization of reactive textile dyes,[27] simultaneous removal of NO_x and SO_2 from flue gas in a coal-combustion power plant,[28] degradation of herbicides,[29,30] removal of ibuprofen from aqueous solutions,[31] degradation of textile azo dye,[32] as well as the degradation of anionic surfactants.[33]

Herein, we report for the first time, the degradation of diazepam and alprazolam, as well as of their respective finished products Bensedin® and Ksalol®, depending on the number of passes through the DBD reactor.

EXPERIMENTAL

For the purpose of this paper, the APIs (diazepam and alprazolam) and the finished products (Bensedin® and Ksalol®) of Galenika a.d., Belgrade, Serbia, were used. All solutions were prepared immediately before their use.

Diazepam solution

A solution of 50 mg L^{-1} concentration was prepared by dissolving 100 mg of diazepam in 2 L of water (double-distilled), and adding 0.5 mL of concentrated hydrochloric acid (Merck *p.a.*), due to its poor solubility.

Bensedin® solution

Bensedin® product containing 5 mg of diazepam, as active ingredient, was used. Twenty tablets were dissolved in 2 L of water, adding 0.5 mL of concentrated hydrochloric acid in order to obtain the same concentration of diazepam (50 mg L^{-1}).

Alprazolam solution

A solution of 50 mg L^{-1} was prepared by dissolving 100 mg of alprazolam in 2 L of water, and adding 1.7 mL of concentrated hydrochloric acid due to its poor solubility.

Ksalol® solution

Ksalol® product containing 1 mg of alprazolam, as active ingredient, was used. One hundred tablets were dissolved in 2 L of water, adding 1.7 mL of concentrated hydrochloric acid, in order to obtain the same concentration of alprazolam (50 mg L^{-1}).

The reagents used for high performance liquid chromatography (HPLC) analysis were: acetonitrile (J. T. Baker, HPLC grade), methanol (J. T. Baker, HPLC grade), potassium dihydrogen phosphate (Merck), sodium hydroxide (Fluka), ammonium acetate (Fluka) and glacial acetic acid (Merck).

Iodometric procedure

Prior to the experiment, the concentration of dissolved ozone was determined using the standard iodometric procedure. The concentration of dissolved ozone was measured by sampling from the upper reservoir and calculated for one pass through the ozone generator.[24,25]

In the ozonated water sample 5 mL of 20 vol. % solution of sulfuric acid (Merck) and potassium iodide (Sigma-Aldrich) were added in excess. The sample was left for 10 min in a dark place and titrated with 0.1 mol L^{-1} solution of sodium thiosulfate. The titrant was added until the yellow color of liberated iodine faded. After the addition of 4 mL of starch indicator solution titration was continued until the blue colour disappeared.

Degradation procedure

Degradation of APIs (diazepam and alprazolam) and their respective finished products (Bensedin® and Ksalol®) was carried out by means of an AOP, using the non-thermal plasma reactor based on coaxial DBD.[24,25]

This coaxial DBD reactor is of fairly simple structure. The both coaxial electrodes are coated with glass as a dielectric and located at the discharge side. The system comprises off three reactors connected in parallel. The length of one DBD reactor, *i.e.*, the length of an electrode is 40 cm and the distance between the electrodes is 3 mm. The electrode diameter is 20 mm.

Solutions of APIs and of their respective finished products were pumped to the top of the reactor through a hollow central electrode using a peristaltic pump. From the top of the reactor, the solutions flowed as a thin film over the glass that was coating the inner electrode. The treated solutions were collected in a receptacle at the bottom of the reactor. The total flow rate through the system of three parallel DBD reactors was 210 mL min^{-1}.

One series of passes of diazepam and alprazolam solutions was carried out without the pH adjustment (pH 3.00). The treated samples were recirculated 12 times for diazepam and

alprazolam, with a 100 mL aliquot withdrawn after each pass of the solution through the DBD reactor.

After a single series of passes of Bensedin® and Ksalol®, where the initial pH was 3.00, and was not modified, the treated sample was recirculated 12 times. After each pass of the solution through the DBD reactor a 100 mL aliquot was withdrawn.

For a series of experiments with diazepam and alprazolam with the pH adjustment, one series of passes was carried out with an initial pH of 3.00. The treated sample was recirculated 7 times for diazepam and alprazolam. After each pass of the solution through the DBD reactor a 100 mL aliquot was withdrawn, while the pH of the remaining solution was adjusted to 3.00 (using 0.1 mol L^{-1} hydrochloric acid), and the solution returned for recirculation.

Analytical procedure

The determination of degradation rate was performed by HPLC technique using a photodiode array detector (Hewlett Packard 1100, Belgrade, Serbia).

A Zorbax SB-C8 column (250 mm×4.6 mm, 5μm) was used at 30 °C for chromatographic separation in diazepam and Bensedin®. The mobile phase was obtained by mixing acetonitrile, methanol and 0.34 g/L aqueous solution of potassium dihydrogen phosphate (its pH being previously adjusted to 5 by the addition of sodium hydroxide solution) at the volume ratio of 22:34:44. The flow rate of the column was 1 ml/min in the isocratic mode, the injection volume being 100 μL. The detection wavelength was set to 254 nm.

A Zorbax SB-Phenyl (250 mm×4.6 mm, 5μm) column was used at 40 °C for chromatographic separation in alprazolam and Ksalol®. The mobile phase consisted of a buffer solution (a 0.77 g/L aqueous solution of ammonium acetate in water, its pH being adjusted to 4.2 using glacial acetic acid) and methanol at the volume ratio of 44:56, as the component A and a buffer solution (0.77 g/L aqueous solution of ammonium acetate in water, its pH being adjusted to 4.2 using glacial acetic acid) and methanol at the volume ratio of 5:95 as the component B. The flow rate of the column was 2 ml min^{-1} in the gradient mode: 2 % B, 15 min, 2–99 %, 20 min, 99 % B, 5 min. The injection volume was 100 μL. The detection wavelength was set to 254 nm.

RESULTS AND DISCUSSION

As the emission of ozone takes place in a closed system there are no losses of ozone during the generation and dissolution in water.[25] D. Manojlović *et al.*[25] applied this reactor for the removal of phenol from water samples. Depending on the experimental conditions, the concentration of dissolved ozone was about 7-40 mg L^{-1}. These values were higher than 0.2 mg L^{-1} obtained by using the reactor based on the corona needle-to-plate discharge.[25]

In our experiment, after approximately 1 h of work, the determined concentration of dissolved ozone in water was 12.9 mg L^{-1}.

In the first part of the paper we presented the degradation rate of diazepam and alprazolam APIs, as well as of their respective finished products Bensedin® and Ksalol®, depending on the number of passes through the DBD reactor. The rate of degradation of starting compounds was determined by means of HPLC technique, using the standard compendial method.

The results are presented in Tables I and II.

TABLE I. Increase of the degradation rate (%) of active ingredient (diazepam and alprazolam) by passing through the DBD reactor

Number of passes	Active ingredient	
	Diazepam	Alprazolam
0	0	0
1	11.00	13.06
2	21.40	20.95
3	28.87	32.39
4	31.18	42.89
5	38.00	51.21
6	39.96	64.05
7	43.76	81.15
8	46.94	84.95
9	52.07	89.31
10	51.97	91.47
11	55.87	93.89
12	60.76	95.17

TABLE II. Increase of the degradation rate (%) of active ingredient (diazepam and alprazolam) in Bensedin® and Ksalol® by passing through the DBD reactor

Number of passes	Active ingredient	
	Diazepam in Bensedin®	Alprazolam in Ksalol®
0	0	0
1	2.59	1.92
2	4.62	3.45
3	7.44	4.90
4	8.35	5.65
5	9.01	6.24
6	10.69	7.34
7	11.76	7.68
8	12.91	9.84
9	14.28	10.34
10	14.63	9.91
11	15.41	11.17
12	32.23	11.83

DBD reactor we used [24,25] can produce oxidative species such as ozone, the ultraviolet (UV) radiation, free electrons, short-lived radicals and ions[26,27]. The trend of decrease in diazepam and alprazolam concentration, in our experiment, may be explained by the fact that the fall of concentration decreases the possibility of the effective collision of the test substance molecules with the oxidizing agent. On the other hand, each subsequent pass of solution through the DBD reactor increases the amount of degradation products, which may also further react with the oxidizing agent, additionally diminishing the possibility of the effective collision of the test substance molecules with the oxidizing agent.

What is evident in alprazolam is a far higher rate of degradation, achieved with fewer passes through the DBD reactor. Considering that the experimental conditions were identical, the explanation of this phenomenon might be related to the alprazolam structure. It has been shown that during benzodiazepine oxidation a cleavage in nitrogen-carbon double bond occurs most commonly.[34] Besides that, the alprazolam carbon C4 (Fig. 1)[35] is more susceptible to oxidation than the diazepam carbon C3 (Fig. 1),[36] and the probability of the effective collision, that would result in oxidation, is by far higher in alprazolam.

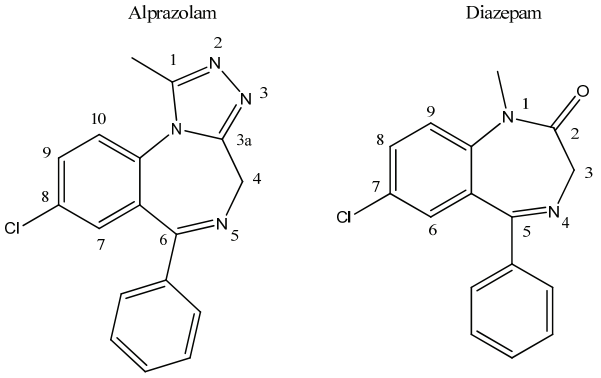

Fig. 1. Diazepam and alprazolam structure.

The hydrolysis of the benzodiazepines ring is the most frequently observed degradation routes for benzodiazepines.[35] The hydrolysis of diazepam in both acidic and basic media was observed, and it may occur in two ways. However, either of these ways results in the same end products of hydrolysis.[34]

In the case of alprazolam, the hydrolysis, even under several different conditions, was not a major degradation source.[35] The aromatic diazo ring of alprazolam probably protects it from hydrolysis, ensuring its better stability in both acidic and alkaline environment.[34]

Some authors describe the degradation of this kind of compounds using a photodegradation method, such as UV irradiation,[34] light-stress exposure testing with a medium-pressure metal halide lamp and mirrors[35] or photolysis under conditions simulating the natural sunlight.[36] This kind of degradation could produce some oxidative species.[37]

It is shown in the Table II that the rate of diazepam and alprazolam degradation in Bensedin® and Ksalol® finished products was not identical when compared to the degradation of the APIs themselves. With the same number of passes, a lower percentage of the API degradation in the finished product was observed, which may be ascribed to the oxidation agent being spent on the excipients contained in the finished products. The oxidative species produced during

the DBD reactor operation are extremely reactive, nonselective, producing an almost instantaneous reaction. The results presented in the Table II show an abrupt rise in the rate of diazepam degradation in Bensedin® at one point, indicating that the oxidation of excipients already occurred, after which the considerable degradation of diazepam began.

This phenomenon was also described in some other papers. After phenol was treated by DBD reactor, the lower removal from samples prepared with Danube river water could be explained by the protective effect of fulvic and humic acids which also reacted with ozone. It could be concluded that ozone reacted with different organic components present in the water.[24,25]

Liu *et al.* reported removal of carbamazepine in an aqueous solution using *ex situ* and *in situ* discharge DBD reactors.[18] The ozone concentration was fixed at the same value of 40 mg L^{-1} for the two systems. The absorbance decrease, measured on UV detector, shows that the degradation of carbamazepine in *ex situ* discharge was rapid (decrease of absorbance for about 80 %) according to the degradation in the *in situ* discharge, where degradation was very slow (decrease of absorbance for about 40 %).[18]

Magureanu *et al.* investigated the decomposition of pentoxifylline in aqueous solution, using a dielectric barrier discharge (DBD), where oxygen was introduced through a separate entrance in the upper lid of the reactor.[19] After plasma treatment (for concentration of 50 mg L^{-1}) about 90 % removal of pentoxifylline was achieved.[19]

After ozonization in DBD reactor, the percentage of removed phenol, 2-chlorophenol, 4-chlorophenol and 2,4-dichlorophenol, 2,6-dichlorophenol from bidistilled water was between 84.9 and 99.9 %.[25,26]

While working with diazepam and alprazolam samples, used in our experiment, an increase of the solution pH value was observed after the sample passing through the DBD reactor. Such observations were contrary to the previous observations on this reactor, when the pH of distilled water decreased as well, which might be explained by the cleavage of water molecules, *i.e.*, by the participation of hydroxyl groups in the ozone generation.[24] In the case of diazepam and alprazolam, it might be assumed that during the molecule disintegration, a protonation of certain negatively charged atoms, produced by bonds cleavage, occurs along with OH ions formation. That was the reason for performing the experiment with the pH adjustment to the initial value (3.00) after each pass through the DBD reactor and the testing of the solution pH influence on the rate of degradation.

The initial pH value of the solution was 3.00. After each pass a 100 mL aliquot of solution was withdrawn, while the remaining solution was acidified to pH 3.00. The pH was measured after each pass through the DBD reactor and was, with minor fluctuations, approximately about 4.5 of pH units. Diazepam and alprazolam samples were passed through the DBD reactor for 7 times.

Table III shows the rate of diazepam degradation depending on the number of passes through the DBD reactor and pH adjustment between the passes.

TABLE III. Increase of the degradation rate (%) of diazepam and alprazolam (with corrected pH) by passing through the DBD reactor

Number of passes	Active ingredient	
	Diazepam	Alprazolam
0	0	0
1	12.28	15.04
2	23.09	25.11
3	31.24	42.62
4	37.87	49.45
5	42.67	54.07
6	49.73	63.36
7	53.15	74.91

The results which are presented in the tables Tables I and III show that the acidification of a solution, after each pass, has no important impact on the rates of diazepam and alprazolam degradation.

CONCLUSIONS

The rate of diazepam and alprazolam degradation, depending on the number of passes through the DBD reactor, was tested, as well as the influence of excipients contained in Bensedin® and Ksalol® finished products, on the rate of degradation. Based on the results obtained, it may be concluded that DBD for AOP has been proved as a highly effective method for the removal of tested APIs from the water, since high degradation rate was obtained for the otherwise poorly degradable compounds (diazepam: 61 %, alprazolam: 95 %).

This method has not been proved effective enough in the degradation of finished products, containing the above mentioned active substances, due to a great consumption of oxidative species (*e.g.*, ozone) on degradation of the excipients contained in the finished products. A large amount of energy was spent on these readily biodegradable compounds, which reduced the cost-effectiveness of this procedure.

It has been demonstrated that the pH adjustment, between the passes of diazepam and alprazolam sample through the DBD reactor, has no important influence on the rate of degradation process.

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ИЗВОД

ДЕГРАДАЦИЈА БЕНЗОДИАЗЕПИНА У РЕАКТОРУ СА ДИЕЛЕКТРИЧНИМ БАРИЈЕРНИМ ПРАЖЊЕЊЕМ КРОЗ ТАНКИ ВОДЕНИ ФИЛМ

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Класичне методе пречишћавања отпадних вода често нису погодне за третирање фармацеутског отпада. Досадашња истраживања су показала да употреба унапређених оксидационих поступака (AOP) може довести до ефикасније деградације различитих билошки активних једињења, која представљају активне фармацеутске супстанце примењиваних лекова. Циљ овог рада је примена плазма технологије за деградацију две активне фармацеутске супстанце (диазепам и алпразолам) и готових производа (Bensedin® and Ksalol®) у реактору са диелектричним баријерним пражњењем (DBD), као унапређеног оксидационог процеса (AOP). Испитиван је степен деградације ових фармацеутика, у зависности од броја пролаза кроз реактор. Овај метод деградације се показао ефикасним: за диазепам 61 %, а за алпразолам 95 %. Испитиван је и утицај pH подешавања између пролаза APIs кроз DBD реактор. Степен деградације API и готових производа праћен је HPLC техником помоћу фотодиодног детектора. Концентрација раствореног озона одређена је јодометријским поступком.

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