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OXIDATIVE DEGRADATION OF NITROFURAN DERIVATIVES

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The inactivation of furacilin and furagin preparations by the Fenton reagent was studied in this work. The effect of different concentrations of the oxidative system on the degradation of drugs was compared, the optimal conditions of destructive processes were determined. The characteristics of oxidative degradation of two drugs were compared; a substantiation of differences on the basis of the chemical structure of the active substances was proposed.
The efficiency of Fenton system for destruction of nitrofuran class drugs has been confirmed. Chemical methods of destruction of organic pollutants are advanced and can be used for wastewater treatment of medical and pharmaceutical enterprises, as well as for local treatment facilities.
Keywords: inactivation, Fenton's reagent, pharmaceutical pollutants.

INTRODUCTION

In the last decade, the problem of pharmaceutical pollution of the environment has increased significantly. The rapid development of the pharmaceutical industry has been the basis for increasing concentrations of various pharmaceuticals in natural objects [1–4]. Due to the high toxicometric index of many drugs, the process of their degradation is difficult, especially in significant concentrations. A particularly toxic group is represented by antibiotics and broad-spectrum antimicrobials such as furacilin and furagin [5–7]. These substrates are derivatives of nitrofuran, certainly less toxic than antibiotics, but in high concentrations provoke dyspeptic and neurotoxic disorders, and therefore certainly have a negative effect on the ecosystem and its inhabitants. The option of degradation of such drugs can be chemical destruction, with complete decomposition of organic pollutants. The search for effective methods of inactivation of organic pollutants of different structure is an urgent task of modern chemistry [8–10].

It is known that hydroxyl radicals produced during the interaction of hydrogen peroxide with some metal ions have a significant oxidative capacity. Such activators are metal ions of secondary groups of the periodic system of chemical elements that have fewer valence electrons than the number of orbitals, such as iron ions with different valence. Of particular interest are iron divalent cations, as a variant of an efficient and reproducible system paired with hydrogen peroxide - the Fenton system [11].

The main stage of the mechanism of formation of hydroxyl radicals:

$$H_2O_2+Fe^{2+} \rightarrow HO^{\cdot}+Fe^{3+}+HO^{-}.$$

Earlier at the Department of General Chemistry (BSU) studies of the oxidation process of a number of drugs by different oxidation systems were performed [12–14]. The

aim of this study was to investigate the inactivation of nitrofuran group drugs by hydrogen peroxide in the presence of iron(II) ions.

MATERIALS AND METHODS

Oxidation of substrates with Fenton's reagent was carried out in aqueous solutions at a constant temperature of 23 °C in a volume of 50 ml.

Medical" hydrogen peroxide with a mass fraction of 37.3 % was used to prepare Fenton's reagent, the exact concentration of which was determined by permanganatometry in acidic medium. The concentration of aqueous hydrogen peroxide solutions varied in the values of four concentrations 4.0, 8.0, 16.0, and 32.0 mmol/L.

Mohr's salt was used as a source of divalent iron ions in Fenton's reagent, and the concentration of iron ions was varied in two concentration values of 0.125 and 0.25 mmol/L.

The initial concentration of the active substance in all experiments was 0.25 mmol/L. Structural formulas of the active substances are shown in Fig. 1.

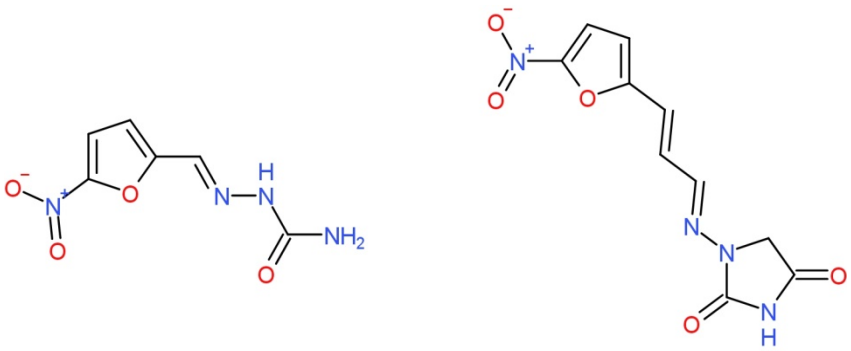

Fig.1. Structural formula of the active substance furacilin (a) and furagin (b).

The pH value was controlled in all cases, since the destructive processes using Fenton's reagent are most optimal at pH values of 2.7–3.5 [11]. In this range and conducted the experiment.

RESULTS AND DISCUSSION

Changes in substrate concentration were observed spectrophotometrically by changes in absorbance intensity. The absorption maximum for each substrate was determined (Fig. 2). Spectra were recorded on a Solar spectrofluorimeter (CM2203). The concentrations of the substrates were determined by calibration graphs in their linear range.

For hydrogen peroxide, the optical density contribution is high up to 285 nm, so the drugs were chosen with absorption maxima above this value. The absorption of Mohr's salt was neglected. Fig. 3 shows absorption spectra of working concentrations of hydrogen peroxide (a) and iron (II) ions. As can be noted from the spectra, these working solutions do not give a significant contribution of optical density at the selected absorption maxima of substrate bands.

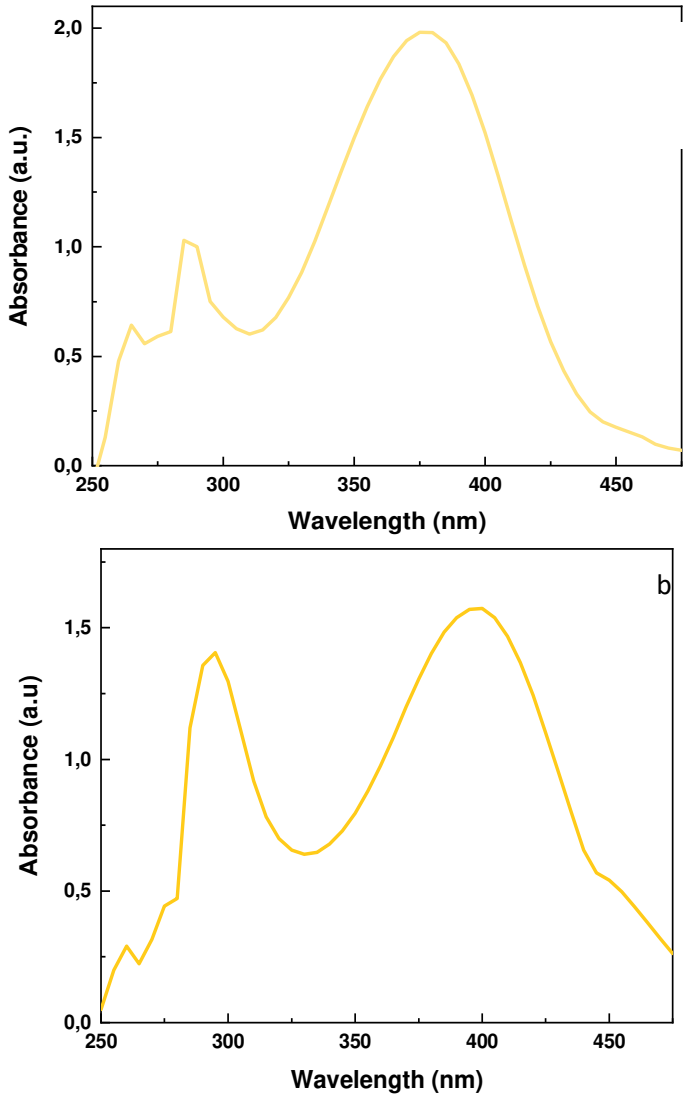

Fig. 2. Absorption spectrum of 0.25 mmol/L aqueous solution of the active substance furacilin (a) λ_{max}=375 nm, furagin (b) λ_{max} =395 nm.

The process of inactivation by the oxidative system of the active substance furacilin was investigated using a wide range of combinations of oxidizing reagents for 60 minutes (Table 1). Full spectra were studied throughout the process to exclude the appearance of new components in the system, that are other forms of organic substances or "fragments" of substrates.

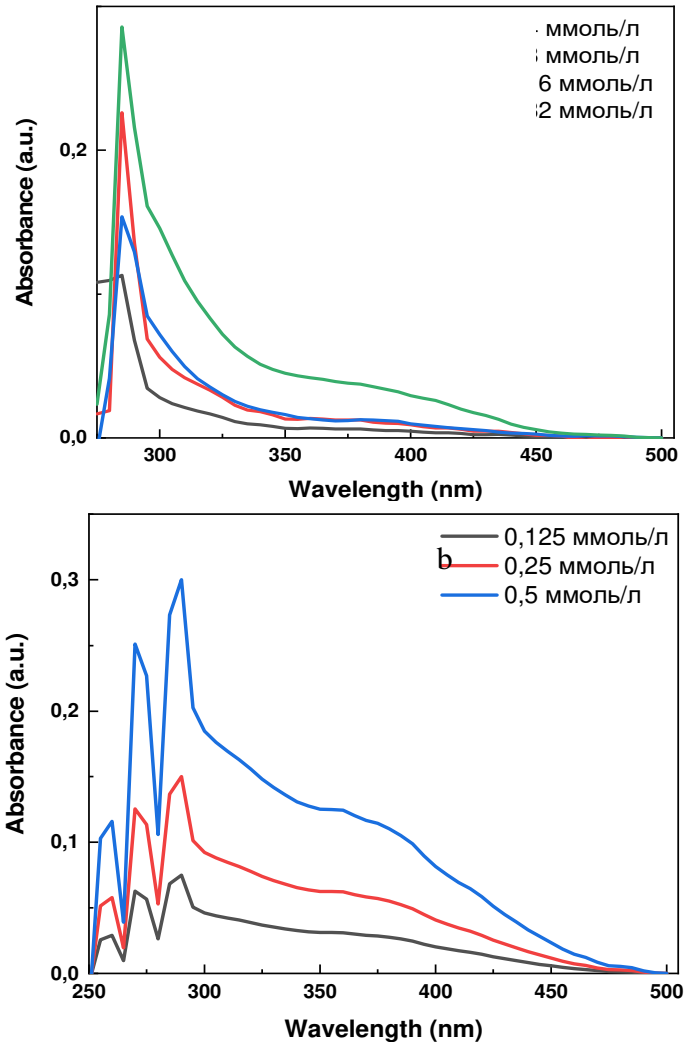

Fig.3. Absorption spectrum of working solutions of hydrogen peroxide (a) and Mora's salt (b).

As can be seen from the data, the greatest degree of degradation is achieved at the optimal reagent ratios [Furacilin]:[Fe^{2+}]:[H_2O_2]=1:1:128 and is 89%, the initial rate of the process at this maximum 10.7 mmol/L×min.

Further oxidative degradation of the active substance of furagin was carried out similarly to furacilin. According to the data obtained (Table 2), the maximum degree of destruction reaches 94% during the first 10 minutes and then changes insignificantly, the maximum initial rate of destruction corresponds to 4.7 mmol/L min. Optimal is the ratio of the reagents [Furagin]:[Fe^{2+}]:[H_2O_2]=1:1:64.

Table 1

Kinetic characteristics of the furacilin degradation process after one hour of oxidation

Reagent ratio	v_0, mmol/L×min	F, %
$[H_2O_2]$=4 mmol/L $[Fe^{2+}]$=0.125 mmol/L	1,6	42
$[H_2O_2]$=8 mmol/L $[Fe^{2+}]$=0.25 mmol/L	3,9	61
$[H_2O_2]$=8 mmol/L $[Fe^{2+}]$=0.125 mmol/L	2,7	45
$[H_2O_2]$=16 mmol/L $[Fe^{2+}]$=0.25 mmol/L	1,1	75
$[H_2O_2]$=16 mmol/L $[Fe^{2+}]$=0.125mmol/L	6,5	54
$[H_2O_2]$=32 mmol/L $[Fe^{2+}]$=0.25mmol/L	10,7	89

Table 2

Kinetic characteristics of the degradation process of furaginafter one hour of oxidation

Reagent ratio	v_0, mmol/L×min	F, %
$[H_2O_2]$=4 mmol/L $[Fe^{2+}]$=0.125 mmol/L	0,13	79
$[H_2O_2]$=4 mmol/L $[Fe^{2+}]$=0.25 mmol/L	1,2	84
$[H_2O_2]$=8 mmol/L $[Fe^{2+}]$=0.125 mmol/L	1,31	81
$[H_2O_2]$=8 mmol/L $[Fe^{2+}]$=0.25 mmol/L	2,6	88
$[H_2O_2]$=16 mmol/L $[Fe^{2+}]$=0.25 mmol/L	4,7	94
$[H_2O_2]$=32 mmol/L $[Fe^{2+}]$=0.25mmol/L	0,18	60

A comparison of the degradation processes revealed that the active substance of furagin undergoes oxidative degradation by the Fenton reagent much easier compared to the active substance of furacilin. In the structure of the active substance of furacilin, the nitrofuran group is connected through a methyl bridge to the carboxamide hydrazine, which makes the heterocycle most resistant to destructive transformations. In the case of furagin, the nitrofuran group is connected to 2,4-imidazolidinedione, the second

heterocycle, via a propenylidene bridge. Being a large molecule with two heterocycles, furagin is less stable and breaks down quickly when exposed to oxidizing agents. To compare the data with the theoretically possible oxidation abilities of the structures, COD values were calculated (Table 3).

Table 3

Calculated chemical oxygen demand of the studied substances

Name of the drug	Molecular formula of the active substance	M, g/mol	COD, mg/mg
Furacilin	$C_6H_6N_4O_4$	198	0,8
Furagin	$C_{10}H_8N_4O_5$	264	1.15

In spite of the fact that the value of COD of furagin is higher than that of furacilin, it was experimentally shown that furagin is oxidized more easily at the expense of a smaller amount of oxidizer. This fact indicates that the number of atoms in the composition of the molecule does not determine the "oxidizability" of drugs.These processes are determined by the complexity of the molecule structure, the stability of bonds in the structure, the mutual influence of substituents.

CONCLUSIONS

1. Thus, it was found that the active substances of furacilin and furagin can be degraded in aqueous solutions at room temperature and atmospheric pressure by hydrogen peroxide in the presence of iron(II) ions. This method can be recommended for the inactivation of pharmaceutical pollutants of the nitrofuran series.
2. Optimal conditions for substrate oxidation were determined: pH, concentration of substrate/hydrogen peroxide/iron(II) ions.
3. It was shown that the active substance of furagin undergoes oxidative degradation by Fenton's reagent much easier in comparison with the active substance of furacilin. The regularity is related to the structure of the active substance, which is confirmed by calculations of the COD value, which do not agree with the data of real oxidative processes, indicating that the oxidant consumption depends on the structure and mutual influence of the substituents of the organic molecule, rather than being limited to the number of atoms in the composition.

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Увеличение концентраций фармацевтических загрязнителей в окружающей среде является серьезной экологической проблемой. Поиск методов их обезвреживания - важная задача современной химии.

В работе проведено исследование инактивации действующих веществ фурацилина и фурагина (производных нитрофурана) пероксидом водорода в присутствии ионов железа (II). Рассчитаны кинетические характеристики окислительной деструкции обоих препаратов. Проведено сравнение воздействия различных концентраций окислительных агентов на деструкцию препаратов. Определены оптимальные условия деструктивных процессов: для фурацилина $[S]:[Fe^{2+}]:[H_2O_2]=1:1:128$, степень деструкции составляет 89 %, начальная скорость процесса – 10,7 мкмоль/л×мин. Для фурагина оптимально соотношение $[S]:[Fe^{2+}]:[H_2O_2]=1:1:64$, степень деструкции при этом достигает 94 %, максимальная начальная скорость деструкции соответствует 4,7 ммоль/л мин. Предложено обоснование различий на основе химического строения действующих веществ изучаемых субстратов, рассчитаны ХПК.

Установлено, что действующие вещества фурацилина и фурагина могут быть деструктированы в водных растворах при комнатной температуре и атмосферном давлении реактивом Фентона. Данный метод можно рекомендовать для инактивации фармацевтических поллютантов нитрофуранового класса.

Ключевые слова: инактивация, реактив Фентона, фармацевтические загрязнители.