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STUDY OF THE DEGRADATION BEHAVIOR OF ENISAMIUM IODIDE, TILORONE DIHYDROCHLORIDE, MORPHOLINIUM THIAZOTATE IN THE SOIL BY THE GC-FID METHOD

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The aim. *To study the behaviour of enisamium iodide, thiloron dihydrochloride, morpholinium thiazotate, and the suitability of the previously developed GC-FID methodology in soil.*

Materials and methods. *The determination of the Enisamium iodide, Tilorone dihydrochloride, and Morpholinium thiazotate in soil gas chromatography with a flame ionization detector using the Rxi-5 ms (30 m long, 0.25 mm outer diameter and 0.25 µm liquid stationary phase thickness).*

Results. *A study was conducted on the behaviour of enisamium iodide, thiloron dihydrochloride, and morpholinium thiazotate in soil, along with the assessment of the suitability of the developed GC-FID methodology for determination in soil. The half-life in soil was investigated, which amounted to 45 days for enisamium iodide, 30 days for thilorone dihydrochloride, and 7 days for morpholinium thiazotate, with corresponding decay rate constants of 0.001 mg/mL, 0.001 mg/mL, and 0.0005 mg/mL, respectively.*

Conclusions. *The previously developed GC-FID methodology is suitable for the determination of enisamium iodide, thilorone dihydrochloride, and morpholinium thiazotate in soil, with necessary analysis conditions established. Under aerobic conditions, the selected pharmaceutical preparations' dispersion rate followed the following decreasing order: enisamium iodide>thilorone dihydrochloride>morpholinium thiazotate in soil*

Keywords: *GC-FID, environmental, soil, enisamium iodide, tilorone dihydrochloride, morpholinium thiazotate*

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1. Introduction

Pharmaceuticals constitute a distinct group of chemical substances that are an integral part of modern human life. Yet, they also emerge as new pollutants in the environment due to their inherent ability to induce various physiological effects in humans. After their use, pharmaceuticals may enter the environment, where they can accumulate and pose harm to both the environment and human health, becoming part of PPCPs [1, 2].

In the last decade, serious concerns have arisen regarding the presence of PPCPs in various parts of ecosystems in quantities capable of eliciting adverse consequences for the environment.

One of the most common ways pharmaceuticals enter the environment is through improper waste disposal. When we discard used medications, they can end up in soil or water bodies. Pharmaceuticals can harm the environment and human health by affecting plants, animals, and microorganisms, entering food and water sources, leading to human poisoning [3].

In 2022, a large-scale study on pharmaceutical pollution of global rivers revealed significant environmental and human health risks in over 25 % of the surveyed areas. This comprehensive investigation covered 1052 sampling locations along 258 rivers in 104 countries, demonstrating pollution affecting 470 million people. The study highlighted that the highest pollution levels were observed in low- and middle-income countries, especially in regions lacking adequate infrastructure for wastewater treatment and waste disposal, often associated with pharmaceutical manufacturing [4].

In recent years, a series of studies have been conducted on the accumulation of pharmaceuticals in soil. These studies have shown that pharmaceuticals can accumulate in soil and persist in it for long periods. One of the key factors influencing the accumulation of pharmaceuticals in soil is their persistence. Persistent pharmaceuticals can remain in the soil for many years without degrading [3, 4].

To better characterize the risks of pharmaceuticals in the soil environment, it is important to understand the factors and processes that influence their persistence.

Laboratory studies indicate that the degradation rate of pharmaceutical compounds in soil varies widely, with half-lives ranging from days to years [5–7]. Within a single therapeutic class, elimination half-lives can vary significantly [9–11].

Enisamium iodide, tilorone dihydrochloride, and morpholinium thiazotate are three innovative pharmaceuticals developed in Ukraine and successfully introduced to the global market. They have many therapeutic indications, including treating viral diseases, cardiovascular, and other conditions.

However, the large-scale production of these drugs poses a threat of increasing pharmaceutical waste. According to the World Health Organization, over 20 million tons of pharmaceutical waste are produced worldwide annually [8, 12–14]. Some of these wastes enter the environment, where they can have a negative impact on human health and the environment.

This issue is particularly relevant for Ukraine, as the country is one of the largest pharmaceutical producers in Europe and shares water bodies. Therefore, developing methodologies and approaches for determining pharmaceuticals in the environment is one of the priority tasks for Ukrainian scientists and manufacturers.

Currently, the most common methods for determining pharmaceuticals in the environment are chromatographic methods [14, 15]. They allow for accurately determining the concentration of pharmaceutical substances in various matrices, such as water, soil, air, and food products.

We have previously developed a quantitative method for simultaneous determination of HPLC [16]. However, GC is the most common method for determining LP in the environment as it is the most environmentally friendly, economical, and widely used method of analysis in environmental laboratories compared to LC-MS/MS. GC has significant advantages over HPLC methods, including better resolution, sensitivity, specificity, and the absence of the need for organic solvents for mobile phases compared to LC-MS/MS measurements [9, 17, 18].

We have developed a GC-FID method to simultaneously determine enisamium iodide, tilorone dihydrochloride, and Morpholinium thiazotate. We utilized a Rxi-5 ms column (Restek Corporation, Bellefonte, PA, USA, capillary column (30 m long, 0.25 mm outer diameter, and 0.25 µm liquid stationary phase thickness), with a mobile phase consisting of an acetonitrile solution, at a flow rate of 1.0 mL/min. The analytes were identified. Our proposed method is characterized by excellent substance separation and suitability for use in “eco-pharmacy,” as it has been analyzed in terms of “greenness” using the AGREE scale [19, 20].

The aim of this study is to conduct chromatographic methods GC-FID for the determination of Enisamium iodide, Tilorone dihydrochloride, and Morpholinium thiazotate in soil, and to assess the behavior of pharmaceuticals and the suitability of the methodology [21].

2. Planning (methodology) of research

The methodology for studying the suitability of the previously developed GC-FID technique for the simultaneous determination of Enisamium iodide, Tilorone dihydrochloride, and Morpholinium thiazotate in soil includes:

1. Analysis of scientific literature.
2. Studying the monographs of SPhU and Ph. Eur.
3. The experiment was developed for the placement of Enisamium iodide, Tilorone dihydrochloride, and Morpholinium thiazotate in soil.
4. Conduct an analysis and check the suitability of the GC-FID method.

3. Materials and methods

3. 1. Soil Collection

For the experiments, Ukrainian soil (Table 1) was chosen, which represented chernozem. The soil was collected from the top 20 cm in the city of Kharkiv in September 2021. After collection, the soil was sieved to 2 mm and dried. The properties of the soil in Ukraine, Kharkiv, are characterized in Table 1. Soil samples were stored at room temperature for less than a month before the start of the study.

APIs and Standard samples of Enisamium iodide manufactured by JSC Farmak batch 07–16; of tilorone hydrochloride manufactured by Interchim, Ukraine No. 2922197000; of morpholinium thiazotate manufactured by Ukraine No, UA/5819/01/02 PAT “Kyivmedpreparat”. Acetonitrile (99.9 %) was purchased from Sigma–Aldrich Co., UK. The GC equipment was run with helium (purity 5.0) as the carrier gas was purchased from Gazchema (Lithuania).

Table 1

Characterization of soil properties in Kharkiv, Ukraine [13]

Soil	Soil texture	pH	Silt	micromineral
Kharkiv soil	Typical chernozems	6.0–6.5	4.6±0.5 %	Carbon content – 2.84±0.35 %, nitrogen – 0.2±0.03 %

The GC-2010 Plus Shimadzu chromatograph operated using helium (purity 5.0), and the carrier gas was procured from Gazchema company (Lithuania).

3. 2. Batch degradation experiment

The basic solutions of enisamium iodide, morpholinium thiazotate, and tilorone dihydrochloride were prepared by dissolving each of the tablets containing 0.125 mg of enisamium iodide, 0.060 mg of tilorone dihydrochloride, and 0.200 mg of morpholinium thiazotate in 10.00 mL of acetonitrile and adjusting to a final volume of 25.00 mL. To ensure uniform distribution of pharmaceuticals in the soil, each preparation was added in the form of a solution. Five grams of air-dried and sieved soil were placed in separate 10.00 mL plastic containers and treated with each of the solutions (at a concentration of 0.002 mg/mL for each substance) previously filtered through a 0.45 µm pore size filter.

The plastic containers were incubated in darkness at 22±1 °C for 45 days. The experiments were conducted at 25 °C. Samples were collected according to the established sampling time after shaking the containers. Before measurement, the volume of the containers was adjusted to 10.00 mL with water, centrifuged at 3000 rpm for 10 minutes. The supernatants were filtered through a 0.45 µm pore size filter and decanted.

3. 3. Equipment

GC/FID method analyses were performed using a GC-2010 Plus Shimadzu with flame ionization detector and autosampler AOC-20i+s (Shimadzu Technologies, Kyoto, Japan). The separation of analytes was carried out on a with Rxi-5 ms (Restek Corporation, Bellefonte, PA, USA, capillary column (30 m long, 0.25 mm outer diameter and 0.25 µm liquid stationary phase thickness). A robotic autosampler and a split/splitless injection port were used.

3. 4. Methods (chromatographic conditions, preparation of standards and samples)

Chromatographic conditions GC/FID method.

Injection port temperature was kept at 250 °C until the end of the analysis. The separation of analytes was carried out on a with Rxi-5 ms (Restek Corporation, Bellefonte, PA, USA, capillary column (30 m long, 0.25 mm outer diameter and 0.25 µm liquid stationary phase thickness) with a liquid stationary phase) 5 % diphenyl and 95 % polydimethylsiloxane) with helium at a purity of 99.999 % as the carrier gas in a constant flow of 1.49 mL/min. The oven temperature was programmed at 75 °C for 5 min, then increased to 290 °C at 10 °C/min and increased to 320 °C at 20 °C/min and kept for 10 min. The total time was 41 min. The injection volume was 1.0 µl, the injection mode was split (split ratio 10), carrier gas – helium [19, 20].

4. Results

The chemical properties, structures, and applications of the investigated compounds are provided in Table 2.

The chromatogram of the solution of pure soil and the tested solution is presented in Fig. 1, 2.

The graphs of linear dependence of peak areas on the concentration of components are shown in Fig. 3.

The conducted research has demonstrated that the dispersion of the selected compounds in the soil occurred, as depicted in Fig. 2. The curves in Fig. 2 represent the fitting of experimental data to a linear decay model (Table 3), and the regression was successful. The corresponding values of the degradation rate constant k (*d1*) and the half-life period $t^{\frac{1}{2}}$ (*d*) are provided in Table 3.

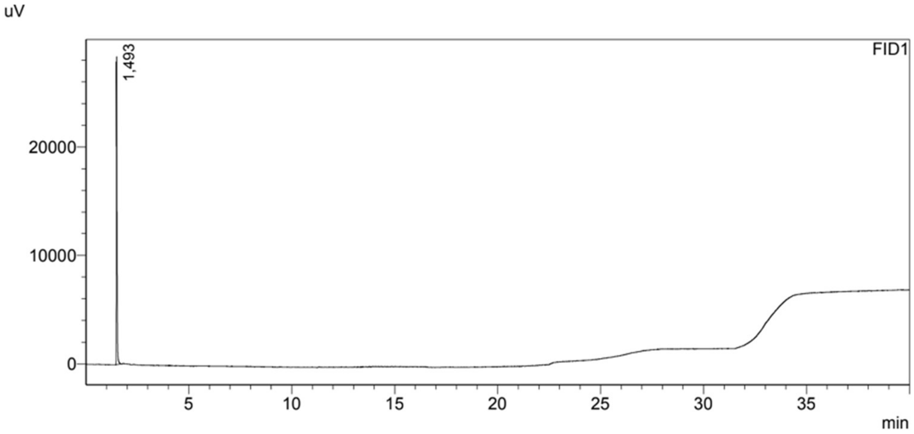


Fig. 1. Pure soil without components

Table 2

The chemical properties, structures, and applications of the investigated compounds

Compound	Water solubility (mg/L)	Solubility	Log KOW*
Enisamium iodide	39.3 mg /mL	In buffer solutions from pH 1.2 to 7.5 is approximately 60 mg/mL at 25 °C	1.8
Tilorone dihydrochloride	96 mg/mL	Ethanol (96 %): 96 mg/mL, DMSO: 43 mg/mL	4.7
Morpholinium thiazotate	0.007 mg/mL	Water soluble, moderately soluble in 96 % alcohol, from 5.5 to 6.7	–0.9

Note: Log KOW values and water solubility were obtained from the Syracuse Research Corporation–Physprop Database [20]

Table 3

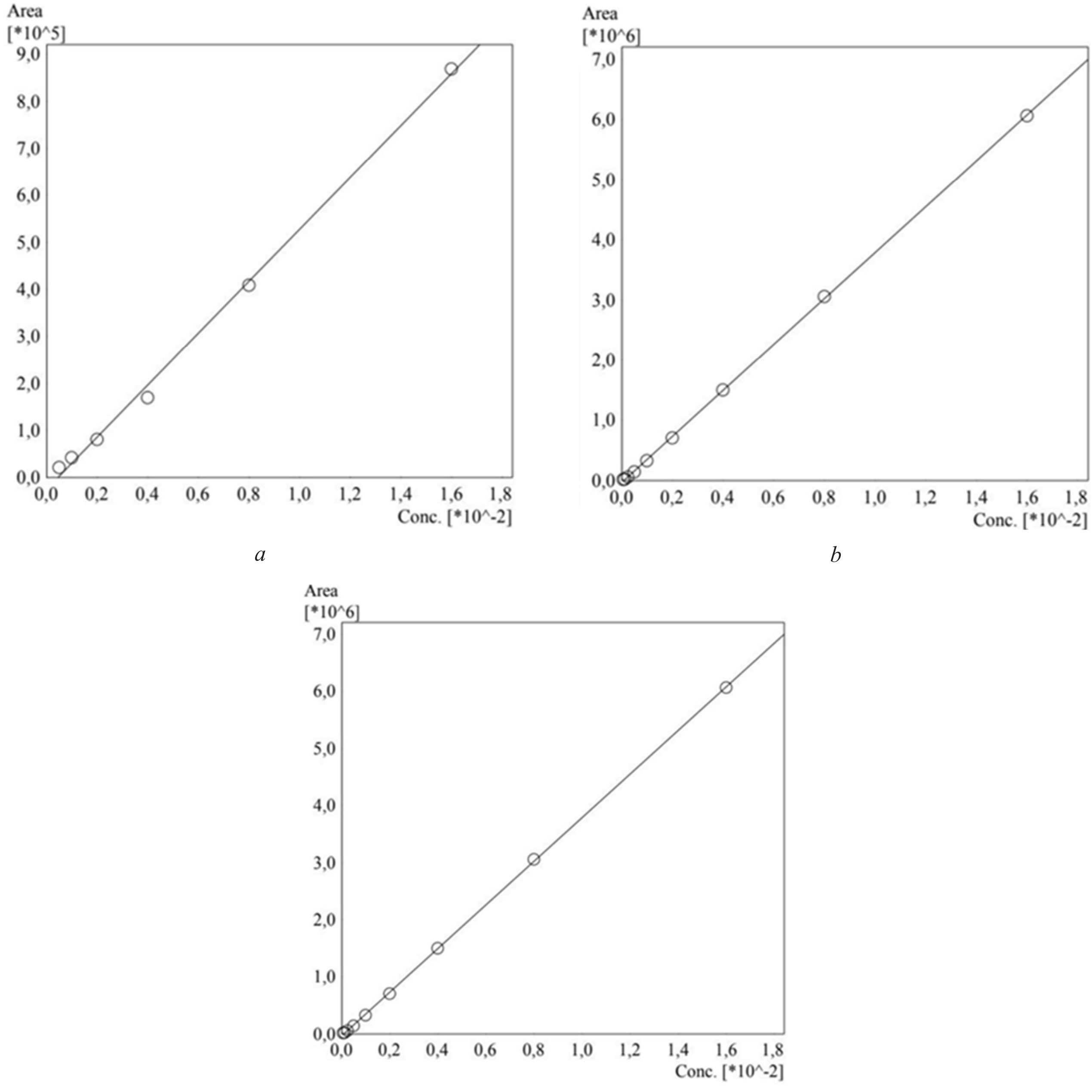
Metrological characteristics of the linear dependence

Magnitude	Acceptance criteria for linear dependence parameters	The obtained values		
		Enisamium iodide	*Tilorone dihydrochloride*	*Morpholinium thiazotate*
$a \pm (S_a)$	$a \le \Delta a = t(95\ \%; 3)$; $S_a = 141$	$-\lvert 221.014 \rvert$	$-\lvert 10892.7 \rvert$	$-\lvert 288.34 \rvert$
b	–	–35059.0	–24968.4	–8747.55
Sb	$\le \Delta As$ (%)/t(95 %; 3)=1.36	0.52571	0.799	0.0004
r	≥0.990	0.9999	0.9987	0.9999
LOD	–	0.008 mg/ml	0.0076 mg/ml	0.0079 mg/ml
LOQ	–	0.025 mg/ml	0.023 mg/ml	0.024 mg/ml

Table 4

Degradation rate constants $\left(k^{d-1}\right)$ and half-lives $\left(t^{\frac{1}{2}}, d\right)$ for the selected pharmaceuticals in the soils

Compound	Incubation conditions	k^{d-1}	$t^{\frac{1}{2}}(d)$	R^2
Enisamium iodide	Soil aerobic	0.001 mg/ml	45	0.9908
Tilorone dihydrochloride	Soil aerobic	0.001 mg/ml	30	0.9802
Morpholinium thiazotate	Soil aerobic	0.0005 mg/ml	8	0.9891



a *b*

c

Fig. 3. The graphs of linear dependence of peak area on the concentration of analytes: *a* – enisamium iodide; *b* – tilorone dihydrochloride; *c* – morpholinium thiazotate) are presented in Fig. 2

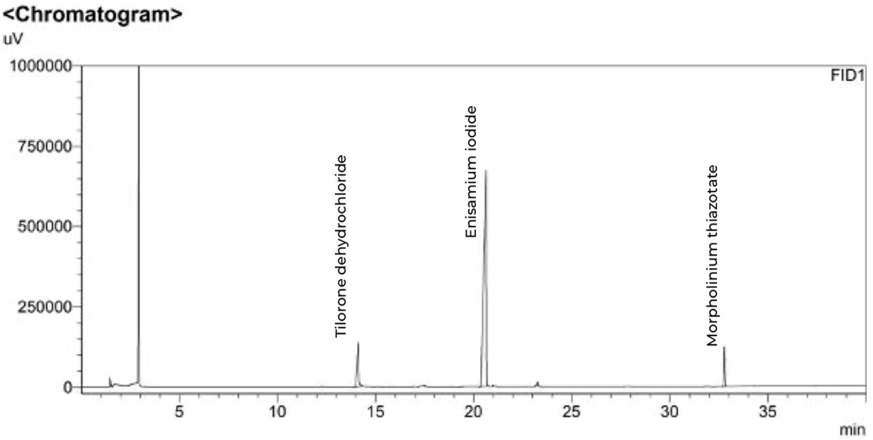


Fig. 2. Soil with Enisamium iodide, Tilorone dihydrochloride, and Morpholinium thiazotate, where the concentration was 0.013 mg/ml

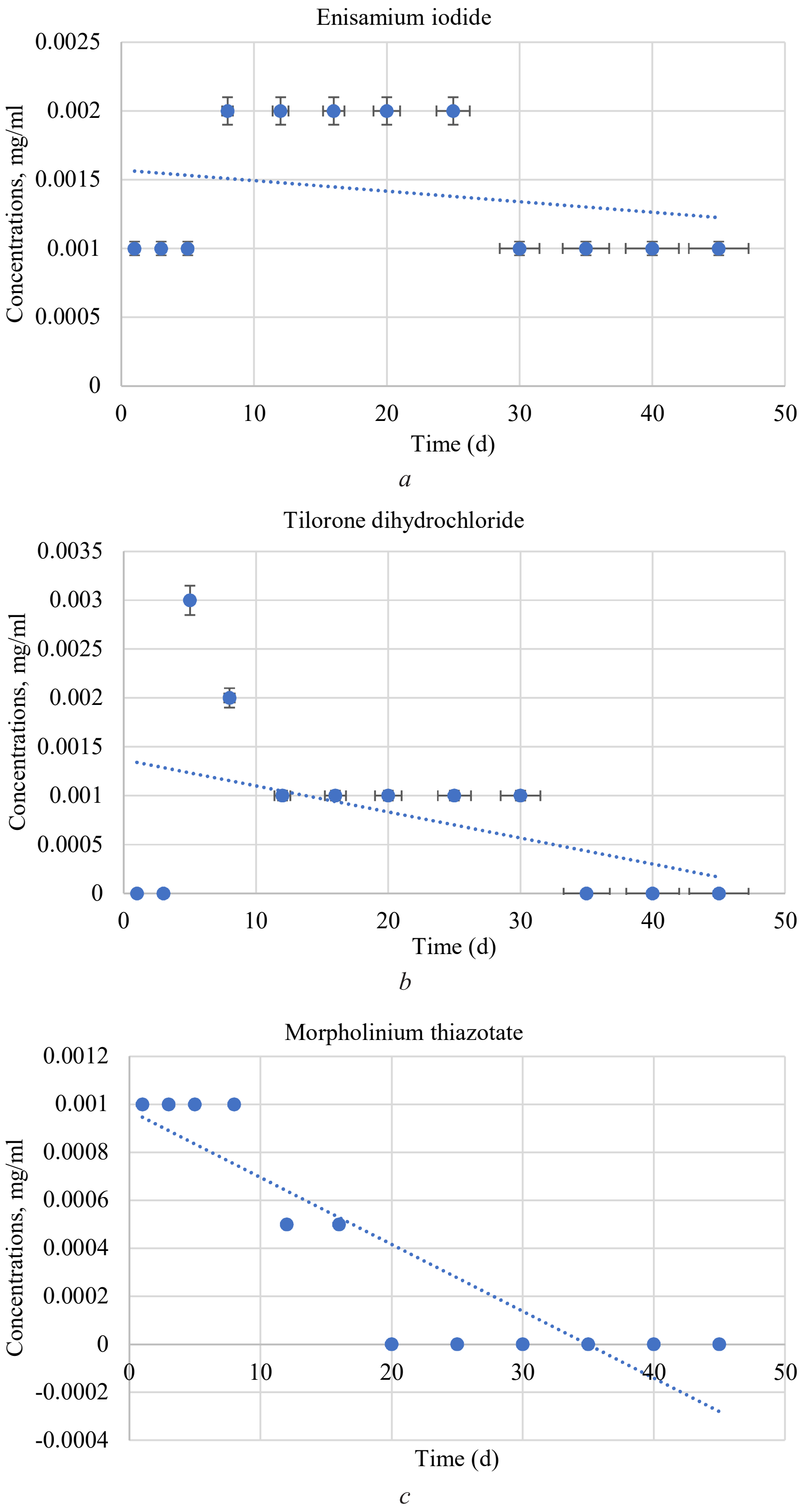


Fig. 4. Dispersion over a period of 45 days: *a* – enisamium iodide; *b* – tilorone dihydrochloride; *c* – morpholinium thiazotate

4. Discussion

The previously developed method [19] is suitable for determining Enisamium iodide, Morpholinium thiazotate, and Tilorone dihydrochloride in soil.

To confirm the specificity of the method, chromatography of the following solutions was conducted: a model solution of pure soil and a solution with substances.

The metrological characteristics of the linear dependence meet the acceptability requirements stipulated by the State Pharmacopoeia. High correlation coefficient values confirm the linearity of the relationship between the "introduced" and "found" quantity of the API. The intercept of the linear dependence for the calculated regression line does not exceed 5.0.

Optimal concentrations of the medicinal preparations were selected, as the higher their initial concentration in the soil, the lower the rate constant of degradation, resulting in a longer decomposition time. When choosing the concentrations of the determined APIs, we were guided by the previously determined minimum concentrations according to the GC-FID method in the detection range of 0.12–16 (μg/mL). When preparing solutions to verify the suitability of the GC-FID method, we used minimum concentrations, which we experimentally determined based on the amount of active substance in the respective pharmaceutical forms.

The use of low concentrations is ecologically important for determining the half-life as a function of the initial concentration in the soil; using unrealistically high concentrations tends to overestimate the half-life periods, deviating from real scenarios.

Under aerobic conditions, a significant portion of enisamium iodide remained in the soil after 45 days (Fig. 1, *a*), indicating minimal dispersion and resistance to microbial degradation. Similarly, enisamium iodide did not show a noticeable decrease in concentration in the soil, indicating that microorganisms play an important role in degradation under aerobic conditions.

The initial decrease was likely caused by the formation of non-extractable residues, as demonstrated by compounds labelled with 14C [14]. After the initial decrease, the amount of enisamium iodide remained unchanged in the soil under aerobic conditions.

The observed decrease also mainly occurred during the first 8 days, with minimal decline thereafter (Fig. 1, *b*). After the initial decrease, the level of Tilorone dihydrochloride remained unchanged in the soil (Fig. 1, *a*, *b*).

Tilorone dihydrochloride demonstrated evident dispersion in the soil, with corresponding half-life values $t^{\frac{1}{2}}$ of 12, 16, and 20, 30 days respectively (Table 4). After 45 days of incubation, it was completely dissipated.

In the case of Morpholinium thiazotate, no decrease occurred (Fig. 1, *c*), but it dispersed rapidly and demonstrated evident dispersion in the soil, with corresponding half-life values $t^{\frac{1}{2}}$ of 3, 3, and 10 days respectively (Table 4). After 45 days of incubation, it was completely dissipated.

Despite selecting optimal low concentrations of the analytes for analysis, the methodology proved suitable, as higher initial concentrations of the pharmaceuticals in the soil resulted in lower degradation rates and, consequently, longer degradation times.

Higher concentrations of the pharmaceuticals upon their introduction will decrease the rate of their degradation and prolong their stability in the soil, as this will inhibit the activity of degrading microorganisms [15, 21].

The results of this study clearly indicate that microbial activity, soil oxygen status, soil type, and compound characteristics all influence the degradation of selected pharmaceuticals in the soil.

With the exception of Morpholinium thiazotate, all other pharmaceutical compounds demonstrated relatively prolonged stability under aerobic conditions, with $t^{\frac{1}{2}} > 45\ d$.

Practical Relevance. The proposed analytical method can be used to determine Enisamium iodide, Tilorone dihydrochloride, and Morpholinium thiazotate in soil**.**

Research limitations. The determination was limited in time, so the time of complete dissipation for enisamium iodide was not determined.

Prospects for further research. The next stage of research is planned to improve the experiment to study the behaviour of Enisamium iodide, Tilorone dihydrochloride, Morpholinium thiazotate in the soil.

5. Conclusions

All methods were accurate and reliable. We confirmed the suitability of the previously developed GC-FID methodology for determining Enisamium iodide, Tilorone dihydrochloride, and Morpholinium thiazotate in soil. Under aerobic conditions, the rate of dispersion of the selected pharmaceutical preparations followed the following decreasing order: Enisamium iodide>Tilorone dihydrochloride>Morpholinium thiazotate in soil.

The stability of Enisamium iodide, Thiotriazoline, and Tilorone dihydrochloride in soil under aerobic conditions implies that these compounds may behave conservatively when reaching subsurface soil layers or the groundwater horizon, where anaerobic environments may prevail. Although these compounds may undergo microbial degradation on the soil surface in aerobic conditions, the clean sorption of Enisamium iodide, Morpholinium thiazotate, and Tilorone dihydrochloride in soil additionally suggests that they can easily migrate downward during irrigation or surface spreading (for groundwater recharge) of treated wastewater, leading to an increased risk of soil water contamination.

These results demonstrate that pollutants can be bioavailable to plants and microorganisms exposed to their influence and may enter groundwater through leaching.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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Data availability

Data will be made available at a reasonable request.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

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