# STUDY OF ANTICHOLINESTERASE PROPERTIES OF LORATADINE AND DESLORATADINE

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**Introduction.** Allergic reactions currently constitute a significant medico-social problem, owing to their high prevalence and the steadily increasing incidence of various allergies worldwide [1, 2]. Consequently, antihistamine drugs have become one of the most frequently prescribed pharmacological drug groups [2, 3]. Given their widespread use across various age groups, accessibility, and low cost, antihistamine drugs are of considerable research interest for a more detailed investigation of their pharmacological potential, with a view to their possible use in the treatment or prevention of other diseases and, accordingly, to reducing the risk of adverse reactions associated with polypharmacy.

Scientific and literary sources indicate that antihistamine drugs exhibit a significantly broader spectrum of pharmacological activity, extending beyond their anti-allergic effects [4, 5]. Moreover, several have emerged as promising candidates for repurposing, demonstrating efficacy in the treatment of various pathological disorders, including inflammatory and autoimmune diseases, oncological processes, neurodegenerative and cardiovascular diseases,as standalone agents or in combination with other active pharmaceutical ingredients (APIs) and/or medicinal products [4-7]. Based on analysis conducted using SemNet 2.0 software, antihistamine APIs were identified as promising candidates for use in adjuvant, combination therapy with levodopa derivatives in the treatment of Parkinson's disease [6]. The work of a research group led by Ayaz M. [5] confirmed that combining ebastine and levocetirizine with levodopa preparations contributed to increased levels of neurotransmitters, including dopamine. It also reduced acetylcholinesterase (AChE) activity, inhibited oxidative stress and reduced neurotoxic damage caused by haloperidol.

Therefore, research aimed at studying the various pleiotropic properties of antihistamines and medicinal products based thereon is promising.

According to marketing research of the product portfolio of antihistamine medicinal products as of July 2024, on the Ukrainian pharmaceutical market, group R06 "Antihistamines for systemic use" comprised 196 trade names (TN) of preparations [8]. Of these, medicinal products of the first generation constitute 26.5%; those of the second, 26.0%; and those of the third, 47.5% of the total number of items. Within the considerable range of antihistamines available on the pharmaceutical market, desloratadine-based medications currently predominate (23.5% of all antihistamines on the market), with levocetirizine- and loratadine-based medications occupying second and third positions, respectively [8]. In light of marketing analysis outcomes pertaining to experimental studies investigating and comparing the pleiotropic properties of antihistamine compounds, desloratadine, along with its metabolic precursor loratadine, was chosen.

Butyrylcholinesterase (BuChE) belongs to the carboxylic ester hydrolase enzyme family. This enzyme is present in nearly all human tissues and organs, although it is most abundant in the liver and blood plasma (hence its alternative designations 'plasma cholinesterase' and 'pseudocholinesterase') [9, 10]. BuChE plays an important role in the breakdown of several neurotransmitters and xenobiotics [11-14]. This enzyme in blood plasma serves as the first line of defence against toxic compounds, particularly organophosphates, which enter the bloodstream and can reduce the activity of its sister enzyme, acetylcholinesterases, also known as true cholinesterase, found in neuromuscular junctions and in cholinergic synapses in the brain, as well as in erythrocytes. AChE plays a well-established role in the hydrolysis of the neurotransmitter acetylcholine in cholinergic synapses. Reduced acetylcholine neurotransmission in specific brain regions constitutes the pathophysiological basis of the cognitive impairments characteristic of patients with Alzheimer's disease, the most prevalent neurodegenerative disorder. During the progression of this disease, an increase in acetylcholinesterase activity is observed, leading to a reduction in acetylcholine levels in the brain and disruption of cholinergic transmission, which plays a key role in the mechanisms of learning and long-term memory formation [15]. Initially, therapeutic strategies to augment impaired cholinergic neurotransmission in Alzheimer's disease focused on the use of AChE inhibitors. However, over the past several years, it has been demonstrated that with the progression of Alzheimer's disease, AChE levels gradually decline, whereas BuChE levels increase, ultimately becoming the most prevalent cholinesterase in the brain. It has been reported that in patients with late-stage Alzheimer's disease, AChE levels decrease to 55-67%, while BuChE levels increase to 120% of normal levels [15]. Thus, BuChE activity likely plays a more significant role in cholinergic transmission during the later stages of the disease [16]. Furthermore, certain scientific studies suggest a potential role for BuChE in the conformational transformation of beta-amyloid from its initial non-aggregated form to pathogenic oligomeric or fibrillar structures, which are associated with the neuropathological signs of Alzheimer's disease and the clinical manifestations of dementia [17]. It is therefore posited that molecules targeting BuChE may also be beneficial in the treatment of this neurodegenerative disorder.

Human serum butyrylcholinesterase is known to play a significant role in the biotransformation of several medicinal products, including muscle relaxants (mivacurium, suxamethonium) and ester-type local anaesthetics (e.g. procaine) [14]. The hydrolysis of these

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compounds involving BuChE accounts for their short-acting pharmacological effect. In this regard, reversible BuChE inhibition may be considered a promising strategy for modifying the kinetic parameters and prolonging the effects of these agents.

Various methods have been developed to determine BuChE activity, but the most prevalent assays are based on Ellman's method [18], owing to its rapid and simple nature, and its ease of adaptation for high-throughput analysis.

**The aim of this work** is to investigate and compare the effects of loratadine and desloratadine on the activity of the human serum butyrylcholinesterases enzyme.

**Materials and methods**

*Materials*. During the experimental studies, LIONORM GUM N control serum (Czech Republic, Erba Lachema s.r.o.) was used. This was manufactured from human serum as a lyophilisate with parameter values corresponding to normal or moderately elevated levels. Butyrylthiocholine iodide was purchased from Tokyo Chemical Industry Co. (Japan), and potassium hexacyanoferrate (III) and dimethyl sulfoxide (DMSO) were obtained from Sigma-Aldrich (USA). Disodium hydrogen phosphate dodecahydrate and sodium dihydrogen phosphate dihydrate, used to prepare the phosphate buffer solution (pH = 7.6), were also obtained from Sigma-Aldrich (USA). The antihistamine active pharmaceutical ingredients loratadine and desloratadine were purchased from Vasudha Pharma Chem Ltd. (India).

For the studies, a potassium hexacyanoferrate(III) solution at a concentration of 2.4 mmol/L (reagent A) in phosphate buffer (pH 7.6), and a butyrylthiocholine iodide solution at a concentration of 30 mmol/L (Reagent B) were prepared beforehand.

*Investigation of serum BuChE activity.*

Human serum butyrylcholinesterase activity was determined *ex vivo* spectrophotometrically using a SPECORD 200 UV spectrophotometer (Analytic Jena, Germany) according to a modified Ellman method [18]. This method is based on the ability of thiocholine, the reaction product catalysed by butyrylcholinesterase, to reduce yellow potassium hexacyanoferrate (III) to virtually colourless potassium hexacyanoferrate (II). This permits direct photometric registration of the enzymatic reaction rate. The rate of decrease in optical density of the reaction solution at a wavelength of 405 nm is proportional to the BuChE activity in the sample under analysis.

The spectrophotometer was initially zeroed against a phosphate buffer solution at a wavelength of 405 nm and a temperature of 37.0 ± 0.5 °C, using a cuvette with an optical path length of 1.0 cm.

To determine butyrylcholinesterases activity, a series of solutions with a fixed amount of serum sample and varying ratios of reagent A and reagent B were measured. The total volume of the reaction mixture was 1530 µL, with the serum sample constituting 30 µL. The amount of reagent A was gradually reduced from 1400 to 1050 µL in increments of 50 µL, whilst the amount of reagent B was increased from 100 to 450 µL in similar increments. A total of 8 variations of reaction mixtures were prepared, each of which was analysed in triplicate.

Initially, reagent A was added to the cuvette, followed by the addition of the blood serum sample. The cuvette containing the sample was incubated for 5 minutes at 37.0 ± 0.5 °C, after which Reagent B was added. Absorbance measurements of the resulting solutions were performed against a buffer solution at a wavelength of 405 nm for 7 minutes, with readings taken at 30-second intervals. A correction factor of 0.54054 mmol/L was used for the calculations.

*Determination of the effect of loratadine and desloratadine on the activity of BuChE in serum.*

Butyrylcholinesterase activity determination in the presence of loratadine and desloratadine was performed using the method described above; however, prior to the addition of reagent B, 10 µL of antihistamine API solution, prepared in dimethyl sulfoxide, was added. The initial concentrations of loratadine and desloratadine were 3.83 mM, 7.65 mM and 15.30 mM, ensuring final concentrations of 25, 50 and 100 µM, respectively, in the reaction mixture with a total volume of 1530 µL.

Reagent A was initially added to the quartz cuvette, followed by 30 µL of the serum sample, and then 10 µL of the antihistamine API under investigation, at a specific concentration. The cuvette containing the sample was incubated for 5 minutes at 37.0 ± 0.5 °C, after which reagent B was added to the cuvette. A total of eight variants of reaction mixtures were prepared for each concentration of the antihistamines under investigation (25, 50, 100 µM). The amount of reagent A was gradually decreased from 1390 to 1040 µL in increments of 50 µL, with a concomitant increase in the amount of reagent B from 100 to 450 µL using similar increments. The measurement of each of the eight reaction mixtures was repeated three times. A correction factor of 0.54054 mmol/L was used in the calculations.

*Processing of experimental data*.

For graphical and statistical processing, analysis, and visualisation of data, the licensed software product SigmaPlot 14.0 was employed. Within this software, various mathematical models of enzyme-inhibitor interaction were tested to determine the most appropriate kinetic model and corresponding type of inhibition, including linear mixed-type associations, competitive and non-competitive binding interactions. A series of calculations were performed under varying conditions, with results ranked according to the coefficient of correlation $R^2$. Using the data obtained, Michaelis-Menten and Lineweaver-Burk plots were constructed, from which initial information regarding the mechanism of inhibition was derived. Based on the data obtained, the following kinetic parameters were determined: maximum reaction rate ($V_{max}$), Michaelis constant ($K_m$), and inhibition constant ($K_i$).

To quantify the inhibitory capacity of antihistamine APIs with respect to the enzyme butyrylcholinesterases, the half-maximal inhibitory concentration ($IC_{50}$) was calculated, based on the results obtained using the Cheng-Prusoff equation (formula 1).

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$$IC_{50} = Ki + \frac{Ki \cdot [S]}{Km}, \qquad (1)$$

where $K_i$ – the inhibition constant;
$K_m$ – the Michaelis constant;
[S] – the maximum substrate concentration in the reaction.

This equation expresses the concentration of the ligand-inhibitor required to inhibit the catalytic activity of an enzyme by 50% relative to its native state.

*Statistical analysis of data.*

Results were expressed as the mean ± standard deviation, estimated from three independent replicates. Data were analysed for statistical significance using a one-way analysis of variance with Tukey's HSD post hoc test. Values of $p \leq 0.05$ were considered significant.

**Results and discussion.**

A spectrophotometric study of the effect of loratadine on the activity of human serum butyrylcholinesterases established that loratadine is an enzyme inhibitor, as illustrated by the Michaelis-Menten plot (Figure 1).

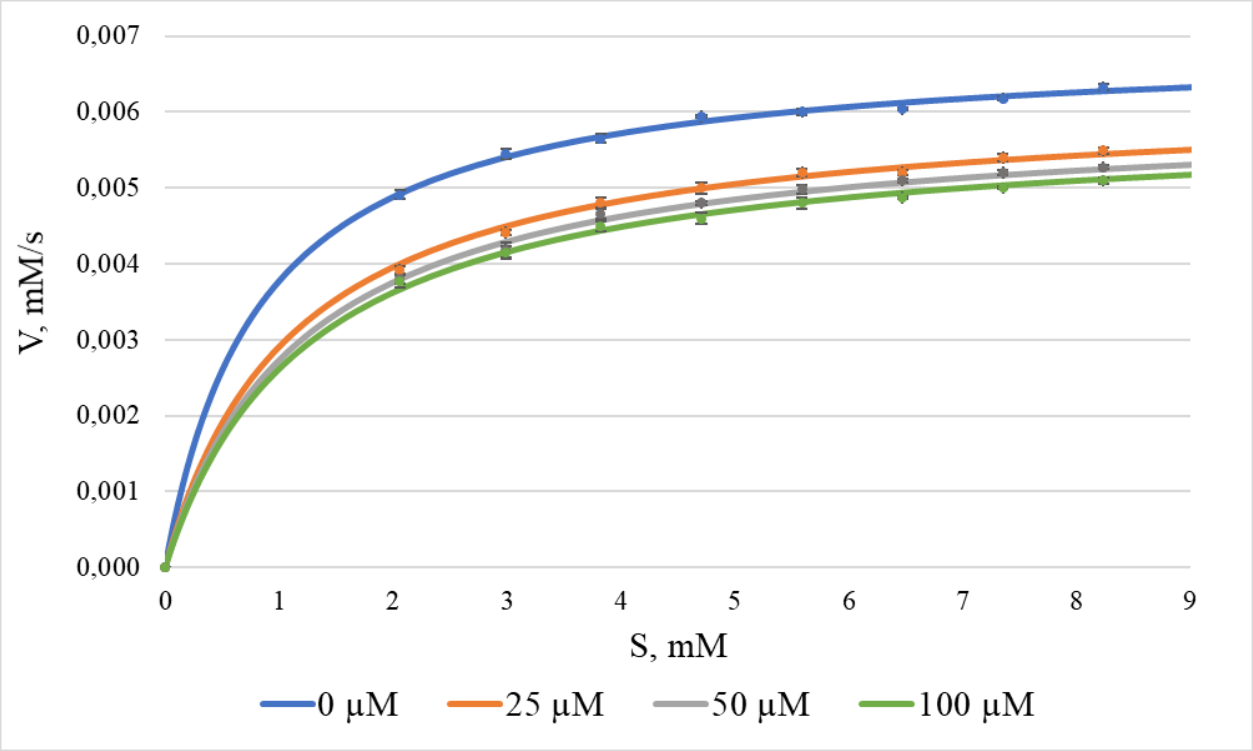


**Fig. 1. The dependence of the substrate conversion rate by butyrylcholinesterases on its initial concentration and the concentration of loratadine, presented in Michaelis-Menten equation coordinates**

It has been demonstrated that loratadine, as an inhibitor of butyrylcholinesterases, reduces the maximum rate of the enzymatic reaction of substrate conversion by butyrylcholinesterases and increases the Michaelis constant ($K_{m(0)}$ = 0.76 ± 0.02 mM, $K_{m(loratadine)}$ = 0.86 ± 0.07 mM). These effects are clearly illustrated in Figure 2, which presents the relationship between the rate of substrate conversion by butyrylcholinesterase and its initial concentration, as well as the inhibitor (loratadine) concentration, in Lineweaver-Burk reciprocal coordinates.

In investigating the inhibitory effect of loratadine on butyrylcholinesterase, the Mixed (Partial) type of inhibition model proves most suitable based on the correlation coefficient value ($R^2$=0.9608). This type of inhibition is observed when the inhibitor binds both at the active site of the enzyme and at an external site. In this instance, the enzyme-substrate complex retains partial activity compared with the native enzyme [19].

The kinetic constants for loratadine, calculated using the chosen model, are as follows: $K_i$ = 10.15 ± 1.20 µM, $K_m$ = 0.86 ± 0.07 mM, $V_{max}$ = 6.94 ± 0.09 µM/sec. Under these conditions, the half-maximal inhibitory concentration of loratadine for butyrylcholinesterases is $IC_{50}$ = 117.78 ± 10.01 µM.

A spectrophotometric study of the effect of desloratadine on human serum butyrylcholinesterases activity revealed that it, like its metabolic precursor loratadine, acts as an inhibitor of the enzyme, as demonstrated in the Michaelis-Menten plot (Fig. 3).

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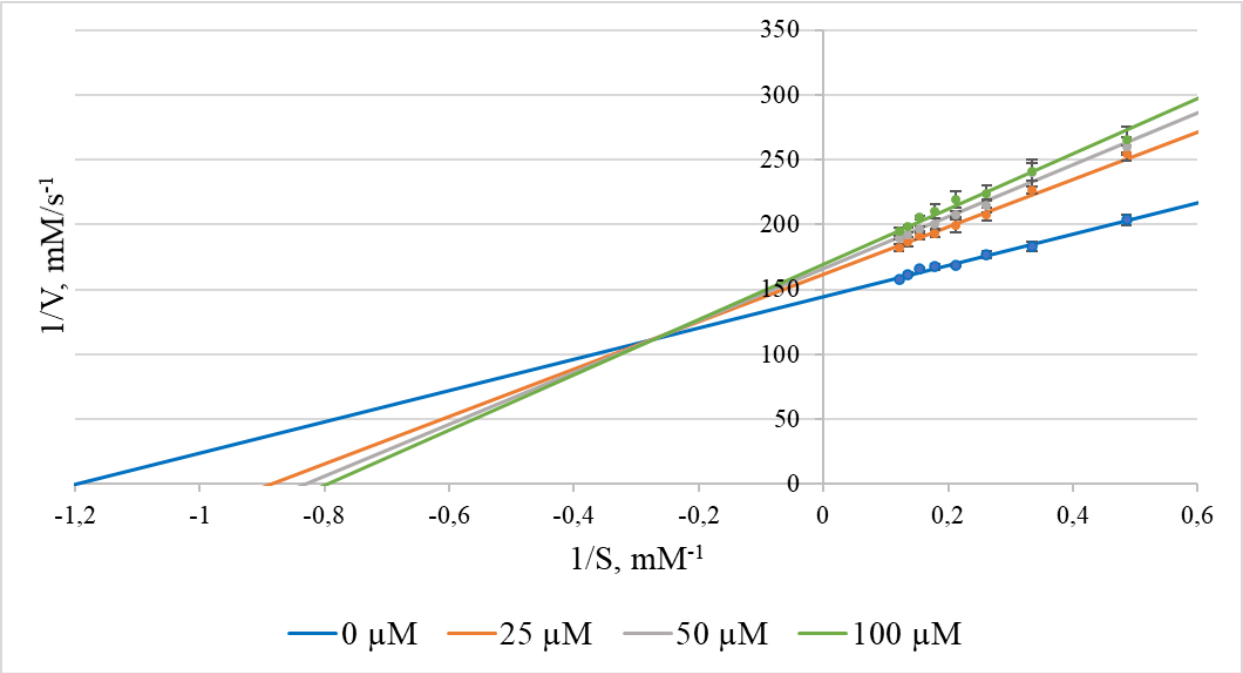


**Fig. 2. Relationship between the rate of substrate conversion by butyrylcholinesterase and its initial concentration, as well as the concentration of loratadine, in Lineweaver-Burk reciprocal coordinates**

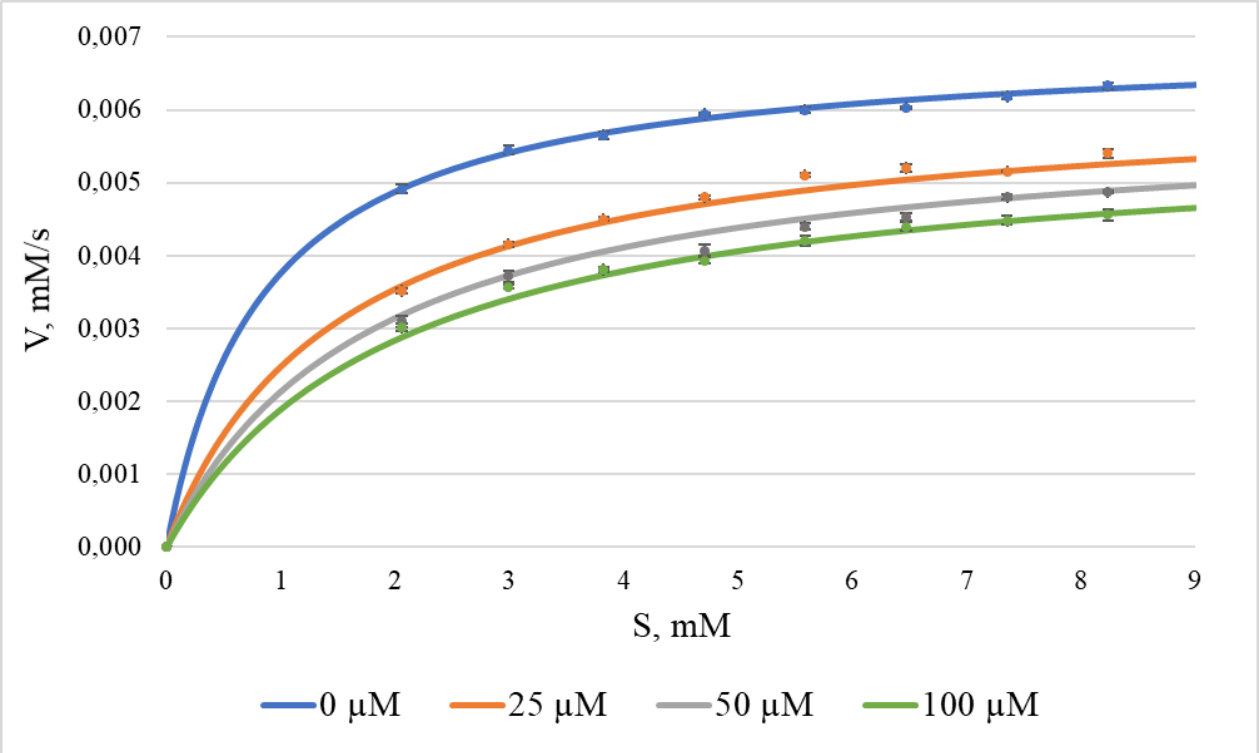


**Fig. 3. The dependence of substrate conversion rate by butyrylcholinesterase on its initial concentration and the concentration of desloratadine, presented in Michaelis-Menten equation coordinates**

Kinetic plots of the substrate conversion rate by butyrylcholinesterase, as a function of its initial concentration and the concentration of desloratadine, in Lineweaver-Burk reciprocal coordinates, are shown in Figure 4.

In studying the inhibitory effect of desloratadine on butyrylcholinesterase, the mixed (partial) type of inhibition model also proved to be the most suitable, according to the correlation coefficient value criterion ($R^2$=0.9809). The kinetic constants calculated using this model for desloratadine have the following values: $K_i$ = 11.50 ± 1.30 µM, $K_m$ = 0.85 ± 0.07 mM, $V_{max}$ = 6.93 ± 0.08 µM/s. For desloratadine, the concentration required to achieve 50% inhibition of butyrylcholinesterases is $IC_{50}$ = 131.40 ± 13.03 µM.The scientific literature also contains The findings of another research group [5] corroborated that the antihistamine API levocetirizine demonstrated an inhibitory effect on acetylcholinesterases, the sister enzyme BuChE, and contributed to the regulation of neurotransmitter levels,

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suggesting the potential utility of this antihistamine compound for adjuvant pharmacotherapy in neurodegenerative disorders.

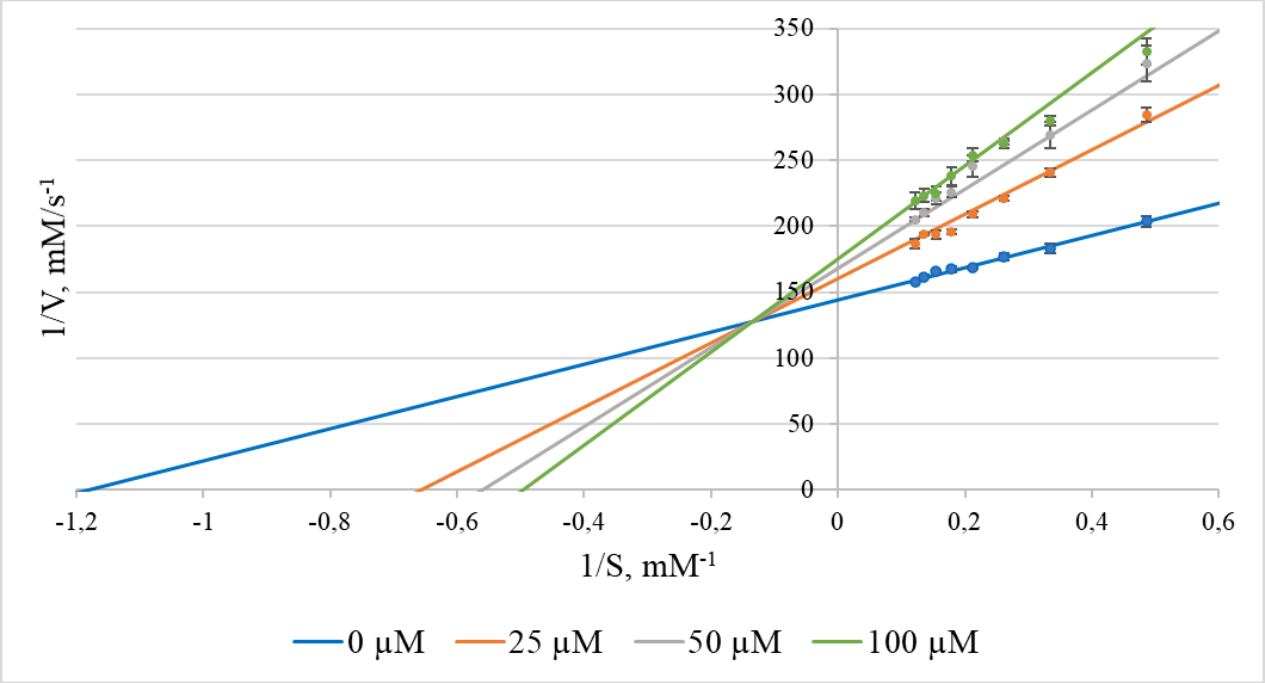


**Fig. 4. The dependence of the substrate conversion rate by butyrylcholinesterase on its initial concentration and the concentration of desloratadine, in Lineweaver-Burk reciprocal coordinates**

Our previous work [21] investigated the activity of loratadine and desloratadine with respect to another enzyme, specifically soybean 15-lipoxygenase (15-sLOX), and found that desloratadine, unlike loratadine, acts as a dose-dependent inhibitor of the enzyme, exhibiting mixed (partial) type inhibition, thereby corroborating its anti-inflammatory properties. Conversely, loratadine demonstrated pro-inflammatory activity in this system [21]. Furthermore, desloratadine and levocetirizine effectively inhibit dopamine oxidation in an *in vitro* model chemical system and exhibit significant concentration-dependent antioxidant activity [22].

Therefore, the results obtained confirm the pleiotropic properties of the antihistaminic active pharmaceutical ingredients loratadine and desloratadine, suggesting the potential for expanding their pharmacological profile. Given that human serum butyrylcholinesterase plays a key role in the metabolism of several medicinal products, including muscle relaxants and ether-type local anaesthetics, mediating their short-lived effect, the observed inhibitory effect of loratadine and desloratadine on BuChE could potentially slow this process, which is likely to prolong the therapeutic action of these substances. Consequently, these findings may provide a foundation for further research investigating the potential mechanisms by which antihistamines prolong the effects of muscle relaxants and local anaesthetics when used in combination.

**Conclusion**

1. It has been established that both loratadine and desloratadine act as concentration-dependent inhibitors of butyrylcholinesterases. Both antihistamine APIs reduce the maximum rate of the enzymatic reaction and increase the Michaelis constant, which is entirely consistent with the effect of mixed (partial) inhibition.
2. It was established that, for loratadine, the concentration required to achieve 50% inhibition of butyrylcholinesterases is $IC_{50}$ = 117.78 ± 10.01 µM, and for desloratadine it is 131.40 ± 13.03 µM.
3. Given that human serum butyrylcholinesterase plays a key role in the metabolism of several medicinal products, including muscle relaxants and ether-type local anaesthetics, mediating their short-lived effect, the observed inhibitory effect of loratadine and desloratadine on BuChE could potentially slow this process, which is likely to prolong the therapeutic action of these substances.

**Prospects for further research.** Further scientific investigations may be directed at studying the rate of degradation of muscle relaxants and local anaesthetic compounds by butyrylcholinesterase when used in combination with loratadine and desloratadine.

**Conflict of interest:** None.

**Study of anticholinesterase properties of loratadine and desloratadine**

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Given that antihistamines are among the most commonly used drugs among different age groups, availability and low cost of drugs, it is important to have complete information about their pharmacological profile and pleiotropic effects. The identification of new

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pharmacological properties of antihistamines may help to expand the indications for their use, improve treatment efficacy and reduce the risk of adverse reactions associated with polypharmacy. **The aim of the work** is to investigate and compare the effect of loratadine and desloratadine on the activity of the human serum butyrylcholinesterases enzyme. **Materials and methods.** The activity of butyrylcholinesterase and the effect of the antihistamine active pharmaceutical ingredients loratadine and desloratadine on this enzyme were determined *ex vivo* spectrophotometrically at a wavelength of 405 nm using the modified Ellman method. Experimental data processing included the calculation of steady-state velocities and kinetic parameters of inhibition and was performed according to standard methods. The kinetic characteristics of the studied process were analyzed and visualized in the SigmaPlot 14.0 software package. **Results.** It was found that both loratadine and desloratadine are dose-dependent inhibitors of butyrylcholinesterase. The both antihistamines inhibit butyrylcholinesterase by a mixed (partial) mechanism. The value of the enzyme inhibition constant ($K_i$) for loratadine is 10.15 ± 1.20 μM, and for desloratadine – 11.50 ± 1.30 μM. It was established that for loratadine the concentration required to achieve 50% inhibition of butyrylcholinesterase is $IC_{50}$ = 117.78 ± 10.01 μM, and for desloratadine – 131.40 ± 13.03 μM. **Conclusions.** Given that human serum butyrylcholinesterase is involved in the metabolism of a number of drugs, including muscle relaxants and local anesthetics of the ether type, which causes their rapid inactivation and short-term effect, the inhibitory activity of loratadine and desloratadine against this enzyme is important for modifying the pharmacokinetic parameters of these compounds. The data obtained can serve as a basis for further studies aimed at studying the rate of decomposition of muscle relaxants and local anesthetic compounds by butyrylcholinesterase when used in combination with loratadine or desloratadine.
**Key words:** antihistamines, active pharmaceutical ingredient, loratadine, desloratadine, pleiotropic properties, butyrylcholinesterase, molecular mechanism, kinetics

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