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Modeling of Desloratadine release process from alloys with Polyethylene glycol-6000 by Molecular dynamics method

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Abstract

Purpose: Desloratadine is a drug with proven antihistaminic activity, is currently presented on the pharmaceutical market only in dosage forms: tablets, solution and syrup. A significant factor limiting the development of new drugs of desloratadine is its low solubility in water. The actual direction of pharmaceutical technology in this regard is research on creation of dosage forms of desloratadine, aimed at increasing its water solubility. Currently, a promising direction in pharmaceutical technology in the development of drug composition is the use of computer modeling. The use of molecular dynamics modeling method is very relevant in the development of solid dispersions of drugs. The aim of this study was to carry out molecular dynamics modeling of desloratadine release from alloys with polyethylene glycol-6000 (desloratadine: polymer ratio 1:1, 1:2, 1:5) into the dissolution medium.

Experimental: modeling of desloratadine release from alloys with polyethylene glycol-6000 was carried out by molecular dynamics method (Gromacs 2023 program, Amber 99 force field). The van der Waals interaction energies of desloratadine with polyethylene glycol-6000 and with water were calculated; the fraction of desloratadine molecules that lost the bond with polyethylene glycol-6000. It was found that the average energy of interaction of desloratadine with polyethylene glycol -6000 and with water. Polyethylene glycol-6000 decreases as the content of desloratadine in the alloy decreases. Desloratadine in the alloy, while the interaction energy with water increases.

Conclusions: The studies on the release rate of desloratadine from alloys with polyethylene glycol-6000 by molecular dynamics method showed that the highest release rate of desloratadine was achieved at 1:1 (5.47±1.11 %), 1:2 (5.39±0.51 %) ratios and the lowest at 1:5 (3.03 ± 0.00 %). The obtained results indicate the promising use of solid dispersions “desloratadine – polyethylene glycol-6000” (1:1 ratio).

Keywords: Modeling, release, Desloratadine, Polyethylene glycol-6000, Molecular dynamics

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1. Introduction

Desloratadine, a histamine H1-receptor antagonist, has a proven safe and effective non-sedative antihistaminic activity and finds use in allergic rhinitis, allergic asthma and urticaria [1, 2]. Desloratadine is available on the pharmaceutical market in the following dosage forms: film-coated tablets, solution and syrup. A significant factor limiting the use of desloratadine is its extremely low solubility in water, which significantly reduces the therapeutic effect of pharmaceutical substances from dosage forms [3, 4].

Several studies have attempted to improve the solubility of Desloratadine by complexing desloratadine with β-cyclodextrin in solution [5].

Currently, various approaches such as salt formation, solubilization with co-solvents, reduction of particle size or preparation of solid dispersions are used to improve the solubility and dissolution rate of poorly water-soluble pharmaceutical substances. A promising and relevant direction in pharmaceutical science is the preparation of solid dispersions [6]. Amorphous solid dispersions are single phase amorphous systems in which drug molecules are molecularly dispersed (dissolved) in a polymer matrix [7]. Obtaining solid dispersions is the most promising method for solubility enhancement because it overcomes the limitations of the above approaches, such as the need to use organic solvents [8].

The class of polymeric carriers widely used in the technology of solid dispersions includes polyethylene glycols (PEG) of different molecular weights [9,10]. In particular, PEG-6000 has been used as a carrier to increase the dissolution rate of poorly water-soluble drugs such as tacrolimus, diclofenac, itraconazole and rofecoxib [11-14]. The conducted literature analysis revealed no information on the use of PEG as carrier polymers to produce solid dispersions with desloratadine in order to increase its water solubility in the creation of dosage forms. Thus, the development of an oral capsulated dosage form with Desloratadine with an increased bioavailability will expand the nomenclature of antihistaminic drugs, which is undoubtedly an urgent task for the development of the modern pharmaceutical market.

A promising direction in pharmaceutical technology is the following obtaining and research of solid dispersions with PEG-6000, including the method of molecular dynamics [15]. The application of molecular modeling, which is important for optimizing formulations and predicting drug release profiles, can provide insight into the interactions between drugs and excipients, including complexation. The aim of this work is to carry out Molecular dynamics simulations of desloratadine release from alloys with PEG-6000 (desloratadine: polymer ratio 1:1, 1:2, 1:5) into dissolution medium.

2. Experimental

Modeling of the release of desloratadine from alloys with PEG-6000 was carried out by molecular dynamics method (Gromacs 2023 program [16], Amber 99 force field). Desloratadine molecules, spatial structures of monomers were constructed in HyperChem program. Polymer chains assembly, force field parameterization for the molecules of the components of the simulated systems was carried out using the ParmEd program [17–19].

PEG molecules (Figure 1) with a length of 136 monomers with a molar mass of 6009, as well as desloratadine molecules in the form of cation and Cl^- ions were included in the components of the modeled systems (Figure 2).

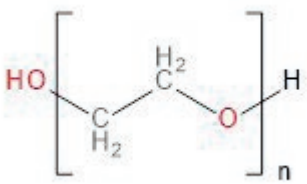

Fig. 1. Structure of the PEG molecule

In the first step of the work, models of desloratadine alloys with PEG-6000 were constructed. Using periodic boundary conditions in all coordinate axes, models of desloratadine alloys with PEG-6000 were prepared by means of molecular dynamics simulations [20, 21].

The van der Waals interaction energy (VDWIE) of desloratadine with PEG-6000 and with water was calculated; the fraction of desloratadine molecules that lost their bond with PEG-6000. A desloratadine molecule was considered to

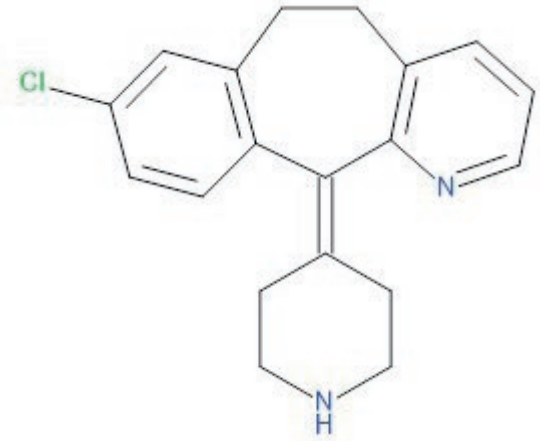

Fig. 2. Chemical structure of the desloratadine molecule

be released into water if it did not bind to the polymer and bound to water.

3. Results and discussion

Starting to discuss the results obtained from modeling, it is necessary to present those possible physicochemical interactions that will occur during the absorption and desorption of desloratadine by the polymer. It should be noted that we are dealing with a heterogeneous system in which the polymer in the polymer (polyethylene) matrix contains polar -OH-groups that do not possess ion-exchange properties. Desloratadine reacts as a doubly charged cation upon absorption of PEG-6000. Consequently, the uptake of desloratadine by PEG will be due to the formation of dispersion, induction and hydrogen bonds (with the participation of water molecule as an active reagent). This was the reason for the composition of the modeled systems (Table 1).

The release of desloratadine from the alloy with PEG-6000 1:1 occurs partially, and the formation of associates of desloratadine molecules in the aqueous medium was observed. The percentage of release of desloratadine during the first 20 ns is 8% (Figure 3), while ΔE in the interaction energies of "Desloratadine-PEG-6000" and "Desloratadine - Water" interaction energies reach –70; –40 kJ/mol (Fig. 4), and clear transitions of desloratadine to water are observed.

Release rate of desloratadine from the fusion with PEG-6000 at a 1:2 ratio of desloratadine to polymer by mass occurs to a small extent over a simulation time of more than 20 ns. The VDWIE between desloratadine and polymer less than –100 kJ/mol and between desloratadine and water greater than –40 kJ/mol indicate no high involvement of desloratadine in solvent interaction and significant binding to the polymer (Fig. 5).

The percentage of desloratadine release within the first 18 ns is 8 % (Fig. 6), although the ΔE in the interaction energies of "Desloratadine-PEG-6000" and "Desloratadine-Water" reaches –140; –30 kJ/mol (Fig. 4), and clear desloratadine-to-solvent transitions at distinct time intervals are observed.

At the ratio of desloratadine with PEG-6000 1:5 by mass, the release of desloratadine into the aqueous medium is insignificant (more than 3 %) (Fig. 7). The VDWIE between desloratadine and polymer less than –140 kJ/mol and between desloratadine and water greater than -30 kJ/mol indicate little involvement of desloratadine in interaction with the solvent and strong binding to the polymer (Fig. 8).

The mean values of VDWIE of desloratadine with PEG-6000 and with water, and the mean values of release rate into water from the fusion with PEG-6000 were calculated (Table 2).

The average interaction energy of desloratadine with polymers decreases as the desloratadine content of the alloy decreases, while the interaction energy with water increases. This trend indicates that the involvement of desloratadine in the solvation and desorption processes decreases as its content in the mixture with the polymer decreases.

Table 1. Amounts of molecules of components of simulated systems

Substance	Desloratadine-PEG-6000 1:1	Desloratadine-PEG-6000 1:2	Desloratadine-PEG-6000 1:5
Desloratadine cation	328	164	66
Cl^- ion	328	164	66
PEG-6000	17	17	17
Water	20056	20425	20086

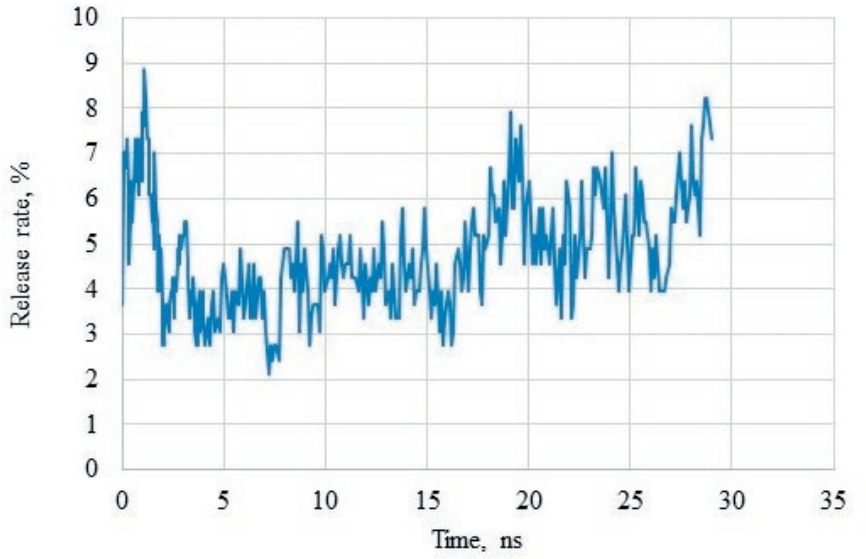

Fig. 3. Extent of release of desloratadine molecules not bound to PEG-6000 in water (desloratadine: PEG-6000 1:1)

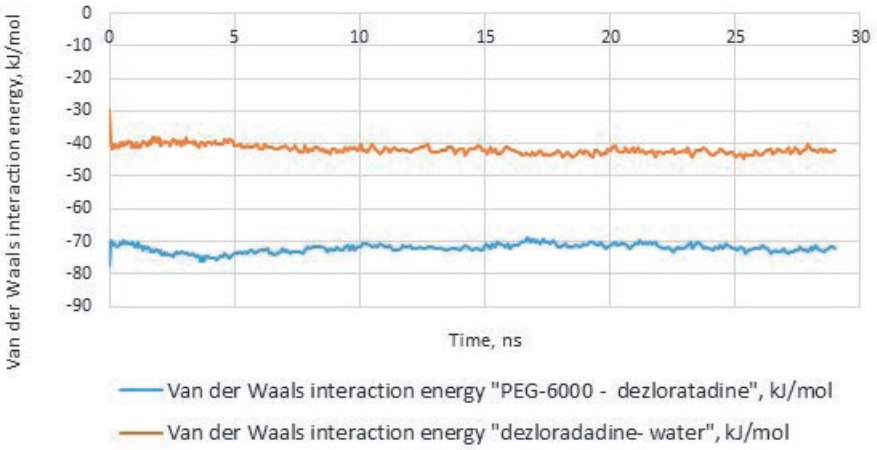

Fig. 4. VDWIE of desloratadine with PEG-6000 and with water (desloratadine: PEG-6000 1:1)

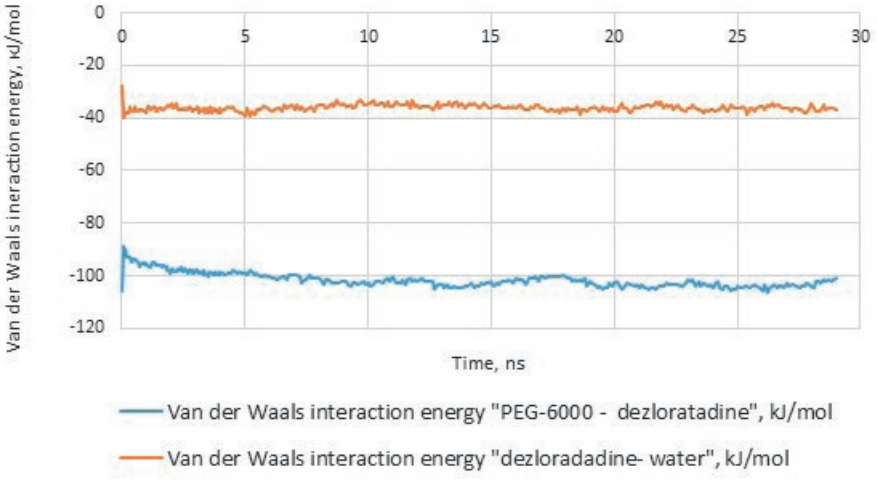

Fig. 5. VDWIE of desloratadine with PEG-6000 and with water (desloratadine: PEG-6000 1:2)

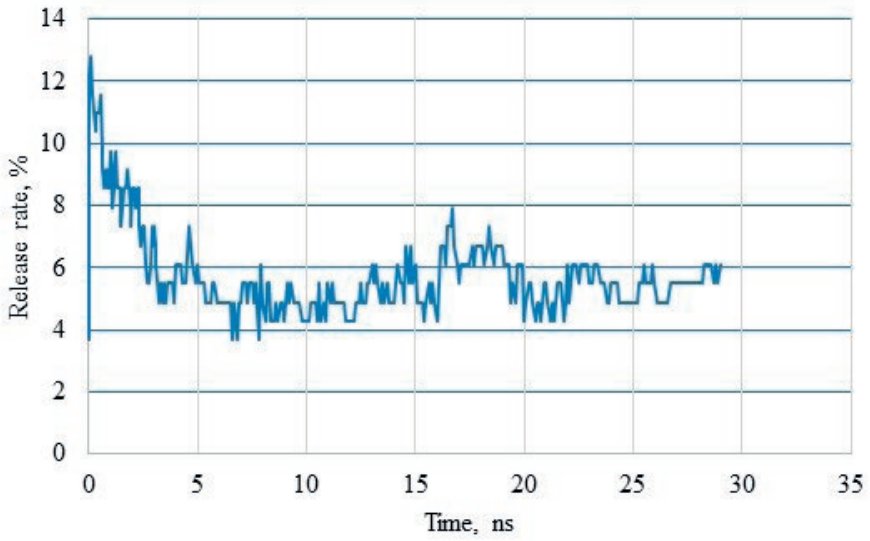

Fig. 6. Extent of release of desloratadine molecules not bound to PEG-6000 in water (desloratadine: PEG-6000 1:2)

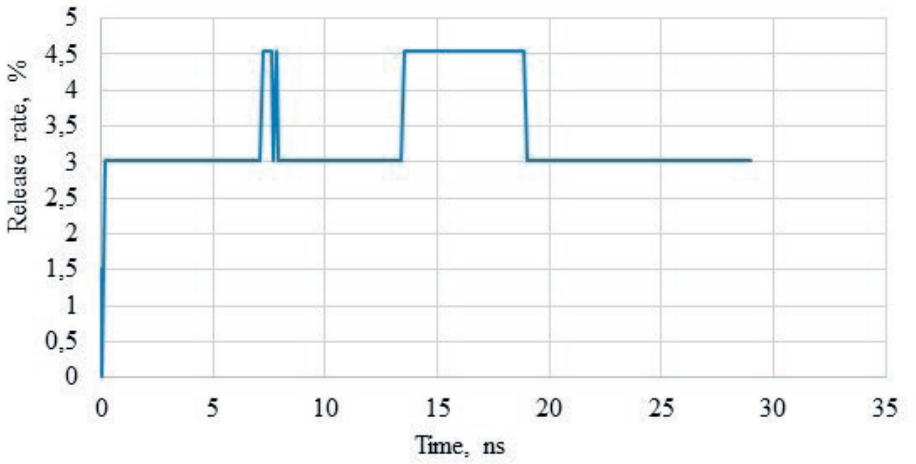

Fig. 7. Extent of release of desloratadine molecules not bound to PEG-6000 in water (desloratadine: PEG-6000 1:5)

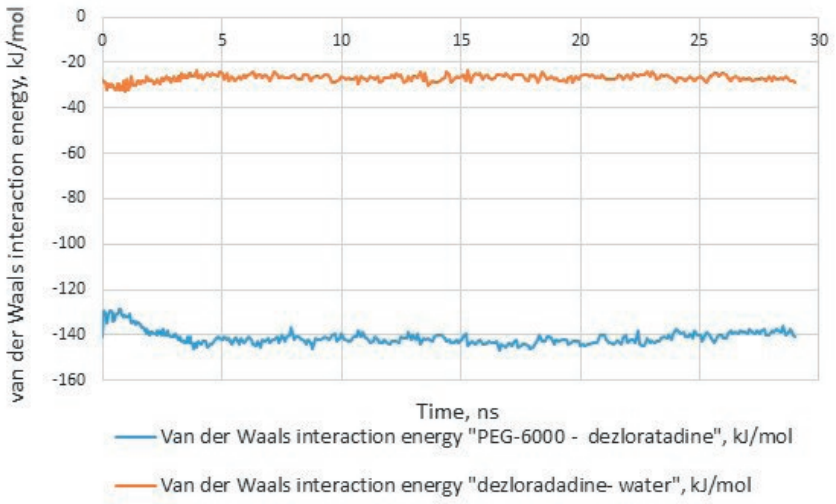

Fig. 8. VDWIE of desloratadine with PEG-6000 and with water (desloratadine: PEG-6000 1:5)

Table 2. Release parameters of desloratadine from alloys with PEG-6000

System	Average EVDWI of desloratadine with PEG-6000, kJ/mol	Average EVDWI of desloratadine with solvent, kJ/mol	Average release rate, %
Desloratadine-PEG-6000 1:1	–72.02±0.87	–42.49±0.78	5.47±1.11
Desloratadine-PEG-6000 1:2	–103.68±1.09	–36.20±0.96	5.39±0.51
Desloratadine-PEG-60001:5	–140.38±2.02	–26.68±1.11	3.03±0.00

4. Conclusions

The studies of desloratadine release from alloys with PEG-6000 by molecular dynamics method showed that the highest release rate of desloratadine from PEG-6000 into aqueous medium was achieved at a ratio of 1:1, and the lowest at a ratio of 1:5. At ratios of 1:1 and 1: 2, the average interaction energy of desloratadine with PEG-6000 per desloratadine molecule was the highest (–72.02±0.87 kJ/mol) and (–103.68±1, 09 kJ/mol), respectively, while the interaction energy of desloratadine with water was low (–42.49±0.78 kJ/mol) and (–36.20±0.96 kJ/mol), respectively, indicating the greatest involvement of desloratadine in the solvation and desorption at this ratio. The results obtained indicate that the use of solid dispersions "Desloratadine – PEG" (1:1 ratio) is promising. The computer modeling data will be subsequently used to establish the value of the computer modeling results characteristics, allowing to obtain solid dispersions of desloratadine with specified biopharmaceutical characteristics.

Contribution of the authors

The authors contributed equally to this article.

Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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