Chimica Techno Acta
published by Ural Federal University
eISSN 2411-1414; chimicatechnoacta.ru

ARTICLE
2022, vol. 9(2), No. 202292S11
DOI: 10.15826/chimtech.2022.9.2.S11

PEG-4000 increases solubility and dissolution rate of vinpocetin in solid dispersion system

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This paper belongs to the MOSM2021 Special Issue.

Abstract

In the present work, we determined the optimal ratio of vinpocetine and polyethylene glycol within a solid dispersion (1:2 or 1:5) according to the simulation results in the framework of molecular dynamics associated with the release of the reactant into aqueous medium. For the simulation of vinpocetine release from its alloy with polyethylene glycol, a technique of coarse-grained molecular dynamics in the force field of Martini 2.2 was applied using the Gromacs 2018 computer program. The results of the simulation demonstrated that at pH 6.8 polyethylene glycol facilitated vinpocetine solubilization and thus considerably enhanced its solubility in water. The data obtained show that the values of the energies of van der Waals interaction between vinpocetine and the polymer are similar to those vinpocetine and water, both at a ratio of 1:2 and at a ratio of 1:5.

Keywords

vinpocetin
solid dispersion system
PEG- 4000
dissolution rate
molecular dynamics

Received: 05.04.22
Revised: 26.06.22
Accepted: 27.06.22
Available online: 30.06.22

1. Introduction

Vinpocetine is a vasoactive and nootropic preparation that is a semisynthetic derivative of the common periwinkle plant alkaloid. Vinpocetine is practically insoluble in water [1, 2]. It provides certain problems in provision of the bioavailability, particularly, the rate of attaining its therapeutic concentration in blood.

Recently, keeping in mind an increase of bioavailability of poorly soluble pharmaceutical preparations, solid dispersed systems have attracted more and more attention as a new basis for the elaboration of new rational drug formulations [3]. Solid dispersions are bi- or multicomponent systems composed of the pharmaceutical substances and a carrier, representing a highly-dispersed solid phases of the pharmaceutical substances or alloys with a partial formation of the complexes of variable composition with a carrier material [4–6].

Fabrication of the solid dispersions is considered as one of the most efficient ways for decreasing the particle sizes to the colloid and/or molecular level values. Under the effect of environment, the soluble matrix of a polymer is dissolved and colloid particles or molecules of the pharmaceutical substances are immediately released into the solution medium, resulting in a rapid solubilization of the pharmaceutical substance [7–9]. Solid dispersions are of a great importance when establishing peroral solid drug formulations with enhanced dissolution rate for the pharmaceutical substances that are weakly dissolved in water. Thus the application of solid dispersions facilitates bioavailability under peroral medication [10–12].Various soluble polymer matrices on the basis of polyvinylpyrrolidone, polyethylene glycols, methyl cellulose, as well as rather simple sub-stances, for example, urea, lactose, were proposed as carriers for soluble dispersions [13].

In the present work , we investigated the optimal ratio between vinpocetine and PEG-4000 in the drug formulation (1:2 or 1:5) using the simulation employed for the molecular dynamics release of the reactant into aqueous medium.

2. Experimental

In order to simulate vinpocetine release from its alloy with polyethylene glycol, the method of coarse-grain molecular dynamics in a force field of Martini 2.2 was applied using the Gromacs 2018 software suite [14]. The method of coarse-grain molecular dynamics consists in representing the groups of atoms (consisting of 2–6 atoms) in the mole-

cule by the particles of different types. In the same way, a group of molecules can be represented by a single particle.

An assembly of the simulated systems, alloys of vinpocetine with polyethylene glycol, was performed with Gromacs 2018 program.

To simulate vinpocetine diffusion process using the coarse-grain molecular dynamics method, the model of the vinpocetine molecule was designed in the HyperChem program; after that geometry of the molecule was optimized by mm+ method [15, 16]. The vinpocetine molecule was nominally divided into the fragments corresponding to the cycles and functional groups.

The compositions of the simulated systems are presented in Table 1.

Table 1 The number of molecules of the components of the simulated alloys.

Substance	Vinpocetine-PEG 1:2	Vinpocetine-PEG 1:5	Vinpocetine cation-PEG 1:2	Vinpocetine cation-PEG 1:5
Vinpocetine	119	48	–	–
Vinpocetine-cation	–	–	119	48
Cl^- ion	–	–	119	48
PEG-4000	21	21	21	21
Water	10968	7228	11860	9484

3. Results and discussion

The modeled system included molecules of polyethylene glycol (Figure 1) with a length of 90 monomers with the atomic mass of 3.978 kDa, as well as molecules of vinpocetine base or its cations and Cl- ions (Figure 2).

During the simulation, the diffusion of PEG-4000 into water was observed. When the ratio of vinpocetine and PEG-4000 is 1:2, some of the vinpocetine molecules lose their bond with the polymer and combine into clusters (Figure 3).

The energies of van der Waals interaction of vinpocetine with the polymer and with the solvent are stabilized after the 40th nanosecond of simulation. An increased proportion of vinpocetine molecules unbound with PEG-4000 is due to the formation of clusters of substance molecules (Figures 4, 5).

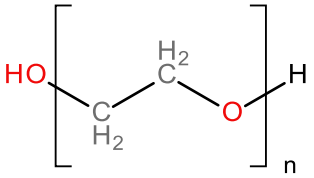

Figure 1 The structure of the polyethylene glycol molecule and its representation in the Martini force field 2.2. SNa–SH_2–...–SH_2–SNa; SNa – terminal OH group; SH_2 is a polyethylene glycol monomer.

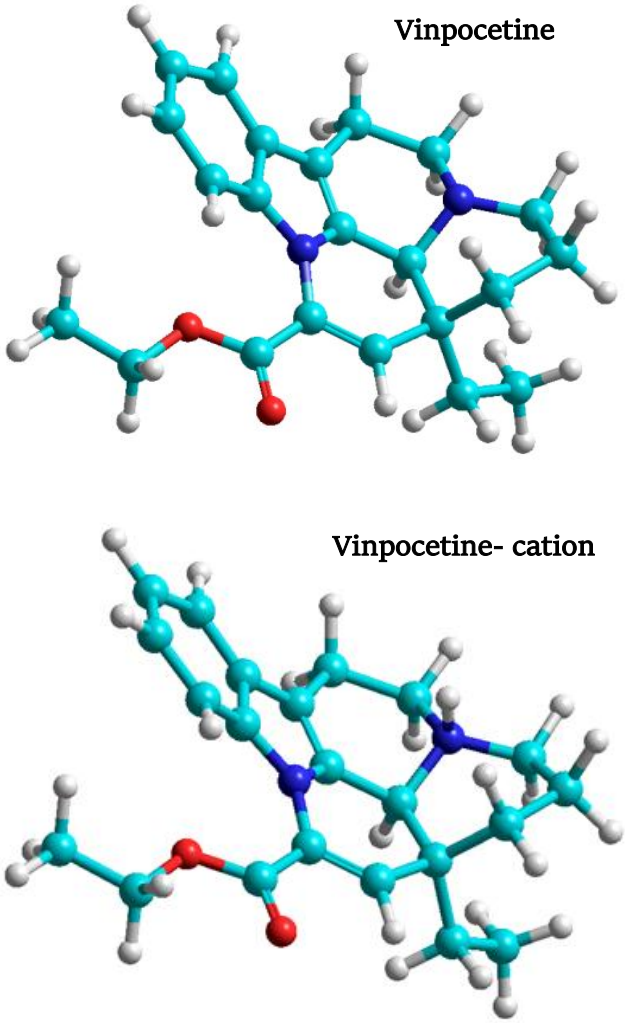

Figure 2 Chemical structure and spatial structure of vinpocetine and vinpocetine cation and their representation in the Martini 2.2 force field.

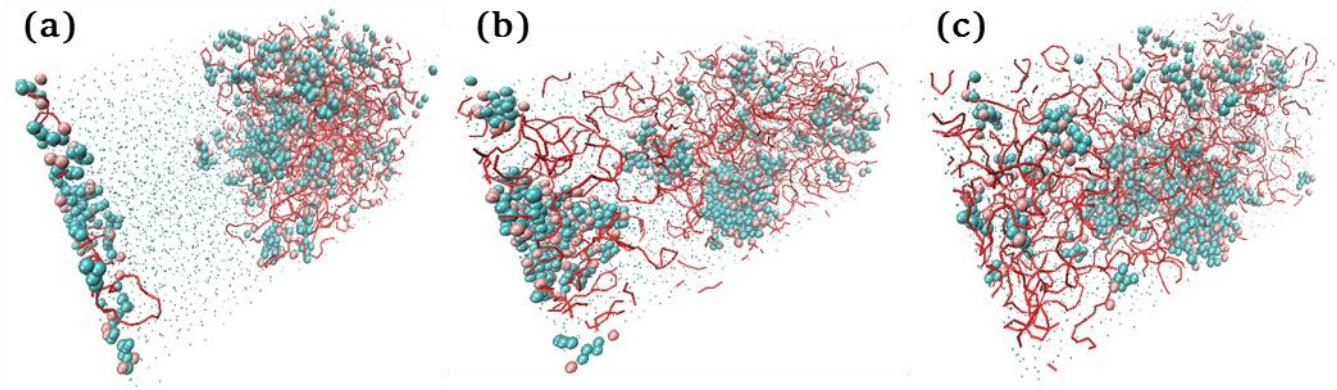

Figure 3 Simulation of the molecular dynamics of the release of vinpocetine from an alloy with PEG-4000 1:2 by weight into water. Time is 0 ns (a), 40 ns (b), 100 ns (c).

When modeling the release of vinpocetine from PEG-4000 into water at a substance-to-carrier ratio of 1:5, the formation of clusters is also observed, but their size is much smaller (Figure 6).

The energy of van der Waals interaction of vinpocetine with PEG-4000 at a ratio of 1:5 stabilizes faster – at the 20th nanosecond of simulation (Figures 7, 8). This is due to the smaller number of vinpocetine molecules in the system.

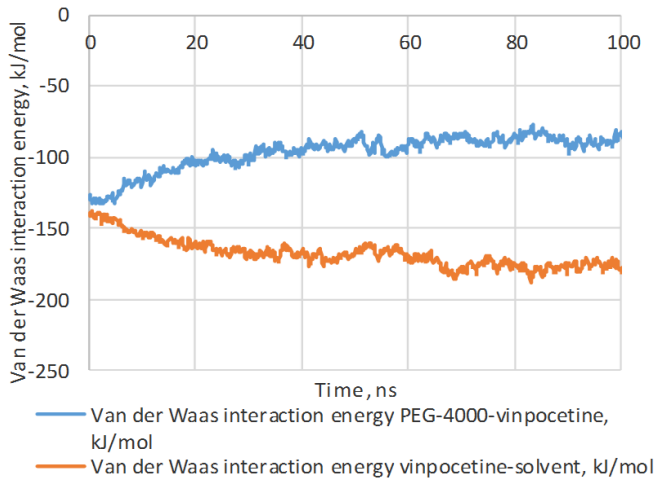

Figure 4 Van der Waals interaction energy of vinpocetine with PEG-4000 and solvent in terms of one molecule of vinpocetine at a ratio of vinpocetine and PEG-4000 1:2 by weight.

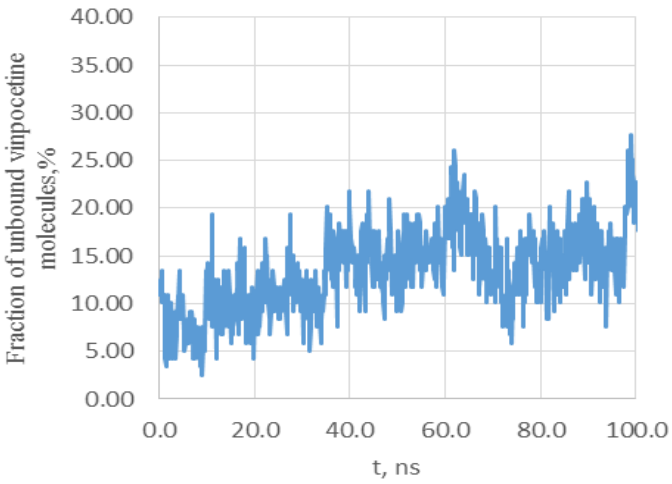

Figure 5 Estimation of the proportion of vinpocetine molecules not bound to PEG-4000 in water at a ratio of vinpocetine to PEG-4000 1: 2 by weight.

When simulating the release of vinpocetine from PEG-4000 in an acidic medium, no significant formation of clusters of substance molecules is observed, but a uniform distribution of vinpocetine molecules over the volume of the simulated system occurs (Figure 9).

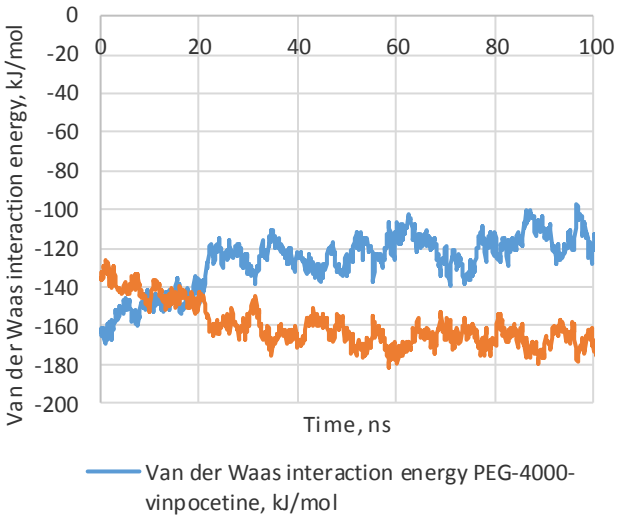

Figure 7 Van der Waals interaction energy of vinpocetine with PEG-4000 and solvent in terms of one molecule of vinpocetine at a ratio of vinpocetine and PEG-4000 1:5 by weight.

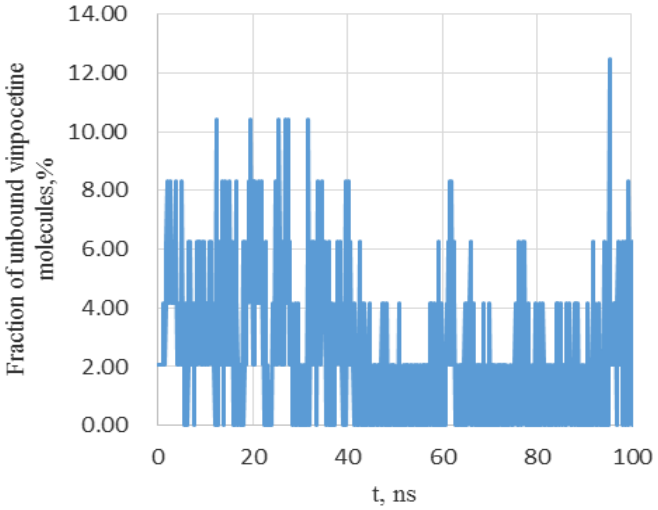

Figure 8 Estimation of the proportion of vinpocetine molecules not bound to PEG-4000 in water at a ratio of vinpocetine to PEG-4000 1:5 by weight.

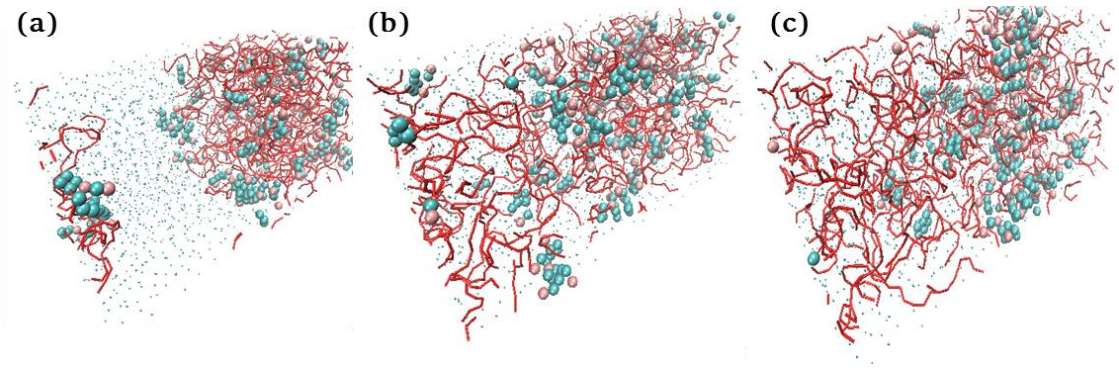

Figure 6 Simulation of the molecular dynamics of the release of vinpocetine from an alloy with polyethylene glycol-4000 1:5 by weight into water. Time is 0 ns (a), 40 ns (b), 100 ns (c).

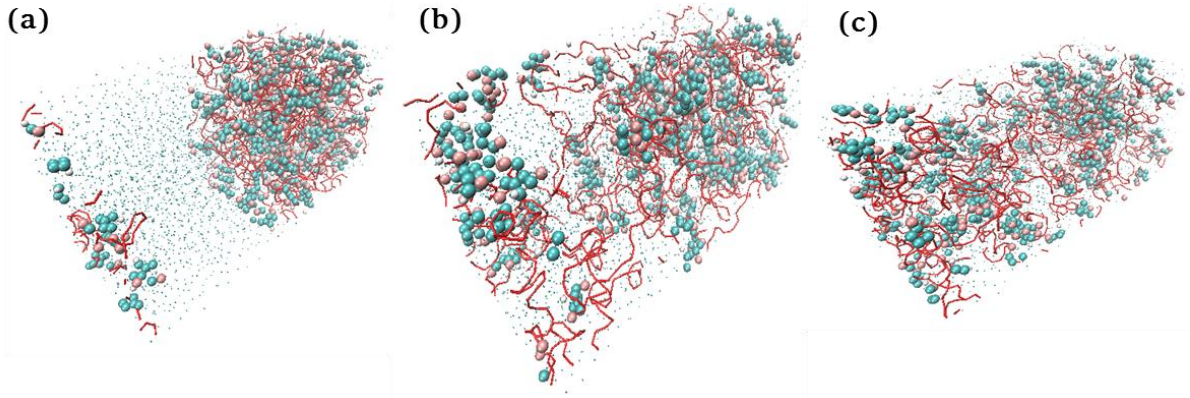

Figure 9 Modeling of the molecular dynamics of the release of vinpocetine from an alloy with PEG-4000 1:2 by weight into water with pH 2.0. Time is 0 ns (a), 40 ns (b), 100 ns (c).

The energy of van der Waals interaction of vinpocetine with PEG-4000 when released in an acidic medium is stabilized after 40 ns of simulation at a ratio of 1:2 (Figures 10, 11).

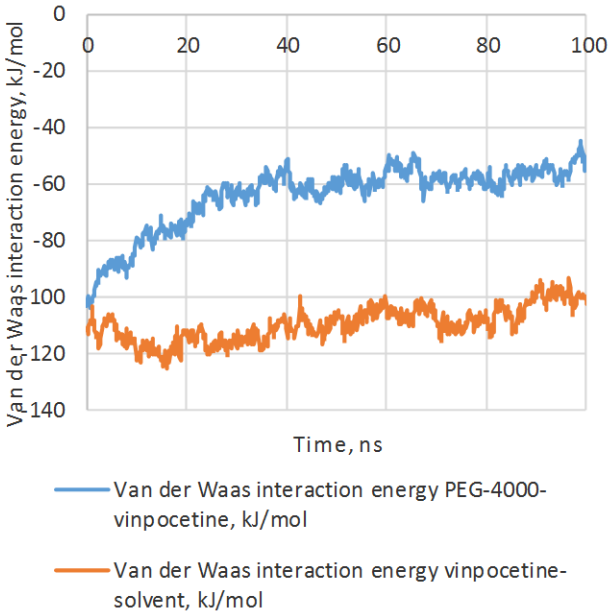

Figure 10 Van der Waals interaction energy of vinpocetine with PEG-4000 and with a solvent (water at pH 2.0) in terms of one molecule of vinpocetine at a ratio of vinpocetine and PEG-4000 1:2 by weight.

When the ratio of vinpocetine and PEG-4000 is 1:5 in an acidic medium, vinpocetine is also evenly distributed in the volume of the modeled system without the formation of large clusters (Figure 12).

Van der Waals interaction energy between Vinpocetine and PEG-4000 stabilizes after 30 ns of simulation (Figures 13, 14).

Based on the results of the computational experiments, the average values of the van der Waals binding energies of vinpocetine with carriers and with the solvent, as well as the average fraction of vinpocetine molecules not bound to the carrier, were calculated (Table 2).

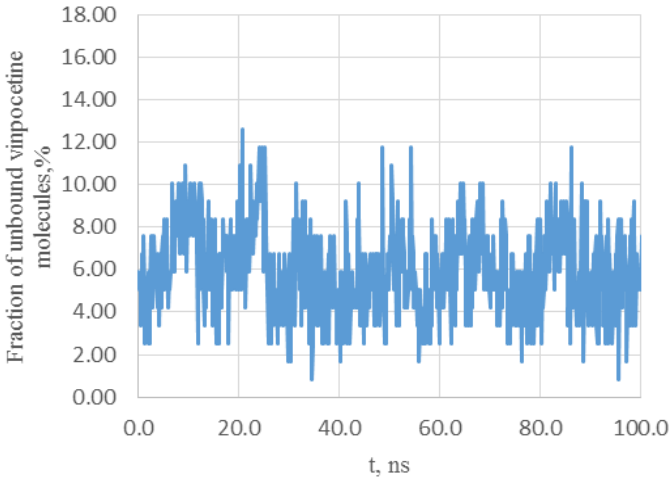

Figure 11 Estimation of the proportion of vinpocetine molecules not bound to PEG-4000 in water at pH 2.0 at a ratio of vinpocetine to PEG-4000 1: 2 by weight.

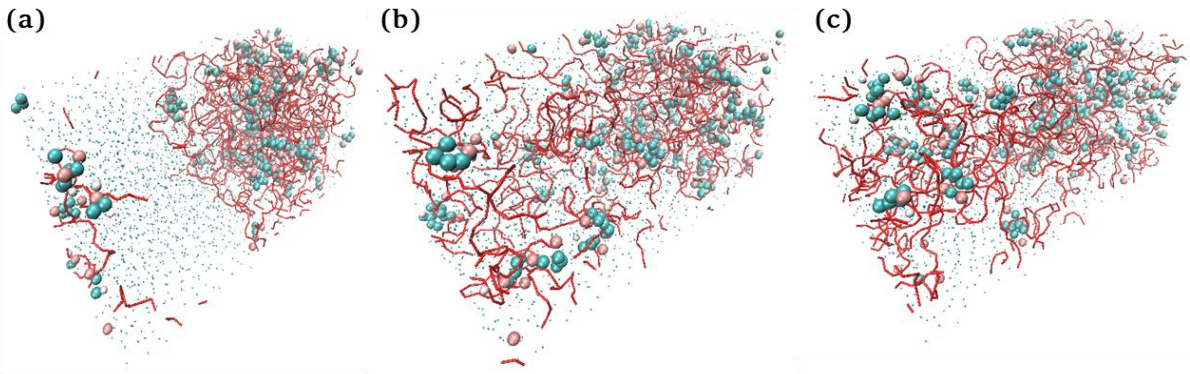

Figure 12 Simulation of the molecular dynamics of the release of vinpocetine from an alloy with PEG-4000 1:5 by weight into water with a pH of 2.0. Time is 0 ns (a), 40 ns (b), 100 ns (c).

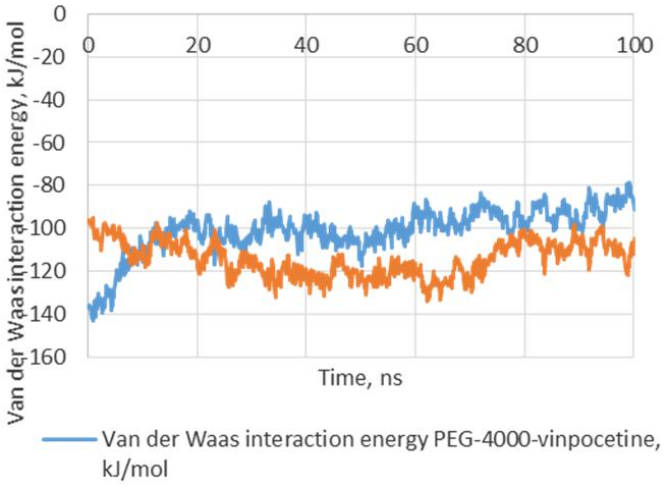

Figure 13 Van der Waals interaction energy of vinpocetine with PEG-4000 and with a solvent (water at pH 2.0) in terms of one molecule of vinpocetine at a ratio of vinpocetine and PEG-4000 1:5 by weight.

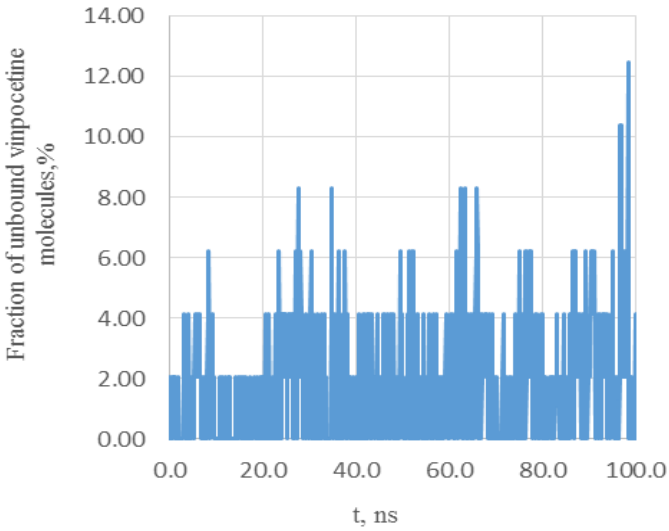

Figure 14 Estimation of the proportion of vinpocetine molecules not bound to PEG-4000 in water at pH 2.0 at a ratio of vinpocetine to PEG-4000 1: 5 by weight.

Table 2 Average values of vinpocetine release parameters from the studied complexes with polymers.

System	Average energy of van der Waals interaction vinpocetine with polymer, kJ/mol	Average energy of van der Waals interaction of vinpocetine with a solvent, kJ/mol	The average proportion of vinpocetine molecules not associated with the carrier, %
Vinpocetine-PEG-4000 1:2	−57.88±3.80	−106.25±4.75	15.274±3.44
Vinpocetine-PEG-4000 1:5	−97.74±6.93	−116.21±7.64	2.060±2.24
Vinpocetine-PEG-4000 1:2 pH 2.0	−88.58±4.18	−173.95±5.60	5.893±1.00
Vinpocetine-PEG-4000 1:5 pH 2.0	−120.51±8.41	−165.37±6.10	1.898±2.06

4. Conclusions

The data obtained show similar values of the energies of van der Waals interaction between vinpocetine and the polymer, as well as vinpocetine and water, both at a ratio of 1:2 and at a ratio of 1:5. In a neutral medium, when released from PEG-4000, clusters of vinpocetine molecules are formed. There is an increased release of vinpocetine molecules in an acidic medium and with an increase in the ratio in the alloy towards vinpocetine.

Supplementary materials

No supplementary materials are available.

Funding

This research had no external funding.

Acknowledgments

None.

Author contributions

Conceptualization: Y.A.P., T.N.G., N.N.S.
Data curation: Y.A.P.
Formal Analysis: Y.A.P., N.N.S.
Methodology: Y.A.P., T.N.G.
Resources: Y.A.P., T.N.G., N.V.A.
Supervision: Y.A.P.
Visualization: Y.A.P., T.N.G.
Writing –original draft: Y.A.P., N.V.A.
Writing –review & editing: Y.A.P.

Conflict of interest

The authors declare no conflict of interest.

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