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A molecular dynamics simulation of the release of desloratadine from alloys containing polyvinylpyrrolidone

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Abstract

Computer modeling is currently a promising technique used in pharmaceutical technologies to develop drug compositions. Molecular dynamics has provided space and time resolutions unavailable during experiments and thus has greatly extended the capabilities of chemistry and some other areas. Molecular dynamics stimulations are very important for the development of solid drug dispersions. The purpose of this study is to simulate the molecular dynamics of the release of desloratadine from alloys containing polyvinylpyrrolidone-10000 into the dissolution medium.

The release of desloratadine from alloys containing polyvinylpyrrolidone-10000 was simulated by the method of molecular dynamics (Gromacs 2023 program, Amber 99 force field). The study involved calculating van der Waals energies of interaction between desloratadine and PVP and desloratadine and water and the proportion of desloratadine molecules that lost their bonds with PVP. The desloratadine molecule was considered released into water provided that it did not bind either to the polymer or water.

It was found that the degree of desloratadine release from PVP into the aqueous medium was the highest at a ratio of 1:1 (24.56±2.08%), and the lowest at ratios of 1:2 and 1:5 (8.27±1.79 and 8.65±0.98%, respectively). At a ratio of 1:1, the average energy of interaction between desloratadine with PVP per one molecule of desloratadine was the highest (–36.13±0.62 kJ/mol) when the energy of interaction between desloratadine and water was low (–52.03±0.82 kJ/mol), which indicates that desloratadine involvement in the solvation and desorption processes was the highest at this ratio. The average energy of interaction between desloratadine and the polymer was the lowest at a ratio of 1:5 (–52.03±0.82 kJ/mol) when the energy of interaction between desloratadine and water was –44.45±1.60 kJ/mol. This fact indicates a low intensity of the desorption and solvation processes at this ratio.

Keywords: release, desloratadine, polyvinylpyrrolidone, molecular dynamics

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1. Introduction

Currently, a large percentage of medicines on the pharmaceutical market (~ 40%) and medicines under development (~ 90%) are poorly soluble in water [1,2]. Substances poorly soluble in water include desloratadine, which has proven safe and effective non-sedative antihistamine activity that is useful for allergic rhinitis, allergic asthma, and urticaria [3, 4]. Several studies have attempted to improve desloratadine solubility by the formation of a complex inclusion of desloratadine with β-cyclodextrin in a solution [5].

The solubility and dissolution rate of medicines poorly soluble in water can be increased with solid dispersions [6, 7]. Solid dispersions with amorphous carriers usually exhibit higher solubility and dissolution rates due to the high energy of the amorphous phase of the medicine [8–10]. Among amorphous polymer carriers widely used in solid dispersion technologies are polyvinylpyrrolidone (PVP), polyvinylpyrrolidone vinyl acetate, and hydroxypropylmethylcellulose [11 13]. An analysis of scientific literature did not reveal information on the use of PVP as carrier polymers to prepare solid dispersions with desloratadine in order to increase its solubility in water during the development of semi-solid formulations.

The preparation and study of solid dispersions with PVP, including by the method of molecular dynamics, is a promising area of pharmaceutical technology. Molecular dynamics has significantly extended the capabilities of chemistry and some other areas by providing space and time resolutions unavailable during experiments [14]. Molecular modeling allows calculating the physical properties of the medicine/excipient without conducting costly experiments. Molecular modeling, which is important for optimizing formulations and predicting drug release profiles, can provide information about interactions between medicines and excipients, including their complexation. The understanding of these interactions allows researchers to develop optimal filler compositions to increase drug stability and bioavailability [15–17].

The purpose of the study is to simulate the molecular dynamics of the release of desloratadine from alloys containing polyvinylpyrrolidone-10000 (desloratadine ratio: PEG-6000 1:1, 1:2, 1:5 by weight) into the dissolution medium.

2. Experimental

The release of desloratadine from alloys containing PVP-10000 was simulated by the method of molecular dynamics (Gromacs 2023 program [16,18], Amber 99 force field [19]). Desloratadine molecules and spatial structures of monomers were built in the HyperChem program [20]. The assembly of polymer chains and parametrization of the force field for the molecules of the components in the simulated systems was completed using the ParmEd program [21].

The simulated system included PVP molecules (Fig. 1) with a length of 90 monomers with a molar mass of 10.005 kDa (PVP), desloratadine molecules in the form of a cation, and Cl ions (Fig. 2).

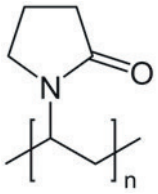


Fig. 1. Structure of the PVP molecule

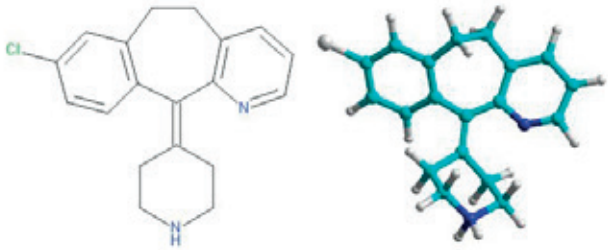


Fig. 2. Chemical structure and spatial structure of the desloratadine molecule

Models of desloratadine alloys containing PVP were built to study the release of desloratadine. Alloy models were prepared by a molecular dynamics simulation of desloratadine and PVP mixtures using periodic boundary conditions along all coordinate axes [16, 22–25]. The geometries of the systems were preliminarily optimized by the gradient method. Further, the molecular dynamics of desloratadine and PVP mixtures was simulated using thermostatting (Berendsen thermostat) and barostatting (Berendsen barostat, 1 atm.) [13, 23] with a step of 2 fs for 25 ns.

The study involved calculating van der Waals energies of interaction between desloratadine and PVP and desloratadine and water and the proportion of desloratadine molecules that lost their bonds with PVP. The desloratadine molecule was considered released into water provided that it did not bind either to the polymer or water.

3. Results and discussion

The molecular compositions of the simulated systems are given in Table 1.

The desloratadine alloy with PEG-6000 was prepared with the ratios of 1:1, 1:2, and 1:5 by weight, since these ratios are the most widely used in the solid dispersion technology [11,12].

During the simulation, there was partial diffusion of desloratadine and PVP into water (Table 2). At a ratio of desloratadine and PVP of 1:1, some of the desloratadine molecules lost their bonds with the polymer and clustered, and some of the PVP molecules passed into the dissolution medium.

The graph (Fig. 3) shows that the van der Waals energies of interaction between desloratadine, the polymer, and the solvent stabilized 20 ns after the beginning of the simulation.

Fig. 4 shows a graph of the dependence of the proportion of desloratadine molecules not bound to the polymer over time. During the first 5 ns of the simulation, over 30% of desloratadine molecules released into the aqueous medium.

The simulation of the release of desloratadine from PVP into water at a ratio of desloratadine to the carrier of 1:2 was accompanied by the formation of clusters and a partial transition of polymer molecules into the solvent (Table 3). During the molecular dynamics simulation, some of the desloratadine molecules released into the aqueous medium, and others retained their bonds with PVP and interacted with water which penetrated into the alloy.

The average energy of the van der Waals interaction between desloratadine and PVP was close to the average energy of the van der Waals interaction between desloratadine and water (Fig. 5).

Fig. 6 provides information on the number of desloratadine molecules not bound to PVP in

Table 1. Amounts of molecules of components of simulated systems

Substance	Desloratadine-PVP 1:1	Desloratadine-PVP 1:2	Desloratadine-PVP 1:5
Desloratadine cation	321	160	64
Cl^- ion	321	160	64
PVP	10	10	10
Water	20264	20064	20960

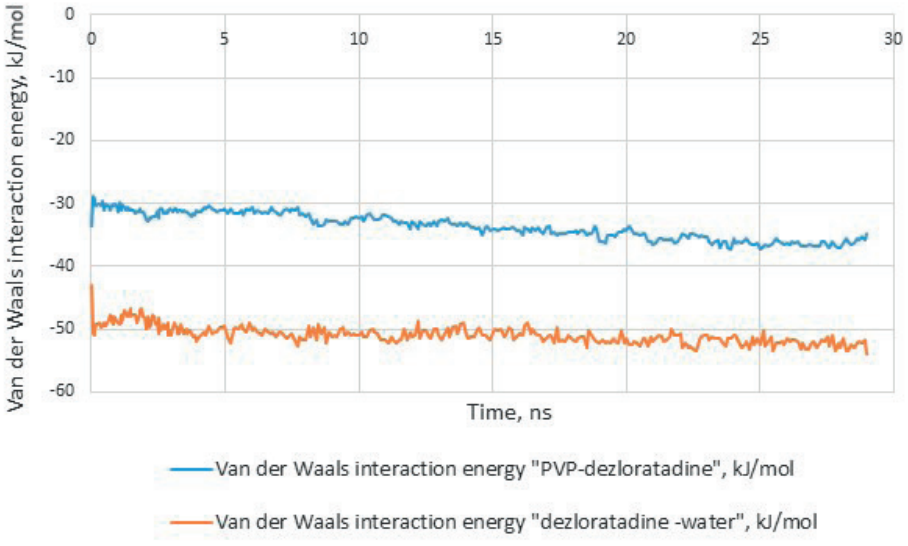


Fig. 3. Energy of van der Waals interaction of desloratadine with PVP and with water (desloratadine: PVP 1:1)

Table 2. Molecular dynamics simulation of the release of desloratadine from a 1:1 PVP alloy by mass into water

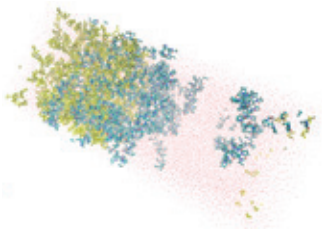
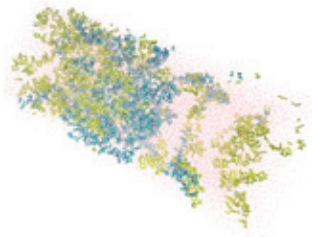
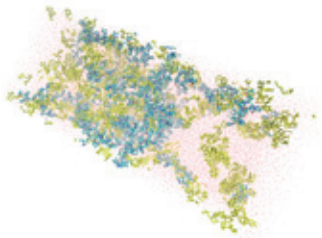
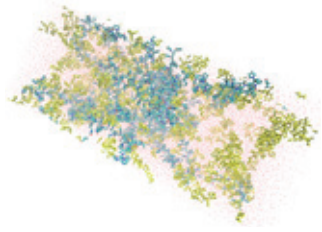
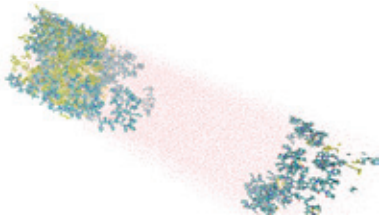
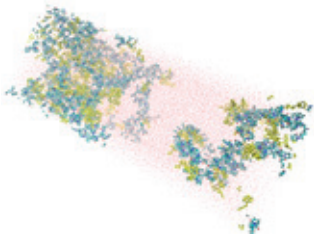
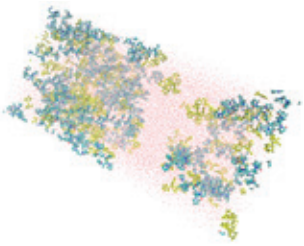
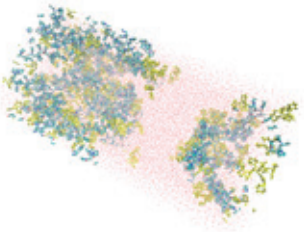
Time, ns	Structure
0	
9	
19	
29	

Table 3. Molecular dynamics simulation of the release of desloratadine from a 1:2 PVP alloy by mass into water

Time, ns	Structure
0	
9	
19	
29	

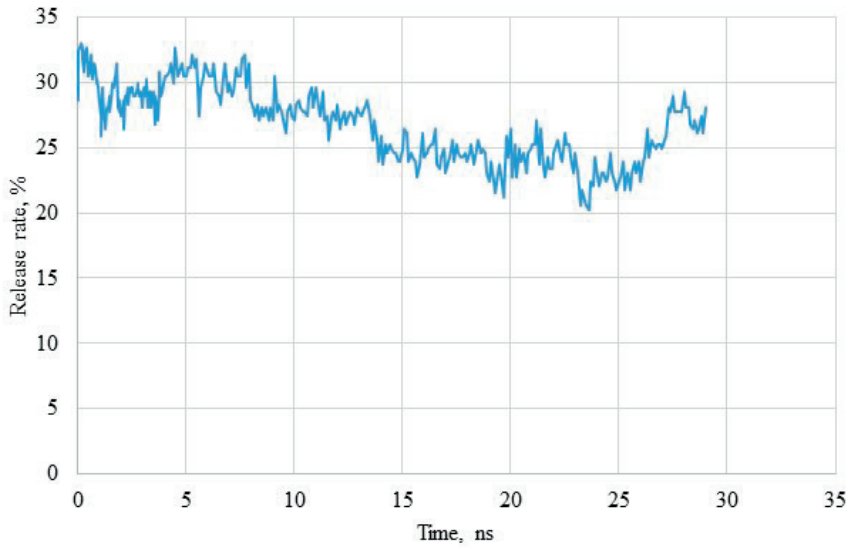


Fig. 4. Release rate of desloratadine (desloratadine: PVP 1:1)

water at a ratio of desloratadine to PVP of 1:2 by weight. It was found that during the first 25 ns of simulation, more than 12% of desloratadine molecules were released into the aqueous medium.

During the simulation of the release of desloratadine from PVP into water at a ratio of desloratadine to carrier of 1:5, a small number of individual desloratadine molecules were released from the polymer into the aqueous medium (Table 4).

The energy of the van der Waals interaction between desloratadine and PVP at a ratio of 1:5 stabilized 20 ns after the beginning of the simulation (Fig. 7).

Fig. 8 shows a graph of the dependence of the proportion of desloratadine molecules not bound to the polymer over time. During the first 25 ns of the simulation, over 10 % of desloratadine molecules were released into the aqueous medium.

The average values for the parameters of the release of desloratadine from the studied PVP complexes are shown in Table 5. According to the results of the molecular dynamics simulation, it was found that the highest degree of desloratadine release from PVP into aqueous medium was achieved at a ratio of 1:1 (24.56±2.08%), and the lowest at ratios of 1:2 and 1:5 (8.27±1.79% and 8.65±0.98%, respectively). The average energy of interaction between desloratadine and the polymer was the lowest at a ratio of 1:5 (–52.03±0.82 kJ/mol), and the energy of

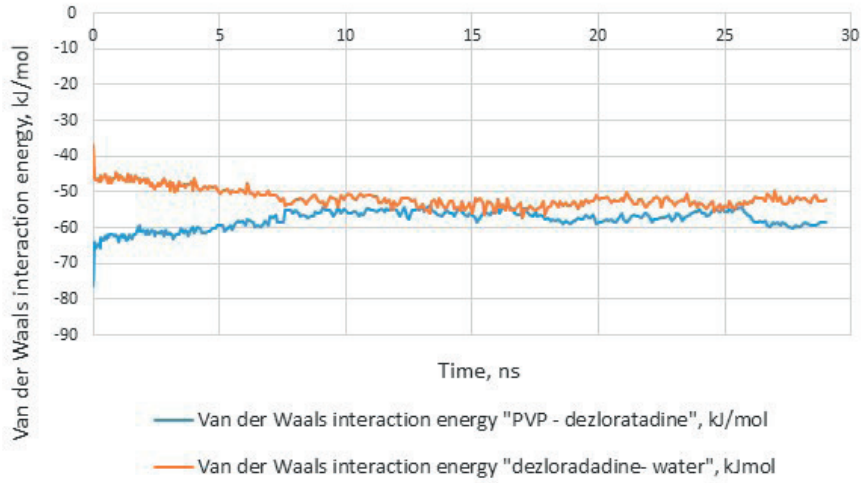


Fig. 5. Energy of van der Waals interaction of desloratadine with PVP and with water (desloratadine: PVP 1:2)

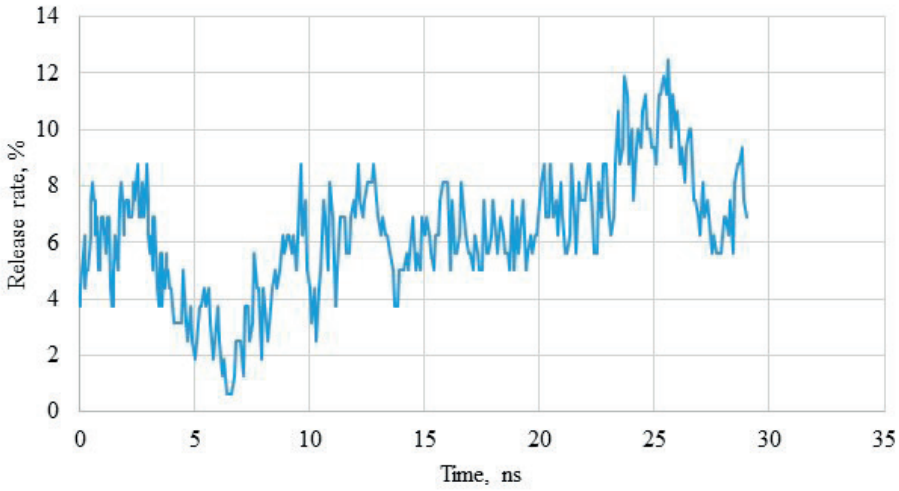
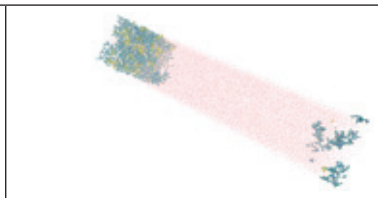
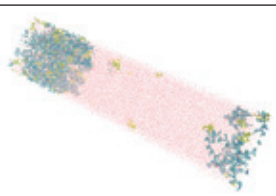
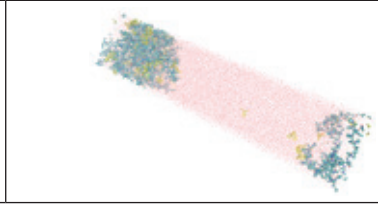
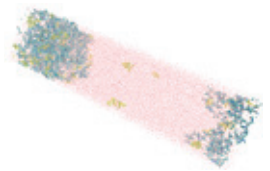


Fig. 6. Release rate of desloratadine (desloratadine: PVP 1:2**)**

Table 4. Molecular dynamics simulation of the release of desloratadine from a 1:5 PVP alloy by mass into water

Time, ns	Structure	Time, ns	Structure
0		19	
9		29	

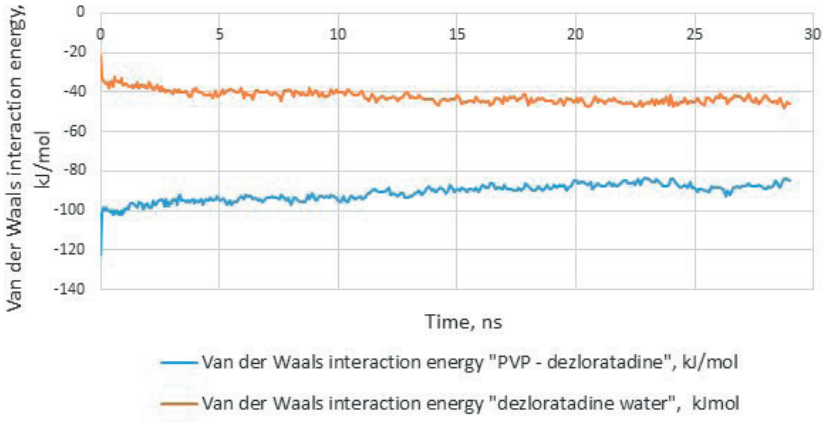


Fig. 7. Energy of van der Waals interaction of desloratadine with PVP and with water (desloratadine: PVP 1:5)

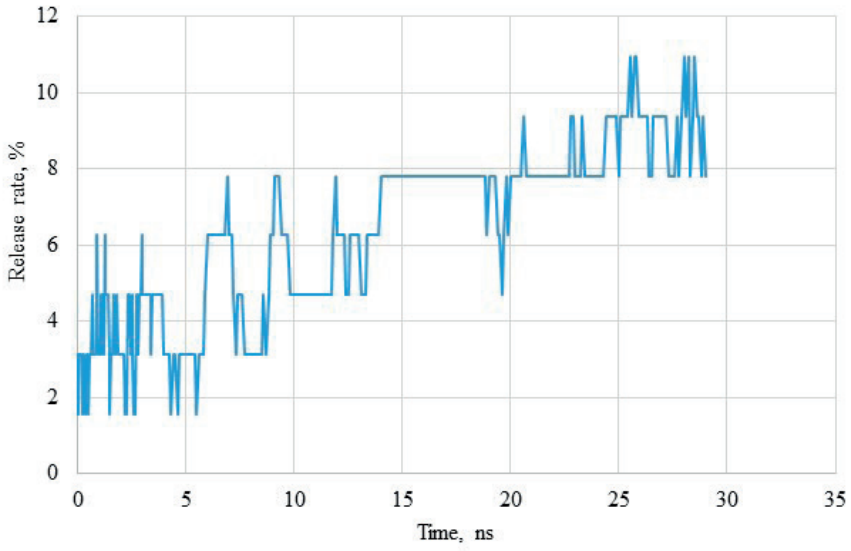


Fig. 8. Release rate of desloratadine (desloratadine: PVP 1:5)

Table 5. Average values of parameters for the release of desloratadine from the studied complexes with PVP

System	Average energy of van der Waals interaction of desloratadine with a polymer, kJ/mol	Average energy of van der Waals interaction of desloratadine with solvent, kJ/mol	Average release rate, %
Desloratadine-PVP 1:1	−36.13±0.62	−52.03±0.82	24.56±2.08
Desloratadine-PVP 1:2	−57.26±1.59	−52.63±1.14	8.27±1.79
Desloratadine-PVP 1:5	−87.07±1.86	−44.45±1.60	8.65±0.98

interaction between desloratadine and water was −44.45±1.60 kJ/mol, which indicates a low intensity of the desorption and solvation processes at this ratio.

4. Conclusions

The conducted study of the release of desloratadine from PVP alloys by the method of molecular dynamics showed that the highest degree of desloratadine release from PVP into the aqueous medium was achieved at a ratio of 1:1, and the lowest at ratios of 1:2 and 1:5. At a ratio of 1:1, the average energy of interaction between desloratadine and PVP per one molecule of desloratadine was the highest (−36.13±0.62 kJ/mol) when the energy of interaction between desloratadine and water was low (−52.03±0.82 kJ/mol), which indicates that desloratadine involvement in the solvation and desorption processes was the highest at this ratio.

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.

References

1. Babu N. J., Nangia A. Solubility advantage of amorphous drugs and pharmaceutical cocrystals. *Crystal Growth & Design*. 2011;11: 2662–2679. https://doi.org/10.1021/cg200492w

2. Benet L. Z., Broccatelli F., Oprea T. I. BDDCS applied to over 900 drugs. *The AAPS Journal*. 2011;13: 519–547. https://doi.org/10.1208/s12248-011-9290-9

3. Popović G., Čakar M., Agbaba D. Acid-base equilibria and solubility of loratadine and desloratadine in water and micellar media. *Journal of Pharmaceutical and Biomedical Analysis*. 2009;49: 42–47. https://doi.org/10.1016/j.jpba.2008.09.043

4. DuBuske L. M. Review of desloratadine for the treatment of allergic rhinitis, chronic idiopathic urticaria and allergic inflammatory disorders. *Expert Opinion on Pharmacotherapy*. 2005;6: 2511–2523. https://doi.org/10.1517/14656566.6.14.2511

5. Ali S. M., Upadhyay S. K., Maheshwari A. NMR spectroscopic study of the inclusion complex of desloratadine with β-cyclodextrin in solution. *Journal of Inclusion Phenomena and Macrocyclic Chemistry*. 2007;59: 351–355. https://doi.org/10.1007/s10847-007-9335-y

6. Ku M. S. Use of the biopharmaceutical classification system in early drug development. *The AAPS Journal*. 2008;10: 208–212. https://doi.org/10.1208/s12248-008-9020-0

7. Jatwani S., Rana A. C., Singh G., Aggarwal G. An overview on solubility enhancement techniques for poorly soluble drugs and solid dispersion as an eminent strategic approach. *ChemInform*. 2013;44(13). https://doi.org/10.1002/chin.201313244

8. Di L., Fish P. V., Mano T. Bridging solubility between drug discovery and development. *Drug Discovery Today*. 2012;17: 486–495. https://doi.org/10.1016/j.drudis.2011.11.007

9. Polkovnikova Yu. A. Study of the release of vinpocetine from solid dispersions with polyvinylpyrrolidone. *Russian Journal of Biopharmaceuticals*. 2021;13(4): 29–32. (In Russ.). https://doi.org/10.30906/2073-8099-2021-13-4-3-6

10. Nair A. R., Lakshman Y. D., Anand V. S. K., Sree K. S. N., Bhat K., Dengale S. J. Overview of extensively employed polymeric carriers in solid dispersion technology. *AAPS PharmSciTech*. 2020;21(8): 309. https://doi.org/10.1208/s12249-020-01849-z

11. Krasnyuk (Jr.) I. I., Belyatskaya A. V., Krasnyuk I. I., ... Odintsova E. B. Prospects for using solid polyvinylpyrrolidone dispersions in medicine and pharmacy. *Pharmacy*. 2016;6: 7-11. (In Russ.). Available at: https://www.elibrary.ru/item.asp?id=26603689

12. Belyatskaya A. V., Krasnyuk (Jr.) I. I., Elagina A. O., ... Kannieva D.R. The study of the solubility of furazolidone from solid dispersions with

polyvinylpyrrolidone. *Moscow University Chemistry Bulletin*. 2020;61(1): 52–56. (In Russ.). Available at: https://www.chem.msu.ru/rus/vmgu/201/52.pdf

13. Polkovnikova Yu. A. Simulation of the release process of vinpoceteine from an alloy with β-cyclodextrin. *Russian Journal of Biopharmaceuticals*. 2022;14(6): 16–20. (In Russ.). https://doi.org/10.30906/2073-8099-2022-14-6-16-20

14. Eastman P., Swails J., Chodera J. D., Pande V. S.OpenMM 7: Rapid development of high performance algorithms for molecular dynamics. *PLOS Computational Biology*. 2017;13: 1–17. https://doi.org/10.1371/journal.pcbi.1005659

15. Walden D. M., Bundey Y., Jagarapu A., Antontsev V., Chakravarty K., Varshney J. Molecular simulation and statistical learning methods toward predicting drug-polymer amorphous solid dispersion miscibility, stability, and formulation design. *Molecules*. 2021;26(1): 182. https://doi.org/10.3390/molecules26010182

16. Polkovnikova Yu. A., Glushko A. A., Slivkin A. I. Molecular dynamics modeling of the release of aminophenylbutyric acid from sodium alginate. *Vestnik of the Smolensk State Medical Academy*. 2023;22(3): 152–157. (In Russ.). https://doi.org/10.37903/vsgma.2023.3.20

17. Chan T., Ouyang D. Investigating the molecular dissolution process of binary solid dispersions by molecular dynamics simulations. *Asian Journal of Pharmaceutical Sciences*. 2018;13(3): 248–254. https://doi.org/10.1016/j.ajps.2017.07.011

18. Abraham M. J., Murtola T., Schulz R., ... Lindahl E. GROMACS: High performance molecular simulations through multi-level parallelism from laptops to supercomputers. *SoftwareX*. 2015;1–2: 19–25. https://doi.org/10.1016/j.softx.2015.06.001

19. Sorin E. J., Pande V. S. Exploring the helix-coil transition via all-atom equilibrium ensemble simulations. *Biophysical Journal*. 2005;88(4): 2472–2493. https://doi.org/10.1529/biophysj.104.051938

20. Teppen J. B. HyperChem, release 2: molecular modeling for the personal computer. *Journal of Chemical Information and Computer Sciences*. 1992;32: 757–759. https://doi.org/10.1021/ci00010a025

21. Shirts M. R., Klein C., Swails J. M., ... Zhong E. D. Lessons learned from comparing molecular dynamics engines on the SAMPL5 dataset. *Journal of Computer-Aided Molecular Design*. 2017;31: 147–161. https://doi.org/10.1007/s10822-016-9977-1

22. Bekker H. E., Dijkstra J., Renardus M. K. R., Berendsen H. J. C. An efficient, box shape independent non-bonded force and virial algorithm for molecular dynamics. *Molecular Simulation*. 1995;14: 137–152. https://doi.org/10.1080/08927029508022012

23. Berendsen H. J. C., Postma J. P. M., van Gunsteren W. F., Di Nola A., Haak J. R. Molecular dynamics with coupling to an external bath. *The Journal of Chemical Physics*. 1984;81(8): 3684–3690. https://doi.org/10.1063/1.448118

24. Braga C., Travis K. P. A configurational temperature Nosé-Hoover thermostat. *The Journal of Chemical Physics*. 2005;123(13): 134101. https://doi.org/10.1063/1.2013227

25. Parrinello M., Rahman A. Polymorphic transitions in single crystals: A new molecular dynamics method. *Journal of Applied Physics*. 1981;52: 7182–7190. https://doi.org/10.1063/1.328693

26. Polkovnikova Yu. A., Slivkin A. I., Glushko A. A. Simulation of the molecular dynamics of the release of gamma-aminobutyric acid from gelatin. *Bulletin of Voronezh State University. Series: Chemistry. Biology. Pharmacy*. 2023;2: 110–116. Available at: https://www.elibrary.ru/item.asp?id=54070189

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