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Modelling Study on Parameters Influencing Binding Affinity in Drug-Polyurethane Nanoparticle Assembly

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Abstract: *Polyurethanes are widely used in different industries, as insulators, coating or adhesive agents. Several of their medical applications include various implants, artificial heart valves, surgical instruments or catheters. The versatility and biocompatibility of these polymer products lead to their application as drug or genetic material delivery systems. We aim to evaluate different parameters that affect the encapsulation efficiency of polyurethanes, using a computational approach, in order to improve the transmembrane transfer and the bioavailability of an active agent loaded inside a drug delivery system. 2D structures of different etheric- and esteric-PU macromolecular chains were modeled in ChemBioDraw, while molecular structures of the three active agents (Deoxyribonucleic acid, Guanidine,1'-[(methylethanediylidene)dinitrilo]di-, mixt. with Calf Thymus DNA, and 2'-Deoxycytidine-5'-phosphonic acid) were imported from PubChem database. Open software such as Open Babel and PyRx were used to convert files and to analyze the binding affinity based on the predicted dissociation constants. Structural parameters of the tested compounds were calculated in HyperChem 8.0. The polymer chains showed very large values for van der Waals potentials, refractivity and polarizability compared to the active agents. Even if there were no major differences in terms of binding affinities between the tested assemblies, the best orientation ligand-macromolecule was the 2'-Deoxycytidine-5'-phosphonic acid encapsulated inside LDI and PEG-based polyurethane carrier. On the other hand, the values of Root Mean Square Deviation have identified that the best geometric fit to be the Deoxy-ribonucleic acid encapsulated inside IPDI and PCL-based polyurethane macromolecule. The assemblies between genetic materials and polyurethane drug delivery systems are not experimentally known and this study could orientate towards new potential therapies. These results indicate that there is no significant change in the values of the docking parameters with different PU synthesis precursors; however, a good compatibility between LDI and PEG-based chain and 2'-Deoxycytidine-5'-phosphonic acid was identified. Further studies are needed to evaluate the in vitro and in vivo utility of this finding.*

Keywords*: dissociation affinity, drug carrier, drug delivery, isocyanate, polymer, structure*

1. Introduction

Polyurethane (PU) compounds have been discovered by Prof. Otto Bayer in 1937; they contain macromolecular chains with the specific urethane functional group (-NH-CO-O-) that are obtained in polyaddition reactions between compounds with active hydrogen such as etheric or esteric polyols and di- or tri-isocyanates. Aromatic compounds are often used in the synthesis due to the enhanced mechanical and physical properties of the final products used in industry. However, they are often replaced with aliphatic substances due to their lower cancer risk for human health [1, 2]. Nano- and micro-scale particles based on PU or PU-copolymers and used as drug delivery systems (DDS) have been developed since the last years of the 20th century, when K. Hong and S. Park have reported the obtaining of PU microcapsules with an average size around 10 μm based on 2,4-tolylene-diisocyanate, poly(ethylene glycol) and ethylene - diamine [3] and respectively Y. Frère has prepared PU particles

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between 50 and 200 μm [4]. Five years later, K. Bouchemal and her research team used an interfacial polycondensation combined with a spontaneous emulsification to synthesize PU nanocapsules for the transport of α-tocopherol [5]. Our research team has begun to obtain PU structures since the beginning of the last decade [6-11]. Here we aim to optimize the encapsulation efficiency and study on the behavior of drug-PU assemblies.

Drug delivery systems can be classified based on: the routes of drug administration (nasal, topical, oral, parenteral, etc.), their forms (solid as powders, tablets, capsules, semisolid as lotions, ointments, creams, and liquid as syrups, solutions, tinctures, etc.), their permeability (intestinal) and solubility, their pharmacokinetics, and the drug release kinetics [12]. Another important classification criteria is represented by the type of the active agent that is encapsulated inside the DDS; it can be a drug recognized in official pharmacopoeia (API) or different genetic materials; the transfer of genetic materials as DNA, RNA and genes are used in various gene therapies.

Gene therapy is based on viral and non-viral vectors, who can transfer foreign DNA inside the cells. The viral vectors used in gene therapy include lentiviral vectors (retroviruses), adenoviruses, and adeno-associated viral vectors, while the non-viral vectors are hemocompatible synthetic or natural compounds as lipids, polymers and nanoparticles. A viral vector presents a "virus' natural design" and it is able to pass through the cell membrane and to disassemble itself at the nucleus; the non-viral vectors have a few advantages, as their lack of pathogenicity and the possibility to transfer much larger nucleic acid molecules [13]. On the other hand, the disadvantages of viruses include replication competence, lack of targeting, non-integration, and low immunogenicity [14], while the non-viral vectors present a low transfection (the ability to introduce nucleic acids into cells) efficiency. J. Luten *et al.* have presented a few examples of polymers that can be used as biodegradable non-viral vectors for plasmid DNA (pDNA) delivery: polyesters, polylysine- or poly(ethylene imine)- based degradable cationic polymers and poly(lactic-co-glycolic acid) micro- and nanoparticles [15]; pDNA, isolated from bacteria such as *Escherichia coli*, is a small, circular, double-stranded DNA molecule used in transfection, sequencing, and screening clones [16]; on the contrary, standard double stranded DNA (dsDNA), the major form of genetic material in most organisms, is often found in SARS-CoV-2 detection and in many experiments with antibodies.

Many small peptides-, cationic polypeptides- and lipid-based gene carriers have been investigated and they show promising results in gene therapy [17]. Although J. Cheng *et al.* have found that cationic PU have a higher transfection efficiency in MCF-7 and SKOV-3 cells than its cationic polyamide analogue, many other *in vitro* and *in vivo* studies on this kind of polymer are necessary [18].

Computational methods are widely used in drug discovery and drug development, due to their good prediction and reduced need for resources (high cost-efficiency). Molecular docking is a computational method that predicts the preferred orientation of an active molecule to a transporter molecule when it binds to each other to form a stable assembly. Knowing the preferred orientations as well as other parameters that influence the association of these molecules or the binding affinity is very important and relatively easy to predict using a computational approach. Considerable efforts have been made to improve the already developed in silico methods based on the biological and pharmaceutical importance of molecular docking [19].

The present study aims to evaluate the etheric vs. esteric character of the polyol used as a precursor in the synthesis of DDS, and structural parameters (energies, surfaces, volumes, logP, refractivity, and polarizability) that affect the encapsulation efficiency of polyurethanes, using a computational approach, in order to improve the transmembrane transfer and the bioavailability of hydrophilic molecules, that carries genetic information, loaded inside a drug delivery system. Standard dsDNA was used instead of pDNA due to its easy way to obtain and to use in further experiments; the future perspectives of this research include the obtaining and the physico-chemical and toxicological characterization of these products.

2. Materials and methods

Three different PU chains were modeled at atomistic level using ChemBioDraw Ultra 14 Suite (CambridgeSoft / PerkinElmer - CheMicro Ltd. Budapest, Hungary) and HyperChem Release 8.0 for Windows (Hypercube, Inc. - CheMicro Ltd. Budapest, Hungary): *structure_1* based on isophorone-diisocyanate (IPDI) and polyethylene glycol (PEG), *structure_2* based on IPDI and epsilon-polycaprolactone (PCL), and *structure_3* based on lysine-diisocyanate (LDI) and PEG.

Open Babel 3.1.1 (http://openbabel.org), an open source chemistry toolbox, was used to convert, analyze, and to store molecular modeling data according to O'Boyle *et al.* [20]. PyRx - Python Prescription 0.8 (Molecular Graphics Laboratory, The Scripps Research Institute, La Jolla, CA, USA), an open source software, was used to import the structures of the active agents (Deoxyribonucleic acid - compound CID: 44135672, labeled *L1*, Guanidine,1'-[(methylethanediylidene)dinitrilo]di-, mixt. with Calf Thymus DNA - compound CID: 54600453, labeled *L2*, and respectively 2'-Deoxycytidine-5'-phosphonic acid - compound CID: 42626896, labeled *L3*). Molecular structure data files of the active agents were downloaded from PubChem database (https://pubchem.ncbi.nlm.nih.gov). Their structures were converted to PDBQT format using PyRx. The strength of the interaction was predicted using the Autodock Vina algorithm [21-23].

All calculations and computational simulations were performed on a 64-bit Windows 10 operating system with Intel® Core(TM) i7-9750H (@ 2.60GHz) as the processors and 16.00 GB of RAM. Data are represented as the mean with standard error of the mean. Statistics were calculated using IBM SPSS Statistics for Windows v.27 (IBM Corp., Armonk, N.Y., USA).

3. Results and discussions

First of all, the macromolecular chains were modeled in 2D (minimum 420 atoms and/or molecular weight 4750 amu) as MOL files and they were imported in HyperChem; an initially "add H and model build" procedure was perform to obtain a fast optimization of the molecular geometry based on the standard bond lengths and angles, then the geometry optimization was done under MM+ (electrostatic – bond dipoles and cutoffs – none, including all components of force field) and Polak-Ribiere as algorithm; the structural parameters of every compound are presented in Table 1.

Table 1. Calculated structural parameters

Parameter, M.U.	Compound (macromolecule / ligand)					
	structure_1	*structure_2*	*structure_3*	*L1*	*L2*	*L3*
E_{tot}, kcal/mol	218.76	254.05	263.67	151.14	241.49	142.62
E_{bond}, kcal/mol	116.00	276.21	72.95	0.36	0.12	1.65
E_{angle}, kcal/mol	173.63	162.28	99.76	116.53	172.53	74.21
Edihedral, kcal/mol	29.76	51.38	54.76	43.06	69.63	13.65
E_{VDW}, kcal/mol	305.06	311.77	389.21	-8.80	-0.41	2.55
AAS, Å^2	7131.04	7954.48	7583.66	541.48	499.45	391.59
VAS, Å^3	12832.20	15448.99	13442.62	1286.09	786.51	771.76
VVDW, Å^3	4486.58	5538.93	4639.68	408.85	223.94	227.75
SVDW, Å^2	5725.14	6838.15	6271.67	507.92	307.41	281.05
E_{hy}, kcal/mol	-89.37	-38.35	-26.25	-35.72	-32.68	-28.55
logP	13.99	44.36	-32.45	-1.94	-8.41	-1.20
Refractivity, Å^3	1210.48	1496.81	1696.76	97.25	61.15	58.48
Polarizability, Å^3	480.47	597.07	276.15	40.63	23.72	23.62
Mass, a.m.u.	4775.84	5786.30	4911.21	527.40	382.16	293.22

M.U. (measurement unit), Etot (total energy), Ebond (H2 bonding potential), Edihedral (dihedral angle potential), EVDW (van der Waals potential), AAS (solvent accessible surface area), VAS (solvent accessible volume), VVDW (van der Waals volume), SVDW (van der Waals surface area), Ehy (hydration energy).

The potential energy of a molecular system is: $E = E_{covalent} + E_{non\text{-}covalent}$, where $E_{covalent} = E_{bond} + E_{angle} + E_{dihedral}$ and $E_{non\text{-}covalent} = E_{van\ der\ Waals} + E_{electrostatic}$ according to Jing Yu [24]. Thus, our macromolecular chains present the following values of $E_{covalent}$: 319.39 kcal/mol (*structure_1*), 489.87 kcal/mol (*structure_2*), and 227.47 kcal/mol (*structure_3*), while the active agents: 159.95 kcal/mol (*L1*), 242.28

kcal/mol (*L2*), and 89.51 kcal/mol (4262896). Covalent bonds are considered as the strongest bonds in nature; this is due to the equal distribution of electrons between the bonded atoms and, as with any equal sharing, there is no conflict that would weaken the arrangement [25]. It must be mentioned that E_{bond} and E_{angle} are typically modeled as harmonic potentials centered about equilibrium bond length values, while $E_{dihedral}$ is modeled with the appropriate potentials, however they tend not to be harmonic oscillators and their various functional forms tend to vary with the specific implementation of the potential function [26].

On the other hand, the partition coefficient (logP) is crucial for understanding the behavior of drug molecules in the body, in the pharmaceutical/biotech industries [27]. Positive and high values of logP were calculated for the polyurethane chains based on IPDI (*structure_1* and *structure_2*), while a negative value was obtained in the case of LDI-based macromolecule (-32.45). A negative value for logP is specific to a compound with a higher affinity for the aqueous phase (it is more hydrophilic). Compared to the logP values of the active agents, the carriers present more hydrophobic (IPDI-based chains) and respectively hydrophilic (LDI-based chain) character.

The structures were exported as MOL files and they were converted to mol2 in Open Babel GUI and then a molecular docking software (PyRx with Autodock Vina) was used to predict the relative binding affinities of the chosen active agents for the three different PU macromolecular chains. The active agents were individually simulated to determine minimal binding energy configurations with either etheric- and esteric-PU as the target host macromolecule (Figures 1-3).

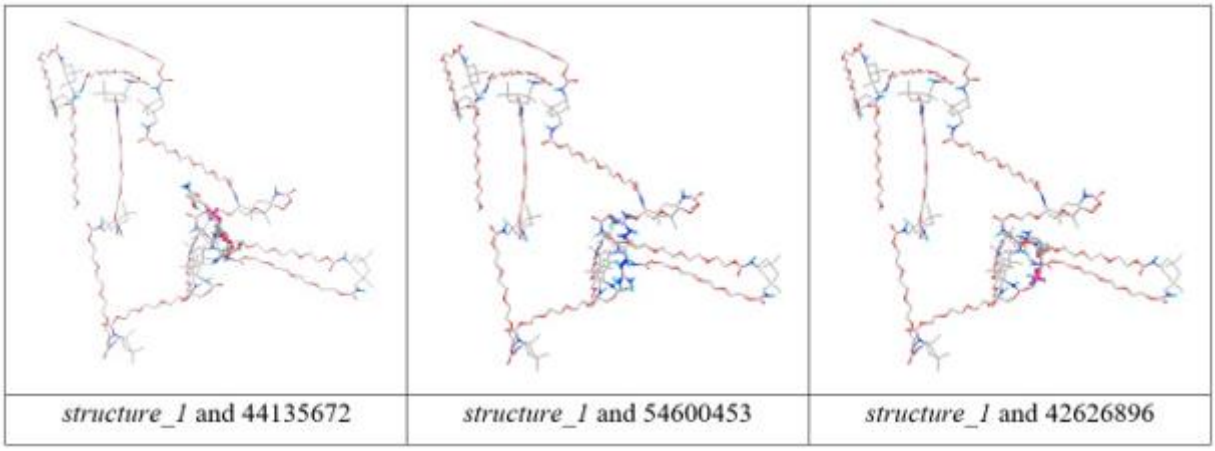

Figure 1. Molecular structures of *structure_1*-based assemblies with: (A) *L1*, (B) *L2*, and (C) *L3*

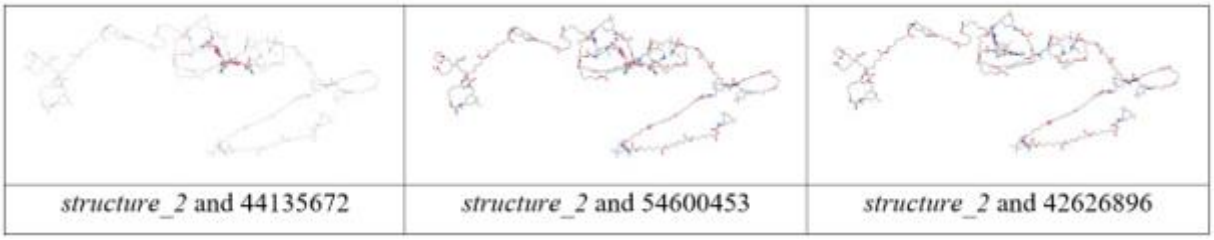

Figure 2. Molecular structures of *structure_2*-based assemblies with: (A) *L1*, (B) *L2*, and (C) *L3*

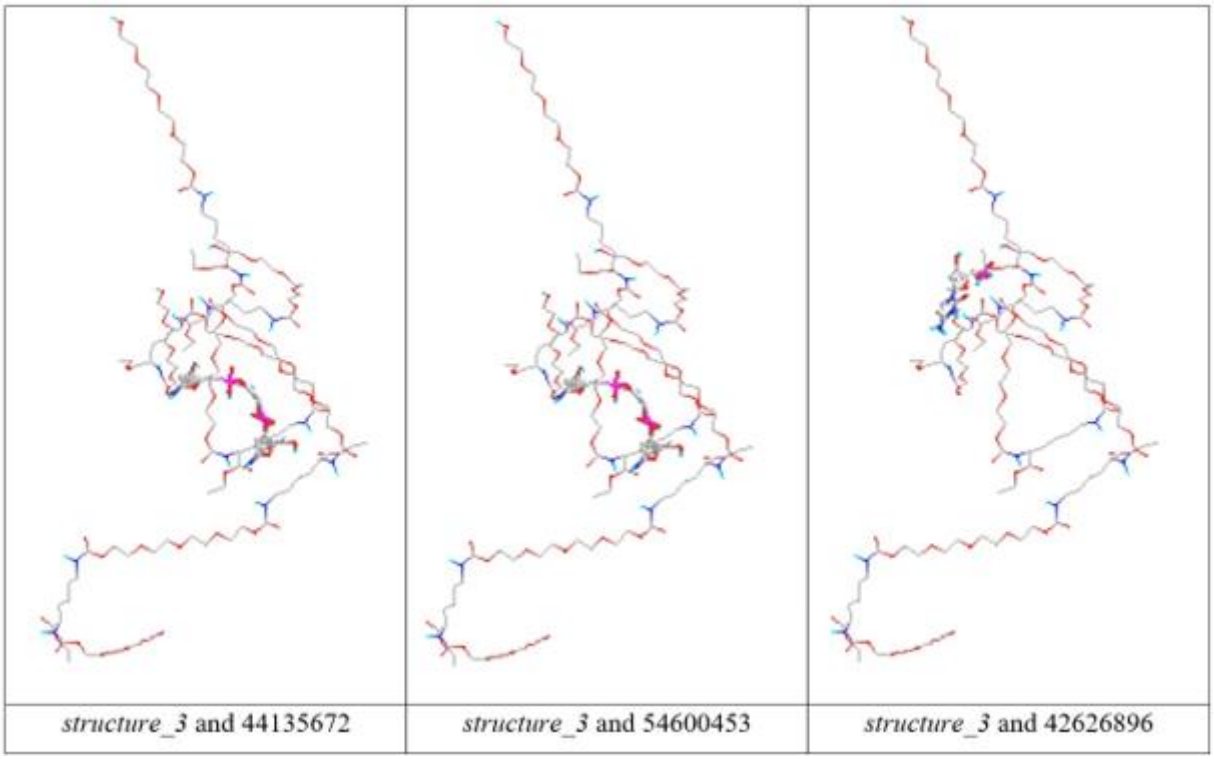

Figure 3. Molecular structures of *structure_3*-based assemblies with: (A) *L1*, (B) *L2*, and (C) *L3*

The lowest values of the binding affinity were identified for *structure_3* and 42626896 (-5.05 kcal/mol), respectively for *structure_2* and 44135672 (-5.02 kcal/mol) (Table 2). The differences between all nine binding affinities are very small and they cannot be correlated with the chemical structures, logP or mass values. Herein, these results predict that 54600453 will have the greatest affinity for *structure_1*.

Table 2. Predicted docking parameters

Molecule (macromolecular chain)	Ligand	Binding affinity (kcal/mol)	rmsd/ub (Å)	rmsd/lb (Å)
structure_1	*L1*	-4.62 ± 0.04	7.62 ± 1.14	4.24 ± 0.70
	L2	-3.56 ± 0.04	9.30 ± 2.78	7.29 ± 2.64
	L3	-4.57 ± 0.04	7.08 ± 1.37	5.69 ± 1.21
structure_2	*L1*	-5.02 ± 0.06	5.31 ± 0.91	2.20 ± 0.33
	L2	-4.43 ± 0.06	6.32 ± 0.91	3.54 ± 0.33
	L3	-4.82 ± 0.06	7.03 ± 1.34	6.05 ± 1.28
structure_3	*L1*	-4.91 ± 0.03	6.36 ± 0.99	3.37 ± 0.95
	L2	-4.58 ± 0.03	6.07 ± 1.00	3.60 ± 0.95
	L3	-5.05 ± 0.04	4.52 ± 1.17	3.45 ± 1.04

The importance of the upper bound limit (rmsd/ub) and the lower bound limit (rmsd/lb) for Root Mean Square Deviation (rmsd) in computational studies was presented by EP Istyastono [28] and O Trott and AJ Olson algorithm [22] as follows: the values of rmsd are highly correlated with the average distance between atoms in a position relative to the best matching position. Thus, $rmsd_{ab} = \max(rmsd'_{ab}, rmsd'_{ba})$ and $rmsd' = \sqrt{[(1/N) \cdot \Sigma \min r^2_{ij}]}$, where N is the number of heavy atom in structure *a* and min is over all atoms in structure *b* with the same element type as atom *i* in structure *a* [29]. Figure 4 presents a comparative graph of these rmsd values.

The IPDI and PEG-based macromolecular chain (*structure_1*) with all three active agents seems to have higher values of rmsd, while the values obtained in the other two PU macromolecules are quite similar.

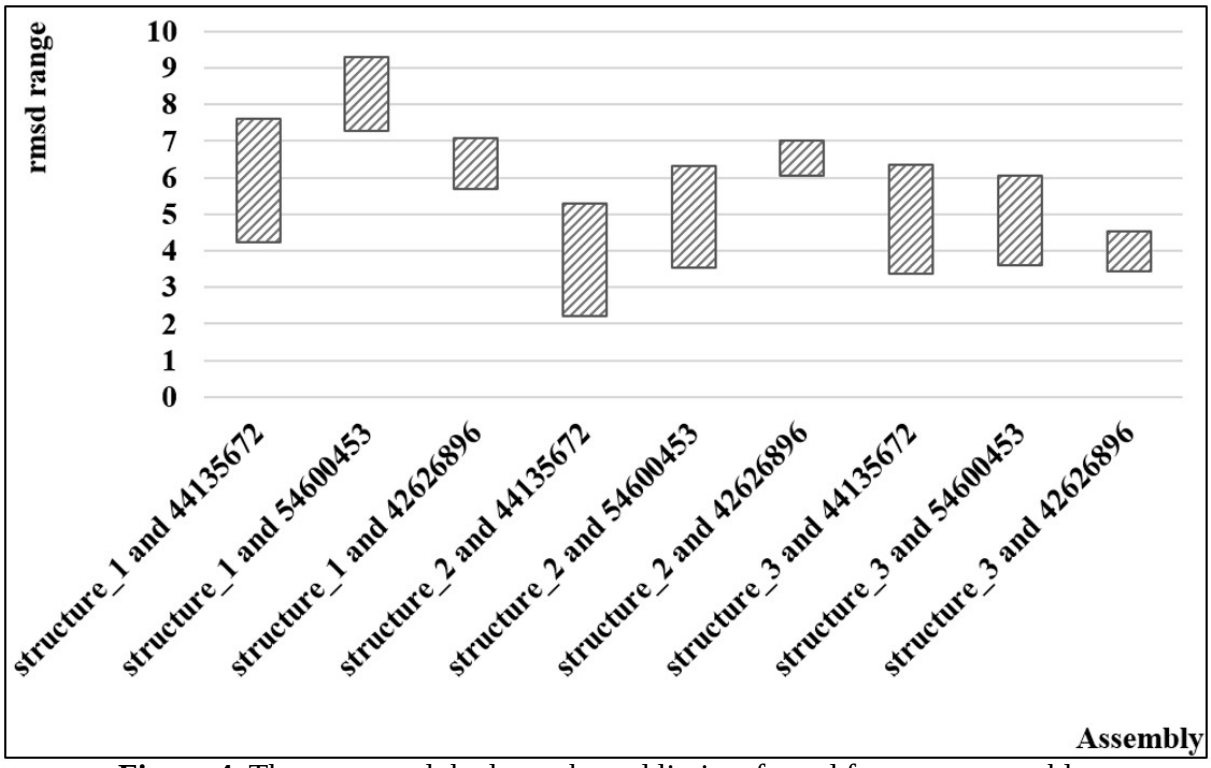

Figure 4. The upper and the lower bound limits of rmsd for every assembly

Docking software are often used as virtual tools in compound optimization [30]. This study shows that the best geometric fit of the tested ligands is in the case of IPDI and PCL-based chains with Deoxyribonucleic acid, while the worst value was obtained in the case of IPDI and PEG-based chain with Guanidine,1'-[(methylethanediylidene)dinitrilo]di-, mixt. with Calf Thymus DNA. On the other hand, the obtained values for the binding affinity indicate a better orientation of all three active agents inside the carrier based on LDI and PEG (average value: -4.87 kcal/mol). The best value was observed for LDI and PEG-based chain with 2'-Deoxycytidine-5'-phosphonic acid, while the worst value was observed for IPDI and PEG-based chain with Guanidine,1'-[(methylethanediylidene)dinitrilo]di-, mixt. with Calf Thymus DNA.

These polyurethane / active agent assemblies are not experimentally known and this study could propose a direction towards new potential therapies. Our previous studies on polyurethane drug delivery systems [6-11] have shown that these structures can have a delayed drug release by changing the ester / ether ratio in the hydroxylic component during the synthesis, and the size of the particles can be easy modified by changing the amount of the chain extender (diols or diamines with low molecular weight such as ethylene glycol, 1,4-butandiol, 1,6-hexanediol, ethylenediamine, etc.). These materials may become an alternative in the drug delivery domain, due to their good biodegradability and hemo-compatibility [31], however safety toxicological trials should be performed in future.

A complete study on the synthesis and characterization of a polyurethane carrier used for the trans-membrane transfer of genetic materials can last for months, while a simulation can be a powerful, quick and economical alternative.

Future directions

In this study, we noted that, despite the change of the genetic material, the etheric vs. esteric character of the polyol used as a precursor, the values of binding affinity were almost similar. Investigating the role of hydrogen bonds interactions between the ligands and different polymeric chains and their change of directions, have the potential to further enhance the scoring function. We are also interested in developing and testing cross-linking macromolecular chains with extensive experimental information about *holo*

structures and binding affinities. On the other hand, the effect of the molecular descriptors (electronic, hydrophobic, steric, hydrogen bond donor/acceptor character) must be also studied. A complete investigation on a larger series of polyurethane-drug assemblies, containing descriptors of physical properties (solvent accessible area and volume and van der Waals area and volume), atom and bond counts (donor/acceptor atoms, rigid and rotatable bonds, hydrophilic/hydrophobic character), electronic (polarizability, refractivity), the potential energy and critical descriptors (logP, count of rotatable bonds, count of hydrogen-bond acceptor/donor atoms and topological polar surface area) can make a reliable prognosis of the binding affinity.

4. Conclusions

The research on the physico-chemical interactions between a drug delivery system and an active substance is the first step to obtain improved carriers. Nowadays, the pharmaceutical industry is more interested to increase the bioavailability of already known active substances, rather than to develop new active agents. Hereby we report a comparative computational study on different esteric- and etheric-PU macromolecular chains loaded with active agents in order to find the parameters that can be correlated with the binding affinity. The results indicate that there is no significant change in the values of the docking parameters with different synthesis precursors; however, a good compatibility between LDI and PEG-based chain and 2'-Deoxycytidine-5'-phosphonic acid was identified. Further studies are needed to evaluate the *in vitro* and *in vivo* utility of this finding.

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