Modeling Polymer-Drug Interactions in Biodegradable Tyrosine-Derived Nanospheres Using Molecular Dynamics Simulations and Docking Studies

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ABSTRACT

The intensive labor and high cost of developing new vehicles for controlled drug delivery highlights the need for a change in their discovery process. Predictive computational models can be used to accelerate the selection process of lead candidates from large polymer libraries prior to their synthesis and biological characterization. Tyrosine-derived nanospheres composed of an ABA-type block copolymer, where the A blocks are poly (ethylene glycol) and the B-blocks are hydrophobic low molecular weight polyarylates, have previously shown an effective binding to lipophilic drugs [1]. To better understand the interaction and binding affinity of drugs with these nanospheres, we have developed a computational method that combines Molecular Dynamics (MD) simulations and docking studies. Preliminary results demonstrate the feasibility of the proposed model and the predicted relative binding affinity is in agreement with experimental values.

Keywords: drug delivery, molecular dynamic simulations (MD), docking

1 INTRODUCTION

Current research suggests that efficient and stable incorporation of drugs into nanoparticles is governed not only by solubility and hydrophobicity, but also by physical factors such as rigidity, conformation and/or configuration of the nanospheres-forming polymer and drug [2]. In this scope, computational methods can help in visualizing and understanding the physical properties that drives the compatibility between the drug and its carrier.

Our previous experimental studies showed that tyrosine-derived nanospheres composed of desaminotyrosyl-tyrosine ester cores and poly (ethylene glycol) shells act as an effective carrier for absorbing and binding lipophilic drugs [1]. In the current study Molecular Dynamics (MD) simulations and docking calculations were combined to better understand the drug interactions with these nanospheres and to rank order them in terms of binding free energy. Nutraceutical curcumin and anti-cancer drug paclitaxel were used as model compounds and predicted outcome was compared with experimental data regarding their binding to the nanospheres made of poly(desaminotyrosyl–tyrosine octyl ester suberate) and 5000Da PEG blocks, (abbreviated here as DTO-SA/5K). The proposed method successfully rank orders the drugs based on binding efficiency experimentally determined.

2 METHODS

2.1 Computational Methods

Molecular dynamics (MD) simulations were performed for the three dimensional (3D) structures of polymer strand(s) (11 repeat units of DTO-SA and 57 repeat units of PEG/5K on each side) using the MOE [3] (Molecular Operating Environment) program and the MMFF94x force field as distributed in MOE (Chemical Computing Group). MD simulations were performed for 1, 2, 4 and 8 strands (different molecular weights of the polymer). In the MD simulations, both implicit and explicit water models were used. The explicit water model was added using the "soaking" option in the MOE program. In both the fully hydrated and the implicitly hydrated simulations, the canonical ensemble (NVT) was used with a target temperature of 300 K. An integration time step of 2 fs was used and structures were saved to disk every 0.5ps. The total simulation time was 5 ns. The polymer strands were included with no atoms restrained or held fixed during the simulations.

Thereafter, each drug (curcumin or paclitaxel) was docked into the pre-minimized polymer structures using Autodock4 [4] software. The three search methods implemented in Autodock4 were tested and the estimated binding energies, defined as the lowest energy found, were compared with experimentally determined binding efficiencies.

2.2 Experimental Methods

Nanospheres with entrapped drugs were prepared by combining 60 mg of triblock copolymer with either 3.6 mg of paclitaxel or curcumin in 600 µL of DMF. These solutions were added drop-wise to 14.4 mL of PBS with constant stirring. The resulting suspensions were filtered (0.22 µm pore size), and purified drug containing nanospheres were obtained by ultracentrifugation and re-suspension of the resultant pellet, followed again by filter sterilization. To determine the drug binding efficiency, a predetermined aliquot of the purified drug-loaded nanosphere suspension was withdrawn and freeze-dried; paclitaxel and curcumin concentrations within the nanospheres were determined by extraction (vigorous vortexing in MeOH for 1 h) and high-performance liquid chromatography methods [1]. For further details on materials, instruments, and methods, refer to Biomacromolecules, 8(3), 998-1003, 2007 [1]. The binding efficiency experimentally determined (eq.1) is defined as the ratio (%) of the mass of the drug in the nanospheres compared to the mass of the drug in feed (initial input).

$$\text{Binding efficiency (\%)} = \frac{\text{mass of drug in nanoparticles}}{\text{total drug of mass input}} \times 100\% \qquad (1)$$

3 RESULTS

3.1 Theoretical Calculations

The structures of the tyrosine derived triblock (DTO-SA/5K) (Fig. 1) and of curcumin and paclitaxel (Fig. 2 a) and b) were optimized starting from its 3D coordinates, as described in methods section. These studies confirmed that the spontaneous self-assembly of tyrosine-derived triblock copolymers leads to formation of core (B-block)-shell (A-blocks) architecture.

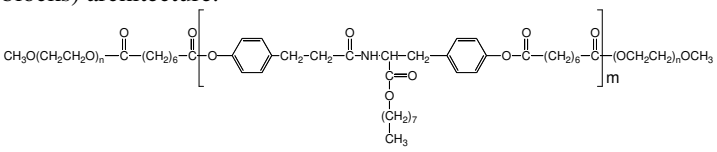
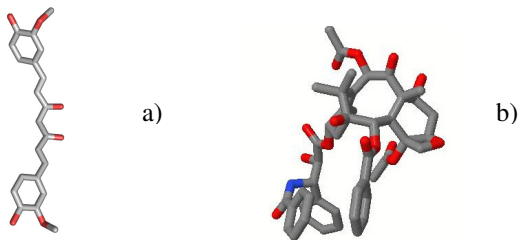


Figure1: General structure of tyrosine-derived triblock copolymers [1]



a) b)

Figure 2: 3D structures of a) curcumin and b) paclitaxel

Initially, a grid refinement study was performed for the docking calculations (Fig. 3) to insure convergence of the computed expected value (*i.e.*, most probable value) of the binding energy. As expected, the binding energies converged with the decreased size of the grid spacing points.

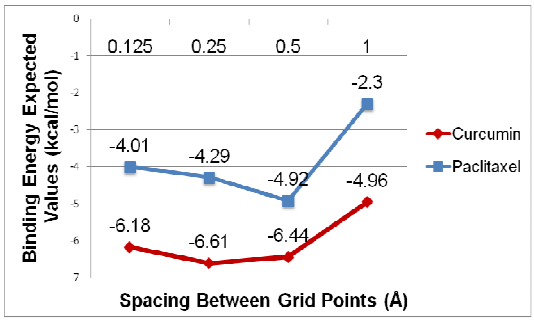


Figure3: Expected values for binding affinities of curcumin (red) and paclitaxel (blue) in complex with oligo (DTO-SA).

The three search algorithms built in Autodock4 were used (Genetic Algorithm-GA, Lamarckian Genetic Algorithm-LGA and Simulating Annealing-SA) to find the most favorable drug-polymer complex geometry (interactions). Comparing the values of binding energy, LGA algorithm predicted a stronger affinity of both of the drugs to the nanosphere core (Table 1). The 1, 2 4, 8 in front of each searching algorithm represent the number of strands used in MD simulations and further in docking calculations.

Estimated binding energies		
Method	**Paclitaxel**	**Curcumin**
1-GA	-3.6 Kcal/mol	-5.1 Kcal/mol
2-GA	-3.36 Kcal/mol	-3.6 Kcal/mol
4-GA	-3.94 Kcal/mol	-4.7 Kcal/mol
8-GA	-4.35 Kcal/mol	-5.38 Kcal/mol
1-LGA	-3.6 Kcal/mol	-6.62 Kcal/mol
2-LGA	-3.24 Kcal/mol	-4.92 Kcal/mol
4-LGA	-4.68 Kcal/mol	-7.36 Kcal/mol
8-LGA	-4.55 Kcal/mol	-7.39 Kcal/mol
1-SA	-1 Kcal/mol	-3.68 Kcal/mol
2-SA	-1.3 Kcal/mol	-3.32 Kcal/mol
4-SA	-1.34 Kcal/mol	-3.77 Kcal/mol
8-SA	-1.45 Kcal/mol	-4.03 Kcal/mol

Table 1: Estimated binding energy values using three searching algorithms built in Autodock4. Grid space between 0.375 Å and 0.5 Å

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3.2 Comparison with Experimental Data

The calculated expected average values of binding energy for curcumin and paclitaxel are -6.2 ± 0.2 and -4.6 ± 0.3 kcal/mol, respectively; thereby indicating curcumin's stronger affinity to DTO-SA/5K nanospheres. This is consistent with the experimentally determined binding efficiency of 94% and 66% wt/wt for curcumin and paclitaxel, respectively (Table 2)

	Curcumin	Paclitaxel
Binding efficiency (experimental) , % wt/wt	94	66
Binding energy (calculated) , kcal/mol	-6.2±0.2	-4.6±0.3

Table2: Comparison between binding efficiency and binding energy for curcumin and paclitaxel

3.3 Physical Interactions

As shown in Figure 4, in all four cases, the binding position of curcumin and paclitaxel are inside and at the interface of the nanosphere's core, respectively. The bulkier conformation of paclitaxel, 17 Å diameter and 2 internal H-bonds, does not allow its penetration inside the core of the oligo (DTO-SA). The smaller size of curcumin, 5 Å diameter, and its chemical similarity to the oligo(DTO-SA) unit highly contribute to stronger binding interactions and better distribution within the nanosphere core.

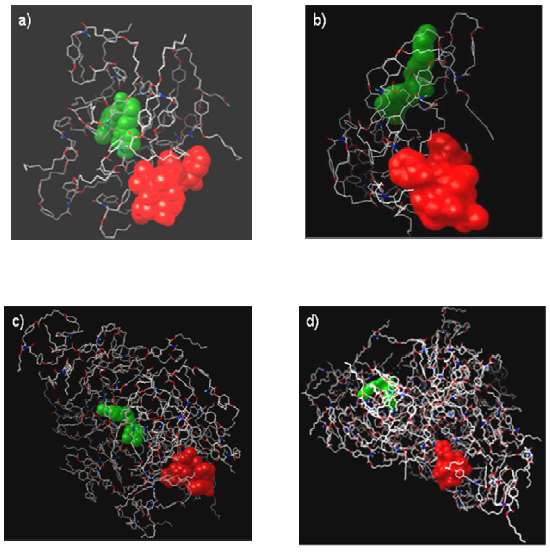

Figure 4: Poses of curcumin (green) and paclitaxel (red) docked in a) 1 strand, b) 2 strands, c) 4 strands and d) 8 strands of 11 repeat units of (DTO-Suberate) core.

Curcumin's stronger affinity to this particular polymer composition may be attributed to two H-bond interactions with DTO-SA and four π-π interactions with the benzene rings of same unit. Paclitaxel has only one H-bond and only two possible π-π interactions. These fewer interactions and much bulkier conformation are the possible explanation of the interface binding of paclitaxel as compared to inside-the-nanosphere's core binding and stronger interactions of curcumin.

4 CONCLUSIONS

A model for predicting binding of drugs to polymeric nanospheres was developed based upon Molecular Dynamics simulations and docking calculations. The model predicts correctly the relative binding efficiency of two different drugs to DTO-SA strands, as measured experimentally for DTO-SA/5K nanospheres. These preliminary results demonstrate that the proposed model can accurately predict the relative binding affinity of drugs in tyrosine-derived nanospheres even if a small part of the nanosphere was simulated.

The proposed method has the potential to become an important step in prescreening studies. The computational approach can accelerate the discovery of suitable polymers for specific drug delivery systems without the need to synthesize the polymers first. In this way the cost of development can be reduced.

Current research focuses on extending the model to additional drugs and polymers, as well as predicting the stability and release based on the physical characteristics of the system.

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