International Journal of Drug Delivery 7 (2015) 27-31
http://www.arjournals.org/index.php/ijdd/index

Original Research Article

ISSN: 0975-0215

Insilico modeling of chitosan as a drug delivery system

Ann Elizabeth Silviya[1], Kavitha G[2,3], K Narayanan Kutty[3] , Krishnan Namboori PK[4]*

*Corresponding author:

Krishnan Namboori PK

[1]Department of ECE, AMRITA Vishwa Vidyapeetham, Coimbatore-641 112
[2]Research and development centre, Bharathiar University, Coimbatore-641 046
[3]Department of Physics, AMRITA Vishwa Vidyapeetham, Amritapuri, Kollam-690525
[4]Computational Chemistry Research Group, AMRITA Vishwa Vidyapeetham, Coimbatore-641 112.

Abstract

Computational modeling of polymeric nanoparticles as drug carriers have been extensively studied due to their varied functionalities, tunable structures and the capability of controlled drug release. Nano particulate polymeric drug delivery systems enable a cell specific targeting with negligible side effects and drug release based on change in physiological conditions. Eight common polymers are modeled and the various properties have been predicted. ADMET, QSAR, thermodynamic and electronic properties have been predicted and compared using SAR as well as quantum mechanical density functional methods. Comparison of the predicted properties suggests that chitosan, which is a natural polymer and has some advantages over others is a promising drug carrier candidate for tumor.

Keywords: Drug delivery systems, chitosan, QSAR, quantum mechanical modeling

Introduction

Drug delivery systems (DDS) have been developed to carry the drugs to specific targets,especially to tumor sites without being exposed to other normal tissues or organs. The administrated drug may interact with the biomolecules that they pass through and may damage the normal cells also [1]. Moreover, rapid clearance from the bloodstream and the inability to cross certain membrane barriers are some additional problems faced by the drug molecules. This may lead into a decrease in bioavailability, limit the efficacy and leave few tumor cells from not exposing to the entire dose. A proper drug delivery system may overcome the difficulties and prevent the drug from rapid clearance and improve the availability at the target site. The drug carrier properties[2] amounting to its efficiency include solubility, stability, molecular weight, molecular volume, interaction with drug molecules, charging and discharging of drugs etc. The drug carriers should be stable to biological fluids, free from rapid degradation and clearance from the bloodstream and should be biocompatible and non-toxic.2 The design of an efficient drug carrier system depends on several factors like drug-carrier interaction, transport of drug molecules through the body to the desired site and the drug release profile. The development of such systems mainly aims at delivering drugs to specific target cells, necessitating biological efficiency and smartness. With the outburst of nano-systems, a number of efficient novel drug delivery systems have entered into the scene. Polymeric nanoparticles are advantageous [3,4] systems because of their varied and efficient properties like biocompatibility, increased efficacy and capability of controlled drug release. Proper optimization of the drug carrier system for each drug is a time consuming and difficult task. Moreover, in most cases, the suggested systems fail to work properly in the biological real environments, necessitating a proper designing phase before the systems are really developed. Computational modeling and simulation may provide a design phase for the 'Drug Delivery System' to be considered. The natural polymer chitosan has conquered the scene recently due to its biocompatibility, low toxicity, and biodegradability. The advanced development of chitosan nano systems has led to new smart drug delivery systems that release their drug payloads under varying environmental stimuli. Computational analysis of these nano-systems facilitates prediction of properties in the design phase itself helping in developing smart drug delivery systems. A preliminary computational analysis of common drug delivery systems to assess the efficiency of each system has been taken up in this work. Structure-Activity Relationship (SAR) studies and quantum mechanical modeling are two important methods in designing and developing a drug delivery system. The structure could be described by using descriptors or by physicochemical properties like logP, logD, solubility etc.

Major pharmacophoric attributes among them are ADMET descriptor [5] .The toxicity analysis has a very important role in the designing of a drug delivery system. The initial prediction of the pharmacokinetic properties helps in the optimization and testing of the most eligible candidates. Quantum mechanical modeling [6] helps in predicting electronic descriptors and can be used for studying the interactional efficiency of the molecules with the drug delivery systems. DFT computational technique is an efficient quantum mechanical level computation used to investigate the structural and electronic properties of molecules, materials and defects. In this manuscript, eight common drug delivery materials have been taken and compared their various properties using SAR studies and quantum mechanical modeling.

Materials and Methods

Common drug delivery systems targeting tumor cells, chitosan, oxyethylene, alkylcyanoacrylate, hydroxy-ethyl-methacrylate, isopropyl-acrylamide, vinyl pyrrolidone, Poly Lactic Acid-Poly Ethylene Glycol (PLA-PEG) and polylactic-co-glycolic acid (PLGA) have been taken for the analysis. The structures of molecules have been optimized within Hartree-Fock (HF)[7] level with 6-31G* basis set.

Quantum mechanical modeling

The optimized structures are further subjected to modeling in the DFT/B3LYP level using the same basis set. Thermodynamic properties such as free energy change (ΔG), enthalpy change (ΔH) and entropy change (ΔS) and electronic properties such as dipole moment, HOMO and 3 LUMO have been generated (Tables I).

Structure activity relationship (SAR) studies

Drug delivery related properties, pharmacokinetic and pharmacodynamic properties of the systems such as volume, mass, log *P*, log *D*, log *X* (where *P* -partition coefficient, *D* – distribution coefficient and *X* -solubility), absorption and hepatotoxicity have been generated using 'structure activity relationship-SAR' approach (Table II). Variations in logD values with pH have also been found computationally using Associative Neural Network (ASNN) algorithm which is a combination of feed-forward neural network and K- nearest neighbor method (Table III).

Results and Discussion

Quantum mechanical modeling

The modeling of all the selected polymers (Figure 1) generates properties such as changes in entropy, enthalpy and free energy, dipole moment and HOMO and LUMO. Chitosan is found to be thermodynamically stable.

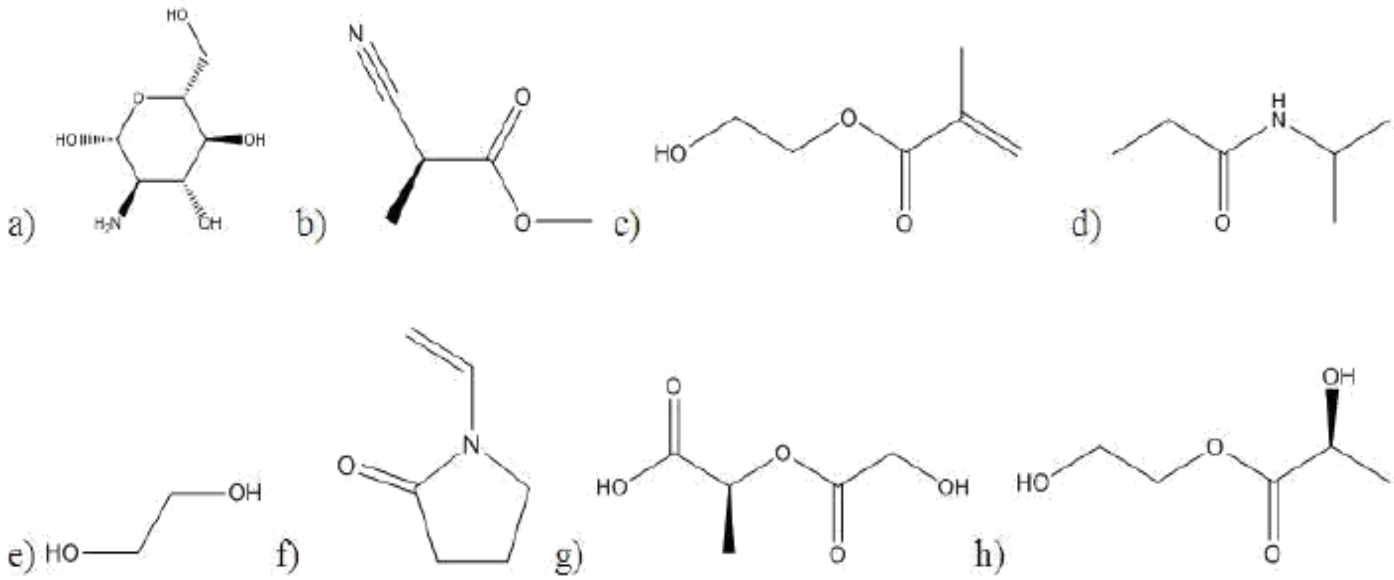

Figure1: a)chitosan b)alkylcyanoacrylate c) hydroxy ethyl methacrylate d) isopropyl acrylamidee) oxyethylene f) vinyl pyrolidone g) PLGA h) PLA-PEG

Table 1 displays the thermodynamic and electronic properties of the drug delivery systems. The negative values of ΔH and ΔG indicate that all the systems are thermodynamically stable and are spontaneous at all temperatures. The HOMO and LUMO energy levels help to predict the possibility for an interaction. Also the frontier orbital energy gap helps to determine the chemical reactivity and kinetic stability of a species. Oxy ethylene and chitosan shows the higher HOMOLUMO energy gap which shows their greater stability and low reactivity. Vinyl pyrrolidone shows the lowest energy gap and thus it shows a higher chance for reactivity. Dipole moment also gives the interaction ability of the molecule with the surrounding medium. The lower values of dipole moment for isopropylacrylamide, chitosan and oxyethylene show their lower ability for interaction and higher stability.

Table 1: Thermodynamic properties

Drug delivery system	ΔH (kJ/mol) $\times 10^4$	ΔS (J/mol^0)	ΔG (kJ/mol) $\times 10^4$	Dipole Moment (Debye)	HOMO (eV)	LUMO (eV)
Chitosan	-155.39	428.74	-155.40	2.85	-6.27	1.31
Alkylcyanoacrylate	-104.96	370.65	-104.98	5.44	-8.08	-1.15
Hydroxy ethyl methacrylate	-120.81	378.8	-120.82	4.15	-7.31	-1.33
Isopropylacrylamide	-96.15	389.26	-96.16	2.02	-6.28	-0.86
Oxyethylene	-60.43	301.8	-60.44	2.66	-7.22	1.91
Vinyl pyrrolidone	-95.42	366.25	-95.43	10.11	-3.48	-0.66
PLGA	-159.41	386.16	-159.42	3.43	-7.49	-1.26
PLA-PEG	-130.56	402.96	-130.57	4.55	-7.39	-0.71

SAR analysis

ADMET descriptors and physicochemical properties of the drug carriers are given in Table 2. It is very clear that all the systems are nontoxic in nature.

Table 2: ADMET descriptors& physicochemical properties

Drug delivery system	Absorption Level	Hepatotoxicity	LogS	Volume (A^3)	Weight (amu)	LogP
Chitosan	3	0	-0.38	155.31	163.173	-2.68
Alkylcyanoacrylate	0	0	0.19	120.47	113.116	0.42
Hydroxy ethyl - methacrylate	0	0	0.098	141.15	130.143	0.62
Isopropylacrylamide	0	0	-0.18	139.35	115.176	0.67
Oxyethylene	1	0	-1.1	66.58	62.068	-1.21
Vinyl pyrrolidone	1	0	0.58	120.11	111.144	0.15
PLGA	0	0	-0.26	137.15	148.114	-0.85
PLA-PEG	0	0	-0.48	134.63	134.131	-1.02

The predicted value of aqueous solubility shows that some drug carriers have low solubility values compared to others [8,9]. If the solubility is high, there is a chance for the carrier to disintegrate before reaching the target and release the drug molecule anywhere else. This may affect the bioavailability of drug molecule near the target. But the drug carriers with low solubility values such as PLA-PEG, chitosan and PLGA are stable towards dissolution. The log X values of all the drug delivery systems are included in Figure 2.

LogP value is a measure of lipophilicity of the compound [10]. From Table I, the log P (-2.62) value of chitosan [11] supports the molecule to be more dispersed in water than in lipophilic medium. This accounts for its low absorption value. The dissociation rates at different pH values for chitosan have been included in Table 3. The hydrolysis and dissociation of chitosan in acidic and alkaline media can be attributed on the basis of this variation.

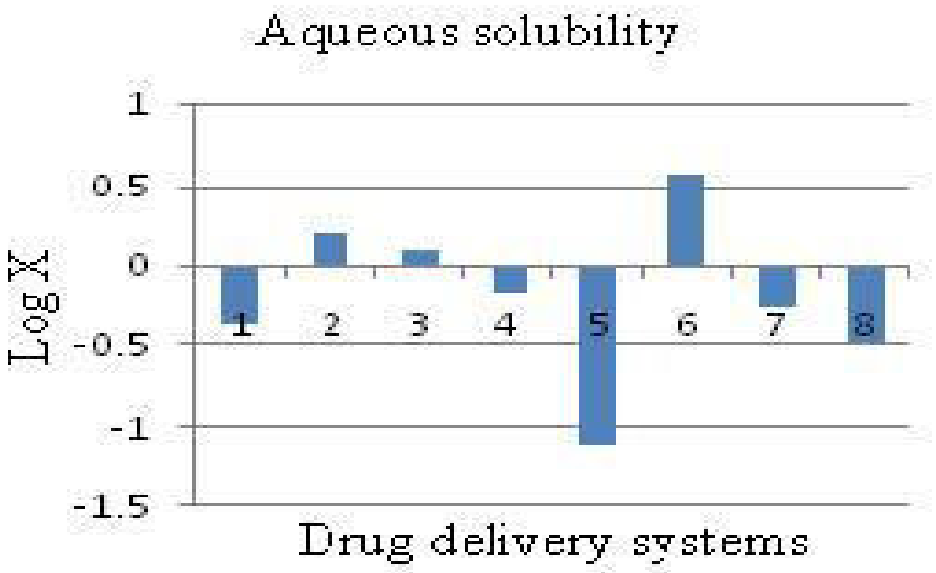

Figure 2: Aqueous solubility; 1-chitosan 2-alkylcyanoacrylate 3- hydroxy ethyl methacrylate4- isopropyl acrylamide 5- oxyethylene 6- vinyl pyrolidone 7- PLGA 8- PLA-PEG

Table 3: pH versus logD

pH	logD							
	chitosan	oxyethylene	alkylcyano-acrylate	hydroxy-ethyl methacrylate	isopropyl-acrylamide	vinyl pyrrolidone	PLA-PEG	PLGA
7.4	-4.08	-1.21	0.42	0.62	0.67	0.15	-1.02	-4.73
0	-5.71	-1.21	0.42	0.62	0.55	0.15	-1.02	-1.27
1	-5.71	-1.21	0.42	0.62	0.65	0.15	-1.02	-1.27
2	-5.71	-1.21	0.42	0.62	0.67	0.15	-1.02	-1.3
3	-5.71	-1.21	0.42	0.62	0.67	0.15	-1.02	-1.54
4	-5.7	-1.21	0.42	0.62	0.67	0.15	-1.02	-2.25
5	-5.64	-1.21	0.42	0.62	0.67	0.15	-1.02	-3.2
6	-5.27	-1.21	0.42	0.62	0.67	0.15	-1.02	-4.1
7	-4.45	-1.21	0.42	0.62	0.67	0.15	-1.02	-4.65
8	-3.53	-1.21	0.42	0.62	0.67	0.15	-1.02	-4.78
9	-2.89	-1.21	0.42	0.62	0.67	0.15	-1.02	-4.79
10	-2.7	-1.21	0.42	0.62	0.67	0.15	-1.02	-4.8
11	-2.68	-1.21	0.42	0.62	0.67	0.15	-1.02	-4.8
12	-2.72	-1.21	0.41	0.62	0.67	0.15	-1.06	-4.83
13	-3.02	-1.22	0.39	0.61	0.67	0.15	-1.32	-5.09
14	-3.97	-1.27	0.18	0.58	0.67	0.15	-2.09	-5.82

In tumor sites, the pH will be less and will be acidic in nature. The chitosan carrier will dissociate in this lower pH, leading into discharge of the drug near the target. PLGA is another monomer which shows a noticeable change in the logD values. But, PLGA is a synthetic polymer which gets separated to glucolic acid and lactic acid with change in pH. Chitosan hydrolyzes to glucose which is an energy provider. This makes the drug carrier using chitosan more favorable. The pH versus logD graph for chitosan is given in Figure 3.

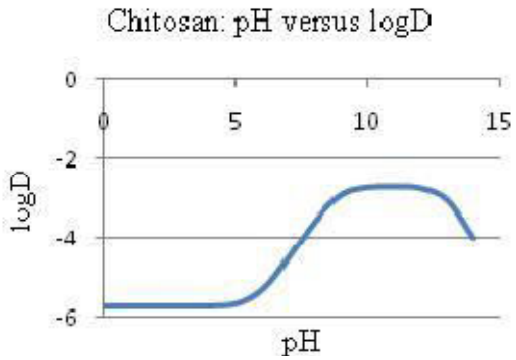

Figure 3: pH versus logD graph of chitosan

Conclusions

In silico prediction of molecular, QSAR, thermodynamic and ADMET properties of eight different monomers have been done in this paper. The properties of all the common drug carriers were compared and found that chitosan is a good candidate to be used as a drug carrier for tumor. A low solubility of the compound under normal body pH prevents the possibility for the carrier to discharge the drugs anywhere else. The hydrolysis of Chitosan is found to be pH dependent and it supports the possibility for discharge near the tumor target.

Abbreviations

ADMET – Absorption, Distribution, Metabolism, Elimination and Toxicity
QSAR – Quantitative Structure Activity Relationship
DDS – Drug Delivery System
DFT – Density Functional Theory
HOMO – Highest Occupied Molecular Orbital
LUMO – Lowest Unoccupied Molecular Orbital

References

[1]. Zhang et al. Design of Nanoparticles as Drug Carriers for Cancer Therapy.Cancer Genomics and Proteomics.2006; 3: 147–158.

[2]. Agnieszka Z. Wilczewska et al. Nanoparticles as drug delivery systems.Pharmacol.Reports.2012; 64: 1020–1037.

[3]. Mostafavi SH, Jayachandra Babu R. Nano-Sized Drug Delivery. J Mol Pharm Org. Process Res. 2013; 1(4): 1–2.

[4]. Sanjeeb K Sahoo, VinodLabhasetwar. Nanoparticle Interface:An Important Determination Nanoparticle-Mediated Drug/ Gene Delivery. In: Nanoparticle Technology for drug delivery. New York:Taylor & Francis Group; 2006. p. 139-154.

[5]. van de Waterbeemd H, Gifford E. Admet InSilico Modeling : Towards Prediction Paradise?.Nat Rev Drug Discov. 2003; 2(3): 192–204.

[6]. Ramachandran KI, Deepa G, Krishnan Namboori PK. The Modeling of Molecules through Computational Methods. In: Computational Chemistry and Molecular Modeling- Principles and Applications. Germany: Springer International; 2008; p. 229-274.

[7]. Malbouisson LAC et al. Optimization of Geometry at Hartree-Fock Level Using the Generalized Simulated Annealing. Applied Mathematics.2012; 2: 1526-1531.

[8]. Wang J, Hou T. Recent Advances on Aqueous Solubility Prediction. Comb Chem High Throughput Screen. 2011; 14(5):1-11.

[9]. James L. McDonagh et al. Uniting Cheminformatics and Chemical Theory To Predict the Intrinsic Aqueous Solubility of Crystalline Drug like Molecules. J. Chem. Inf. Model. 2013; 54(3): 844-856.

[10]. Kujawski J, Popielarska H, Myka A, Drabi ska B, Bernard MK. The log P Parameter as a Molecular Descriptor in the Computer-aided Drug Design – an Overview. Comput. Methods Sci. Technol. 2012; 18(2): 81–88.

[11]. Park JH, Saravanakumar G, Kim K, Kwon IC. Targeted delivery of low molecular drugs using chitosan and its derivatives. Adv. Drug Deliv. Rev. 2010; 62(1): 28–41.

[12]. Kean T, Thanou M. Biodegradation, biodistribution and toxicity of chitosan. Adv Drug Deliv Rev. 2010; 62(1): 3–11.