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International Journal of Current Research
Vol. 7, Issue, 06, pp.16840-16843, June, 2015

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

EFFICIENCY OF CHITOSAN DRUG DELIVERY SYSTEM-A COMPUTATIONAL ANALYSIS

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ARTICLE INFO

Article History:
Received 20th March, 2015
Received in revised form
23rd April, 2015
Accepted 24th May, 2015
Published online 27th June, 2015

Key words:

Chitosan, Modeling and simulation,
Drug delivery system, Anticancer drugs.

ABSTRACT

The natural polysaccharide chitosan has been extensively studied for predicting its efficiency as drug delivery systems for tumor. The 'smartness' of chitosan to release drug molecules specifically near to the tumor sites; makes it different from other drug carriers. The computational modeling and simulation technique has been adopted to predict the efficiency of the drug delivery system with different anti-cancer drugs. Interaction profile, stability profile, surface profile, potential profile and drug-release profile have been studied. The results highlight the efficiency of chitosan in using as a drug delivery system for anticancer drugs.

***Citation*:** Ann Elizabeth Silviya, Kavitha, G., Narayanan Kutty, K. and Krishnan Namboori, P. K. 2015. "Efficiency of Chitosan drug delivery system-A computational analysis", *International Journal of Current Research*, 7, (6), 16840-16843.

INTRODUCTION

Delivering the drug molecule to the specific site is a vital issue in many of the treatment methodologies, especially in cancer treatment. In most cases, the drugs will not give the desired therapeutic action and create undesirable side effects or may result in poor bioavailability. Delivering these drugs by using biocompatible nano drug delivery systems is a promising method to avoid these limitations and to obtain efficient results (Liu *et al*., 2012). The development of polymeric drug carriers is now in active research and has got several promising advantages over other delivery systems. The researches suggest that polymeric drug delivery systems help in 'site specific' targeting and discharge of drugs and thereby reducing the side effects (Vilar *et al*., 2012). The biocompatible and biodegradable polysaccharides like chitosan are found to be biologically smart in delivering drug molecules to the specific target site. The designing of drug carriers to the specific target for the specific drug molecule requires much preliminary analysis. Normally, the designing phase will be set up with modern computational techniques such as molecular modeling, interactional studies, simulation, potential analysis and complementarity analysis.

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The major properties to be taken care of while designing a proper drug delivery system will be the interaction between the drug molecules and the drug delivery system, stability of the system, potential or capacity of the system in effective drug delivery, the surface interaction between the molecules, toxicity and bio-compatibility and the drug release efficiency of the system (Bagheri *et al*., 2012). In this connection, chitosan has been considered as a potential drug delivery system, as its hydrolysis product is glucose. Moreover, dissociation of chitosan and discharge of drug from the drug delivery system occur only at a low pH which favors the use of chitosan as a drug carrier to the tumor cells.

The interaction between the polymeric nanoparticle and the drug molecule has an important role in deciding the properties of the drug delivery systems. Binding energy represents the most distinctive contribution to the receptor – ligand interaction affinity. The prediction of the time evolved behavior of a system is another important property to be looked into and can be studied through 'molecular dynamics (MD)' simulation (Ramachandran *et al*., 2008). It helps in predicting the properties like stability of the molecules, binding probabilities and the energy dependence at each instance of time during the simulation process.

The electrostatic potential maps are helpful in the visualization of the molecular charge distribution and to determine the various interactions between molecules (Ahmed *et al*., 2013). Since it is a complicated task to predict the interaction of each electron, computational calculations will help to find the net charge and the calculations can be simplified to a certain extend. The interaction/reactive sites can be predicted by plotting the potential maps and calculating the potential energy at each region.

The surface analysis gives an additional scope of knowledge to the drug – carrier binding evaluation. The study of adsorption isotherms helps in the successful design of an adsorption system (Ng *et al*., 2003). The ion transport across the cell membrane is another important mechanism in maintaining the ionic composition in the cells and has great importance in pharmaceutical research. It helps to predict the diffusion of drug across the cell membrane. The 'Monte Carlo' simulation techniques can be used to study the stability of 'drug-drug delivery system' complexes. The present manuscript gives way to prediction of efficiency of chitosan drug delivery system with the help of these computational techniques. The present analysis introduces a systematic designing phase for predicting the efficiency of drug delivery system. This emphasizes the need for "Computer Aided Drug Delivery Systems". The various factors to be considered while designing a drug delivery system have been clearly pointed out.

MATERIALS AND METHODS

Chitosan polymer and ten anti cancer drugs, viz. *bexarotene, methadone, flavopiridol, erlotinib, lapatinib, gemcitabine, pemetrexed, tretinoin, vinorelbine,* and *cisplatin* have been taken for investigation. The drug – polymer complexes are generated by allowing them to establish secondary interactions (Jay *et al*., 2003). The structures of both the drug-polymer complexes and the individual molecules are then structurally optimized within the molecular mechanics level of computation using Compass forcefield until they are converged. These input structures have been used for further analysis.

To study the interaction profile of the drug-carrier complexes, binding energy has been computed. An atom based simulation technique is used with an energy bin width of 0.2kcal/mol at 298K temperature within the CHARMm forcefield using the 'Blends' module of the Accelrys Material Studio (M. Subashini *et al*., 2011). The Flory-Huggins model along with molecular simulation has been used to predict the binding energy between chitosan and drug molecules. The stability profile has been investigated by studying the time evolved and temperature evolved behavior of the molecules within the NVE ensemble. The drug – polymer complex has been subjected to Molecular Dynamics (MD) simulation with MM+ forcefield (Krishnan Namboori *et al*., 2010). The simulation was made to run at constant temperature of 310K with 1000 steps and 0.001ps step size. The simulations have been characterized with the help of kinetic energy, potential energy and the total energy at different time steps. Electrostatic potential maps of poly-chitosan and the individual drug molecules have been generated in the quantum mechanical Hartree – Fock level of computation with 6-31G* as the basis set.

Surface profile of the drug-carrier complexes has been predicted using the sorption algorithm of the Material Studio. The adsorption isotherms have been generated and the calculations have been done at a constant temperature of 298K with Universal forcefield and within 50 sample intervals. The adsorption isotherm graphs are generated to study the type of adsorption of the drug molecules with chitosan polymer.

All the ten polymer – drug complexes have been subjected to Monte Carlo simulation to study the drug release properties using the BioMoca suit of NanoHub, upto a membrane potential of 240mV and a time step of 10fs. The radius of the membrane pore has been adjusted as $6A^0$.

RESULTS AND DISCUSSION

One of the basic methods to study the interaction profile is to predict the binding energy between the drug and chitosan polymer. The binding energy of drug – polymer complex is the difference in the energies of unbound and bound molecules (S. Hamedani *et al*., 2014). The results are given in Table 1. A forcefield based approach is utilized here to find the binding energy which is a sum of Van der Waals, electrostatic and hydrogen bonding contributions. From the table, it is clear that all the ten drugs are having a negative binding energy with chitosan and are thermodynamically supportive. However, the low interaction supports for the possibility of weak biomolecular interactions, a characteristic requirement of drug delivery systems.

Table 1. MD simulation results of chitosan-drug complexes

S. No.	Name of Drugs	Potential Energy (kcal/mol)	Kinetic Energy (kcal/mol)	Total Energy (kcal/mol)	Time (ps)	Binding Energy (kcal/mol)
1	*Bexarotene*	373.23	230.48	603.71	0.668	-2.608
2	*Methadone*	408.58	239.24	647.82	0.791	-2.378
3	*Flavopiridol*	396.86	230.46	627.32	0.702	-2.744
4	*Erlotinib*	399.24	245.11	644.34	0.693	-2.534
5	*Lapatinib*	442.74	264	706.74	0.618	-2.986
6	*Gemcitabine*	355.5	214.48	569.99	0.809	-2.347
7	*Pemetrexed*	445.41	267.99	713.4	0.95	-3.005
8	*Tretinoin*	386.24	236.7	622.94	0.679	-2.526
9	*Vinorelbine*	560.21	298.4	858.6	0.617	-2.973
10	*Cisplatin*	304.84	193.44	498.3	0.864	-1.299

The time evolved and temperature evolved behavior of the drug-carrier complexes have been studied using MD simulation (Discher *et al*., 2007) and the corresponding results are included in Table1. All the molecules are found to be converged fast and are not dissociated during the simulation process. The drug *pemetrexed(0.95ps), cisplatin(0.864ps)* and *gemcitabine(0.809ps)*require more time to attain stability with chitosan whereas *vinorelbine(0.617ps)* and *lapatinib(0.618ps)* attain stability at a faster rate.

The secondary interactions up to a distance of $3A^0$ have been considered in the computations and charge distribution complementarity has been maintained to the maximum possible level to ensure maximum biomolecular interactions. It has been found that in the chitosan-drug complexes, maximum complementarity has been maintained supporting prominent weak interactions of the drug molecules with the carriers. The molecules allow both hydrophilic and lipophilic interactions.

The surface characteristics are one of the most important properties, contributing towards efficiency of any drug delivery system. The adsorption isotherms of chitosan polymer with ten anti-cancer drugs have been generated. The enthalpy of adsorption and the behavior of isotherms are favoring the process to be physisorption. The biomolecular interaction within the 'drug-drug delivery complex' can be studied through the isotherms. Among the drugs taken up for the analysis, variation of loading (L) with respect to pressure (P) (Fig. 1& Fig. 2) is found to be linear and in accordance with Henry's law for only *cisplatin,* suggesting the molecular interaction to be of non specific long range van der Waal's type. The hydrogen bonding sites present in *cisplatin* might have been made unavailable due to the 'pi-lone pair' interaction possible in the molecule. However, for other drug molecules, P-(P/L) isotherms (Fig.3) are found to be linear suggesting Langmuir behavior at low pressure and Freundlich at high pressure (Ahmad *et al*., 2010). These drug molecules may be adsorbed mainly due to the specific short range hydrogen bonding besides the possible van der Waal's interaction.

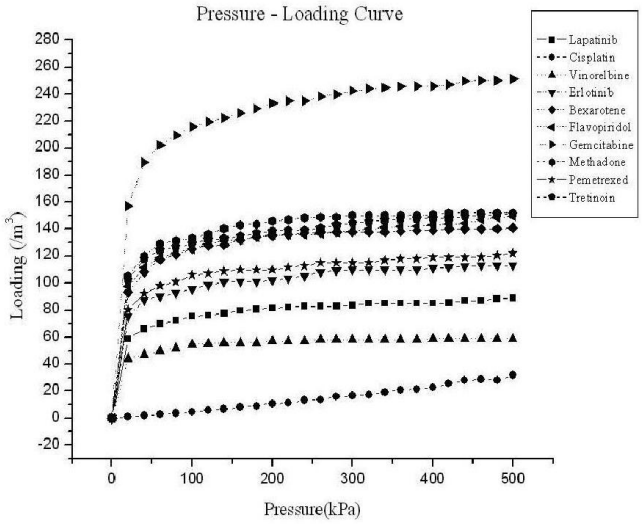

Fig. 1. Pressure versus loading curve

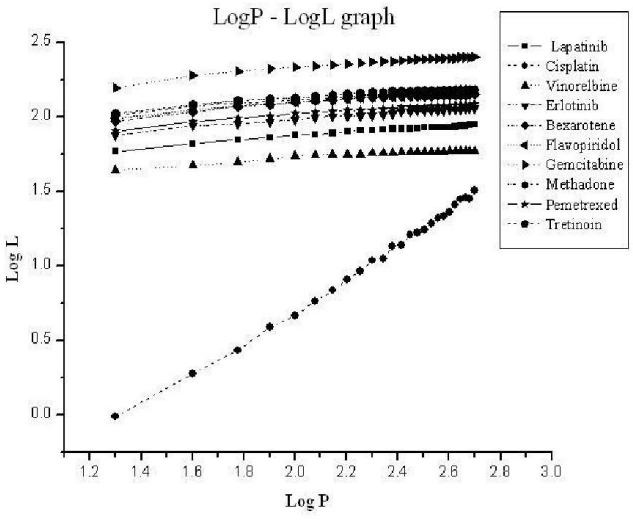

Fig.2. Log P versus logL graph

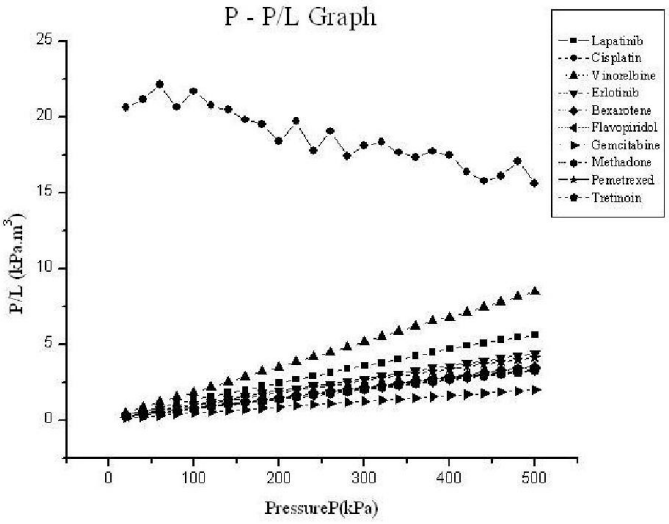

Fig. 3. P versus P/L graph

To study the possibility for passive diffusion within the potential head possible in the cell membrane, drug discharge studies have been done using Monte-Carlo simulation technique. The dissociation of drug-drug delivery system under different potentials and concentration gradients has been studied. The dissociation of the complex was possible only at a high potential of 200-280 mV, supporting the drug molecules to be stable under normal cellular conditions. However, the chitosan drug delivery system is found to be hydrolyzed at acidic pH conditions (Leo *et al*., 1996) supporting the drug to be discharged at the specific smart sites of tumor, which makes the drug delivery system highly promising and unique towards delivery of antitumor drug molecules.

Conclusion

Insilico modeling and simulation predicting the possibility of using chitosan polymer as a drug delivery system for ten anti-cancer drug molecules have been studied. The drug delivery system is found to be stable in the normal body conditions, while the discharge of drug molecules takes place near the tumor cells due to the variation in pH. This smartness in drug carrying property as well as drug delivery makes chitosan favorable for anticancer drugs. A computational strategy for comparing the efficiency of drug delivery systems has been set up by taking drug delivery property of chitosan with anticancer drug molecules.

REFERENCES

Ahmad S. *et al*. 2010. Insilico modeling of drug–polymer interactions for pharmaceutical formulations. *J. R. Soc. Interface*, 7: 423–433.

Ahmed A. *et al*. 2013. In Vivo Anti-Leukemia, Quantum Chemical Calculations and ADMET Investigations of Some Quaternary and Isothiouronium Surfactants. *Pharmaceuticals*, *6*: 634-649.

Bagheri *et al*. 2012. A Computational Method for Predicting the Solubility of Doxorubicin-PLLA-PEG.*Asian J Pharm Clin Res.*, 5(3):1-3.

Discher *et al*. 2007. Emerging Applications of Polymersomes in Delivery: from Molecular Dynamics to Shrinkage of Tumors. *ProgPolym Sci.,* 32(8-9): 838–857.

Hamedani S. *et al*. 2014. A DFT study of interaction of folic acid drug on functionalized single-walled Carbon Nanotubes. *J. Phys. Theor. Chem.*, 11 (1): 21-27.

Jay W. Ponder and David A. Case. 2003. Force Fields for Protein Simulations. *Advances in Protein Chemistry*, 66: 27-78.

Krishnan Namboori P. K. *et al*. Thermal analysis of Nanofluids using modeling and molecular dynamics simulation, *AIP Conference Proceedings*, Guwahati, 1276(2010), pp. 407-412.

Krishnan Namboori P. K. *et al*. 2013. Computational modeling of environmentally responsive hydrogels (ERH) for drug delivery system. *Current Computer-Aided Drug Design*, 9: 76-82.

Leo E. Gerweck and Kala Seetharaman. 1996. Cellular pH Gradient in Tumor versus Normal Tissue: Potential Exploitation for the Treatment of Cancer. *Cancer Research*, 56: 1194-1198.

Liu *et al*. 2012. Computational Modeling of Nanoparticle Targeted Drug Delivery, *Rev. Nanosci. Nanotechnol.*, 1(1): 66–83.

Ng J.C.Y. *et al*. 2003. Equilibrium studies for the sorption of lead from effluents using chitosan. *Chemosphere*, 52: 1021–1030.

Radhika R. *et al*. 2010. Insilico Analysis of Nano Polyamidoamine (PAMAM) Dendrimers for Cancer Drug Delivery. *Int. J. of Recent Trends in Engineering and Technology*, 4: 142-144.

Ramachandran K.I. 2008. The Modeling of Molecules through Computational Methods. In: Computational Chemistry and Molecular Modeling- Principles and Applications. Germany: Springer International, 229-274.

Subashini M. *et al*. 2011. Molecular dynamics simulation of drug uptake by polymer. *J Mol Model*, 17: 1141–1147.

Vilar *et al*. 2012. Polymers and Drug Delivery Systems. *Current Drug Delivery*, 9(4): 1-28.

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