International Journal of ChemTech Research
CODEN (USA): IJCRGG ISSN: 0974-4290
Vol.7, No.2, pp 700-705, 2014-2015

ICONN 2015 [4th -6th Feb 2015]
International Conference on Nanoscience and Nanotechnology-2015
SRM University, Chennai, India

Simulation and Modeling of Micelle as Nano-Drug Carrier for Targeting of Anticancer Drugs

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Abstract : The field of drug delivery is advancing rapidly. By controlling the precise level and location of a given drug in the body, side effects are reduced, doses are lowered, and new therapies are possible. Nonetheless, substantial challenges remain for delivering specific drugs into specific cells. Computational methods to predict the binding and dynamics between drug molecule and its carrier are increasingly desirable to minimize the investment in drug design and development. Significant progress in computational simulation is making it possible to understand the mechanism of drug delivery. By using Polymeric micelles composed of (Val, Leu, Ile) is simulated using Packmol (molecular modeling software) and the anti-cancer drugs such as (Anastrozole; Cyclophosphamide; Daunorubicin; Ixabepilone; Docetaxel) structures are incorporated into the simulated micelle and they are docked. Their binding affinity, stability and their pharmaceutical properties and used in the advancement in cancer therapy to achieve tumor targeting and site-specific drug release.
Keywords : Drug delivery, Molecular modelling, Polymeric micelles, tumour targeting

1. Introduction

Current chemotherapy of cancer is still facing a major problem of lack of selectivity of anticancer drugs toward neoplastic cells, thus cells of the bone marrow and gastrointestinal tract which are rapidly proliferating are getting affected by the cytotoxic action of these drugs. This results in a narrow therapeutic index of most anticancer drugs[1]. Along with this, increasing resistant types of tumors require high dose of anticancer drugs which in turn enhances the toxicity of treatment.By increasing the delivery of drug to the therapeutic sites and reducing delivery to the unwanted sites, an improved therapeutic index can be obtained with enhanced drug action at the therapeutic sites. Polymeric micelles possess several strong advantages because of their physicochemical properties for tumor targeting by passive targeting mechanism called enhanced permeability and retention (EPR) effect[2]. In addition, polymeric micelles can be engineered by means of ligand coupling or addition of pH-sensitive moieties according to the biological characteristics of the diseased site for active targeting. For targeting the tumor at the inaccessible sites, the drug should be administered by parenteral route. Pharmaceutical drug carriers carrying drug in plasma should possess properties such as biodegradability, small particle size, high loading capacity, prolonged circulation, and accumulation in required pathological site in the body[3]. All these properties are mostly executed by polymeric micelles.Poorly water soluble, hydrophobic agents are known to be associated with problems in therapeutic applications such as poor absorption and bioavailability, and drug aggregation-related complications such as embolism[4,5]. On the other hand, poor

solubility in water is associated with many drugs including anticancer drugs. Also, drugs should have hydrophobicity to penetrate a cell membrane and presence of hydrophobic group for sufficient affinity toward the target receptor[6,7]. To overcome these problems, amphiphilic copolymers are used to encapsulate poorly water-soluble anticancer drugs in polymeric micelles which have inner core made up of hydrophobic block of copolymer in which drug gets entrapped and outer shell of hydrophilic block of copolymer which reduces the interactions of drug with the outer aqueous environment keeping them stable. Also, the hydrophilic micelle corona keeps the polymeric micelle stable in plasma for longer duration and also prevents their opsonization and capture by reticuloendothelial system[9]. Polymeric micelles are very stable as having low critical micelle concentration (CMC) values comparative to surfactant micelles, as low as 10^{-6} M[8]. The purpose of this review is to provide a concise, yet detailed, introduction to the use of polymeric micelles as delivery agents [1].

Nanoparticle drug delivery systems present exciting opportunities for safer and more effective anti-cancer drug therapy. By engineering intelligent biomaterials for these applications, it is possible to develop platform technologies that can be used to target and destroy more cancer cells, and with greater specificity. Toxic chemotherapeutics given in their free form distribute broadly throughout the body, but by redirecting more of the drug dose towards tumour sites, reduced systemic side effects are expected, making anti-cancer treatment safer than conventional approaches.

2. Molecular Dynamics

Molecular dynamics simulation consists of obtaining initial coordinates for all the atoms of the system. For example, in order to run a simple simulation consisting of 300 water molecules with experimental density, we need the positions of the 300 molecules inside an adequately sized box. Furthermore, since molecular dynamics force fields contain repulsive terms that increase abruptly for short atom-to-atom distances, the distances between atoms from different molecules must be large enough so that repulsive potentials do not disrupt the simulations. Frequently, the instability and non-differentiability of the potential energy resulting from overlapping atoms is hard to overcome.For a simple system such as a water box, we can obtain an adequate configurations simply by ordering the molecules in a regular lattice. However, for slightly more complex systems such as a solvated peptide, regular configurations would almost certainly contain overlapping atoms. However, when the complexity of the system increases, the work for building a starting configuration may be very tedious.

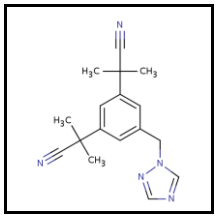
Building ordered molecular systems, such as micelles, double layers, or interfaces, require lots of trials, manipulation of files, small ad-hoc codes, etc., and, so, the very first steps of the simulation turn out to be quite cumbersome. Packmol creates an initial point for molecular dynamics simulations by packing molecules in defined regions of space. The packing guarantees that short range repulsive interactions do not disrupt the simulations. The great variety of types of spatial constraints that can be attributed to the molecules, or atoms within the molecules

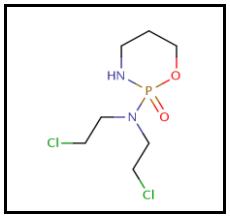
3.Results and Discussions

3.1 Retrieval of Drug Compounds from Drugbank

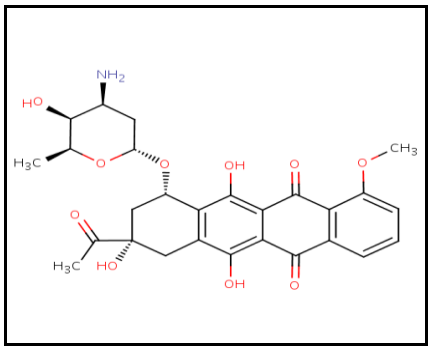
The DrugBank database is a unique bioinformatics and cheminformatics resource that combines detailed drug (i.e. chemical, pharmacological and pharmaceutical) data with comprehensive drug target (i.e. sequence, structure, and pathway) information.

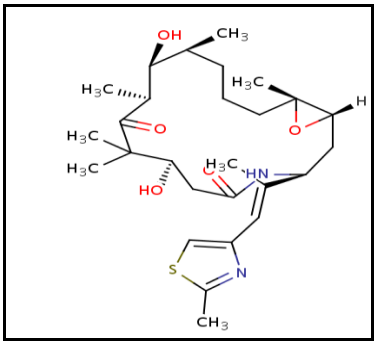
The database contains nearly 4800 drug entries including more than 1,350 FDA-approved small molecule drugs, 123 FDA-approved biotech (protein/peptide) drugs, 71 nutraceuticals and more than 3,243 experimental drugs. Additionally, more than 2,500 non-redundant protein (i.e. drug target) sequences are linked to these FDA approved drug entries. Each DrugCard entry contains more than 100 data fields with half of the information being devoted to drug/chemical data and the other half devoted to drug target or protein data.



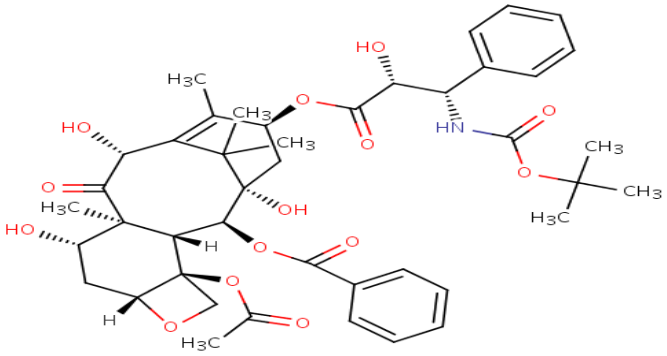


AnastrozoleCyclophosphamide





DaunorubicinIxabepilone



Docetaxel

Figure 1Thestructure of drugs like Anastrozole, Cyclophosphamide, Daunorubicin, Ixabepilone and Docetaxelwere retrieved from Drug Bank by specifying the common name of the drug in the search box provided.

3.2 Construction of Dipeptide

The structure of Boc-Val-Gln dipeptide was drawn using Chemsketch tool. Structure mode is used for drawing chemical structure. The structure of the elements are readily available in the chemsketch tool. Template window offers the structures of Alkaloids, carbohydrates, DNA/RNA, steroids and sugars. Using the template structures, the chemical structure of the above mentioned dipeptide was drawn. SMILES notations of the structure was generated using the 'Generate SMILES notation' option in Chemsketch.

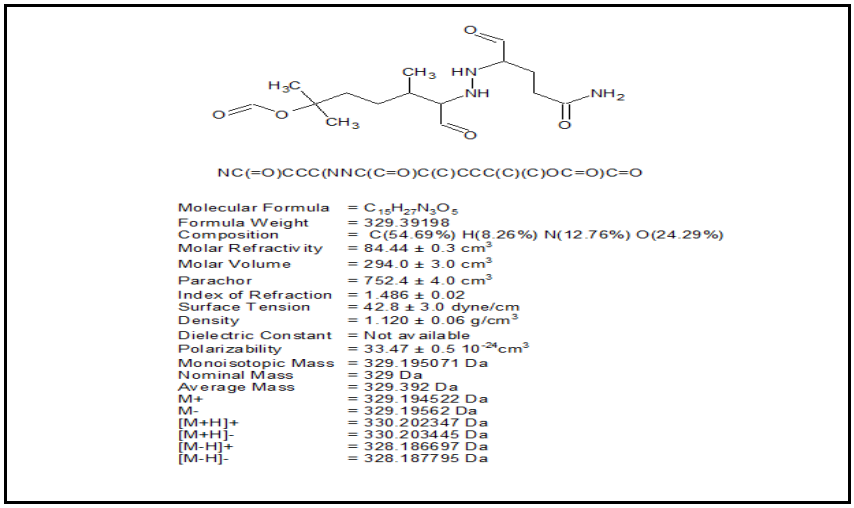


Figure 2- Constuction of dipeptide using chemsketch.

The chemical structures of Boc-Val-Gln group were drawn using Chemsketch and the SMILES notation was generated for structure. The SMILES notations were further submitted to ChemDB to retrieve 2D and 3D structures.

3.3 Conversion of Chemical Structures to 3D Format using Smi2depict

Smi2Depict is available in the ChemDatabase. It generates 2D images from the SMILES notation, from which the structure can be easily converted to 3D format. The SMILES notation of the dipeptide structure was provided as input for Smi2Depict. The obtained 2D format is converted to 3D format with the help of the options provided in Smi2Depict Generated 2D structure and SMILES notation

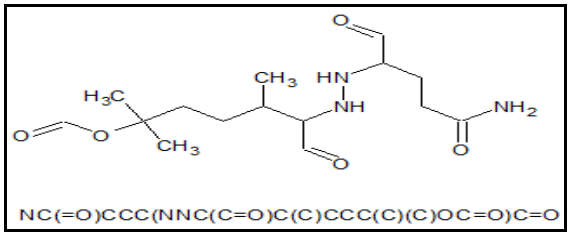
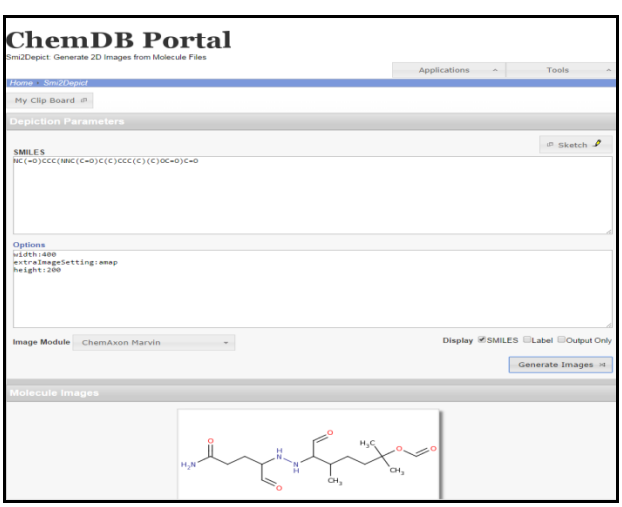


Figure 3-Boc-Val-GlnDipeptide(generated 2D structure with SMILES notation)



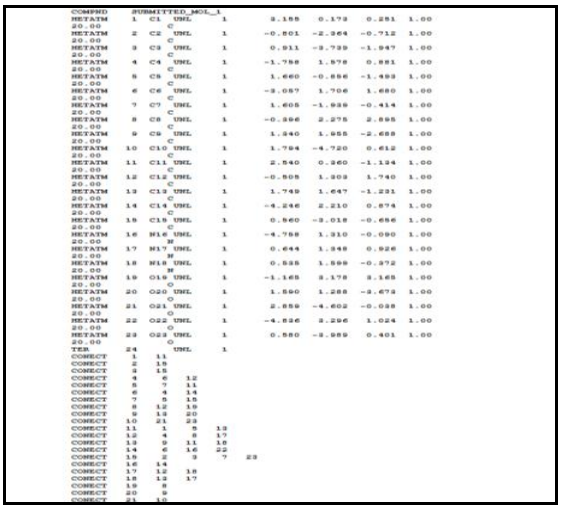


Figure 4-Boc-Val-GlnDipeptide(SMILES notations submitted at ChemDB)

The 3D structure of the dipeptide is given below in figure 5.

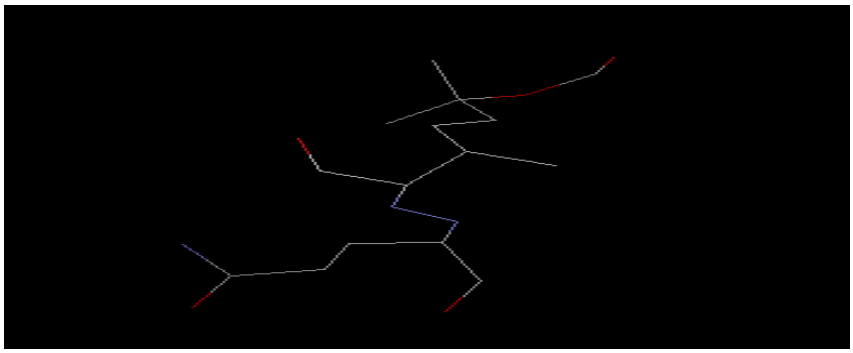


Figure 5-Boc-Val-GlnDipeptide(3D-pdb-file)

3.4 Construction of Micelle using Packmol

Packmol creates an initial point for molecular dynamics simulations by packing molecules in defined regions of space. The packing guarantees that short range repulsive interactions do not disrupt the simulations. The great variety of types of spatial constraints that can be attributed to the molecules, or atoms within the

molecules, makes it easy to create ordered systems, such as lamellar, spherical or tubular lipid layers. The micelle structure of the Boc-Val-Glnwas created using the packmol package. Which is shown as figure 6

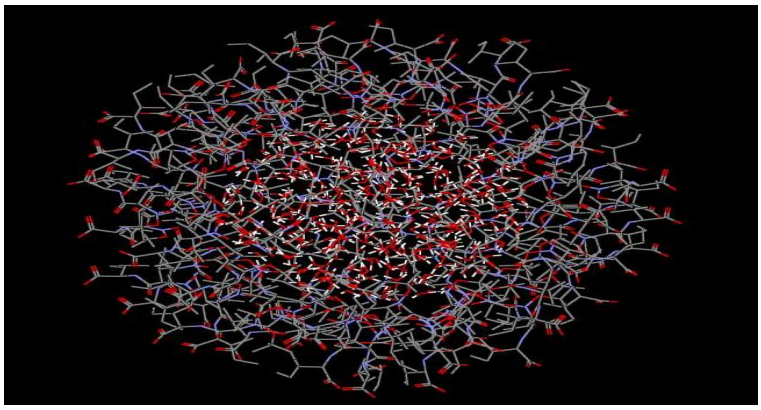


Figure 6-Micelle structure of the Boc-Val-Gln

3.5 Encapsulation of Drugs into the Micelle:

The micelle has been constructed again along with the drugs using the Packmol software. Here the drugs are encapsulated into the innercore of the micelles. The micelles along with the drugs are given below in figure 7.

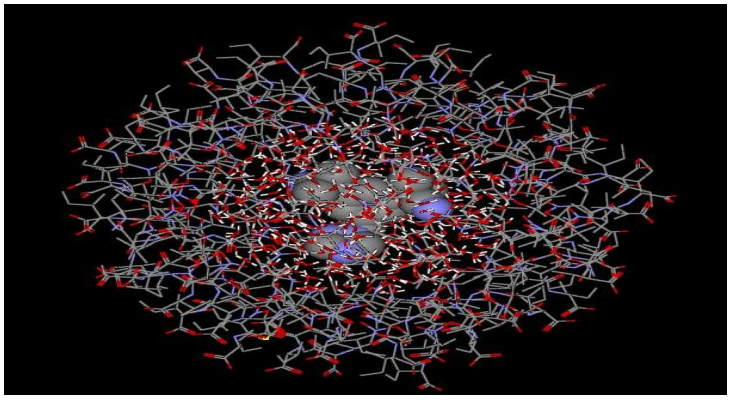


Figure 7-micelle with the drug incorporated at the core

4. Conclusion

The Micelles with an Aggregation number 69 was constructed with the dipeptide Boc-Val-Gln. The initial configuration was done using packmol package. As one of the application of micelles was to deliver the drug, So the drugs were searched in Drugbankbased upon inner volume of micelles and also based on the property and we have screened five different drug molecules (Anastrozole, Cyclophosphamide**,** Daunorubicin**,** Ixabepilone andDocetaxel) which has been encapsulated to the inner core of Micelles using Packmol package. Its energy has to be minimized for the stability of the molecular structure and their pharmacophore properties and ADMENT properties has to be analysed using (ALMOND and ALOGPS) for a novel carrier and used in the advancement in cancer therapy to achieve tumor targeting and site-specific drug release.

5. References

1. Monica, L., Adams, Afsaneh Lavasanifar, Glen, s., Kwon “Amphiphilic Block Copolymers for Drug Delivery” Division of Pharmaceutical Sciences, School of Pharmacy, University of Wisconsin–Madison
2. Caldorera-Moore, M., Guimard, N., Shi, L., Roy, K., Designer nanoparticles: incorporating size,shape and triggered release into nanoscale drug carriers. Expert Opin Drug Del 2010;7:479-495.

3. Aggarwal, P., Hall, J.B., McLeland, C.B., Dobrovolskaia, M.A., McNeil, S.E., Nanoparticle interaction with plasma proteins as it relates to particle biodistribution, biocompatibility andtherapeutic efficacy. Adv Drug Deliver Rev 2009;61:428-437.
4. Karyn Susana Ho., "Targeted drug delivery to breast cancer using polymeric nanoparticle micelles" Yokoyama, M., Svenson, S., Particulate drug carriers: Polymeric drug delivery, Oxford University press (Book) Volume 1. 2006;924:27-36
5. Gref, R., Minamitake, Y., Percocchia, M., Trubetskoy, V., Torchillin, V.P., Langer, R., Polymeric miscelles for targeted delivery. Science 1994;263:1600-9.
6. Fernandez, A.M., Van Derpoorten, K., Dasnois, L., Lebtahi, K., Dubois, V., Lobl, T.J., Carriers for particlulate drug delivery. J Med Chem 2001;44:3750-61.
7. Hageluken, A., Grunbaum, L., Numberg, B., Harhammer, R., Schunark, W., Scifert, R., Drug targeting with nanoparticles as carriers. BiochemPharmacol 1994;47:1789-96

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