# Investigation of Flutamide@Ethyleneimine as Drug Carrier by Nanocone and Nanotube Theoretically

***Nazar Ali, Zhila; Ahmadi, Sayed Ali*[+]; Ghazanfari, Dadkhoda; Sheikhhosseini, Enayatollah***

*Department of Chemistry, Kerman Branch, Islamic Azad University, Kerman, I.R. IRAN*

***Razavi, Razieh***

*Department of Chemistry, Faculty of Science, University of Jiroft, Jiroft, I.R. IRAN*

**ABSTRACT:** *Flutamide is used with a luteinizing hormone-releasing hormone agonist, a type of hormonal injections such as leuprolide, goserelin, or triptorelin to treat certain types of prostate cancer. Flutamide is in a class of medications called nonsteroidal antiandrogens. Ethyleneimine is used in polymerization products; as a monomer for polyethyleneimine; as a comonomer for polymers and in paper and textile chemicals, adhesives, and binders. This study applied ethyleneimine to modify Flutamide as an anti-cancer drug. Therefore, an investigation of the adsorption behavior and electronic properties of carbon nanotubes and nanocones against flutamide @ ethyleneimine was carried out by calculation of the density functional theory. The N atom of flutamide @ ethyleneimine helps its adsorption on the nanotubes and nanocones, showing adsorption energies of around - 30.1 and - 20.5 kcal/mol, correspondingly. Chemical activities of the nano complexes were specified through electronic parameters such as electronegativity, electron affinity, softness, and hardness. All calculated data obtained good behavior of flutamide @ ethyleneimine with nanotubes and nanocones adsorption as carriers.*

**KEYWORDS:** *Carbon nanotube; Carbon nanocone; Adsorption behavior; Electronic sensitivity; Density functional theory calculations.*

## INTRODUCTION

The rapid development of nanotechnology provides new prospects for solving the existing limitations in biomedicine. The increased number of researchers dedicated to using nanomaterials biotechnology and genetic engineering to diagnose, treat, and prevent diseases. Carbon NanoTubes (CNTs) were discovered in 1991 and shown to have certain unique physicochemical properties, attracting considerable interest in their application in various fields including drug delivery. The unique properties of CNTs such as ease of cellular uptake, high drug loading, andthermal ablation, among others, render them useful for cancer therapy. Ever since, there has been intense interest in allotropes of carbon due to their unique physical and chemical properties, emerging as promising candidates for multimodal drug delivery systems. They not only allow for the attachment of multiple copies of drug molecules but can also be equipped with targeting agents and stealth molecules to

***** *To whom correspondence should be addressed.*
*+ E-mail: ahmadi.iauk58@gmail.com*
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evade clearance by the immune system. Furthermore, they hold several potential advantages over other nano-sized delivery systems, such as an exceptionally high drug loading capacity due to their high surface area and the possibility for incorporating additional therapeutic and diagnostic moieties, either on the surface or in their inner cavity. In addition, they interact with cellular membranes in a unique way: some types of Carbon NanoTubes (CNTs) have been reported to enter mammalian cells by an endocytosis-independent, "needlelike" penetration mechanism, which allows for direct cytoplasmic delivery of therapeutic payloads. Carbon NanoTubes (CNTs) are allotropes of carbon with a cylindrical nanostructure. The discovery and subsequent widespread characterization of carbon nanotubes (CNTs) have opened up a class of materials with unexpected electrical, mechanical, and thermal properties. The research for polymeric drug delivery has been progressing for a long time since 1980's . A drug delivery system combines one or more traditional drug delivery systems with engineered technologies. The systems create the ability to specifically target points where a drug has been released in the body and/or the rate at which it has been released. Ethyleneimine is one of the drug carriers and the chemical, as well as physical behaviors of ethyleneimine, are determined by their amine group functionalities. Among organic molecules, ethyleneimine shows the greatest cationic charge density. An amine group makes up each third atom across a chain while every 6th nitrogen atom of each is protonated in the physiological state [1]. Such high charge densities facilitate interaction with phosphate groups in genetic materials, forming the toroidal complexes whose endocytosis takes place promptly by the cells [2, 3]. Accordingly, ethyleneimine has high efficiency in the delivery of oligonucleotides in vitro as well as in vivo [4] because of this special property. There are two various forms of linear and branched ethyleneimine [5]. The synthetic nonsteroid antiandrogen of 4-nitro-3-trifluoromethyl-isobutilanilide which is known as Flutamide (FLT) has applications in treating the early stages of prostate cancer. FLT facilitates controlling the development of cancerous cells as it jams the male hormone testosterone secretion [6]. The chemical formulation of FLT consists of the nitro group, which is significantly important in metabolism biological mechanisms. Pharmaceutical industries in India have recently paid considerable attention to the application of FLT to treat cancers [7]. Inorganic nanostructures such as nanocones, nanosheets, nano-chains, nanotubes, as well as nanoclusters are currently considered by researchers due to their unique stability in terms of thermal and chemical properties, along with their extraordinary mechanical as well as electronic features [8-28]. In the present work, nanocone and nanotube interaction parameters are calculated theoretically. Nanotubes and nanocones are used as drug carriers. The interaction of FLT- FLT-ethyleneimine with nanocones and nanotubes is examined using the DFT technique B3LYP/6-311 by Gaussian 03 software.

## COMPUTATIONAL METHOD

The framework of DFT in 6-311g basis sets were used to carry out full geometry optimization for equilibrium geometries(by Guassian03 software), overall energies, as well as electronic densities. The relation below was used to calculate the FLT@$E_{th}$ adsorption energies on nanocones and nanotubes through the site with the highest activity:

$$E_{ads} = E_{T(EFLT@Eth-NC/NT)} - \left(E_{TNC/NT} + E_{TFLT@Eth}\right) \quad (1)$$

In which, $E_T$($E_{FLT}$@$E_{th\text{-}NC/NT}$) indicates the FLT@$E_{th}$ overall energy adsorbed on nanocones and nanotubes, E($_{TNC/NT}$) and $E_{FLT}$, indicate the overall energies of nanocones and nanotubes and flutamide@Ethyleimine correspondingly. As the proposed frequencies are absent in the vibrational spectra of the structure under study, their stability is supported. The reactivity descriptors based on DFT were investigated using the theory of Frontier molecular orbital. The total molecular charge distribution was described by calculating the Molecular Electrostatic Potential (MEP) energies. Equations (2) through (5) were used based on the Koopmans theorem to calculate the chemical reactivity based on DFT along with the stability descriptors including chemical potential (μ), hardness (η), and softness (S) as well as electrophilicity (ω):

$$\mu = -\chi \quad (2)$$

$$\eta = \left(\frac{I - A}{2}\right) \quad (3)$$

$$S = \frac{1}{\eta} \quad (4)$$

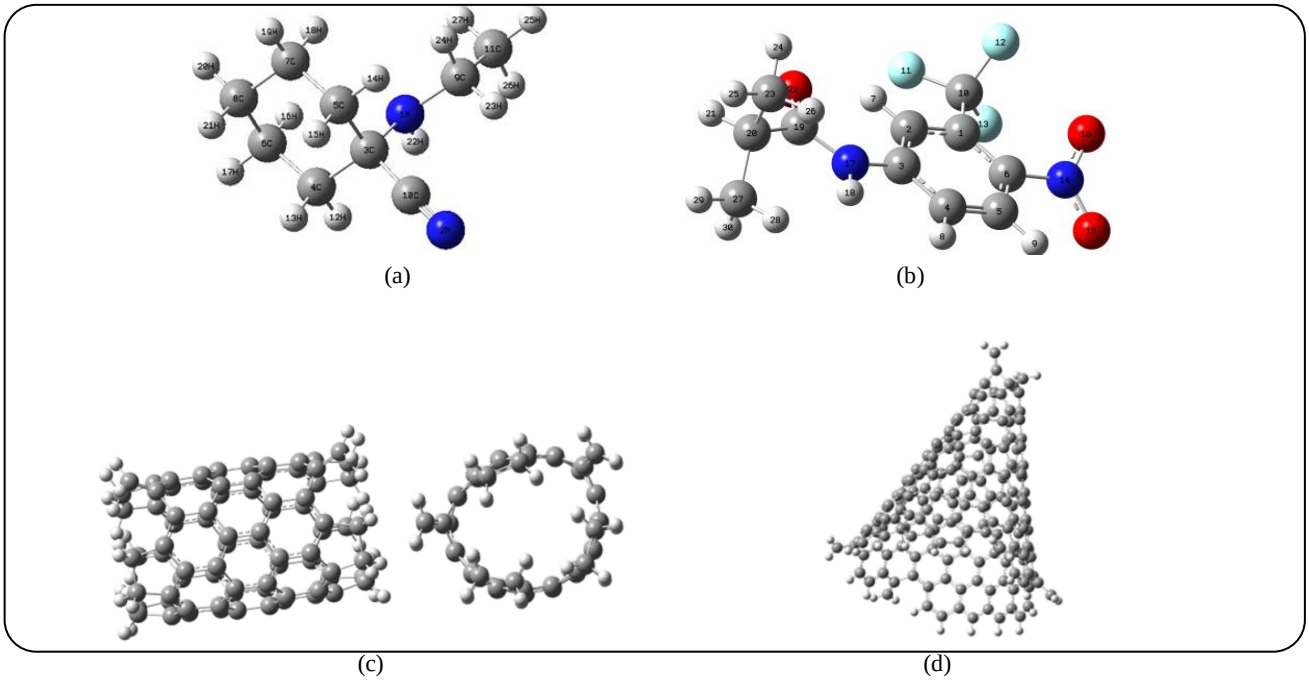


***Fig. 1: Geometry structure of all molecules Ethylamine(a), Flutamide (b), Nanotube(c), and Nanocone(d)).***

$$\omega = \left( \frac{\mu^2}{2\eta} \right) \quad (5)$$

In which μ, η, S, and ω show chemical potential, chemical hardness, global softness, and electrophilicity index, respectively.

## RESULTS AND DISCUSSION

Different potential primary geometries such as drug charge distribution near the surface of nanotubes and nanocones went under examination to identify complexes of nanotubes and nanocones that had stability (Fig. 1). The properties that make CNTs ideal drug carriers are multiple. CNTs have a high specific surface area per unit weight, offering enhanced loading capacity compared with conventional nanomaterials of spherical shape. They have been used for the delivery of several anticancer drugs, with doxorubicin (DOX) being the most extensively studied. The possibility of forming π–π interactions between DOX and the surface of CNTs makes loading simple and efficient; furthermore, the high surface area offered by CNTs allows for a high degree of loading that cannot be achieved by other carrier systems. Using a noncovalent loading mechanism means that loading is not limited to the type and number of functional groups present on the drug molecule and the carrier; moreover, it allows for the loading of other lipophilic aromatic compounds.

Very elegant, multifunctional, engineered CNT derivatives and conjugates for drug delivery have been extensively described in the literature. Constructs that combine drug-loading properties with enhanced biocompatibility, targeting ability, and imaging or tracking options have been developed to both exploit the positive and counteract the negative intrinsic properties of CNTs. However, the translational potential of nanomedicine so far has been achieved only by the simplest systems. Therefore, a paradigm shift is required; we need to move from sophisticated and elaborated ways of modifying CNTs to more simplified and flexible approaches. For example, favoring noncovalent modification could present an adaptable approach for the functionalization of different types of CNTs, and developing one-pot functionalization methods could reduce development time and cost. Furthermore, despite intense research on carbon nanotubes, there is still a wealth of unanswered questions about their interaction with the human body, more detailed and systematic studies need to be undertaken in this direction. Clinical applications are still not a reality however strategies to harvest the full potential of carbon nanotubes are continually invented,

***Table 1: Charge distribution of molecules/ B3LYP/6-311G.***

| FLT | Charge | Ethyeimine | Charge | NT | Charge | NC | Charge |
|---|---|---|---|---|---|---|---|
| C23 | -0.563 | C10 | -0.002 | C Head | -0.318 | C Head | -0.412 |
| C27 | -0.585 | N2 | -0.127 | C Wall | 0.021 | C wall | -0.13 |
| C19 | 0.678 | C3 | 0.014 | | -0.031 | | 0.009 |
| O22 | -0.596 | C5 | -0.307 | | | | -0.001 |
| N17 | -0.593 | C4 | -0.321 | | | | 0.002 |
| C6 | 0.085 | N1 | -0.562 | | | | -0.01 |
| C5 | -0.159 | C9 | -0.178 | | | | |
| N14 | 0.437 | C11 | -0.542 | | | | |
| F13 | -0.348 | | | | | | |
| C10 | 1.066 | | | | | | |
| O15 | -0.367 | | | | | | |

developed, and refined as testified by the wealth of literature regularly published by experts in various biomedical specialties.

According to Table 1, the atom charge shows a positive electrostatic potential, making it prone to nucleophilic attack. Ultimately, the site of complexes of nanotubes and nanocones, where molecule adsorption from O22, N17, and F heads on an O atom takes place, respectively, was predicted.

Table 1 indicates the relevant data, according to which stronger interaction can be observed for the drug from its side effect head with- 38.2 kcal/mol adsorption energy (interaction distance * 2.00 Å) compared to other sites. Based on calculations, the adsorption energies are around - 30.1 and - 22.5 kcal/mol, correspondingly. The entropic effect has led to fewer negative values for Gibbs free energies compared to the case of the adsorption energies, indicating a decrease in the entropy due to the adsorption process.

Every atom's charge distribution in the molecule indicates positive as well as negative sites through which the molecule can interact with others. The negative charge of C27, N17 makes them good donors in FLT. Accordingly, they play the role of active sites in which molecules interact. On the other hand, the positive charge of N14 and C10 makes them good receivers when molecules interact in FLT. N1, C5, and C11 are donors in
Eth. The charge of some carbon is positive and some negative in the NT wall;

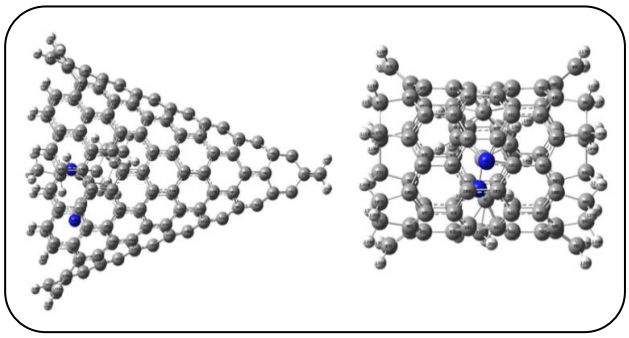

***Fig. 2: Complex of Drugs and NC –NT.***

however, their values are lower than the nanotube head charge. Thus, the nanotube head functions in molecule interactions. The same function was observed in NC again, leading to molecule interactions at NC and NT heads (Fig. 2).

Despite the drug sensitivity of the electronic characteristics of nano complexes, there is significantly large adsorption energy capable of inhibiting the process of desorption. Calculation of electronic parameters was performed according to Table 2 for a more detailed analysis of this matter.

The HOMO energy reflects the molecule's capability of electron donation and therefore the probability of electron donation by the molecule increases at higher values of $E_{HOMO}$. The LUMO energy reflects the molecule's capability to accept electrons and therefore the probability of electron acceptance by the molecule increases at lower values of $E_{LUMO}$. The gap in the

***Table 2: Molecular parameters of all compounds and complexes.***

| Molecular parameters | FLT | Ethyleimine | NT | NC | FLT-Ethy-NT | FLT-Ethy-NC |
|---|---|---|---|---|---|---|
| E HOMO | -0.24680 | -0.23834 | -0.14476 | -0.19838 | -0.11452 | -0.17889 |
| E LUMO | -0.02768 | +0.01914 | -0.08765 | -0.04190 | -0.08922 | -0.12655 |
| ΔE HOMO-LUMO | -0.21912 | -0.25748 | 0.05711 | -0.15648 | 0.0253 | 0.05234 |
| IP(ioniziation energy) | 0.24680 | +0.23834 | 0.14476 | 0.19838 | 0.11452 | 0.17889 |
| Electron affinity(EA) | 0.02768 | -0.01914 | 0.08765 | 0.04190 | 0.08922 | 0.12655 |
| Electronegativity(χ) | 0.1086 | 0.1096 | 0.116205 | 0.1385 | 0.10187 | 0.15272 |
| Chemical potential(μ) | -0.1086 | -0.1096 | -0.116205 | -0.1385 | -0.10187 | -0.15272 |
| Chemical softness(s) | 8.541281 | 7.7675935 | 35.0201365 | 10.685472 | 79.0513833 | 38.21169277 |
| Chemical hardness(η) | 0.1354 | 0.12874 | 0.028555 | 0.065421 | 0.032140 | 0.02617 |
| Global electrophilicitiyindex(ω) | 0.05214 | 0.0466527 | 0.2364489 | 0.1392425 | 0.4101777 | 0.4456132 |

molecule HOMO and LUMO energy levels have great importance since it acts as a function of the reactivity of the molecule. Ionization potential can be a fundamental description of the chemical reactivity of atoms and molecules high IP is associated with increased stability. Larger energy gaps are observed in hard molecules. Soft molecules show higher reactivity compared to hard molecules because of readily offer electrons to the acceptors. Description of the molecules' capability of accepting electrons can be carried out using the electrophilicity index.

As shown in Table 2, electron donation takes place from FLT to Eth, NT, and NC. Thus, it can start biological and chemical reactions. Besides, Eth donates in chemical reactions with NT and NC which function as better acceptors in chemical reactions. The data relating to the distribution of charges support the results. According to the energy band gap, FLT shows reactivity in chemical media. According to the electronic data of the complexes, the higher stability of the structure supports its function as the targeted carrier of nanostructures.

## CONCLUSIONS

DFT in order to turn the partial differential equations of the model into algebraic equations suitable for efficient implementation on computer calculations is used to investigate the FLT drug interaction with ETh nanotubes and nanocones. The B3LYP function was also used as a good basis set for optimizing and calculating the chemical parameters. According to the results, unlike the carbon nanotubes, its nanocones can be successful candidates to detect FLT drugs due to significant adsorption energy equal to - 30.1 kcal/mol along with the low adsorption energy equal to– 22.5 kcal/mol in nanocones. The Eg of the carbon nanocones will implicitly decrease from 3.01 to 1.22 eV because of LUMO's significant stabilization. Accordingly, the exponential increase of the conduction electrons' population happens, which consequently increases the carbon nanotube's electrical conductivity which is changeable to electrical signals. As the %HF exchange of the functional increases, more negativity of the adsorption energy is observed while it becomes less sensitive.

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