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Cyclophosphamide@CNT: *In Silico* Exploration of Nano Drug Delivery System

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ABSTRACT. Within this work, cyclophosphamide (CP) anticancer drug was loaded at the surface of a representative carbon nanotube (CNT) to examine the formation and features of such CP@CNT hybrid model system. Density functional theory (DFT) calculations were performed to provide required information to reach the aim of this work *in silico*. The obtained results indicated that the formation of CP@CNT could be possible regarding the calculated adsorption energy and electrostatic potential (ESP) surface representation. Additionally, the reactivity of CP was significantly reduced in the hybrid showing the reduction of unfavorable side effects of CP consumption for cancerous patients. As a remark of this work, it could be mentioned that such CP@CNT hybrid model system could be proposed for further investigation of nano-based targeted drug delivery processes to reduce negative impacts of anticancer consumption for the cancerous patients.

KEYWORDS. Cyclophosphamide; CNT; Anticancer; Adsorption; DFT.

INTRODUCTION. Several diseases have been always arisen with known and unknown reasons in current years of technological life style; therefore, drug design and discovery has been seen as a non-stop process.[1] Among which, cancer is one of the most important risk factor for health making trouble for so many people all around the world.[2] Indeed, discovery of drugs for cancer therapy or even improvement of available drugs might help such deathful crisis all around the world.[3] Cyclophosphamide (CP) (Fig. 1) has been using as one of the useful drugs for medication of cancer with remarkable effects for immune system suppressing too.[4] CP has been prescribed for patients with various types of cancer such as lymphoma, multiple myeloma, leukemia, ovarian cancer, breast cancer, small cell lung cancer, neuroblastoma, and sarcoma.[5] Despite of advantages of CP consumption, patients have always complaining side effects after medication by this drug.[6] Therefore, it is important to improve the features of CP for more efficient consumption for cancerous patients.[7] One of the ways to improve a drug efficacy is how to deliver it to the correct target through targeted drug delivery process.[8] In this case, carriers are needed to deliver the drug up to the correct target.[9] By the innovation of nanostructures, they have been always expected to work as proper carriers in the targeted drug delivery processes.[10] Carbon nanotubes (CNTs) have been seen to do such functions in living systems because of their unique structural and electronic properties for such purposes.[11] Indeed, several efforts have been devoted to provide them for drug carries using computational

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and experimental aspects.[12-15] Among which, computer-based *in silico* works could always reveal insightful information for the complicated nano-bio hybrid structures especially for nano based drug delivery processes.[16-20]

In this work, CP was loaded at the surface of a representative CNT to explore such nano carrier for this drug (Fig. 2). To this aim, quantum chemical computations were performed for molecular systems to run an *in silico* computer-based work to achieve the purpose. Several types of quantitative descriptors and qualitative representations and spectra were evaluated for describing the investigated CP@CNT system (Table 1 and Figs. 1-3). The major goal of this work was examining the advantage of CNT carrier for CP, in which the results of singular and hybrid forms of molecular systems were carefully obtained and discussed to possibly answer this problem. Previously, nanostructures have been seen for good adsorbing function of other substances in different applications.[21] From gas sensors up to drug carries have been all seen the possible functions of nanostructures.[22-25] Moreover, non-carbon based nanostructures and even metal based have been considered for such adsorption processes.[26] To this point, it could be an important aim to examine such novel advantage of nanostructures carry CP cancer drug to may reduce its side effects in a novel way of targeted drug delivery process.

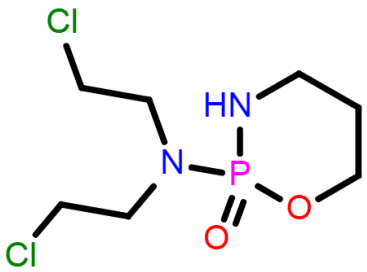

Fig. 1: Cyclophosphamide (CP) from ChemSpider (ID: 2804).

METHODOLOGY. This computer-based *in silico* work was done employing density functional theory (DFT) calculations at the level of B3LYP method and 6-31G* basis set as implemented in the Gaussian program.[27] First, all the individual structures of CP and CNT were optimized to achieve the minim energy structures. Next, the global minimum achievement was approved by the vibrational calculation of the optimized structures avoiding the existence of any imaginary frequency. The original structure of CP (Fig. 1) was obtained from the ChemSpider structural bank.[28] A representative (4,0) CNT was modelled to be considered for the drug carrier of targeted drug delivery process. By obtaining optimized structures of singular models, their combination were investigated to create CP@CNT hybrid system through another optimization calculations and exclusion of imaginary frequency confirmations. The quantitative descriptors including energy values for the highest occupied and the lowest unoccupied molecular orbitals (HOMO and LUMO), energy difference of HOMO and LUMO levels in energy gap (EG), Fermi energy (FE) as the average energies of HOMO and LUMO levels, dipole moment (DM), adsorption energy (AE) as the energy differences of hybrid system from each of singular models, and minimum value of adsorption distance between CP and CNT (AD) all exhibited in Table 1. Qualitative representations of HOMO and LUMO distribution patterns in addition to electrostatic potential (ESP) surfaces were all exhibited in Fig. 2. Furthermore, computed infrared (IR) spectra were shown in Fig. 3 for the investigated model systems. All obtained result were discussed carefully to reach the goal of this work.

Table 1: Molecular descriptors.*

Descriptor	CP	CNT	CP@CNT
HOMO eV	-7.01	-4.77	-5.10
LUMO eV	0.09	-3.94	-4.11
EG eV	7.10	0.83	0.99
FE eV	-3.45	-4.36	-4.60
DM Debye	5.05	0	5.52
AE eV	N/A	N/A	-0.22
AD Å	N/A	N/A	2.51

*See Figs. 1 and 2 for models details.

RESULTS & DISCUSSION. Loading CP drug at a representative model of CNT was investigated in this work employing the DFT computed results for singular and hybrid system structures (Table 1 and Figs. 1-3). The optimization processes yielded global minimum energy structures for both of singular and hybrid models. It is worth to note that the dispersion effects correction was included in the DFT calculations of optimization for CP@CNT hybrid system structure.[29] Indeed, examining the role of CNT for carrying CP drug in targeted drug delivery process was the main goal of this work, in which the models and results were collected to reach such achievement of a possible

solution for such problem. Hence, the goal was defined to investigate such nano-based drug delivery system because of deficiency of CP drug to arise side effects for the cancerous patients. [6]

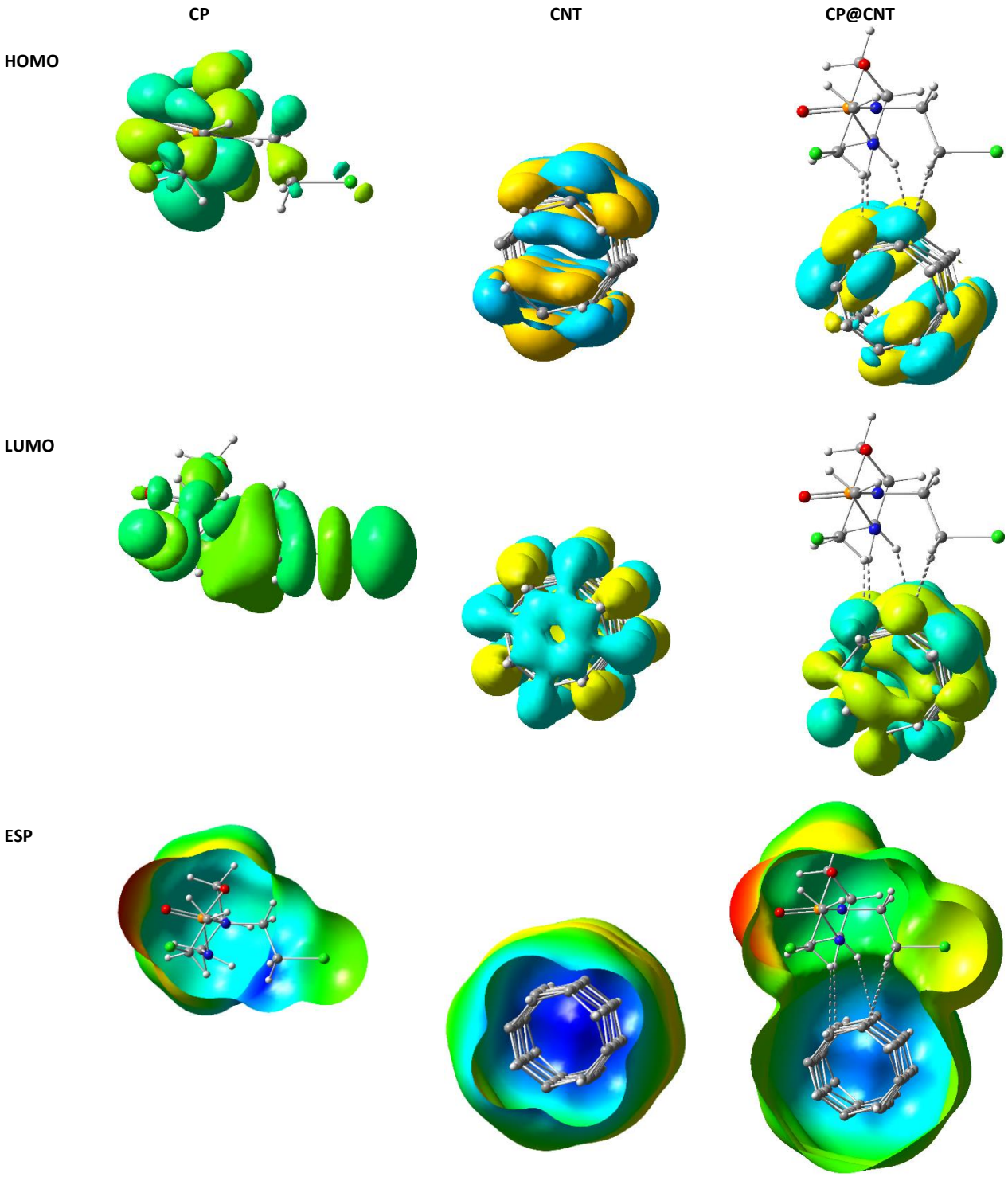

Fig. 2: Molecular orbital representations.

The values of HOMO and LUMO are very much important for designating the reactivity of a chemical structure regarding electron transferring in side of outside the molecule. Additionally, distribution patterns could recognize the localization of such molecular orbitals for the investigated model structures. Within this work, both of quantitative and qualitative features were obtained for HOMO and LUMO of singular and hybrid model systems to examine the role of CNT for carrying the loaded CP drug. It was very much interesting that the localization of HOMO and LUMO distributions were moved to CNT in hybrid model system meaning the serious role of carrier to neutralize the reactivity mode of the loaded substance. As seen in Fig. 2, both of HOMO and LUMO patterns were active in the singular CP as used for

conventional drug delivery processes to arise side effects. However, in the hybrid model system, the loaded CP could not significantly contribute to possible interaction with other substances, in which CNT could do such function instead. This trend is important to be considered according to the biosensor role of nanostructures for detecting the correct target of targeted drug delivery processes. Here with such results, the role was seriously seen for CNT in carrying the loaded CP drug. Examining the quantitative values of HOMO and LUMO (Table 1) could also approve that the molecular orbital features of CP@CNT were more related to singular CNT than singular CP. The obtained values of EG and FE also approved the dominant role of CNT for carrying CP drug in a targeted drug delivery process to probably reduce the unfavorable side effects of consumption for the patients. The obtained values of DM indicated the effects of such non-covalent functionalization on the electronic properties of CP@CNT in comparison with each of singular counterparts. Additionally, the evaluated ESP surfaces confirmed reality of such intermolecular adsorption process to produce of hybrid model system. The adsorption strength of such CP@CNT hybrid was shown by the value of AE in a reasonable state of such non-covalent interaction between two molecular systems. The nearest adsorption distance between two CP and CNT counterparts was designated by 2.51 Å of AD. As a consequence of this part, the formation of CP@CNT hybrid model system could be achievable and the side effects of CP could be reduced through its delivery by CNT up to the correct target avoiding any extra interaction for the loaded CP.

For showing a more precise recognition procedure, the evaluated IR spectra for all three investigated models were exhibited in Fig. 3. Yes, it could be evident that the formation of such CP@CNT hybrid model system could be possible according to the obtained spectra of singular and hybrid models. It is worth to note that, the obtained IR spectra could reveal that the original chemical features of CP could be still remained safe in the CP@CNT hybrid model system avoiding any worry about missing the drug property in such adsorption process. However, it should be noticed that such properties could be protected at the carrier and they could be released again during delivery process to the correct target. Indeed, combinations of such insightful results at the lowest molecular scale could yield reasonable consequences for proposing to be involved in further practical or extra computational works.[30-38]

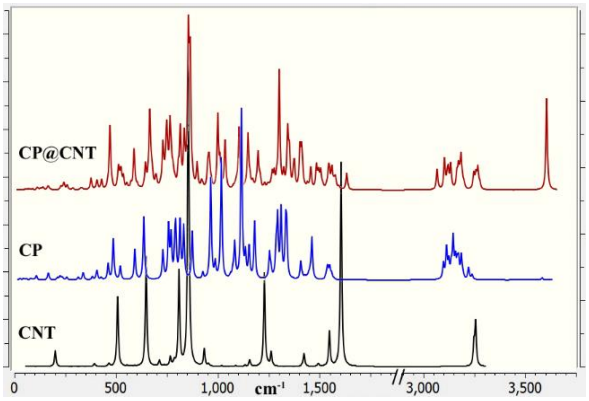

Fig. 3: IR spectra.

CONCLUSION. Within this work, the features for CP@CNT hybrid model system was investigated to show the role of CNT carrier to be used in targeted drug delivery purpose of the loaded CP avoiding unfavorable side effects for the patients. The obtained results of DFT calculations indicated that the formation of CP@CNT hybrid model system could be achievable regarding the values of energies and also ESP surfaces. Moreover, the reactivity of CP was reduced at the hybrid due to movement of molecular orbital localization mainly to CNT and the loaded CP was free of such points to interact with other substances. This was a good consequence of this work to show first the achievability of CP@CNT hybrid model system and next the non-reactivity of CP counterpart of such hybrid. The trend could help that the drug could be remained safe from other interferers up to reaching to the correct target. The carrier showed the function of biosensor to detect the correct target. As a final remark, such CP@CNT hybrid model system could be proposed for further investigations of reducing CP side effects through nano-based targeted drug delivery processes.

DISCLOSURE STATEMENT. The author(s) did not report any potential conflict of interest.

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