Drug delivery by SiC nanotubes as nanocarriers for anti-cancer drugs: investigation of drug encapsulation and system stability using molecular dynamics simulation

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Abstract

Since much attention has been paid to the targeted drug delivery system, using the molecular dynamics simulation, the present work has been devoted to clarify the potential of the silicon carbide nanotubes (SiCNTs) as a new carrier for the three common anti-cancer drugs temozolomide, carmustine, and cisplatin. Three zigzag single-walled nanotubes with different diameters, i.e. SiC(18,0), SiC(20,0), and SiC(22,0), in pure and decorated with the hydroxyl and carboxyl functional groups are selected to assess the effect of the functional groups as well as the diameter effect on the drug encapsulation process. The effects of binding energy, probability of finding the drugs along the nanotube length, mean square displacement, and body temperate as well as the zeta potential for the stability of the drug delivery system in the blood stream are evaluated. The results showed that the cisplatin does not encapsulate into the selected SiCNTs. However, the pure nanotubes show a high stability in the blood stream but the magnitude of their interaction energies with the temozolomide and carmustine drugs is less than $-10$ kcal mol$^{-1}$, which does not guarantee that the drug will remain bonded to the nanotubes in the blood stream. Also the presence of the carboxyl functional group on the nanotube surface only has no significant effect on the interaction energies but also decreases the stability of the drug delivery system. Decorating the edge nanotubes with the hydroxyl group causes the interaction between temozolomide and SiCNTs into chemisorption ($-10$ to $-40$ kcal mol$^{-1}$) while the variation in binding energy of the carmustine is not remarkable. Finally, the zeta-potential results showed that the edge nanotubes decorated with the hydroxyl group due to a high stability in the blood stream as well as the strong interaction with the drugs temozolomide and carmustine is an appropriate carrier for the targeted drug delivery.

1. Introduction

Cancer is the second leading cause of death in the world, and its treatment remains a major therapeutic challenge for humanity. Generally, cancer includes a group of diseases in which a number of cells in one part of the body start to grow abnormally. These cells have the potential to spread or invade the other organs of the body [1]. Consequently, finding an effective treatment for cancer has been the main goal of the scientific research works during the previous years [2]. Surgery, radiotherapy, and chemotherapy are the most common forms of cancer treatment. Among these treatments, chemotherapy is more popular because it cures a widespread of cancers due to travel throughout the body using the systemic blood circulation [3]. Nevertheless, this process is not a targeted treatment because not only a low concentration of medication reaches the cancered organs but also the side-effects resulting from the interaction of the drug with a normal tissue are inevitable. These disadvantages...
indicate the importance and valubility of the targeted drug delivery systems in cancer treatment. The main considered aspects of the targeted drug delivery involve increasing the anti-cancer drug effect, controlling the drug dosage, and reducing the toxicity [4, 5].

The nanocarriers with different shapes are good candidates for the drug delivery systems. These type of carriers are able to encapsulate the anti-cancer drugs and release them in the diseased tissue. Among the introduced drug nanometer carriers, the nanotubes have shown a great potential for the drug delivery system [6]. Carbon nanotubes (CNTs) with outstanding properties such as the structural stability, high drug loading capacity, and penetrating through the targeted cancerous cell walls have been utilized in the field of cancer therapy [7, 8]. Another kind of nanotubes is the boron nitride nanotubes (BNNTs). The non-toxic and biocompatible properties along with stable binding make BNNTs an efficient candidate as a drug delivery vehicle for cancer treatment [9, 10]. Despite the high potential of the nanotube families in the field of cancer treatment, silicon carbide nanotubes (SiCNTs) have not been considered as the other members. The most stable SiCNTs can be constructed by rolling up the SiC graphene sheet, in which the Si to C ratio is 1:1. These structures consist of the alternating C and Si atoms so that each C atom is surrounded by three Si atoms, and vice versa [11]. According to the previous reports, SiCNTs have more advantages compared to CNTs [12]. These structures possess a reactive exterior surface that facilitates their functionalization in comparison with CNTs [13, 14]. Also the difference between the electronegativities of the Si and C atoms leads to the hydrophilic surface of SiCNTs in contrast to the hydrophobic surface of CNTs [12]. Furthermore, SiC has been long known as one of the best biocompatible substances, especially in the blood-contacting implants, and cardiovascular and biomedical devices [15]. The structural stability, high solubility, and biocompatibility along with other excellent properties such as blood compatibility, low density, and high rigidity in SiCNTs make them attractive candidates for the targeted drug delivery. Except for the very few studies such as computer simulation of DNA bases with Li-doped SiCNTs in aqueous solutions [16] and the comparative investigation of encapsulation of carboplatinum anti-cancer drug into CNT and SiCNT for the drug delivery system [12], not much attention has been paid to SiCNTs as an effective carrier for the drug delivery system. Therefore, the main goal of the present work is the ability of SiCNTs to encapsulate the three common anti-cancer drugs temozolomide, carmustine, and cisplatin. These anti-cancer drugs, as alkylating antineoplastic agents, are used mainly in the treatment of brain tumors. The effects of different parameters on the drug encapsulation process such as the diameter of SiCNTs and the functional groups present in it, and the ambient and the body temperatures were investigated. In order to accurately interpret the encapsulation process, the binding energy between the drugs and the nanotubes, the probability of finding a drug along the nanotube length, and the mean square displacement after drug encapsulation were studied. In addition, the zeta potential was evaluated for the stability of the drug delivery system in the blood.

2. Computational details

The classic molecular dynamics (MD) simulation was applied using the LAMMPS package supplied by the Sandia National Laboratory [17] in order to scrutinize the potential of the selected nanocarriers (i.e. SiCNTs). NPT ensemble (constant particle number, temperature, and pressure) through a Parrinello–Rahman barostat [18] and a Nose-Hoover thermostat [19] was implemented in order to control a pressure of 1 bar and a temperature of 298 K, respectively. The intramolecular interactions of SiCNTs were given by a consistent valence force field (CVFF) [20] model, and its force field parameters were adapted from the previous work [21]. The applied force field parameters are reported in table 1. Also the drug atoms interacted with each other via Chemistry at Harvard Macromolecular Mechanics (CHARMM) (MacKerell et al 1998). The transferable intermolecular potential functions (TIP3P) implemented in the CHARMM force field were selected for the water molecules. The global cut-off radius for the Van der Waals and electrostatic forces were considered to be 12 Å and 13 Å, respectively. In order to calculate the long-range electrostatic interactions, the particle mesh Ewald (PME) method [22] was used. Through the hybrid pair_style [23], the drug/SiCNT, drug/water, and SiCNT/water intermolecular interactions were modeled by the CHARMM potential (S1 of the supplementary file available online at stacks.iop.org/MRX/8/105012/mmedia).

To achieve the aims of this work, three zigzag single-walled SiCNTs with different diameters, i.e. SiC(18,0), SiC(20,0), and SiC(22,0), were selected in order to clarify the SiCNT diameter effect on the drug encapsulation. Accordingly, the three common anti-cancer drugs temozolomide (TMZ), carmustine (bis-chloroethyl nitrosourea, BCNU), and cisplatin were considered. Since the zigzag hetero-nanotubes are polar materials in contrast to the armchair nanotubes, a polar adsorbent is better than a non-polar one for the selected polar drug (S6 of the supplementary file). The encapsulation simulation was carried out by the pure nanotubes, and the surface/edge nanotubes were decorated with the carboxyl/hydroxyl functional group. Based on our DFT calculation results, the carboxyl and hydroxyl functional groups were bonded to the Si and C atoms of SiCNTs,
The number of carboxyl functional groups was equal to 5% of the total number of Si atoms on the nanotubes in the order pattern (the reasons for the 5% and the order pattern are discussed in S3 of the supplementary file). The nanotube length was estimated in such a way that the edge effects of the nanotubes were eliminated. This meant that when a drug was placed in the middle of the nanotubes, the distance between the drug and the nanotube edge was out of the considered cut-off radius. Technically speaking, the designed nanotubes acted like long-length nanotubes in our MD simulations. At the onset of a stimulation, the drugs were placed about 10–12 Å from the nanotube entrance as the initial configuration. Also the water

![Figure 1. Pure nanotubes (a), surface decorated nanotubes with the –COOH functional group (b), and edge decorated nanotubes with the –OH functional group (c).](image)

**Table 1.** Applied force field parameters in the molecular dynamic simulations.

| Atom type                      | σ (Å) | ε (kcal mol⁻¹) | Atomic charge |
|--------------------------------|-------|----------------|---------------|
| Si of nanotube                 | 3.808 | 0.585          | +0.60         |
| C of nanotube                  | 3.820 | 0.056          | -0.60         |
| C of –COOH                     | 3.617 | 0.148          | +0.41         |
| O of double bond in –COOH      | 2.860 | 0.228          | -0.38         |
| O bonded to H in –COOH         | 2.860 | 0.228          | -0.38         |
| H of –COOH                     | 0.000 | 0.000          | +0.35         |
| O of –OH                       | 2.860 | 0.228          | -0.38         |
| H of –OH                       | 0.000 | 0.000          | +0.35         |

**Table 2.** Encapsulation simulation results for TMZ, BCNU, and cisplatin.

| Nanotube         | TMZ | BCNU | cisplatin |
|------------------|-----|------|-----------|
| SiC(18,0)        | X   | ✓    | X         |
| SiC(20,0)        | ✓   | ✓    | X         |
| SiC(22,0)        | ✓   | ✓    | X         |
| SiC(18,0)–OH     | ✓   | ✓    | X         |
| SiC(20,0)–OH     | ✓   | ✓    | X         |
| SiC(22,0)–OH     | ✓   | ✓    | X         |
| SiC(18,0)–COOH   | ✓   | ✓    | X         |
| SiC(20,0)–COOH   | ✓   | ✓    | X         |
| SiC(22,0)–COOH   | ✓   | ✓    | X         |

respectively (see figure 1). The number of carboxyl functional groups was equal to 5% of the total number of Si atoms on the nanotubes in the order pattern (the reasons for the 5% and the order pattern are discussed in S3 of the supplementary file). The nanotube length was estimated in such a way that the edge effects of the nanotubes were eliminated. This meant that when a drug was placed in the middle of the nanotubes, the distance between the drug and the nanotube edge was out of the considered cut-off radius. Technically speaking, the designed nanotubes acted like long-length nanotubes in our MD simulations. At the onset of a stimulation, the drugs were placed about 10–12 Å from the nanotube entrance as the initial configuration. Also the water
molecules of the TIP3P model (with density of 1 g cm$^{-3}$) were loaded in the simulation box. The variation in the mean square displacement of the drug during the simulation was considered as a criterion for the system equilibration. Finally, the effects of the diameter and functional group of the nanotube as well as the temperature on the binding energy between the drug and SiCNTs after encapsulation, the probability of finding the drug along the nanotube length, the mean square displacement, and the zeta potential were calculated for about 0.2 ns after the system equilibration (discussed in the next section).

3. Results and discussion

An overview of the MD simulation results indicated that only TMZ and BCNU were encapsulated into SiCNTs. Nonetheless, all the selected nanotubes with different diameters and functional groups were not the appropriate carriers for the cisplatin drug, and cisplatin encapsulation did not occur. The estimation interaction between SiCNTs and cisplatin revealed that the repulsive interaction was dominated between them according to the positive values of binding energy (figures 2S in S5 of the supplementary file). Table 2 shows a summary of the encapsulation results. Hereupon, the TMZ and BCNU results are discussed below.

3.1. Binding energy (BE)

The reactivity of the SiC nanotubes (SiCNTs) with different electronegativities of the Si and C atoms in its six member rings in sensing a large variety of molecules is considerable in comparison with the carbon nanotubes (CNTs) [24]. It is obvious that SiCNTs can be an appropriate material for CO$_2$ detection [25] as well as for hydrogen storage at the ambient condition [26]. A comparative investigation using the MD simulation study illustrated that the binding interaction of SiCNT/cholesterol was about 1/4 larger than that of CNT/cholesterol [27]. Also in the drug delivery field, based on the molecular dynamics results illustrated for platinum-based anticancer drug, SiCNTs are a more appropriate drug delivery system than CNTs [12]. In this regard, the encapsulation process was analyzed from the interaction viewpoint between the drug and the SiCNTs.
Although TMZ did not enter pure SiC(18,0) during an MD simulation, the diameter increase of SiCNTs or surface/edge decoration by the carboxyl/hydroxyl functional group of the pure nanotube solved this problem. On the other hand, the BCNU encapsulation occurred in all SiCNTs. The BE frequency for 0.2 ns after the system equilibration is illustrated in figure 2. In more details, a constant slope for the plot of mean square displacement (MSD) versus time was considered as a criterion for the system equilibration. After the system equilibration during 2 ns, BE between a drug and the nanotubes was estimated every 500 time steps over 0.2 ns of the sampling procedure (i.e. 400 values of BE). Since the drug encapsulated into the nanotubes is a dynamic system, the BE values are not necessarily equal. Hereupon, the frequency plot of the BE values obtained is depicted in figure 2. Referring to figure 2(a), it is clear that the diameter increase in the case of pure SiCNTs does not cause a significant change in the BE values for the two drugs TMZ and BCNU. In the case of pure nanotubes, the BE values approximately fall in the range of 0 to −10 kcal mol$^{-1}$. Considering the value of 0.5 eV ($\approx 11.53$ kcal mol$^{-1}$) as the threshold separating the physisorption from the chemisorption interaction [28], it can be deduced that the BE values for pure SiCNTs do not guarantee that the drug will remain bonded to the nanotubes in the blood stream until it reaches the targeted cells. After the surface/edge decoration of the nanotube by the carboxyl/hydroxyl functional group, the magnitude of the interaction energies between the drugs and the nanotubes are remarkable. As depicted in figure 2(b), in the presence of the hydroxyl functional group on the nanotube edge, the interaction between TMZ and SiCNTs turns into chemisorption. In more details, the BE values between SiCNTs and TMZ fall in the range of −10 to −40 kcal mol$^{-1}$ after nanotube edge decoration with the hydroxyl functional group. In contrast, there is no difference in BE between the pure form and the hydroxyl-functionalized nanotube for BCNU. Also the carboxyl functional group on the surface of SiC(18,0) causes a significant change in the binding energy compared to the pure nanotubes, and the magnitude of BE falls in the range of chemisorption, as shown in figure 2(c). Nonetheless, the effect of the hydroxyl functional group on BE is more than the effect of the carboxyl functional group. Since the encapsulation MD simulations were carried out at the room temperature (298 K), the effect of body temperature (310 K) on the encapsulated drugs into SiCNTs was assessed. Due to the negative effect of the increasing temperature on BE, only the effect of body temperature on the BEs of SiC(18,0)−COOH/TMZ, SiC(18,0)−COOH/BCNU, and SiCNT−OH/TMZ are reported in figure 2(d). As expected, an increase in the temperature from 298 K to 310 K decreases the magnitude of BE to the range of physisorption. Hence, it can be said that SiC(22,0)−OH is the best carrier for TMZ, and there is no appropriate carrier for BCNU among the selected nanotubes at the body temperature.
However, according to the range of BE under our simulation conditions at 310 K, the challenge of drug-release before reaching the targeted cells will remain.

### 3.2. Mean square displacement (MSD)

After the system equilibration, the MSD and diffusivity of the drugs inside the nanotubes were estimated. In order to estimate the MSD and diffusion coefficient, equation (1) \[29\] was used.

\[
MSD = \langle (x_t - x_0)^2 \rangle = \frac{1}{N} \sum_{n=1}^{N} (x_n(t) - x_n(0))^2 = 2nDt
\]

where \(N\), \(x_n(0) = x_0\), \(x_n(t) = x_t\), \(n\), \(D\), and \(t\) are the average number of particles, reference position of each particle, position of each particle in the specified time \(t\), dimension of the simulation box \((n = 3)\), diffusion coefficient, and time, respectively. Furthermore, the center of mass of a drug was considered as the position of the drug. It is worth noting that the calculated diffusivity is self-diffusion. The self-diffusion coefficient is a measure of the translational mobility of the individual molecules at thermodynamic equilibrium. Technically speaking, self-diffusivity arises from the adsorption effects and intermolecular interactions. Therefore, the diffusivity (or MSD) calculation reveals a worth information. Like the previous section, the effects of diameter, functional group, and body temperature on MSD were investigated (figures 3(a)–(f)). What is important to keep in mind is that although the MSD states says nothing about the magnitude of the intermolecular interaction, the variation in MSD says about increasing or decreasing the BE implicitly. Accordingly, the round-trip pattern in figure 3 indicates that the drugs are encapsulated into the nanotubes based on equation (1). By referring to figure 3(a), it is clear that the diameter increase has a different effect on MSD of the TMZ drug in the case of pure nanotubes. The MSD fluctuation of TMZ into SiC(22,0) is more than that of SiC(20,0). It means that the diameter increase causes a decreasing interaction between the nanotubes and TMZ. This trend is observed for the case of SiCNTs decorated with the carboxyl and hydroxyl functional groups (figures 3(c) and (e)). Consequently, there is a direction relationship between the diameter of the related nanotubes and MSD fluctuation of TMZ. However, the fluctuation of MSD for pure nanotubes is higher than that of functionalized nanotubes. It is worth noting that the mentioned MSD trend of TMZ corresponds to the BE results in the previous section. In comparison to the TMZ drug, the BCNU drug illustrates different trends. Unlike TMZ, the MSD fluctuation of BCNU for the case of pure nanotubes decreases with diameter increase, which corresponds
to BE in the case of BCNU. The higher fluctuation means less attraction between BCNU and SiCNTs. Nonetheless, the MSD trend in the case of SiCNTs decorated with the carboxyl and hydroxyl functional groups is the same as that of TMZ. Furthermore, the MSD plot provides a more useful information. It is evident that surface functionalization of SiC(18,0) by the carboxyl functional group causes that MSD of the two drugs TMZ and BCNU leads to a value of nearly zero (figures 3(c) and (d)). This means that the carboxyl functional group, especially SiC(18,0) - COOH, increases the interaction between a drug and the nanotubes. However, MSD in the presence of a carboxyl functional group on the surface of other nanotubes does not change considerably. This phenomenon can be observed for BE in the previous section (figure 2(b)). Compared to BCNU, the MSD of TMZ after nanotube edge decoration by the hydroxyl functional group significantly leads to a value of nearly zero. Falling the TMZ mean square displacement value toward zero can be interpreted as a remarkable increase in BE between TMZ and SiCNTs with the hydroxyl functional groups. Figure 2(c) numerically illustrates this increase in BE. Finally, as expected, the temperature increase from 298 K to 310 K has a negative effect on MSD, like BE. In other words, BE between a drug and the nanotubes decreases with a temperature increase, as shown in section 3.1. BD reduction leads to an increase in the drug mobility. Consequently, MSD of the drug increases.

3.3. Probability of finding encapsulated drugs along nanotube length

As mentioned earlier, the length of the nanotubes was considered in such a way that when a drugs was located in the middle of the nanotubes, the drug position could not be affected by interaction with the edge of the nanotubes. Under these conditions, it can be said that the created nanotubes are representative of long-length nanotubes. Accordingly, the probability of finding a drug along the nanotube length (Prdrug) after encapsulation was scrutinized. Albeit, the BE between a drug and the nanotubes is a crucial parameter for the targeted drug delivery; understanding the position of the encapsulated drug along the nanotube length can be effective too. What is useful to know is that with increase in the distance of an encapsulated drug from the nanotube edge, the probability of drug-release decreases. Referring to figure 4(a), Prdrug far away from the center of the nanotubes increases along with a diameter increase. Encapsulations of TMZ into SiC(20,0) and BCNU into SiC(18,0) were found around the middle of the nanotubes compared to the pure nanotubes. The presence of the carboxyl functional group on the SiCNT surface decreases the mobility of TMZ and BCNU into SiC(18,0). The narrow and sharp peak for Prdrug of TMZ and BCNU into SiC(18,0) proves this phenomenon (figure 4(b)). This pattern is consistent with the effect of the carboxyl functional group on BE (refer to figure 2(b)). Despite the consistency
between BE and Pr\text{drug}, the weak interaction (physisorption) of TMZ/BCNU with SiC(18,0) is a serious problem for a drug delivery system. Decoration of the nanotube edge with the hydroxyl functional group causes an increase in Pr\text{drug} around the middle of nanotube, as depicted in figure 4(c). In more details, it can be observed that Pr\text{drug} of TMZ/BCNU around the middle of SiC(18,0)-OH/SiC(22,0)-OH is more than that for the others. Albeit, the sharpest and highest peak attributed to BCNU into SiC(22,0)-OH, its BE is in the physisorption range. Based on figure 2(c), there is a consistency between BE and Pr\text{drug} for TMZ into SiC(18,0) and SiC(22,0) decorated with the hydroxyl functional group. Finally, by considering the temperature effect on BE (figure 2(d)) and Pr\text{drug} together clarifies that SiC(22,0)-OH is an appropriate carrier for the targeted drug delivery.

Accordingly, the distance between the center of mass of a drug and the nanotubes (DBCOM) was defined as another parameter in order to study Pr\text{drug} from other viewpoints. DBCOM was calculated using equation (2).
The results obtained are shown in treatment through the targeted drug delivery. Accordingly, the silicon carbide (SiC) nanotubes as a new high potential carrier was investigated for the common anti-cancer drugs temozolomide, carmustine, and cisplatin.

### 3.4. Zeta potential (ZP)

The major obstacle after drug encapsulation into SiCNTs is the reticuloendothelial system (RES), especially in the spleen and liver of the body. RES can recognize and eliminate the drug delivery systems (in this case, the drug and nanotubes) from the blood stream [30]. Hence, a long-time stability of the drug delivery system in blood circulation is a crucial parameter for cancer treatment. On the other hand, it is well-known that the drug delivery system acts as a colloidal system in the blood flow [31]. The stability of the colloidal system is measured by a key parameter called ZP. Technically speaking, the repulsive interaction forces between the charged particles are illustrated by this parameter in the dispersion. If the degree of ZP decreases below a defined threshold, the aggregation tends to occur because of the Van der Waals interactions [32]. With increase in the size of particles resulting from aggregation, the probability of uptake by the reticuloendothelial system will increase [33]. Hereupon, ZP becomes an essential factor in the targeted drug delivery field. Theoretically, when the particles disperse into the fluid medium, a layer of fluid is attached to them. The plane that is the interface of the attached fluid to the particle and mobile fluid is called a slipping plane. The electrical potential at the slipping plane is ZP. From the theoretical viewpoint, the potential between the stationary layer of the fluid (Stern layer) attached to the dispersed particle and dispersion medium (diffuse layer) is called ZP [34]. In other words, the diffuse layer/Stern layer is equivalent to the outer/inner region of the loosely/strongly bound ions around the dispersed particle.

In this regard, the cylindrical distribution function (CDF) for the oxygen atoms of the water molecules around the nanotubes with the aim of ZP estimation was obtained. Based on the theoretical viewpoint, the closest peak (Stern peak) of CDF to the outside wall of the nanotubes corresponds to the Stern layer. Likewise, the farthest peak (diffuse peak) of CDF from the exterior wall of the nanotubes can be considered as a diffuse layer. Consequently, the ratio of Stern peak to diffuse peak is proportional to the magnitude of ZP. Note that CDF was estimated the same as the radial distribution function (RDF), except that a cylindrical shell was applied instead of a radial shell. The results obtained are shown in figures 6(a)–(c). Moreover, the Stern to diffuse peak ratio is reported in table 3. From this table, it is clear that more stability in the blood stream belongs to the pure nanotubes (without a functional group). Among the pure nanotubes, SiC(18,0) has the maximum ratio of Stern to diffuse peak. However, the type of interaction between the drugs and pure SiC(18,0) will be physisorption (refer to figure 2(a)). In addition, decoration of the nanotubes with the carboxyl functional group significantly decreases the ratio of Stern to diffuse peak. Considering the diminishing of the stability of the drug delivery system as well as the weak interaction of the drug with the nanotubes functionalized with a carboxyl functional group, we can deduce that SiCNTs with a carboxyl functional group is not an appropriate carrier for TMZ and BCNU. The stability of SiC(18,0) and SiC(20,0), edge decorated with a hydroxyl functional group, is remarkable, like the pure nanotubes. In addition to the stability, the interaction energy of SiCNTs-OH with the drugs falls into the range of chemisorption. By considering the consistency between the drug-nanotube interaction and stability of SiCNTs in the presence of the hydroxyl functional group, we can conclude that SiCNTs-OH is an ideal candidate as the carrier for the targeted drug delivery among the selected nanotubes.

### 4. Conclusion

The classic molecular dynamics simulation was implemented in order to introduce a new carrier for cancer treatment through the targeted drug delivery. Accordingly, the silicon carbide (SiC) nanotubes as a new high potential carrier was investigated for the common anti-cancer drugs temozolomide, carmustine, and cisplatin. Three nanotubes with different diameters (i.e. SiC(18,0), SiC(20,0), and SiC(22,0)) in two forms (i.e. pure and functionalized with the carboxyl and hydroxyl functional groups) were selected. The effects of the nanotube
diameter and the functional group on the drug encapsulation was studied. The binding energy, probability of finding the drug along the nanotube length, and mean square displacement after drug encapsulation were calculated. Since the encapsulation process was carried out under the ambient temperature, the human body temperature effect on the drug delivery system (i.e. nanotubes and drugs) was examined. Besides, the zeta potential, as a scientific term used for the stability of the drug delivery system in the blood stream, was evaluated. The results obtained show that the SiC nanotubes are not suitable carriers for cisplatin. Furthermore, the data obtained show that although the pure SiC nanotubes have a high stability in the blood flow, it is not a good candidate for encapsulation of the two drugs temozolomide and carmustine due the weak interactions between these drugs and the SiC nanotube. Adding the carboxyl functional group to the pure nanotubes not only has no significant effect on the interaction energy but also decreases the stability of the drug delivery system. Unlike the pure and carboxyl functionalized nanotubes, the edge decorated nanotubes with the hydroxyl functional group due to the high stability system in the blood stream as well as the strong interaction with the two drugs TMZ and BCNU is an appropriate candidate for the targeted drug delivery.

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Data availability statement

All data that support the findings of this study are included within the article (and any supplementary files).

Declarations

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References

[1] Liu Y, Niu T-S, Zhang L and Yang J-S 2010 Review on nano-drugs Nat. Sci. 2 41
[2] Sinha R, Kim G J, Nie S and Shin D M 2006 Nanotechnology in cancer therapeutics: bioconjugated nanoparticles for drug delivery Mol. Cancer Ther. 5 1909–17
[3] McKinnell R G, Parchment R E, Perantoni A O, Pierce G B and Damjanov I 2006 The Biological Basis of Cancer (Cambridge: Cambridge University Press)
[4] Sharma A, Jain N and Saroo R 2013 Nanocarriers for diagnosis and targeting of breast cancer BioMed Res. Int. 2013 1–10
[5] Weisleder R, Kelly K, Sun E Y, Shtatland T and Josephson L 2005 Cell-specific targeting of nanoparticles by multivalent attachment of small molecules Nat. Biotechnol. 23 1418–23
[6] Fabbro C, Ali-Boucetta H, Da Ros T, Costarelos K, Bianco A and Prato M 2012 Targeting carbon nanotubes against cancer Chem. Commun. 48 3911–26
[7] Tripisciano C, Kraemer K, Taylor A and Borowiak- Palen E 2009 Single–wall carbon nanotubes based anticancer drug delivery system Chem. Phys. Lett. 478 200–5
[8] Prakash S, Malhotra M, Shao W, Tomaro–Duchesneau C and Abbasi S 2011 Polymeric nanohybrids and functionalized carbon nanotubes as drug delivery carriers for cancer therapy Adv. Drug Deliv. Rev. 63 1340–51
[9] Xu H, Wang Q, Fan G and Chu X 2018 Theoretical study of boron nitride nanotubes as drug delivery vehicles of some anticancer drugs Theor. Chem. Acc. 137 1–15
[10] Ciofani G, Dani S, Nitti S, Mazzoli B, Mattei V and Giorgi M 2013 Biocompatibility of boron nitride nanotubes: an up-date of in vivo toxicological investigation Int. J. Pharm. 444 85–8
[11] Menon M, Richter E, Mavrandonakis A, Froudakis G and Andriotis A N 2004 Structure and stability of SiC nanotubes Phys. Rev. B 69 115322
[12] Khatti Z, Hashemianzadeh S M and Shafiei S A 2018 A molecular study on drug delivery system based on carbon nanotube compared to silicon carbide nanotube for encapsulation of platinum–based anticancer drug Adv. Pharm. Bull. 8 163
[13] Wu L and Guo G 2007 Optical properties of SiC nanotubes: an ab initio study Phys. Rev. B 76 035343
[14] Miyamoto Y and Yu B D 2002 Computational designing of graphitic silicon carbide and its tubular forms Appl. Phys. Lett. 80 586–8
[15] Sahu T, Ghosh B, Pradhan S and Ganguly T 2012 Diverse role of silicon carbide in the domain of nanomaterials Int. J. Electrochem. 2012 1–7
[16] Ketabi S, Hashemianzadeh S M and Moghim/Waskasi M 2013 Study of DNA base-Li doped SiC nanotubes in aqueous solutions: a computer simulation study J. Mol. Model. 19 1605–15
[17] Plimpton S 1995 Fast parallel algorithms for short-range molecular dynamics J. Comput. Phys. 117 1–19
[18] Parrinello M and Rahman A 1981 Polymorphic transitions in single crystals: a new molecular dynamics method J. Appl. Phys. 52 7182–90
[19] Kusnezov D, Bulgac A and Bauer W 1990 Canonical ensembles from chaos Ann. Phys. 204 155–85
[20] Dauber-Osguthorpe P, Roberts V A, Osguthorpe D J, Wolff J, Genest M and Hagler A T 1988 Structure and energetics of ligand binding to proteins: Escherichia coli dihydrofolate reductase-trimethoprim, a drug-receptor system Proteins 4 31–47
[21] Moradi G F and Kalantarinejad R 2012 A molecular dynamics simulation of water transport through C and SiC nanotubes: application for desalination Int. J. Nano Dimens. 2 151–7
[22] Darden T, York D and Pedersen L 1993 Particle mesh Ewald: an N·log(N) method for Ewald sums in large systems J. Chem. Phys. 98 10089–92
[23] Khorsandi-Langol A and Hashemianzadeh S M 2019 Distinct understanding of constant-volume/variable-pressure experimental method on CO2 capture using graphatriyne membrane through an atomistic approach J. Phys. Chem. C 123 15523–33
[24] Daoust Mohammad F and Hanziehoo M 2018 The adsorption of bromomethane onto the exterior surface of aluminum nitride, boron nitride, carbon, and silicon carbide nanotubes: a PBC-DFT, NBO, and QTAIM study Comput. Theor. Chem. 1144 26–37
[25] Zhao J X and Ding Y H 2009 Can silicon carbide nanotubes sense carbon dioxide? J. Chem. Theory Comput. 5 1099–105
[26] Mukherjee S and Ray A K 2008 An ab initio study of molecular hydrogen interaction with SiC nanotube—a precursor to hydrogen storage J. Comput. Theor. Nanosci. 5 1210–9
[27] Raczyński P, Górn K, Samios J and Gburzki Z 2014 Interaction between silicon-carbide nanotube and cholesterol domain. A molecular dynamics simulation study J. Phys. Chem. C 118 30115–9
[28] Frenkel D, Smit B and Ratner M A 1996 Understanding Molecular Simulation: From Algorithms To Applications (San Diego: Academic)
[29] Lyklema J 1995 Fundamentals of Interface and Colloid Science: Solid-Liquid Interfaces With Special Contributions by ed A de Keizer et al (London: Academic) vol 2