Fluid-Solid Interaction Analysis of Drug Delivery Mechanism to Damaged Cancer Cellules in the Shape of Single-Walled Carbon Nanocone by Molecular Mechanics Approach

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Abstract: Drug delivery systems able to deliver the required dose of the drug to the target level use active or passive nano metric designed systems. In the earlier researches, carbon nanocones are used for transferring the serum to damaged proteins and damaged cancer cellules. In this lecture, stability analysis of drug delivery to damaged cancer cellules is studied in the shape of single-walled carbon nanocone. In this method, each atom is considered as node and interactions between them are supposed as 3D-beam elements. By supposing that potential energy in macro relations is equal to the nano relations, nano-drug characteristics can be calculated. Then shape functions can be extracted to use in blood's FEM model and using reduced-order method, divergence velocities of carbon nanocone can be found. In this lecture, carbon nanocones are modeled with different dimensions and boundary conditions and stability of them in blood flow is studied and optimized carbon nanocone is selected in blood flow. Results show that conical nano-drug structures have more efficiency in blood flow rather than tube nano-drug structures and by increasing length of carbon nanocones, dimensionless stability parameter decreased and by increasing declination angle of carbon nanocones, dimensionless stability parameter increased.

Keywords: Conical Nano-Drugs, molecular mechanics, drug delivery.

1. Introduction

The pharmaceutical industry in terms of drug delivery using nanotechnology achievements has been remarkable. In addition, from the perspective of the pharmaceutical industry, nanotechnology drug delivery capabilities and providing available materials at very small scales are very important. In ancient medical system due to unrealistic doses of the drug in terms of the amount needed to treat, much of the digestive system, blood circulation and tissue interface are wasted and required amount to reach the desired cells or tissue are absorbed along the side effects, If the patient does not interfere as sleepiness, whereas diseases such as cancer and diabetes cause hair loss and

many events will be repeated injection may be painful tissues that is unbearable to the patient.

The new delivery system (nano) will solve all these problems. The new delivery system is a drug delivery at a specified time and with controlled doses of specific medicinal purposes, it's significantly safer and more effective than drug distribution in the body. One of the problems is that the targets are very small and scattered. New drug delivery reduces side effects and lower doses be used. Drug delivery systems are able to deliver the required dose of medication on time to the target level of designed nano scale systems.

Experimental results showed that by cohering anti-cancer drugs to nano particles, drug can be reached to cancer cellules purposefully and time of treatment will be increased. Once this research showed that coherent drugs to nano particles will go out of

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bloodstream and they will be concentrated inside the cancer cellules and their biological effects on tumor cells is applied to animals. Also by targeting the drug directly to cancer cells, receiving amount of these drugs by normal cells will be decreased and by increasing the therapeutic index of anticancer drugs, cancer can be turned into a controllable disease.

In this paper, by using molecular mechanics approach, drug delivery mechanism to damaged cancer cells is designed in the form of carbon nanocone and it can be seen that the structure of the carbon nanocone is more efficient than nanotube structure in the bloodstream. In another hand, structure of carbon nanocone to transfer serum to damaged proteins and delivering drugs are used and dynamic stability analysis of these carriers inside the bloodstream was studied.

After synthesizing the carbon nanocones, some structures can be obtained that lengths of them are optional, but apex angles have some specific values like: 123.6° , 86.6° , 60° , 38.9° and 19.2° . Naess et al. [1] verified these apex angles experimentally.

Some methods are applied in order to model the mechanical behavior of molecular structures. Among of these techniques, atomistic modeling is the most popular method and it's divided to two branches: 1- Molecular Mechanics for modeling atoms, 2- Quantum Mechanics for modeling electrons [2].

Atoms in the molecular mechanics are described as the point mass. In addition spring-like interactions and the van der Waals forces are used between each two atoms [3].

Furmaniak et al. [4] studied the first atomistic modeling of defective single walled carbon nanohorns morphologically. In this report, a new model of SWNHs was considered to anticipate the properties of Ar adsorption and also the fundamentals of the adsorption mechanism were investigated.

Hawelek et al. [5] studied the structural modeling of Dahlia-Type single walled carbon nanohorn using molecular dynamics. In this report, two parameters

were computed: the diffracted intensity and the pair correlation function. Finally they were compared with neutron diffraction experimental data and proper results were obtained.

Wei et al. [6] investigated some researches to determine the mechanical behaviors of carbon nanocone with apex angle 19.2° . In one of their articles, they studied the elastic modulus and poisson's ratio of the carbon nanocones by MD (molecular dynamics) [6]. In another report, the axial buckling of the mentioned structures was presented in Ref. [7]. In the present article, axial buckling of these structures was studied by MD method.

In another report, buckling and competition of energy and entropy lead conformation of SWCNC (single-walled carbon nanocones) was studied by Zhang et al. [8]. In this research, buckling analysis of SWCNC during synthesizing was studied.

In addition, chiral inversion of a microscale three-dimensional object of mechanical manipulation of carbon nanocones was studied by Jordan et al. [9].

In the present article, absorption of five hydrogen atoms on the apex of nanocone was studied.

Mechanical behavior of carbon nanocones using MD method was simulated in Ref. [10]. In the present article, stress-strain behavior of SWCNC was studied.

Vibration analysis of single-walled carbon nanocone using molecular mechanics method was studied in Ref. [11]. In the present article, each atom of carbon was modeled as point mass or node and covalent forces were noticed as space-truss elements. Frequency parameters of carbon nanocones with different lengths and apex angles were obtained by FEM (finite element method).

In addition, free vibration analysis of SWCNC using a nonlocal continuum model was presented in Ref. [12]. In the present article, an exciting method that it's known as Galerkin technique was used to obtain the natural frequencies and mode shapes.

Therefore fluid-solid interaction for nano materials has been an important issue for using in the carrier role

of drug delivery. In addition dynamic stability of carbon nanotube for delivering nanodrug is an interesting problem for some researchers.

In addition some literatures presented fluid-solid interaction for carbon nanotube. Shell-like instability of large diameter SWCNTs (single-walled carbon nanotubes) conveying fluid was presented in Ref. [13]. In this letter, molecular mechanics method was applied to make a FEM model for SWCNC.

The results showed that the vibration behavior of large diameter SWCNTs conveying fluid was different for several lengths and diameters of carbon nanotubes. In addition, the equivalent wall thickness of large diameter SWCNTs was verified according to the results of continuum shell theory.

Furthermore, wave propagation of fluid-conveying SWCNTs by gradient elasticity theory was studied in Ref. [14]. This report studied vibration properties of fluid-conveying SWCNTs according to the strain gradient elasticity theory.

Results showed that in the lowest wave numbers, effect of internal fluid flow on the velocity of upstream wave was considerable. However, in the highest wave numbers, this effect may be neglected.

In another report, vibration and instability of SWCNTs conveying fluid was presented [15]. In the present article, motion equations could be separated by DQM (differential quadrature method). The results showed that the coupled modes of utter could be appeared at the highest flow velocities.

In addition, dynamic behavior of TWCNTs (triple-walled carbon nanotubes) conveying fluid was studied in Ref. [16]. In this study, the Euler-Bernoulli beam was applied in order to model the covalent forces between the atoms of carbon. In addition, the van der Waals interactions between different TWCNTs were considered by Lennard-Jones potential energy. Results showed that the van der Waals interactions were considerable for TWCNTs.

The present work is a survey into dynamic stability of SWCNCs conveying fluid in bloodstream as a drug

delivery carrier. For this study, mode shapes and natural frequencies of carbon nanocone extracted using molecular mechanics approach. In addition mechanical properties of SWCNC were obtained by MM method. These obtained parameters are used for extraction of conical shell virtual model of nanocone with the same dimensions. The equations of coupled fluid-structural dynamics of SWCNCs are derived using the modal expansion of conical shell structural displacements and velocity potential flow field solution simultaneously. Boundary element method is used for separating the flow field and developing reduced order model for the fluid dynamics. The coupled fluid-structure interaction equations are solved using reduced order method and coupled system frequencies at different values of fluid velocity are obtained.

2. Objectives

In molecular mechanics method, basic structure of conical nano-medicine is clear. The structure and properties of drug delivery vehicle such as the atoms, atomic bond distance and location of each atoms is known. Usually conical structure of carrier is composed of two parts. A section of that is the conical structure with carbon atoms which only task of that is delivering drugs to the damaged cells and it must have proper stiffness to move into the bloodstream. Another section includes the basic structure of nano-drug carriers that can be used to repair damaged cells. This structure is usually based on Pharmacophore with Ligand based that is produced under laboratory conditions and includes the structure of atoms and with different properties which are located side by side and form the basic structure of a nano-drug. Also this part has a database or map for damaged cancer cells and according to this map, basic structure of nano-drug will be located on damaged cells and it will repair them.

The basic structure of delivery carriers in this study are carbon nanocones that synthetic polymer molecules (Dendrimers) are functionalized on the surface of carbon nanocones. These Dendrimers with diameters

less than 5 nm are able to pass from very small cell membranes. Dendrimers have a tree-like structure with many branches that different kinds of molecules can bind to them. In several experiments, methotrexate can be attached to Dendrimer branches. In other branches, fluorescence imaging agents and other needed components like Folic acid will be connected. Folic acid or Folate, is an important required vitamin for the function of cancer cells but it seems that cancer cells need to this vitamin exceedingly and cancer cells may be able to receive it, so special places as a Folate receptors are specified on their surface. The current researchers are using this advantage that cancer cells have a large appetite for Folate, they are able to prevent the resistance of cancer cells to chemotherapy. The connected Folate molecules on Dendrimers will be attached on the membranes of certain cancer cells and then Folate molecules can be entered into the cells because cell identifies it as a needed vitamin but actually entered Folate into the cancer cells will enter methotrexate with itself. In usual method of chemotherapy, drugs like methotrexate to enter into the cell must be passed from membrane that this process is very slow and requires a high concentration of drug in the extracellular space and the high concentration itself is harmful to normal cells.

In this report, single-walled carbon nanocones can carry Dendrimers and Folate to damaged cancer cells and dynamic stability analysis of these structures in bloodstream to prevent failures was studied.

3. Materials and Methods

3.1 Review to Molecular Mechanics Approach

One of the simplest methods for modeling the molecular systems is molecular mechanics approach. Generally, molecular mechanics method has three features:

1. Atoms are modeled as some nodes or point masses.
2. Bonded interactions between the two atoms are modeled as structural elements or springs with the certain stiffness.

3. Non-Bonded interactions between the two atoms are modeled as structural elements or springs with the certain stiffness that it can be obtained from the Lennard-Jones potential energy equation.

Therefore in the present article, carbon bonds of SWCNC were modeled using three-dimensional elastic beams (structural elements), atoms of carbon were considered as point masses (nodes). According to this method, modeling of SWCNC is feasible and mode shapes and frequencies of it, are extracted using MM approach. In addition mechanical properties of SWCNC were obtained by this simplification method.

3.2 Atomistic Modeling of Single-Walled Carbon Nanocone Using MM

In this section, MM method is used for modeling of SWCNC. Finite element modeling of SWCNC is used in this report to obtain its mode shapes, frequencies and mechanical properties. In addition four views of the predicted topologies on the conic tips are shown in Fig. 1 and Schematic representation of carbon nanocone is shown in Fig. 2.

Fig. 1 Four views of the predicted topologies on the conic tips with the length of 20Å°.

Fig. 2 Schematic representation of nanocone.

Fig. 3 Graphical representation of carbon nanocone and various bonds between carbon atoms.

The discrete structure of carbon nanocone is shown in Fig. 3. This carbon structure with different lengths and apex angles is used in finite element method. At first, the type of the element which is required in order to model the bonded interactions between the two atoms is determined and then features of these elements using MM must be obtained. In order to model the SWCNC, the covalent bonds between the two carbon atoms are considered as the three dimensional elastic beam elements. These elements should tolerate the torsional, bending and stretching loads as well as the van der Waals forces.

In addition the total potential energy of carbon atoms as called steric energy, according to Fig. 3, is obtained

from Eq. (1) [17, 18]:

$$E_{\text{StericEnergy}} =$$

$$E_{\text{str}} + E_{\text{bend}} + E_{\text{out of plane}} + E_{\text{dihedral}} + E_{\text{vdW}} \quad (1)$$

where, E_{str} , E_{bend} , $E_{\text{out of plane}}$, E_{dihedral} and E_{vdW} are the stretching, bending, out of plane, dihedral, torsional, and vdW energies, respectively. E_{str} represents the energy that it's needed to stretch or compress a covalent bond. A carbon bonded interaction can be considered as a spring with its own equilibrium length, r_0 . In addition the required energy to stretch or compress of this spring can be estimated by the Hookean potential in Eq. (2) [19]:

$$E_{\text{str}} = \frac{1}{2} k_{s,ij} (r_{ij} - r_0)^2 \quad (2)$$

In addition E_{bend} is the required energy to bend a bond from its equilibrium angle, θ_0 , and it can be estimated in Eq. (3) [19]:

$$E_{\text{bend}} = \frac{1}{2} k_{b,ijk} (\theta_{ijk} - \theta_0)^2 \quad (3)$$

$$E_{\text{outofplane}} = \frac{1}{2} k_{o,ijkl} (\omega_{ijkl} - \omega_0)^2 \quad (4)$$

E_{dihedral} is the needed energy of dihedral torsion to rotate about bonds that identifies as φ and it can be estimated in Eq. (5) [19]:

$$E_{\text{dihedral}} = \frac{1}{2} k_{\text{dihedral},1} (1 - \cos \varphi) + \frac{1}{2} k_{\text{dihedral},2} (1 - \cos 2\varphi) + \frac{1}{2} k_{\text{dihedral},3} (1 - \cos 3\varphi) \quad (5)$$

E_{vdW} is the long-range attraction energy and according to Lennard-Jones relation, this energy can be approximated in Eq. (6) [19]:

$$E_{\text{vdW}}(R) = 4\epsilon_{ij} \left(\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right) \quad (6)$$

Therefore according to these potentials, total potential of steric energy comes in Eq. (7) [19]:

$$E_{\text{Total}} = \frac{1}{2} \left[\sum_{\text{bonds}} k_b (b - b_0)^2 + \sum_{\text{angles}} k_\theta (\theta - \theta_0)^2 + \sum_{\text{torsion}} k_\varphi (\varphi - \varphi_0)^2 \right] \quad (7)$$

where, b , θ and φ are linear, bending and torsional terms, respectively. Value of the vdW energy is small therefore it can be ignored in comparison with the other energies.

In addition, k_b , k_θ and k_φ are stretching, bending and torsional stiffness, respectively. These constants can be obtained from computational chemistry. Therefore numerical values of them are $6.52 \times 10^{-7} \text{ N.nm}^{-1}$, $8.76 \times 10^{-10} \text{ N.nm.rad}^{-2}$ [20] and $2.78 \times 10^{-10} \text{ N.nm.rad}^{-2}$ [21], respectively.

From simplification of the structural and molecular energies in Eq. (7), the following formulations can be achieved in Eq. (8):

$$\frac{EA}{L} = k_b, \frac{EI}{L} = k_\theta, \frac{GJ}{L} = k_\varphi \quad (8)$$

where E and G are the elastic and shear modulus, and A , L , I and J are the cross-section, length, moment of

inertia and polar moment of inertia of the mentioned beam element, respectively. After some simplifications, the mechanical elastic characteristics of three dimensional beam elements with circular cross-section are calculated in Eq. (9) [17, 18]:

$$d = 4 \sqrt{\frac{k_\theta}{k_b}}, E = \frac{k_b^2 L}{4\pi k_\theta}, G = \frac{k_b^2 k_\varphi L}{8\pi k_\theta^2} \quad (9)$$

where d is the diameter of the beam element. In addition the elastic features of the beam element are obtained by substituting the MM constants into Eq. (9) and they presented in Eq. (10) [17, 18]:

$$d = 14.66 \text{ nm}, E = 5.448 \text{ Tpa}, G = 0.8701 \text{ Tpa} \quad (10)$$

These obtained characteristics can be used for obtaining the natural frequencies and applying in conical shell which is the virtual model of nanocone with the same dimensions.

3.3 Modal Analysis of SWCNC

According to obtained parameters of MM, natural frequencies of SWCNC can be obtained by the space-frame modeling of the carbon nanocone structure. The natural frequencies and corresponding mode shapes for an un-damped structure can be obtained from the solution of the eigenvalue problem that it introduced in Eq. (11):

$$(K_{sf} - \omega^2 M_{sf}) \bar{\delta} = 0 \quad (11)$$

where M_{sf} and K_{sf} are the global mass and stiffness matrices of the space-frame model of SWCNCs, respectively, $\bar{\delta}$ represents for the mode shapes and ω stands for the corresponding natural frequencies. These obtained frequencies and mode shapes can be applied for developing fluid-solid interaction model and obtaining dimensionless instability velocity of SWCNC.

3.4 Shell Model of Carbon Nanocone

To obtain dynamics instability velocities of carbon nanocone conveying Methotrexate and Folic Acid, SWCNC assumed as a conical shell model with the same dimensions and equivalent wall thickness [13]

but before that, natural frequencies of SWCNC were calculated in ANSYS.

Thus, covalent bonds and carbon atoms were considered as BEAM188 and MASS21 elements, respectively. Then, the dimensions of the parameters were further adjusted (Table 1) to avoid errors during the computation with ANSYS. After adjustment, the numerical parts of the input data were showed in Table 2 for the BEAM188 and MASS21 elements [22]. Then, using modal analysis, natural frequencies of SWCNC were obtained in ANSYS.

In this simulation, SWCNC can be considered as a conical shell with equivalent density of $N_{mc}/2\pi R t L$ where N_c , m_c are the total numbers of the carbon atoms in the network of SWCNC and mass of carbon atom, respectively. In addition t and L are thickness and length of carbon nanocone, respectively, and R is the equivalent radius of carbon nanocone which is given in Eq. (12):

$$R = \frac{R_1 + R_2}{2} \quad (12)$$

where as a simplification, R_1 and R_2 are tip and end radius of shell model of SWCNC, respectively. In addition equivalent thickness for carbon nanocone can be assumed the same as carbon nanotube that it introduced in Ref. [23]. Therefore according to these

features for SWCNC, nanocone space frame modeled. Then mode shapes and natural frequencies of it interpolated to the conical shell model which is shown in Fig. 4.

For a peculiar case, applied mode shapes to conical shell with the height of $10 \text{ \AA}$ and declination angle of 60° comes in Fig. 5.

In addition, in this moment notice to this issue is significant that equivalent shell doesn't play any structural role in the solution of the problem. The virtual

Table 1 Adjusted dimensions for ANSYS [22].

Division	Units	Scale
Length	m	$\times 10^{-10}$
Force	N	$\times 10^{-20}$
Mass	kg	$\times 10^{26}$
Youngs Modulus	Pa	1
Shear Modulus	Pa	1
Natural Frequency	Hz	$\times 10^{-8}$

Table 2 The input data prepared for the BEAM188 and MASS21 elements [22].

Division	Units	Values
C-C bond diameter	m	0.1466
Poisson ratio	-	0.3
Density	kg/m^3	2.3×10^3
Youngs Modulus	Pa	5.448×10^{12}
Shear Modulus	Pa	0.8701×10^{12}
Mass of carbon atom	kg	2

Fig. 4 Transferring nanocone space frame model to the shell model.

Fig. 5 Interpolated mode shapes of carbon nanocone with the height of $10 \text{ \AA}$ and declination angle of 60° in Clamped-Clamped (C-C) BCs, (A, B, C): Three mode shapes.

shell transfers the modal displacements of the hexagonal SWCNCs network into a quadrilateral mesh which is then used to apply the wall boundary condition to the flow inside the conical shell.

3.5 Structural Dynamic Modeling

By taking the modal expansion of the SWCNC deformations as $e = \sum_{n=1}^{N_s} \bar{e}_n \xi_n(t)$, the equation of the generalized modal coordinate vector ξ for analyzing the structural dynamics can be written as[24]:

$$\ddot{\xi} + \Omega \xi = F \quad (13)$$

In which Ω is a diagonal matrix defined as $\Omega_{ii} = \omega_i^2$ where ω_i is the natural frequency of the i^{th} mode. Furthermore, F stipulates the vector of the generalized structural force due to the flow pressure distribution p over the inside wall of the carbon nanocone and can be written as:

$$F = \int_s \tilde{e}_i \cdot n p ds, \quad i = 1, 2, \dots, N_s \quad (14)$$

where n is the normal vector at each point of the wall surface and N_s is the number of structural modes.

3.6 The Coupled Fluid-Structural Dynamic Model

In this study, blood flow assumed inside SWCNC as a carrier in drug delivery system. The applied pressure on the fluid-wall interface of the cylindrical shell can be calculated using the model of Paidoussis and Deise [23] as follows:

$$p_R = -\rho_f C_{mn} \left(\frac{\partial}{\partial t} + U \frac{\partial}{\partial x} \right)^2 w, \quad (15)$$

$$C_{mn} = \frac{L}{m\pi} \frac{I_n(m\pi R / L)}{I'_n(m\pi R / L)}$$

where U and ρ_f are the steady state flow speed and fluid density, respectively, and w is the radial displacement of the wall, m is the longitudinal half-wave number and n is the circumferential wave number. In addition I_n is the modified Bessel function of order n and I'_n is its derivative. For arbitrary geometries, Eq. (15) can be separated using finite

element approach as:

$$p = -\rho_f C_{mn} (N_w \ddot{e} + 2UN'_w \dot{e} + U^2 N''_w e) \quad (16)$$

where N_w explains the shape function matrix for the displacement w , i.e., $w = N_w e$, and the prime represents for derivation respect to x . After substituting interpolated displacement vector e into Eq. (15) and inserting the result into Eq. (14), the generalized forces can be calculated as:

$$F_i = -\left(\sum_{j=1}^{N_s} C^j_{mn} \tilde{e}^T_{m_j} \tilde{e}_j \ddot{\xi}_j + 2U \sum_{j=1}^{N_s} C^j_{mn} \tilde{e}^T_{c_j} \tilde{e}_j \dot{\xi}_j + U^2 \sum_{j=1}^{N_s} C^j_{mn} \tilde{e}^T_{k_j} \tilde{e}_j \xi_j \right) \quad (17)$$

where m_f , c_f and k_f are the flow related mass, damping and stiffness matrices, respectively, which are calculated by assembling the corresponding sub-matrices as:

$$m^e_f = \rho_f \int N_w^T N_w ds$$

$$c^e_f = \rho_f \int N_w^T N'_w ds \quad (18)$$

$$k^e_f = \rho_f \int N_w^T N''_w ds$$

Therefore the final form of Eq. (16) can be summarized as follows:

$$F = -(M_f \ddot{\xi} + 2UC_f \dot{\xi} + U^2 K_f \xi) \quad (19)$$

where the flow mass, damping and stiffness matrices are calculated as:

$$M^{(ij)}_f = C^j_{mn} \tilde{e}^T_{m_j} m_f \tilde{e}_j$$

$$C^{(ij)}_f = C^j_{mn} \tilde{e}^T_{c_j} c_f \tilde{e}_j \quad (20)$$

$$K^{(ij)}_f = C^j_{mn} \tilde{e}^T_{k_j} k_f \tilde{e}_j$$

After substituting Eq. (19) into Eq. (13), the fluid-structure equation obtains as:

$$\begin{bmatrix} 0 & \mathbf{I} + \mathbf{M}_f \\ \mathbf{I} & 0 \end{bmatrix} \begin{bmatrix} \dot{\xi} \\ \eta \end{bmatrix} + \begin{bmatrix} \Omega + U^2 \mathbf{K}_f & 2\mathbf{U} \mathbf{C}_f \\ 0 & -\mathbf{I} \end{bmatrix} \begin{bmatrix} \xi \\ \eta \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix} \quad (21)$$

where $\dot{\xi} = \eta$. Equation (20) can be used to analyze the coupled fluid structural dynamics and stability of SWCNC conveying fluid via their natural frequencies and structural mode shape vectors.

4. Results and Discussion

4.1 Validation

In this section, developed model for calculating dynamics instability velocity must be validated. For this purpose a specific carbon nanotube is selected and by this model, instability dimensionless velocity calculated and these results compared with those in Ref. [13]. Dimensionless parameters are introduced in Eq. (22):

$$w_0 = \sqrt{\frac{EI}{(m + m_f)L^4}}, \quad U_0 = \sqrt{\frac{EI}{m_f L^2}} \quad (22)$$

where EI is stiffness of bending, m is nanocone mass, m_f is fluid mass and L is nanocone length. Selected carbon nanotube has a length of 6.9nm with chirality of (88,0) with C-C BCs. For this case, reduced order model calculates the dimensionless instability velocity. The calculated dimensionless instability velocities are compared those in Ref. [13] in table 3 that it presents good agreement between obtained results and the literature in Ref. [13].

4.2 Results

Consider a SWCNC conveying Methotrexate and

Folic Acid with declination angle of 60° and length of $5A^\circ$ with C-C BCs at both ends. According to molecular mechanics approach, mechanical properties of SWCNC and the natural frequencies and mode shapes are obtained. The values of the reference Young modulus and wall thickness for all cases are assumed to be $E = 5.448 \text{ Tpa}$ and $t = 0.34 \text{ nm}$ respectively.

Using shell-like, mode shapes and frequencies a conical shell model for coupling the fluid-structural and the dimensionless divergence velocity for this structure can be obtained. These results are illustrated in Fig.6 for $\beta = 0.8$.

By increasing the flow speed, the fundamental frequency decreases and in dimensionless velocity of 3 becomes zero. Fig. 6 shows the behavior of the first four dimensionless frequencies versus the dimensionless velocity for this nanocone.

Table 3 Dimensionless instability velocities of (88,0) SWCNC conveying fluid.

SWCNT	Dimensionless Velocity	
	Ref. [13]	Present work
First mode	0.65	0.68
Second mode	0.88	0.90
Third mode	1.06	1.09

Fig. 6 Dimensionless frequency versus the dimensionless flow velocity for SWCNC conveying bloodstream with the length of $5A^\circ$ and declination angle of 60° .

Fig. 7 Dimensionless damping versus the dimensionless flow velocity for SWCNC conveying bloodstream with the length of $5A^0$ and declination angle of 60^0 .

Fig. 8 Dimensionless divergence velocity of SWCNC with declination angle of 60^0 versus different axial lengths in three modes of instability.

In addition, it can be seen that the dimensionless damping versus the dimensionless flow velocity for SWCNC conveying bloodstream with the length of $5A^0$ and declination angle of 60^0 is shown in Fig. 7. It shows that first dimensionless damping is negative and SWCNC is stable but in some dimensionless velocities it goes to positive values and SWCNC becomes

unstable. These dimensionless velocities are corresponded to the divergence velocities shown in Fig. 7.

In addition, dimensionless divergence flow velocity for SWCNC with declination angle of 60^0 versus axial lengths of SWCNC in three modes of instability is shown in Fig. 8.

Results show that by increasing the length of SWCNCs, the dimensionless divergence flow velocity decreases. In addition, by increasing the mode number, the dimensionless divergence flow velocity increases.

Now consider SWCNC with declination angle of 120° with C-C BCs at both ends. The dimensionless

divergence flow velocity for SWCNC with declination angle of 120° versus axial lengths of SWCNC in three modes of instability is shown in Fig. 9.

In addition dimensionless divergence flow velocity for SWCNC with declination angle of 240° versus axial lengths of SWCNC in three modes of instability is shown in Fig. 10.

Fig. 9 Dimensionless divergence velocity of SWCNC with declination angle of 120° versus different axial lengths in three modes of instability.

Fig. 10 Dimensionless divergence velocity of SWCNC with declination angle of 240° versus different axial lengths in three modes of instability.

In addition, the dimensionless divergence velocity for SWCNC with declination angles of 60° , 240° at the first mode of instability is plotted versus different axial lengths in Fig. 11.

Results show that by increasing the length of SWCNCs, dimensionless divergence velocity decreases. In addition, by decreasing declination angle of SWCNC, dimensionless divergence velocity decreases.

Finally, according to the nonlocal shell theory,

natural frequencies of SWCNC conveying Methotrexate and Folic Acid can be obtained for the different small scale factors (e_0a). Then reduced order method calculated divergence velocity of SWCNC conveying bloodstream. Therefore instability conditions of SWCNC conveying fluid were obtained for different small scale factors. The dimensionless divergence velocities for SWCNC with declination angle of 60° at the first mode of instability are plotted in Fig. 12.

Fig. 11 Dimensionless divergence velocity for SWCNC with declination angles of 60° , 240° at the first mode of instability.

Fig. 12 Dimensionless divergence velocities for SWCNC with declination angle of 60° at the first mode of instability and different e_0a .

Fig. 13 Dimensionless divergence velocities for SWCNC with declination angle of 240° at the first mode of instability and different $e0a$.

Fig. 14 Calibrated small scale factor of SWCNC by using the nonlocal shell theory and molecular approach.

Results show that by increasing the length of SWCNCs, the dimensionless divergence flow velocity decreases in all of small scale factors. In addition, by increasing small scale factors, the dimensionless divergence flow velocity decreases. In addition, Dimensionless divergence velocities for SWCNC with declination angle of 240° at the first mode of instability

are plotted in Fig.13.

In addition, by using the nonlocal shell theory and molecular mechanics approach, small scale factors can be calibrated in different length to radius ratios and declination angles of SWCNC. The calibrated small scale factor of SWCNC is plotted in Fig. 14.

Results show that by increasing the length to radius

ratio of SWCNCs, calibrated small scale factor increases in all of declination angles. In addition, by increasing the declination angle of SWCNC, calibrated small scale factor increases.

5. Conclusion

The dynamic stability of single walled carbon nanocone conveying Methotrexate and Folic Acid in bloodstream for some axial lengths and declination angles of 60° , 120° and 240° was studied according to the shell-like method.

In addition, carbon nanocone can be simulated as truncated conical shell with C-C BCs. Then coupled fluid-structural dynamic equations governed and for a velocity field, dimensionless frequencies were drawn versus dimensionless velocities and dimensionless divergence velocity was obtained. In addition, dimensionless divergence velocities were drawn versus axial length of carbon nanocone. Results show that by increasing the length of SWCNCs, dimensionless divergence velocity decreases. This behavior of SWCNC could be the result of the small-scale effect as same as the nanotube behavior in Ref. [13]. In addition, by decreasing the declination angle of SWCNC, dimensionless divergence velocity decreases; because stiffness of SWCNC will be decreased by decreasing the declination angle. Therefore SWCNC conveying Methotrexate and Folic Acid in bloodstream with axial length of $5A^\circ$ and declination angle of 240° is the more stable than other cases. In addition, by increasing the small scale factors or increasing the length of SWCNCs, the dimensionless divergence flow velocity decreases. Finally, by increasing the length to radius ratio of SWCNCs, calibrated small scale factor increases in all of declination angles and by increasing the declination angle of SWCNC and increasing the stiffness of SWCNC, calibrated small scale factor increases.

Also as an experimental work, some tests were conducted on laboratory mice that human epithelial cancer cells were injected to them. Results showed that drug therapy based on carbon nanocones in

reducing tumor growth is 10 times more effective than using only folic acid.

Also the toxic effects observed with nanocone-based therapy have been far less than treatment with usual medications.

In long-term experiments that lasted 99 days, 30 to 40 percent of the rats were survived that received carbon nanocones as carriers with methotrexate. Tumor growth in rats can be put off until 30 days using nanocone carriers. Also results showed that all mice treated quickly carbon nanocones from blood and they are excreted in the urine. No evidence was found to enter these carriers into the brain and carbon nanocones had no effect on the immune system of mice.

In addition to described experimental method in this paper, carrier structures as carbon nanocones were designed by molecular mechanics method. Results showed that these drug structures have a high effectiveness than nanotube drugs and in less time can deliver drugs to damaged cells and have a greater effect than previous nano drugs.

So, Experimental results showed that by attaching anticancer drugs to carbon nanocones, therapeutic response increases.

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