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Three model shapes of Doxorubicin for liposome encapsulation

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Abstract Targeted drug delivery provides a possible method for the transfer of drug molecules into cancer cells. Liposomes together with a drug, such as Doxorubicin (DOX) inside the liposomes, can be formed as a nano-capsule. In this study, we are interested in finding a favorable size of liposome and an appropriate shape of DOX cluster: sphere, cylinder or ellipsoid. Using mathematical modeling, the interaction energy of the system is obtained from the Lennard-Jones potential and the continuum assumption which assumes that discrete atomic structure can be replaced by an average atomic density spread over a surface. The numerical results show that the spherical shape gives the lowest energy at the equilibrium configuration amongst the three shapes. In the case of equivalent surface areas, the spherical shape gives the energy lower than −4,000 kJ/mol at the equilibrium while the energies for the other cases do not come close to this level. Further in the case of a liposome of 50 nm in radius, the sphere of radius 49.726 nm, equivalent to 31,072 nm^2 surface area, gives the minimum energy at −6,642 kJ/mol. However, an equivalent cylindrical shape is not possible due to geometric constraints. The lowest minimum energy for the ellipsoid occurs for equal major and minor axes, namely for the spherical case. The results presented here are a first step in the design and implementation of a drug molecule for a targeted drug delivery system.

Keywords Liposome · Doxorubicin · Lennard-Jones potential · Drug delivery

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Introduction

Cancer remains a major health problem around the world, even though many successful treatments have been developed so far. Based on GLOBOCAN 2008 report [1], there were over 10 million patients suffering from cancer, and about seven million of them died. Chemotherapy is an accepted treatment that can cure cancer and has raised the survival ratio in patients. A new approach for chemotherapy using nanotechnology is progressing in many research groups [2]. Using nanotechnology, nanocarriers can be designed to carry multiple drugs to the target cells based on size and shape of materials, surface functionality and the surrounding environment. There are many advantages for the use of nanocarriers over free drugs; that are; drugs can be protected from premature degradation and from interacting with the biological environment; the absorption of the drugs into selected target cells is increased, and the penetrating ability into other healthy cells is removed.

Doxorubicin(DOX) is a well known drug that has been widely used in cancer treatment. It has become well-known from its utilization of DOX primary form, adriamycin, to cure breast cancer, and the results show that adriamycin has more potential in the treatment [3]. A number of researchers have tried to directly transport DOX to targeted cells in order to reduce side effects from the chemotherapy treatment, and to investigate the capability of DOX in the cancer treatment. Meng et al. [4] and Heister et al. [5] utilize carbon nanotubes and decorated carbon nanotubes as a carrier for DOX. These authors find that both *in vitro* and *in vivo*, DOX encapsulated in carbon nanotubes is more effective than free DOX. Heister et al. [5] propose that single-walled carbon nanotubes have the potential to carry drug molecules to cancer cell sites. Lu et al. [6] utilize multi-walled carbon

nanotubes together with a magnetic field to load and unload DOX to the target. The efficiency of unloading depends on a pH condition. Wang et al. [7] investigate the efficiency of DOX transportation worn by laponite nanodisks. Further, Prabaharan et al. [8] use gold nanoparticles stabilized with a monolayer of copolymer as a carrier, where DOX is combined with other kind of chemical molecules [9, 10]. Meng et al. [11] design a new method to carry DOX to overcome a drug resistance in a cancer cell line using mesoporous silica as a drug vehicle. Their conclusion states that the mesoporous silica nanoparticles is applicable and the toxicity is less than the use of free DOX. Lankelma et al. [12] derive a simple mathematical model to predict the extent of cancer cell growth and the effect of DOX concentration in comparison to experimental data. They find that their model can be used to describe the findings in the experiment.

Liposome, a spherical structure comprising of two layers of lipid, is used as a delivery vehicle for gene therapy [13] and drug treatment [14] due to the ability of penetrating through the cell membrane. It is also considered as a carrier of DOX for cancer treatment. The suitable size of a liposome used as a nanocapsule ranges from 70 to 200 nm in diameter [15–17]. The shapes of DOXs, such as cylinder and ellipsoid, encapsulated in the liposome are varied depending on the method of the syntheses and the intensity of the solution. Furthermore, the size and shape of the liposome can also be modified to accommodate the shapes of those DOXs [18, 19]. Gordon et al. [20] study phase II stealth liposomal DOX in platinum- and paclitaxel-refractory ovarian cancer. The results suggest that stealth liposomal DOX has an activity in a refractory epithelial ovarian cancer, and the toxicity is low. Johnston and Gore [21] investigate the effect of Caelyx, a drug molecule consisting of DOX hydrochloride encapsulated in the stealth liposome, in phase II ovarian cancer. Caelyx has significantly affected the activity for the second-line treatment of ovarian cancer. Vaage et al. [22] utilize DOX encapsulated in sterically stabilized liposomes to treat human ovarian carcinoma xenografts, where mice tumor is used as a model. This study shows that not only DOX contained in liposomes can cure the cancer cell but it is also more effective than the use of free DOX. Hong et al. [23] compare the results of efficiency of DOX encapsulated in liposome between with and without surface coating, polyethylene glycol coating in C-26 tumor-bearing mice. They find that there is no difference between the two cases, and they conclude that surface coating with polyethylene glycol is not suitable for C-26 tumor-bearing. Lee and Low [24] study three conditions of DOX which are folate tumor cell targeting liposomal DOX, non-targeting liposomal DOX, and free DOX *in vitro*. The first case has 45 times of DOX loading higher than that in the DOX in non-targeting case, and 1.6 times of DOX loading higher than that in the case of free DOX. However, the toxicity of the first case is also higher than the latter two cases. Moreover, Ahmad et al. [25] state that a liposome encapsulating DOX is highly successful in the treatment of lung cancer in mice.

In terms of mathematics, Baowan et al. [26] study the energy behavior of liposomes encapsulating silica compound as a representative of a drug molecule. Their results show that the equilibrium radius of liposome is in a relationship with the location of the silica compound. Their study inspires us to progressively study the drug molecule contained inside a liposome. Here, we consider a cluster of DOX molecules as a drug molecule, and employ a principled mathematical technique to calculate the energy of the system. The configuration of a lipid molecule in a liposome is taken from the Martini coarse grain model [27] and the Lennard- Jones parameters are taken from the work of Baowan et al. [26]. Our liposomal systems do not consider the effect from the solution both inside and outside the liposomes. We assume first that DOX and liposomes are stable then we investigate the energy between them from the Van der Waals force between non-bonded atoms. In other words, this is the interaction energy of the system.

In this paper, the molecular interaction between two molecules is given in the next section. Then a mathematical derivation is presented, and the calculation of the interaction energy between a drug and a liposome is detailed in section "Interaction energy between drug and liposome". Furthermore, the numerical result is given in section "Numerical result and discussion". Finally, a discussion of this study is presented in section "Summary".

Molecular interaction

The non-bonded interaction energy between two molecules of discrete structures is obtained by a summation of all non-bonded atomic pairs

$$E = \sum_i \sum_j \Phi(\rho_{ij}),$$

where $\Phi(\rho_{ij})$ is the potential function of atom i and atom j and ρ_{ij} is the distance from the atom i to atom j. When the number of atomic pairs tends to infinity, the summation can be replaced by the integration, hence the total potential energy can be calculated using the continuous approximation. In this study, we consider two cases of the integration depending on the structural layers of the liposome which can be either spherical surface or spherical volume. Firstly, we assume that atoms are uniformly distributed over the surface of a drug molecule and of a layer of a liposome, then we

employ double surface integral instead of double summation to give

$$E = \eta_1 \eta_2 \int_{S_2} \int_{S_1} \Phi(\rho) \mathrm{d}S_1 \mathrm{d}S_2,$$

where η_1 and η_2 are the mean surface densities of the drug and the intermediate layer of a liposome, respectively. S_1 and S_2 are surface elements of the drug and of the intermediate layer of a liposome. Secondly, we assume the surface integral for a drug molecule whereas atoms on a layer of a liposome are assumed to be distributed over a spherical volume. Then we utilize a volume integral of liposome where we may deduce

$$E = \eta\omega \int_V \int_S \Phi(\rho) \mathrm{d}S \mathrm{d}V,$$

here η is the mean surface density of the drug, and ω is the mean volume density of the liposome. S is the surface element of the drug, and V is the volume element of a thick layer of a liposome.

In this research, we use 6–12 Lennard-Jones potential to calculate the energy of system. The function can be written in a form

$$\Phi(\rho) = 4\epsilon \left[-\left(\frac{\sigma}{\rho}\right)^6 + \left(\frac{\sigma}{\rho}\right)^{12} \right],$$

where ϵ is the well depth and σ is the Van der Waals diameter. For the different types of atoms, we can use an empirical mixing rule for ϵ and σ which are given by $\epsilon = (\epsilon_1 \epsilon_2)^{1/2}$ and $\sigma = (\sigma_1 + \sigma_2)/2$, where number 1 and number 2 are assigned to atomic type 1 and 2, respectively. The Lennard-Jones potential function can also be rewritten as

$$\Phi(\rho) = -\frac{A}{\rho^6} + \frac{B}{\rho^{12}},$$

where $A = 4\epsilon\sigma^6$ and $B = 4\epsilon\sigma^{12}$ are the attractive and repulsive constants, respectively. Throughout this study, we utilize the second form of the function to calculate the energy of the system.

In this work, we only consider the van der Waals interaction arising from the Lennard-Jones function. It has been shown that the electrostatic energy plays only a minor role in the system involving a liposome encapsulating a charged particle [26].

Mathematical derivations

In this research, we study three different shapes of a drug molecule; that are, sphere, cylinder, and ellipsoid, encapsulated at the centre of a liposome. Further, we assume that the energy contribution of the drug arising only from the surface, hence a surface integral is used. In terms of the liposome, it comprises of six layers which are two head groups, two intermediate layers and two tail groups. The intermediate layers are modelled as spherical surfaces, whereas the head groups and the tail groups are represented by the spherical shell shape. Hence, both surface and volume integrals are utilized to determine the energy contribution arising from the liposomal capsule. To start, we introduce the calculations for surface and volume integrals for the capsule and they are presented in the following sections. Then the surface integrals for the three shapes of the drug are determined.

Spherical surface integral of the capsule

The interaction energy between a spherical surface and a point is given by

$$E = \eta \int_S \Phi(\rho) \mathrm{d}S,$$

which can be written in the spherical coordinates as,

$$\begin{aligned} E &= \eta \int_{-\pi}^{\pi} \int_0^{\pi} \Phi(\rho) a^2 \sin\phi \, \mathrm{d}\phi \mathrm{d}\theta \\ &= \eta \int_{-\pi}^{\pi} \int_0^{\pi} \left(-\frac{A}{\rho^6} + \frac{B}{\rho^{12}} \right) a^2 \sin\phi \, \mathrm{d}\phi \mathrm{d}\theta, \end{aligned} \tag{1}$$

where η is the mean atomic surface density of the sphere and a is the radius of the sphere. A schematic model for an atom interacting with a spherical surface is depicted in Fig. 1a. Now we consider

$$I_n^S = \int_{-\pi}^{\pi} \int_0^{\pi} \frac{a^2 \sin\phi}{\rho^{2n}} \mathrm{d}\phi \mathrm{d}\theta, \quad n = 3, 6.$$

Noting that $E = \eta(-AI_3^S + BI_6^S)$. The coordinates for a point and a spherical surface centred at the origin are given by

$$\begin{aligned} (x_p, y_p, z_p) &= (0, 0, \delta), \quad \text{and} \\ (x_s, y_s, z_s) &= (a\sin\phi\cos\theta, a\sin\phi\sin\theta, a\cos\phi). \end{aligned}$$

Consequently, the distance ρ^2 between the two points can be given by $\rho^2 = a^2 + \delta^2 - 2a\delta\cos\phi$. Hence, I_n^S becomes

$$I_n^S = a^2 \int_{-\pi}^{\pi} \int_0^{\pi} \frac{\sin\phi}{(a^2 + \delta^2 - 2a\delta\cos\phi)^n} \mathrm{d}\phi \mathrm{d}\theta.$$

We let $t = a^2 + \delta^2 - 2a\delta\cos\phi$ and change the integration variable to obtain

$$I_n^S = \frac{\pi a}{\delta(n-1)} \left[\frac{1}{(a-\delta)^{2(n-1)}} - \frac{1}{(a+\delta)^{2(n-1)}} \right].$$

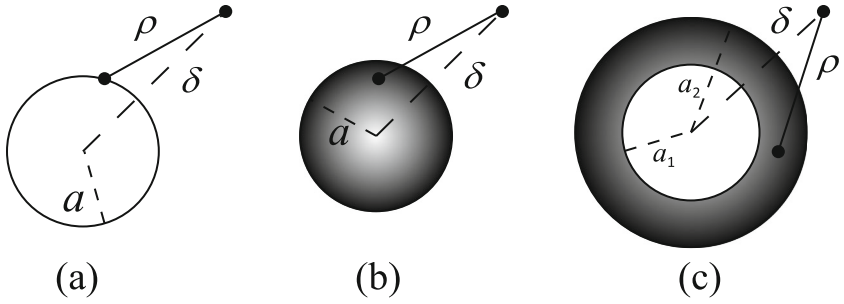

Fig. 1 An atom interacting with (**a**) spherical surface, (**b**) spherical volume, and (**c**) spherical shell volume

Next, we use a binomial expansion for the terms $(a-\delta)^{2(n-1)}$ and $(a+\delta)^{2(n-1)}$, and eliminate the zero summation, so we get

$$I_n^S = \frac{2\pi}{n-1}\sum_{k=0}^{n-2}\binom{2(n-1)}{2k+1}\frac{a^{2(n-k-1)}\delta^{2k}}{(a^2-\delta^2)^{2(n-1)}},\quad n=3,6. \tag{2}$$

We note that

$$(a+\delta)^{2(n-1)} = \sum_{k=0}^{2(n-1)}\binom{2(n-1)}{k}a^{2(n-1)-k}\delta^k.$$

Spherical volume integral of the capsule

The interaction energy between a spherical volume and a point, as illustrated in Fig. 1b, is given by

$$E = \omega\int_V \Phi(\rho)\mathrm{d}V = \omega\int_0^{\pi}\int_{-\pi}^{\pi}\int_0^a \Phi(\rho)r^2\sin\phi\,\mathrm{d}r\mathrm{d}\theta\mathrm{d}\phi,$$

where ω is the mean volume density of the sphere. Similar to a previous case, we consider

$$I_n^V = \int_0^{\pi}\int_{-\pi}^{\pi}\int_0^a \frac{r^2\sin\phi}{\rho^{2n}}\mathrm{d}r\mathrm{d}\theta\mathrm{d}\phi,\quad n=3,6.$$

In this case, the coordinates for a point and a typical volume element of a sphere centred at the origin are given by

$$\begin{aligned}(x_p, y_p, z_p) &= (0,0,\delta),\quad \text{and}\\ (x_v, y_v, z_v) &= (r\sin\phi\cos\theta, r\sin\phi\sin\theta, r\cos\phi).\end{aligned}$$

Then, we have $\rho^2 = r^2+\delta^2-2r\delta\cos\phi$ and I_n^V becomes

$$\begin{aligned}I_n^V &= \int_0^{\pi}\int_{-\pi}^{\pi}\int_0^a \frac{r^2\sin\phi}{(r^2+\delta^2-2r\delta\cos\phi)^n}\mathrm{d}r\mathrm{d}\theta\mathrm{d}\phi\\ &= \frac{\pi}{\delta(n-1)}\int_0^a\left[\frac{r}{(r-\delta)^{2(n-1)}}-\frac{r}{(r+\delta)^{2(n-1)}}\right]\mathrm{d}r.\end{aligned}$$

We use a by parts integral technique to integrate each term, and then combine the coefficients of the same polynomials to obtain

$$\begin{aligned}I_n^V = &-\frac{\pi a}{\delta(n-1)(2n-3)}\left(\frac{1}{(a-\delta)^{2n-3}}-\frac{1}{(a+\delta)^{2n-3}}\right)\\ &-\frac{\pi}{\delta(n-1)(2n-3)(2n-4)}\left(\frac{1}{(a-\delta)^{2n-4}}-\frac{1}{(a+\delta)^{2n-4}}\right).\end{aligned}$$

Next, we employ a binomial expansion for $(a-\delta)^{2n-3}$, $(a+\delta)^{2n-3}$, $(a-\delta)^{2n-4}$, and $(a+\delta)^{2n-4}$ then eliminate the zero summation, so we have

$$\begin{aligned}I_n^V = &-\frac{2\pi}{(n-1)(2n-3)}\sum_{k=0}^{n-2}\binom{2n-3}{2k+1}\frac{a^{2(n-k-2)+1}\delta^{2k}}{(a^2-\delta^2)^{2n-3}}\\ &-\frac{\pi}{(n-1)(n-2)(2n-3)}\sum_{k=0}^{n-3}\binom{2(n-2)}{2k+1}\\ &\times\frac{a^{2(n-k-2)-1}\delta^{2k}}{(a^2-\delta^2)^{2(n-2)}},\quad n=3,6.\end{aligned}$$

For the spherical shell shape as shown in Fig. 1c, the interaction energy may obtain by subtracting the interaction energy between a point and a smaller spherical volume from that of a larger spherical volume. We assume that a_1 and a_2 are the radii of an inner and an outer spheres, respectively, therefore, we may deduce

$$\begin{aligned}I_n^V = &-\frac{2\pi}{(n-1)(2n-3)}\sum_{k=0}^{n-2}\binom{2n-3}{2k+1}\\ &\times\left[\frac{a_2^{2(n-k-2)+1}\delta^{2k}}{(a_2^2-\delta^2)^{2n-3}}-\frac{a_1^{2(n-k-2)+1}\delta^{2k}}{(a_1^2-\delta^2)^{2n-3}}\right]\\ &-\frac{\pi}{(n-1)(n-2)(2n-3)}\sum_{k=0}^{n-3}\binom{2(n-2)}{2k+1}\\ &\times\left[\frac{a_2^{2(n-k-2)-1}\delta^{2k}}{(a_2^2-\delta^2)^{2(n-2)}}-\frac{a_1^{2(n-k-2)-1}\delta^{2k}}{(a_1^2-\delta^2)^{2(n-2)}}\right],n=3,6.\end{aligned} \tag{3}$$

Note that both Eqs. 2 and 3 have the terms $\delta^{2k}/(a^2-\delta^2)^m$ which involve a distance between two elements where m and k are integers. For convenient, we define $I_m^* = \delta^{2k}/(a^2-\delta^2)^m$, and next we need to integrate I_m^* with

respect to a shape of the drug molecule to obtain a molecular interaction between a drug and a spherical capsule.

Spherical drug molecule

We consider both the interaction energies between a spherical drug molecule and an outer spherical surface, and that between a spherical drug molecule and an outer spherical shell volume as shown in Fig. 2. The coordinates for atoms on a drug molecule are given by

$$(x, y, z) = (b\sin\phi\cos\theta, b\sin\phi\sin\theta, b\cos\phi),$$

where b is a radius of the drug. Next we calculate

$$J_{m,a} = \int_{-\pi}^{\pi}\int_{0}^{\pi} I_m^* b^2 \sin\phi \,\mathrm{d}\phi\mathrm{d}\theta = \int_{-\pi}^{\pi}\int_{0}^{\pi} \frac{\delta^{2k}}{(a^2-\delta^2)^m} b^2 \sin\phi \,\mathrm{d}\phi\mathrm{d}\theta.$$

For the spherical shape, $\delta^2 = b^2$ is the distance from the centre of a liposome to a surface of the drug molecule, so we may deduce

$$J_{m,a} = \int_{-\pi}^{\pi}\int_{0}^{\pi} \frac{b^{2k}}{(a^2-b^2)^m} b^2 \sin\phi \,\mathrm{d}\phi\mathrm{d}\theta.$$

By straightforward integration technique, we get

$$J_{m,a} = \frac{4\pi b^{2(k+1)}}{(a^2-b^2)^m}. \tag{4}$$

The interaction energy I_n^S between the outer spherical surface and the drug can be obtained by substituting $J_{m,a}$ given by Eq. 4 into Eq. 2, whereas the interaction energy I_n^V between the outer spherical shell volume and the drug can be determined by substitute $J_{m,a}$ defined by Eq. 4 into Eq. 3. Further, the total energies of the two systems can be evaluated by $\eta_1\eta_2(-AI_3^S + BI_6^S)$ and $\eta\omega(-AI_3^V + BI_6^V)$, respectively.

Cylindrical drug molecule

In the case of a cylindrical drug molecule, we consider both the cylindrical surface area and the two circular areas at the ends. The details are as follows.

Cylindrical surface area

The coordinates for atoms on a cylindrical surface are given by

$$(x, y, z) = (b\cos\varphi, b\sin\varphi, z),$$

where b is a radius of the cylindrical drug molecule with length L as depicted in Fig. 3. Next we evaluate

$$J_{m,a}^1 = \int_{-L/2}^{L/2}\int_{-\pi}^{\pi} I_m^* b \,\mathrm{d}\varphi\mathrm{d}z = \int_{-L/2}^{L/2}\int_{-\pi}^{\pi} \frac{\delta^{2k}}{(a^2-\delta^2)^m} b \,\mathrm{d}\varphi\mathrm{d}z.$$

For the cylindrical shape, we have $\delta^2 = b^2 + z^2$, so that we may deduce

$$J_{m,a}^1 = \int_{-L/2}^{L/2}\int_{-\pi}^{\pi} \frac{(b^2+z^2)^k}{[a^2-(b^2+z^2)]^m} b \,\mathrm{d}\varphi\mathrm{d}z.$$

We then expand $[a^2-(b^2+z^2)]^m$ using a binomial expansion to obtain

$$J_{m,a}^1 = 4\pi b \sum_{l=0}^{\infty} \binom{m+l-1}{l} \frac{1}{a^{2(m+l)}} \int_0^{L/2} (b^2+z^2)^{k+l} \mathrm{d}z.$$

Let $z = b\tan\alpha$, then $J_{m,a}^1$ becomes

$$J_{m,a}^1 = 4\pi \sum_{l=0}^{\infty} \binom{m+l-1}{l} \frac{b^{2(k+l+1)}}{a^{2(m+l)}} \int_0^{\arctan(L/2b)} \frac{1}{(\cos^2\alpha)^{k+l+1}} \mathrm{d}\alpha.$$

We use the integral expression from the formula TI (240) given in [28] which is

$$\int \frac{\mathrm{d}x}{(\cos^2 x)^\nu} = \frac{\sin x}{2\nu-1} \times \left[\sec^{2\nu-1}x + \sum_{i=1}^{\nu-1} \frac{2^{2i-1}\Gamma^2(\nu)\Gamma(2\nu-2i-1)}{(\nu-1)\Gamma^2(\nu-i)\Gamma(2(\nu-1))} \sec^{2\nu-2i-1}x\right].$$

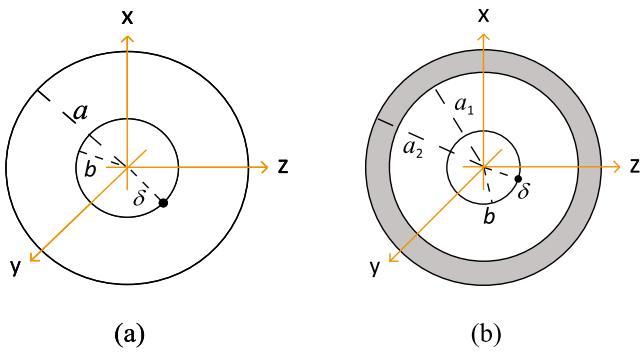

Fig. 2 Spherical drug molecule interacting with (**a**) outer spherical surface and (**b**) outer spherical shell volume

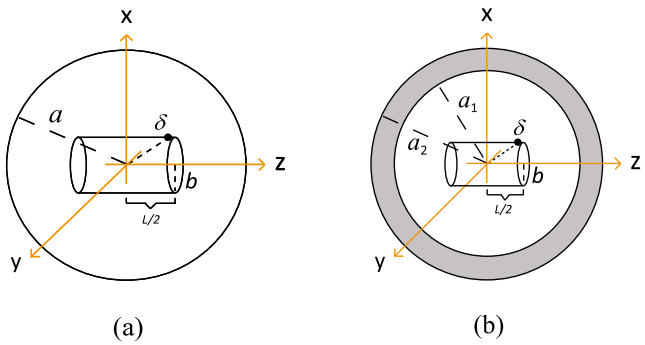

Fig. 3 Cylindrical drug molecule interacting with (**a**) outer spherical surface and (**b**) outer spherical shell volume

Now we define $D_\nu(x) = \int(\cos^2 x)^{-\nu}\mathrm{d}x$, so we have

$$J^1_{m,a} = 4\pi \sum_{l=0}^{\infty} \binom{m+l-1}{l} \frac{b^{2(k+l+1)}}{a^{2(m+l)}} \times \Big[D_{k+l+1}(\arctan(L/2b)) - D_{k+l+1}(0) \Big],$$

and if $k=0$ and $l=0$ then $D_1(x) = L/2b$ for any value of x.

Circular areas at the two ends

The coordinates for atoms on the open ends of the cylinder are given by

$$(x, y, z) = (r\cos\varphi, r\sin\varphi, \pm L/2),$$

Now, we have $\delta^2 = r^2 + L^2/4$, so that we may deduce

$$J^2_{m,a} = \int_0^{2\pi}\int_0^b \frac{(L^2/4+r^2)^k}{[a^2-(L^2/4+r^2)]^m} r\,\mathrm{d}r\mathrm{d}\varphi.$$

Follow the similar method, we expand $[a^2-(L^2/4+r^2)]^m$ using a binomial expansion to obtain

$$J^2_{m,a} = 2\pi \sum_{l=0}^{\infty} \binom{m+l-1}{l} \frac{1}{a^{2(m+l)}} \int_0^b (L^2/4+r^2)^{k+l} r\,\mathrm{d}r.$$

Let $t = L^2/4 + r^2$, then the equation can be straightforwardly integrated to obtain

$$J^2_{m,a} = \pi \sum_{l=0}^{\infty} \binom{m+l-1}{l} \times \frac{a^{-2(m+l)}}{k+l+1} \Big[(L^2/4+b^2)^{k+l+1} - (L^2/4)^{k+l+1} \Big].$$

Therefore, we have

$$J_{m,a} = J^1_{m,a} + 2J^2_{m,a} = \pi \sum_{l=0}^{\infty} \binom{m+l-1}{l} \frac{1}{a^{2(m+l)}} \times \Big[4b^{2(k+l+1)} \big[D_{k+l+1}(\arctan(L/2b)) - D_{k+l+1}(0) \big] + 2\frac{1}{k+l+1} \Big[(L^2/4+b^2)^{k+l+1} - (L^2/4)^{k+l+1} \Big] \Big]. \quad (5)$$

Ellipsoidal drug molecule

The coordinates for atoms on an ellipsoidal surface are given by

$$(x, y, z) = (b\sin\phi\cos\theta, b\sin\phi\sin\theta, c\cos\phi),$$

where b is a minor axis of the ellipsoid and c is a major axis of the ellipsoid as shown in Fig. 4. Next we determine

$$J_{m,a} = \int_{-\pi}^{\pi}\int_0^{\pi} I^*_m b\sin\phi \Big[(b\cos\phi)^2 + (c\sin\phi)^2 \Big]^{1/2} \mathrm{d}\phi\mathrm{d}\theta = \int_{-\pi}^{\pi}\int_0^{\pi} \frac{\delta^{2k}}{(a^2-\delta^2)^m} b\sin\phi \Big[(b\cos\phi)^2 + (c\sin\phi)^2 \Big]^{1/2} \mathrm{d}\phi\mathrm{d}\theta.$$

For the ellipsoidal shape, $\delta^2 = (b\sin\phi)^2 + (c\cos\phi)^2$, so we may deduce

$$J_{m,a} = \int_{-\pi}^{\pi}\int_0^{\pi} \frac{[(b\sin\phi)^2 + (c\cos\phi)^2]^k}{[a^2-(b\sin\phi)^2-(c\cos\phi)^2]^m} b\sin\phi \times \Big[(b\cos\phi)^2 + (c\sin\phi)^2 \Big]^{1/2} \mathrm{d}\phi\mathrm{d}\theta.$$

The above integrand is independent of θ, therefore we have 2π, and then we rearrange the above integral to obtain

$$J_{m,a} = 4\pi b(-1)^m (b^2+c^2)^k \times \int_0^{\pi/2} \frac{\sin\phi \Big[1 - \frac{(b\cos\phi)^2+(c\sin\phi)^2}{b^2+c^2} \Big]^k [(b\cos\phi)^2+(c\sin\phi)^2]^{1/2}}{[-(a^2-b^2)+(c^2-b^2)\cos^2\phi]^m} \mathrm{d}\phi.$$

On expanding $\Big[1 - \frac{(b\cos\phi)^2+(c\sin\phi)^2}{b^2+c^2} \Big]^k$ in terms of a binomial expansion then $J_{m,a}$ becomes

$$J_{m,a} = \frac{4\pi b}{(a^2-b^2)^m} \sum_{i=0}^{k} \binom{k}{i} (-1)^i (b^2+c^2)^{k-i} c^{2i+1} \times \int_0^{\pi/2} \frac{\sin\phi(1-\alpha\cos^2\phi)^{i+1/2}}{(1-\beta\cos^2\phi)^m} \mathrm{d}\phi,$$

where $\alpha = (c^2-b^2)/c^2$ and $\beta = (c^2-b^2)/(a^2-b^2)$. Next we let $t = \cos^2\phi$, so

$$J_{m,a} = \frac{2\pi b}{(a^2-b^2)^m} \sum_{i=0}^{k} \binom{k}{i} (-1)^i (b^2+c^2)^{k-i} c^{2i+1} \times \int_0^1 t^{-1/2}(1-\alpha t)^{i+1/2}(1-\beta t)^{-m}\mathrm{d}t.$$

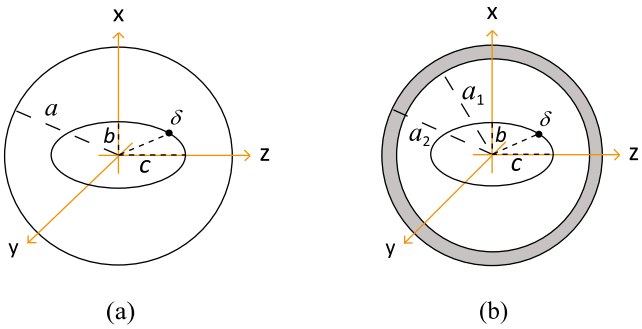

Fig. 4 Ellipsoidal drug molecule interacting with (**a**) outer spherical surface and (**b**) outer spherical shell volume

On using a relationship of an Appell hypergeometric function F_1 as given in eq.5 page 231 of [29] where

$$F_1(\alpha;\beta,\beta';\gamma;x,y)=\frac{\Gamma(\gamma)}{\Gamma(\alpha)\Gamma(\gamma-\alpha)}\times\int_0^1 u^{\alpha-1}(1-u)^{\gamma-\alpha-1}(1-ux)^{-\beta}(1-uy)^{-\beta'}\mathrm{d}u,$$

we may deduce

$$J_{m,a}=\frac{4\pi b}{(a^2-b^2)^m}\times\sum_{i=0}^{k}\binom{k}{i}(-1)^i(b^2+c^2)^{k-i}c^{2i+1}\times F_1(1/2;-i-1/2,m;3/2;\alpha,\beta).$$

Further, it can be written as a usual hypergeometric function F as

$$J_{m,a}=\frac{4\pi b}{(a^2-b^2)^m}\sum_{i=0}^{k}\binom{k}{i}(-1)^i(b^2+c^2)^{k-i}c^{2i+1}\times\sum_{l=0}^{\infty}\frac{(1/2)_l(-i-1/2)_l}{l!(3/2)_l}\times F(l+\frac{1}{2},m;l+\frac{3}{2};\beta)\alpha^l, \quad (6)$$

where $(a)_l$ is a Pocchammer's symbol. We note that

$$F_1(a;b,b';c;x,y)=\sum_{m=0}^{\infty}\frac{(a)_m(b)_m}{m!(c)_m}F(a+m,b';c+m;y)x^m,$$

and $(a)_l=\frac{\Gamma(a+l)}{\Gamma(a)}=(a)(a+1)...(a+l-1)$.

Completed formulae for liposome encapsulating drug molecule

For the surface integral of the outer sphere referring to Eq. 2, the energy for each case of the three shapes of the drug molecule is obtained as

$$E=\eta\eta^*\left(-AI_3^S+BI_6^S\right), \quad (7)$$

where

$$I_n^S=\frac{2\pi}{n-1}\sum_{k=0}^{n-2}\binom{2(n-1)}{2k+1}a^{2(n-k-1)}J_{2(n-1),a},$$

and η^* is the mean surface density of the drug. The three cases of the drug configurations correspond to the function $J_{m,a}$ given by Eqs. 4, 5 and 6 for the spherical, cylindrical and ellipsoidal drug molecules, respectively.

Similarly, for the case of the outer spherical shell volume given by Eq. 3, the interaction energies for the three cases of the drug molecules can be obtained as

$$E=\omega\eta^*\left(-AI_3^V+BI_6^V\right), \quad (8)$$

where

$$I_n^V=-\frac{2\pi}{(n-1)(2n-3)}\sum_{k=0}^{n-2}\binom{2n-3}{2k+1}\times\left[a_2^{2(n-k-2)+1}J_{2n-3,a_2}-a_1^{2(n-k-2)+1}J_{2n-3,a_1}\right]-\frac{\pi}{(n-1)(n-2)(2n-3)}\sum_{k=0}^{n-3}\binom{2(n-2)}{2k+1}\times\left[a_2^{2(n-k-2)-1}J_{2(n-2),a_2}-a_1^{2(n-k-2)-1}J_{2(n-2),a_1}\right],$$

and $J_{m,a}$ for the spherical, cylindrical and ellipsoidal molecules can be found in Eqs. 4, 5 and 6, respectively.

Interaction energy between drug and liposome

The Dipalmitoylphosphatidylcholine (DPPC) molecular structure is utilized in this study. We employ the coarse grain configuration proposed by Martini et al. [27], where Q_0 and Q_a represent a choline and a phosphate positions, respectively, which are assumed to be a head group. A glycerol group is referred as N_a and it is an intermediate layer. Further, the carbon tail group is defined as C_1. The values of the Lennard-Jones parameters σ and ϵ corresponding to Q_0, Q_a, N_a and C_1 are taken from the work of Martini et al. [27], and they are given in Table 1.

A liposome consists of two layers of lipid, hence the summation of six interaction energies belonging to the six component layers of lipid are needed to determine the total energy of the system. These six layers comprise two spherical surfaces, that are two intermediate layers, and four volume spherical shells, that are two head group layers and two tail group layers. The physical dimensions of the lipid layer and the structure of a liposome are detailed in Fig. 5.

In this study, Doxorubicin (DOX) is employed to demonstrate the interaction behavior for a drug in a liposomal capsule, where its chemical formula is $C_{27}H_{29}NO_{11}$. The

Table 1 Values of well depth ϵ and Van der Waals diameter σ used in this model

	ϵ (kJ/mol)	σ (nm)
Q_0	5.0000	0.4700
Q_a	5.6000	0.4700
N_a	4.5000	0.4700
C_1	2.3000	0.4700
C	0.4393	0.3431
H	0.1841	0.2571
O	0.2510	0.3118
N	0.2887	0.3261

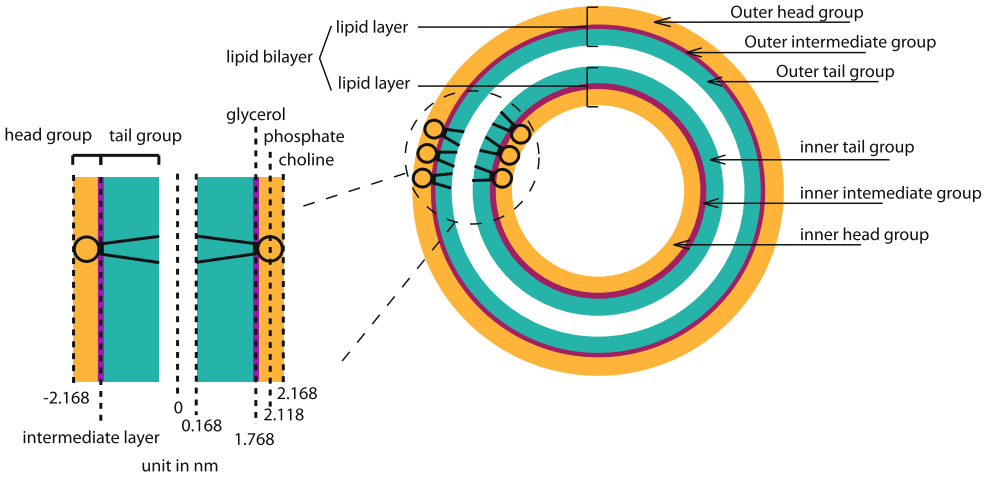

Fig. 5 A liposome comprising two layers of lipid

Van der Waals parameters σ and ϵ for each atomic type of the drug molecule, which are C, H, N, and O, are taken from Rappé et al. [30], and are presented in Table 1. Further, we assume that the drug is comprised of uniformly distributed DOX molecules, therefore the atomic proportion of the molecule is used to present the chemical structure of the drug.

The attractive and the repulsive energies are calculated from entire possible matching between atoms from the drug molecule and atoms from each layer of the liposome. Therefore, the Lennard-Jones constants A and B can be determined as follow. Firstly, the head group has eight possible matching that are C, H, N, and O interacting with Q_0 and Q_a. Additionally, there are 27 carbon atoms, 29 hydrogen atoms, one nitrogen atom and 11 oxygen atoms, so the total interaction pairs are $2(27+29+1+11) = 136$. Next, the intermediate group has one type of lipid molecule that is N_a hence the total interaction pairs are 68. Finally, a number of an atomic group of the tail group is similar with the intermediate group where it comprises of only C_1. Therefore, there are 68 interaction pairs for the tail group.

The attractive and repulsive constants A and B for each layer interacting with DOX can be obtained by employing an empirical mixing rule. Table 2 shows applicable values A and B used in this study where A_H, A_I, and A_T are total attractive constants for the head group, the intermediate group, and the tail group, respectively, and B_H, B_I, and B_T are total repulsive constants for the head group, the intermediate group, and the tail group, respectively.

Table 2 Attractive and Repulsive constants for three layers of liposome interacting with DOX

	A (kJ nm^6 mol^{-1})	B (10^{-5} kJ nm^{12} mol^{-1})
Head (H)	0.01778	6.90489
Intermediate (I)	0.01639	6.36178
Tail (T)	0.01172	4.54817

According to Martini et al. [27], there are two interaction sites for the head group and the intermediate layer, where there are eight interaction sites for the tail group. These interaction sites will contribute to the mean surface and the mean volume densities of the system. Hence, the mean surface density η and the mean volume density ω for each layer of the liposome can be obtained by

$$\omega_H(r) = \frac{2N_{lipids}(r)}{4\pi(r+4.336)^3/3},$$
$$\eta_I(r) = \frac{2N_{lipids}(r)}{4\pi(r+4.336)^2},$$
$$\omega_T(r) = \frac{8N_{lipids}(r)}{4\pi(r+4.336)^3/3},$$

where r is the inner radius of the liposome, ω_H and ω_T are the mean volume densities of the head and the tail, respectively, and η_I is the mean surface density of the intermediate layer. Further, $N_{lipids(r)}$ represents a number of lipid molecules which can be obtained by $N_{lipids}(r) = [4\pi(r+4.336)^2 + 4\pi r^2]/0.64$, where the value of 4.336 nm is the thickness of a lipid bilayer and 0.64 nm^2 is one lipid head group area. For the mean surface density of DOX, η^*, we derive from the molar volume by assuming a spherical shape of DOX cluster, so it is 0.3047 molecule/nm^2. The total energy for each of the three shapes of drug encapsulated in a liposome is given by

$$E_{tot} = E_{outerH} + E_{outerI} + E_{outerT} + E_{innerT} + E_{innerI} + E_{innerH}, \quad (9)$$

where each energy term refers to E in the completed formulae subsection as defined by Eqs. 7 or 8. In other words, the total energy of each system comprises of

– Two interaction energies between a drug molecule, and the inner and the outer head groups, E_{innerH} and E_{outerH}.

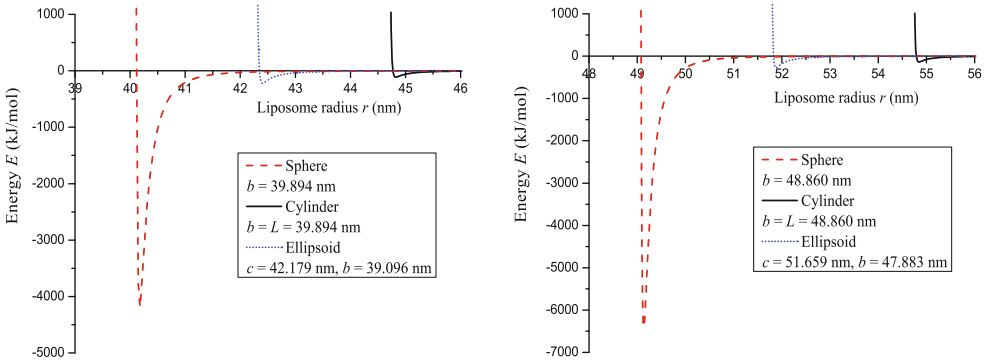

Fig. 6 First assumption: energy versus radius of liposome where (*left*) surface area of drug is 20,000 nm^2 and (*right*) surface area of drug is 30,000 nm^2

– Two interaction energies between a drug molecule, and the inner and the outer intermediate groups, E_{innerI} and E_{outerI}.
– Two interaction energies between a drug molecule, and the inner and the outer tail groups, E_{innerT} and E_{outerT}.

Numerical result and discussion

We consider two hypotheses for the encapsulation of DOX inside a liposome. Firstly, we fix the surface area of the drug molecule and vary the radius of the liposome. Secondly, we fix the radius of the liposome and vary the sizes of the drug molecules.

Fix surface area of drug molecule

In this subsection, we also have two assumptions. Firstly, on the equality of the surface area we assume that the radius of the cylindrical drug molecule is equal to the radius of the spherical molecule, and the minor axis of the ellipsoidal drug molecule is 49/50 times the radius of the sphere where the energy profiles are presented in Fig. 6. Secondly, we assume that the length of the cylindrical drug molecule is twice the radius of the spherical molecule, and the major axis of the ellipsoidal drug molecule is 16/15 times the radius of the sphere where the energy profiles are presented in Fig. 7. The purpose of both assumptions is to manage their sizes to give rise to similar shapes. Further, the values 49/50 and 16/15 are chosen to present the ellipsoidal structures that closely related to the spherical ones.

From Figs. 6 and 7, the spherical case gives the lowest energy value at the equilibrium position. However, the appropriate shape of a drug molecule also depends on the the size of the liposome. That is when the radius of the liposome is larger than that giving the minimum energy for the spherical-shaped drug, we may use ellipsoidal or cylindrical shape since they give lower energies at the equilibrium configurations and the system will be more stable. Moreover, our two assumptions give similar result that is a spherical drug is suitable for a small liposome and once a liposome gets larger, a cylindrical or an ellipsoidal molecule is needed.

Fix inner radius of liposome to be $r = 50$ nm

In this subsection, we choose $r = 50$ which is a radius of the liposome found in experiments.

From the previous subsection, we find that the spherical drug molecule gives the lowest energy value comparing to the cylindrical and the ellipsoidal ones. For the liposome of radius 50 nm, the most suitable radius for the spherical drug molecule is approximately 49.726 nm as shown in Fig. 8. This minimum energy is around −6,642 kJ/mol, which is a potential well for the DOX encapsulated in the liposome. We comment that the liposome will form without the

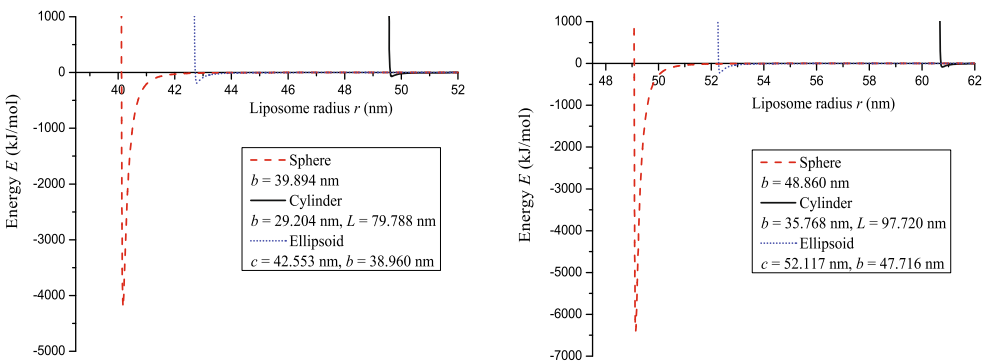

Fig. 7 Second assumption: Energy versus radius of liposome where (*left*) surface area of drug is 20,000 nm^2 and (*right*) surface area of drug is 30,000 nm^2

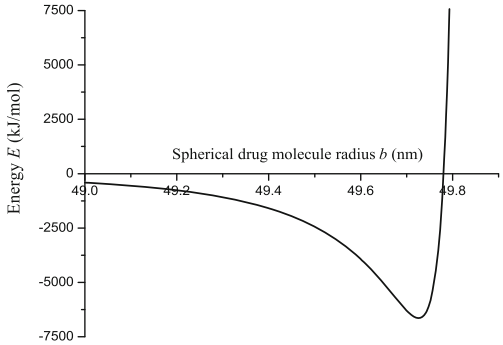

Fig. 8 Energy profile for a spherical drug molecule encapsulated in the liposome of radius 50 nm

presence of DOX molecule, and the value of potential well is determined for the comparison purpose between different shapes of DOX. At this radius, the interacting surface area of the sphere is 31,072 nm^2. Next, we investigate the ellipsoidal drug molecule where its surface area is equal to the spherical case. Noting that the surface areas for the three shapes of the drug molecules are calculated from

$$\begin{aligned} Area(sphere) &= 4\pi b^2, \\ Area(cylinder) &= 2\pi bL + 2\pi b^2, \\ Area(ellipsoid) &= 2\pi b^2\left[1 + \frac{c\sin^{-1}(1-b^2/c^2)}{b(1-b^2/c^2)}\right]. \end{aligned}$$

Figure 9 shows that the energy decreases when the value of minor axis b increases. We note that the value of the major axis c is varried to give the total surface area of 31,072 nm^2. The trend of the minimum energy is depended on the ratio between the major axis c and the minor axis b. We find that the lowest energy occurs at the ratio of the ellipsoidal axes being 1 which turns to be a spherical structure.

However, the cylindrical drug molecule cannot have the surface area up to 31,072 nm^2. For the liposome radius 50 nm, there is no b such that $31072 = 2\pi bL + 2\pi b^2$ and $(L/2)^2 + b^2 < 50^2$ where the inequality represents the

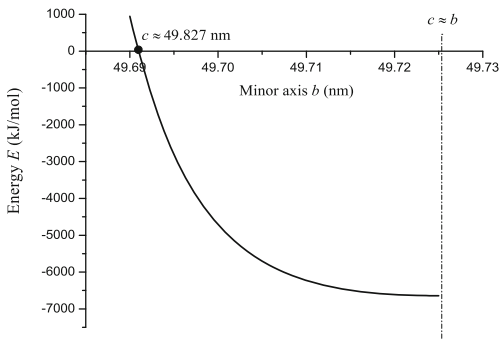

Fig. 9 Energy profile for an ellipsoidal drug molecule of various minor axis with the fixed surface of 31,072 nm^2 and $r = 50$ nm. Noting that the value of the major axis is varied to give the total surface of 31,072 nm^2

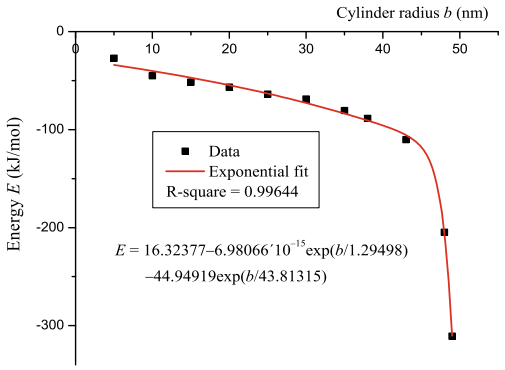

Fig. 10 The minimum energy of the system for each radius b of cylindrical drug molecule with $r = 50$ nm

largest possible of a cylinder encapsulated in a liposome of radius 50 nm. Then we investigate the possible minimum energy for various sizes of cylindrical drug molecules that can be encapsulated in the liposomal capsule of radius 50 nm. We find that the energy cannot be lower than −400 kJ/mol as graphically shown in Fig. 10. From Figs. 9 and 10, these graphs confirm that the spherical shape has the lowest minimum energy at the equilibrium position.

All in all, we find that the spherical drug is the best choice among these three structures. In mathematical point of view, we can choose an appropriate size of a liposome when we have a restriction on the drug size and shape, and we can determine an appropriate size of a drug when we have a restriction on the liposome size.

Summary

This study examines the liposome system filled with a DOX cluster as a drug transporter. We assume three shapes for the DOX which are a sphere, a cylinder, and an ellipsoid. The objectives of the study are to determine the energy for each shape of DOX, and to obtain the best shape of the drug among those three possible ones. Further, we also investigate the appropriate size of the DOX cluster and the liposome. To accomplish these objectives, we utilize elementary mathematical modelling together with special functions. We obtain a mathematical model for the system of the liposome encapsulating DOX inside, and we compare the energy profiles. Two conditions are studied here which are (i) fixing the surface area of the drug and (ii) fixing the radius of the liposome. In this study, the spherical DOX is found to be the most suitable shape for the system under both conditions. In terms of varying liposome radius, the appropriate shape of the drug is dependent on the size of the liposome. Once the liposome radius is fixed to be 50 nm, a suitable radius of the spherical DOX is approximately

49.726 nm with the energy −6,642 kJ/mol. For the ellipsoidal case, its axes can be modified to allow the system to give this minimum energy. However, there is no equivalent cylinder with this spherical surface area. On using the mathematical model, we can predict a size and a shape of a drug molecule that can be encapsulated inside a liposome for the use in a drug delivery system. These results can be used by experimentalists in the sense that we can predict an appropriate size of a liposome for any specific size and shape of a DOX cluster. Moreover, the energy values calculated here can be considered as an optimum energy used to load and unload the DOXs from the nanocapsule.

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