Molecular interactions between PAMAM dendrimer and some medicines that suppress the growth of hepatitis virus (Adefovir, Entecavir, Telbivudine, Lamivudine, Tenofovir): a theoretical study

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Abstract

Viral hepatitis is a common viral infection, can be dangerous, involves the body and leads to inflammation and destruction of tissue and normal function of the liver. Viral hepatitis is a major cause of premature death in human beings. According to the World Health Organization, it was assumed that there are more than 385 and 170 million carriers of hepatitis B and C in the world, respectively, and more than a million deaths occur due to hepatitis each year. There are a few specific drugs to treat hepatitis. To overcome some of these problems, nanoparticle systems containing organic and inorganic compounds are used for pharmaceutical purpose. One of these nanostructures is dendrimer. Dendrimers are repetitively branched nanomolecules. In this study, a theoretical study of the structural probabilities of nanostructure complex formation between polyamidoamine dendrimers (PAMAM) and some drugs that suppress the growth of hepatitis virus (Adefovir, Entecavir, Telbivudine, Lamivudine, Tenofovir: **1–5**) has been carried out. The possibility of drug release, drug delivery and drug separation by PAMAM has been investigated. MMFF94 method has been used to provide results and medical solutions. In all the drug–PAMAM complexes, the relative energy levels of the complex energy have been calculated by the RHF/PM6 method. Medicine delivery, release process of drugs and separation of drugs from the in vivo and in vitro real sample were the main enforceable results obtained from this theoretical study of medicines **1–5** & PAMAM. This model has predicted an imaginary method to separate the medicines from real samples and study the drug release process of the discussed complexes. The imaginary separation procedure that suppresses the growth of hepatitis virus–**1–5** medicine mixture in in vitro samples is discussed. It is possible to collect compounds **1** and **2** by PAMAM and separate Adefovir, Telbivudine and Tenofovir (**3–5**) from the mixture of the sample of medicines **1–5**.

Keywords Hepatitis · PAMAM dendrimers · Adefovir · Entecavir · Telbivudine · Lamivudine · Tenofovir · Molecular modeling

Introduction

One of the main families of three-dimensional polymers is dendrimers, which are in the nanoscale dimension in the solution and recognized by a spherical pattern. Investigation

of these structures was started in 1970s. In 1984, Tomalia et al. had discovered the first class of the polymers with many derivatives. These molecules with a lot of ramifications are called dendrimers. The structural forms of these compounds have demonstrated an important efficacy of their characteristics [1, 2]. Although the origin of dendrimers is known to be linear polymers and branched polymers, amazing structural features of dendrimers and macromolecules with many branches are quite different from that of traditional polymer characteristics. Despite the use of polymers in pharmaceutical systems, dendrimers have more benefits compared to them. They have limited poly-dispersity and dimensions in nanometer range, which make it easier to cross biological barriers. Dendrimers can encapsulate guest

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Fig. 1 The polyamidoamine dendrimer (PAMAM) **a** with six zooms (0.5–3) and **b** with three generations. “A-area” includes zoom 3–2.5, “B-area” includes zoom 2–1.5, and “C-area” involves zoom 1–0.5

molecules with receptors existing on their surface or in holes between their branches [1–3].

Unlike linear polymers, dendrimers are macromolecules that are derived from one core and all ramifications are finally reached to the central core, and for building dendrimers, size, weight and molecular mass should be controlled precisely. The presence of large numbers of end ramifications increased the solubility, mixing and reactivity of the dendrimers. The solubility effect of dendrimers was strongly affected by the nature of the surface functional groups. Existence of hydrophilic groups makes the dendrimers soluble in polar solvents, and hydrophobic end groups lead to higher solubility of dendrimers in non-polar solvents [2, 3]. The importance of dendrimers becomes clear here as the therapy influence of any drug depends on its good solubility in the aquatic environment of the body. A great number of medicines with strong medical properties have been discovered but because of being insoluble they are not used for therapeutic purposes; water-soluble dendrimers have an ability to connect with hydrophobic molecules with anti-fungal or anti-bacterial properties. There is a possibility of release of the attached drug when exposed to targeted organisms; therefore, these complexes are considered as drug delivery systems. Unique features such as controlled mono-dispersity and mutable surface groups make these molecules ideal for biomedical applications. Dendrimers can be functionalized by modifying their end groups with different therapeutic agents, which in turn is the potential for their use as targeted drug. In addition, the existence of empty

holes in the dendrimers is used to encapsulate hydrophobic drug molecules [2, 3].

The applications of dendrimer polymers were investigated as one of the interesting subjects to deliver the medicinal compounds. Due to the solubility limitations in the aqueous media, some of the medicines were not used in treatments [2, 4]. The applications of dendrimer polymers have investigated as one of the interesting subjects for delivering the medicinal compounds. One of these classes is the construction of a covalent bond between medicines and the dendrimers. In this case, the obtained complex of the medicine–dendrimer was known as a prodrug. The non-covalent interaction of medicines with the dendrimer functional groups (such as amines and –COOH groups) was introduced as another class of dendrimer applications. The possibility of dendrimer–medicine encapsulation operation creates a micelle dendrimer–medicine supermolecular structure, which is the third introduced class in this subject [5, 6]. The antiviral activity of dendrimers gives rise to their property as efficient carrier agents in antiretroviral compounds [7, 8]. Overall, the discussed properties have made them an interesting compound to design medicine delivery systems in clinical treatment applications [6–9]. Here we applied the modeled PAMAM (polyamidoamine dendrimer) as one of the polymers as they have attracted the attention of researches in drug delivery processes. Figure 1 shows three generations of PAMAM.

Among dendrimer structures, polyamidoamine (PAMAM) is very popular that it has been considered a lot

Scheme 1 The chemical structures of Lamivudine, Entecavir, Adefovir, Telbivudine and Tenofovir (1–5)

in drug delivery. Many of the PAMAM dendrimers with altered levels, not stimulating the immune system. They are dissolved in water and containing ending amines that could be changed to the different targeted or guest's molecules [2]. Their unique structure and the internal space of PAMAMs that contain triple junctions of amines and amides can attract guest molecules such as medicines.

The amine functional groups in dendrimers form hydrogen bonds causing non-covalent interactions with encapsulated host medicines.

These features have made dendrimer polymers a suitable medium to solubilize hydrophobic medicines [1, 9].

The use of computational methods of quantum mechanics (QM) and molecular mechanics (MM) for this kind of investigation has its own innovation; although the large size of the biochemical and pharmaceutical molecules make it difficult to use quantum computing, theoretical studies in these types of investigation have been widely performed. Since modeling of processes prior to empirical implementation is considered an economical method in terms of cost savings of chemical tests and the time of investigations. Therefore, in this study, the polyamidoamine (PAMAM) dendrimers were applied for modeling to adsorb and gradually release the discussed medicines 1–5 (Lamivudine, Entecavir, Adefovir, Telbivudine and Tenofovir). By using the results of this study, it was found that there are three main areas (A–C) in the PAMAM dendrimers to adsorb all medicines 1–5. The release rates of each medicine is differ from the other medicine in these three regions (A–C) of the discussed PAMAM dendrimer due to the difference in molecular drug absorption capacities in areas A–C of the discussed PAMAM dendrimer and the effective factors in the establishment of the medicines. These differences are also different for medicines 1–5 that they involved in the PAMAM dendrimer regions. In addition to investigating the release of the discussed medicines in the modeled structure of the PAMAM dendrimers, this

feature can be used to separate them in a real sample containing medicines 1–5. It is possible to apply the obtained results to real-sample experiments.

Medicine compounds 1–5 (Lamivudine, Entecavir, Adefovir, Telbivudine and Tenofovir) are known as inhibitors of reverse transcriptase of hepatitis virus that cause viral DNA chain termination. These drugs are rapidly absorbed after ingestion and their biocompatibility average is about 59%, and less than 4% binds to plasma proteins. These were applied as useful medicines for the treatment of hepatitis B. The chemical structures of Lamivudine, Entecavir, Adefovir, Telbivudine and Tenofovir (1–5) are shown in Scheme 1. [10].

Computational and theoretical methods

The quantum chemical computational operations of the molecular geometries of the ground states, dipole moment factor, and $\text{Log}K_{ow}$ (logarithm of octanol–water distribution coefficient factor or $\text{Log}P$) of the selected medicines Lamivudine, Entecavir, Adefovir, Telbivudine and Tenofovir (1–5) that suppress the growth of hepatitis virus were carried out by hybrid *ab initio* and UHF/PM6 semiempirical method [11–34]. The geometries and energy optimization stages of the suppression of the growth of hepatitis virus by medicines (1–5) were studied by the UHF/PM6 method using *Spartan '10* package [35].

To investigate the diffusion of medicines 1–5 that suppress the growth of hepatitis virus in the PAMAM areas A–C of dendrimer, the MMFF94 molecular mechanics method (MM) has been applied in this modeling. The MM method (MMFF94) provides a good condition for construction and analysis of the chemical molecules. Optimization of structures 1–5 was done in the next step of the study. The complexes of the selected medicines (1–5) that suppress the growth of hepatitis virus with the areas A–C of PAMAM

dendrimer at different ratios (1:1 and 1:18) were calculated by MMFF94 method. The calculations have been performed using *Spartan '10* package [35].

The extracted results have demonstrated appropriate data. The results were appropriately compared and investigated. To calculate the free energies and discuss the changes of the structures of drugs **1–5** that suppress the growth of hepatitis virus with areas **A–C** of PAMAM dendrimer (at different ratios, 1:1 and 1:18, at 298 K), the following equations were applied:

$$\Delta G^\ddagger = G_{\text{TS}} - G_{\text{Reactants}}, \quad (1)$$

$$\Delta_r G = \Sigma G_{\text{products}} - \Sigma G_{\text{reactants}}. \quad (2)$$

The dipole moment (μ) value depends on the amount of the atom charges and the distance between them. The μ factor increases with decrease in the energy gap of the HOMO–LUMO orbitals. The total dipole moment (static) as a summation vector of the bonds' dipole moments is shown as follows:

$$\mu = \left(\mu_x^2 + \mu_y^2 + \mu_z^2 \right)^{1/2}. \quad (3)$$

Mulliken charge introduces approximated partial charges of atoms. Equation (4) demonstrates the method to calculate the density matrix terms.

In Eq. (4), in a molecular orbital that is doubly occupied (closed shell system), the character $C_{\mu i}$ is defined for μ th basis function in the i th molecular orbital as a basis function in MO [36–50]:

$$D_{\mu\nu} = 2 \Sigma_i C_{\mu i} C_{\nu i}^*. \quad (4)$$

Therefore, the population matrix is defined as follows [41–49]:

$$P_{\mu\nu} = D_{\mu\nu} S_{\mu\nu}. \quad (5)$$

K_{ow} (octanol–water partition coefficient) is inversely related to the solubility of a compound in water media. This factor was applied to environmental investigations to determine the environmental fate of chemical compounds. This coefficient determines the equilibrium concentration of chemicals between phases of the water and octanol. This factor has indicated the partitioning of soil organic compounds. The high value of K_{ow} factor introduces a chemical which will be preferentially soluble in soil organic matter rather than water [51–53].

Results and discussion

Although the theory and mathematics of computational chemistry could be very specialized and tedious, due to the endless applications of this newly established field, it gains a

high reputation rapidly among all chemists around the world, even experimental chemist who call the computational software as “dry lab”. Its applications have been widely used to describe all of chemistry, biology, nanosystems, biochemistry, and even educational chemistry. The application of the theoretical and computational chemistry benefits science economy, is time saving, boosts scientific confidence and creation of new interdisciplinary sciences, and bridges the scientific limitations and other effective aspects to improve the quality of human lifestyle.

The properties of the discussed medicines **1–5** (Lamivudine, Entecavir, Adefovir, Telbivudine and Tenofovir) that suppress the growth of hepatitis virus have been reported before [54–56]. There are not serious investigations on the complex structures of the selected drugs (**1–5**) that suppress the growth of hepatitis virus with PAMAM dendrimer, at ratios 1:1 and 1:18, and the imaginary.

Interactions of Medicine–PAMAM complexes in the structures were investigated. The growth of hepatitis viral medicine **1–5** (Lamivudine, Entecavir, Adefovir, Telbivudine and Tenofovir) transfer performance, a realization of the physical and chemical characters and structural interaction properties were studied. These theoretical studies have allowed to determine the relative energies of the most stable structures of medicines **1–5** individually that suppress the growth of hepatitis virus and the geometries of the drug–PAMAM complexes at 1:1 and 1:18 ratios.

The geometrical data and the optimized structures of the selected inhibitors, drugs (**1–5**), of the growth of hepatitis virus and the complexes with PAMAM dendrimer, at 1:1 and 1:18 ratios, have been depicted in Table 1 and Figs. 2, 3, 4, 5, 6, 7, 8, 9 and 10.

The location of medicines **1–5** in the discussed PAMAM dendrimer areas (**A**, **B** and **C**, see Fig. 1) to produce 1:1 of medicines–PAMAM complexes is demonstrated in Figs. 2, 3, 4, 5, 6 and 7. The results also show the relative $\Delta\Delta G_f^\circ$ (in kcal mol^{−1}), which was calculated by the MMFF99 method. The results of the calculations for the PAMAM(**B**)–Adefovir (**3**) complex are shown in Fig. 4. This modeled complex was the most stable form among the predicted **A–C** forms. The obtained results of PAMAM(**B**)–Telbivudine (**4**) complex are demonstrated in Fig. 5. Form **B** among the predicted forms **A–C** was the most stable case. PAMAM(**B**)–Tenofovir (**5**) was obtained as the most stable case among the obtained **A** and **C** forms.

Table 1 shows the obtained data related to medicines **1–5** that suppress the growth of hepatitis virus and their locations in **A**, **B** and **C** areas of PAMAM dendrimer of the medicine–PAMAM complexes at 1:1 and 1:18 ratios. The obtained data of $\Delta\Delta G_f^\circ$ show that the stability of the complex of Lamivudine (**1**) at 1:1 mol ratio with PAMAM in the **C** area was more than **A** and **B** areas. But the stability of complexes Entecavir, Adefovir and Tenofovir (**2–3**, **5**)

Table 1 The calculated results related to the medicines Lamivudine, Entecavir, Adefovir, Telbivudine and Tenofovir (1–5) that suppress the growth of hepatitis virus and their locations in A, B and C areas

Drugs that suppress the growth of hepatitis virus	S: molecular surface V: molecular volume LogP(LogK _{ow}) of drugs that suppresses the growth of hepatitis virus			Dipole moment (D) of medicine–PAMAM complexes			ΔG_f^0 (kcal mol ⁻¹) medicine–PAMAM complexes (1:1) ^a			ΔG_f^0 (kcal mol ⁻¹) medicine–PAMAM complexes (1:18) All areas (A–C) have been occupied ^b	
	S(A ⁰²)	V(A ⁰³)	LogP	Area A	Area B	Area C	Area A	Area B	Area C		
Lamivudine	227.26	204.40	70.85	43.53	30.21	29.62	–43.53	–30.21	–29.62	–40.92	
Entecavir	283.52	260.70	104.30	206.39	144.25	83.60	–18.13	–10.78	–18.05	–19.75	
Adefovir	277.60	236.90	117.60	183.01	111.14	80.58	67.49	41.56	64.22	122.06	
Telbivudine	250.78	226.02	85.80	180.03	121.06	72.63	83.64	84.15	103.60	131.99	
Tenofovir	294.99	254.75	117.90	101.26	136.93	80.34	84.00	74.00	85.66	41.98	

^aFor the $\Delta\Delta G_f^0$ in kcal mol⁻¹ amounts, see Figs. 2, 3, 4, 5, 6 and 7^bSee Fig. 8^cThe drug–PAMAM (I) and the differences of the PAMAM volume and medicine–PAMAMs **Fig. 2** The Lamivudine (1) location in A, B and C areas of PAMAM dendrimer at 1:1 ratio of Lamivudine–PAMAM and the comparison of their $\Delta\Delta G_f^0$ (in kcal mol⁻¹)

Fig. 3 The Entecavir (2) location in **A**, **B** and **C** areas of PAMAM dendrimer at 1:1 ratio of Entecavir–PAMAM and the comparison of their $\Delta\Delta G_f^o$ (in kcal mol^{-1})

with PAMAM (1:1 mol ratio) in the area **B** are more than **A** and **C** and the stability of the complex of Telbivudine (4) with PAMAM (1:1 mol ratio) in the area **B** was more than **A** and **C** areas. The stability of Telbivudine–PAMAM (1:1) in **A** is more than **B** and **C** areas. The sequence of stability was related to the three important factors: (a) the H bonds between the medicine structure and PAMAM dendrimer, (b) the vacancies of the **A**, **B** and **C** areas the main steric restraints of PAMAM dendrimer and medicine structures. The factors have provided that in so far as it may be best electrostatic H bonds interactions. The vacancies of the areas and the steric restraints was created with minimal interruptions. Due to the folding of PAMAM around medicines 1–5 and the occupation of PAMAM's **A**, **B** and **C** areas by the anti-hepatitis viral medicines, some changes have been made in the PAMAM structures. While 1–5 have settled inside one of the dendrimer holes, the upcoming forces withdraw other holes to it. This situation has created an opportunity to open other hole areas to attract the other molecules inside.

Figure 7 represents the complexes of the medicines Lamivudine, Entecavir, Adefovir, Telbivudine and Tenofovir (1–5) that suppress the growth of hepatitis virus in the **A**, **B** and **C** areas of PAMAMs at 1:18 ratio of the complexes of medicine–PAMAM and comparison of ΔG_f^o in kcal mol^{-1} . The calculated ΔG_f^o values of 1–2 complexes with PAMAM were negative and it demonstrates that the complex construction between Lamivudine and Entecavir (1–2) are theoretically possible. The values of ΔG_f^o for (1–5)–PAMAM complexes (at a ratio of 1:18) were obtained to be -40.92 , -19.75 , 122.06 , 131.99 and $41.98 \text{ kcal mol}^{-1}$, respectively. The values of ΔG_f^o for Adefovir, Telbivudine and Tenofovir (3–5)–PAMAM complex were positive. It demonstrates that the construction of these complexes with PAMAM was not theoretically possible. The results have depicted that the best H bond interactions, the area vacancies and the hindered steric effects with minimal interruptions space were created for the 1:18 ratio complexes between 1–2 and PAMAM. The results of the modeling have shown that the folding of the

Fig. 4 The Adefovir (3) location in A, B and C areas of PAMAM dendrimer at 1:1 ratio of Adefovir–PAMAM and the comparison of their $\Delta\Delta G_f^\circ$ (in kcal mol⁻¹)

A–C areas of PAMAM dendrimers around medicines 1 and 2 was better than medicines 3–5. In these cases, it seems that the rotation of the medicines 1 and 2 inside the A–C areas (in both ratios 1:1 and 1:18) has made a better condition to complexation and increases the attraction forces inside the PAMAM. The medicines Adefovir, Telbivudine and Tenofovir do not have good conditions to construct the complex of Adefovir, Telbivudine and Tenofovir–PAMAM, see Table 1 and Fig. 7. The values of ΔG_f° for (1 and 2)–PAMAM complexes (at a ratio of 1:1) with the areas A–C were obtained to be -43.53 (A), -30.21 (B), -29.62 (C) and -18.13 (A), -10.78 (B) and -18.05 (C) in kcal mol⁻¹ for 1–PAMAM and 2–PAMAM complexes, respectively. The obtained results demonstrated that in both the complexes, area A has made the most stable interactions with medicines 1 and 2. Medicine 1 has made better interactions with area B than medicine 2. But medicine 2 has made better interactions with area C than medicine 1. These results return back to the complexation patterns of the discussed medicines with the areas of the OAMAM dendrimers. The different folding patterns of the A–C areas of PAMAM dendrimers around 1 and 2 medicines, H bond interactions, the area vacancies and the hindered steric effects with minimal interruptions

space are the factors from which the above stabilities could be interpreted. In this case, medicines 1 and 2 have shown different behaviors than medicines 3–5 with PAMAM dendrimers. The obtained results have demonstrated that the construction of these complexes between medicines 1–2 and PAMAM was theoretically possible, and it is also possible to determine the sequences of the medicine release in the discussed patterns by the theoretical calculations.

Figure 8 shows the relationships between ΔG_f° (kcal mol⁻¹) and Log K_{ow} ; volume of molecules ($\text{\AA}^3$) and moments of dipoles of 1–5. The values of Log K_{ow} (Log P) for medicines 1 and 2 were obtained as 70.85 and 104.30, respectively. Also, the calculated values of the molecular volume ($\text{\AA}^3$) coefficient of 1 and 2 were obtained as 204.40 and 260.70 $\text{\AA}^3$, respectively. In regard to the complexation (at ratio 1:1) of all the area capacities A–C of PAMAM dendrimer with medicines 1 and 2, the combination relationships between the above data and ΔG_f° have shown similar patterns. In all diagrams, two medicines Lamivudine and Entecavir (1 and 2) that suppress the growth of hepatitis virus displayed similar properties, and Adefovir, Telbivudine and Tenofovir (3–5) have depicted different properties. The graphs in Fig. 8 represent the similarities and/or

Fig. 5 The Telbivudine (4) location in **A**, **B** and **C** areas of PAMAM dendrimer at 1:1 ratio of Telbivudine–PAMAM and the comparison of their $\Delta\Delta G_f^\circ$ (in kcal mol⁻¹)

differences in the discussed properties of drugs **1–5** that suppress the growth of hepatitis virus in the presence of PAMAM dendrimer. Figure 8 (line-1) demonstrates the relationships between ΔG_f° and $\text{Log}K_{ow}$ ($\text{Log}P$) in different types of occupation of the anti-hepatitis viral drugs **1–5** in **A**, **B** and **C** areas of PAMAM dendrimer. As discussed above, the obtained values of $\text{Log}K_{ow}$ coefficient determine the equilibrium concentration of octanol–water partition coefficient of a chemical compound such as the selected anti-hepatitis viral medicines **1–5** between octanol and water media. In the shown graphs, the relationships between ΔG_f° and $\text{Log}K_{ow}$ ($\text{Log}P$) of Lamivudine (**1**) and Entecavir (**2**) were near together and they show similar behavior to each other (**3–5**). They have shown high different properties in respect to the discussed relationship. Figure 8 (line-1) also represents that Lamivudine (**1**) and Entecavir (**2**) have shown the most similarities among **1–5** drugs. Figure 8 (line-2) represents the relationships of the molecular volume ($\text{\AA}^3$) of **1–5** with ΔG_f° in the different occupation types of medicines **1–5** that suppress the growth of hepatitis virus in **A**, **B** and **C** areas of the dendrimer. The obtained results for the molecular volume ($\text{\AA}^3$) coefficient of **1–5** have shown the effects of hindered

steric properties between the spaces of **A**, **B** and **C** PAMAM areas and the discussed drugs **1–5**. In all of the graphs, for the relationships between ΔG_f° and $V(\text{\AA}^3)$ relationships of Lamivudine (**1**) and Entecavir (**2**) has shown that the results are near together. The results have also shown similar behavior to each other for Lamivudine (**1**) and Entecavir (**2**). But for **3–5** has demonstrated very different properties in the obtained relationships. Figure 8 (line-3) shows the relationships of the calculated dipole moment values of **1–5** and ΔG_f° in different occupations of drugs **1–5** of PAMAM dendrimer. The data of **1–5** molecular volume ($\text{\AA}^3$) coefficient determine the effect of polar interactions between **1–5** and the hole of the **A**, **B** and **C** of PAMAM areas. The graphs of the relationships of ΔG_f° and dipole moments of Lamivudine (**1**) and Entecavir (**2**) show that the obtained points were near together and show similar behavior to each other. But for **3–5**, the results have demonstrated very different properties in the relationships.

Figure 9 represents the release steps of drugs **1–2**. The results of the medicine release priorities for **1–2** (Lamivudine and Entecavir) with PAMAM (in 1:18 mole ratio) were shown in this figure. The patterns of the discussed release

Fig. 6 The Tenofovir (5) location in A, B and C areas of PAMAM dendrimer at 1:1 ratio of Tenofovir–PAMAM and the comparison of their $\Delta\Delta G_f^\circ$ (in kcal mol^{-1})

have shown that Lamivudine (1) and PAMAM, and Entecavir (2) and PAMAM with similar priority of release have different forms with each other (3–5) and PAMAM complexes. The medicine release priority process for Lamivudine(1)–PAMAM was obtained as [A → B → C] and Entecavir (2)–PAMAM [A → C → B], respectively. The drug (1–2) release steps were related to the hydrogen bond interactions, the area vacancies and the hindered steric effects with minimal interruption factors. The process of medicine release for 1–2 from the complexes of (1–2)–PAMAM occurred in the three explained steps. The complexes of Adefovir, Telbivudine and Tenofovir (3–5)–PAMAM (at 1:18 mol ratio) do not have enough stability for their release steps to be investigated, see Figs. 2, 3, 4, 5, 6, 7 and 9 and also Table 1.

Due to the obtained results and the discussions, it could be supposed that the release of the medicines from (1–5) and PAMAM complexes and the partitioning of medicines 1–5 (from an in vitro sample) may be possible as an important application of the results of this study. Figure 10 represents the imaginary drug 1–5 collection and/

or separation method from in vivo and in vitro samples. In the imaginary separation procedure that was predicted on the basis of the discussed theoretical study, it is possible to find the feasibility of separation of the discussed medicine in a sample mixture. In this predicted procedure, a sample with medicines 1–5 could be added to the PAMAM sample vessel. After complete mechanical mixing, the mixture could be filtered. The remaining liquid contains Adefovir, Telbivudine and Tenofovir (3–5) medicines and medicines 1 and 2 (Lamivudine and Entecavir) with which 1 and 2–PAMAM complexes were made could be separated. So, it is possible to collect 1 and 2 by PAMAM and separate Adefovir, Telbivudine and Tenofovir (3–5) from the in vitro and/or in vivo samples of medicine (1–5) mixtures. The release process of the medicines 1 and 2 from 1 and 2–PAMAM complexes agrees with the sequence of the medicine release that has been shown in Fig. 9. This model has predicted and demonstrated the feasibility to separate the discussed medicines from the samples, and the medicine release process from the discussed complexes. The results of this research could be important in establishing

Lamivudine- PAMAM
(A)

Entecavir- PAMAM
(B)

Adefovir- PAMAM
(C)

Telbivudine- PAMAM
(D)

Tenofovir- PAMAM
(F)

Fig. 7 The complexes of the medicines Lamivudine, Entecavir, Adefovir, Telbivudine, Tenofovir (1–5) that suppress the growth of hepatitis virus in A, B and C areas of the dendrimer (PAMAM) at 1:18 ratio of drug–PAMAM structures and the comparison of their ΔG_f^0 in kcal mol⁻¹. The obtained values of ΔG_f^0 for 1–2 with PAMAM were negative and for 3–5 PAMAM was positive

the effects of hepatitis virus growth in general and may, therefore, be used in pharmaceutical science.

Conclusion

The dynamic process of drug delivery, release and isolation of the discussed medicinal compounds shown by this theoretical research model is ideal for biomedical applications. In this theoretical investigation, the different properties of 1–5 and PAMAM (1:1 and 1:18 mol ratios) complexes demonstrated the abilities of the discussed PAMAM dendrimer to adsorb the discussed medicines 1–5 (Lamivudine, Entecavir, Adefovir, Telbivudine and Tenofovir) that suppress the growth of hepatitis virus. The feasibility

of this dendrimer was investigated to separate the medicine molecules 1–5 in real samples. The three areas (A, B and C) and their structural properties of the discussed PAMAM structure were also discussed. These locations have different capacities to adsorb the medicine molecules 1–5. The H bonding effects, electrostatic interactions, vacancies of these areas, the hindered steric effects and the least interruption space were the main factors to devise a variety of discussed medicine molecules and the structural properties of the modeled (1–5)–PAMAM complexes. The obtained results demonstrated that the construction of these complexes between medicines 1 and 2 and PAMAM was theoretically possible, and also it is possible to determine the sequences of the medicine release in the discussed patterns by the applied theoretical calculations. The other aspects of these investigations discussed the relationships between free energies (ΔG_f^0) and $\text{Log}K_{\text{ow}}$ with volume of the medicinal molecules ($\text{\AA}^3$) and their dipole moments in medicine (1–5)–PAMAM complexes. This modeling has predicted an imaginary method to separate the medicines from real samples and studied the drug release process from the discussed complexes.

Fig. 8 The relationships between line-1) ΔG_f^0 in kcal mol⁻¹ and $\text{Log}P$ ($\text{Log}K_{\text{ow}}$); line-2) ΔG_f^0 in kcal mol⁻¹ and the volumes ($\text{\AA}^3$) of the molecules; and line-3) ΔG_f^0 in kcal mol⁻¹ and dipole moments (in Debye). In the diagrams, the two medicines Lamivudine and Entecavir (1–2) that suppress the growth of hepatitis virus displayed same properties and Adefovir, Telbivudine and Tenofovir (3–5) have demonstrated different behavior

Fig. 9 Stages of release of medicines 1–2. The priority of medicine release process from A, B and C areas of 1–2 (Lamivudine and Entecavir) with PAMAM at 1:18 ratio of medicines–PAMAM structures.

The release patterns demonstrate that Lamivudine–PAMAM and Entecavir–PAMAM with same release priority have different patterns with together. See Figs. 2, 3, 4, 5, 6 and 7, and Table 1

Fig. 10 The imaginary collection of 1–5 medicines that suppress the growth of hepatitis virus and/or procedure of separation from in vivo and in vitro samples. It is possible to collect 1 and 2 compounds by

PAMAM and separate Adefovir, Telbivudine and Tenofovir (3–5) from the mixture of the sample of medicines (1–5)

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Compliance with ethical standards

Conflict of interest Masoomeh Bayat, Avat Taherpour and Seyed Mohammad Elahi declare that they have no conflict of interests.

Ethical approval This article does not contain any investigations with human participants or animals performed by any of the authors.

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