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The mechanism of interaction of a new drug coating components for medical stents based on polyvinylpyrrolidone with introduced carbon nanotubes and drugs

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Abstract: Almost all stents with medicinal coatings used in Russia are manufactured abroad and have a high cost, which cannot meet the needs of Russian patients and their financial capabilities. The search and development of new types of medical stent coatings, as well as the establishment of their production in the Russian Federation is relevant. It is necessary to create thin-film drug coatings of stents with an extended time of drug emission for the treatment of various diseases. As a component providing prolonged and dosed desorption of the drug from the surface of the stent, it is best to use a carrier polymer. The paper investigates the possibility of using a promising modern material – carbon nanotubes – as a component of the medicinal coating of a medical stent, which will provide not only an improvement in the physical and mechanical properties of the coating, but also a prolonged effect of the drug by increasing its desorption time. Theoretical studies on the mechanisms of creating drug coatings for stents based on the polyvinylpyrrolidone copolymer, which include drugs (tegafur, dexamethasone) and carbon nanotubes, have been carried out. The quantum chemical calculation method – the density functional theory DFT, which is applied worldwide for calculating nanosystems, was used for research.

Keywords: medical stents; drug coating; carbon nanotubes; tegafur; dexamethasone; polyvinylpyrrolidone.

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Механизм взаимодействия компонентов нового лекарственного покрытия медицинских стентов на основе поливинилпирролидона с введенными углеродными нанотрубками и лекарственными препаратами

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Аннотация: Практически все используемые в России стенты с лекарственными покрытиями произведены за рубежом и имеют высокую стоимость, что не может удовлетворять потребностям российских пациентов и их финансовым возможностям. В связи с этим актуальным является поиск и разработка новых типов покрытий медицинских стентов, а также налаживание их производства в РФ. Необходимо создание тонкопленочных лекарственных покрытий стентов с увеличенным временем испускания лекарственного препарата для лечения различных заболеваний. В качестве компонента, обеспечивающего пролонгированную и дозированную десорбцию лекарственного препарата с поверхности стента, лучше всего использовать полимерный носитель. В работе исследована возможность применения перспективного материала современности – углеродных нанотрубок – в качестве компонента лекарственного покрытия медицинского стента, который обеспечит не только улучшение физико-механических свойств покрытия, но и пролонгированное действие лекарственного препарата за счет увеличения времени его десорбции. Выполнены теоретические исследования механизмов взаимодействия

компонентов лекарственных покрытий стентов на основе биополимера поливинилпирролидона, в состав которых входят лекарственные препараты (тегафур, дексаметазон) и углеродные нанотрубки. Исследования выполнены в рамках квантово-химического расчетного метода теории функционала плотности (DFT), который широко используется во всем мире для расчета наносистем.

Ключевые слова: медицинские стенты; лекарственное покрытие; углеродные нанотрубки; тегафур; дексаметазон; поливинилпирролидон.

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1. Introduction

The development of medicine today is associated with the introduction of high-tech types of care. Among such types of care for patients, one can name stenting, which is used to expand the lumen of blood vessels and ducts in the human body. Thus, stenting is used in cardiology and gastroenterology practice. One of the reasons for the need to use stents may be narrowing of ducts or vessels due to oncological neoplasms. In oncological diseases, a local drug delivery system through a stent with a coating that releases antitumor drugs can be successfully used, which allows for treatment without adverse systemic effects [1]. However, at present, almost all stents with drug coatings used in Russia are manufactured abroad and are expensive, which cannot meet the needs of Russian patients and their financial capabilities. It is necessary to search for new types of stent coatings and establish their production in the Russian Federation. The search and study of new composite coatings for medical stents related to the selection of drug coating components (polymer carrier, drugs corresponding to the stenting tasks, possible modifying elements) used in cardiac surgery for stenting of blood vessels, gastroenterology for endobiliary prosthetics and oncology to increase the lumen of various ducts compressed as a result of tumor growth, which can provide a high-quality, durable thin-film coating with an increased drug desorption time, are extremely relevant.

One of the main disadvantages of the medical stenting procedure is the risk of serious complications such as thrombosis and restenosis. It is believed that the polymer coating on the stent surface causes an inflammatory reaction at the site of injury creating the potential for restenosis. Drug-eluting stent reduces the percentage of restenosis to less than 10% in initial clinical trials [2].

Recently, the introduction of nanomaterials into drugs has been increasingly used for safer and more effective treatment of tumors. Nanomaterial-based therapy that provides target selectivity in action has been used since traditional chemotherapy faces several inevitable problems such as short half-life, cytotoxicity, lack of selective targeting, poor solubility and multidrug resistance [3].

The analysis of the available literature and in vitro results have shown that carbon nanotubes (CNTs) incorporated into the coating play an important role in stent bioactivity. Such coatings can significantly reduce the loss of therapeutic agents as they pass through the vessel during stent deployment, which significantly affects the occurrence of restenosis [4]. It can be assumed that the use of nanomaterial as a component of the stent drug coating can change the solubility, drug release profiles, diffusion, bioavailability and immunogenicity. This can lead to lower toxicity, fewer side effects, improved biodistribution and a longer life cycle of drugs [5, 6]. Known inexpensive biopolymers into which the drug is introduced can be used as a polymer matrix of the stent drug coating. The authors have previously conducted comparative theoretical and practical studies in which various polymer matrices of stent coatings were considered, including polylactic acid, polycaprolactone and chitosan, which proved the possibility of creating a thin-film drug coating that also uses a drug and carbon nanotubes [7, 8]. In this paper, polyvinylpyrrolidone is considered as a base polymer.

We assume that carbon nanotubes, which act as a modifying component of the coating, due to their unique strength and adhesive properties [9–11], can provide greater mechanical resistance of the coating and prolonged release of the drug.

The analysis of literary sources showed that chemotherapy is best at slowing down and stopping the growth of malignant neoplasms. The use of chemotherapeutic drugs on stent coatings can contribute to local (point) prevention of the disease without affecting other vital organs [12, 13]. Medicines such as tegafur and dexamethasone are the most suitable for the treatment of cancer at various stages of the disease, as their use prevents the cell from growing from the inside. Dexamethasone can also be used as a post-chemotherapy treatment to counteract certain side effects. That is why these medicines (tegafur, dexamethasone) were chosen as a

component of the drug coating of the stent used in oncological practice created on the basis of the biopolymer polyvinylpyrrolidone modified with carbon nanotubes. To prove the possibility of creating a thin-film stent coating with an increased drug desorption time that can be used in oncology practice, we created models of drug coating based on the selected polymer matrix (polyvinylpyrrolidone) doped with carbon nanotubes, with the introduced antitumor drugs dexamethasone or tegafur. Then theoretical studies of the mechanisms of interaction of the main components of the ultra-thin drug coating of stents using quantum chemistry tools were conducted within the framework of density functional theory.

2. Materials and Methods

2.1. Initial materials

Polyvinylpyrrolidone (PVP) is a vinyl polymer obtained by radical vinyl polymerization from the monomer N-vinylpyrrolidone. The presence of a double bond and a heterocycle with a nitrogen atom in the elementary unit of the polymer, which is part of the amide group, impart unique properties to PVP [14, 15]. The use of PVP as a carrier polymer is of particular interest, since it fully meets the necessary requirements: PVP is indifferent to the human body, it is not broken down by enzymes in the body and is excreted through the kidneys unchanged, which minimizes the risk of toxicity and side effects [16].

CNTs in small quantities can be used to improve the strength coefficient and binding capacity of the components included in the thin-film coating of medical stents, as well as to ensure prolongation of the process of drug release from the coating [17, 18]. The unique antimicrobial activity of CNTs forms the basis for developments in protecting human health, and one of the main areas of using antimicrobial properties is the creation of bionanofilms [19]. Carbon nanotubes improve the adhesion of the coating to the stent surface, which in turn prevents the coating from peeling off during implantation [20, 21].

Tegafur is a cytostatic antitumor chemotherapeutic drug. Cytostatics, translated from Greek, mean “making the cell immobile” and have been used in oncology since 1947. These drugs disrupt the vital activity of the cell, forcing it to commit suicide – apoptosis [22, 23]. Tegafur has high lipophilicity, which ensures rapid passage through biological membranes and distribution in the body. It intensively penetrates most tissues and fluids, including the central nervous system and cerebrospinal fluid. Tegafur can enhance the effect of other antitumor drugs. The use of the drug tegafur allows for more “targeted” delivery of the drug to tumor cells [24–26].

Dexamethasone belongs to a group of synthetic hormones, which is a synthetic analogue of prednisolone. When interacting with specific cytoplasmic receptors, it forms a complex that penetrates the cell nucleus, causes expression or depression of mRNA, changing the formation of proteins on ribosomes that mediate cellular effects [27]. In the treatment of cancer, dexamethasone can be prescribed to people undergoing chemotherapy to counteract certain side effects of their anticancer treatment. Dexamethasone can enhance the antiemetic effect of 5-HT3 receptor antagonists, such as ondansetron (an antiemetic) [28]. Dexamethasone can also be used as a direct chemotherapeutic agent in certain hematological malignancies [29]. The drug can be administered in various ways: by aerosol inhalation, subcutaneously, intramuscularly, and intravenously. Intravenous and systemic drug therapy usually fails due to one or more of the following factors: low drug solubility, toxicity, short-term drug stability in vivo, poor drug pharmacokinetics, poor biodistribution, low bioavailability, rapid metabolism, and lack of selectivity for the disease target.

2.2. Density functional theory

In order to prove the possibility of creating a drug coating for stents with improved properties, such as biocompatibility and resistance to external influences, as well as predicting the physicochemical properties of materials before their synthesis and experimental study, we carried out quantum-chemical calculations of the interaction processes of the components of the drug coating (PVP, drug, CNT) using the density functional theory (DFT) [30, 31], which can significantly reduce the time and costs of experimental development of the coating.

The calculation method of the DFT from a quantum-mechanical point of view is the most convenient method and is widely used throughout the world for calculating nanosystems. The essence of this method is to use the electron density distribution in describing atomic-molecular systems. Due to the fact that any property of the ground state of a bound system of interacting electrons can only be described by the electron density ρ(r), the electron energy in the DFT method can be calculated as follows:

$$E[\rho] = T[\rho] + V_{en}[\rho] + V_{ee}[\rho], \quad (1)$$

where $T[\rho]$ is kinetic energy, $V_{en}[\rho]$ is potential energy of electron-nuclear interactions, $V_{ee}[\rho]$ is energy of interelectronic interactions.

The used hybrid functional B3LYP is unique in that three exchange components are taken with weighting coefficients selected on the basis of experimental data, as a result of which the B3LYP method acquires the features of a semi-empirical method and its accuracy in most cases is significantly higher than in the case of methodologically "pure" functionals [31].

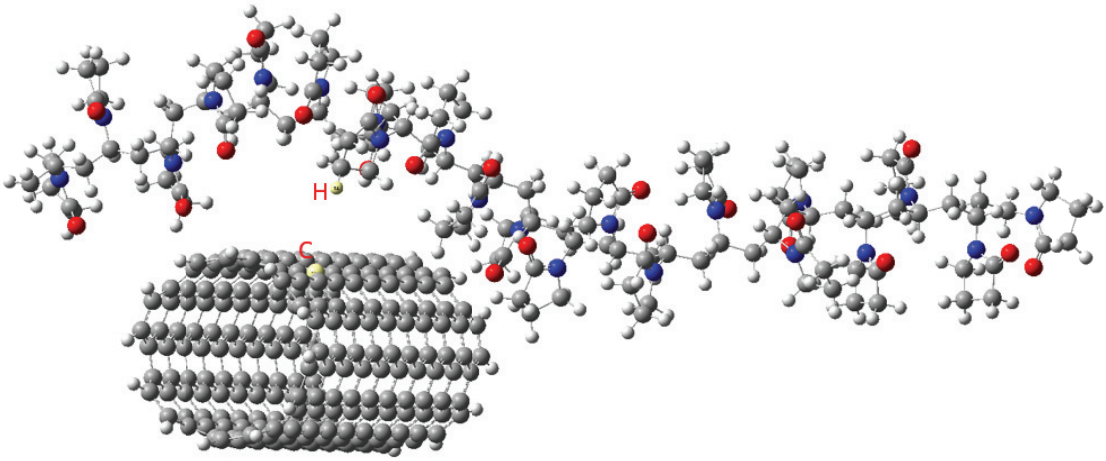
3. Results and Discussion

3.1. Interaction of polyvinylpyrrolidone with carbon nanotube

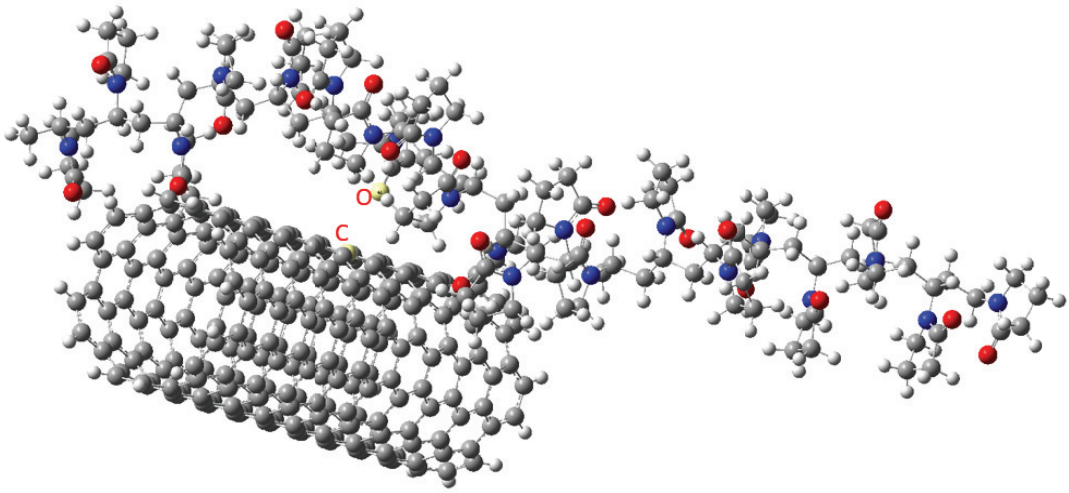
The first stage of geometry optimization of the polyvinylpyrrolidone fragment containing 21 elementary polymer units (21 monomers) revealed the presence of a certain region (the so-called half-cavity), which can act as an effective place for placing modifying systems in it. In our case, a single-walled carbon nanotube of the (6, 6) type is considered as such a system. The process of surface modification of the carbon nanotube with polyvinylpyrrolidone oriented with the named region to the nanotube was performed and analyzed with three possible locations of the PVP fragment relative to the CNT surface:

1) perpendicular to the nanotube axis, the polyvinylpyrrolidone fragment is oriented with the hydrogen atom (H) to the carbon atom (C) of the nanotube surface (Fig. 1*a*);

2) perpendicular to the nanotube axis, the polyvinylpyrrolidone fragment is oriented with the oxygen atom (O) to the carbon atom (C) of the nanotube surface (Fig. 1*b*);

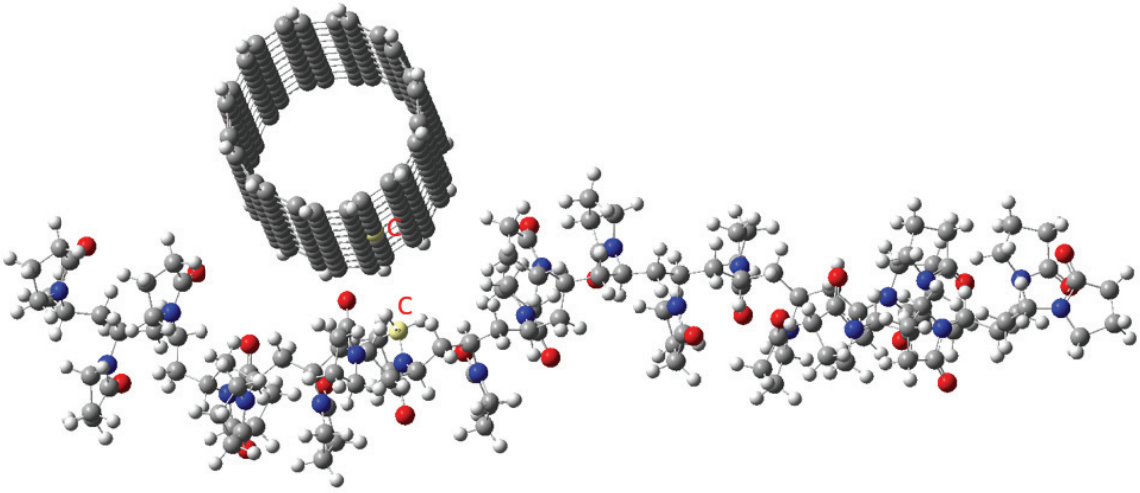


(a)



(b)

Fig. 1. Model of surface modification of (6, 6) carbon nanotube with polyvinylpyrrolidone when oriented:
a – by a hydrogen atom (H) to a carbon atom (C) of the nanotube surface;
b – by an oxygen atom (O) to a carbon atom (C) of the nanotube surface;

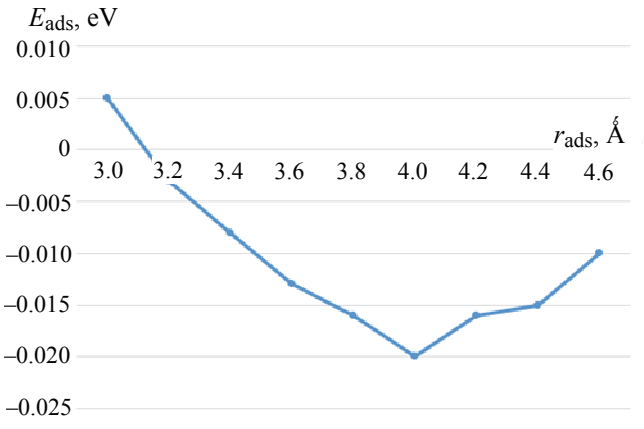


(c)

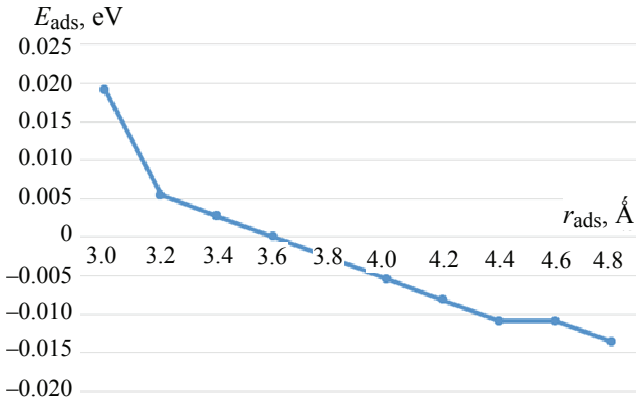
Fig. 1. *c* – by a carbon atom (C) to a carbon atom (C) of the nanotube surface

3) perpendicular to the nanotube axis, the polyvinylpyrrolidone fragment is oriented with the carbon atom (C) to the carbon atom (C) of the nanotube surface (Fig. 1*c*).

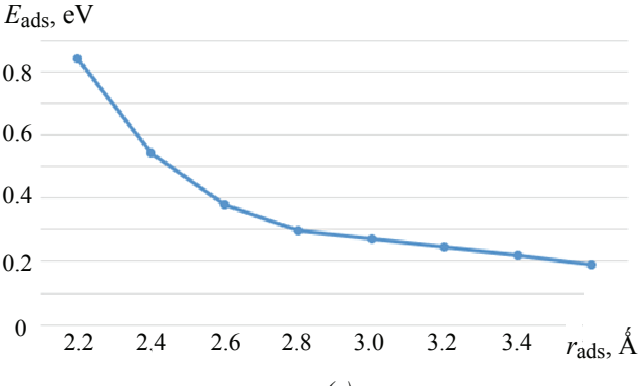
The length of the CNT molecular cluster was 22.16 Å. The cluster included nine layers of carbon hexagons along the longitudinal axis of the nanotube. To compensate for the broken chemical bonds along the cluster boundaries, pseudoatoms with a suitable valence were used. In this case, hydrogen atoms were chosen. The PVP fragment was approached step by step (with a step of 0.1 Å) to the selected atom of the nanotube surface, which made it possible to construct potential energy profiles of the considered processes for three possible orientation options (Fig. 2).



(a)



(b)



(c)

Fig. 2. Surface profiles of the potential energy of the process of a PVP fragment and CNT interaction (6, 6) when oriented: *a* – by the hydrogen atom (H) to the carbon atom (C) of the nanotube surface; *b* – by the oxygen atom (O) to the carbon atom (C) of the nanotube surface; *c* – by the carbon atom (C) to the carbon atom (C) of the nanotube surface

Table 1. The main parameters of the interaction of a PVP fragment with a carbon nanotube: *r* is interaction distance, *E* is interaction energy, *q* is charge of the active center after interaction

Orientation options	*r*, Å	*E*, eV	Charge of the active center after interaction, *q*
1) **H** – C	4,0	–0.02	0.081
2) **O** – C	–	–	–
3) **C** – C	–	–	–

The analysis of the curves allows us to establish the possibility of implementing the interaction of polyvinylpyrrolidone with a carbon nanotube, obtain the main parameters of the process and determine the most probable options for the arrangement of components during such interaction.

Table 1 shows the results of calculating the main parameters of the interaction between the polyvinylpyrrolidone fragment and the carbon nanotube.

The findings showed that the interaction is possible only for variant 1 of the arrangement of the PVP fragment relative to the CNT surface (with the orientation of the polyvinylpyrrolidone fragment by the H atom to the C carbon atom of the carbon nanotube): the curve has a minimum, which corresponds to a distance of 4 Å and energy of 0.02 eV. For the other orientation variants, there are no minima on the curves, which indicates the impossibility of interaction between PVP and CNT in such arrangements. A fairly large distance between polyvinylpyrrolidone and the nanotube corresponds to physical interaction between them without the formation of a chemical bond.

3.2. Polyvinylpyrrolidone complexes with carbon nanotube and drug

The mechanisms of creating a three-component complex including polyvinylpyrrolidone, a carbon nanotube and a drug (tegafur or dexamethasone) were studied by modeling the interaction process between the components of the complex. To perform theoretical calculations of the interaction of the components of the drug coating, a nanotube of the (6, 6) type was chosen, the length of the molecular cluster of which was also equal to 22.16 Å, and the dangling bonds at the cluster boundary were closed by pseudo-hydrogen atoms.

The dexamethasone (or tegafur) molecule was brought closer with a step of 0.1 Å to a stable complex consisting of a carbon nanotube cluster and a polyvinylpyrrolidone fragment including 21 monomer units orienting the oxygen atom of the molecule to the carbon atom of the CNT surface with its perpendicular arrangement relative to the longitudinal axis of the nanotube (Figs. 3, 4).

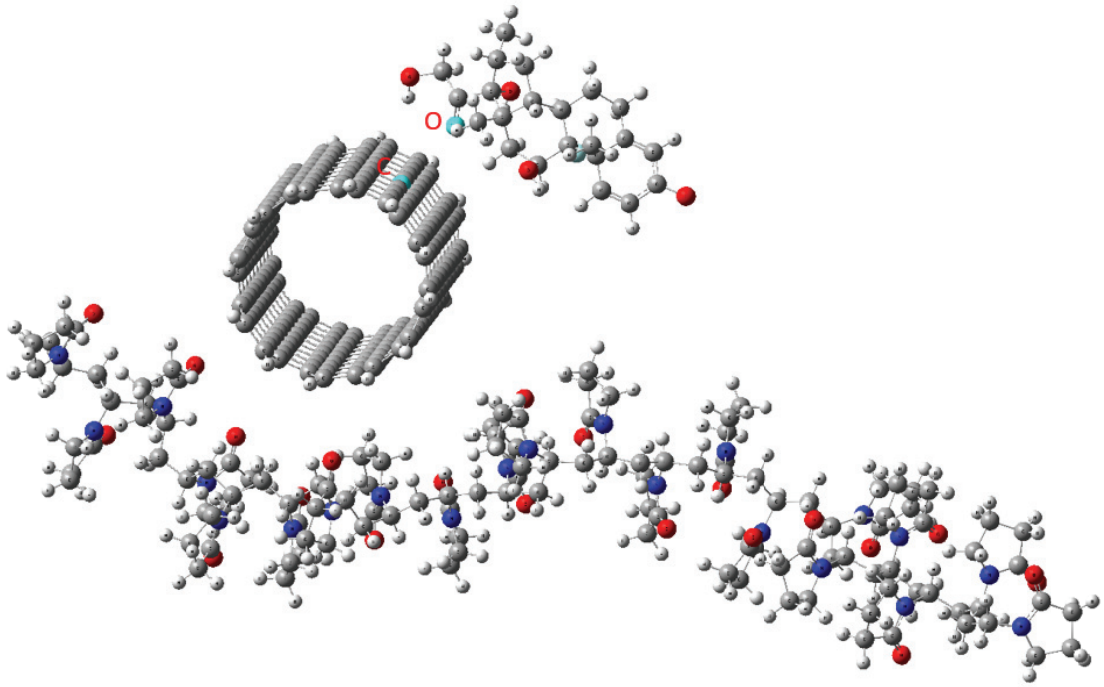


Fig. 3. Model of interaction of dexamethasone with the complex “polyvinylpyrrolidone + CNT”

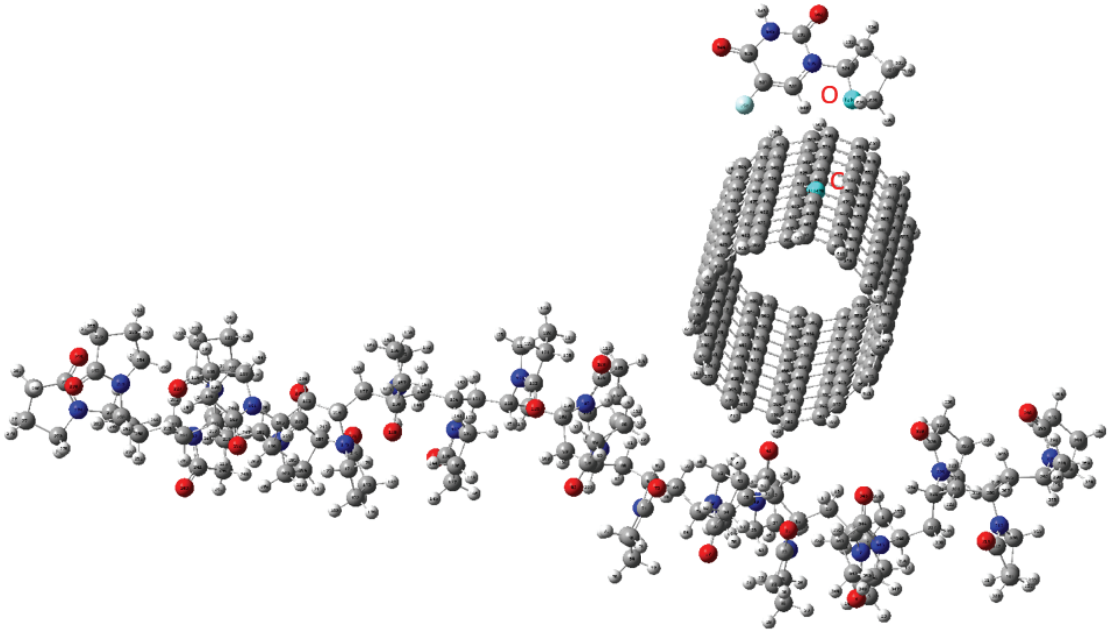


Fig. 4. Model of interaction of the tegafur molecule with the "polyvinylpyrrolidone + carbon nanotube" complex

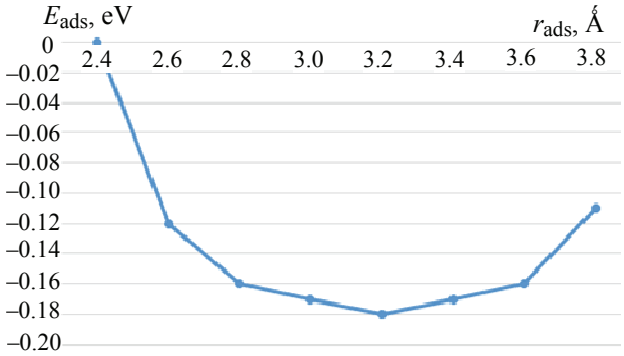


Fig. 5. The energy curve of the interaction of the dexamethasone molecule with the "polyvinylpyrrolidone + carbon nanotube" complex

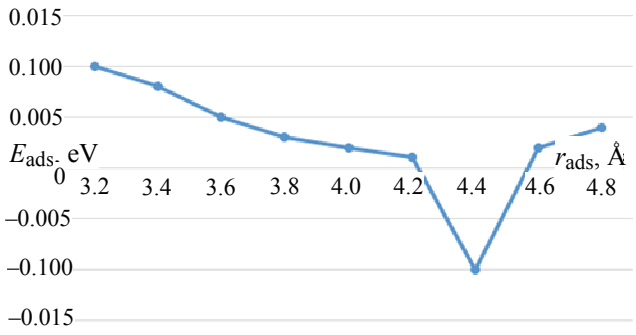


Fig. 6. Energy curve of the interaction of the tegafur molecule with the "polyvinylpyrrolidone + + carbon nanotube" complex

The obtained energy curves of the interaction process of the dexamethasone molecule with the "polyvinylpyrrolidone + carbon nanotube" complex are shown in Fig. 5. The optimal variant of PVP orientation relative to the CNT surface, determined in the previous step of the research, was chosen as the complex, when the polyvinylpyrrolidone fragment is located with the H atom to the C carbon atom of the carbon nanotube.

When analyzing the energy dependence, a minimum of the potential interaction energy (E = –0.18 eV) was found at a distance of 3.2 Å, which indicates the formation of a stable complex during physical interaction.

Similarly, the process of interaction of the complex components was studied when the tegafur drug approaches the stable complex "polyvinylpyrrolidone + + carbon nanotube", as a result of which an energy curve of the process was constructed (Fig. 6).

The analysis of the curve revealed the presence of a minimum at a distance of 4.4 Å, corresponding to the energy of –0.01 eV, which proves the possibility of implementing the process of interaction of the drug with polyvinylpyrrolidone and a carbon nanotube.

The study of the interaction mechanisms of the complexes "dexamethasone + povinylpyrrolidone + + CNT" and "tegafur + polyvinylpyrrolidone + CNT" proved the possibility of physical interaction between the components of the complex. The addition of carbon nanotubes to the coating composition provides not only an increase in the durability of the coating on the surface of the medical stent, its mechanical strength, but also increases the duration of action of

Table 2. Main parameters of the interaction of the PVP + CNT complex with dexamethasone/tegafur drug molecules: r is the interaction distance of the drug molecule and the PVP + CNT complex when the oxygen molecule of the drug is oriented to the carbon atom of the nanotube

Interacting components	*r*, Å	*E*, eV	Charge of the active center after interaction, *q*
PVP + CNT+ Dexamethasone	3.2	–0.18	–0.261 **(O)**
PVP + CNT+ Tegafur	4.4	–0.01	–0.199 **(O)**

dexamethasone and tegafur due to their desorption from the CNTs surface included in the polymer complex "PVP + CNT + drug", as evidenced by the fact of physical, not chemical interaction of the drug molecule with the complex.

The results obtained during the model experiment containing the main parameters of the processes of interaction of the components of the drug coating are presented in Table 2.

The obtained calculation results are consistent with the conclusions presented in the works [32–34], which presented the results of an experimental study of the possibility of creating a drug coating based on PVP containing a drug and carbon nanotubes. In the works, the composition of a stable drug coating based on PVP was identified and the optimal concentration of carbon nanotubes was determined. A comparative analysis of various concentrations of CNTs introduced into the drug coating proved that applying a solution to the stent surface that includes PVP and contains, in addition to the drug, 0.01 wt. % carbon nanotubes leads to the creation of a high-quality coating that is sufficiently resistant to the effects of the external environment compared to the version without the addition of CNTs and including only polyvinylpyrrolidone and the drug [32–34].

Thus, it can be stated that the addition of carbon nanotubes to the coating composition provides an increase in the coating's resistance to external environments, better coupling of the coating with the surface of the medical stent itself, its mechanical strength, and also provides a prolonged action of the drug, as also evidenced by the results of the theoretical study. This allows us to recommend the use of carbon nanotubes as a modifying component of thin-film drug coatings of medical stents, leading to the creation of effective and inexpensive systems.

4. Conclusion

Medical stenting is one of the treatment methods in modern practice. The study of the interaction mechanisms of the components of complexes consisting of a polymer matrix of polyvinylpyrrolidone doped with carbon nanotubes with the introduced drugs dexamethasone or tegafur revealed the possibility of creating such drug coatings of stents due to the implementation of physical interaction between the components, which ensures the possibility of prolonged entry of the drug into the body during its desorption from the thin-film coating of the stent.

The study and comparison of the main characteristics of the interaction processes in the components of complexes consisting of CNTs and a carrier polymer allowed us to conclude that the best interaction of PVP with CNTs occurs when the polyvinylpyrrolidone fragment is oriented with a hydrogen atom to a carbon atom of the nanotube surface. For complexes including, in addition to PVP and CNTs, the antitumor drugs dexamethasone or tegafur, stable systems are formed at distances of 4.4 Å and 3.2 Å between "PVP + CNTs" and drug molecules (corresponding to interaction energies of –0.01 eV and –0.18 eV), and the fact of physical, rather than chemical, interaction of the drug molecule with the complex allows us to conclude that it is possible to increase the duration of action of the drugs dexamethasone and tegafur during their desorption from the surface of CNTs included in the polymer complex "PVP + CNTs + drug".

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6. Conflict of interests

The authors declare no conflict of interests.

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