

Article

Interaction of BSA with Ta₂O₅ Nanoparticles: The Effect of Polydopamine Pre-Coating

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Abstract

The modification of tantalum oxide (Ta₂O₅) nanoparticles (NPs) with biocompatible polymers is crucial for their biomedical use. Such modification can prolong NP circulation in the bloodstream by minimizing salt-induced aggregation and reducing nonspecific protein adsorption onto their surface. Understanding the features of polymer–NP interactions is a key issue in the fabrication of nanostructures with required characteristics. The present work aims to provide a comprehensive comparative study of bovine serum albumin (BSA) adsorption on bare and polydopamine (PDA)-coated Ta₂O₅ NPs. The synthesized NPs were characterized via transmission electron microscopy, Fourier transform infrared spectroscopy, dynamic light scattering, and zeta potential measurements. Fluorescence and circular dichroism spectroscopy were also employed for the first-time investigation of the interactions of Ta₂O₅ NPs and Ta₂O₅@PDA NPs with BSA. The results obtained show that PDA coating significantly enhances the protein-binding affinity. Time-resolved measurements revealed signatures of Förster resonance energy transfer, confirming complex formation between NPs and BSA. Moreover, colloidal stability tests in phosphate-buffered saline indicated that the presence of adsorbed BSA improves the dispersion stability of bare and PDA-coated Ta₂O₅ NPs. These findings advance the understanding of protein–NP interactions and highlight the potential of PDA coatings for designing stable and functional nanostructures for biomedical applications.

Keywords: tantalum oxide nanoparticles; polydopamine coating; bovine serum albumin; fluorescence spectroscopy; protein adsorption; colloidal stability



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1. Introduction

Nowadays, a lot of drug forms based on nanoparticles (NPs) have either entered clinical practice or are undergoing clinical trials [1]. Among the variety of NPs being

studied for medical purposes, those made of tantalum pentoxide (Ta_2O_5) attract special attention. This material is known as an inert, highly biocompatible, and radiopaque. Owing to its high chemical stability and minimal adverse effects, it seems to be an ideal material for coating surgical implants [2–4]. Furthermore, in the nanoparticulate form, tantalum oxide is promising for the development of drug-delivery systems [5], biosensors [6], contrast agents [7,8], and antitumor radiosensitizers [9,10].

One of the key limitations in the development of effective products based on NPs is the difficulty in predicting their behavior *in vivo*. Getting into the body presents a serious problem for NPs, since the environment there is far from “friendly” for them. For example, when administered intravenously, NPs encounter not only high ionic strength, molecular crowding, and whatever follows but also the immune defense system (for more information on opsonization, phagocytic attacks, etc., see [11,12]. In this regard, special attention should be paid to the physical or colloidal stability of NPs, as well as how to make them “stealthy” to the immune system, since, among others, these factors largely determine biodistribution, pharmacokinetics, and toxicity [13].

A promising strategy to ensure the stability of nanodrugs in physiological environments and prevent opsonization is the preliminary coating of NP surface with proteins [14–16]. These molecules may provide both steric and electrostatic stabilization to NPs due to their large number of charged groups. Among various proteins, bovine serum albumin (BSA) is one of the most commonly used for these purposes due to its abundance, high biocompatibility and non-toxicity to cells. However, BSA, very similar in structure and function to its human analog, is much cheaper and more available on the market. In principle, BSA molecules can be adsorbed onto the surface of metal oxide NPs through hydrogen bonding, electrostatic and hydrophobic interactions [17]. Also, to ensure effective binding of BSA molecules, a special functional layer may be formed on the NP surface. For this purpose, various polymers, such as, for example, polydopamine (PDA), can be used. PDA interacts with BSA through Michael addition, Schiff base reaction, and several non-covalent interactions [18,19], and, by the way, coating PDA NPs with BSA has been previously demonstrated as an effective strategy to prevent particle aggregation [20]. PDA also contains diverse functional groups, including catechol, amine, and imine, which enable it to form coatings on inorganic surfaces and provide a versatile platform for further modification.

It is especially important to note here that practically nothing is known about the interaction of Ta_2O_5 NPs with BSA. There are some works devoted to the adsorption of this protein on tantalum oxide films (for example, see [21]), but for its nanoparticulate form, there is an absolute lack of corresponding information. By the way, this problem concerns the NPs of many metal oxides. If many such works are known for metallic NPs (e.g., gold or silver), then only a few are known for those made, for example, of zinc, zirconium or cerium oxide (see [22,23]). From this point of view, the most studied among them, apparently, are iron and titanium oxide NPs (this is in good agreement with the data by Goodilin et al. [24]). Thus, the lack of systematic data on the interaction of metal oxide NPs with albumin and other serum proteins represents a serious challenge given how many factors influence this process (see in detail in [25]) and, therefore, how difficult it is to extrapolate the known results.

In the present work, we studied, for the first time, the interaction of Ta_2O_5 NPs with BSA, tested the possibility of facilitating the adsorption of its molecules onto the particle surface by its pre-coating with PDA, and also carried out a preliminary assessment of how coating such NPs with protein affects their stability under conditions close to physiological ones, since like a number of other NPs, those made of tantalum oxide are unstable in electrolyte solutions with high ionic strength [26,27].

2. Results and Discussion

Tantalum oxide NPs were synthesized via the solvothermal method, followed by replacing the alcohol dispersion medium with water [27]. During this process, Ta–O–Ta bonds are formed through the reaction of two tantalum ethoxide molecules via ether elimination. Among various synthesis methods for producing tantalum oxide NPs, this approach offers a significant advantage by enabling the formation of stable aqueous dispersions of nanoscale particles without requiring stabilizers. This allowed us to study the properties of the bare surface, since the absence of stabilizers preserved the intrinsic characteristics of the material, providing valuable insights into its behavior. This was especially essential for conducting a rigorous comparative analysis between coated and uncoated nanomaterial samples.

To visualize the synthesized NPs, a transmission electron microscopy (TEM) analysis was performed (Figure 1a). The uncoated Ta₂O₅ NPs exhibited a spherical morphology with an average core size of 29.7 ± 9.3 nm (the corresponding size distribution is shown in Figure 1b). The hydrodynamic diameter of the NPs was measured in distilled water and phosphate-buffered saline (PBS) using dynamic light scattering (DLS; Figure 1c). In water, it was found to be 70.4 ± 0.3 nm with a corresponding polydispersity index (PDI) of 0.235. In this case, the NPs were characterized by a zeta potential value of -49.3 ± 1.5 mV. This parameter is one of the key features indicating the colloidal stability of dispersed systems. For these NPs, as well as for their various modifications described below, all results on hydrodynamic diameters and PDI are summarized in Table S1. In turn, in PBS, the hydrodynamic diameter of the NPs increased to 129.1 ± 0.7 nm, with the PDI increasing to 0.191. Their electrical double layer was compressed, resulting in a decrease in the zeta potential to -30.4 ± 1.3 mV. All this clearly indicated the aggregation of the uncoated Ta₂O₅ NPs. However, no noticeable differences were observed between the studied solutions by the extinction spectra (Figure 1d).

According to the literature, DA and PDA attach to the surface of metal oxides NPs through the complexation reaction, which involves the replacement of surface oxide hydroxyl groups by deprotonated catechol groups from the ligand [28,29]. Thus, to coat the NPs with a PDA layer, a dopamine (DA) solution was mixed with Ta₂O₅ hydrosol. Then, the pH of the mixture was then adjusted to approximately 8.5 to initiate DA polymerization. The results of the study of the tantalum oxide NPs before and after their coating with PDA via Fourier transform infrared spectroscopy (FTIR) are presented in the Supplementary Materials (Figure S1). A series of new peaks which appeared in the range of $1250\text{--}1550\text{ cm}^{-1}$ clearly indicated the adsorption of PDA on the NP surface [30]. The formation of the PDA coating was further confirmed by XPS analysis, which revealed nitrogen-containing functional groups characteristic of polydopamine (Figure S2).

The corresponding TEM image for the PDA-coated NPs is presented in Figure 2a. It can be seen that after the deposition of PDA, the NP surface became quite rough. According to the statistical analysis, the average size of the NPs increased to 35.0 ± 11.4 nm after their modification (Figure 2b). After coating, the hydrodynamic diameter measured in water also increased to 86.5 ± 0.4 nm (Figure 2c). In turn, the values of PDI and zeta potential reached 0.104 and -46.9 ± 1.8 mV, respectively. Thus, coating the NPs with PDA did not lead to a decrease in their stability in distilled water. However, a significantly different picture was observed in PBS. Here, the PDA-modified NPs exhibited a drastic growth to 911.8 ± 44.0 nm. Such sharp increase in the average particle size, as well as the broadening of the size distribution clearly indicated the strong aggregation of the NPs. This finding was further supported by the alterations in the extinction spectrum upon changing the solvent from distilled water to PBS (Figure 2d). The observed increase in the signal, especially in the visible region of the spectrum, where there is no absorption by the NPs

themselves, may be associated with an increase in the contribution from light scattering by their large aggregates. In turn, the shoulder observed near 300 nm corresponded to the 5,6-dihydroxyindole units in the PDA molecules [31]. Herewith, the zeta potential of the Ta₂O₅@PDA NPs in PBS was -30.9 ± 0.3 mV, indicating that electrostatic interactions are not the only factor affecting their stability. In general, such behavior was consistent with the report for the PDA-coated gold NPs [32]: they also suffered a salt-induced aggregation, the effect of which was enhanced by the PDA layer.

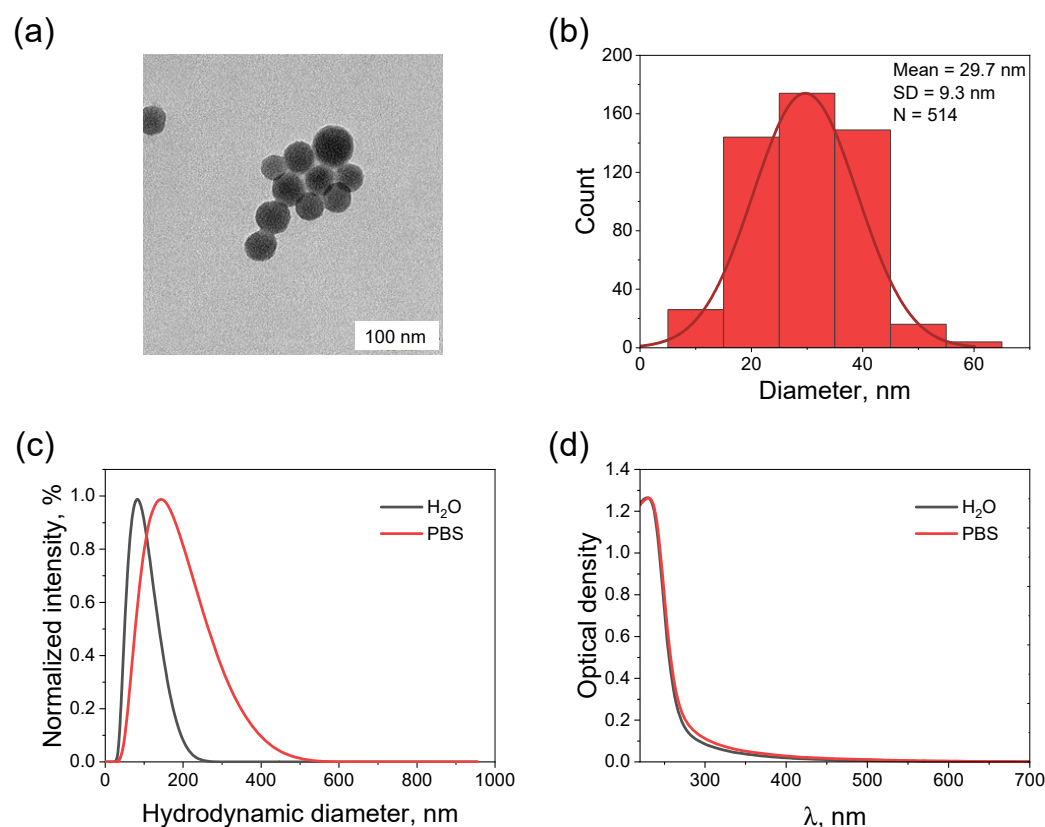


Figure 1. Characterization of the synthesized Ta₂O₅ NPs. (a) TEM image and (b) corresponding size distribution histogram (514 particles were analyzed). (c) Size distributions measured by DLS and (d) extinction spectra of Ta₂O₅ NPs (1.5×10^{-9} M). The color legends in figures (c,d) are identical: gray curves correspond to distilled water, and those of red—to PBS.

Interaction of BSA with the uncoated and coated tantalum oxide NPs was investigated by measuring the quenching of its fluorescence. It is well-known that photophysical properties of serum albumins are determined by their composition, namely, by the presence of such amino acids as tryptophan (Trp), tyrosine (Tyr) and phenylalanine (Phe) [33]. The main contribution to the signal comes from Trp residues. In native proteins, Tyr emission is often suppressed, presumably by its interaction with the peptide chain or via energy transfer to Trp. In turn, Phe has a low quantum yield and thus contributes minimally. Upon excitation at 280 nm, both Trp and Tyr residues fluoresce, while irradiation at 295 nm selectively excites Trp. Thus, data obtained at both wavelengths may provide complementary information about the microenvironment of these residues [34]. Based on this rationale, for both NP types, the efficacy of BSA fluorescence quenching was investigated at excitation wavelengths of 280 and 295 nm.

In order to eliminate the inner-filter effects, the fluorescence intensities were corrected by the formula below [35,36]:

$$F_{corr} = F_{obs} \times 10^{\frac{A_{ex}}{2} + \frac{A_{em}}{2}} \quad (1)$$

where F_{corr} and F_{obs} are the corrected and observed fluorescence intensities, A_{ex} and A_{em} are the absorption intensities at the given excitation and emission wavelengths, respectively.

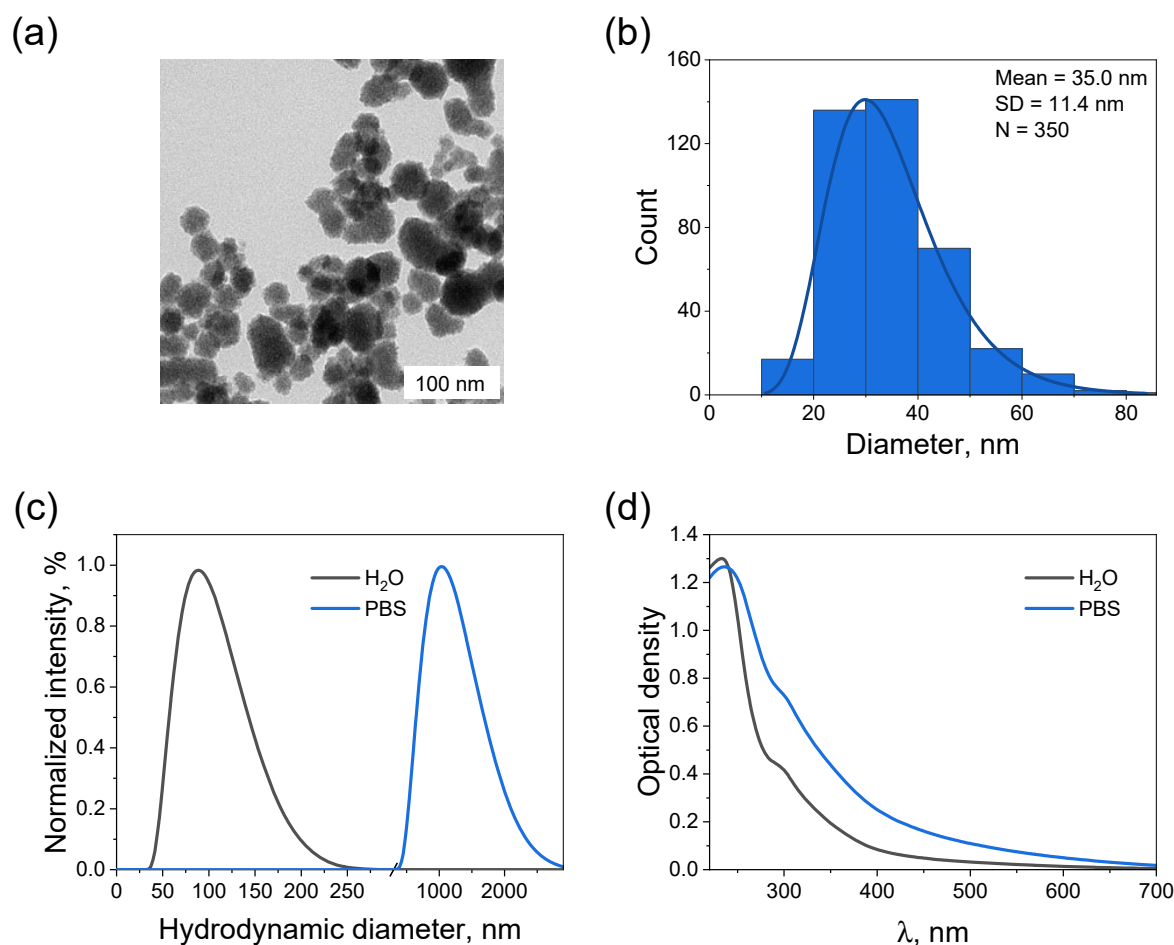


Figure 2. Characterization of the obtained Ta₂O₅@PDA NPs. (a) TEM image and (b) corresponding size distribution histogram (350 particles were analyzed). (c) Size distributions measured by DLS and (d) extinction spectra of Ta₂O₅ NPs (1.1×10^{-9} M). The color legends in figures (c,d) are identical: gray curves correspond to distilled water, and those of blue—to PBS.

The quenching data were analyzed by the Stern–Volmer equation [35]:

$$\frac{F_0}{F} = 1 + K_{SV} [Q] \quad (2)$$

where F_0 and F are the fluorescence intensities of BSA in the absence and presence of the NPs, K_{SV} is the Stern–Volmer constant, and $[Q]$ is the NP concentration.

The quenching constant k_q was determined as follows:

$$k_q = \frac{K_{SV}}{\tau_0}, \quad (3)$$

where τ_0 is the average excited state lifetime of BSA (6.19 ns), measured in the absence of NPs.

Figure 3a–d present the normalized fluorescence spectra of aqueous solutions of BSA (2×10^{-6} M) in the presence of increasing concentrations of Ta₂O₅ or Ta₂O₅@PDA NPs (up to 1.54×10^{-9} M and 1.14×10^{-9} M, respectively). It can be seen that both when the protein fluorescence was excited at a wavelength of 280 nm, and when it was excited at 295 nm, the signal intensity decreased with an increase in the content of NPs in the

system. In both cases, a significantly stronger drop was observed for Ta₂O₅@PDA NPs. Thus, upon excitation at 295 nm, the fluorescence intensity decreased by 1.5 times at the bare NP concentration of 1.32×10^{-9} M, whereas for PDA-coated ones, a similar effect was observed at 0.25×10^{-9} M (upon excitation at 280 nm, the corresponding concentrations were 1.33×10^{-9} M and 0.57×10^{-9} M, respectively). Plotting the $\frac{F_0}{F}$ ratio against the NP concentration provided a much clearer comparison (Figure 3e,f). The corresponding values of Stern–Volmer constant, estimated from linear sections of these dependencies, are summarized in Table 1. The values of quenching constant are also given there. Note that for both types of NPs, a slight shift in the spectral maximum to the blue region was noted. Among others, this could be due to changes in the microenvironment of the fluorophores due to the particle binding [34].

For the case of fluorescence excitation at 295 nm, the K_{SV} value for the PDA-coated NPs was approximately 2.5-fold higher than that for the uncoated particles. A less pronounced difference was found when it was excited at a wavelength of 280 nm. This variation may indicate a stronger affinity of Ta₂O₅@PDA NPs for BSA compared to bare Ta₂O₅ NPs. In turn, the k_q values for both types of the NPs significantly exceeded the diffusion-controlled limit $(1\text{--}2) \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ [37,38], indicating that the observed quenching of BSA fluorescence might have not only collisional nature, but also involve binding interactions [35].

The Stern–Volmer and quenching constants for Ta₂O₅ ($K_{SV} = 1.25 \times 10^9 \text{ M}^{-1}$) and Ta₂O₅@PDA ($K_{SV} = 3.12 \times 10^9 \text{ M}^{-1}$) NPs exceed those reported for titanium dioxide ($K_{SV} \approx 0.5 \times 10^4 \text{ M}^{-1}$) [39] and iron oxide ($K_{SV} \approx 10^4\text{--}10^8 \text{ M}^{-1}$) [40–42] NPs, which are among the most extensively studied metal oxide systems. At the same time, these values are lower than or comparable to those of plasmonic NPs such as gold and silver ($K_{SV} \approx 10^7\text{--}10^{10} \text{ M}^{-1}$) [43], which exhibit enhanced quenching efficiency due to localized surface plasmon resonance effects. Comparative studies on uncoated and PDA-coated iron oxide NPs [34] and functionalized metal–polyphenol NPs [44] reported differences in quenching efficacy related to surface modification. Thus, a slight decrease in the effect was observed for PDA-coated NPs in these studies. This result may be due to a reduction in the surface area of NPs available for adsorption, which in turn could be a result of their aggregation in buffer solutions [44]. Additionally, the coating formation may stimulate small particles to cluster into larger aggregates [34]. Such aggregation reduces the total surface area accessible for protein binding, thereby lowering the fluorescence quenching efficiency. However, as we noted above, the efficacy of fluorescence quenching can be affected by various factors (e.g., particle size, crystallinity, surface charge, etc. For more detail, see [25]); therefore, even within the same class of NPs, the values of the corresponding constants may differ by many orders of magnitude.

Let us now consider the quenching of BSA fluorescence in more detail. For both studied types of NPs, the signal dropped rapidly at low concentrations and decreased noticeably more slowly at higher concentrations, resulting in a downward-curving Stern–Volmer plot. The observed negative deviation from linearity suggested heterogeneity in the fluorophore population, where only a fraction of fluorophores contributes significantly to the fluorescence signal [45]. To estimate the fraction of fluorophores accessible to quenching, the modified Stern–Volmer equation can be used [35,46]:

$$\frac{F_0}{F_0 - F} = \frac{1}{f_a} + \frac{1}{f_a K_q} \frac{1}{[Q]}, \quad (4)$$

where f_a represents the fraction of fluorophore accessible to the NPs and K_q is the apparent quenching constant; F_0 , F and $[Q]$ are the same as in Equation (2).

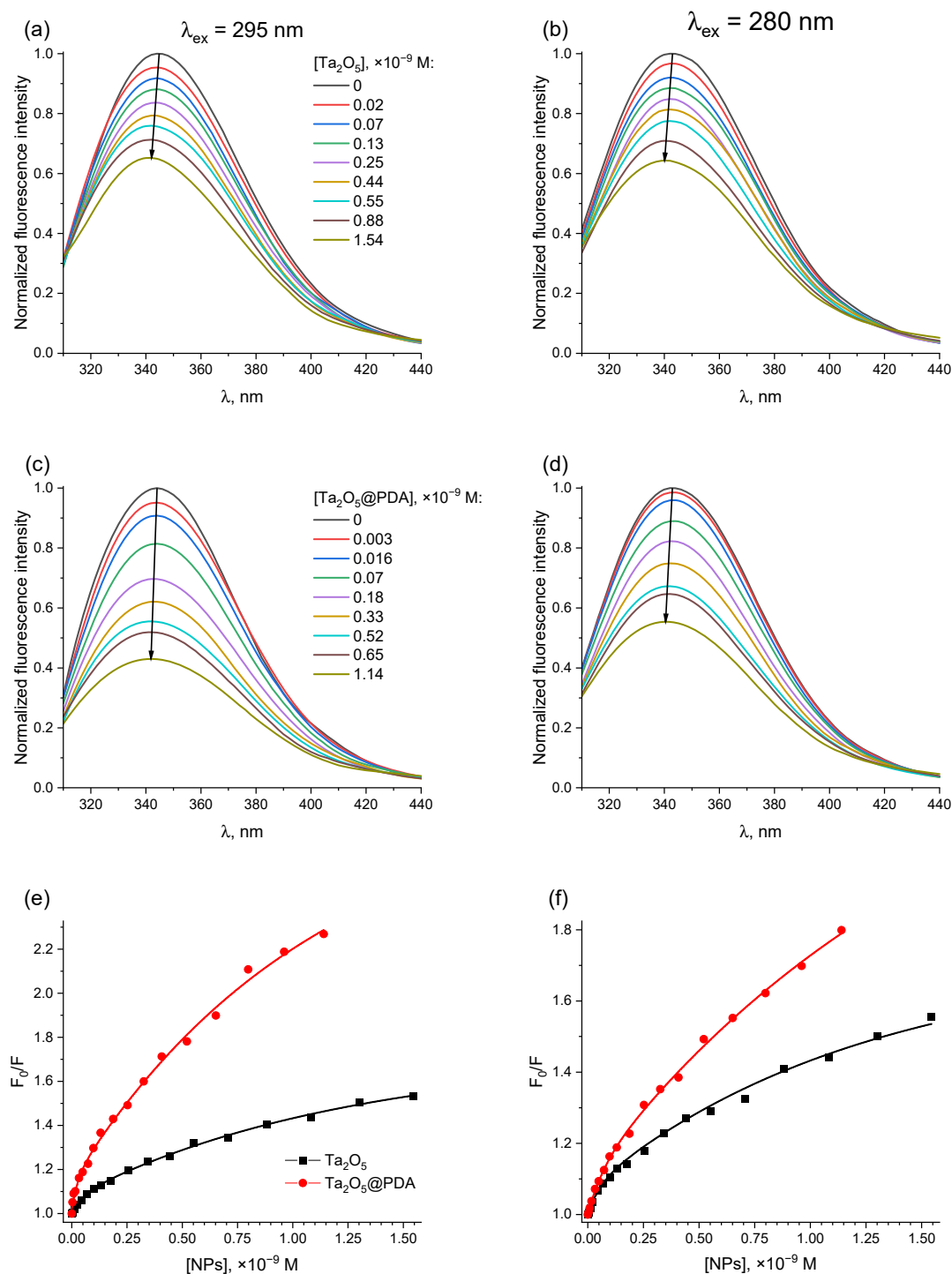


Figure 3. (a–d) Normalized fluorescence spectra of BSA (2×10^{-6} M) in distilled water in the presence of $(0\text{--}1.53) \times 10^{-9}$ M of Ta₂O₅ NPs (a,b) and $(0\text{--}1.14) \times 10^{-9}$ M of Ta₂O₅@PDA NPs (c,d). (e,f) Stern–Volmer plots for the quenching of BSA fluorescence by Ta₂O₅ (black curves) and Ta₂O₅@PDA (red curves) NPs. The left column shows the data for the case of the protein excitation at 295 nm, and the right one—for 280 nm, respectively.

The analysis using Equation (4) did not provide us with convincing data, as the results were heavily distorted by errors. This is most likely due to the fact that Equation (4) is a linear transformation of the equation describing the quenching of heterogeneously emitting systems [47]:

$$\frac{F}{F_0} = \sum_{i=1}^n \frac{f_i}{1 + K_{q,i}[Q]}, \quad (5)$$

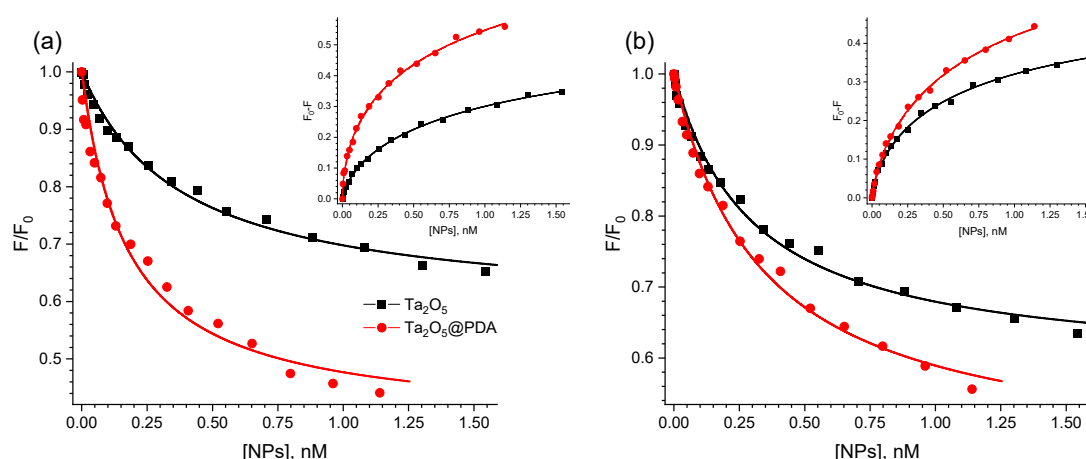
Table 1. Calculated values of Stern–Volmer and quenching constants for the Ta₂O₅ and Ta₂O₅@PDA NPs.

NPs	$K_{SV}, \times 10^9, (M^{-1})$		$k_q, \times 10^{17}, (M^{-1} s^{-1})$	
	$\lambda_{ex} = 280 \text{ nm}$	$\lambda_{ex} = 295 \text{ nm}$	$\lambda_{ex} = 280 \text{ nm}$	$\lambda_{ex} = 295 \text{ nm}$
Ta ₂ O ₅	1.17 ± 0.04	1.25 ± 0.06	1.89 ± 0.06	2.02 ± 0.10
Ta ₂ O ₅ @PDA	1.93 ± 0.11	3.12 ± 0.23	3.12 ± 0.18	5.04 ± 0.37

This is consistent with the fact that linear transformations can sometimes distort data and lead to unsatisfactory results [48,49]. Therefore, the use of non-linear approximation methods may be more appropriate in some cases [49]. For analysis, we used Equation (6) [50], which is a mathematically equivalent non-linear transformation of Equation (4). This equation is also a special case of Equation (5), assuming the presence of only two types of fluorophore populations:

$$\frac{F}{F_0} = (1 - f_a) + \frac{f_a}{1 + K_q[Q]}, \quad (6)$$

The plots of $\frac{F}{F_0}$ as a function of $[Q]$, constructed based on the mathematical model represented by Equation (6), are shown in Figure 4. The respective quantitative parameters K_q and f_a calculated according to this model are summarized in Table 2.

**Figure 4.** Modified Stern–Volmer plots for the quenching of BSA fluorescence by Ta₂O₅ (black curves) and Ta₂O₅@PDA (red curves) NPs. Panel (a) shows the data for the case of the protein excitation at 295 nm, and panel (b)—for 280 nm, respectively. The insets show the corresponding Hill plots for the quenching by Ta₂O₅ (black curves) and Ta₂O₅@PDA (red curves) NPs at 295 nm (a) and 280 nm (b).**Table 2.** Calculated values of apparent quenching constants and accessible fraction of the fluorophore for the Ta₂O₅ and Ta₂O₅@PDA NPs.

NPs	$\lambda_{ex} = 280 \text{ nm}$		$\lambda_{ex} = 295 \text{ nm}$	
	$K_q, \times 10^9, (M^{-1})$	f_a	$K_q, \times 10^9, (M^{-1})$	f_a
Ta ₂ O ₅	2.39 ± 0.19	0.42 ± 0.01	2.63 ± 0.24	0.45 ± 0.02
Ta ₂ O ₅ @PDA	3.32 ± 0.29	0.55 ± 0.02	4.94 ± 0.69	0.61 ± 0.03

The values of constant calculated according to Equation (6) were higher compared to those calculated by Equation (2). Modification of the NPs with PDA led to a slight increase of f_a : from 0.42 to 0.55 and from 0.45 to 0.61 upon excitation of the protein fluorescence

at wavelengths of 280 and 295 nm, respectively. Thus, it did not drastically influence the accessibility of fluorophores in BSA molecules.

Continuing the discussion regarding the mechanisms of protein–NP interaction, we suggest that the Hill equation could provide valuable additional information about these mechanisms:

$$\log\left(\frac{F_0 - F}{F}\right) = \log K_b + n \log [Q], \quad (7)$$

In the literature, this is sometimes termed the double log Stern–Volmer equation [51]. However, it is fundamentally a linear transformation of the original Hill equation [52]. The conventional form of Equation (7) describes the limiting case of a completely quenched complex. Since we observed incomplete fluorophore accessibility, the equation must be corrected for the residual fluorescence intensity at saturation (F_∞) [53]. Additionally, we directly used the non-linear form of the modified Hill equation, as the linear regression of transformed data is not the optimal method for parameter estimation [54]. Despite the widespread use of the linear transformation form, the application of non-linear fitting to fluorescence quenching data, particularly for NP systems, remains relatively uncommon [55]. The adapted non-linear equation is given as

$$\frac{F_0 - F}{F_0 - F_\infty} = \frac{[Q]^n}{(1/K_b)^n + [Q]^n}, \quad (8)$$

where n is the Hill coefficient, K_b is the overall binding constant, F_∞ —intensity of residual fluorescence; F_0 , F and $[Q]$ are the same as in Equations (2) and (6). The corresponding plots are shown in Figure 4 (inset), and the calculated values of n and K_b are presented in Table 3.

Table 3. Calculated values of Hill coefficient and binding constant for Ta₂O₅ and Ta₂O₅@PDA NPs.

NPs	$\lambda_{ex} = 280 \text{ nm}$		$\lambda_{ex} = 295 \text{ nm}$	
	$K_b, \times 10^9, (\text{M}^{-1})$	n	$K_b, \times 10^9, (\text{M}^{-1})$	n
Ta ₂ O ₅	0.44 ± 0.12	0.65 ± 0.02	0.46 ± 0.10	0.68 ± 0.03
Ta ₂ O ₅ @PDA	0.63 ± 0.15	0.67 ± 0.03	1.33 ± 0.03	0.59 ± 0.02

Although many studies interpret the coefficient n as the number of binding sites [51,56], there is substantial evidence that n is not a stoichiometric coefficient but a phenomenological parameter (the Hill coefficient), which is often lower than the actual number of binding sites [52,54,57]. The Hill coefficient serves as a model-independent measure of cooperativity within a system under equilibrium conditions and quantifies cooperative interactions between binding sites [58]. The value of $n < 1$ indicates negative cooperativity, where the binding of one ligand molecule impedes the binding of another one. For instance, in the context of protein adsorption onto NPs, this manifests as a gradual decrease in the binding affinity for additional protein molecules on the same particle surface. Conversely, $n > 1$ indicates positive cooperativity, meaning the adsorption of one protein molecule enhances the attachment of others to the same NP surface. Interestingly, the Hill coefficients n in our systems were found to be significantly below unity, suggesting negative cooperativity in the binding process. This observation is consistent with the downward-curving shape of the Stern–Volmer plots (Figure 3e,f). The more pronounced difference in quenching constants observed at 295 nm excitation compared to 280 nm across all three analytical approaches (Stern–Volmer, modified Stern–Volmer, and Hill equations), likely indicates a stronger interaction between the coated NPs and the tryptophan residues of the protein.

Figure 5 represents the fluorescence decay kinetics of BSA in distilled water in the presence of various concentrations of Ta₂O₅ NPs and Ta₂O₅@PDA NPs. The curves were analyzed using the two-exponential model, with the exception of native protein samples, which were analyzed using a single-exponential model:

$$I(t) = A_1 e^{-t/\tau_1} + A_2 e^{-t/\tau_2}, \quad (9)$$

where τ_1 and τ_2 are the lifetime components, A_1 and A_2 are their contributions to the total fluorescence amplitude.

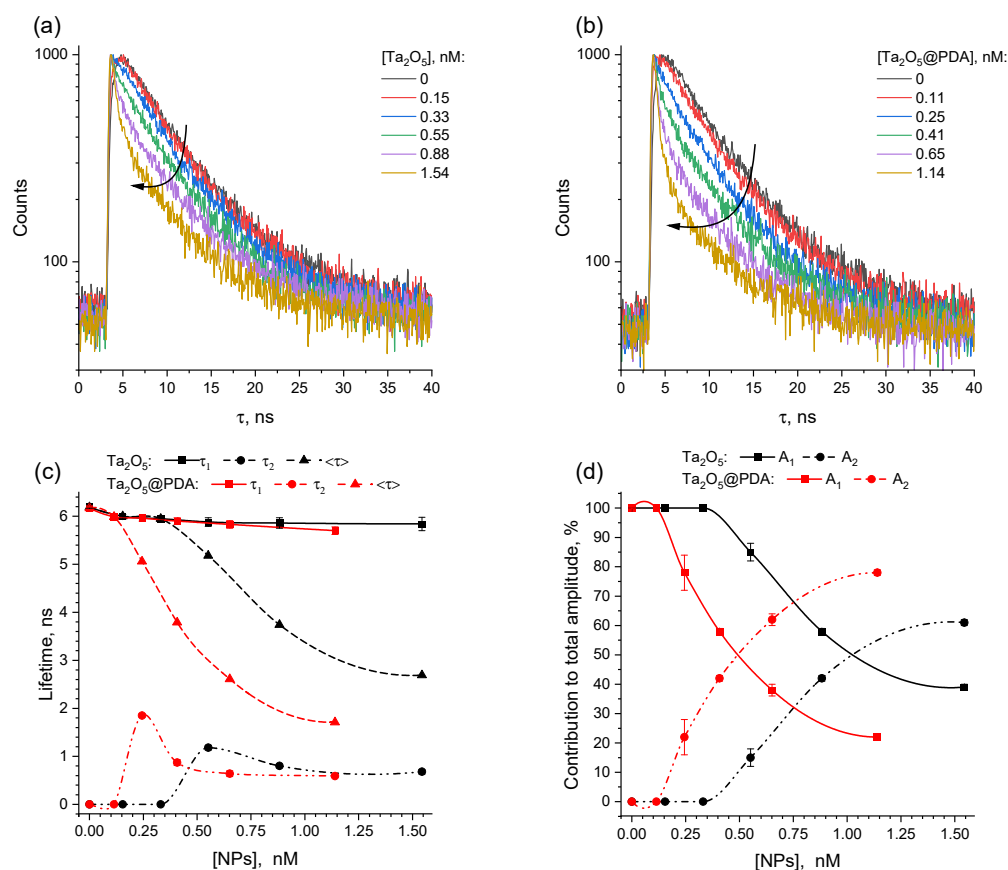


Figure 5. (a,b) Fluorescence decay kinetics of BSA ($\lambda_{\text{ex}} = 300$ nm, $\lambda_{\text{em}} = 345$ nm) in distilled water in the presence of $(0\text{--}1.53) \times 10^{-9}$ M of Ta₂O₅ (a) and $(0\text{--}1.14) \times 10^{-9}$ M of Ta₂O₅@PDA (b) NPs. The color legend in these figures is identical. The arrow indicates the increase of concentration of NPs. (c,d) Dependences of the lifetimes ((c); τ_1 —squares, τ_2 —circles, $\langle \tau \rangle$ —triangles) and their contributions to the total fluorescence amplitude ((d); A_1 —squares, A_2 —circles) on the concentration of Ta₂O₅ NPs (black curves) and Ta₂O₅@PDA NPs (red curves).

The average fluorescence lifetime $\langle \tau \rangle$ was calculated from the following equation:

$$\langle \tau \rangle = \frac{\sum_i A_i \tau_i^2}{\sum_i A_i \tau_i} \quad (10)$$

The variations of τ_1 and τ_2 , as well as A_1 and A_2 , are shown in Figure 5c,d. In the absence of NPs, the decay curve for BSA in water is monoexponential, with a single lifetime $\tau \approx 6.19$ ns, which is in good agreement with the literature [59,60]. A similar shape of the curves was also observed at low concentration of the NPs. However, in these cases, the lifetime gradually decreased from 6.19 ns to 5.95 ns (bare Ta₂O₅) and from 6.17 ns to 5.99 ns (Ta₂O₅@PDA). In turn, to accurately fit the experimental curves at increasing NP concentration, a two-component exponential model was required. Herewith, the short-lived

component can be attributed to bound BSA molecules, thereby supporting the existence of binding interactions. Indeed, as the NP concentration increases, its contribution to the total fluorescence amplitude increased, while that of the long-lived one gradually decreased. Moreover, the average fluorescence lifetime $\langle \tau \rangle$ demonstrated a noticeable reduction with rising NP concentration, particularly for coated particles.

It is also well-known that a change in the lifetime is the characteristic feature of Förster resonance energy transfer (FRET). Since FRET occurs at very close distances (≤ 10 nm), it may also be a marker of complex formation between the NPs and BSA. For the PDA-coated NPs, the corresponding changes were more pronounced, which may indicate more efficient energy transfer (note that the contribution of the short-lived component to the total intensity is also greater for Ta₂O₅@PDA).

Further experiments were carried out using circular dichroism (CD) spectroscopy, which is an excellent method for analyzing the structure (conformation) of proteins and peptides in a solution [61]. The CD spectra recorded for 4.5×10^{-6} M BSA in the absence and presence of varying concentrations of Ta₂O₅ and Ta₂O₅@PDA NPs are shown in Figure 6. Native BSA exhibited characteristic CD minima at 211.5 nm and 222 nm (black curve). The slight shift in the shorter-wavelength minimum from the typically reported 208 nm (in buffered solutions) to 211.5 nm is attributed to the usage of water as a solvent. Upon addition of NPs, the intensity of both minima decreased, indicating a loss of α -helical content and suggesting structural changes [62] consistent with NP-BSA complex formation [63]. The α -helix content in native BSA was 54% (it was calculated at wavelength 222 nm, according to [64]), which is consistent with literature values [65,66]. CD spectroscopy revealed partial unfolding of BSA upon interaction with NPs, characterized by a substantial loss of α -helical content and CD-signal intensity at 222 nm [67,68]. The effect was concentration-dependent and significantly more pronounced for PDA-coated NPs. At 1 nM, Ta₂O₅@PDA induced a $\approx 40\%$ reduction in helicity and a red shift in the longer-wavelength minimum to ≈ 227 nm, whereas bare Ta₂O₅ caused a similar change only at 2 nM. This indicates that the PDA coating may enhance the unfolding of BSA by the NPs. The decrease in the 208/220 nm ellipticity ratio from 0.83 (native) to 0.55 (Ta₂O₅) and 0.36 (Ta₂O₅@PDA) further confirms the loss of ordered structure [69]. In contrast, no such structural changes were detected for iron oxide nanoparticles, either coated with PDA or uncoated [34].

Then, knowing that BSA successfully binds to studied NPs, let us assess their colloidal stability. After modification, the hydrodynamic diameter of Ta₂O₅ and Ta₂O₅@PDA NPs in distilled water increased to 72.4 ± 0.7 nm and to 89.1 ± 0.4 nm, respectively. The corresponding PDI values were 0.190 and 0.101. The zeta potential values for Ta₂O₅-BSA and Ta₂O₅@PDA-BSA NPs remained highly negative (-40.3 ± 2.4 and -47.3 ± 1.1 mV), which favored electrostatic stabilization. The formation of the adsorbed BSA layer was also supported by FTIR spectroscopy, as evidenced by the intensified absorption band at 1648 cm^{-1} , characteristic of the C=O stretching vibrations in the amide I region (Figure S1) [70]. The colloidal stability of Ta₂O₅-BSA and Ta₂O₅@PDA-BSA NPs was studied in PBS (Figure 7). Overall, it can be seen that being coated with BSA significantly improved their stability in this medium. However, there were some differences in their behavior. While the size distributions of the double-modified NPs in PBS closely matched those measured in distilled water (Figure 7c), Ta₂O₅-BSA NPs showed signs of slight aggregation, as evidenced by a minor broadening of the size distribution peak and the appearance of a very broad band at higher diameters (Figure 7a). The zeta potentials values of Ta₂O₅-BSA and Ta₂O₅@PDA-BSA NPs in PBS were found to be -39.0 ± 3.5 and -25.2 ± 2.1 mV, respectively. Considering that the zeta potential of the latter was relatively low, it can be assumed that a steric mechanism makes a significant contribution to the stability of the system. In

turn, no noticeable difference in the absorption spectra of the BSA-modified particles was observed between water and PBS (Figure 7b,d).

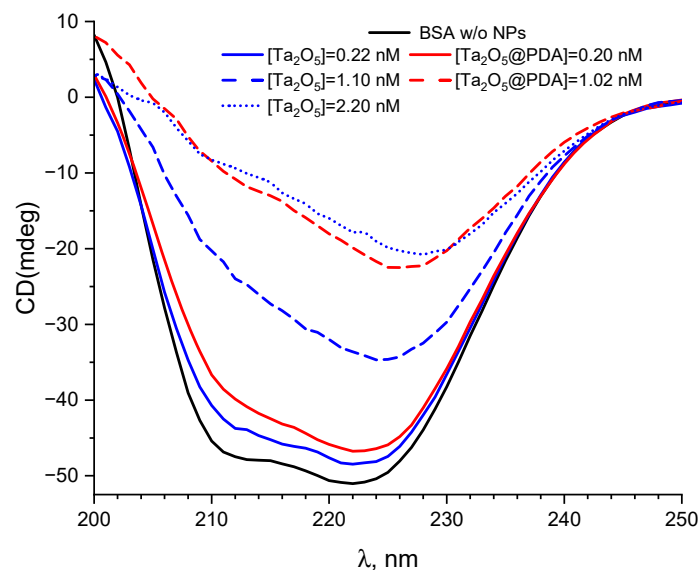


Figure 6. CD spectra of 2×10^{-6} M BSA in the absence (black line, BSA w/o NPs) and presence of varying concentrations of bare Ta_2O_5 NPs (blue lines) and Ta_2O_5 @PDA NPs (red lines).

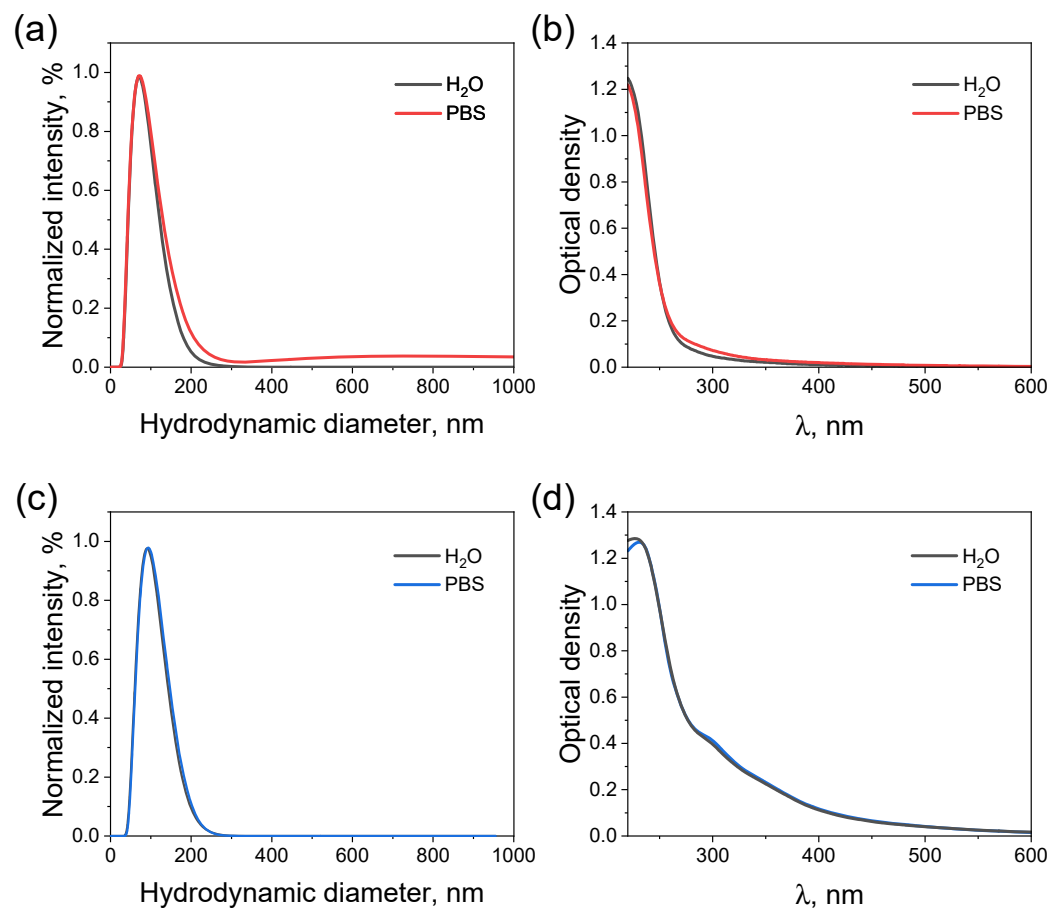


Figure 7. Characterization of the synthesized BSA-coated Ta_2O_5 and Ta_2O_5 @PDA NPs. (a,c) Size distributions measured by DLS and (b,d) extinction spectra of the NPs ($\approx 1.5 \times 10^{-9}$ M for Ta_2O_5 and $\approx 1.1 \times 10^{-9}$ M for Ta_2O_5 @PDA NPs). The top row shows the data for Ta_2O_5 NPs coated with BSA, and the one—for Ta_2O_5 @PDA NPs. The black curves correspond to distilled water, and those of red and blue—to PBS.

3. Materials and Methods

3.1. Materials

Tantalum (V) ethoxide (99.98%; Sigma-Aldrich, St. Louis, MO, USA), isopropyl alcohol (IPA; Chimmed, Moscow, Russia), sodium hydroxide solution (1 M) and DA hydrochloride (ACS Reagent; Sigma-Aldrich, USA), ready-made PBS with pH of 7.2–7.6 (Eco Service, Moscow, Russia), and BSA (PanEco, Moscow, Russia) were used as received. The protein concentration was determined spectrophotometrically using the known extinction coefficient $\epsilon_{280} = 44,720 \text{ M}^{-1} \text{ cm}^{-1}$ [71].

3.2. Synthesis of Ta_2O_5 NPs

Ta_2O_5 NPs were synthesized via the solvothermal method according to the protocol described in detail by Koshevaya et al. [27]. Briefly, 0.468 mL of tantalum (V) ethoxide was added in a drop-wise manner to 45 mL of anhydrous IPA. All manipulations with $\text{Ta}(\text{OC}_2\text{H}_5)_5$ were performed under a nitrogen atmosphere to prevent uncontrolled hydrolysis reaction. Next, a Teflon cup filled with the resulting solution was transferred to a stainless-steel autoclave and carefully sealed. The autoclave was placed in a furnace and heated to 200 °C for 12 h. This resulted in a transparent sol of primary particles in IPA. To obtain a hydrosol of Ta_2O_5 NPs, the sol of primary particles in IPA was mixed with water deionized using Arium 611 device (Sartorius, Göttingen, Germany) in such a volume ratio as to ultimately achieve a tantalum oxide content of 10 mg/mL ($1.5 \times 10^{-7} \text{ M}$ of Ta_2O_5 NPs). Then, the obtained mixture was slowly heated to remove IPA. During evaporation, the temperature was kept below the boiling point of IPA (82.5 °C).

3.3. Surface Modification of Ta_2O_5 NPs with PDA

To prepare Ta_2O_5 @PDA NPs, the Ta_2O_5 hydrosol (3 mg/mL or $4.4 \times 10^{-8} \text{ M}$) and DA solution (0.5 mg/mL) were mixed at a volume ratio of 1:1. To start the polymerization of DA, NaOH solution of 0.1 M was added to the dispersion in a drop-wise manner until its pH reached ≈ 8.5 . Then, the mixture was placed in a Rotamix shaker (Elmi, Riga, Latvia) and slowly rotated (20 rpm) at room temperature for 3 h. The prepared PDA-coated NPs were centrifuged at 14,000 rpm for 20 min using 320R centrifuge (Hettich, Tuttlingen, Germany). After that, the precipitated particles were resuspended in deionized water (30 s of ultrasonication using a Elmasonic S10H device (Elma, Singen, Germany)). This cycle was repeated 3 times.

3.4. Determination of NP Molar Concentration

The molar concentration of Ta_2O_5 and Ta_2O_5 @PDA NPs was calculated based on the particle number. Individual particle diameters were obtained from TEM, yielding mean diameters of $\langle d \rangle = 29.7 \text{ nm}$ and $\langle d \rangle = 35.0 \text{ nm}$, respectively. Assuming spherical geometry, the average particle volume was calculated as

$$V = (\pi/6) \times \langle d \rangle^3$$

Particle mass for Ta_2O_5 NPs was determined as $m(\text{NP}) = \rho \times V$, where ρ is the density of Ta_2O_5 (8.2 g/cm³) and V is the average particle volume.

Particle mass $m(\text{NP})$ for Ta_2O_5 @PDA NPS was determined as the sum of the oxide core mass and PDA-layer mass. The PDA-layer mass is determined as $m(\text{PDA}) = \rho \times V$, where ρ is the density of PDA-layer (1 g/cm³) and V is the average layer volume. The PDA-layer volume was calculated as the difference between the volumes of spheres with diameter of 35.0 nm (oxide core + PDA shell) and 29.7 nm (oxide core), corresponding to a shell thickness of approximately 2.7 nm.

The particle number in a given solution volume was determined from

$$N = m(\text{total})/m(\text{NP})$$

where $m(\text{total})$ is the mass of Ta_2O_5 and $\text{Ta}_2\text{O}_5\text{@PDA}$ determined gravimetrically. The molar concentration was finally calculated as $c = N/N_A$, where $N_A = 6.022 \times 10^{23} \text{ mol}^{-1}$ is Avogadro's number.

This calculation did not consider the polydispersity of the particle size distribution, which is a limitation of the approach used.

3.5. Surface Modification of Ta_2O_5 and $\text{Ta}_2\text{O}_5\text{@PDA}$ NPs with BSA

Ta_2O_5 -BSA and $\text{Ta}_2\text{O}_5\text{@PDA}$ -BSA NPs were prepared by mixing hydrosols of NPs, aqueous solutions of BSA and NaOH at the following concentrations: 0.75 mg/mL of NPs ($1.1 \times 10^{-8} \text{ M}$ of Ta_2O_5 NPs and $1.0 \times 10^{-8} \text{ M}$ of $\text{Ta}_2\text{O}_5\text{@PDA}$ NPs), 3.3 mg/mL of BSA (50 μM), 3 mM of NaOH. The resulting mixtures were characterized by a pH of ≈ 8.5 . Then, they were placed in the shaker and slowly rotated at room temperature for 4 h using the same settings as above. Finally, the NPs were centrifuged and washed three times with deionized water to remove unbound BSA and impurities.

3.6. Characterization of NPs

3.6.1. Transmission Electron Microscopy

The size and morphology of Ta_2O_5 and $\text{Ta}_2\text{O}_5\text{@PDA}$ NPs were determined using a high-resolution transmission electron microscope (HRTEM) Libra 120 (C. Zeiss, Oberkochen, Germany) operating at an accelerating voltage of 120 kV. For this purpose, a drop of the corresponding dispersion was placed on a formvar-coated copper grid for 1 min and then removed with filter paper. Particle size distribution histograms were obtained by counting at least 350 particles. The particle size was analyzed using an ImageJ.JS software (National Institutes of Health, Bethesda, MD, USA).

3.6.2. FTIR Spectroscopy

The formation of PDA and BSA layers on the NPs was qualitatively evaluated using Nicolet 380 FTIR spectrometer (Thermo Electron Corporation, Waltham, MA, USA). The spectra were measured in the diffuse reflectance mode in the wavenumber range of 400–4000 cm^{-1} .

3.6.3. Dynamic Light Scattering and Laser Doppler Electrophoresis

The hydrodynamic diameters of the synthesized NPs, as well as their zeta potentials in various solvents, were determined via Zetasizer Nano ZS spectrometer (Malvern, Malvern, UK) with solid state He–Ne laser generating light at a wavelength of 633 nm (scattering angle of 173°). In all cases, the concentration of NPs in the samples was $(1.5\text{--}3.0) \times 10^{-8} \text{ M}$ of Ta_2O_5 NPs and $(1.1\text{--}2.2) \times 10^{-8} \text{ M}$ of $\text{Ta}_2\text{O}_5\text{@PDA}$ NPs). The measurements were carried out in the special quartz cells at 25 $^\circ\text{C}$. The presented results were averaged over five independent measurements.

3.6.4. Absorbance, Fluorescence and Circular Dichroism Measurements

Absorption and steady-state fluorescence spectra were recorded using a UV-3101 PC spectrophotometer and an RF5301PC spectrofluorimeter (Shimadzu, Kyoto, Japan). In this case, BSA fluorescence was excited at wavelengths of 280 and 295 nm. Time-resolved fluorescence measurements were performed by the time-correlated single photon-counting (TCSPC) method using a FluoTime 300 spectrometer (Picoquant, Berlin, Germany; a pulsed 300 nm laser light source was used for the protein excitation, and its fluorescence was

detected at a wavelength of 345 nm). The decay curves were fitted by the exponential model using EasyTau 2 software. When calculating the excited state lifetimes, χ^2 did not exceed 1.3. In all cases, the measurements were performed in rectangular quartz cells (Hellma, Müllheim, Germany) with 1 cm path length for excitation light. Circular dichroism (CD) measurements were carried out on a J-715 spectropolarimeter (Jasco, Tokyo, Japan) at 20 °C using a quartz cell with 0.1 cm path length (Hellma, Müllheim, Germany).

4. Conclusions

This study provides the first comprehensive investigation of the interactions between tantalum oxide NPs and BSA. Using spectroscopic methods, we demonstrated that both bare and PDA-coated Ta₂O₅ NPs bind BSA quite effectively. Our findings revealed that the PDA coating acts as a crucial functional layer, significantly enhancing the binding affinity to BSA, as evidenced, among other things, by the increase in Stern–Volmer constant. The existence of FRET between BSA molecules and NPs also confirmed our assumptions. Analysis via Hill equation showed a negative binding cooperativity ($n < 1$) for both Ta₂O₅ and Ta₂O₅@PDA NPs, suggesting steric hindrance as a limiting factor for fluorophore accessibility. CD data demonstrated a significant disruption of BSA's secondary structure upon NP binding, consistent with partial unfolding. The PDA-coated NPs (Ta₂O₅@PDA) induced a markedly greater loss of α -helical content and a more drastic change in the 208/220 nm ellipticity ratio compared to bare Ta₂O₅ NPs. This indicates that the PDA coating may enhance the unfolding of BSA by the NPs.

Moreover, it was shown that surface modification with BSA significantly enhances the colloidal stability of the studied NPs in high-ionic strength environments. While bare Ta₂O₅ and Ta₂O₅@PDA NPs exhibited considerable aggregation in PBS, those coated with BSA demonstrated markedly reduced aggregation or its complete absence. The enhanced stability may be attributed to the synergism of electrostatic and steric stabilization mechanisms provided by the adsorbed BSA layer.

In conclusion, this work fills a critical knowledge gap in understanding the interaction between Ta₂O₅ NPs and albumins and establishes an effective strategy for NP stabilization in high ionic strength environments via sequential PDA and BSA coatings. The functional groups present in both PDA and BSA offer versatile platforms for further modification, enabling the fabrication of multifunctional nanostructures suitable for advanced biomedical applications such as targeted imaging, therapeutic delivery, and stimuli-responsive systems [72–75].

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/molecules31020241/s1>, Table S1: Hydrodynamic diameters and polydispersity index of NPs in water and PBS; Figure S1: FTIR spectra of Ta₂O₅, Ta₂O₅@PDA, Ta₂O₅-BSA and Ta₂O₅@PDA-BSA NPs; Figure S2: XPS spectra in the N1s region for bare Ta₂O₅ NPs and Ta₂O₅@PDA NPs.

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