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Preparation and properties of Miramistin–hyaluronic acid coatings on the nanodiamond surface

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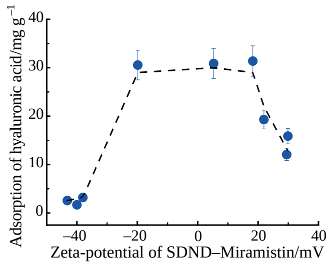
Hyaluronic acid is a promising coating for imparting biocompatibility to nanodiamond–antibiotic composites. It has been found that the adsorption of Miramistin on nanodiamonds with an initial negative zeta-potential increases the adsorption of hyaluronic acid, which remains lower than on positively charged nanodiamonds that are not affected by the pre-adsorption of Miramistin. The highest adsorption of hyaluronic acid is observed when Miramistin neutralizes the surface charge of nanoparticles.



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The variety of structures and unique properties make nanodiamonds a promising material in various fields of modern technologies.[1] Due to the high sorption capacity provided by the developed particle surface, nanodiamonds can potentially be used in medicine, in particular, for drug delivery.[2–4] Encapsulation is a convenient approach to solving problems associated with unacceptable bioavailability of a drug, its stability both individually and on the surface of a nanocarrier, taste, odor, *etc*. This procedure often consists in the co-precipitation of a drug, for example, with a polymer as an alternative to drug carrier.[5] Since the biocompatibility of the nanodiamond–drug composite may differ from the compatibility and toxicity of the initial components, it seems promising to use easily destructible additional coatings to keep the drug in a specific form for the required time. Coating with a biological material is considered as a promising tool for imparting biocompatibility to a nanodiamond–antibiotic composite. Hyaluronic acid appears to be a suitable material in this capacity. In this research, benzyldimethyl[3-(1-oxotetradecylamino)propyl]-ammonium chloride, known under the commercial name Miramistin®, was used as a model drug.[6] The aim of this study is to prepare and characterize adsorption complexes nanodiamond–Miramistin–hyaluronic acid.

We have concentrated our efforts to get answers to the questions listed below. (1) How does Miramistin coating affect the adsorption of hyaluronic acid in a wide range of biopolymer concentrations? To do this, we considered the adsorption isotherm of hyaluronic acid on nanodiamonds modified with Miramistin, provided that all nanodiamond samples have the same surface coverage with Miramistin. (2) How does the surface concentration of Miramistin affect the adsorption of hyaluronic acid? In these experiments, nanodiamond samples contained different amounts of Miramistin. Finally, (3) how stable are the adsorption complexes in biological media? To clarify this, we determined the amounts of both Miramistin and hyaluronic acid using compounds labeled with tritium.

Nanodiamonds in the form of a powder (DND) or suspension (SDND), as well as sodium hyaluronate with a molecular weight of 200 kDa, were used to prepare nanodiamond–Miramistin–hyaluronic acid complexes (for details, see Online Supplementary Materials).

At the first stage, nanodiamonds were modified with Miramistin. In the case of DND, the adsorbed amount of Miramistin increased almost linearly with increasing concentration, while for SDND, adsorption reached a constant value at a concentration of Miramistin of *ca*. 2 mmol dm^{-3} (Figure S1, see Online Supplementary Materials). At concentrations below 2 mmol dm^{-3}, the adsorption of Miramistin on DND is lower than on SDND, which is in good agreement with the previously obtained data for positively and negatively charged nanodiamonds.[7,8] At higher concentrations, micelles can affect the adsorption process. The surface concentration of tightly bound Miramistin (Γ_1) was also determined (Figure S2). In the region of low concentrations, adsorption was described using the Langmuir model to identify adsorption parameters for comparing nanodiamond samples with each other and with the previously obtained results.[8] It was found that for DND and SDND the values of maximum adsorption Γ_{max} were 0.04 and 0.18 mmol g^{-1}, and the Langmuir constants K_L were 0.41 and 4.2 dm^3 $mmol^{-1}$, respectively.

Surface coverage with Miramistin leads to a change in the zeta-potential of nanodiamonds of both types. Figure 1 shows the dependence of the zeta potential on the surface coverage. Upon reaching a surface coverage of SDND with Miramistin of 0.11 mmol g^{-1}, the zeta potential becomes zero and then positive with increasing surface concentration. It should be noted that the SDND–Miramistin suspension has the maximum colloidal stability in the plateau region on the curve of dependence of the zeta potential on the surface concentration of Miramistin.[9] The modification of DND with Miramistin retains the zeta-potential in the positive region but demonstrates significant stabilization of

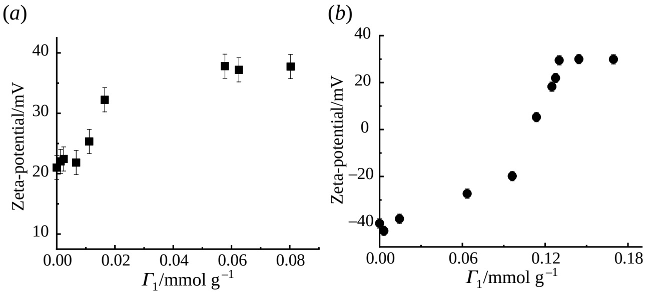

Figure 1 Dependence of the zeta-potential of nanodiamonds on the surface concentration of Miramistin adsorbed on (*a*) DND and (*b*) SDND.

nanoparticles in the aqueous suspension. With a surface coverage of 0.04 mmol g^{-1}, the zeta-potential becomes close to 36 ± 1 mV and remains constant with a further increase in surface coverage.

Therefore, this region of constant values of the zeta-potential was chosen to compare the adsorption of hyaluronic acid on nanodiamonds modified with Miramistin. SDND and DND were modified with Miramistin at a surface concentration of about 0.18 and 0.02 mmol g^{-1}, respectively, where the zeta-potential is close to +30 mV for both samples. Figure 2 shows the adsorption of hyaluronic acid depending on its equilibrium concentration. It was found that the pre-adsorption of Miramistin does not change the DND surface coverage with hyaluronic acid at its concentrations less than 0.5 g dm^{-3}, while the adsorption of hyaluronic acid on the SDND surface modified with Miramistin was 18 times higher than on the initial one. Despite the positive zeta-potentials of both modified samples, the adsorption of hyaluronic acid on these surfaces is not the same.

To determine the effect of the Miramistin content in the complex on the coverage of the surface with hyaluronic acid, an SDND sample was selected. The experiment was carried out with 0.16 g dm^{-3} of tritium-labeled hyaluronic acid, the surface concentration of Miramistin varied from 0.2 to 175 μmol g^{-1}, which led to a change in the zeta-potential from −40 to +30 mV. Figure 3 shows the surface concentration of hyaluronic acid as a function of the zeta-potential of the SDND–Miramistin surface.

The low adsorption values of hyaluronic acid on initially negatively charged particles can be explained by electrostatic repulsion. The formation of complexes in this case occurs due to bound water molecules.[10–13] It was found that the surface concentration of hyaluronic acid is higher for composites with a zeta-potential of −20 to +20 mV, while for positively charged particles with higher zeta-potential values, polymer adsorption is reduced. Being a weak polyelectrolyte (polyanion), hyaluronic acid has more elongated conformations on the neutral and negatively charged surfaces due to repulsion from the surface and bonds, while the positively charged surface adsorbs the polyanion in a flat conformation due to electrostatic attraction.[14]

The retention of hyaluronic acid in adsorption complexes was determined in phosphate-buffered saline (PBS) with and without

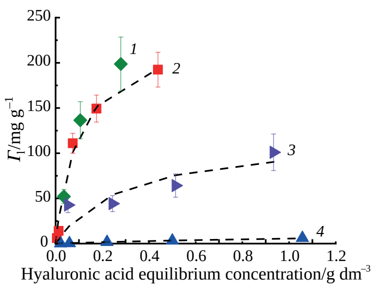

Figure 2 Concentration dependence of nanodiamond surface coverage with hyaluronic acid for initial nanodiamonds and nanodiamond–Miramistin complexes: (*1*) DND–Miramistin, (*2*) DND, (*3*) SDND–Miramistin and (*4*) SDND.

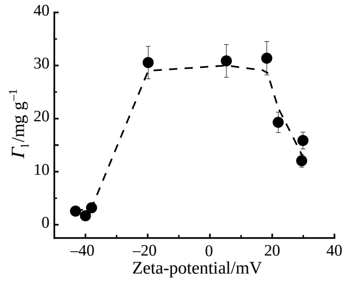

Figure 3 Dependence of the surface concentration of hyaluronic acid on the zeta-potential of the SDND–Miramistin surface. The dotted line is a guide to the eye.

Table 1 Desorption of hyaluronic acid from nanodiamond-containing particles.

Nanodiamond particles	Zeta-potential in aqueous suspension/ mV	Amount of hyaluronic acid on nanodiamond surface/mg g^{-1}		
		Before desorption	After desorption in PBS	After desorption in PBS + BSA
DND	14 ± 2	238 ± 10	82 ± 9	22 ± 3
DND–Miramistin	31 ± 1	210 ± 17	56 ± 4	17 ± 3
SDND	−50 ± 1	3.6 ± 0.8	2.6 ± 0.2	1.5 ± 0.4
SDND–Miramistin	4 ± 2	50 ± 4	16 ± 2	2.9 ± 0.4
SDND–Miramistin	25 ± 1	23 ± 5	14 ± 1	2.0 ± 0.6

40 g dm^{-3} of bovine serum albumin (BSA). The desorption experiment was carried out at an equilibrium concentration of hyaluronic acid of 0.7 g dm^{-3}, which is four times higher than in the previous experiment (Table 1). It was found that the pre-adsorption of Miramistin on the SDND surface increases both the total amount of hyaluronic acid on the surface of nanodiamonds and its residual amount after storage in a 0.9 wt% NaCl solution. Being a good desorbing agent, albumin removes a significant amount of coverage from the surface of nanodiamonds. Note that in the cases of DND and DND–Miramistin, the residual amount of hyaluronic acid was higher than in the case of SDND modified with Miramistin to a positive zeta-potential.

Thus, it can be concluded that hyaluronic acid can successfully encapsulate nanodiamond–drug adsorption complexes and be partially removed from adsorption complexes in the presence of serum proteins. We believe that the data obtained can be used in the development of drug nanocarriers.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.07.023.

References

1 V. Yu. Dolmatov, A. N. Ozerin, I. I. Kulakova, O. O. Bochechka, N. M. Lapchuk, V. Myllymäki and A. Vehanen, *Russ. Chem. Rev.*, 2020, **89**, 1428.

2 J. Xiao, X. Duan, Q. Yin, Z. Zhang, H. Yu and Y. Li, *Biomaterials*, 2013, **34**, 9648.

3 V. Vaijayanthimala, D. K. Lee, S. V. Kim, A. Yen, N. Tsai, D. Ho, H.-C. Chang and O. Shenderova, *Expert Opin. Drug Delivery*, 2015, **12**, 735.

4 E. Perevedentseva, Y.-C. Lin and C.-L. Cheng, *Expert Opin. Drug Delivery*, 2021, **18**, 369.

5 C. J. Martínez Rivas, M. Tarhini, W. Badri, K. Miladi, H. Greige-Gerges, Q. A. Nazari, S. A. Galindo Rodríguez, R. Álvarez Román, H. Fessi and A. Elaissari, *Int. J. Pharm.*, 2017, **532**, 66.

6 H. S. Skrabkova, M. G. Chernysheva, A. M. Arutyunyan and G. A. Badun, *Mendeleev Commun.*, 2020, **30**, 645.

7 M. G. Chernysheva, N. S. Melik-Nubarov, I. D. Grozdova, I. Yu. Myasnikov, V. N. Tashlitsky and G. A. Badun, *Mendeleev Commun.*, 2017, **27**, 421.

8 M. G. Chernysheva, A. G. Popov, V. N. Tashlitsky and G. A. Badun, *Colloids Surf., A*, 2019, **565**, 25.

9 N. Gibson, O. Shenderova, T. J. M. Luo, S. Moseenkov, V. Bondar, A. Puzyr, K. Purtov, Z. Fitzgerald and D. W. Brenner, *Diamond Relat. Mater.*, 2009, **18**, 620.

10 A. M. Vervald, K. A. Laptinskiy, S. A. Burikov, T. V. Laptinskaya, O. A. Shenderova, I. I. Vlasov and T. A. Dolenko, *J. Colloid Interface Sci.*, 2019, **547**, 206.

11 A. V. Shvidchenko, E. D. Eidelman, A. Ya. Vul', N. M. Kuznetsov, D. Yu. Stolyarova, S. I. Belousov and S. N. Chvalun, *Adv. Colloid Interface Sci.*, 2019, **268**, 64.

12 S. Stehlik, T. Glatzel, V. Pichot, R. Pawlak, E. Meyer, D. Spitzer and B. Rezek, *Diamond Relat. Mater.*, 2016, **63**, 97.

13 A. V. Sinolits, M. G. Chernysheva, A. G. Popov, A. V. Egorov and G. A. Badun, *Colloids Surf., A*, 2021, **618**, 126461.

14 F. Carnal and S. Stoll, *J. Phys. Chem. B*, 2011, **115**, 12007.

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