



QD–APTAMER BIOCOMPLEXES WITH SPECIFICITY TO THE EPIDERMAL GROWTH FACTOR RECEPTOR

Cite this: *INEOS OPEN*,
2025, 8 (1–3), XX–XX
DOI: 10.32931/ioXXXXXx

Received XX Month 20XX

Accepted 6 April 2025

<http://ineosopen.org>

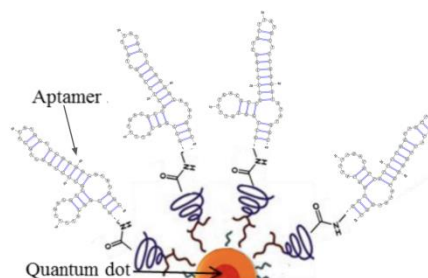
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Abstract

Complexes based on quantum dots (QDs) and aptamers can combine the luminescence properties of nanoparticles and the specificity of interaction of an aptamer with a target. In this work, a method for obtaining the complexes of QDs of various types (CdSe/ZnS and InP/ZnS) with DNA aptamers Gol1 and U8 was proposed. These aptamers determine the specificity of interaction with the epidermal growth factor receptor (EGFR). The complexes obtained have great potential in the field of optical visualization and diagnostics of oncological diseases.

Key words: quantum dot, aptamer, luminescence.



Introduction

Owing to the unique optical properties and stability, quantum dots are increasingly considered as luminescent markers in the development of new biosensors for clinical diagnostics and various immunobiological studies [1, 2]. Along with high stability, these systems may also exhibit specific interactions with certain targets. To create them, QDs of various structures were used, including CdSe/ZnS and InP/ZnS bearing functional groups on the particle surface, which offer the possibility of further modification with ligands such as aptamers [3]. Aptamers are oligonucleotides with a complex tertiary structure, which ensures the ability to perform diverse functions, for example, molecular recognition—the ability to structurally bind with both small and large molecules [4, 5]. Oligonucleotide aptamers offer a number of advantages such as the versatile and rapid synthesis, chemical stability, non-toxicity, as well as the possibility to modify the structure and introduce difference functional groups into the main chain. The aptamers Gol1 [6] and U8 [7] are known for their specificity to bind with the epidermal growth factor receptor. The EGFR is a transmembrane protein of both healthy and cancerous cells and acts as a receptor for the epidermal growth factor (EGF) normally required to stimulate healthy cell growth and differentiation. However, the presence of the EGFR on the cell surface in larger quantities is a globally recognized marker of oncological diseases [8].

Results and discussion

This work was aimed at obtaining QD–aptamer complexes featuring the luminescence properties of QDs and selectivity of aptamers. Two different types of nanoparticles were used:

CdSe/ZnS with a high quantum yield and stability and InP/ZnS based on low-toxicity atoms.

The QDs are coated with hydrophilic high-molecular ligands, which, in addition to the ability of imparting water solubility, have functional carboxy groups, ensuring the possibility of their further modification. In order to create the complexes with high affinity to the EGFR, two DNA aptamers, namely, Gol1 and U8 were selected in order to provide specific interaction with the EGFR protein on the cell surface. For binding with carboxy groups on the QD surface, the aptamers were additionally modified with amino groups. The sequences of the aptamers in use were as follows:

- amino-Gol1: $\text{NH}_2\text{-C}_6\text{H}_{12}\text{-gcc-ggc-att-ttg-acg-ccg-ccc-cgg-ctg-ctt-att-atg-ctcc-ggg-gca-tat-ggc}$,
- amino-U8: $\text{NH}_2\text{-C}_6\text{H}_{12}\text{-atc-cag-agt-gac-gca-gca-tga-atc-ttt-tct-ttt-ggt-ttt-gat-att-tat-agt-tgg-tga-atg-gac-acg-gtg-gct-tagt}$.

The reactions between carboxy groups of the QDs and amino groups of the aptamers were accomplished using *N*-(4-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC) and *N*-hydroxysuccinimide (NHS) as activators (Fig. 1).

The aptamer binding with the QD was confirmed by the results of light scattering studies, which revealed a change in the hydrodynamic radius of the particles before and after the reaction. As an example, Fig. 2 shows the dependences for InP/ZnS QDs with Gol1 and U8 aptamers in water.

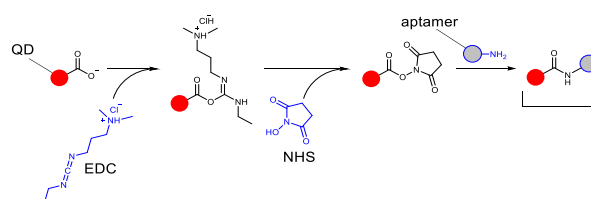


Figure 1. Synthesis of the QD–aptamer complexes.

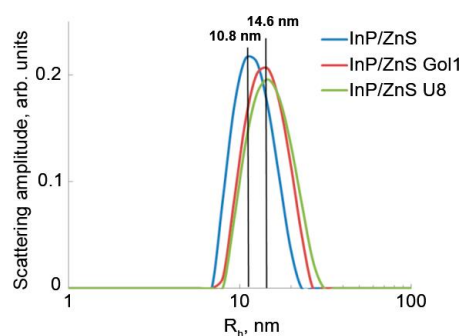


Figure 2. Hydrodynamic radii of InP/ZnS quantum dots before and after attachment of Gol1 and U8 aptamers.

The initial hydrodynamic radius of InP/ZnS QD was 10.8 nm. The particle radius increased to 14.6 nm after binding of the QD with both of the aptamers. The hydrodynamic radius of CdSe/ZnS QD in pure form without aptamers was 10.8 nm. The radius of the particles of CdSe/ZnS–Gol1 complex was 14.6 nm and that of CdSe/ZnS–U8 complex was 17.0 nm (Table 1).

Upon the aptamer interaction with the surface of the quantum dots, an increase in the hydrodynamic radius of the nanoparticles was observed in all cases, which is associated with the attachment of the aptamer to the polymeric stabilizer through an amide bond.

Table 1. Hydrodynamic radii of the QDs and QD–aptamer complexes

QD	$R_{hs} \pm 0.5$ nm		
	Pure QD	QD–Gol1	QD–U8
CdSe/ZnS	10.8	14.6	17.0
InP/ZnS	10.8	14.6	14.6

Experimental section

The QD–aptamer complexes were synthesized using the following procedure based on the material from Ref. [9].

N-(4-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.8 mM, 20 μ L) and *N*-hydroxysuccinimide (0.8 mM, 20 μ L) were added to a solution of the QD in water (5 μ M, 12 μ L). The mixture was incubated in the dark at room temperature for 90 min and then purified from the activators by the dialysis using an Amicon Ultra 30 kDa centrifugal concentrator (centrifuged 3 times, washing with water, 10000 rpm for 10 min). Then an aptamer solution (50 μ L) was added to the activated QD solution. The mixture was incubated in the dark at room temperature for 90 min and then purified from the excess aptamer and activators by the dialysis using an Amicon Ultra 100 kDa centrifugal concentrator (centrifuged 3 times, washing with water, 10000 rpm for 10 min).

Conclusions

Hence, the method for obtaining and isolating the aptamer complexes with nanoparticles *via* a strong amide bond was elaborated. For this purpose, the QDs of different structures (CdSe/ZnS and InP/ZnS) with active COOH groups on the surface were obtained and bound with the aptamers bearing NH₂ groups. An increase in the hydrodynamic radius of the nanoparticles after modification indicated the formation of the QD–aptamer complexes.

Acknowledgements

This work was supported by the Russian Science Foundation (project no. 24-23-00551).

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