Synthesis of thermoresponsive polymer pNIPAM for drug delivery system using gold nanostructures

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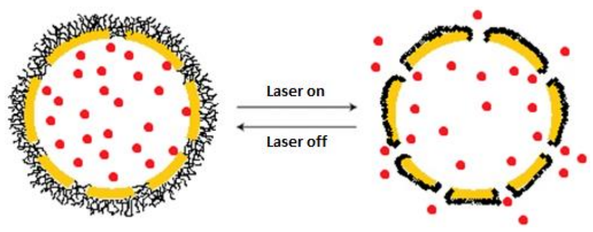
Introduction

Over the past two decades, many ways to create controlled drug delivery systems have emerged, among which systems based on metals, particularly gold, stand out. Due to its bioinertness, ability to be heated under laser irradiation at different wavelengths depending on size and morphology, surface functionalization to improve properties, ability to accumulate in tumors, gold nanoshells have become one of the best solutions for use in the fight against cancer cells.



The main idea is to create a drug delivery system based on gold nanoshells covered by thermoresponsive polymer pNIPAM. When a nearinfrared laser irradiates the nanoparticle, the gold heats up and polymer changes its structure from hydrophilic to hydrophobic opening pores and releasing downloaded drugs outside.

In this work, the processes of synthesis of poly-N-isopropylacrylamide (pNIPAM) by RAFT polymerization on the surface of gold nanoshells and silver nanoparticle seeds were investigated. The studies were performed by means of absorption spectroscopy technique. The absorption spectra of the aqueous solutions were measured before and after the addition of monomer and iniferter, and also were compared depending on different concentrations of components and ultraviolet irradiation time.

Materials and methods

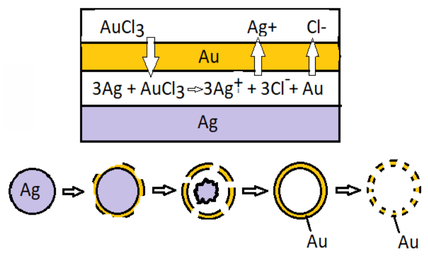


Fig. 1. Scheme of prolonged Au/Ag galvanic replacement reaction.
P. V. Demydov et al. "LSPR Tuning by Variable Morphology of Gold Nanoshells," *2021 IEEE 11th International Conference (NAP)*, 2021

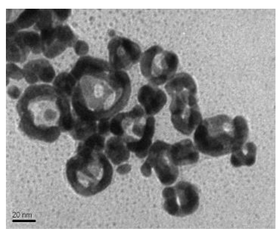


Fig. 2. TEM photograph of citrate-coated gold nanoshells prepared by standard protocol with three reaction stages.
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In the first experiment citrate-coated gold nanoshells were prepared by standard protocol with three reaction stages.
In the second experiment only the first stage was used. To synthesize seed silver nanoparticles there were taken aqueous solution of silver nitrate, sodium citrate or NIPAM aqueous solutions as stabilizers, $NABH_4$ as reductant and saturated solution of 3-mercaptopropyl diethyl carbamodiciatate in isopropanol as iniferter and heated. The last one was developed by our colleagues from University of Leicester (England) for molecular imprinting via RAFT polymerization.

According to IUPAC RAFT is reversible-addition-fragmentation chain-transfer polymerization. The mechanism is related to iniferter dormant and active group exchange. A radical of polymer chain interacts with sulfur-carbon double bond of iniferter and goes to carbon of SH-end group, which forms new polymer chain. Then the last one interacts with sulfur-carbon double bond of iniferter again and radical goes to the previous polymer chain bounded with iniferter at first step etc. SH-end group helps to bind with silver and gold nanoparticles.

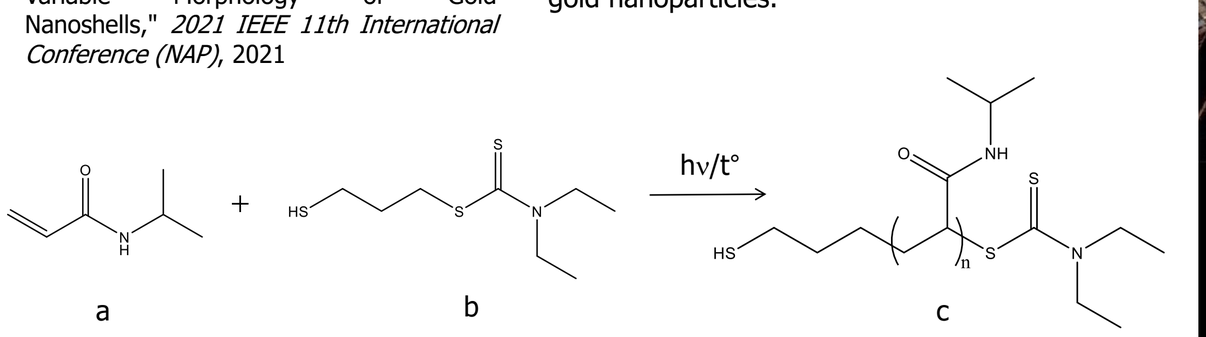

Fig. 3. Scheme of Poly(N-isopropylacrylamide) (pNIPAM) synthesis by RAFT polymerization via UV irradiation or temperature. (a) – NIPAM, (b) – 3-mercaptopropyl diethyl carbamodiciatate (iniferter), (c) – pNIPAM.

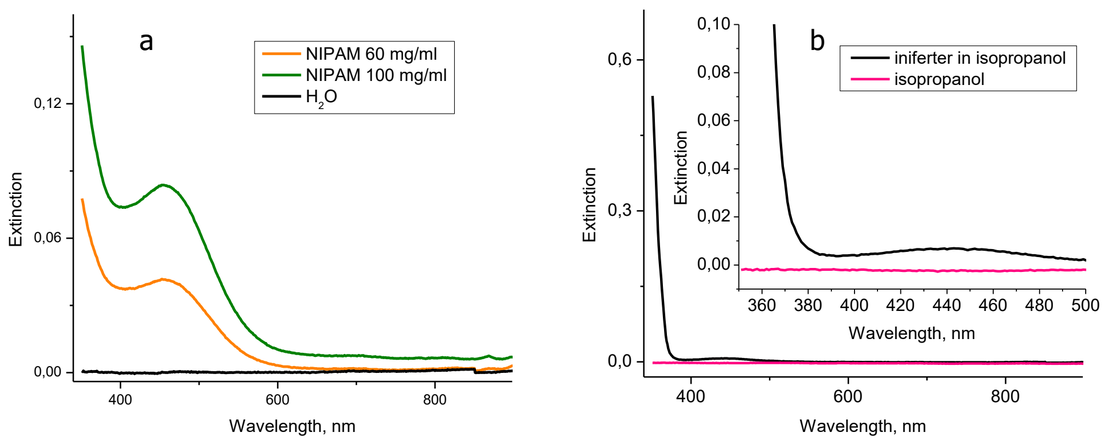

Fig. 4. Extinction spectra of pure monomer NIPAM (a) and iniferter (b).

Citrate-coated gold nanoshells

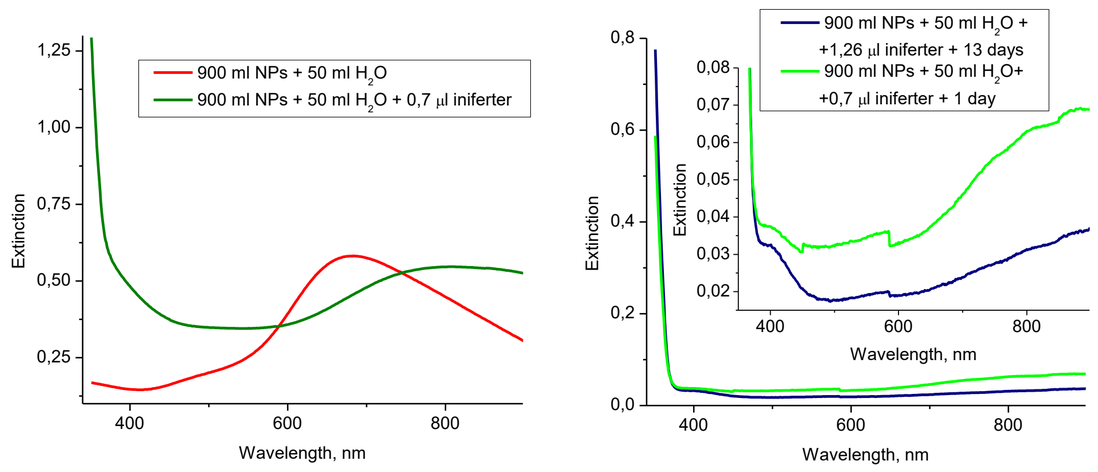

Fig. 5. Extinction spectra of citrate-coated gold nanoshells solutions with different concentrations of iniferter. Measurements were carried out immediately and in a few days after the addition of iniferter.

- Gold nanoshells absorb light in the wavelength region near 700 nm.
- Aggregated gold nanoshells absorb light in the wavelength region near 800 nm.
- After a few days an absorbance peak shifted to 900 nm and intensity decreased.

So, addition of iniferter to gold nanoshells solution leads to their aggregation.

Seed silver nanoparticles

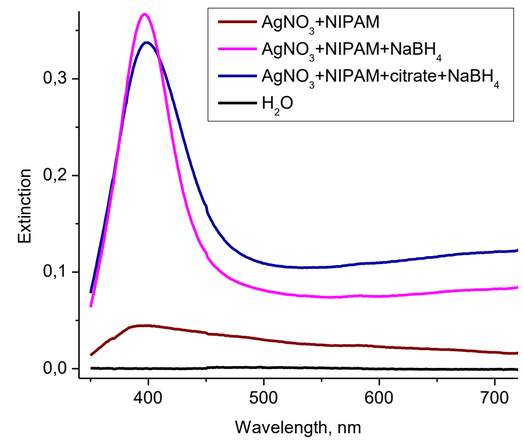

Fig. 6. Extinction spectra of $AgNO_3$ solutions with and without citrate before and after the addition of $NABH_4$.

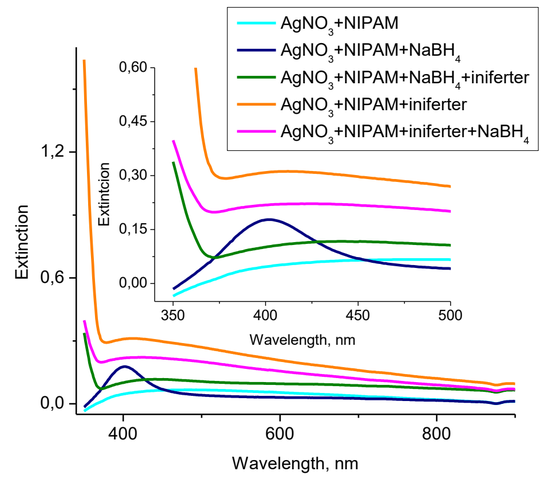

Fig. 7. Extinction spectra of $AgNO_3$ solutions and AgNPs with NIPAM before and after the addition of iniferter.

- Seed silver nanoparticles absorb light in the wavelength region near 400 nm.
- NIPAM absorb light in the wavelength region near 450 nm.
- Iniferter absorb light in the wavelength region near 430 nm.

- After the addition of NIPAM to silver nitrate, an absorbance peak near 400 nm appeared, which may indicate the reduction of Ag^+ ion.
- After the addition of $NABH_4$, solution became yellow, that indicates the formation of AgNPs.
- After the addition of iniferter to seed silver nanoparticles, they aggregated. The solution became colorless.
- After the addition of iniferter to solution of silver nitrate and NIPAM, an absorbance peak near 420 nm appeared and solution became yellowish, that indicates the formation of AgNPs. The addition of $NABH_4$ didn't change the situation. Wider peak may indicate a polymerization.

Conclusion

Drug delivery based on gold nanoshells covered by smart polymer is a novel approach to threat cancer due to their unique physicochemical properties. Thanks to our universal iniferter in a role of RAFT-agent with SH- group for binding with metal this method makes polymerization much easier and with fewer stages.
In spite of that it was established that using an iniferter with citrate-coated gold nanoparticles leads to their aggregation, it was found that the creation of a thermoresponsive polymer layer simultaneously with the synthesis of seed silver nanoparticles leads to the formation of nanoparticles with a polymer coating.
Due to the performed studies, it is proposed to create a thermosensitive polymer layer simultaneously with the synthesis of nanoparticles, which showed a positive result on the example of the synthesis of silver nanoparticles.