Temperature control during nanoparticle-sensitized hyperthermia

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Abstract. Hyperthermia is one of the mild cancer treatment approaches, which can be realized via a non-invasive way. It has been established that nanoparticles are effective for local hyperthermia enhancement when stimulated by an external stimulus. We show that silicon-based nanoparticles can be used as sensitizers for radiofrequency-induced hyperthermia and propose a thermographic method to control the temperature during the treatment.

1. Introduction

One of the most difficult problems of modern medicine is the treatment of cancer. Due to the complex nature of oncological diseases, it often requires an interdisciplinary approach and uses the latest developments in biology, chemistry, physics and nanotechnology. The approaches for the treatment of several types of tumors may include, surgery, high-energy beam treatment or chemotherapy and still not guarantee the positive result. To improve the cancer treatment, the set of novel and combined methods are explored. One of the promising methods for cancer treatment is based on an application of nanoparticles (NPs) for simultaneous diagnostics and therapy, i.e. theranostics [1,2].

NPs themselves can be accumulated in certain types of tumors because of so-called Enhanced-Permeability and Retention (EPR) effect [3]. Other approach is to target NPs using the chemical compounds specific to the malignant cell receptors attached to the surface of the cells. It has been established that pure silicon (Si) NPs have low overall toxicity and moderate biodegradability with the formation of non-toxic silicic acid [4]. Such physical properties as the absorbance in near-IR range and responsivity to the radiofrequency (RF) electromagnetic waves turn Si NPs to one of the most promising inorganic agents for theranostics [1,5,6].

Hyperthermia is a promising method in cancer therapy, which is based on the heating of a tumor within the clinically accepted range of 40-45 °C [7]. Such application evidently has a drawback due to close thresholds of the damage in cancer and non-cancer cells. So, the whole-body hyperthermia is not usually used for the cancer therapy, and local hyperthermia seems to be more promising for different types of cancer [7]. Recently, Si NPs were shown to act as an efficient light absorber to control the spatially-temporally localized photoinduced heating in aqueous suspension and living cells for hyperthermia application [8,9].
In this work, we explore porous silicon (PSi) NPs under RF irradiation with therapeutic frequency and intensities [6,7]. In contrast to the optical range, the RF-electromagnetic waves have a large penetration depth and therefore, their application is not limited by the skin treatment or shallow-located tumors. The efficiency of RF heating depends on the RF frequency, electrical conductivity and polarizability of the tissue and NPs [10]. Experiments with phantoms showed that Si NPs could lead to the heating above 43°C even at relatively low intensity of the clinically approved RF source at 27 MHz [5]. The usage of such setup among with biocompatible and bioresorbable Si NPs can make the RF hyperthermia safer and more efficient. The purpose of our work is to evaluate both the effectiveness of Si-based NPs as hyperthermia sensitizers and temperature controllability using thermography-based feedback.

2. Experimental part

Samples of mesoporous (mPSi) NPs were formed by means of the electrochemical etching of crystalline (100) Si wafers (p-type, doped with boron to a resistivity of 20 mΩ·cm) in a mixture of hydrofluoric acid (48%) and ethanol (1:1) for 60 min with a current density of 60 mA/cm². The etching was carried out in a Teflon cell with a platinum counter electrode at room temperature. Films of mPSi were separated from the substrate using a short electric current pulse of increased density (500-600 mA/cm²), washed in deionized water, and dried at room temperature. Next, the prepared mPSi films were ground in an agate mortar to obtain powders of micrometer-sized particles followed with their fine milling in a planetary ball mill to obtain aqueous suspensions of mPSi NPs (see for details Ref.[6]).

We used human serum albumin solution as a model for biological fluids such as blood or lymph at various protein concentrations. In this experiment, the protein composition of the blood was simulated by a solution of human albumin with a concentration of about 50 mg/ml. Experimental studies were carried out separately for aqueous suspensions of mPSi NPs, albumin and albumin with mPSi NPs. The pH level of the solution was adjusted by adding drops of hydrochloric acid.

RF heating was carried out by using an UHF-60-MedTeKo (MedTeKo LLC, Russia) RF-therapy apparatus (frequency 27 MHz, maximal power 60 W) [5]. The temperature measurements were performed in 4.5 ml polystyrene cuvettes filled with 1.5 ml of solution. Also, we carried out experiments with a piece of beef liver with injected concentrated suspension (20 mg/mL) of mPSi NPs. The liver sample on a plastic Petri dish was placed between the electrodes of the RF-therapy apparatus. The temperature was monitored and controlled by using a Flir C3 thermal imager (FLIR Systems, Inc., USA), which had the feedback with the RF generator.

3. Results and discussion

3.1. Estimation of heating rate in silicon NPs suspensions

To evaluate the difference in heating of the solution with mPSi NPs from physiological fluids in the human body, an experiment was carried out using human blood model. For this, four solutions with a volume of 1.5 ml were prepared in spectrometric plastic cuvettes. The first cell contained only distilled water. The second cuvette contained physiological saline and human albumin with a concentration of 50 g/L. The third cell contained mPSi NPs with a concentration of 20 g/L. In the fourth cuvette - human blood model with mPSi NPs with a concentration of 20 g/L.

Figure 1 shows that solutions containing mPSi NPs exhibit the higher heating rates. In 5 minutes, a temperature of 44 °C from the initial 19 °C was reached. That temperature is enough for the local hyperthermia (>42 °C).
The solution imitating the blood model, in turn, in 5 min was heated only to a safe value of 26°C, i.e. below the denaturation temperature of some types of proteins (40°C). Thus, the hypothesis of the effectiveness of mPSi NPs as sensitizers for the RF hyperthermia has been confirmed.

3.2. RF hyperthermia experiments with beef liver

In this experiment, a piece of beef liver (15 g) was placed on a 6 mm plastic Petri dish. Two injection solutions were prepared for comparison. The first one was a 200 μl aqueous solution of mPSi NPs with a concentration of 20 mg/mL. The second one was a 200 μl of distilled water. The heating was performed by the RF apparatus for 5 min. The corresponding temperature transients and thermal image are shown in Figures 2 and 3, respectively.

It can be clearly seen that temperature increases into the region of NPs injection, while the heating of the rest areas remains relatively small. The temperature difference at the most heated area is 20 deg higher than the average temperature of untreated part of the liver (Figure 2). This fact indicates that the mPSi NPs can be potentially used for the RF hyperthermia.
3.3. Temperature control during nanoparticle-sensitized hyperthermia

Maintaining the temperature at a given level is very important for achieving a therapeutic effect when using the hyperthermia method. Therefore, an experiment was carried out aimed at testing the possibility of long-term maintenance of the therapeutic temperature required for hyperthermia. An albumin solution was used as a sample for heating, since it is a natural protein that is an integral part of the protein fraction of human blood. This solution was placed between the electrodes of the RF therapy apparatus. And then heating was carried out at a maximum power of 60 W. Figure 4 shows the temperature data obtained during the experiment. The temperature was maintained at 42.5°C with a fluctuation less than 0.5°C.

![Figure 4](image-url)

**Figure 4.** Heating kinetics of mPSi NPs colloid in physiological solution in the mode of maintaining the solution temperature at the level of 46°C under RF (27 MHz, 60W) irradiation

It follows from Figure 4 that the use of the RF therapy device for the heating of aqueous suspension of mPSi NPs allows us to maintain the object temperature at the value required for hyperthermia for a long time.

4. Conclusions

It was found that Si-based NPs exhibited properties of the sensitizers for local hyperthermia under RF irradiation. The temperature above 42 °C was achieved with the usage of mesoporous Si NPs and relatively low radiation power densities. The hyperthermia experiment with model organ showed that the temperature difference between NPs-reach and NPs-depleted areas could reach 20°C. The combination of Si-based NPs and RF irradiation with thermographic feedback allowed maintaining the temperature at the value required for hyperthermia for relatively long periods of time (>30 min). The obtained results reveal a great potential of the NP-sensitized RF-hyperthermia for cancer therapy.

Acknowledgement

The work was partially supported by the Russian Science Foundation (Project no. 19-14-00171) for the nanoparticle preparation and temperature control optimization.
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