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# 암치료를 위한 약물전달 자성 나노리포좀 제작 및 근적외선 레이저에 의한 약물방출에 관한 연구

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# The study of magnetic nanoliposome fabrication and NIR light triggered drug release for cancer therapy

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**Key Words**: Magnetic nanoliposome, near infrared (NIR) light, drug delivery.

**Abstract**

Recently, stimuli-controlled drug release and design of biocompatible micro-nanoparticles have been received significant attention to improve the drug delivery efficiency and reduce the side-effect in cancer therapy. Near infrared (NIR) light has been demonstrated as promising trigger of drug release because of easy to control and non-invasive. In this study, we synthesized superparamagnetic iron oxide (SPIO) and doxorubicin (DOX) loaded magnetic nanoliposomes (MNL) as a thermal sensitive nanocarriers. In addition, near inferred light (NIR) was introduced to control the release of entrapped DOX. Based on the DOX releasing rate results, an irreversible release under NIR irradiation was proposed. In addition, tumor cell killing effect of MNL combined with NIR laser irradiation was evaluated. As a result, significantly enhanced tumor cell killing effect was achieved by irradiating with NIR light. We expect that enhanced localized drug accumulation and antitumor therapy can be achieved through NIR irradiation

## 1. Introduction

Photothermal therapy (PTT) kills the cancer cells by converting the near infrared (NIR) light energy to heat without affecting healthy tissues [1]. However, complete tumor treatment with PTT alone is difficult due to the distribution of photothermal agents is often uneven, which induces the heterogeneous heat distribution [2]. Herein, we proposed a photothermal-chemotherapy for cancer treatment. We synthesized a novel NIR light sensitive magnetic nanoliposomes (MNL) containing DOX and SPIO. The liposomes were designed based on a thermal sensitive liposome (DPPC) and SPIO were entrapped into the liposomes. The temperature increase of MNL media by NIR irradiation was determined with a thermal camera. Then, controlled release of entrapped drug in MNL combined with NIR irradiation was confirmed. Finally, through evaluate the tumor cell killing effect of MNL combined NIR laser irradiation was evaluated. We expect that drug loaded MNL combined with NIR laser irradiation will be the best promising method to improve the cancer treatment efficiency.

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## 2. Methods

2.1 synthesis of magnetic nanoliposome (MNL)

First, we prepared hydrophilic super paramagnetic iron oxide (SPIO) nanoparticles using a chemical co-precipitation method of ferrous and ferric salts in alkaline medium [3]. Next, we synthesized MNL by thin film method. Briefly, Liposome colloidal suspension was prepared by dissolving the 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) in chloroform and transferred into round bottom flask. The organic solvent for the lipid solution was evaporated in a fume hood and completely removed in a vacuum for an additional 1h to obtain a dry film. The dried lipid film was then hydrated with 0.5wt% glycerol dissolved phosphate buffered saline (PBS, pH 7.4) to obtain a clear solution with final lipid concentration of 15mg/ml. Aliquots of this lipid solution were transferred into 5ml chromatography vials and mixed with DOX (1mg/ml) and SPIO (10mg/ml). MNL

was synthesized by sonication for 5min (VC750, Sonics & Materials, Newtown, CT). The emulsion was centrifuged for 3min at 3000 rpm. The underlying liquid phase was removed from the top foam with a syringe and re-dispersed with fresh PBS buffer. This washing step was performed three times.

2.1 characterization of photothermal effect

To investigate temperature increase, we adopt NIR light irradiation in the presence of MNL. We used a continuous wave fiber coupled diode light (center wave length; 808nm) with an external adjustable power (CNI, Changchun New Industries Optoelectronics Tech. Co. Ltd). The light power and intensity were measured with an optical power meter (PM200, Thorlabs, NK, USA). The MNL samples upon to various concentration of iron were placed in cuvette tube and irradiated by the light. The distance between the sample and the light was set to be 5cm and the light power was adjusted to 2W/cm2. The photothermal transduction photographs were obtained through a thermal camera (America, FLIR E60; thermal sensitivity is 0.05℃).

2.2 NIR irradiation induced DOX Release

Drug release behavior from MNL was evaluated using dialysis method. DOX loaded MNL was put in dialysis bag (MW: 3500), immersed in PBS buffer solution (pH 7.4) and then the solution was placed in a shaking incubator (37℃, 150rpm). Then, at determined time period, 1 ml release medium was sampled and the equal volume of fresh medium was added to maintain the sink conditions. After the certain period of 12h, the sample with PBS solution was placed in heating mantle to keep the surround temperature at 37℃, and then irradiated with NIR light for 3 min. 1ml of release medium was collected and replaced with fresh medium before NIR irradiation. The negative control group was tested with the same process without NIR irradiation. The released DOX was measured by HPLC system.

2.3 In vitro Cytotoxicity Test

4T1 breast cancer cells were seeded at a density of 104 cell per well in 96-well plates. Next day, the used medium was replaced with different formulation solutions: fresh medium, MNL and DOX loaded MNL with different DOX concentrations (11.5μg/ml and 23μg/ml), where the DOX concentration was based on the corresponding SPIO concentration when DOX and SPIO are co-loaded (Fe concentrations: 100μg/ml and 200μg/ml). After 12h, the cell wells were placed on sample holder at 37℃ and the certain cell line group was irradiated with NIR light for 3min. After following incubation for 12h, supernatants were removed. Then, the wells were washed twice with PBS and incubated with DMEM containing MTT (5mg/ml) for an additional 2h. The MTT solution was removed and dimethylsulfoxide (DMSO) was added to dissolve the formasan crystals. The absorbance at 570 nm was measured by a microplate reader and the untreated cells were taken as a negative control groups.

## 3. Results

3.1 Characterization of Drug-loaded MNL

Fig. 2a shows the temperature profiles for 5 min NIR irradiation of MNL solutions with iron concentration of 100 and 200 μg/ml (iron concentration was normalized by considering the ICP-OES results). At an iron concentration of 200μg/ml, the MNL solution shows significant temperature elevation about more than 7℃ and 10℃, when the NIR irradiation time were 3min and 5min, respectively, which are much higher than transient

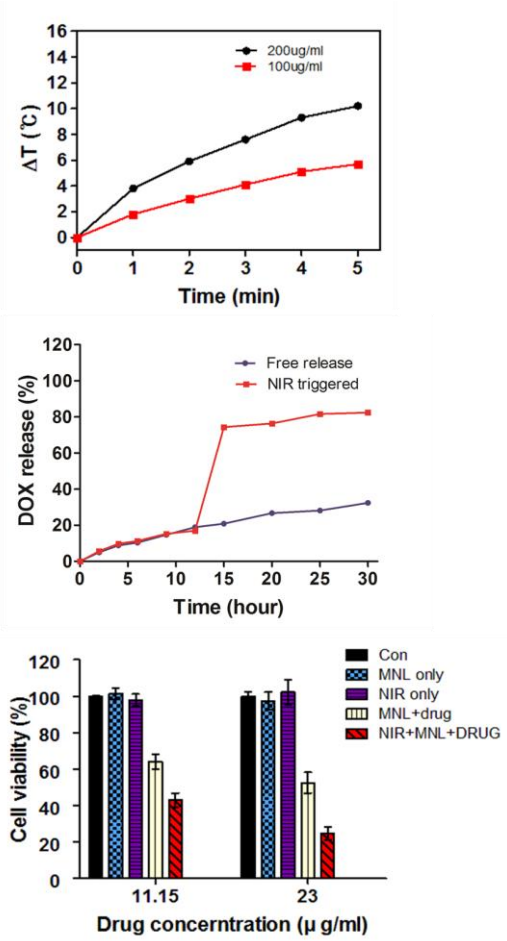


Fig. 2. a) Temperature increase induced by NIR laser irradiation when the Fe concentration are 100μg/ml and 200μg/ml. b) In-vitro DOX release profiles. c) Tumor cell viability test of MNL combined with NIR irradiation

temperature of liposome (41℃), sufficient to control drug release from DOX-loaded MNL.

(Fig. 2b) shows the in vitro drug release profiles. Two drug release samples were prepared, one sample was freely released in shaking incubator, and the other was triggered with NIR irradiation for 3min when the time interval was 12 h. The drug release behavior of MNL at 37℃ was very slow and the drug release rate was only 32% even 30 hours later. In contrast, the drug release of NIR light triggered sample was similar slow release before NIR irradiation and the drug release rate was increase more than 56% after irradiate NIR light for 3min. And then, the drug release was retained slow release mode again without NIR irradiation. This result shows the drug release from MNL combined with NIR light triggering almost meets the requirement of controlled drug release that can stably retain drug in physiological conditions and release it with stimuli existence.

3.2 In vitro Cytotoxicity

In addition, the tumor cell killing effect of MNL combined with NIR irradiation was evaluated (Fig. 2c). The cell survival rates of control group and MNL only group showed no significant differences. However, the drug loaded MNL group showed obvious tumor cell killing effect. Furthermore, the drug loaded MNL combined with NIR irradiation group showed much higher tumor killing effect. It may be caused by the enhanced drug release, the increased cell permeability and the photothermal therapy effect by NIR light irradiation [1, 4].

## 4. Conclusion

We provided a novel NIR light sensitive MNL, which contains SPIO nanoparticles and DOX, and evaluated the photothermal effect and the controlled release of DOX by NIR light irradiation. A significantly enhanced tumor cell killing effect of DOX and SPIO loaded MNL combined with NIR irradiation was achieved, which could be attributed the PTT effect, the increased intracellular DOX concentration due to the triggered release of DOX from MNL and the synergistic interaction between the photothermal effect and the cytotoxic effect of DOX. Therefore, we expect that this study can be used for a promising application of drug-loaded MNL using NIR irradiation for photothermal-chemotherapy in cancer treatment.

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