Examination and development of magnetic nanoparticle based tumour therapies

PhD thesis book

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Introduction

Cancer is one of the deadliest illnesses of the world that causes death of millions of people worldwide. There are several conventional and novel methods for the humanity to cure this illness; however, there is still no generally successful procedure therefore development of new methods is highly desired.

One of the promising methods is the nanomagnetic hyperthermia where intensive research began during the past 10-15 years. Nanoparticles have a magnetic moment that interacts with the external magnetic field, therefore positioning them to the malignant tissues and placing them in an alternating magnetic field (typically at a few 100 kHz), they absorb energy from the external magnetic field, thus their temperature increases. The optimal temperature of the nanoparticles is 42-46 °C. As the malignant tissues are more sensitive to the heat than the healthy ones, the process leads to either direct apoptosis (dell death) or combining hyperthermia with the conventional chemo- or radiotherapy, they enhance the effect of each other. The advantage of the procedure is that the heat is localized and happens under well-controlled conditions; furthermore, it is applicable in case of deeply situated tumours, too.

Recently the therapy has been under clinical phase investigations and at the submission of this dissertation, the appropriate administration has not validated the results, therefore this therapy is recently not applied in the hospitals.

Hyperthermia is an interdisciplinary procedure involving biology, chemistry, and physics. From the physics perspective, the most important challenge is the determination of the power dissipated by the nanoparticles or its local version, the specific absorption rate (SAR). There are more conventional methods for this purpose but the methods are mainly invasive, remarkably inaccurate, and furthermore expensive and are time consuming. Therefore, it is necessary to develop further methods that are more accurate and non-invasive in order to determine the absorbed power.

Objectives

The goal of my PhD work was to further study the physical background of the nanomagnetic hyperthermia, beyond the known results. I proposed the development of a new method which enables determination of the absorbed power without the calorimetric method. A further goal was the accurate localization of a buried sample and the controlling of the absorbed power. I found furthermore that there is no satisfactory information about to the complex, frequency-dependent magnetic susceptibility of the nanoparticles that is one of the important parameters of the hyperthermia, which motivated a study of this parameter.

Methods

I obtained the power absorbed by the sample using reflectometry from a resonant circuit which contains the fluid with the nanomagnetic particles. I determined the absorbed power from the quality factors of the resonators. At the measurements mentioned in thesis point 1 and 2, I applied frequency sweep for irradiation, and at thesis point 3 and 4, I used short pulses at near the resonance frequency, and I determined the quality factor from the measurements of the transients.

At the last thesis point, I used resonant and non-resonant circuits, too. In the latter case, I determined the impedance of the circuits using a vector network analyzer, and I obtained the frequency-dependent magnetic susceptibility from these data.

Thesis points

1. I developed a new method for the measurement of the power absorbed by magnetic nanoparticles. It is based on placing the sample in a resonant circuit; one obtains the absorbed power directly from the quality factor of the resonator. This method is more accurate than the conventional ones and it does not require modelling or calibration. I compared and thus validated the method with the conventional calorimetric procedure. [S1]
2. I studied the dependence of the adsorbed power of the nanoparticles during RF magnetic irradiation as a function of a static magnetic field. The importance of the measurement

is that the static magnetic field allows the control of the absorbed power, thereby that of the temperature rise. I found that the absorbed power significantly decreases even at a 0.1 T magnetic field.

3. I significantly improved the accuracy of the absorbed power measurement using radiofrequency pulses to determine the quality factor. The method is based on the use of a nuclear magnetic resonance console as a transceiver-receiver system, which enables the acquisition of the response of the resonator to the pulses. This method improves the accuracy of the quality factor determination by 1-1.5 orders of magnitude as compared to the case of the frequency swept method. [S2]
4. I developed a method for mapping the buried sample for *in-vivo* conditions. The method is based on movin the coil of the resonator with respect toa the phantom that represents the *in-vivo* organ and contains the sample. I measured the detuning rate of the resonator with the pulse method. I developed the method for one- and two-dimensions. [S2]
5. I studied the broadband frequency-dependent magnetic susceptibility of the magnetic nanoparticles using two different methods with resonant and non-resonant approaches. I found that the magnetic relaxation of the nanoparticles does not follow a single exponential function. This observation is based upon that for both cases, the ratio of real and imaginary the components of the susceptibility was identical. [S3]

Publications related to the thesis points

S1 **Gresits I.**, Thuróczy Gy., Sági O., Gyüre B., Márkus B. G., Simon F.: *Non-calorimetric determination of specific absorption rate during magnetic nanoparticle based hyperthermia,* Scientific Reports **8** 12667 (2018).

S2 **Gresits I.**, Thuróczy Gy. Sági O., Homolya I., Bagaméry G., Gajári D., Babos , Major P., Márkus B. G., Simon F.: *A highly accurate determination of absorbed power during magnetic hyperthermia,* Journal of Physics D: Applied Physics, **52**, 37 (2019).

S3 **Gresits I.**, Thuróczy Gy. Sági O., Kollarics S., Csősz G., Márkus B. G., Nemes N. M., García-Hernández M., Simon F.*: Non-exponential magnetic relaxation in magnetic nanoparticles for hyperthermia,* Journal of Magnetism and Magnetic Materials, **526**, 167682 (2021).

Publications not related to the thesis points

S4 **Gresits I.**, Necz P., Jánossy G., Thuróczy Gy.: *Extremely low frequency (ELF) stray magnetic fields of laboratory equipment: a possible co-exposure conducting experiments on cell cultures*, Electromagnetic Biology and Medicine, **34**, 32 (2015).