Physica Medica 29 (2013) 624–630

Contents lists available at SciVerse ScienceDirect

Physica Medica

journal homepage: http://www.physicamedica.com

Original paper

# Control of the temperature rise in magnetic hyperthermia with use of an external static magnetic field

Kenya Murase*, Hiroshige Takata, Yuki Takeuchi, Shigeyoshi Saito

*Department of Medical Physics and Engineering, Division of Medical Technology and Science, Faculty of Health Science, Graduate School of Medicine, Osaka University, 1-7 Yamadaoka, Suita, Osaka 565-0871, Japan*

ARTICLE INFO

*Article history:*
Received 1 May 2012
Received in revised form
19 August 2012
Accepted 25 August 2012
Available online 15 September 2012

*Keywords:*
Magnetic hyperthermia
Alternating magnetic field
Static magnetic field
Field-free point

ABSTRACT

Our purpose in this study was to investigate the usefulness of a method for controlling the temperature rise in magnetic hyperthermia (MH) using an external static magnetic field (SMF), and to derive an empirical equation for describing the energy dissipation of magnetic nanoparticles (MNPs) in the presence of both the alternating magnetic field (AMF) and SMF through phantom experiments.

We made a device that allows for MH in the presence of an SMF with a field-free point (FFP) using a Maxwell coil pair. We measured the temperature rise of MNPs under various conditions of AMF and SMF and various distances from the FFP ($d$), and calculated the specific absorption rate (SAR) from the initial slope of the temperature curve.

The SAR values decreased with increasing strength of SMF ($H_s$) and $d$. The extent of their decrease with $d$ increased with an increase of the gradient of SMF ($G_s$). The relationships between SAR and $H_s$ and between SAR and $d$ could be well approximated by Rosensweig's equation in which the amplitude of AMF ($H_{ac}$) is replaced by $H_{ac}^2/\sqrt{H_{ac}^2+H_s^2}$, except for the case when $G_s$ was small.

In conclusion, the use of an external SMF with an FFP will be effective for controlling the temperature rise in MH in order to reduce the risk of heating surrounding healthy tissues, and our empirical equation will be useful for estimating SAR in the presence of both the AMF and SMF and for designing an effective local heating system for MH.



## Introduction

Hyperthermia is one of the most promising approaches in cancer therapy. The most commonly used heating method in the clinical setting is capacitive heating that uses a radiofrequency (RF) electric field [1]. However, a major technical problem with hyperthermia is the difficulty of heating the targeted tumor to the desired temperature without damaging the surrounding tissues, as the electromagnetic energy must be directed from an external source and penetrate normal tissue. Other hyperthermia modalities, including RF ablation and ultrasound hyperthermia, have been reported [2,3], but the efficacies of these modalities depend on the size and depth of the tumor, and disadvantages include the ability to target the tumor and control the exposure.

Hyperthermia with use of magnetic nanoparticles (MNPs) (magnetic hyperthermia) was developed in the 1950s [4] and is still under development in an effort to overcome the above disadvantages [5]. MNPs generate heat in an alternating magnetic field (AMF) as a result of hysteresis and relaxational losses, which results in heating of the tissue in which MNPs accumulate [6]. The degree to which magnetic hyperthermia can be applied to cancer therapy depends on the ability to deliver MNPs systematically to tumor cells in sufficient concentrations. If MNPs were adsorbed only to tumor cells, the MNPs could be administered intravenously. This feature would be of great advantage in terms of the quality of life of patients. However, because the administered MNPs migrate passively to a reticuloendothelial system such as the Kupffer cells of the liver and spleen, the passive targeting of MNPs for cancer is a very important issue for the establishment of cancer therapy with use of magnetic hyperthermia.

With regard to the delivery of MNPs, magnetoliposomes (MNPs encapsulated within liposomes) may be a promising tool for passive targeting. Shinkai et al. [7] developed magnetite cationic liposomes (MCLs) with improved absorption and accumulation properties within tumors. Administration of the MCLs, however, is limited to direct injection into the tumor tissue [8].

* Corresponding author. Tel./fax: +81 6 6879 2571.
*E-mail address:* murase@sahs.med.osaka-u.ac.jp (K. Murase).

1120-1797/$ – see front matter 
http://dx.doi.org/10.1016/j.ejmp.2012.08.005

The conjugation of antibodies to MNPs is a possible approach to achieving the passive targeting of MNPs for cancer. Le et al. [9] and Shinkai et al. [10] have developed MNPs conjugated to the Fab' fragments of anti-human MN antigen-specific antibody. DeNardo et al. [11] developed $^{111}$In-chimeric L6 monoclonal antibody-linked MNPs for magnetic hyperthermia. However, because the target concentration is very low in antibody targeting tumors and particle penetration to the surrounding healthy tissues still has not been significantly prevented, producing considerable adverse effects [12], this approach cannot yet be translated successfully from research to the clinical stage. In contrast, the combination of thermosensitive liposomes and local heating has been shown to improve anticancer drug delivery in both animal and human patients [13]. Thermosensitive magnetoliposomes (MNPs encapsulated within thermosensitive liposomes) appear to be a versatile delivery system due to their biocompatibility, chemical functionality, and potential for use in a combination of drug delivery and hyperthermia treatment of cancers [13]. To establish this approach and to minimize the side effects, it will be necessary to focus the heat deposition into the targeted tissue or organ.

Besides the above-mentioned approaches, gene-based therapies are promising tools with which to treat a wide range of diseases. However, the efficient and specific delivery of a therapeutic gene to an identified tissue or organ and its controlled activation remain important challenges [14]. Spatial and temporal control of gene expression is made possible through the use of local heat deposition coupled with the use of a thermosensitive promoter [14]. Thus, to focus the heat deposition into the targeted tissue or organ will also be essential for establishing a gene-based therapeutic approach with use of a thermosensitive promoter.

Recently, Tasci et al. [15] proposed and designed a system that focuses the heat into very small regions using a static magnetic field (SMF) with a field-free point (FFP) generated by two solenoid coils, and reported that this method will be useful for making magnetic hyperthermia a more effective approach to cancer therapy with a decreased risk of heating surrounding healthy tissues. Although this approach appears to be useful for focusing the heat deposition into the targeted tissue or organ, it would be necessary to investigate the effectiveness of this approach under various conditions of AMF and SMF. Furthermore, it would be desirable to derive an equation describing the energy dissipation of MNPs in the presence of both the AMF and SMF for estimating and controlling the heat deposition into the targeted tissue or organ and for designing an effective local heating system.

Our purpose in this study was to investigate the usefulness of a method for controlling the temperature rise in magnetic hyperthermia with use of an external SMF under various conditions of AMF and SMF through phantom experiments. We also attempted to derive an empirical equation for describing the energy dissipation of MNPs in the presence of both the AMF and SMF, and validated this equation by comparing the energy dissipation estimated by this equation with the specific absorption rate measured experimentally under various conditions of AMF and SMF.

## Materials and methods

### *Theory*

Rosensweig [6] developed analytical relationships and computations of the energy dissipation of MNPs subjected to an AMF in the case when an SMF is not applied. From this theory, the energy dissipation ($P$) can be given by [6]

$$P = \pi\mu_0\chi_0 H_{ac}^2 f \frac{2\pi f\tau}{1+(2\pi f\tau)^2}, \tag{1}$$

where $\mu_0$ is the permeability of free space, $\chi_0$ is the equilibrium susceptibility, and $H_{ac}$ and $f$ are the amplitude and frequency of the AMF, respectively. $\tau$ is the effective relaxation time given by $1/\tau = 1/\tau_N + 1/\tau_B$, where $\tau_N$ and $\tau_B$ are the Neel relaxation time and Brownian relaxation time, respectively [6]. $\tau_N$ and $\tau_B$ are given by $\tau_N = \tau_0\sqrt{\pi}e^{\Gamma}/2\sqrt{\Gamma}$ and $\tau_B = 3\eta V_H/k_BT$, respectively [6], where $\tau_0$ is the average relaxation time in response to a thermal fluctuation, $\eta$ is the viscosity of the medium, $k_B$ is the Boltzmann constant, $T$ is the absolute temperature, and $\Gamma = KV_M/k_BT$ with $K$ being the anisotropy constant of MNP. $V_H$ is taken as the hydrodynamic volume of MNP that is larger than the magnetic volume $V_M = \pi D^3/6$ for MNP of diameter $D$. As a model for $V_H$, it is assumed that $V_H = (1+2\delta/D)^3 V_M$, where $\delta$ is the thickness of a sorbed surfactant layer. Since the actual equilibrium susceptibility $\chi_0$ is dependent on the magnetic field, $\chi_0$ is assumed to be the chord susceptibility corresponding to the Langevin equation given by $\chi_0 = \chi_i \frac{3}{\xi}\left(\coth\xi - \frac{1}{\xi}\right)$, where $\chi_i = \mu_0\phi M_d^2 V_M/3k_BT$, $\xi = \mu_0 M_d H_{ac} V_M/k_BT$, $M_d$ is the domain magnetization of a suspended particle, and $\phi$ is the volume fraction of MNPs. In this study, we assumed $M_d$, $K$, and $\eta$ as 414 kA/m, 4.7 kJ/m$^3$, and 0.00235 kg/m/s, respectively, for Resovist® (maghemite, $\gamma$-$Fe_2O_3$) [16], and $T$ as a room temperature (20 °C = 293.15 K).

When the SMF is applied, we hypothesized that the energy dissipation ($P_s$) is given by

$$P_s = \pi\mu_0\chi_0 \tilde{H}_{ac}^2 f \frac{2\pi f\tau}{1+(2\pi f\tau)^2}, \tag{2}$$

where $\tilde{H}_{ac}$ is the amplitude of AMF corrected for the effect of SMF and is assumed to be given by $\tilde{H}_{ac} = CF \cdot H_{ac}$, with CF being a correction factor. In this study, CF was empirically assumed to be $CF = H_{ac}/\sqrt{H_{ac}^2 + H_s^2}$. It should be noted that when $H_s$ is equal to 0, CF becomes unity. The validity of this assumption will be investigated by comparing the energy dissipation estimated by Eq. (2) with the experimental data of the specific absorption rate.

Because not all particles in a certain volume have the same diameter $D$, the energy dissipation $P_s$ given by Eq. (2) should be averaged based on the particle size distribution as

$$\langle P_s(x)\rangle = \int_0^\infty P_s(D,x)\rho(D)\mathrm{d}D, \tag{3}$$

where $P_s(D,x)$ denotes the energy dissipation of an MNP having a diameter $D$ and located at $x$, and $\rho(D)$ denotes the probability density function of the particle size distribution. The result of a natural growth process during particle synthesis yields particles that do not have a single diameter $D$, but a polydisperse particle size distribution [17]. A reasonable and commonly used approach for modeling is the log-normal distribution [17]. Thus, $\rho(D)$ is given by [17]

$$\rho\left(D\right) = \frac{1}{\sqrt{2\pi}\sigma D}\cdot\exp\left[-\frac{1}{2}\left(\frac{\ln(D)-\mu}{\sigma}\right)^2\right], \tag{4}$$

where $\mu$ and $\sigma$ are given by $\mu = \ln[E(D)] - \frac{1}{2}\ln\left[\frac{Var(D)}{E^2(D)}+1\right]$ and $\sigma = \sqrt{\ln\left[\frac{Var(D)}{E^2(D)}+1\right]}$, respectively. $E(D)$ and $\sqrt{Var(D)}$ denote the mean and standard deviation (SD) of $D$, respectively. The integration in Eq. (3) was performed by use of the trapezoidal rule [19].