Investigation properties of superparamagnetic nanoparticles and magnetic field-dependent hyperthermia therapy

Z Hedayatnasab, F Abnisa, W M A Wan Daud

1 Department of Chemical Engineering, Faculty of Engineering, University of Malaya, 50603 Kuala Lumpur, Malaysia
2 Department of Chemical Engineering, Faculty of Engineering, University of Malikussaleh, Lhokseumawe 24351, Indonesia

E-mail: faisal.abnisa@gmail.com

Abstract. The application of superparamagnetic nanoparticles as heating agents in hyperthermia therapy has made a therapeutic breakthrough in cancer treatment. The high efficiency of this magnetic hyperthermia therapy has derived from a great capability of superparamagnetic nanoparticles to generate focused heat in inaccessible tumors being effectively inactivated. The main challenges of this therapy are the improvement of the induction heating power of superparamagnetic nanoparticles and the control of the hyperthermia temperature in a secure range of 42 °C to 47 °C, at targeted area. The variation of these hyperthermia properties is principally dependent on the magnetic nanoparticles as well as the magnetic field leading to enhance the efficiency of magnetic hyperthermia therapy at targeted area and also avoid undue heating to healthy cells. The present study evaluates the magnetic hyperthermia therapy through the determination of superparamagnetic nanoparticles properties and magnetic field parameters.

1. Introduction

Hyperthermia has been considered as a therapeutic method for the treatment of cancerous tumors when a sarcoma had been disappeared after a very high fever [1, 2]. This finding had been the reaction of the immune system towards a bacterial infection. Based on this observation, the fact of the cancer cells is vulnerable to high temperatures and their growth can be terminated at temperatures ranging from 42 °C to 47 °C has been established [3, 4]. Meanwhile, local hyperthermia has been used for such cases that cancers have not spread the whole body in order to avoid side effects as well as enhance the treatment efficiency. However, this technique has not much more effective for deep-seated tumors due to the distribution of heterogeneous temperature and also incapability in preventing overheating nearby healthy cells consequently, superparamagnetic nanoparticles (SPMNP) have been applied. As a matter of fact, SMNPs have been attracted attention for this cancer treatment due to easy controllability, biological compatibility, physicochemical properties, and superior magnetic properties to enhance the hyperthermia efficiency. Technically, SPMNPs can be injected locally or through the intravascular region within the vicinity of external alternating current magnetic field (ACMF). This technological procedure produces focus-generated heat by the stable colloidal suspensions of the NPs.
on the affected cells which is called magnetic hyperthermia or magnetic nanofluid hyperthermia therapy (MNFHT) [5, 6].

This cancer treatment was first experimentally performed in 1957 [7], to cure carcinoma in lymphatic nodes through maghemite (γ-Fe₂O₃) NPs, with 20-100 nm particle size heated between 43 °C to 47 °C by 1200 kHz ACMF. Subsequently, MNFHT has been well established for the application of the SPMNPs in treating prostatic and esophagus cancers and brain and neck tumors beside the investigation of the clinical prophase and animal-based experiment stages of different cancers [8]. The proper functionality of MNFHT depends on two crucial factors; heat power of SPMNPs known as specific absorption rate (SAR) as well as heat temperature called hyperthermia temperature (T_H) which can be achieved by applying the appropriate stable SPMNPs and the ACMF’ parameters (frequency and amplitude) [9]. These considerations can provide SPMNPs with high magnetic capability to destroy cancerous cells while the temperature controlled in the secure range of 42 °C to 47 °C to protect healthy cells being overheated. This present paper tries to investigate the crucial properties of SPMNPs as well as ACMF’ parameters that have direct effects on the factors of MNFHT to improve its efficiency.

2. Magnetic nanofluid hyperthermia therapy

Hyperthermia therapy commonly remedies cysts, inflammation and arthritis pains through the raising of the blood flow to deliver nutrition to the affected cells then muscle spasms are released. In regards to the sensitivity of cancerous cells towards the high temperature (above 42 °C) which derive from deficiency of oxygen and subsequently blood flow in their own cells; hence, they are incapable to dissipate the extra heat via the heat transfer phenomenon resulted in being destroyed. Indicating, the viability of cancerous cells will be reduced by increasing the body temperature [10]; however, such increased-temperature is inadequate to destroy serious cancers. Therefore, strong magnetic mediates required to not only produce satisfactory heat but even focus on the affected area to prevent disorders for patients. Magnetic nanofluid hyperthermia therapy applies SPMNPs as magnetic mediators in the presence of ACMF through the attachment of SPMNPs on the cancer cells while stimulating the body’s active immunity.

Figure 1 experimentally shows, magnetic nanofluids are placed in a micro-centrifuge tube in the center of a circular coil exposed to ACMF to measure the temperature changes over the time (dT/dt) via a thermocouple connected to a data processing system in order to record T_H [3, 4]. The desirable case in this procedure is achieving the T_H between 42 °C and 47 °C since SPMNPs within this secure range are prone to burn cancerous cells while the healthy cells are unaffected. Meanwhile, the induction heating power of SPMNPs plays effectively to burn and eradicate cancerous cells. Hence, determination the factors affect these magnetic hyperthermia parameters will assure to perform a promising cancer treatment such as particle size and shape of SPMNPs, the surface modification of SPMNPs, frequency and amplitude of ACMF.
2.1. The parameters of ACMF

The variation of frequency (f) and amplitude (H) of ACMF have directly effects on SAR and $T_H$ values. Generally, the SAR values rise by increasing these parameters and can be beneficial until the temperature being stable in the hyperthermia range; otherwise, disorders may be occurred. Atkinson et al. [11], suggested that there was a criterion for induction field’ parameters that should not be exceeded value of $4.85 \times 10^8$ A/(ms). This value obtained by the multiplication of the coil diameter of 30 cm, amplitude (A/m) and the frequency of 200 kHz to protect healthy cells from overheating by eddy currents. However, they ignored to consider some measurement in this heating process which can diminish the eddy currents including smaller coils with inhomogeneous fields and off-axis field directions and also SPMNPs as magnetic mediators with Neel and Brownian heating mechanism which are varied from the ones that Atkinson used. This criterion cannot be acceptable; thus, a new criterion proposed [12], that $H \times f = 5 \times 10^9$ A/(ms) considering SPMNPs with small coil diameter.

According to the latter criterion, polyethylene glycol-coated rod-shaped NiFe$_2$O$_4$ NPs were synthesized with 16 nm length and 4.5 nm diameter by Iqbal et al. [13]. $T_H$ values of coated NiFe$_2$O$_4$ (8.7 mg/mL) increased by the increase of the amplitude which were 35, 42 and 47 °C in accordance with $2.3 \times 10^3$, $3.9 \times 10^3$ and $5.5 \times 10^3$ A/m with the frequency of 260 kHz. Although coated NiFe$_2$O$_4$ with 5.5 KA/m amplitude was appropriate to protect the normal cells, low value of SAR, 18 W/g, indicated incapability of heating power to destroyed cancerous cells. Different values of amplitudes (20, 30, 40, 50 and $60 \times 10^3$ A/m) were performed on 1.5 mg ml$^{-1}$ chitosan-coated MnFe$_2$O$_4$ NPs at 307 kHz [14]. The SAR and $T_H$ values improved by increasing the amplitude from 57.2 to 278.69 W/g and from 44.10 to 65.38 °C respectively; however, two SAR values of 57.2 and 97.5 W/g that were acceptable for MNFHT measured in 20 and $30 \times 10^3$ A/m amplitudes at 307 kHz which were beyond than allowable criterion value.

Sakellari et al. [15], opposed these criteria and believed that those values were inadequate for the biological tissues in clinical. They compared the SAR values of nanorods magnetite NPs in low ($12 \times 10^3$ A/m and 210 kHz, $H \times f = 2.5 \times 10^9$ A/(ms)) and high (24 $\times 10^3$ A/m and 765 kHz, $H \times f = 18.3 \times 10^9$ A/(ms)) magnetic field. These values were measured of 10W/g and 759W/g, respectively. The large values of ACMF parameter made nanorod MNPs appropriate candidate for MNFHT which beyond the presented criteria. Similarity, comprehensive experiments performed have indicated that the permissive value of $H \times f$ have been considerably larger than both criteria ranging between 1.8 $\times 10^9$ A/m to $18.7 \times 10^9$ A/m [16, 17]. Consequently, a new criterion of $H \times f$ value is required to perform the promising clinical MNFHT without heating disorders for patients. Interestingly, Salunkhe et al. [18], mentioned the key point that besides the amplitude and frequency, the concentration of SPMNPs plays important role in the variation of the magnetic hyperthermia factors. They observed that the SAR values decreased with increasing concentrations, the trend of $T_H$ values was in the
opposite of SAR values due to the enhancement in exchange coupling energy derived from dipole–dipole interactions.

2.2. Coating of SPMNPs
Uncoated SPMNPs display commonly low capability to retain the stability in a colloidal suspension and also make some difficulties during their synthesis and then hyperthermia therapy; consequently, their surface modification is acquired to provide a proper coater to

- Reduce the sensitivity of the SPMNPs surface toward air and moisture and make more appropriate surface for further functionalization and absorption of proteins.
- Create the hydrophilic molecules on the surface to improve the dispersity of SPMNPs (prevent agglomeration then control the particle size and reduce the risk of blood capillary obstruction) and enhance blood circulation (transport SPMNPs to targeted area).
- Preserve the physiochemical properties of SPMNPs.
- Prevent the opsonization of SPMNPs by reticuloendothelial system causes their fast clearance from the blood stream before reaching the targeted
- Make a biocompatible and nontoxic shield around SPMNPs because their surface is directly in contact with blood and tissues [19-21].

Besides, if the coating layer of the SPMNPs is thin, it can increasingly affect the magnetic as well as hyperthermia properties by forming a new material with enhanced magnetic properties. The main difference between coated and uncoated SPMNPs is saturation magnetization (Ms) which derived from their surface areas. In the latter case, due to their large surface-area-to-volume ratio, the attractive force among them increased and become aggregated (particle size increased), thereby larger block temperature occurred and subsequently Ms and SAR values decreased. Whereas, the block temperature of the former is forced to the lower temperature, leading to boost Ms and then SAR values [21]. Therefore, coated SPMNPs (with high SAR) have stronger heating power to burn cancer cells with less settling time in the human body with lower concentration considered the desirable case for clinical trials. Clinically, acceptable doses of SPMNPs (magnetite) are between 0.56-3 mg Fe/kg human body weight that is greatly less than the normal blood iron concentration (~33 mg Fe/kg body weight) as well as total body iron (~3,500 mg) [22].
A wide variety of materials are applied as a coating agent for SPMNPs can be categorized into two main groups, namely, organic and inorganic. Inorganic coating renders the SPMNPs’ surface to bind biological ligands while maintaining the stability of particles to make SPMNPs target specific [19]. The former group functionalizes SPMNPs by functional reactive groups leading to three main supposed structures, core shell [23], matrix (mosaic, shell-core), and shell−core−shell, [24], (as illustrated in figure 2). Among various organic coatings, if the shell of such structure is polymer, it may render more benefits like better dispersion of particles, high colloidal stability, solubility, and drug loading on the shell for further treatments. Moreover, polymeric coating promotes biocompatibility, circulation of MNPs in the blood and reduce the toxicity and risk of blood capillary obstruction [25]. Recently, in situ reduction method applied for core-shell Fe3O4 with the Ag and polyacrylic acid. SPMNPs Fe3O4@Ag and Fe3O4-polyacrylic acid showed Ms values of 75.1 and 82.4 emu/g and SAR values of 76 and 87 W/g, respectively. Indicating, the thin polymer coating layer had a great influence in enhancing of MNFHT efficiency [26]. Shete et al. [27], investigated the effects of chitosan on Fe3O4 SMNPs. Polymer coating did not significantly influence in the reduction of magnetization. The Ms values were 49.96 and 51.68 emu/g for the particle size of 21.8 ± 5.3 and 15.1 ± 5.0 nm, respectively. This finding implies well dispersion and less agglomeration degree of SPMNPs with thin polymer layer coating. Interestingly, the SAR value of coated SPMNPs boosted to 118 W/g at 26.67 × 103 A/m and 265 KHz indicating, in addition to coating, other parameters affect hyperthermia properties. The coated SPMNPs become also saturated in less time as compared with the uncoated ones.

2.3. Particle size and particle shape of SPMNPs

A small particle size leads to high magnetization, as well as high induction heating power, whereas a particle size below 5 nm makes some disorders on the surface spin of NPs consequently, Ms and SAR values decreased. SPMNPs with the optimal particle size of 5<d<20 nm can influence greatly in increasing Ms and SAR values which related to the Neel and Brownian heating mechanism in single-domain state. Muller et al. [28] compared the single-domain SPMNPs with different particle sizes (10.9, 12.6, and 20.9 nm). It showed that by increasing particle size in single-domain, Ms rose from 64.9 emu/g to 79.9 emu/g, and coercivity and residual magnetism appeared gradually, implying that magnetic behavior is changing from superparamagnetic to ferromagnetic with hysteresis heating mechanism. Moreover, they realized that wide size distribution can negatively influence the magnetic properties because of the particles’ statistical orientation. A wide range of particle sizes from 5 nm to 110 nm investigated on the SAR value [29]. While particle size increased moderately from 24 nm to 110 nm, the SAR value decreased from 137 W/g until it become null 1 W/g by reaching the multi-domain state. As matter of the fact when the dispersity of MNPs changes from mono- to poly-, the SAR value decreases due to the reduction in homogeneous particle distribution, which helps in the increase of the total heat generation.

Furthermore, shape anisotropy (spherical, cubic, rod, and facet irregular) is another important parameter in enhancing magnetic as well as hyperthermia properties. Fe3O4 SPMNPs with rod and spherical shapes showed high magnetic and hyperthermia; however, the rod-shaped SPMNPs had higher magnetization as compared to the counterpart with the same material and volume [30]. It can be said that this difference in their magnetization related to the shape anisotropy of nanorods avoided them becoming magnetized in directions apart from magnetization along their easy magnetic axis. Spherical shaped-MNPs as compared to the cubic shaped-ones exhibited lower Ms due to the interface coupling energy of spherical shaped was larger than cubic shaped resulted in larger shape anisotropy [31]. This trend was observed in SAR values of the spherical and cubic shaped-MNPs because of different particle morphologies [29]. The variation of magnetic and hyperthermia properties of spherical and facet shaped-CoFe2O4 NPs with different particle sizes were studied by Joshi et al. [32]. They observed that with increasing particle size in both shapes, the Ms and SAR values increased; whereas, these values of spherical-shaped were significantly smaller than their counterparts which due to the partial attachment of the magnetic moments of the facet shaped-CoFe2O4 and also severity in
their orientation in the direction of ACMF. Hyperthermia temperatures followed the similar trend of above magnetic properties that rose by increasing the particle size of both shapes, while $T_{11}$ of the facet not only was lower than spherical but also could not reach the allowable hyperthermia temperature range 42 °C to 47 °C.

3. Conclusions
Hyperthermia therapy is considerably developed by applying SPMNPs as heating nano-mediators. Magnetic hyperthermia properties, SAR and $T_{11}$, act crucially in the destroying of cancerous cells without damage to nearby healthy cells if the temperature controlled in secure temperature range. The consideration of SPMNPs’ properties as well as magnetic field’ parameters not only can improve the efficiency of this cancer therapy on the affected cells but also avoid undue heating to healthy cells. Application the coating layer on the SPMNPs’ surface meanwhile outweighs the uncoated SPMNPs due to the provided improved properties if the coating layer of SPMNPs is thin. However, a great research is still required in the case of magnetic field’ parameters to present a reliable criterion.

Acknowledgments
The authors appreciate the University of Malaya for financial support through the PPP project number PG065-2015B.

References

[1] Busch W 1867 Aus der sitzung der medicinischen Berl Klin Wochenschr 13 137
[2] Coley W B 1891 Ii. Contribution to the knowledge of sarcoma Annals of surgery 14 199-220
[3] Chiriac H, Petreus T, Carasevici E, Labusca L, Herea D-D, Danceanu C and Lupu N 2015 In vitro cytotoxicity of fe–cr–nb–b magnetic nanoparticles under high frequency electromagnetic field Journal of Magnetism and Magnetic Materials 380 13-9
[4] Moroz P, Jones S K and Gray B N 2002 Magnetically mediated hyperthermia: current status and future directions International Journal of Hyperthermia 18 267-84
[5] Khot V M, Salunkhe A B, Thorat N D, Ningthoujam R S and Pawar S H 2013 Induction heating studies of dextran coated mgfe2o4 nanoparticles for magnetic hyperthermia Dalton Trans 42 1249-58
[6] Hedayatnasab Z, Abnisa F and Daud W M A W 2017 Review on magnetic nanoparticles for magnetic nanofluid hyperthermia application Materials & Design 123 174-96
[7] Gilchrest R K, Medal R, Shorey W D, Hanselman R C, Parrott J C and Taylor C B 1957 Selective inductive heating of lymph nodes Annals of surgery 146 596-606
[8] Pang C L K 2015 Hyperthermia in Oncology: CRC Press)
[9] Hergt R, Dutz S and Roder M 2008 Effects of size distribution on hysteresis losses of magnetic nanoparticles for hyperthermia Journal of Physics: Condensed Matter 20 385214
[10] Jordan A, Scholz R, Wust P, Fähling H and Roland F 1999 Magnetic fluid hyperthermia (MFH): Cancer treatment with AC magnetic field induced excitation of biocompatible superparamagnetic nanoparticles Journal of Magnetism and Magnetic Materials 201 413-9
[11] Atkinson W J, Brezovich I A and Chakraborty D P 1984 Usable Frequencies in Hyperthermia with Thermal Seeds IEEE Transactions on Biomedical Engineering BME-31 70-5
[12] Hergt R and Dutz S 2007 Magnetic particle hyperthermia—biophysical limitations of a visionary tumour therapy Journal of Magnetism and Magnetic Materials 311 187-92
[13] Iqbal Y, Bae H, Rhee I and Hong S 2016 Control of the saturation temperature in magnetic heating by using polyethylene-glycol-coated rod-shaped nickel-ferrite (NiFe2O4) nanoparticles Journal of the Korean Physical Society 68 587-92
[14] Oh Y, Lee N, Kang H W and Oh J 2016 In vitro study on apoptotic cell death by effective magnetic hyperthermia with chitosan-coated MnFe(2)O(4) Nanotechnology 27 115101
Sakellari D, Brintakis K, Kostopoulou A, Myrovali E, Simeonidis K, Lappas A and Angelakeris M 2016 Ferrimagnetic nanocrystal assemblies as versatile magnetic particle hyperthermia mediators *Materials Science and Engineering: C* **58** 187-93

Kossatz S, Ludwig R, Dähring H, Ettelt V, Rimkus G, Mariello M, Salas G, Patel V, Teran F J and Hilger I 2014 High Therapeutic Efficiency of Magnetic Hyperthermia in Xenograft Models Achieved with Moderate Temperature Dosages in the Tumor Area *Pharmaceutical Research* **31** 3274-88

Mamiya H 2013 Recent Advances in Understanding Magnetic Nanoparticles in AC Magnetic Fields and Optimal Design for Targeted Hyperthermia *Journal of Nanomaterials* 2013 17

Salunkhe A B, Khot V M, Ruso J M and Patil S I 2016 Water dispersible superparamagnetic Cobalt iron oxide nanoparticles for magnetic fluid hyperthermia *Journal of Magnetism and Magnetic Materials* **419** 533-42

Salunkhe A B, Khot V M and Pawar S H 2014 Magnetic hyperthermia with magnetic nanoparticles: A status review *Current Topics in Medicinal Chemistry* **14** 572-94

Laurent S, Dutz S, Häfeli U O and Mahmoudi M 2011 Magnetic fluid hyperthermia: Focus on superparamagnetic iron oxide nanoparticles *Advances in Colloid and Interface Science* **166** 8-23

Gupta A K and Gupta M 2005 Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications *Biomaterials* **26** 3995-4021

Huang J, Li Y, Orza A, Lu Q, Guo P, Wang L, Yang L and Mao H 2016 Magnetic Nanoparticle Facilitated Drug Delivery for Cancer Therapy with Targeted and Image-Guided Approaches *Advanced Functional Materials* **26** 3818-36

Ghosh Chaudhuri R and Paria S 2012 Core/shell nanoparticles: classes, properties, synthesis mechanisms, characterization, and applications *Chem Rev* **112** 2373-433

Chomoucka J, Drbohlavova J, Huska D, Adam V, Kizek R and Hubalek J 2010 Magnetic nanoparticles and targeted drug delivering *Pharmacological Research* **62** 144-9

Zhang Q, Lee I, Joo J B, Zaera F and Yin Y 2013 Core–Shell Nanostructured Catalysts *Accounts of Chemical Research* **46** 1816-24

Ding Q, Liu D, Guo D, Yang F, Pang X, Che R, Zhou N, Xie J, Sun J, Huang Z and Gu N 2017 Shape-controlled fabrication of magnetite silver hybrid nanoparticles with high performance magnetic hyperthermia *Biomaterials* **124** 35-46

Shete P B, Patil R M, Thorat N D, Prasad A, Ningthoujam R S, Ghosh S J and Pawar S H 2014 Magnetic chitosan nanocomposite for hyperthermia therapy application: Preparation, characterization and in vitro experiments *Applied Surface Science* **288** 149-57

Müller R, Dutz S, Neeb A, Cato A C B and Zeisberger M 2013 Magnetic heating effect of nanoparticles with different sizes and size distributions *Journal of Magnetism and Magnetic Materials* **328** 80-5

Gonzalez-Fernandez M A, Torres T E, Andrés-Vergés M, Costa R, de la Presa P, Serna C J, Morales M P, Marquina C, Ibarra M R and Goya G F 2009 Magnetic nanoparticles for power absorption: Optimizing size, shape and magnetic properties *Journal of Solid State Chemistry* **182** 2779-84

Mohapatra J, Mitra A, Tyagi H, Bahadur D and Aslam M 2015 Iron oxide nanorods as high-performance magnetic resonance imaging contrast agents *Nanoscale* **7** 9174-84

Salazar-Alvarez G, Qin J, Šepelák V, Bergmann I, Vasilakaki M, Trohidou K N, Ardisson J D, Macedo W A A, Mikhailova M, Muhammed M, Baró M D and Nogués J 2008 Cubic versus Spherical Magnetic Nanoparticles: The Role of Surface Anisotropy *Journal of the American Chemical Society* **130** 13234-9

Joshi H M, Lin Y P, Aslam M, Prasad P V, Schultz-Sikma E A, Edelman R, Meade T and Dravid V P 2009 Effects of Shape and Size of Cobalt Ferrite Nanostructures on Their MRI Contrast and Thermal Activation *The Journal of Physical Chemistry C* **113** 17761-7