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Magnetic nanoparticle based hyperthermia: A review of the physiochemical properties and synthesis methods

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ABSTRACT

Recent years have witnessed a dramatic development in using various types of nanoparticles (NPs) in medical theranostic applications. Among them, magnetic NPs (MNPs) have gained remarkable attention because of their inherent attributes. Some of great attributes of MNPs for medical applications are non toxicity, injectability, biocompatibility, and high-level and tissue specific aggregation in the target tissue. MNP-based hyperthermia is one of the promising applications of MNPs that incorporates an old idea with modern technologies to locally destruct tumoral tissues. This study reviews the basics principles and recent advances of MNP-hyperthermia for cancer treatment. In addition, important physicochemical factors of MNPs for an efficient highly localized and specific hyperthermic treatment are discussed.

Key words: magnetic nanoparticle, therapeutic application, hyperthermia, synthesis methods

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INTRODUCTION

During the recent years, theoretical and experimental studies have shown that micro and nanoscale particles could be useful in biomedical application. Among different small particles, polymeric microparticles could be obtained as highly monosized assemblies. They have the advantages of biocompatibility and large reactive surface for biological applications. In addition, these microparticles have been approved by food industries for selected uses in the food production lines. Polymeric microparticles have shown promising potentials in different clinical applications including immunological diagnostics for malignant proliferative plasma cell disorders; quantification of immunoglobulin molecules in serum by immunodiagnostic assay systems, and fluorescent neuronal markers for studying the visual cortex [1,2]. Nanoparticles (NPs) have been recently introduced as the most important nanomaterials in medical theranostic applications [3-6]. Materials in the nanoscale scale ranging 1–100 nm show remarkably unique size-dependent physical, chemical, and biological properties. From the practical side of NPs applications in medicine, the control, and implementation of magnetic properties are among the most practical applications of nanoparticles for cancer diagnosis and treatment [3-6]. Among different types of NPs, magnetic NPs (MNPs) have received plenty of research interests in medical theranostics because of their inherent attributes. Some of these attributes are their small size, non toxicity, injectability, biocompatibility, high-level and tissue specific aggregation in the target tissue, easy surface functionalization, and inherent ability to be remotely localized and redistributed using external electromagnetic fields[7].

These features made MNPs a great choice for radiology and magnetic resonance (MR) imaging [8]. Some applications of MNPs are: MRI contrast enhancement agents [8-10], drug and gene delivery[11, 12], magnetic cell sorting schemes [13], nano biosensors [14], and magnetic fluid hyperthermia[15]. Currently, the main research

frontlines on developing the MNPs applications in cancer theranostics are in molecular and cellular imaging as contrast agents, intra- and extracellular hyperthermia, and targeted drug and gene delivery. Depending on particle size, composition, structure, and physicochemical properties, MNPs have showed interesting potentials in the aforementioned fields. Although different materials exist that fulfill more appropriately the magnetic requirements for biomedical applications (i.e. materials with higher saturation magnetization), other traits such as biocompatibility or toxicity must be taken into account. Iron oxides not only show interesting size-dependent magnetic properties and can be functionalized with both organic and inorganic compounds, but also they are thought to be biocompatible and non-toxic, which makes them excellent candidates for biomedical applications and in in-vivo experiments.

2. Hyperthermia: Basic principles and definitions

Radiation therapy as a conventional cancer treatment modality is based on the use of ionizing radiation to control or kill tumoral tissue. Tumor cells are generally more vulnerable to radiation compared to normal cells partly because of their increased metabolism and higher rates of glycolysis. The efficiency of radiotherapy relies on the irreversible damage that the ionizing radiation provokes to the DNA of injured cells, which eventually kills them or avoids their reproductive cycle, controlling in this way the progress of the tumor.

The main challenge of any radiotherapy techniques for treatment of tumoral tissues is avoiding radiation exposure of surrounding healthy tissues while keeping the therapeutic dose to the tumoral tissues. During the recent years, various high resolution radiotherapy techniques have been developed to address this challenge. However, the harmful side effects caused by high doses on healthy tissues surrounding the cancer tissues are the main causes of therapeutic inefficiencies of radiotherapy.

Radiotherapy treatment is performed at tissue or organ size scales, not at cellular level, so precise demarcating of the treatment volume containing the tumoral tissue is necessary. However, all of treatment volume delimitation techniques inevitably cover certain normal tissues as they could be somehow affected by tumor cells. Therefore, killing and controlling tumors at cellular level is always a big challenge. To resolve these challenges, specific targets, or markers should be developed that can be able to identify and selectively attach to tumor cells, allowing a more localized treatment and destruction of the tumoral cells, whereas the healthy cell remained intake. NPs and specially MNPs enjoy the basic characteristics for such markers and targets.

National Cancer Institute of the United States defines hyperthermia as a type of treatment in which body tissue is exposed to high temperatures to damage and kill cancer cells or to make cancer cells more sensitive to the effects of radiation and certain anticancer drugs. The main objective in hyperthermia for cancer therapy is raising the temperature of target tissue to 42°C to 44°C. This method can affect the performance of cellular structures, cell membrane, proteins, nucleic acid repair enzymes, and consequently kill cells. Tumor cells have low tolerance of a sudden variation in temperature thus can be destructed. The underpinning idea of hyperthermia is an old as modern era of cancer treatment modalities such as ionizing radiation and laser therapy. Different techniques involving laser, ionizing radiation, and microwaves have been used to apply hyperthermia in tumor regions, but with harmful secondary effects in the healthy tissues. This issue is the main challenge of many other techniques used to heat up malignant body tissues. Although these techniques are able to increase the intracellular temperature up to the cellular death, they also induce harmful side effects that adversely influence the surrounding healthy tissues.

3. MNP- based Hyperthermia

In the case of MNP-based hyperthermia, one of the main goals is to synthesize multifunctional MNPs that exhibit the highest saturation magnetization as possible and have surfaces properly functionalized that allow them to selectively attach to target cells or tissues. To achieve such high demanded selectivity and specificity, DNA probes, antibodies, and other chemical compounds are used. For a wide range of applications, the use of colloidal iron oxide and iron oxide-based core-shell nanostructures have shown promising potentials for these applications.

MNPs, due to their size-dependent physicochemical properties, have demonstrated promising potentials for developing localized hyperthermia techniques [12, 15-19].

High saturation magnetization and functionalizable surface are the two main traits of MNPs making them efficient markers to selectively attach to target cells or tissues. In particular, iron oxide NPs are currently under intensive studies to develop highly localized and efficient MNP-based hyperthermia for treatment of carcinogenic cells.

Hyperthermic techniques have been conventionally used in combination with radiotherapy during the recent years. However, serious harmful secondary effects induced in healthy tissues are the main barrier in developing these techniques. In this regard, nanotechnology introduces a novel and innovative solution with magnetic hyperthermia,

which is based on the use of MNPs to remotely induce local heat through an external radiofrequency magnetic field to increase temperature in the tissues and organs containing the tumoral cells.
Therefore, one important factor that determines the efficiency of this technique is the ability of MNPs to be driven and accumulated in the desired area inside the body.

Surface functionalization is one of the main characteristics of all the NPs used in biomedical applications for several reasons: stability of their physicochemical properties within in the medium because of their resistance against biological pH changes, hydrophobicity or hydrophilicity, etc[20].
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The size of MNPs is the crucial factor determining their uptake of target cell and elimination from the body. For example MNPs which have the diameter size larger than 200 nm are absorbed by spleen and liver while particles of below 10 nm are rapidly removed via renal clearance[21].

Furthermore, the unique and modifiable surfaces of SPIONs make them suitable for local heat induction or hyperthermia.

For any efficient therapeutic applications of MNPs, the particles must be stable in water at pH 7 and in a physiological environment. The colloidal stability of magnetic fluid or MNPs depends on the two factors including: 1- the size of particles which must be small enough to prevent precipitation 2- the charge and surface chemistry, which lead to both steric and coulombic repulsions [22] [23].

A major challenge in applying conventional hyperthermic methods is the difficulty in induction of desired temperature in the target site without damaging to healthy tissue [24-26]. Systems that are constructed to produce hyperthermia, must heat tissue of body to temperature of 42°C to 44.0°C. Nevertheless, higher temperatures can ruin more tumor cells. in this regard, in order to therapeutic cancer by hyperthermia, many various devices have been designed to heat of malignant cell while protecting surrounding healthy tissue [27, 28].

History of experimental studies of hyperthermia using magnetic material backed to 1957 when Gilchrist et al (1957) heated different tissue samples with NPs of γ -Fe_2O_3 that were exposed to magnetic field[23]. Afterward, a lot of experiments have been conducted in order to surveying various methods using several types of magnetic materials, different field strengths and frequencies and different methods of encapsulation and delivery of the particle [29-33]. This method contains defusing magnetic particles all over the desired tissue, and then applied an AC magnetic field with appropriate frequency and strength to induce intended heat in the target. This heat immediately dissipates into the sou of target tissue, as a result, if the temperature maintained above the treatment threshold of 42˚C for 30 min or more, ruining cancer has been occurred. First, Gordon et al (1979) reported the producing intracellular hyperthermia by utilizing dextran magnetite NPs [34]. They injected magnetite NPs intravenously to Sprague–Dawley rats suffering from mammary carcinomas. Also they demonstrated that an alternating magnetic field (AMF) led to generate heating. In this relation, some studies have surveyed “intracellular” hyperthermia and developed MNPs and micro magnetic particles for applying hyperthermia [33, 35, 36]. This concept is based on the principle that under AMF, a magnetic particle can generate heat by hysteresis loss. Afterward Jordan et al suggested the magnetic fluid hyperthermia (MFH) in various experiments [37]. Magnetic particles which are used for hyperthermia must have certain properties such as nontoxicity, injectability, biocompatibility, high aggregation in the desired tumor region and effective absorption of the AMF energy. Then some studies focused on modified dextran magnetite and its hyperthermic effect by using several human carcinoma cell lines in vitro. The specific adsorption rate (SAR) demonstrates the evaluation rate of heat. SAR of conventional dextran magnetite is low. Dextran magnetite have very small size, therefore it acts as a superparamagnetism rather than a ferromagnetic particle; therefore, its hysteresis loss is very low. It was proved that particle size has an important role in achieving a high SAR value [38].The main advantage of MNP-based hyperthermia, in comparison with the other conventional hyperthermia techniques is that it offers a way to ensure just the desired target is heated

CONCLUSION

MNPs have demonstrated promising potentials in developing selective and localized hyperthermia. Size of MNPs is the crucial factor determining their efficacy for efficient hyperthermia through their uptake by target cell as well as their elimination from the body.

Furthermore, the unique and modifiable surfaces of MNPs, especially SPIONs make them suitable for localized hyperthermia. Several initial clinical studies have investigated MNP-based hyperthermia for different cancers and the findings were promising. One of the main goals in MNP-based hyperthermia is to synthesize multifunctional

MNPs that exhibit the highest saturation magnetization as possible and have surfaces properly functionalized that allow them to selectively attach to target cells or tissues.

REFERENCES

[1] Wellinghausen, N., et al., Evaluation of the Hyplex BloodScreen multiplex PCR-enzyme-linked immunosorbent assay system for direct identification of gram-positive cocci and gram-negative bacilli from positive blood cultures. *Journal of clinical microbiology*, **2004**. **42**(7): p. 3147-3152.
[2] Bradwell, A.R., et al., Highly sensitive, automated immunoassay for immunoglobulin free light chains in serum and urine. *Clinical Chemistry*, **2001**. **47**(4): p. 673-680.
[3] Ali, Y., et al., Dye-Doped Fluorescent Nanoparticles in Molecular Imaging: A Review of Recent Advances and Future Opportunities. *Material Science Research India,* **2014**. **11**(2).
[4] Ali, Y., et al., Applications of Upconversion Nanoparticles in Molecular Imaging: A Review of Recent Advances and Future Opportunities. *Biosci., Biotech. Res. Asia*, **2015**. **12**(Spl.Edn.1): p. 131-140.
[5] Yadollahpour, A., Magnetic Nanoparticles in Medicine: A Review of Synthesis Methods and Important Characteristics. *Oriental Journal of Chemistry*, 2015. **31**(Special Issue 1 (**2015**)): p. 271-277.
[6] Yadollahpour, A. and S. Rashidi, Magnetic Nanoparticles: A Review of Chemical and Physical Characteristics Important in Medical Applications. *Oriental Journal of Chemistry*, 2015. **31**(Special Issue 1 (**2015**)): p. 25-30.
[7] Panyam, J. and V. Labhasetwar, Biodegradable nanoparticles for drug and gene delivery to cells and tissue. *Advanced drug delivery reviews*, **2003**. **55**(3): p. 329-347.
[8] Sun, C., J.S. Lee, and M. Zhang, Magnetic nanoparticles in MR imaging and drug delivery. *Advanced drug delivery reviews*, **2008**. **60**(11): p. 1252-1265.
[9] Reimer, P. and R. Weissleder, [Development and experimental use of receptor-specific MR contrast media]. *Der Radiologe*, **1996**. **36**(2): p. 153-163.
[10] Wang, Y.-X.J., S.M. Hussain, and G.P. Krestin, Superparamagnetic iron oxide contrast agents: physicochemical characteristics and applications in MR imaging. *European radiology*, **2001**. **11**(11): p. 2319-2331.
[11] Arruebo, M., et al., Magnetic nanoparticles for drug delivery. *Nano today*, **2007**. **2**(3): p. 22-32.
[12] Dobson, J., Magnetic nanoparticles for drug delivery. *Drug development research*, **2006**. **67**(1): p. 55-60.
[13] Zborowski, M., Physics of magnetic cell sorting, in Scientific and clinical applications of magnetic carriers. **1997**, Springer. p. 205-231.
[14] Fuentes, M., et al., Preparation of inert magnetic nano-particles for the directed immobilization of antibodies. *Biosensors and Bioelectronics*, **2005**. **20**(7): p. 1380-1387.
[15] Latorre, M. and C. Rinaldi, Applications of magnetic nanoparticles in medicine: magnetic fluid hyperthermia. *Puerto Rico health sciences journal*, **2009**. **28**(3).
[16] Trahms, L., Biomedical applications of magnetic nanoparticles, in Colloidal Magnetic Fluids. **2009**, Springer. p. 1-32.
[17] O'Grady, K., Biomedical applications of magnetic nanoparticles. *Journal of Physics D: Applied Physics*, **2002**. **36**(13).
[18] Jordan, A., et al., Magnetic fluid hyperthermia (MFH): Cancer treatment with AC magnetic field induced excitation of biocompatible superparamagnetic nanoparticles. *Journal of Magnetism and Magnetic Materials*, **1999**. **201**(1): p. 413-419.
[19] McBain, S.C., H.H. Yiu, and J. Dobson, Magnetic nanoparticles for gene and drug delivery. *International journal of nanomedicine*, **2008**. **3**(2): p. 169.
[20] Kim, D.-K., et al., Superparamagnetic iron oxide nanoparticles for bio-medical applications. *Scripta materialia*, **2001**. **44**(8): p. 1713-1717.
[21] Pratsinis, S.E. and S. Vemury, Particle formation in gases: a review. *Powder technology*, **1996**. **88**(3): p. 267-273.
[22] Langer, R., Polymeric Delivery Systems, in Targeting of Drugs 2. **1991**, Springer. p. 165-175.
[23] Gilchrist, R., et al., Selective inductive heating of lymph nodes. *Annals of surgery*, **1957**. **146**(4): p. 596.
[24] Cavaliere, R., B. Giogatto, and B. Giovanella, Selective heat sensitivity of cancer cells. *Cancer*, **1967**. **20**(1): p. 351.
[25] Stauffer, P.R., et al., Observations on the use of ferromagnetic implants for inducing hyperthermia. *Biomedical Engineering, IEEE Transactions on*, **1984**(1): p. 76-90.
[26] Ikeda, N., et al., Experimental study on thermal damage to dog normal brain. *International journal of hyperthermia*, **1994**. **10**(4): p. 553-561.
[27] van der Zee, J., Heating the patient: a promising approach? *Annals of oncology*, **2002**. **13**(8): p. 1173-1184.
[28] Moroz, P., S.K. Jones, and B.N. Gray, Status of hyperthermia in the treatment of advanced liver cancer. *Journal of surgical oncology*, **2001**. **77**(4): p. 259-269.
[29] Mosso, J.A. and R.W. Rand, Ferromagnetic silicone vascular occlusion: a technic for selective infarction of tumors and organs. *Annals of surgery*, **1973**. **178**(5): p. 663.

[30] Hilger, I., et al., Heating potential of iron oxides for therapeutic purposes in interventional radiology. *Academic radiology*, **2002**. **9**(2): p. 198-202.
[31] Moroz, P., et al., Targeting liver tumors with hyperthermia: ferromagnetic embolization in a rabbit liver tumor model. *Journal of surgical oncology*, **2001**. **78**(1): p. 22-29.
[32] Minamimura, T., et al., Tumor regression by inductive hyperthermia combined with hepatic embolization using dextran magnetite-incorporated microspheres in rats. *International journal of oncology*, **2000**. **16**(6): p. 1153-1161.
[33] Mitsumori, M., et al., Development of intra-arterial hyperthermia using a dextran-magnetite complex. *International journal of hyperthermia*, **1994**. **10**(6): p. 785-793.
[34] Gordon, R., J. Hines, and D. Gordon, Intracellular hyperthermia a biophysical approach to cancer treatment via intracellular temperature and biophysical alterations. *Medical Hypotheses*, **1979**. **5**(1): p. 83-102.
[35] Wada, S., et al., New local hyperthermia using dextran magnetite complex (DM) for oral cavity: experimental study in normal hamster tongue. *Oral diseases*, **2001**. **7**(3): p. 192-195.
[36] Jordan, A., et al., Inductive heating of ferrimagnetic particles and magnetic fluids: physical evaluation of their potential for hyperthermia. *International Journal of Hyperthermia*, **2009**. **25**(7): p. 499-511.
[37] Jordan, A., et al., Cellular uptake of magnetic fluid particles and their effects on human adenocarcinoma cells exposed to AC magnetic fields in vitro. *International journal of hyperthermia*, **1996**. **12**(6): p. 705-722.
[38] Shinkai, M., Heat properties of magnetoliposomes for local hyperthermia. *Jpn. J. Hyperthermic Oncol.*, **1994**. **10**: p. 168-177.