SELF-REGULATED MAGNETIC FLUID HYPERTHERMIA

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Introduction

The human body naturally uses heat to fight disease. Viruses and bacteria proliferate at normal body temperatures, so the body instinctively defends itself by increasing its temperature several degrees to slow the rapid multiplication of such disease-causing agents. This phenomenon, commonly called a fever, gives the body an advantage while fighting the infection. Fevers form one subset of hyperthermia, an abnormally high body temperature. Hyperthermia also refers to body temperatures elevated for therapeutic reasons. The use of hyperthermia to treat many types of cancer has been a recent topic of research[1].

Hyperthermia treatments elevate the temperatures of cancerous cells. Temperatures within the therapeutic temperature range, 42-45°C, improve the efficacy of other treatments like chemotherapy and radiotherapy[1, 2]. By raising the temperature to ~50°C, hyperthermia alone can kill the cancerous cells. This latter treatment is usually referred to as thermal ablation[3]. Hyperthermia can be performed by focusing laser, microwave, ultrasound or magnetic energy to the infected regions. The challenges faced by hyperthermia cancer treatment include minimizing damage to healthy tissue and treating deep-seated tumors. A non-invasive procedure is also desirable. After considerable research magnetically mediated hyperthermia has been found to live up to these challenges[2].

Gilchrist *et al.*[4] were the first to propose the use of magnetic materials in hyperthermia in 1957. They introduced magnetic microspheres into animal tissues and applied an alternating magnetic field. The alternating magnetic field can provide the energy necessary to reorient the particles' magnetic moments. Due to the phase lag between the magnetic moment and the applied magnetic field, magnetic energy is converted to thermal energy[5, 6]. Hyperthermia cancer treatment uses the heat generated by this conversion to destroy cancerous tissues.

Temperatures above 42°C in healthy tissues can cause burns, blisters, and discomfort. Consequentially, temperatures must be closely monitored during hyperthermia cancer treatment. The temperature that can be achieved in the tissue strongly depends on the properties of the magnetic material used, the frequency and the strength of the applied magnetic field, the blood perfusion in the tissue and the duration of application of the magnetic field. Therefore carefully chosen parameters and the means to monitor the real-time temperature are required. These complications can be eliminated by choosing a magnetic material that has a Curie temperature equal to the therapeutic temperature. At the Curie temperature ferromagnetic or ferrimagnetic materials (strongly magnetic) become paramagnetic (weakly magnetic). A magnetic material with a Curie temperature equal to the therapeutic temperature will act like a self-controller, generating heat only when below the therapeutic temperature. This therapy has been named self-regulated hyperthermia. Brezovich *et al.*[7] were among the earliest to study self-regulated hyperthermia using low Curie temperature Ni-Cu alloy seeds. Later studies included low Curie temperature thermoseeds made of Mn-Cu ferrite [8-9], Fe-P-Cr-C amorphous flakes[10], Ni-Si alloys[11], Co-Pd alloys[12-14] and Ni-Pd alloys[15-16]. These studies show that such materials help control the temperature within the tissue.

More recently another form of magnetically mediated hyperthermia named Magnetic Fluid Hyperthermia (MFH) has been studied. Many studies have confirmed the feasibility of magnetic fluid

hyperthermia cancer treatment[17-18]. The major difference between other magnetically mediated hyperthermia and MFH is the size of the magnetic material used. MFH uses magnetic nanoparticles that are superparamagnetic in contrast to large ferromagnetic thermoseeds used in other forms. Due to their small size, magnetic nanoparticles disperse well within the tissue, thus distributing the heating centers to give more uniform temperatures. In addition, the small size can make it possible to non-invasively introduce the magnetic nanoparticles to the cancerous tissue.

When the benefits of MFH and self-regulated hyperthermia are brought together they result in a highly desirable form of hyperthermia named here as self-regulated MFH. Such a therapy is accomplished by choosing magnetic nanoparticles that have a Curie temperature that equals the therapeutic temperature. Obvious choices of materials for such a therapy are the materials studied earlier for self-regulated hyperthermia namely Ni-Cu alloy, Mn-Cu ferrites, Ni-Pd alloy and Co-Pd alloys. Recently, Chatterjee *et al.*[19] have studied polymer encapsulated Cu-Ni nanoparticles, Brusentsova *et al.*[20] have synthesized low Curie temperature Gd-substituted Mn-Zn ferrite nanoparticles and Giri *et al.*[21] have synthesized $Fe_{1-x}Mn_xFe_2O_4$ nanoparticles for self-regulated MFH. Our research group is interested in studying FePt, NiPt and NiPd[22] nanoparticles.

Two important aspects of nanoparticles should be addressed for biological applications: i) size of the nanoparticles and ii) surface chemistry of the nanoparticles. Earlier reports have discussed the strong dependence of the heat generation from magnetic nanoparticles in an alternating magnetic field on their size[6], indicating the importance of synthesizing monodisperse magnetic nanoparticles. The Curie temperature of the nanoparticles is also expected to vary with the size of the nanoparticles, particularly when the fraction of the surface atoms is high. The surface chemistry of the nanoparticles influences their biocompatibility. Studies to investigate the toxicity of the magnetic material will be important because it may be very difficult if not impossible to extract the nanoparticles from the body after the therapy has been completed. This is unlike hyperthermia conducted using thermoseeds that are introduced into the tissue and removed from the tissue surgically. Further discussions on toxicity studies are beyond the scope of this paper. The discussion of the synthetic procedures to make such magnetic nanoparticles, the modification of their surface chemistry to achieve biocompatibility and the thermal modeling of self-regulated hyperthermia is the subject of this report.

Synthesis of Magnetic Nanoparticles

Several methods to synthesize magnetic nanoparticles are available in the literature. A recent review discusses various synthesis procedures[23]. With the aim of obtaining biocompatible nanoparticles, in general, a synthesis can be classified as a single-step or a two-step procedure. The single-step procedure involves the synthesis of nanoparticles in the presence of ligands like PEG or dextran that will make the nanoparticles biocompatible[23]. However these synthesis routes suffer from a serious disadvantage of making nanoparticles that are highly polydisperse in size. The two step procedure synthesizes highly uniform nanoparticles in an organic medium with hydrophobic ligands and then modifies the particle surface to make them biocompatible.

Several procedures to make uniform sized particles are known. Among them are the synthesis of FePt nanoparticles by Sun *et al.*[24], iron oxide nanoparticles by Hyeon *et al.*[25], and Co nanoparticles by Alvisatos *et al.*[26]. The common theme among these procedures is to isolate the nucleation and the growth regimes that were originally suggested by LaMer *et al.*[27]. Another mechanism called Ostwald ripening is also known to result in the formation of uniform sized large particles, where the large particles grow at the expense of the small particles. Though the exact mechanism of formation of particles by these procedures is not known, the choice of the surfactant for a particular system is very important. For instance, the preparation of FePt nanoparticles requires the presence of both oleic acid and oleyl amine ligands. We have verified that the absence of any one of these surfactants produces poorly dispersed

FePt (unpublished results). In general it can be said that i) carboxylic acid based surfactants like oleic acid make good dispersions of Fe-based nanoparticles, ii) amine and thiol groups ligate well with noble metals like Pt and Au and iii) phosphine ligands make good dispersions of Ni, Pd, Cd-based nanoparticles. The science behind why certain surfactants work and others don't is not yet well understood.

We have been evaluating the potential of NiPd and FePt nanoparticles for self-regulated hyperthermia applications. The Curie temperature of these alloy systems can be tuned by changing their composition as shown in figure 1. From the figure bulk $Fe_{27}Pt_{73}$ and $Ni_{28}Pd_{72}$ alloys will have a Curie temperature near 45ºC.

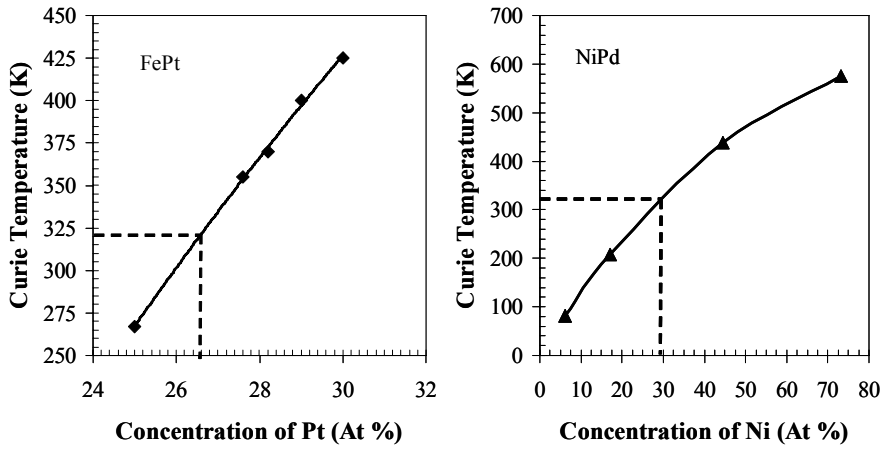

Figure 1. T_c plots of bulk FePt[28] and NiPd[29] alloys in the disordered fcc state as a function of their composition.

Based on studies conducted on various nanoparticles, the heating potential[6] of FePt and NiPd nanoparticles is likely to change with their size. The Curie temperature is also expected to change with the size and certainly with the composition of the nanoparticles. Therefore, it is of interest to make nanoparticles with different sizes and composition. Methods to make FePt nanoparticles of different sizes (2-9nm) [24, 30] are available. We have been modifying these procedures to achieve the desired composition and size. Hyeon *et al.* [31] have reported on the synthesis of 3 nm NiPd particles. Procedures to make different sized NiPd nanoparticles are under investigation[22].

Tailoring the Surface of Nanoparticles

The synthesis of uniform sized particles described above yields particles that have a hydrophobic surface due to the surfactants. Several techniques described in recent reviews[23, 32, 33] can make these particles water soluble and biocompatible by modifying their surface chemistry. Among them are coating the surface of the particles with i) Au[34] shells or non-magnetic oxides like SiO_2 [35, 37], which can then be made biocompatible ii) biocompatible polymers like polyethylene glycol, polyvinyl pyrrolidone or polyvinyl alcohol [32,23] and iii) molecules like carboxylic acids, dextran, phosphorylcholine or chitosan [32, 23]. Our research group has been investigating these options[36, 37].

As an example, we discuss our efforts to introduce carboxylate groups[36] on the surface of FePt nanoparticles to make them water soluble. We carried out ligand exchange[38] on FePt surface to displace the oleic acid and oleyl amine ligands with mercapto alkanoic acid. After ligand exchange, water-soluble FePt nanoparticles were formed[36]. To understand the surface chemistry during the ligand exchange the FePt nanoparticles were characterized before and after the ligand exchange by XPS and FTIR spectroscopy. The results suggest that the mercpato end displaces oleyl amine on Pt atoms and the carboxylic acid end of the mercapto alkanoic acid displaces oleic acid on the Fe atoms. The carboxylate

and sulfate ions then provide the necessary electrostatic repulsion to form water dispersible FePt nanoparticles[39]. The knowledge gained by understanding the surface chemistry reveals the anchor group that can be chosen to introduce functionalities on the particle. Here, thiol is established as the anchor group for Pt atoms and carboxylate for Fe atoms. A ligand with any of these anchor groups at one end and a desired functionality at the other end can then be used to introduce the functionality on the nanoparticles' surface.

Modeling Magnetic Fluid Hyperthermia

Estimates of the amount of the heat that will be required and knowledge of the temperature distribution within the tumor and the healthy tissue will be important for hyperthermia treatment. Modeling the thermal behavior during hyperthermia can help to ascertain these estimates. The thermal model developed by our group[40] consists of two finite concentric spherical regions. The inner sphere represents cancerous tissue containing magnetic particles, and the outer sphere represents healthy tissue. Penne's bioheat transfer equation describes the temperature in the diseased and healthy tissues as functions of the heat generated by the particles, the heat conducted through the tissues, and the heat removed by blood perfusion. The model showed that the proper distribution of magnetic particles throughout the tumor could minimize the damage to the surrounding healthy tissue while still maintaining a therapeutic temperature in the tumor.

Applying this model for self-regulated hyperthermia[41] shows the ability of self-regulated MFH to maintain therapeutic temperatures within the tumor while maintaining near body temperature in the healthy tissue, a highly desirable scenario. The model can also be used to find ways to apply the magnetic field to minimize damage to healthy tissues and the patient's exposure to the field. Future computer simulations could assist doctors in determining how and where to place the magnetic fluids. Precise treatments would increase the likelihood of eliminating the tumor while decreasing the side effects of heating healthy tissue.

Conclusions

Self-regulated MFH is a promising treatment for cancer that can help avoid the complicated control mechanism that is usually required for MFH. Owing to the strong influence of the size of the nanoparticles on the amount of heat generation, synthesis of monodispersed particles is important. A two step approach to synthesize biocompatible particles was discussed that involved making uniform sized particles followed by tailoring of the surface chemistry to achieve biocompatibility. Thermal modeling was discussed as a tool for further advancing self-regulated MFH as a therapy.

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