Magnetic Nanoparticles and their Applications in Biomedicine

Honors Project

University Physics II

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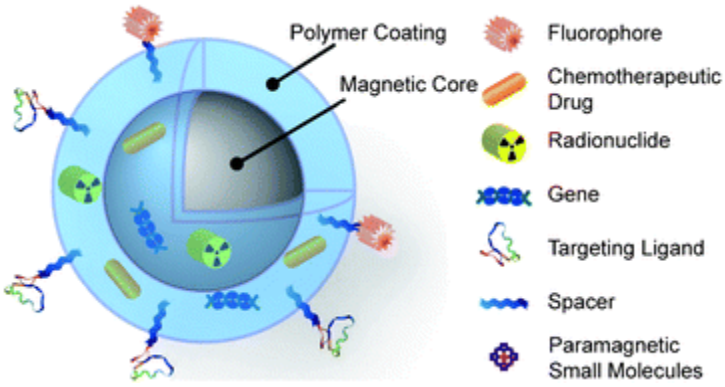
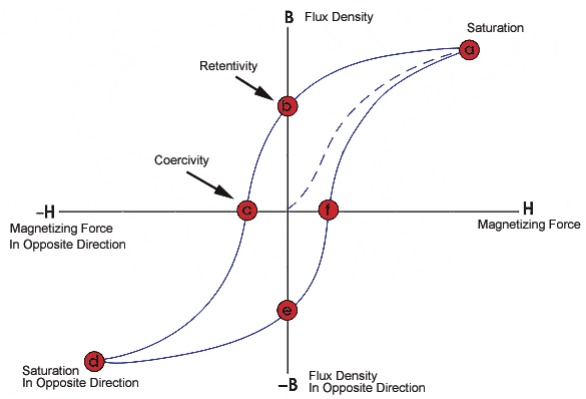
Over the past decade, research in the field of nanotechnology has led to major advancements in the areas of health care and the life sciences. In particular, the synthesis and the functionalizing of magnetic nanomaterials have allowed researchers to better understand biological processes at the molecular level (Tartaj et al 2003, 182).

The magnetic nanomaterials that are commonly used in biotechnology fall into three general categories: nanospheres, nanotubes and nanowires, and thin films. In most biomedical cases, the magnetic nanomaterial is suspended in a carrier liquid, forming magnetic fluids, also called ferrofluids. Among the three types of magnetic particles, magnetic nanospheres are most widely used in biomedicine (Varadan et al 2008, 11). Magnetic nanospheres are approximately 100 nanometers in size and contain a magnetic element such as Ni, Co, or Fe at their core. For biomedical applications, the magnetic material most often used in the core is iron oxide in the form of magnetite (Fe_3O_4). As a result of their magnetic core, these particles obey Coulomb's Law and can be manipulated by an external magnetic field (Conroy et al 2008). For example, magnetic nanoparticles will rotate under an external uniform magnetic field, and will make translational movements under an external field gradient. This property is crucial when transporting magnetically tagged drug molecules to diseased sites (Conroy et al 2008). One of the more attractive properties of magnetic nanospheres is that due to their small size they do not agglomerate due to magnetic dipole interaction. However, because of their size, small interactive forces called Van der Waals interactions become a factor. To mitigate this effect, nanospheres are normally coated with a thin gold or silica based layer. In practical applications, gold serves as an ideal foundation on which a particular nanosphere can be functionalized.



In recent years, functionalizing magnetic nanospheres with targeting ligands and locators has been of great interest in targeted drug delivery (Conroy et al 2008).

In order to understand the benefits of magnetic nanoparticles, it is important to understand the behavior of magnetic nanoparticles under the influence of an external magnetic field. Any magnetic material can be broken up into smaller sub-units called domains. Each domain behaves as a small magnet with a north and south pole (Giancoli 2005, 573). When in the presence of an external magnetic field, the various spins associated with each domain align with the applied field. Naturally, as the applied field gets stronger, more spins align until the saturation magnetization (M_s) is reached. For a ferromagnetic material, even when the applied field goes to zero, the material still has a residual magnetization denoted M_r. If for some reason the material is fully saturated, and needs to be brought to zero magnetization, a magnetic field in the negative direction (H_c) should be applied.



The curve above is referred to as a hysteresis loop and characterizes the relationship between a magnet and an applied field. When a magnetic field of strength **H** is applied to a magnetic material, the individual atomic moments in the material contribute to the overall magnetic induction **B** of the material.

$$B = u_o (H + M)$$

Where M is the magnetization (magnetic moment per unit volume) and u_o is the permeability of free space (Gubin 2009, 200-210).

There are several challenges in synthesizing nanoparticles. First, systems of ultrafine particles often have very high surface energies. This makes it very difficult to maintain these systems during the initial developmental stages due to their tendency to spontaneously reduce their surface area (Varadan et al 2008, 87). Currently, chemical synthesis in solution is the primary method of manufacturing magnetic metal nanoparticles. In principle, approaches to producing magnetic nanoparticles are not that different from approaches to producing metals. For the synthesis of monometallic magnetic nanoparticles, the electrochemical cell (reduction method), is commonly used in which a salt of the metal of interest is dissolved in an ionic solution. The metal ions then migrate over to the cathode and then form clusters which are stabilized by the solvent or a surfactant. Particle size can then be regulated by current density where higher current densities produce smaller particles (Gubin 2009, 296).

Precipitation methods have also shown promise in producing nanoparticles on a large scale and allow for better control of nanoparticle size and shape. In the case homogeneous precipitation, when the constituent species reaches a point of supersaturation, a single, short burst of nucleation occurs. Then, the nuclei are allowed to grow uniformly through the diffusion of

solute particles in solution onto their surface. The nanoparticle growth can then be halted by promptly dropping the temperature (Tartaj et al 2003, 190).

Apart from the “wet” chemical methods, the solvothermal method is a preferred technique when size-selection is of greater importance than mass-scale production. In this method, the metal of interest (usually in the form of organometallic compounds) is injected into a hot solution of surfactants. This stimulates nucleation and growth can then be ended by dropping the temperature. In general, larger particles can be obtained with longer reaction time and higher reaction temperature (Varadan et al 2008, 87).

The synthetic methods described above are only a few of the ways in which magnetic nanoparticles are created for biomedical applications. Furthermore, the methods described are primarily used to generate monometallic magnetic nanoparticles. Synthesis of alloy and oxide nanoparticles are developed similarly to monometallic nanoparticles however additional steps are required to add multiple elements (Gubin 2009, 300).

Magnetic nanoparticles are actively used in the biomedical community. One of the primary applications of magnetic nanoparticles is through their use as MRI contrast agents. Molecular imaging is the technology that allows for the understanding of diseases and finding appropriate treatments. Due to the fact that most diseases have a molecular basis, molecular imaging with better image resolution and image contrast at the molecular level is much needed for better diagnostic differentiations and early disease detection. Among the imaging techniques present, MRI is one of the most widely used (Varadan et al 2008, 132).

The technology of MRI is based on the detection of nuclear spin in molecules. When a magnetic field is applied, the nuclei respond by adopting two different energy states/orientations (spin-up and spin-down orientation). One of these energy states is higher in energy than the other

and as a result there are more spinning nuclei in the lower energy state. When the nuclei are activated by a magnetic field (typically in the form of an oscillating radio frequency), some spinning nuclei jump from the lower energy state to the higher state. These “excited” nuclei eventually return to their original energy state and in doing so emit energy at a frequency called the Larmor frequency. The RF signal of emission can be detected by a RF coil (Varadan et al 2008, 132). In terms of biological tissue, MRI relies upon the counterbalance between the very small magnetic moment of a proton and the very large number of protons present in tissue. This difference leads to a measurable effect in the presence of a large magnetic field (Pankhurst et al 2003, 170).

MRI contrast agents improve image resolution by changing the magnetic resonance relaxation times of water in the tissues around the tissue (Kumar 2009, 120). In MRI and NMR relaxation refers to nuclear spins returning to their original spin state (equilibrium distribution). The rate of relaxation is then measured by MRI (Gubin 2009, 408). Contrast agents are either categorized as either T1 or T2 type. T1, also called the spin-lattice relaxation time, is a time constant that characterizes the mechanism by which the z-component of the magnetization vector comes to thermodynamic equilibrium with its surroundings (the lattice) (Conroy et al 2008). T1 contrast agents (positive-contrast agents) enhance images by reducing the spin-lattice relaxation time and thereby increasing the intensity of the water signal of the tissue in which it is placed. Those tissues in which the agent is located will appear brightly in the final image (Kumar 2009, 121). T2 contrast agents (negative-contrast agents) reduce the relaxation time of the component of the magnetization vector that is perpendicular to the applied field. These agents are called negative because the tissue in which these agents are placed will appear darker on an image (Conroy et al 2008).

For clinical usage, most MRI contrast agents produce positive contrast or signal enhancements. Thus, the T1 agents most often used are gadolinium complexes. However, magnetic nanoparticles have been found to be far more efficient as relaxation enhancers. Superparamagnetic ferrite-based particles represent typical T2 agents. Some of the commonly used magnetic nanoparticles used as contrast agents are magnetic oxide-based nanoparticles, magnetic metal and alloy based particles, and earth metal-loaded nanoparticles (Kumar 2009, 125).

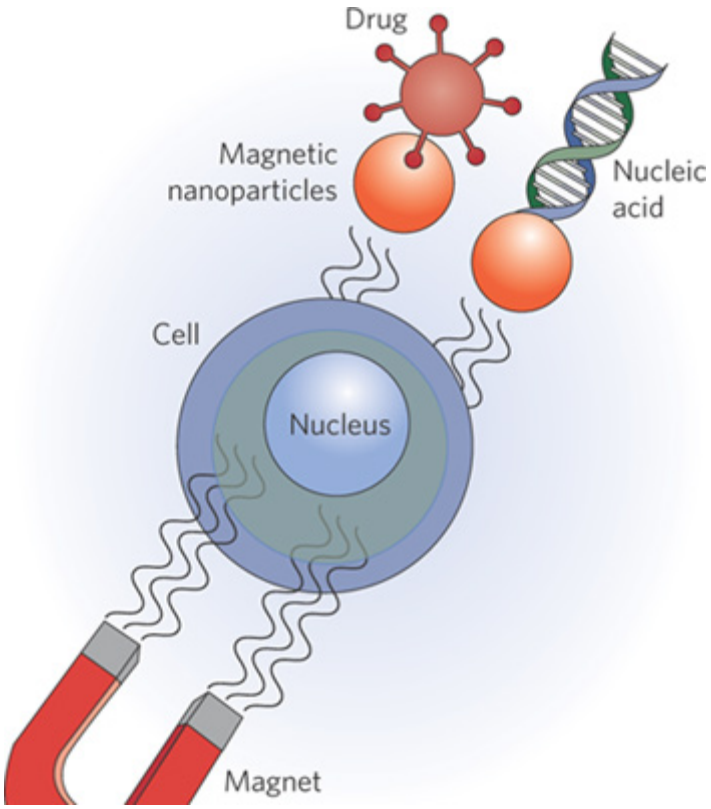
There are however several drawbacks to extensive use of magnetic nanoparticles as T2 contrast agents. One of the main problems is the complexity and difficulty in preparing and functionalizing nanoparticles for placement in biological tissue. Another problem is related to the instability of nanocomposites in solutions. Oftentimes, in biological environments, nanoparticles will aggregate or clump together due to magnetic, electrostatic or chemical interactions with one another. To prevent this problem, very careful design and accurate synthesis is required during the initial preparation stages. Another major problem is the potential of nanotoxicity. Iron-oxide based nanoparticles are fairly biocompatible and show no adverse effects to major organs. But, the long-term usage of magnetic nanoparticles still poses the potential of metal toxicity (Kumar 2009, 121).

Because of their physical properties, and their ability to function at the cellular and molecular level, magnetic nanoparticles have been investigated for decades as the future of targeted drug delivery (Chomoucka et al 2010). The importance of targeted drug delivery is to successfully deliver a drug to the center of a disease thereby treating the disease without any side effects to the body (Conroy et al 2008). Typically a functionalized magnetic nanoparticle contains drugs that are expected to be released into harmful cells. Sensors and actuators on the

MNP (magnetic nanoparticle) govern the release of the drug. Forces between the blood carriers and magnetic forces generated from the magnet also dictate drug localization and release. For example, when the magnetic forces exceed the linear blood flow rates in arteries or capillaries, the magnetic carriers are contained in the target site. Once a drug has been localized in the target site, the drugs are released from carriers by modulation of the magnetic field, enzymatic activity or changes in physiological conditions such as pH, osmolality or temperature (Varadan et al 2008, 24).

One of the key properties of magnetic nanoparticles that make them desirable in targeted drug delivery is their superparamagnetism. This property results from the thermal effects of a material. In targeted drug delivery, it is sometimes necessary to increase the magnetization so that drug transport is performed efficiently. The property of superparamagnetism allows the field to be increased without the agglomeration of MNP's after the field has been stopped. In other words, magnetic nanoparticles have no remanence and therefore no hysteresis. Also, superparamagnetism allows nanoparticles to remain in circulation without being removed from the body's natural filters (liver and immune system) (Chomoucka et al 2010).

Functionalization and coating of magnetic nanoparticles is crucial in drug delivery as it is for any biomedical application of MNP's. Iron oxides are the most commonly used core for drug delivery. In some cases,



DNA displayed corresponds to the MNP's application in gene delivery/therapy.

carbonyl iron, a unique form of elemental iron, is used preferentially because of its small particle size. Fitting magnetic nanoparticles (as illustrated in the figure on page 2) with amino groups, silica, polymers, or other organic compounds is used to give the particle better physical and chemical properties. Polymer coating for example, mitigates the effects of oxidation on metal-core magnetic nanoparticles. Studies also indicate that coating reduces potential nanotoxicity. In drug delivery, it is also very common to add locator molecules on the surface of the nanoparticle. These molecules can then bind to surface receptors near the final destination of the drug. This overall, enhances the effect that the drug has on the patient. Another problem faced in drug delivery is due to strong magnetic dipole-dipole interactions, MNP's will aggregate in solution. The attractive forces are reduced by coating the particles with a hydrophilic polymer such as starch or chitosan (Chomoucka et al 2010).

Finally, the use of magnetic nanoparticles in cancer treatment has led to major improvements in cancer therapy. One of the biggest problems when dealing with cancer is detection. In general, when an individual has a particular malady, the body will respond with pain to let the individual know that there is a problem. However with cancer, the individual experiences no pain in the early stages. The physiological effects of cancer emerge well after metastasis; furthermore, at this stage, treatment is relatively unhelpful in solving the problem. This "lack of pain" aspect of cancer makes early detection even that much more important. Even with detection though, on an MRI scan it can be difficult to discern between malignant tissue and harmless body tissue. This makes the use of contrast agents even more critical. Through better development and understanding of magnetic nanoparticles as contrast agents, carcinogenic tissue could be detected early enough so that it can then be surgically removed (Kumar 2006, 73).

In terms of treatment, researchers have synthesized an arsenal of anticancer drugs that have exhibited therapeutic benefits. However, because anticancer drugs are designed to kill cancer cells in a somewhat non-specific manner, the distribution of anticancer drugs in healthy organs and tissues poses numerous severe side effects (Gubin, 2009 423). Magnetic targeted drug delivery is expected to reduce the unnecessary side effects and improve the efficiency by controlled localized delivery. In magnetic therapy, the cytotoxic drug is placed in a biocompatible magnetic nanoparticle drug/carrier complex system. Then, the biocompatible ferrofluid is injected into the bloodstream of the patient. At this point, a magnet is applied outside the body creating a magnetic field gradient to capture magnetic carriers flowing in the circulatory system and concentrate the complex in the target area. The drug is then released in a controlled manner and the magnetic nanoparticles are metabolized by the spleen and liver. This form of therapy has yet to be tested on human subjects. This is primarily due to the fact that a magnetic field with a safe strength may not be effective due to the large distance between the target site and the magnet. Other issues with this form of treatment are mainly due to the accumulation of the magnetic carriers which may cause a tough embolization of the blood vessels in the treated area (Varadan et al 2008, 159).

The main application of magnetic nanoparticles in cancer is magnetic hyperthermia. As the name suggests the hyperthermia treatment for cancer is the controlled heating of harmful tissues in order to promote cell necrosis. Research has indicated that malignant cells are more responsive to heat than are normal cells. This is the basis behind using hyperthermia. The most commonly used heating method used in a clinical setting involves capacitive heating through a radiofrequency electric field (Kumar 2006, 67).

Through an inductive heating mechanism, magnetic nanoparticles are being investigated as potential agents for the hyperthermia treatment (Gubin 2009, 414). In fact, the inductive heating method of magnetic nanoparticles has a much greater affinity for tumor cells than normal cells (Kumar 2006, 56). Magnetic nanoparticles coated in a lipid bilayer, magnetoliposomes, can combine heat therapy with drug delivery to provide a synergistic treatment.

The hyperthermia theory is based on the idea that when a metallic substance is placed in an alternating magnetic field, there is an induced current in the metal. By resisting the change in field through the establishment of an induced current, the metal heats up (inductive heating). The heating is greatly enhanced if the metal is magnetic, such as iron (Gubin 2009, 417).

Numerous studies have revealed that magnetic hyperthermia has shown therapeutic benefits in animal models. In an experiment, Elsherbini and company, through the use of superparamagnetic iron oxide nanoparticles, were able to reach a maximum temperature of 47 °C in the tumor region for a female mouse with Ehrlich carcinoma. Although the tumor size in the mouse was the same as before the treatment, the rate of tumor growth and proliferation was greatly decreased by magnetic hyperthermia (Elsherbini et al 2010). The challenge that lies in this treatment is in being able to deliver an adequate supply of magnetic particles to generate enough heat to the target area using AC magnetic field conditions that are clinically acceptable. Most of the magnetic field strengths used in animal model studies could not be safely used for a human patient (Gubin 2009, 420).

Developments in nanotechnology for the manipulation and control of biomaterials have greatly improved disease detection and treatment (Varadan et al 2008, 479). In particular, the use of magnetic nanoparticles as MRI contrast agents and drug carriers has greatly enhanced early cancer detection and targeted therapies (Conroy et al 2008). Current research in magnetic

nanoparticles has been in the development of better synthetic routes. New synthetic approaches are needed for magnetic nanoparticles which are either very difficult to produce or simply cannot be made by current methods. Secondly, a large-scale production and cost efficient process for MNP creation has yet to be developed. Additionally, research on better understanding the relationship between the magnetism and crystalline properties of magnetic nanoparticles has also garnered much scientific interest. As illustrated in their numerous applications, functionalization of magnetic nanoparticles is critical. However, only a few functionalization techniques have been developed. Therefore, in order to precisely control the interactions between magnetic nanoparticles and biomolecules, more chemistry about either non-covalent bonding or covalent linkages need to be investigated (Varadan et al 2008, 126). Finally, special interest is also being given to developing strategies for increasing the circulation time of magnetic nanoparticles in blood (Chomoucka et al 2010). Overall, research in magnetic nanoparticles have both further connected and revolutionized the fields of physics, chemistry, and biology. As the area of nanotechnology continues to develop, inevitably more advancement will also be made in the usage of magnetic nanoparticles in biomedicine.

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