BOB THE BUILDER AND HIS ELECTRON SHOVEL: PLANNING AND CONSTRUCTING NANOMAGNETS FOR JOBS FROM DRUG DELIVERY TO ELECTRIC CAR MOTORS

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SUMMARY

We discuss how understanding the physics of magnetism is used to direct the "pushing" of atoms and their electrons to make and enable novel applications.

The earliest known application of any magnetic material is the navigation compass in which naturally occurring lodestone or "leading stone" was used. The applications of magnetic materials are now widespread, including transformers, electric motors, loudspeakers, sensors, tapes (audio and video), floppy disc and hard disc media, giant magnetoresistance (GMR) reading heads for magnetic media, magnetic random access memory (MRAM) devices, permanent magnets, and carriers for targeted drug delivery. The magnetism of a material needs to be tailored for the intended application. For example, for a permanent magnet, materials with a large magnetization (response to an applied magnetic field) remanance (remaining magnetization when there is no applied field) and coercivity (magnetic field necessary to rotate the material's magnetization) are preferable. While designing a transformer core, a magnetic material with a high permeability and a low remanence (e.g. soft iron and silicon steel) is desirable.

One might be wondering: What is the primary origin of magnetism in a magnetic material? It is the motion of electrons at the atomic scale which results in magnetism. The magnetic moment of an electron has two contributions: orbital and spin. For an atom with many electrons, the electrons of partially filled shells contribute to the magnetism. In a material, the mixing of electronic orbitals occurs due to the formation of energy bands or covalence, and sets the overall magnetic behaviour. The electrons of different atomic sites of a material interact with each other via an exchange interaction, which decides the overall nature of the magnetic configuration. Moreover, the exact form of the magnetic coupling between moments depends on the elements present and how those are arranged crystallographically. Let us consider the examples of Fe and Fe_3O_4. In the case of pure Fe metal, the orbitals of its *d*-electrons are delocalized. But, the presence of O^{2-} ions in Fe_3O_4 [(Fe^{3+})tetrahedral (Fe^{3+},Fe^{2+})octahedral$(O^{2-})_4$] localize the *d*-electron orbitals and alter the magnetism in comparison to the pure metal considerably. In Fe_3O_4, the octahedral Fe^{3+} and Fe^{2+} ions are coupled ferromagnetically (moments parallel to each other) via a double exchange mechanism; whereas, the Fe^{3+} ions in the tetrahedral sites are coupled antiferromagnetically (moments antiparallel) to the octahedral sites through a superexchange interaction via the neighbouring O^{2-} ions. Essentially, this is how one can think of a particular electronic configuration to get the desired magnetic property; somewhat similar to the usage of an "electron shovel" by "Bob the Builder".

In this article, we shall concentrate particularly on magnetic nanoparticles and how they can be used individually at the nanoscale or cooperatively to make new bulk (macroscopic) magnets. Over the past hundred years, nanoparticle research has driven a more complete understanding of physics at the nanoscale, inspired new viewpoints on materials production and engineering, and enabled the realization of applications previously only imagined. Due to the extremely small size of nanoparticles (typically ~3–50 nm), a substantial fraction of the atoms that compose the particle reside at the surface (~60% for a 5 nm diameter iron-oxide nanoparticle). Surface atoms have broken coordination; their "frustrated" character is a product of an incomplete number of neighbouring atoms. The associated electronic surroundings, and the reduced symmetry, results in properties (magnetic and electronic) that differ substantially from the interior, well-coordinated "bulk-like" population. These nanoparticle surface atoms therefore behave in different and sometimes unexpected ways, leading to many compelling questions regarding the physics of nanoscale-material properties. Many interesting opportunities arise for making use of these nanoparticle surfaces that are irrelevant in a non-nanostructured systems due to the sparsity of surface atoms compared to those in the bulk. For example, meaningful surface functionalization can be conducted on nanoparticles to attach organic and

biological molecules for biomedical applications. In addition, the specialized reactivity of nanoparticles can be capitalized on to engineer new and fascinating materials.

The evolution of nanoparticle-based magnetism has been driven substantially by materials physics and chemistry in two ways: 1) Exploration of fundamental qualities of materials by the emergence of new, previously unattainable structures, compositions, and morphologies; and 2) The methodology of using nanoparticles as "building blocks" that offers reactivities substantially different from their bulk-form doppelgangers. It is important to note that this has led not only to new nanostructured macro-scale materials, but also much more effective means to synthesize bulk materials that are unfavourable or problematic to produce through traditional top-down approaches. Both 1) and 2) lay out novel bottom-up pathways to new physics by constructing electron configurations that enable novel and useful magnetic properties. We discuss briefly two areas of nanomagnets: First, using the archetypal iron-oxides for biomedical application, and second, a promising candidate for a rare-earth-free permanent magnetic material - manganese bismuth.

NANOMAGNETS MADE FOR TARGETED DRUG DELIVERY: FROM NANOPARTICLE, TO COATING, TO DELIVERY AND DRUG RELEASE

A Brief History

The work on targeted drug delivery was started by the founder of chemotherapy, Paul Ehrlich, who approximately 100 years ago postulated the concept of a "magic bullet" that would carry treatment to a target in the body [1–3]. Ehrlich's goal was to find chemical substances that would have specific affinities for pathogenic organisms, and like a "magic bullet" would go directly to targeted cells [4]. In 1910, Ehrlich and his colleague Sahachiro Hata discovered that drug trial 606 (a synthetic organic compound containing arsenic) could treat syphilis infected laboratory rabbits [5,6]. This first magic bullet was later marketed as Salvarsan [5,6] and the research Ehrlich and his colleagues pioneered became a new area of science now known as "targeted drug delivery" - an interdisciplinary research area now comprising physics, chemistry, engineering, biology, and medicine.

Advantages and Goals of Targeted Drug Delivery

The main advantage of a targeted approach is being able to minimize the exposure of healthy cells to any adverse side effects, permitting a more effective and efficient treatment. The success of a targeted delivery system is based on its capability to manipulate a drug molecule by the following criteria: 1) retain, 2) evade, 3) target, and 4) release [7,8]. Thus, the efficacy of the drug should be retained during the delivery system's synthesis, processing and application. Once administered, the delivery system should be able to evade the body's immunological defences and reach the targeted cells without affecting healthy cells. Finally, the delivery system must have the capability to release the drug in a controlled manner [7].

Planning and Construction

Part 1) Deciding on the drug carrier

Of primary importance is to find a biocompatible carrier for the drug(s). Of the possible magnetic carriers that fit this requirement, the innate biocompatibility of iron-oxide nanoparticles make them the best candidate, currently. This biocompatibility arises from ferritin [9], an iron-oxide nanoparticle that enables blood to be oxygenated by binding oxygen molecules to ionic iron stored by the nanoparticle. The United States Food and Drug Administration (FDA) and the European Commission (EC) have already approved iron oxide nanoparticles for use in clinical trials [10,11]. Examples are the recently introduced Fe-oxide nanoparticle-based magnetic resonance imaging (MRI) contrast agents Combidex, Feridex and Lumirem that are being used in clinical practice [11].

Part 2) Does the particle size and shape matter?

Particle size and shape are very important considerations, especially with regards to nanoparticle functionality. Firstly, nanoscale sizes are necessary to pass inside a living animal without adverse effects, and then to safely penetrate membranes, such as cell walls and the blood brain barrier. It has also been observed that depending upon their size, nanoparticles can accumulate preferentially in different parts of the body. For example, larger particles (>1 μm, including coating) accumulate in the liver and lungs, while medium-sized nanoparticles (10–300 nm) populate the bone marrow, spleen, liver and lymph nodes. Smaller nanoparticles (<10 nm) go preferentially to the kidney directly [11,12].

The shape of the nanoparticles also plays an important role [13–16]. For example, non-spherical nanoparticles (rods, discs, etc.) are known to be more effective when targeting damaged cells compared to spherical nanoparticles [13–16]. A possible explanation for this is the difference in electric (zeta-potential) and magnetic field-gradients from different shapes, shown schematically in Fig. 1.

Comparing a spherical nanoparticle with a nanorod, the field gradient is uniform for a spherical shape, while a rod exhibits a strong axial field gradient at the ends of its long axis. Consequently, it is easier to affect nanorods with an external magnetic field [11]. Both the size and shape of the nanoparticle drug carrier need to be tailored to the intended target location.

Part 3) Nanoparticle synthesis and surface functionalization

The general design of a drug carrier is shown schematically in Fig. 2. Synthesis of the magnetic core, e.g. Fe_3O_4 nanoparticles, can be done using a number of methods (co-precipitation, hydrothermal, sol–gel, microemulsion, and sonochemical synthesis [17]). The typical method for Fe_3O_4 nanoparticles

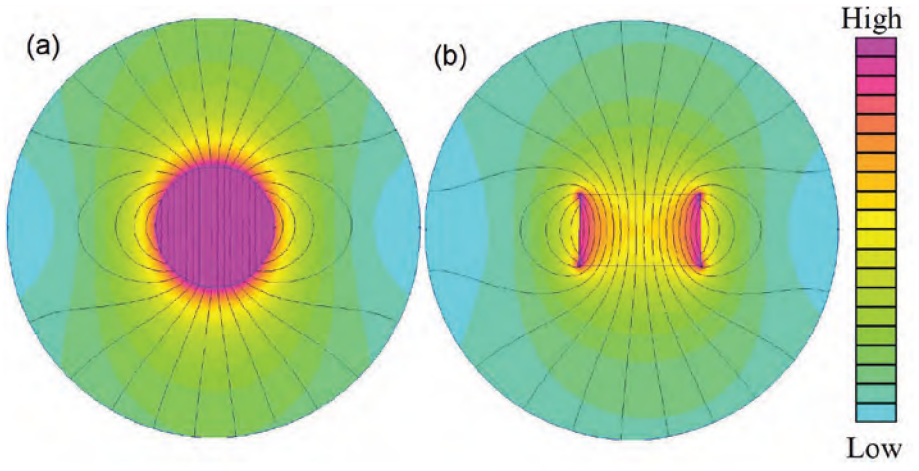

Fig. 1 Magnetic field profiles of (a) spherical and (b) rod-shaped nanoparticles.

synthesis is co-precipitation, pioneered by Massart [18] which is one of the best ways to prepare nanoparticles for drug delivery in gram-scale quantities.

A schematic of the co-precipitation synthesis procedure is shown in Fig. 3. In brief, in this method, Fe_3O_4 nanoparticles are synthesized by mixing an alkaline solution (NaOH, NH_4OH, etc.) with a solution of Fe^{2+} and Fe^{3+} salts (1:2 molar ratio) in the pH range of 8–14. A number of factors determine the final nanoparticle size, such as reaction temperature, mixing rates of the base and salt solutions, the pH of the mixed base-salt solution, and the ratio of Fe^{2+} and Fe^{3+} salts [17,19].

The co-precipitation reaction of Fe_3O_4 proceeds via two stages: 1) nucleation, and 2) growth. The nucleation process is short-lived ($\sim$2 minutes) [19]. A recent report [19] shows that an unstable gel-like network structure is formed at this stage along with aggregates of $\sim$2 nm primary particles. These primary particles mostly consist of iron (hydr)oxide with a Fe^{2+} and Fe^{3+} ratio of $\sim$0.55 [19]. After a few more minutes, these aggregates start growing bigger to form spherical Fe_3O_4 nanoparticles.

Nonspherical nanoparticles (rods, cubes, plates, rings, etc.) can be synthesized using methods like hydrothermal/solvothermal, vapor-phase, thermal decomposition, and polyol [16,17,20]. While the typical synthesis of non-spherical nanoparticles use template-based methods, a non-template based method such as hydrothermal is quite useful for a precise control over the shape of nanoparticles [16,17,20]. This method uses solutions of metal salts subjected to high vapour pressure and temperature (100–250 °C, typically) [17].

Once synthesized, the nanoparticles are coated to prevent agglomeration and allow later attachment of drug molecules via covalent and hydrogen bonds [10,11]. Some commonly used coating materials are carbohydrates (dextran), polymers (polvinyl alcohol), proteins (albumin), gold and silica [10].

The next step in the formation of a drug carrier system is the bonding of a multifunctional linker molecule to the coated nanoparticle surface (typically a bidentate organic molecule). This linker molecule is then used to attach drugs or active biomolecules to the surface of a nanoparticle structure via strong bonding interactions, like dative or hydrogen bonding. The linker molecules chemical functionalities are used to couple the iron-oxide nanoparticle (drug carrier) to the biologically active molecule, and include amines ($-NH_2$, -NHR, $-NR_2$) to form amides with carboxylic acids (-COOH), and aldehydes (-CHO) forming imide with amines ($-NH_2$) [9]. The linker functionality is decided based on the corresponding chemical functionality of the binding site on the drug to be delivered. For example, folic acid is used to target folate receptors, and chlorotoxin when gliomas and neuroectodermal tumors need to be targeted [21].

Evading, Targeting and Releasing

The body's immune system presents the first impediment to the nanoparticle-based drug delivery system. In order to physically reach the target site, these nanoparticles are directed using physical (heat, light, magnetic field), chemical (site specific prodrugs) and biological (antibodies, peptides, proteins) means [7]. The final task is to release the drug at a prescribed rate [22]. It is often preferred to have a release mechanism governed by an external stimulus (i.e. heat or an alternating magnetic field). Poly (N-isopropylacrylamide) [p-NIPAAM] is one of the preferred polymers for controlled drug delivery because it exhibits a very sharp phase transition, known as lower solution critical temperature (LSCT), between 298–310 K. Below the LSCT, the polymeric chains are hydrophilic, and remain

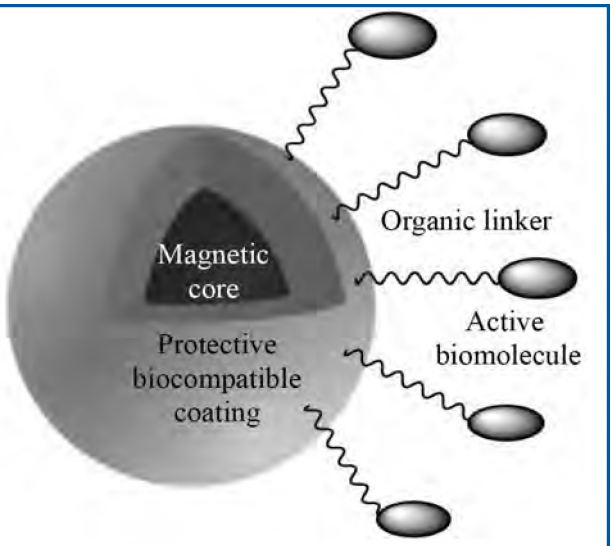

Fig. 2 Schematic of the components necessary for the design of a bio-compatible magnetic nanoparticle.

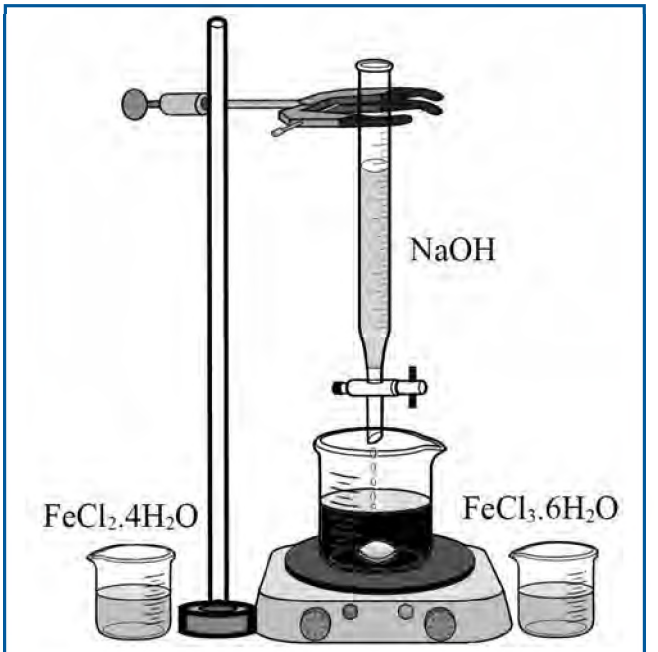

Fig. 3 A schematic illustration of the co-precipitation set-up in a laboratory. Here, NaOH solution is added dropwise to a mixture of Fe^{2+} and Fe^{3+} salt solution, producing black coloured Fe_3O_4 nanoparticles.

hydrated and swollen [21]. However, above the LSCT, the chains become hydrophobic and dehydrated. Therefore, if the final coating of the drug delivery nanoparticle is p-NIPAAM, a small amount of heat or an AC magnetic field (providing inductive heating in a manner similar to hyperthermia) [23], would trigger the release of the drug in the coating.

NANOSTRUCTURED PERMANENT MAGNETS: MANUFACTURE AND DESIGN FROM THE BOTTOM-UP

The essential purpose of a permanent magnet is to produce a strong magnetic field without an additional expenditure of energy. The classic 'refrigerator magnet' is such a permanent magnet, as opposed to a solenoid which requires an electric current. To be a permanent magnet, a material must have 1) a large and stable magnetization, preferably large atomic moments, combined with 2) a single spatial alignment of their spin orientations (e.g., a uniaxial anisotropy). Shown in Fig. 4 is a typical response of the magnetic induction (B) of a permanent magnet to an applied field (H). The standard figure of merit for a permanent magnet is the energy product (abbreviated $(BH)_{max}$), which describes the maximum (magnetostatic) energy that the magnet can store.

To achieve the largest possible overall magnetization one needs the largest possible atomic moments. This calls for a metallic system to be used. Metal ions surrounded by non-metallic neighbours (such as oxygen-ions in the transition metal oxides) suffer quenched orbital moments as the 3d electrons are quite localized about the nucleus, and the associated "circulating currents" from the moving electrons are fragile and easily affected by the associated crystal field effects (due to Coulombic interactions between neighbouring atoms). Moving away from this super-exchange based magnetism, to exchange based magnetism, with transition metal ions, in bands (metallic magnetism, like that of Fe metal discussed above) permits one to take advantage of the resulting delocalized electronic configuration about the atoms. Previously localized 3d electrons are pushed into a band that is superposed onto the 4s band, while crystal fields (charge distributions creating electric fields) enable this intermixing, and larger spin and orbital moments are accessible.

The directional dependence of the magnetic response (magnetic anisotropy) is essentially the reaction of the atomic moments in different crystallographic positions in a material when exposed to an external magnetic field. The spin part of the moments are coupled to the electronic orbital shapes and orientations (spin-orbit coupling) and the chemical bonding (facilitated by the bonding and antibonding of states near the bands) of the orbitals with the crystal field. Thus, to achieve an optimal magnetic anisotropy necessitates positioning the atoms and their electrons so as to generate the best possible anisotropy.

A Brief History

The 20th century was a period of substantial advancement in the design and production of permanent magnets, which helped to drive numerous technological developments. Permanent magnets usefulness ranges from the trivial refrigerator magnet to the ubiquitous computer, to wind powered turbines, to electric motors [24,25]. Improvements hinged on the development of new and better materials (by exploring a variety of

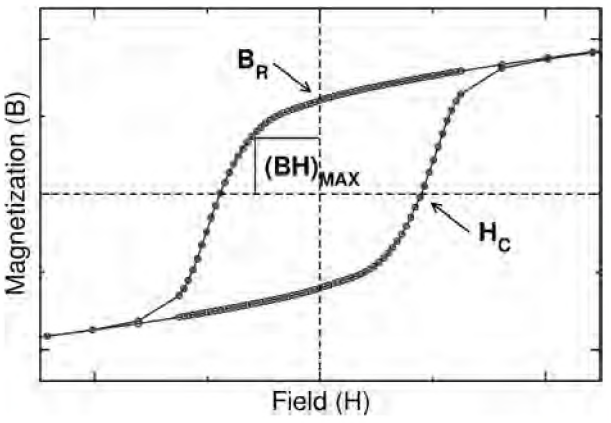

Fig. 4 Hysteresis loop describing the magnetic response of a typical permanent magnet to an applied field.

composition and structures) and by achieving control of the microstructure (e.g., grain size and morphology).

Fe-based steel alloys were the majority of permanent magnets in the first half of the 20th century. The tuning of the electrons' behaviour and resulting magnetism for these materials was limited by the understanding of quantum mechanics and magnetism at that time. Despite Fe atoms having what we now know to be a reasonably large moment, such magnets suffered low $(BH)_{max}$ values as the crystal field effects in these alloys are weak, resulting in low anisotropies. The first notable improvement in permanent magnet $(BH)_{max}$ was in 1931, with the discovery of Alnico. This family of metal alloys (based on aluminum, nickel, cobalt and iron) is an excellent example for the importance of both composition and microstructure in permanent magnets [26,27]. The transition metal ions are in special configurations that permit quite large spin moments, and their spin-orbit interactions with local neighbours permit

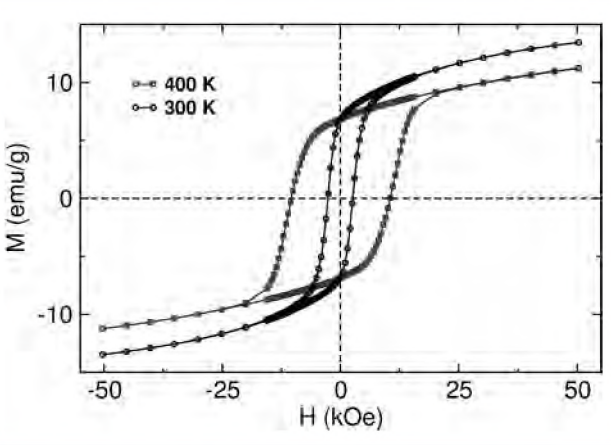

Fig. 5 Hysteresis loop of MnBi made from nanoparticles.

larger anisotropies. In addition, Alnico made as a mixture of nanometer-sized grains of Fe (or Fe/Co) surrounded by a weakly magnetic NiAl matrix (formed by a spinoidal phase separation during processing) permitted much larger $(BH)_{max}$ values. The early Alnicos ($\sim$1 MGOe) were improved to $\sim$5.5 MGOe in the 1930s [26,27].

The 1960s ushered in the era of the strong permanent magnet. $SmCo_5$ was the first compound discovered. Based on metallic Co, these magnets have an intrinsically large magnetization, where exchange coupling with the rare earth element Sm, which has a large unquenched orbital angular momentum, results in a huge intrinsic magnetic anisotropy. Refinements to these magnets resulted in $(BH)_{max}$ values up to 20 MGOe [28]. The high cost and the unpredictable supply of Co during the 1970s, due to geopolitics, re-energized the development of Fe-based magnets.

In 1982, $Nd_2Fe_{14}B$ was discovered [29,30]. Fe, whose 3d electrons ferromagnetically coupled to the 4f electrons of Nd, results in both a large magnetization and a large anisotropy. A small amount of B provides a crystallographic stability, and additional Dy increases high temperature performance by increasing the magnetic ordering temperature. From the 1980s to 90s, $Nd_2Fe_{14}B$ was studied extensively, and microstructure refinement (e.g. grain growth and orientation) led to the current optimal $(BH)_{max}$ of $\sim$60 MGOe [31]. The discovery of $Nd_2Fe_{14}B$ impacted many industries, and the excellent magnetic properties have led to $Nd_2Fe_{14}B$ being the most widely used permanent magnet material to date.

Currently, history is repeating itself as the geopolitical climate causes concern over many rare-earth elements supply chains. Since 2009 with the arrival of the "rare-earth crisis" [32], increasing research focus has been placed on finding new "rare-earth free" permanent magnets.

Planning and Constructing Hard Magnets

The "top-down" approach used for magnet research and development of lodestones up through modern rare-earth permanent magnets has limitations with regards to materials combinations and microstructure control, and therefore what can be realized in overall magnetic properties. Researchers are turning to nanoparticles to address these technological boundaries. Inherent to their size, nanoparticles offer the direct control of composition and microstructure from the "bottom-up" in magnet constructions [25,33]. In particular, the coercivity will increase as the particle size is decreased, with an optimal size depending on the material (e.g., $\sim$10 nm for Fe, $\sim$20 nm for cobalt-rich grains in Alnico). However, when the grains become too small, the energy required to reverse the magnetization may be overcome merely by the thermal energy. When this occurs, the nanoparticle becomes "superparamagnetic" ("super" since the entire magnetization of the particle acts together by comparison with the single atomic moments in a typical paramagnet, yet presents similar magnetization vs field behaviour) and the coercivity becomes zero. Achieving a

delicate balance of grain structure is necessary both in traditional "top-down" approaches, where particle size is controlled indirectly (e.g., by the nature of the alloying mechanisms, or post-synthesis processing like mechanical grinding), and in the "bottom-up" approach using nanoparticles. A considerable advantage of the "bottom-up" approach is the direct control of the grain size necessary for good performance.

Making rare-earth-free permanent magnets using nanoparticles of MnBi

The intermetallic alloy MnBi has been a highly sought "rare-earth free" permanent magnet for over 60 years [34]. When formed in the "low-temperature-phase" (LTP), MnBi has a very large magnetic anisotropy at room temperature that uniquely increases with increasing temperature due to the nature of subtle temperature-dependent changes in the atomic (crystalline) configuration that alter the crystal fields about the atoms. Because many commercially important applications of strong permanent magnets are above room temperatures, LTP-MnBi promises excellent performance at elevated temperatures for uses such as electric motors in cars, generators in turbines, and solenoids in aircraft (potentially replacing the heavy pneumatic control systems used currently). Because of this, substantial efforts by researchers around the world have been directed toward the formation, purification, and large-scale production of LTP-MnBi. However, producing the LTP form of MnBi has proven to be extremely difficult. This is due to two primary aspects of the constituent metals: 1) The peritectic interaction of molten Mn and Bi, and 2) The slow inter-diffusion of Mn and Bi. Historically, these impediments to the successful synthesis of LTP-MnBi have retarded the subsequent understanding of the physics behind the magnetism in this compound. Approaches from mechanical grinding and ball milling, to arc melting and rapid solidification, have seen limited success. This necessitates novel approaches to overcome the materials challenges associated with LTP-MnBi.

We have turned to a "bottom-up" approach using a new wet chemical synthesis method because of these challenges. Fundamentally, nanoparticles are synthesized by the reduction of metal ions in the presence of a surfactant. However, the reduction potential of Mn is too high for such an approach to be practical, so an alternative method is needed. Using a manganese "ligated anionic element reagent complex" (Mn-LAERC) [35,36] to reduce bismuth ions, while simultaneously depositing Mn atoms at room temperature, produces nanoparticles of Mn, Bi and a ferromagnetic MnBi phase, which can then be conveniently annealed to form the desired LTP-MnBi. The hysteresis loops measured at 300 and 400 K show [Fig. 5] the suitability of MnBi nanoparticles for applications as hard magnets.

Importantly, new chemistries have been developed to access challenging metal alloys, in nanoparticle-sizes. Such advancements allow the physics of the nanoparticle magnetism to be investigated and understood, improving the state of the art for a critical magnetic material.

CONCLUSIONS

The present article provides an overview of the strategies involved in designing nanoparticle systems for targeted drug delivery and hard magnets. We have discussed how understanding and tuning the behaviour of atom's electrons, the primary source of magnetism, are the tools necessary for creating materials suitable for an application. The study of nanomaterials has flourished because properties at the nanoscale can produce phenomena that are not otherwise accessible at bulk macroscopic dimensions. But, nanoscale-based magnets require a detailed understanding of the physics to enable the requisite control over atomic electron configurations to achieve the desired magnetism. Such mastery manifests in the laboratory as pushing electrons and atoms around, finally assembling them into nanoparticles, and beyond. From the applications view-point, for nanoparticle-based drug delivery, the amount of drug delivered to targeted cells is typically around 5% [8], which points to the lack of understanding of all the actual mechanisms by which drug carriers interact with a body's cells and organs. Moreover, all the steps involved in the delivery of any drug to the targeted cells are not well characterized for any particular nanocarrier and drug, currently. A plethora of reports are available, but a systematic approach to this challenge has yet to be developed. For permanent magnets, the use of nanoparticles has resulted in novel avenues towards material synthesis (such as with MnBi), the realization of hard/soft material combinations (to take advantage simultaneously of magnetization of one material and the anisotropy of another in one nanostructured magnet), and as a means to control directly the grain structure in traditional materials. Currently, the development of permanent magnets using a nanoparticle-based approach is the focus of substantial ongoing research, and is considered a promising route towards the next generation of permanent magnets.

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