Clinical Applications of Magnetic Nanomaterials

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Abstract—This paper outlines the various clinical applications of magnetic materials in medicine. A historical introduction is provided. Modern applications are the discussed. Many novel approaches are described in the use of magnetic materials in cell separation, immunoassay, as contrast agents in magnetic resonance imaging, drug and gene delivery, minimally invasive surgery, radionuclide therapy and hyperthermia applications.

Keywords—Magnetism, drug targeting, gene therapy, MRI

I. INTRODUCTION

Historical: The diverse applications of magnetism and magnetic materials in medicine have been compiled [1]. The first medical references of using magnetism was made by Hippocrates of Cos (460-360BC). Lodestone, a natural iron core in the chemical form of FeO·Fe₂O₄ (Fe₃O₄) or magnetite, was first medically used to stop bleeding and control hemorrhage. Most ancient medical applications of the lodestones were external. It was either used as the unbroken form of lodestone or in pulverized form of powders. The lodestone was then bound directly to the affected part of the body. This technique was thought to be effective in the treatment of arthritis, gout, poisoning and baldness.

The internal use of magnetite was first introduced by Egyptian physician Avicenna (980-1037). He suggested taking a one-grain-dose of magnetite to treat accidental swallowing of poisonous iron, i.e. rust. This antidote, made up of pulverized magnet together with milk, was believed to make the poisonous iron inert through attracting it and accelerating its excretion through the intestine. An added consequence to making it an effective remedy was due to the fact that it also induced vomiting. Albertus Magnus (1200-1280) used the same formula to treat edema.

The first surgical use of lodestone was believed to be made by a Hindu surgeon Sucruta (~600BC). In his book “Ayu-Veda”, he wrote that magnet can be used to extract an arrow tip. Kirches recommended in 1640 that iron filings could be fed to a patient with hernia, and with an external magnet placed appropriately, the iron could be attracted thus drawing in and restoring the position of the intestine. In subsequent years, medical applications of magnets came to include the removal of iron particles embedded in the eye. In 1627, Wilhelm Fabricius performed the first case of iron splinter removal from an eye chamber. Since then, the use of magnet has become the established procedure for the removal of magnetic objects from the interior of the eye.

II. MODERN APPLICATIONS

Different types of magnetic particles have been used for a variety of applications in biosciences and biotechnologies, for example in immunomagnetic separation of microorganisms in food and clinical microbiology as reviewed by I. Šafarík [2].

A. Immunomagnetic separation of cells
In this application, a ligand is coupled to the magnetic nanoparticles and is applied directly to the sample of cells. During incubation, the magnetic particles are bound to the target cells, and thus stable magnetic complexes are formed, they can then be separated using an appropriate magnetic separator. Magnetic nanoparticles used to label the cells have no negative effect on the viability of the attached cells, and the isolated cells remain phenotypically unaltered. Due to its small size, it is able to avoid mechanical stress for the cells. The particles form a stable colloidal suspension and do not sediment or aggregate in magnetic fields.

B. Determination and detection of biologically active compounds
Magnetic modifications of standard immunoassays can be successfully used for the determination of various biologically active compounds. Specific antibodies or antigens are immobilized on the magnetic particles by chemical bonding. Magnetically based assays are faster than the standard microtitration plate based assays.

C. Immobilization and modification of biologically active compounds
Biologically active compounds immobilized on magnetic carriers can be removed from the system by using an external magnetic field or can be targeted to the desired place. They can be used to express their activities in the process or can be used as affinity ligands enabling the capture or modification of the targeted molecules or cells. This technology can be used to modify antibodies. Magnetically-labelled antibodies have been proposed for clinical applications as a therapeutic agent for the induction of hyperthermia.

D. Contrast agent for MRI investigations
Magnetic particles are being increasingly used to improve the contrast in MRI studies. The use of dextran coated superparamagnetic iron oxide has been shown to be extremely effective as a T2 proton relaxation enhancer, it may be recalled that magnetic relaxation in MRI is characterized by the time constants T1 (longitudinal) and T2 (transverse). Thus magnetic particles can be used as a source of exogenous contrast.

E. Magnetic fluid hyperthermia
Hyperthermia is a promising approach to cancer therapy. It is based on the heating of the target tissue to slightly above body temperature. This can generally reduce the viability of cancer cells and increasing their sensitivity to chemotherapy and radiation. This technology is based on the fact that magnetic particles produce heat through various kinds of energy losses during application of an external AC magnetic field [3].

III. MAGNETIC DRUG TARGETING
In targeted drug delivery or drug targeting as it is commonly called, drugs are directed to cells that need therapy or repair, such as in cancer treatment. Effective treatments of cancer involve either surgery, radiation, immunotherapy, chemotherapy or a combination of these choices. Chemotherapy is useful mostly for disseminated cancers and is often used in combination with the 3 other choices of therapies. Patients receiving chemotherapy treatments often have to suffer many adverse side effects due to a decrease in host defense mechanism against infection as cancer treating drugs are delivered to both the healthy and diseased cells during treatment. Drug targeting which has been an active area in cancer research serves to provide a solution to eliminate these problems.

In drug targeting, the drugs required for treatment are brought to the diseased area and released specifically at that region only. In this way, the drugs would interact only with the diseased cells. Not only can side effects be reduced; this ensures that maximum amount of drugs reached the diseased area eliminating drug wastage.

Using magnetic drug carriers is one method of drug targeting. In this technique, a powerful external magnet is placed over the tumor. After being injected into the bloodstream, the magnetic drug carriers would be pulled by the magnetic field into the tumor region (Fig 1).

Magnetic drug targeting was pioneered by Dr. Kenneth Widder from the United States. Magnetite(Fe₃O₄) together with drugs were formed into albumin coated microspheres. In vivo tests were carried out on rats with tumors, with results showing that more than half of the injected microspheres was retained in the tumor. However, due to the insufficient magnetic susceptibility of Fe₃O₄, the albumin microspheres could not be used for tumors below the body surface.

Fe₃O₄ magnetic carriers have been used commercially in cell separation and protein analysis. The beads are made up of Fe₃O₄ and Fe₃O₄ particles coated with a thin polymer layer and the sizes ranged from approximately 2.5 to 4.5µm [5]. A range of magnetic microspheres have been Streptavidin coated or carboxylate modified to allow binding of proteins on the surface[6].

Another approach in drug delivery is to use microspheres which are made up of metallic Fe and activated carbon. While pure Fe exhibits high magnetic susceptibility, activated carbon has the ability to absorb drugs and release them over time upon entering the body. Preclinical trials on these carriers are planned for treating liver, bladder cancer and gastrointestinal disease.

Success had been achieved by such drug targeting through clinical trials, further opportunities still exist due to the following technical challenges: the rapid separation of drugs from the carrier, the removal of the carriers from blood circulation before reaching the targeted area, since the body identifies intravenously injected particles as foreign. Coating sufficient amount of drugs on the carrier without significantly increasing the size of the microspheres is also yet another challenge. Strong permanent magnets need to be

**Fig 1: Magnetic drug targeting (from [4])**

constructed for providing the magnetic field required at the target site. Not only must the magnet be able to maneuver the magnetic particles against blood flow, it must be high enough to keep the particles magnetized at regions far from the body surface. Fig. 2 shows an example of polymer coated magnetic microspheres for drug targeting applications [7].

**IV ARTIFICIAL MUSCLE**

There have been various attempts to synthesize artificial muscles and many approaches have been developed starting from a robot-like metallic actuator to a more advanced soft actuator. Selected novel approaches to soft actuators are listed here.

Most smart gels are relatively homogenous materials that shrink or swell uniformly, with no dramatic change in shape. But Li et al made gels whose composition is engineered so that, in response to a specific stimulus, they spontaneously bend into a predetermined shape such as a letter of alphabet, a spiral, etc [8].

Two polymers with different sensitivities, PNIPA and polyacrylamide, were employed. The gels (bigel strips) are synthesized in such a way that across the thickness of the gel, its composition changes gradually from pure polyacrylamide to a mixture of polyacrylamide and PNIPA to pure PNIPA. PNIPA shrinks drastically when warmed above 37°C, whereas polyacrylamide shrinks much more than PNIPA when the acetone concentration of the medium increases beyond 34%. Thus, by choosing the appropriate temperature and solvent conditions, the bigel strips can be made to bend into a predetermined shape. The shape changes are reversible.

The picture below shows the examples of the bigel strips. The black bar represents 10 mm. Several of these bigel strips can be joined to make a gel “hand” that grasps objects with its bigel “fingers” and releases them in response to stimuli.

**Fig 3  Bigel strips for artificial muscle application [8]**

The discontinuous volume phase transition in response to external stimuli permits gels to be employed as muscle-like soft actuators. However, the structural changes of gels (shape and volume) are kinetically restricted by diffusion, which is a slow process.

In order to accelerate the response, M. Zrinyi et al developed magnetic field sensitive gels in which magnetic particles of colloidal size are dispersed and incorporated into the gels [9]. These ferrogels then couple the magnetic properties of magnetic fillers and high elastic properties of hydrogel. Thus, shape distortion occurs instantaneously and disappears abruptly when the external magnetic field is applied and removed. The following figure shows the shape distortion (bending) of ferrogel due to nonuniform magnetic field.

**Fig 4  Shape distortion of ferrogel due to nonuniform field [9]**

They then found that when the gels were placed into a spatially nonuniform magnetic field, forces act on the magnetic particles and as a result of strong interaction between magnetic particles and polymer chains, they all move together as a whole.

We have performed some preliminary experiments using solenoids wound around a “finger” prepared from PVA hydrogels loaded with magnetic particles. A solenoid was formed by winding a long wire in the form of a helix. The magnetic field in the interior of a solenoid is measured by the following equation derived from Ampere’s law (\( B = \mu_0 (N/l)I = \mu_0 nI \)) where \( B \) is magnetic flux, \( \mu_0 \) is the permeability of free space, \( N \) is the number of turns in the length \( l \) such that \( n = N/l \) and \( I \) is the current. In order to create different magnitude of magnetic flux at different locations in the artificial finger, separate solenoids were wound on the artificial finger so that it would bend.

V GENE DELIVERY

Magnetic particles can be used as a novel and effective method of enhancing and targeting nucleic acid delivery [10]. One of the primary reasons for the limited efficacy of nucleic acid delivery systems is insufficient contact with target cells. This can be overcome by physical methods of targeting. Nucleic acid vectors are associated with magnetic particles and magnetic fields are used to mediate the rapid contact of these vectors with the target cells. This technique called magnetofection is applicable to viral as well as non-viral vectors. Other key advantages are that saturation level transfection is achieved at low dose, that it is fast and simple.

V CONCLUSIONS

The above discussion clearly shows the wide variety of both conventional and magnetic biomaterials. The applications discussed in this paper include cell separation, immunoassay, magnetic resonance imaging, drug and gene delivery, radionuclide therapy, hyperthermia and artificial muscle applications. Intense research in these areas is expected to widen and deepen the use of such magnetic materials.

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REFERENCES
