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Magnetisable Implants for Targeted Drug Delivery System

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ABSTRACT

The capability to deliver high effective dosages to specific sites in the human body has become the holy grail of drug delivery research. Drugs with proven effectiveness under in vitro investigation often reach a major roadblock under in vivo testing due to a lack of an effective delivery strategy. The review article focusing on targeted drug delivery by applying high magnetic field gradients within the body to an injected super paramagnetic colloidal fluid carrying a drug, with the aid of modest uniform magnetic field. A new method for locally targeted drug delivery is proposed that employs magnetic implants placed directly in the affected area to attract injected magnetic carriers. Theoretical simulations and experimental results support the assumption that using magnetic implants in combination with externally applied magnetic field will optimize the delivery of magnetic drug to selected sites within a subject.

KEYWORDS

Drug delivery; Magnetic implant; Local drug delivery; Targeted

INTRODUCTION

The ability to safely and effectively deliver high dosages of drugs to specific sites in the human body is fundamental to the advancement of drug delivery based therapeutic strategies. Drugs with proven effectiveness under in vitro investigation often reach a major roadblock during in vivo testing due to a lack of an effective delivery strategy. In addition, many clinical scenarios require delivery of agents that are therapeutic at the desired delivery point but otherwise systemically toxic. Thus the ability to adequately localize injected drug is paramount to an effective drug delivery strategy.

The development of more effective drug treatment methodologies is an area of much research. In most drug delivery systems much of any drug administered to patients does not reach its target site.

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The aim of the drug targeting is to decrease the amount of drug delivered to healthy tissue, while maintaining the therapeutic action at the desired site. One such approach is magnetic drug targeting (MDT). For instance magnetic particles can be employed as carriers in a cancer treatment, thereby avoiding the side effects of conventional chemotherapy. MDT typically uses an external magnetic field source to capture and retain magnetic drug carrier particles (MDCPs) at a specific site after being injected into the body.

Various nonmagnetic micro carries are successfully utilized for drug targeting but they show poor site specificity and are rapidly cleared off by reticuloendothelial system (RES) under normal circumstances. Magnetism play an important role in these case, magnetic particles composed of magnetite which are well tolerated by the body, magnetic fields are believed to be harmless to biological systems and adaptable to any part of the body. Up to 60% of an injected dose can be deposited and released in a

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controlled manner in selected non reticuloendothelial organs. So, magnetic microcarriers were developed to overcome two major problems encountered in drug targeting namely RES clearance and target site specificity. This review article discusses the potential applications of magnet in drug targeting, magnet containing particles & mechanism of targeted drug delivery by magnetism.

High gradient magnetic separation (HGMS). When a ferromagnetic element (e.g., an implant) is placed in a magnetic field, it becomes magnetically energized creating a very strong but localized magnetic field that is far more capable of concentrating magnetic particles at the site of the implant compared to the magnetic field alone.

Invasive magnetic implants can be made of needles, wires, stents, catheter tips, and even very magnetic (non-drug carrying) particles. Wires can also be placed just outside the body near the target zone to improve the collection efficiency of the MDCPs.

Popular cancer drugs have been found to have applications in many realms of clinical medicine. The best approach for treating tumours and other localized medical defects is to administer drugs only at the site of complication. By delivering the drug locally, the toxicity of the drug to the rest of the body can be reduced while maintaining the desired therapeutic benefit at the site of interest.

MAGNET SETUP

A photograph of the bulk-type superconducting magnet system used in this experiment is shown in figure 1, while more details are shown in figure 2. The SmBaCuO and YBaCuO bulk superconducting magnet was of cylindrical shape (diameter: 45mm and thickness: 15 mm). Magnetization was performed by the pulse magnetization method (PMM) that can be done with copper wire. The bulk superconductor can generate a strong magnetic field in an open space up to the maximum values shown in figure 2. Clearly, very strong magnetic fields can be generated by bulk superconducting magnet, so using this type of magnet can be a promising technology for realization of MT-DDS.

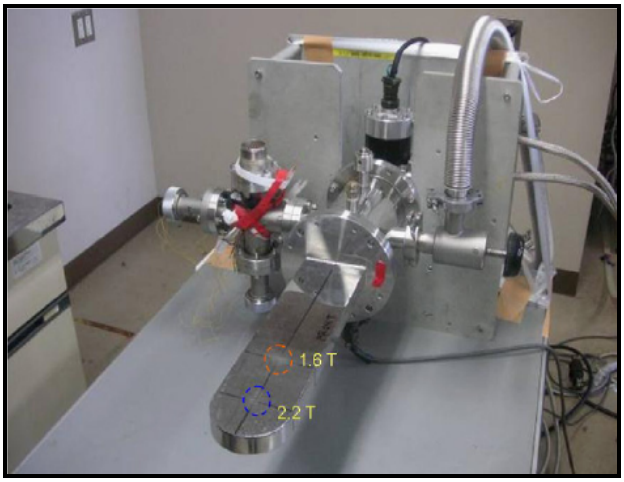

Figure 1: photograph of the SmBaCuO and YBaCuO bulk superconductor

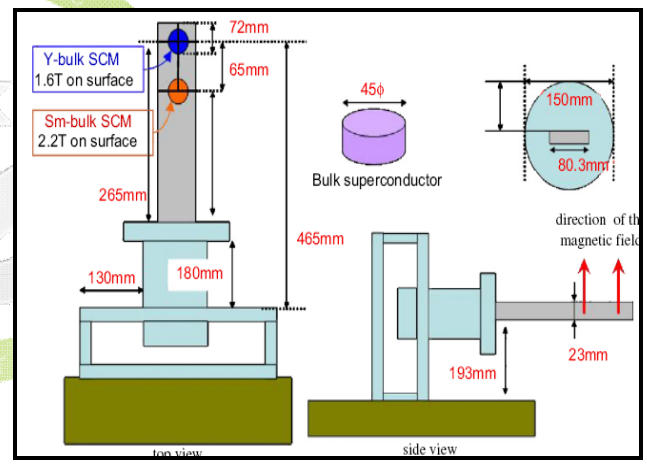

Figure 2: schematic of the SmBaCuO and YBaCuO bulk superconductor

DESIGN FOR THE MAGNETIC TARGETING

One possible approach to this problem is to use magnetic material embedded in blood vessel walls as the source of strong localized magnetic field gradients at defined locations in the body. The proposed design involves seeding magnetic particles onto blood vessel walls at designated sites through specific receptor-ligand recognition typical techniques for drug delivery involve saturation of site receptors with an

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appropriate ligand chemically attached to a desired drug.

In contrast with these techniques, this method relies on saturating receptors with inert superparamagnetic particle anchors coated with specific ligands for the site of interest (containing no drug). High concentrations of anchors can be applied to saturate receptors without fear of harmful side-effects. One can also imagine scenarios in which magnetic anchors can be implanted in blood vessel walls through catheter based insertion methods. Once the anchors or implants are in place, uniform magnetic fields may be used to attract an injected drug-infused superparamagnetic colloidal fluid to the anchored particles, thereby allowing high local concentrations of otherwise systemically toxic drugs to be captured at the site of interest.

MAGNETIC IMPLANT FOR LOCAL DRUG DELIVERY

The therapeutic agents that can be delivered to the implant by this method include Pharmaceutical drugs, radioactive polymers, an cells. For example, in the treatment of coronary atherosclerosis. This drug delivery system could also offer significant benefits in the treatment of hepatic, renal, pancreatic, prostate and other cancers where the ability to provide multiple doses is of enormous importance. It may be possible to adapt currently used devices, such as the FDA approved coronary stent, with a pattern of magnetic material to attract magnetic drug to its surface.

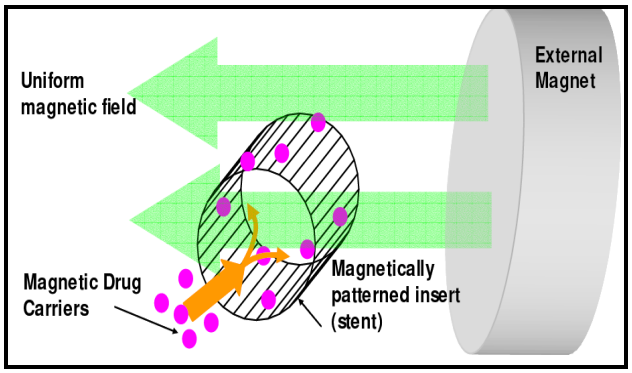

Figure: 3 illustration of the magnetic targeted delivery

MATERIAL SELECTION FOR MAGNETIC IMPLANTS

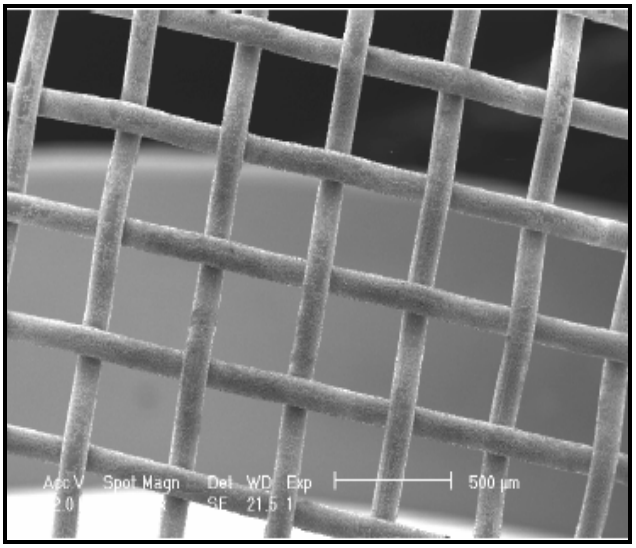

Figure 4: This SEM image depicts the stainless steel mesh electroplated with cobalt- Nickel alloy that was the sole source of magnetic field gradients in experiments

To simulate a stent-like surface as a plane instead of a circular cross-section, the first material selected for electroplating was a woven, 316L stainless steel wire mesh (140µm wire diameter, 400µm apertures). This particular material was selected due to its large strut spacing, and extremely low saturation magnetization. As a result, a large difference in response to applied magnetic fields, and subsequently in capture ability, can be compared between a virtual non-magnetic 316L mesh and a CoNi electroplated 316L mesh. This can be seen in figure 4. The second stent-like material selected was a molded 304 grade stainless steel (150µm wire diameter, 450µm apertures). This material has a more level, consistent surface, as opposed to a woven geometry. In addition, it has stronger inherent magnetic properties than 316L steel. This can be seen in figure 5.

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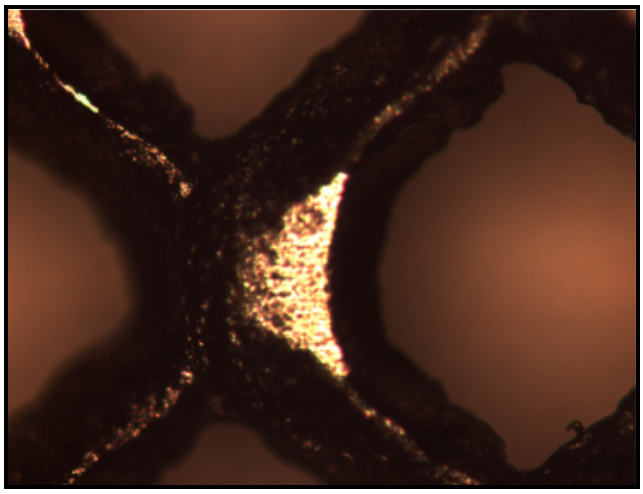

Figure 5: Photograph of 304 Stainless Steel Mesh

With the aid of the Drexel Machine shop, stent-like tubes of this 304 steel were rolled by heating the mesh, and sealing the roll using silver solder. Tubes were rolled to a 5mm external diameter, 2cm in length. Which can be seen in Figure 6.

Figure 6: photograph of 304 Steel mesh as seen

The final material selected were industrial application 302 stainless steel compression springs (2cm long spring, 3mm diameter, 355µm wire diameter). These springs are more stent-like in geometry and flexibility, but their wire diameter is 3-5 times thicker than struts in a typical stent. These springs are highly magnetic, and provide an upper bound for examining different alloys and their inherent abilities to capture particles under the application of external magnetic fields. An image of a 302 steel compression spring can. This can be seen in figure 7.

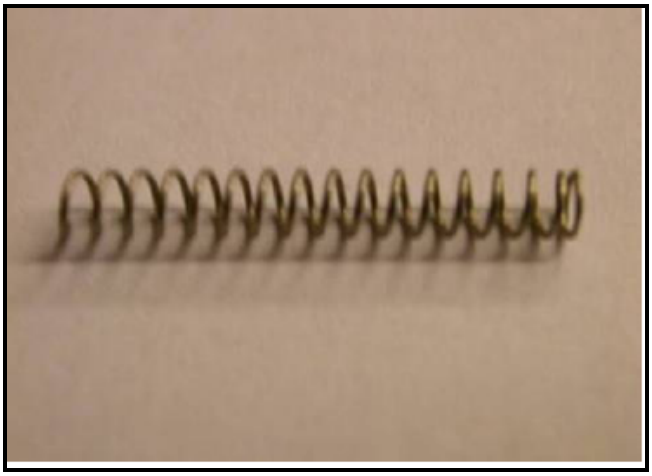

Figure 7: 302 Stainless Steel compression spring

METHODS FOR FORMULATION OF MAGNETIC IMPLANTS

The static magnetic properties of in-situ-formed implants based on the two formulations, hydro gel (Alginate2%w/V in water) or organogel (EVAL8%w/V in DMSO); with increasing magnetic micro particle concentrations appear to well correspond to the magnetic characteristics of the control magnetic particles.

The hysteresis loop so fall implants revealed similarities to those of the control sample, suggesting the preservation of the super paramagnetic behaviour of micro particles in the implants formed in situ. It is important to note that the curves were even more similar when the magnetization values were weighted by the mass of constituting magnetic microparticles (or iron oxide content) determined on the basis of weighing the injections .This was not the case when the magnetization values were weighted by the masses of the wet implants introduced in the SQUID.

The microchip delivery system consists of a substrate containing multiple reservoirs which are capable of holding chemicals in the solid, liquid, or gel form. Each reservoir is capped with a conductive membrane and wired with the final circuitry.

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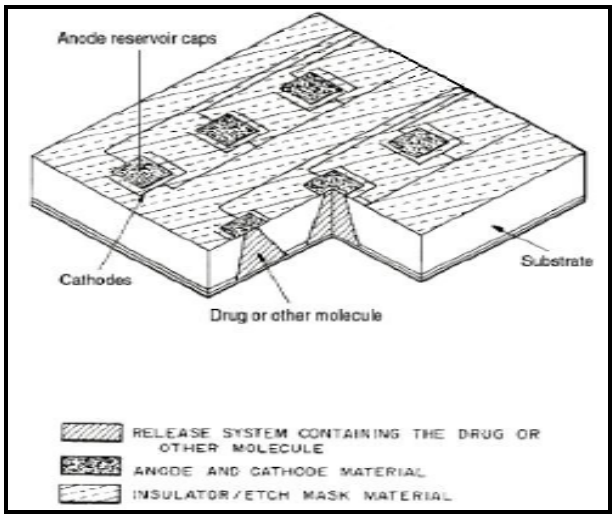

Figure 8: Schematic Representation of Microchip Design

This is controlled by a microprocessor. The central processor should be able to control electrically the exact time of release and the amount of drugs dispersed by controlling the dissolution of the gold membrane. The system should be reasonable to manufacture by standard micro fabrication techniques and should also be cost effective. (Figure. 8)

METHOD OF DEPOSITION OF MAGNETIC PARTICLES ON IMPLANTS

Electroplating is a process of depositing a coating (commonly) of silver, gold, cobalt, or nickel on an inferior metal, by means of electricity.

Electroplating Procedure

Before each electroplating session, a fresh bath was prepared. 100 mL of bath was prepared of the following makeup: 0.45 M NiCl2, 0.65 M CoCL2, 30 g/dm-3 H3BO3 and a trace of Saccharin.

The bath solution was placed in a 1L glass beaker, heated to 55ºC. A thermometer was stabilized for constant temperature measurement. An air bubbler, connected to the house air system, was fixed at the bottom of the beaker. A Princeton Applied Research 363 Potentiostat was used as the current controller for electroplating. To the anode an industrial-grade sheet of cobalt (EMI, CA) 2 x 2 inches in size was connected, and connected to the cathode was the piece of implant-simulating material.

In order to maintain reproducibility, it was entirely necessary to account for how much magnetic material was deposited on a given sample. While this can be calculated loosely by ion concentrations in the bath, the dimensions of the sample, and the applied current, some of these factors may be inconsistent. Plating height was determined by measuring the mass of the sample before and after plating, using a digital balance with a resolution of 10-5 grams. By using an air-bubbler, keeping the sample close to the anode, and rotating the sample 180 degrees at the half time mark of each plating session, it is most reasonable to assume near uniform plating. So assuming uniform plating, with knowledge of the geometry and dimensions of each sample, electroplating height was calculated.

The method for reproducing the same height in each session, was correlating the exact sample size, ion concentrations, and plating time. This was accomplished with ease due to the quality of the electroplating setup, and strict monitoring of these governing factors.

EVALUATION OF MAGNETIC PROPERTIES OF MODEL IMPLANTS

Magnetic properties of model implants were measured using a Princeton Measurements MicroMag Alternating Gradient Magnetometer (AGM).

The MicroMag AGM is a highly sensitive instrument for detecting changes in the magnetic properties of materials. 5mm circular punch-outs of each mesh were made using an industrial hole punch, as well as individual coils from the 302 compression spring. In order to normalize saturation magnetization to mass, each sample was weighed and its mass documented. A piece of mesh or spring was then mounted on the end of a cantilevered rod that incorporates a piezoelectric sensor (the perpendicular probe was selected). A dc field then magnetizes the sample while simultaneously subjecting it to a

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small alternating field gradient. This gradient exerts an alternating force on the sample, which is proportional to the magnitude of the field gradient and to the magnetic moment of the sample. The resulting deflection of the rod is detected by the piezoelectric element. Computer software then generates hysteresis curves and saturation magnetization data. Five samples of each material were measured by AGM, and the normalized results averaged to obtain Ms per gram data.

INVITRO EVALUATION

In all magnetic drug delivery systems, the magnet serves two purposes; first, to magnetize the drug, and secondly to provide magnetic field gradients to capture the drug. Although large magnets held near or implanted in the body provide strong magnetic fields to magnetize the drug, these large magnets inherently produce weak magnetic field gradients. On the other hand, micron-sized magnets provide very strong magnetic field gradients, however their fields are short-range and they cannot by themselves efficiently magnetize the drug.

By using micron-sized magnetic implants in combination with long-range magnetic fields, it is possible to both magnetize the drug and create strong magnetic field gradients for more efficient capture and localization of the drug.

Advantages

As implants are foreign bodies, and we know the body will always recognize them as such, there remains a long-term threat for future inflammation, thrombus formation, and other complications. The long shelf-life of controlled release spheres and non-drug-coated stents, compared to the expensively sterilized and briefly storable drug-eluting stents were other obvious benefits.

Proposed method for local drug delivery does not have to be disruptive, but rather complementary; meaning that it can be paired with drug-eluting stent technology to provide an enhancement for additional doses along the lifetime of the implant. Drug eluting stents are limited by some of their problems: complications related to implantation, cracking of the polymer layer, limited dose size, shelf life, and the fact that they can only provide a single dose. For the other uses of stents (biliary, renal, brain), pacemakers, and orthopaedic implants, a dose at implantation may not be necessary, making the addition of magnetic drug delivery functionality beneficial for prevention of complications in the future as needed. It also considered the use of endovascular and extravascular implants for treatment of localized tumors. Implants in these cases would have the sole or primary function of facilitating local magnetic drug delivery, and could be implanted by catheter, or in cases where open chest surgery is already required to excise tumors, implanted extravascularly over vessels or organs. This could provide a future option for local chemotherapy at the same site should carcinomas be found to be re-growing during remission.

Obviously the benefits of this system must not come at the cost of increased risk in other arenas, such as chemical tolerance of a magnetic coating or final compositions of polymer and magnetite crystals. As biocompatibility surely represent a roadblock in clinical testing, having flexibility in the design will make the system that much more attractive to industry. Development and in vivo testing of final designs should heavily extend efforts to construct a magnetic drug delivery system that will allow for safe and effective MRI procedures for patients receiving the implants.

CONCLUSION

This has provided a proof of concept to the proposed magnetically targeted drug delivery system. This system operates by first embedding magnetic implants, such as a stent; at designated sites in the cardiovascular system, and then attracting injected doses of magnetically susceptible drugs to those implant sites with the aid of a modest external magnetic field. Previous attempts to use magnetic particles in these applications have relied on high gradient magnetic fields produced by magnets external to the body to direct magnetic particles to specific

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locations. This limits the range of their applications. The main disadvantage of this approach is that externally generated magnetic fields apply relatively small and insufficiently local forces on micron and nano-scale magnetic particles. As a result, there has been great interest in devising systems that produce strong and highly localized field gradients in the interior of the body.

Rational magnetic implant design began with the selection of stent-simulating materials of different geometries, mesh sizes, and metallic content, suitable for in vitro flow experimentation. Stainless steel materials ranging from 316 to 302 grade were chosen, in grid-like mesh geometries, as well as in the form of a compression spring. A soft magnetic alloy of Cobalt-Nickel was selected as a practical material for increasing the saturation magnetization of the materials, while retaining a very low state of magnetization in the absence of an externally applied magnetic field. An electroplating setup was developed utilizing a cobalt anode, borate bath containing scaled concentrations of cobalt and nickel, and controlled by a potentiostat. By combining the use of very weakly magnetic materials (316L SS) and highly magnetic materials (302 SS) with varied plating heights of soft magnetic alloy, flow experiments were able to examine the scalability of magnetic capture over a range of saturation magnetizations.

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