Journal of Magnetism and Magnetic Materials 321 (2009) 1586–1590

Contents lists available at ScienceDirect

Journal of Magnetism and Magnetic Materials

journal homepage: www.elsevier.com/locate/jmmm

In vitro study of magnetic particle seeding for implant-assisted-magnetic drug targeting: Seed and magnetic drug carrier particle capture

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ARTICLE INFO

Available online 21 February 2009

Keywords:
Magnetic drug targeting
MDT
Drug delivery
High-gradient magnetic separation
HGMS
Ferromagnetic particle
Nanoparticle
Magnetite
Magnetic seed
Magnetic drug carrier particle

ABSTRACT

An implant-assisted-magnetic drug targeting system using seed particles as the implant to increase the capture of magnetic drug carrier particles (MDCPs) in capillary tissue was studied *in vitro*. Dextran-coated magnetite particles were used as seeds, polydivinylbenzene magnetite particles were used as MDCPs, and a polyethylene porous cylinder was used as surrogate capillary tissue. The results showed that seeds could be magnetically captured first and then used to magnetically capture the MDCPs, causing a significant increase in their collection compared to when the seeds were absent.

1. Introduction

Magnetic drug targeting (MDT) is based on using magnetic drug carrier particles (MDCPs) to selectively deliver drugs to a specific site inside the body by using an external magnet to attract and retain them there [1,2]. However, due to the short range of the magnetic force and the adverse effect of the hydrodynamic force, the progress of this approach has been stalled for more than three decades, leaving potential applications looming. Fortunately, the use of a magnetic implant to augment the magnetic force imparted by the external magnet has recently brought new light to MDT [4–17].

This new MDT approach is called the implant-assisted (IA) MDT and takes advantage of the fact that the magnetic force imparted on a particle (e.g., a MDCP) by a magnetic field depends on both the magnitude (H) and the gradient of the magnetic field (∇H) [3]. In IA-MDT, a ferromagnetic object, e.g., a wire, is placed inside the body at the target site. Under the influence of an external magnetic field, this ferromagnetic implant becomes magnetized, thereby locally increasing the magnetic force exerted on a nearby MDCP. The net effect is that the collection of the MDCPs at the desired site is greatly increased by the presence of this ferromagnetic implant compared to just using the external magnet alone. Several enlightening theoretical [4–12], experimental [11–15], and animal model [16,17] studies have been carried out recently using wires, stents, and even seeds as the implant for IA-MDT.

One of the more interesting approaches was associated with the use of magnetic particles as seeds for the implant [8,12,14]. Compared to wires and stents, which might require a more invasive procedure for implantation, these strongly magnetic seeds could simply be transdermally injected into or near a target organ or tissue prior to injecting the MDCPs. In contrast to the MDCPs, which are composed mostly of the polymer and drug, the seeds are composed mostly of the magnetic element. Hence, depending on their size or extent of agglomeration between them, each seed or cluster can serve as a localized magnetic element with elevated magnetic force density to assist in the collection of the MDCPs, even at relatively low external magnetic field strengths. For the same reasons, the seeds can also be more easily captured than the MDCPs, so they can be readily held in place magnetically to assist in the subsequent collection of the MDCPs. So, once the seeds are in place, the MDCPs can be injected nearby and be captured by seeds located downstream by HGMS principles.

A theoretical study [8] demonstrated the feasibility of using magnetized seeds as the implant. Then, an *in vitro* study [14] was done using a porous polymer as surrogate capillary tissue, but with the magnetite seed particles already held in place by physical adhesion not magnetism. As informative as those theoretical and experimental studies were, they focused only on the conditions necessary for MDCP capture; they both disregarded the capture of the seeds prior to capture of the MDCPs.

Therefore, the objective of this study was to provide additional experimental evidence of the feasibility of using seeds as the

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doi:10.1016/j.jmmm.2009.02.091

implant for IA-MDT, by proving that the superparamagnetic seeds could be magnetically retained in tissue and then subsequently used to increase the capture of MDCPs in that tissue. An *in vitro* study was designed using a porous polyethylene (PE) polymer as surrogate capillary tissue, dextran-coated magnetite particles as seeds, and polydivinylbenzene particles embedded with magnetite as MDCPs. The effects of several important variables on the performance of this IA-MDT approach were studied, including the distance to the magnet, the seed particle diameter, and the seed suspension injection volume.

2. Materials and methods

2.1. Materials

Ultra-high molecular weight polyethylene powder (Sigma-Aldrich, 180 μm), sodium chloride (Sigma-Aldrich, +80 mesh, 98+%), and sodium *n*-dodecyl sulfate (SDS) (Alfa Aesar, 99%) were used as received. Magnetic microspheres, 0.87 μm in diameter, composed of carboxyl-modified polydivinylbenzene (DVB/V-COOH) and containing 24.8 wt% magnetite were obtained in a suspension (Bangs Laboratories, Inc.). Magnetic particles, 130 and 250 nm in diameter and composed of 75–80 wt% magnetite in a matrix of dextran (40,000 D) were also obtained in a suspension (Micromod). De-ionized water was obtained from a Milli-Q purification system.

2.2. Porous polymer preparation and characterization

A porous polymer of cylindrical shape was prepared by a compression melt molding technique, followed by a salt-leaching step [18]. In short, the PE powder and NaCl particles were mixed in a ratio of 1.00 g of PE to 5.37 g of NaCl to obtain a material with about 70% porosity, once all the salt was removed. The materials were mixed for at least 2 h, and then added to a specially designed aluminum mold with a 1 cm diameter by 5-cm-long cylindrical opening. A 1 t manual arbor press was used to compress the sample. The mold was then heated to 170 °C for 2 h, with recompression steps after 1 and 2 h. The mold was cooled to room temperature and the sample was removed. The sample, in the form of a solid rod, was immersed in water for at least 48 h to remove all the salt. The water was changed every hour for the first 4 h, and then every 2–6 h. The resulting porous samples were cut into 1-cm-long cylindrical pieces. The cut samples were dried for 48 h under vacuum at 60 °C.

The morphologies of the porous polymers were imaged by examining cross sections in a FEI Quanta 200 environmental scanning electron microscope (SEM) operated at 30 kV. The porosity of the material was estimated from the apparent geometrical density (ρ_a) and the skeletal density (ρ_s). The apparent geometrical density was measured using the weight of a 1 cm long × 1 cm in diameter porous polymer sample. The skeletal density was measured using a Quantachrome Ultrapycnometer 1000 with helium as the carrier gas. The porosity (ε) was calculated from $\varepsilon = 1-(\rho_a-\rho_s)$.

2.3. Magnetic characterization

The magnetic susceptibilities of the MDCPs and seed particles were measured using a MPMS XL SQUID magnetometer (Quantum Design). For the magnetic measurements, loose particles were placed in a gelatin capsule, which was then placed in a plastic straw. Magnetic field sweeps were recorded between +1 and −1 T at 300 K.

2.4. Particle capture apparatus

The experimental setup is shown in Fig. 1. It consisted of the cylindrical porous polymer, a single NdFeB permanent magnet located adjacent to the porous polymer, a 50 ml syringe to supply the suspension of MDCPs, a 50 ml syringe to supply the SDS solution for flushing, a 1 ml syringe to supply the seed particle suspension, and two KDS200 syringe pumps to control the flow through the polymer matrix. A calibrated Spectronic 20+ spectrophotometer set at 750 nm was used to determine the concentration of the seeds or the MDCPs in suspension as a function of the suspension transmittance. The magnitude and the gradients of the magnetic field were adjusted by varying the distance between the magnet and the porous polymer. The magnetic field was measured using a Model 4048 Bell Gauss/Tesla meter.

The porous polymer was encapsulated inside the flow tube by placing the 1 cm diameter × 1 cm long cylinder inside a 3 cm long piece of shrink tube, along with 4 in pieces of $\frac{1}{8}$ in Tygon tubing at each end. A heat gun was then used to shrink the tube, while taking care not to overheat the polymer to avoid melting. Once the shrink tube was reduced in size, the porous polymer was encapsulated tightly inside, along with the two pieces of Tygon tubing at each end.

2.5. Particle capture procedure

For a typical experiment, a suspension of the MDCPs at a concentration of 50 mg/L was prepared in a 10 mM SDS aqueous solution using the 0.87 μm particles. A suspension of the seed particles was also prepared using either the 130 or 250 nm particles at a concentration of 2000 mg/L in a 10 mM SDS aqueous solution. One of the 50 ml syringes was charged with the 10 mM SDS aqueous solution. The other 50 ml syringe was charged with

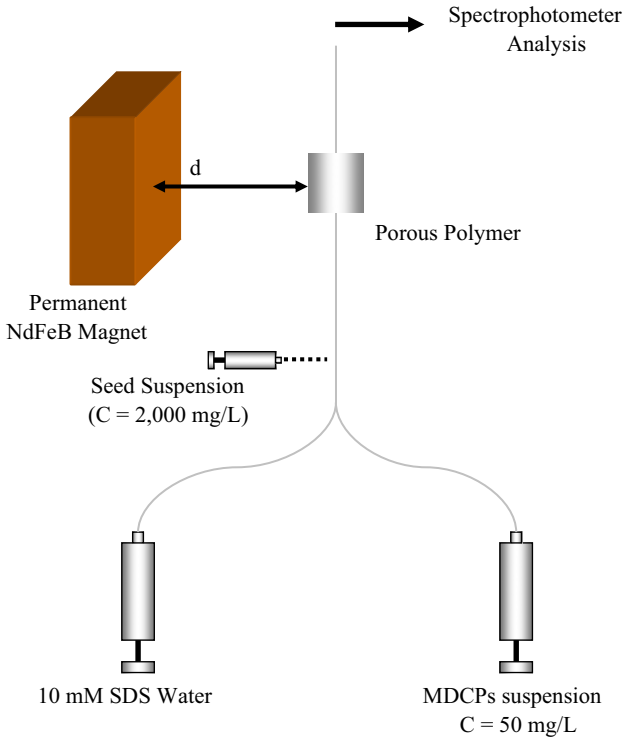

Fig. 1. Experimental apparatus used in the *in vitro* study of the use of magnetic seed particles as the implant for IA-MDT. The system consists of two 50 ml glass syringes, one 1 ml glass syringe, a cylindrical porous polymer 1 cm in length and 1 cm in diameter connected to the syringes using 1/8″ Tygon tubing, and a 50–50–25 mm, 0.3 T NdFeB rectangular permanent magnet.