Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 277 (2004) 19–24
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Magnetically modulated therapeutic systems

U.O. Häfeli*

The Cleveland Clinic Foundation, 9500 Euclid Avenue, T28 Cleveland, OH 44195, USA

Received 13 August 2002; received in revised form 24 November 2002; accepted 18 March 2003

Available online 13 April 2004

Abstract

Magnetically targeted drug delivery by particulate carriers is an efficient method of delivering drugs to localized disease sites, such as tumors. High concentrations of chemotherapeutic or radiological agents can be achieved near the target site without any toxic effects to normal surrounding tissue. Non-targeted applications of magnetic microspheres and nanospheres include their use as contrast agents (MRI) and as drug reservoirs that can be activated by a magnet applied outside the body. Historic and current applications of magnetic microspheres will be discussed, as well as future directions and problems to be overcome for the efficient and beneficial use of magnetic carriers in clinical practice. More information about the field and an extensive bibliography is available at "www.magneticmicrosphere.com."

Keywords: Magnetic targeting; Liver tumor; Magnetic microspheres; Cell separation; Contrast agent; Chemotherapy

1. Principle of magnetic targeting

Magnetic drug delivery by particulate carriers is a very efficient method of delivering a drug to a localized disease site. Very high concentrations of chemotherapeutic or radiological agents can be achieved near the target site, such as a tumor, without any toxic effects to normal surrounding tissue or to the whole body. Fig. 1 highlights the concept of magnetic targeting by comparing systemic drug delivery with magnetic targeting. In magnetic targeting, a drug or therapeutic radioisotope is bound to a magnetic compound, injected into a patient's blood stream, and then stopped with a powerful magnetic field in the target area (see arrow in Fig. 1). Depending on the type of drug, it is then slowly released from the magnetic carriers (e.g. release of chemotherapeutic drugs from magnetic microspheres) or confers a local effect (e.g. irradiation from radioactive microspheres; hyperthermia with magnetic nanoparticles). It is thus possible to replace large amounts of freely circulating drug with much lower amounts of drug targeted magnetically to localized disease sites, reaching effective and up to several-fold increased localized drug levels (Widder et al., 1979; Gupta and Hung, 1989; Häfeli et al., 1997).

Magnetic carriers receive their magnetic responsiveness to a magnetic field from incorporated materials such as magnetite, iron, nickel, cobalt, neodymium–iron–boron or samarium–cobalt. Magnetic carriers are normally grouped according to size. At the lower end, we have the ferrofluids, which are colloidal iron oxide solutions. Encapsulated magnetite particles in the range of 10–500 nm are usually called magnetic nanospheres and any magnetic particles of just below 1–100 μm are magnetic microspheres. In general, magnetic liposomes are also included when speaking about magnetic carriers.

* Tel.: +1-216-445-4480; fax: +1-216-444 2174.
E-mail address: hafeliu@ccf.org (U.O. Häfeli).

0378-5173/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2003.03.002

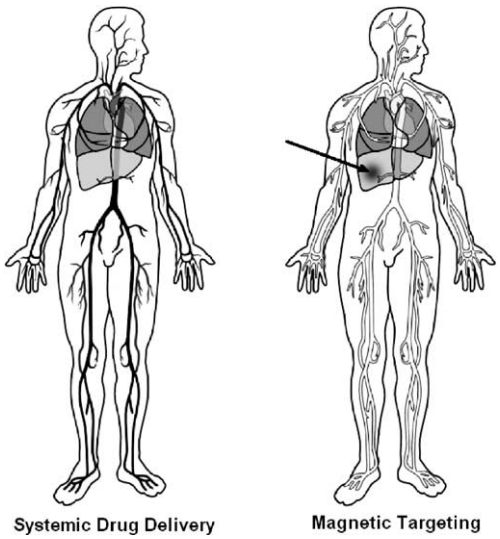

Fig. 1. Concept of magnetic drug targeting.

For biomedical applications, magnetic carriers must be water-based, biocompatible, non-toxic, and non-immunogenic. The first medical applications directly applied magnetite or iron powder. Improved biocompatibility, however, was reached by encapsulating the magnetic materials. The "shell" material determines the reaction of the body to the microsphere. Matrix materials that have been tested for the magnetic microspheres include chitosan, dextran, poly(lactic acid), starch, poly(vinyl alcohol), polyalkylcyanoacrylate, polyethylene imine, carbon, polysaccharides, gelatin and proteins.

2. History of magnetic targeting

Magnetic drug targeting is a young field. The surgeon Gilchrist published a seminal paper in 1956 on the selective inductive heating of lymph nodes after injection of 20–100-nm-sized maghemite particles into the lymph nodes near surgically removed cancer (Gilchrist et al., 1957). Turner and Rand combined then this radiofrequency heating method with embolization therapy (Turner et al., 1975).

Gilchrist apparently did not, however, envision that his magnetic particles could be magnetically guided and delivered to the target area. In 1963, Meyers described how they were able to accumulate small iron particles intravenously injected into the leg veins of dogs, using a large, externally applied horse shoe magnet (Meyers et al., 1963). They imagined that it might be useful for lymph node targeting and as a contrast agent. Hilal then engineered catheters with magnetic ends, and described how they could be used to deposit and selectively embolize arterio-venous malformations with small magnets (Hilal et al., 1974). The use of magnetic particles for the embolization therapy of liver cancer followed and has recently found renewed interest (Wu et al., 1995; Jones and Winter, 2001). More defined spherical magnetic microspheres were made for the first time at the end of the 1970s by Widder et al. (1979). Their magnetic albumin microspheres worked well in animal experiments for tumor therapy and as magnet resonance contrast agents, but were not explored in clinical trials (Widder et al., 1983, 1987).

3. Current applications of magnetic systems

3.1. Magnetic systems for the therapy of diseases

3.1.1. Magnetic delivery of chemotherapeutic drugs to liver tumors

The first clinical cancer therapy trial using magnetic microspheres (MMS) was performed by Lübbe et al. in Germany for the treatment of advanced solid cancer in 14 patients (Lübbe et al., 1996, 2001). Their MMS were small, about 100 nm in diameter, and filled with 4′-epidoxorubicin. The phase I study clearly showed the low toxicity of the method and the accumulation of the MMS in the target area. However, MRI measurements indicated that more than 50% of the MMS had ended up in the liver. This was likely due to the particles' small size and low magnetic susceptibility which limited the ability to hold them at the target organ.

The startup company FeRx in San Diego developed irregularly shaped carbon-coated iron particles of 0.5–5 μm in diameter with very high magnetic susceptibility and used them in a clinical phase I trial for the treatment of inoperable liver cancer (Goodwin, 2000). They have treated 32 patients to date and are able to super-selectively (i.e. well directed) infuse up to 60 mg of doxorubicin in 600 mg MMS with no treatment-related toxicity (Johnson et al., 2002). The

firm recently started a large phase I/II trial for the treatment of hepatocellular carcinoma in China, Korea, and the US (Johnson et al., 2002).

Current preclinical research is investigating the use of magnetic particles loaded with different chemotherapeutic drugs such as mitoxantrone (Alexiou et al., 2000), mitomycin C, etoposide, paclitaxel or oxaliplatin (Johnson et al., 2002).

3.1.2. Magnetic targeting of radioactivity

Magnetic targeting can also be used to deliver therapeutic radioisotopes (Häfeli, 2001). The advantage of this method over external beam therapy is that the dose can be increased, resulting in improved tumor cell eradication, without harm to nearby normal tissue. Different radioisotopes can treat different treatment ranges depending on the radioisotope used—the β-emitters ^{90}Y for example will irradiate up to a range of 12 mm in tissue. Unlike chemotherapeutic drugs, the radioactivity is not released, but rather the entire radioactive microsphere is delivered to and held at the target site to irradiate the area within the specific treatment range of the isotope. Once they are not radioactive anymore, biodegradation of the microspheres occurs (and is desired).

Initial experiments in mice showed that intraperitoneally injected radioactive poly(lactic acid) based MMS could be concentrated near a subcutaneous tumor in the belly area, above which a small magnet had been attached (Häfeli et al., 1997). The dose-dependent irradiation from the β-emitter ^{90}Y-containing MMS resulted in the complete disappearance of more than half of the tumors. Magnetic targeted carriers (MTC; from FeRx), which are more magnetically responsive iron carbon particles, have been radiolabeled in the last couple of years with isotopes such as ^{188}Re (Häfeli et al., 2001), ^{90}Y, ^{111}In and ^{125}I (Johnson et al., 2002) and are currently undergoing animal trials. As an example, a preliminary in vivo investigation of binding stability and localization was performed in normal swine. Eleven millicurie of ^{90}Y-MTC was administered intra-arterially to a swine liver via catheterization of the hepatic artery. Blood samples were taken following the administration, which indicated that less than 3% of the total injected activity was circulating 30 min following the administration and decreased over time. A γ-camera image taken 24 h after the injection using the Bremsstrahlung emission associated with ^{90}Y showed qualitatively a single source of emission in the region of the liver where the ^{90}Y-MTCs were targeted (Fig. 2).

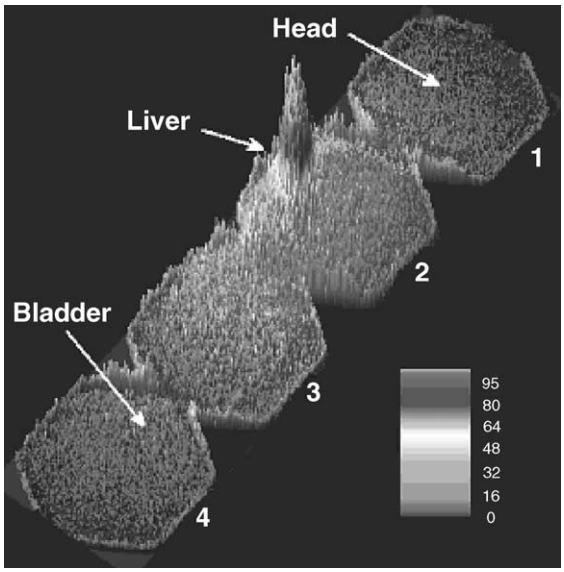

Fig. 2. Bremsstrahlung image taken 24 h after intra-arterial delivery of ^{90}Y-MTCs to the right liver lobe of a swine. The animal was lying on its back. Four consecutive scans were taken and combined in this figure.

3.1.3. Treatment of tumors with magnetically induced hyperthermia

Developments by Jordan and Chan led to the current hyperthermia application of single domain, dextran-coated magnetite nanoparticles in tumors (Jordan et al., 1993; Chan et al., 1993). The first clinical trial is ongoing in Germany (Jordan et al., 2001). Magnetic hyperthermia is also possible with larger magnetic particles, as shown by the group of Moroz et al. (2002). Their 32-μm plastic particles contain maghemite and embolize the arterial blood supply of the tumor, in addition to the magnetic hyperthermia treatment. In an animal study with 10 rabbits, the tumor volumes decreased by 50–94% within 2 weeks.

Ongoing investigations in magnetic hyperthermia are focused on the development of magnetic particles that are able to self-regulate the temperature they reach. The ideal temperature for hyperthermia is 43–45 °C, and particles with a Curie temperature in this range have been described by Kuznetsov et al. (2002).

3.1.4. Other magnetic targeting applications

Similar to chemotherapeutic drugs, many other drugs including peptides and proteins can be adsorbed or encapsulated into magnetic microspheres or nanospheres. Normal pharmaceutical technology is employed to influence release kinetics. Ongoing work describes the encapsulation of the peptide octreotide and the protein tumor necrosis factor alpha (TNF-α) (Johnson et al., 2002).

A very recent development in the field of magnetic targeting is the use of magnetically enhanced gene therapy (Scherer et al., 2002). Advantages of such an approach are targeted gene transfection at rapid speed and high efficiencies.

It is also possible to use only the mechanical-physical properties of magnetic particles or ferrofluids for therapy. One example is the embolization (clogging) of capillaries under the influence of a magnetic field (Flores and Liu, 2002). In this way, tumors could be specifically starved of their blood supply. Another elegant example is the use of magnetic fluids to prevent retinal detachment, thus preventing the patients from going blind (Dailey et al., 1999). A magnetized scleral buckle, similar to a rubber band, is placed around the eye. The magnetic fluid is then injected into the eye and immediately drawn towards the buckle by its magnetic forces. The mechanical forces push the retina back into its original place.

3.1.5. Magnetic control of pharmacokinetic parameters and drug release

The magnetic component in microspheres can also be used for purposes other than targeting. Langer et al. embedded magnetite or iron beads into a drug-filled polymer matrix and then showed that they could activate or increase the release of the drug from the polymer by moving a magnet over it or by applying an oscillating magnetic field (Langer et al., 1980; Edelman and Langer, 1993). The micro-movement within the polymer seemed to have shaken the matrix or produced "micro-cracks," and thus made the influx of liquid, dissolution and efflux of the drug possible. In this way, it was possible to magnetically activate the release of insulin from a depot underneath the skin (Kost et al., 1987). Done repeatedly, this would allow for pulsatile drug delivery.

Another mechanistic approach based on magnetic attraction is the slowing-down of oral drugs in the gastrointestinal system. This is possible by filling an additional magnetic component into capsules or tablets. The speed of travel through the stomach and intestines can then be slowed down at specific positions by an external magnet, thus changing the timing and/or extent of drug absorption in stomach or intestines. Slowing down the passage of magnetic liposomes with a magnet actually increased the blood levels of a drug (Chen and Langer, 1997).

3.2. Magnetic systems for the diagnosis of diseases

The most important diagnostic application of magnetic nanospheres is as contrast agents for magnetic resonance imaging (MRI). Saini et al. tested 0.5–1 μm sized ferrites in vivo for the first time in 1987 (Saini et al., 1987). Since then, smaller superparamagnetic iron oxides (SPIOs) have been developed into unimodular nanometer sizes and have since 1994 been approved and used for the imaging of liver metastases (ferumoxide based Feridex I.V., or Endorem in Europe) or to distinguish loops of the bowel from other abdominal structures (GastroMark, or Lumirem in Europe).

3.3. Magnetic systems for magnetic cell separation

The era of using magnetic particles with surface markers against cell receptors started in 1978 with a seminal paper by Kronick et al. (1978). Currently, many different kits for the sample preparation, extraction, enrichment and analysis of entire cells based on surface receptors, and subcellular/molecular components such as proteins, mRNA, DNA are available (Bosnes et al., 1997). Analytical procedures, such as many different immunoassays, are often based on magnetic separation (Meza, 1997). More information is available from the firms providing these kits, such as Dynal, Miltenyi, Bangs Laboratories, micromod. Many more suppliers are listed on the website "www.magneticmicrosphere.com."

One important application of magnetic cell separation is the purging of malignant cells from autologous stem cell products, depletion of T cells, and selection of specific lymphocyte subsets with potential antileukemic activity. In this way, a cancer patient's stem cells can be extracted, purified, and then injected again after he has gone through a harsh cancer

treatment schedule. The therapeutic applications of immunomagnetic cell selection are based on antibodies that bind to cancer cell antigens such as CD10, CD19 or CD20 (Farag, 2002). Two machines for magnetic cell separation have recently received FDA approval, Cellpro's "Ceprate SC stem cell collection system" and Baxter's "Isolex 300I." A third system is approved in Europe, Miltenyi's "ClinicMACS" system.

4. Future directions

Conceptually, magnetic targeting is a very promising approach. However, there are a number of physical, magnetism-related properties which require careful attention. First, the magnetic force, which is defined by its field and field gradient, needs to be large and carefully shaped to fit the target area. For in vivo applications, this is not trivial, and collaborations with electrical or biomedical engineers are advisable. Second, the magnetic susceptibility of the MMS needs to be as high as possible. More responsive magnetic materials of defined and homogeneous material properties in a (tissue-) stable and defined oxidation state need to be synthesized. Third, the MMS size must be small enough that they do not clog the blood vessels through which they are guided to the target organ. In cases where it may be desirable to circulate particles through the body rather than injecting them in close proximity to the treatment area, additional benefits are obtained if the particles are small enough to minimize their trapping in other organs such as the lungs or liver. Fourth, altering the surface of MMS with appropriate molecules should always be considered to either decrease the interaction of MMS with tissues or organs, using for example PEG; or to specifically bind to target cell populations using for example antibodies or receptor agonists. Finally, the MMS size must be uniform enough to provide an equal probability of magnetic capture for each MMS and constant drug/radioactivity content.

Beside the magnetic properties, the fate of the particles in the body is an important consideration both for local and systemic short- and long-term toxicity. Furthermore, the pharmacokinetic characteristics must be optimized for the specific target organ, taking into account that the normal organ behavior might differ from that of a diseased organ.

References

Alexiou, C., Arnold, W., Klein, R.J., 2000. Locoregional cancer treatment with magnetic drug targeting. Cancer Res. 60, 6641–6648.

Bosnes, M., Deggerdal, A., Rian, A., Korsnes, L., Larsen, F., 1997. Magnetic separation in molecular biology. In: Häfeli, U.O., Schütt, W., Teller, J., Zborowski, M. (Eds.), Scientific and Clinical Applications of Magnetic Carriers. Plenum Press, New York, pp. 269–285.

Chan, D.C.F., Kirpotin, D.B., Bunn, P.A., 1993. Synthesis and evaluation of colloidal magnetic iron oxides for the site-specific radiofrequency-induced hyperthermia of cancer. J. Magn. Magn. Mater. 122, 374–378.

Chen, H., Langer, R., 1997. Magnetically-responsive polymerized liposomes as potential oral delivery vehicles. Pharm. Res. 14, 537–540.

Dailey, J.P., Phillips, J.P., Li, C., Riffle, J.S., 1999. Synthesis of silicone magnetic fluid for use in eye surgery. J. Magn. Magn. Mater. 194, 140–148.

Edelman, E.R., Langer, R., 1993. Optimization of release from magnetically controlled polymeric drug release devices. Biomaterials 14, 621–626.

Farag, S.S., 2002. Therapeutic applications of immunomagnetic cell selection: a review. Eur. Cells Mater. 3, 37–40.

Flores, G.A., Liu, J., 2002. In vitro blockage of a simulated vascular system using magnetorheological fluids as a cancer therapy. Eur. Cells Mater. 3, 9–11.

Gilchrist, R.K., Medal, R., Shorey, W.D., Hanselman, R.C., Parrott, J.C., Taylor, C.B., 1957. Selective inductive heating of lymph nodes. Ann. Surg. 146, 596–606.

Goodwin, S., 2000. Magnetic targeted carriers offer site-specific drug delivery. Oncol. News Int. 9, 22.

Gupta, P.K., Hung, C.T., 1989. Magnetically controlled targeted micro-carrier systems. Life Sci. 44, 175–186.

Häfeli, U., Schütt, W., Teller, J., Zborowski, M., 1997. Scientific and Clinical Applications of Magnetic Carriers, first ed. Plenum Press, New York.

Häfeli, U.O., 2001. Radioactive magnetic microspheres. In: Arshady, R. (Ed.), Microspheres, Microcapsules & Liposomes: Magneto- and Radio-Pharmaceuticals, vol. 3. Citus Books, London, Chapter 18, pp. 559–584.

Häfeli, U.O., Pauer, G.J., Roberts, W.K., Humm, J.L., Macklis, R.M., 2001. Magnetically targeted microspheres for intracavitary and intraspinal Y-90 radiotherapy. In: Häfeli, U., Pauer, G., Failing, S., Tapolsky, G. (Eds.), Radiolabeling of Magnetic Particles with Rhenium-188 for Cancer Therapy. J. Magn. Magn. Mater. 225, 73–78.

Hilal, S.K., Michelsen, W.J., Driller, J., Leonard, E., 1974. Magnetically guided devices for vascular exploration and treatment. Radiology 113, 529–540.

Johnson, J., Kent, T., Koda, J., Peterson, C., Rudge, S., Tapolsky, G., 2002. The MTC technology: a platform technology for the site-specific delivery of pharmaceutical agents. Eur. Cells Mater. 3, 12–15.

Jones, S.K., Winter, J.G., 2001. Experimental examination of a targeted hyperthermia system using inductively heated ferromagnetic microspheres in rabbit kidney. Phys. Med. Biol. 46, 385–398.

Jordan, A., Wust, P., Fahling, H., John, W., Hinz, A., Felix, R., 1993. Inductive heating of ferrimagnetic particles and magnetic fluids: physical evaluation of their potential for hyperthermia. Int. J. Hyperthermia 9, 51–68.

Jordan, A., Scholz, R., Maier-Hauff, K., 2001. Presentation of a new magnetic field therapy system for the treatment of human solid tumors with magnetic fluid hyperthermia. J. Magn. Magn. Mater. 225, 118–126.

Kost, J., Wolfrum, J., Langer, R., 1987. Magnetically enhanced insulin release in diabetic rats. J. Biomed. Mater. Res. 21, 1367–1373.

Kronick, P.L., Campbell, G.L., Joseph, K., 1978. Magnetic microspheres prepared by redox polymerisation used in a cell separation based on gangliosides. Science 200, 1074–1076.

Kuznetsov, A.A., Shlyakhtin, O.A., Brusentsov, N.A., Kuznetsov, O.A., 2002. "Smart" mediators for self-controlled inductive heating. Eur. Cells Mater. 3, 75–77.

Langer, R., Hsieh, D.S.T., Rhine, W., Folkman, J., 1980. Control of release kinetics of macromolecules from polymers. J. Membr. Sci. 7, 333–350.

Lübbe, A.S., Bergemann, C., Riess, H., 1996. Clinical experiences with magnetic drug targeting: A phase I study with 4′-epidoxorubicin in 14 patients with advanced solid tumors. Cancer Res. 56, 4686–4693.

Lübbe, A.S., Alexiou, C., Bergemann, C., 2001. Clinical applications of magnetic drug targeting. J. Surg. Res. 95, 200–206.

Meyers, P.H., Cronic, F., Nice, C.M., 1963. Experimental approach in the use and magnetic control of metallic iron particles in the lymphatic and vascular system of dogs as a contrast and isotopic agent. Am. J. Roentgenol. Radium Ther. Nucl. Med. 90, 1068–1077.

Meza, M., 1997. Application of magnetic particles in immunoassays. In: Häfeli, U.O., Schütt, W., Teller, J., Zborowski, M. (Eds.), Scientific and Clinical Applications of Magnetic Carriers. Plenum Press, New York, pp. 303–309.

Moroz, P., Jones, S.K., Gray, B.N., 2002. Tumor response to arterial embolization hyperthermia and direct injection hyperthermia in a rabbit liver tumor model. J. Surg. Oncol. 80, 149–156.

Saini, S., Stark, D.D., Hahn, P.F., Wittenberg, J., Brady, T.J., Ferrucci, J.T., 1987. Ferrite particles: a superparamagnetic MR contrast agent for the reticuloendothelial system. Radiology 162, 211–216.

Scherer, F., Anton, M., Schillinger, U., 2002. Magnetofection: enhancing and targeting gene delivery by magnetic force in vitro and in vivo. Gene Therapy 9, 102–109.

Turner, R.D., Rand, R.W., Bentson, J.R., Mosso, J.A., 1975. Ferromagnetic silicone necrosis of hypernephromas by selective vascular occlusion to the tumor: a new technique. J. Urol. 113, 455–459.

Widder, K.J., Senyei, A.E., Ranney, D.F., 1979. Magnetically responsive microspheres and other carriers for the biophysical targeting of antitumor agents. Adv. Pharmacol. Chemother. 16, 213–271.

Widder, D.J., Greif, W.L., Widder, K.J., Edelman, R.R., Brady, T.J., 1987. Magnetite albumin microspheres: a new MR contrast material. AJR 148, 399–404.

Widder, K.J., Morris, R.M., Poore, G.A., Howards, D.P., Senyei, A.E., 1983. Selective targeting of magnetic albumin microspheres containing low-dose doxorubicin: total remission in Yoshida sarcoma-bearing rats. Eur. J. Cancer Clin. Oncol. 19, 135–139.

Wu, C.B., Wei, S.L., He, S.M., 1995. Studies on adriamycin magnetic gelatin microspheres. J. Clin. Pharm. Sci. 4, 1–6.