



PHARMACEUTICAL APPLICATIONS OF MAGNETIC PARTICLES IN DRUG DELIVERY SYSTEM

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ABSTRACT

Magnetic seems to serve as a common function of opening a new vista of a multi-step drug delivery. Magnetically targeted drug delivery by particulate carriers is an efficient method of delivering drugs to localized disease sites. High concentrations of chemotherapeutic or radiological agents can be achieved near the target site without any toxic effects to normal surrounding tissue. Magnetic targeting is a process for choice of delivery of about 45-60% of the new peptide and recombinant proteins at a level of 25-50% localization of injected dose in non-reticuloendothelial target tissues. This means targeting has been exploited to achieve adequate drug levels, bioavailability enhancement, localizing the effect of biopharmaceuticals and avoidance of toxic manifestations. 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.

Keywords: Magnetic particles, targeted drug delivery, magnetic drug targeting, Magnetic Microspheres, Magnetic Neutrophils.

INTRODUCTION

Magnetic microcarriers¹⁻⁵ are supramolecular particles that are small enough to circulate through capillaries without producing embolic occlusion (less than 4 micrometers), but are sufficiently susceptible to become captured in microvessels and dragged in to the adjacent tissues by magnetic fields of 0.5-0.8 tesla (T). These microcarriers include microspheres, liposomes, cells, nanoparticles etc. Biological response modifiers (BRMs) alter host, tumor as well as microbial responses in four ways:

- Augmentation of host effectors mechanisms directed against tumor cells or microorganisms.
- Decrease in host responses that interferes that tumor resistance by a quantitative increase in endogenous effector resistance by an increase in endogenous effector molecules or redirecting their sites and duration of action.
- Augmentation of tumor sensitivity to host cells by redifferentiating tumor cells.
- Increase in host tolerance of conventional cancer treatment.

There are basically two types of agents: Indirect and Direct. Indirect agents include white cell chemoattractant/activator peptides, interleukins (1 to 4) and immunomodulators such as the interferons (alpha, beta, and gamma). Indirect BRMs seem to act by enhancing the responses of monocytes, neutrophils, macrophages, B and T lymphocytes and natural killer cells. Direct acting BRMs are the final exemplified by antibodies, lymphotoxin and tumor necrosis factor (TNF also called as cachectin). A potential advantage of these molecules is that they do not have upper limit to their pharmacological actions.²³

Chemoattractant Microspheres

Neutrophil chemoattractant, f-met-leu-phe was the first selected biomodulator for magnetic targeting due to its lethal property when administered freely in the circulation at a concentration exceeding $2 \times 10^{-7} M$. It requires a site specific and local delivery to modulate inflammation and is a small, bacterially derived peptide, stable during microspheres preparation. It can be entrapped successfully in microparticles. F-met-leu-phe microspheres have been used either in disease modeling or clinical therapy. In pulmonary medicine these delivery systems are used as:

- An experimental method to test new agents that prevent neutrophil degradation of lung elastin in smokers,
- A means of studying the contribution of acute alveolar damage to acute type respiratory distress syndrome and
- As an adjuvant method in treating invasive pulmonary aspergillus's suffering patients.¹³

Magnetic Neutrophils

In certain clinical conditions, where patient sera contains chemoactive factor inactivators and neutrophils directed inhibitors of chemotaxis, an indirect approach of targeting white cells by chemoattraction fails.⁸ These disorders include chronic lymphocytic leukemia, alcoholic cirrhosis, cronh's disease, hemodialysis, sarcoidosis and Hodking's disease. Even though failure of chemotaxis is not observed in all patients, such conditions are life threatening. Therefore, a means of making neutrophilingest magnetic base system ought to be developed, so that the sites of severe infection can be selectively approached for therapy.²³



Interleukin 2 Microspheres

Interleukin 2 (IL-2) is an important modulator with a modulator weight 15000. It is chemically glycoprotein made by activating T lymphocytes that enhance immune response in infection and certain tumors. IL-2 activates certain cell types like T-helper cells, cytotoxic T-lymphocytes, natural killer cells and possibly macrophages. It is an appropriate molecule for drug delivery systems due to its attractive properties. It is stable, active in mice and human being and is available as a large quantities as a product of genetic engineering. Studies revealed that high doses of IL-2 lead to regression of pulmonary and hepatic metastasis in several murine tumors. IL-2 has also been found to effective against disseminated human melanomas and renal cell carcinoma, which are generally non-responsive to conventional therapy.²⁴⁻²⁷

Magnetic Nanoparticles

Immunospecific ferromagnetic iron-dextran reagents for the labeling and magnetic separation of cells were studied. Ferromagnetic iron-dextran nanoparticles were prepared by reacting a mixture ferrous chloride and ferric chloride with dextran polymers under alkaline conditions. The particles of average size range (30-40nm) showed little non-specific binding to cells and had a magnetic moment. Protein A from *Staphylococcus aureus* was covalently linked to periodate oxidized ferromagnetic iron-dextran particles. These conjugate were used to indirectly label antigen sites on human red blood cells and thymocytes for visualization by scanning and transmission electron microscopy. Cells labeled with these immunospecific ferromagnetic particles were quantitatively retained by a simple permanent magnet and could be separated from unlabeled cells.

Magnetic carbohydrate nanoparticles have been proposed for use in affinity cell separation. Magnetically responsive nanoparticles were prepared from enzymatically hydrolyzed starch and magnetite. Two different monoclonal antibodies were covalently coupled to the particles. Using these magnetic nanoparticles (average size range 100-300 nm) coupled monoclonal mouse anti-rat Ig kappa light chain antibody, a very high depletion of surface Ig positive cells (mostly B-cells) from one million rat peripheral blood mononuclear cells could be achieved. The separation efficiency of this technique was evaluated by flow cytometric analysis and the technique has been reported to permit the detection of a small number of surface Ig positive among 10,000 negative cells. Indomethacin bearing magnetic nanoparticles of polymethylmethacrylate, were prepared by the emulsion polymerization technique. The controlled growth of ferric hydroxide particles in the presence of non-ionic surfactant was affected to obtain nano-sized particles and these were subsequently heated to obtain magnetite. The effect of various particles, i.e. monomer concentration and magnetite concentration, as well as the stirring rate was studied to characterized the particle

size and its distribution. Then in vivo magnet responsiveness and kinetics of distribution of these magnetic and plain nanoparticles were characterized and reported. Up to 60 min post injection time, 60-fold higher drug concentration in target tail segment was recorded which resulted in considerably reduced drug concentration in other organs as evinced by data from control rats. Following normal administration (without magnetic field) drug concentration was higher in liver and spleen, where endocytosis and phagocytosis takes place. Tumor specific superparamagnetic particles (SMP) were prepared and characterized. Particles of uniform size (9.6 ± 0.8 nm) were prepared from an alkaline solution of ferric and ferrous ions and isolated by different centrifugation. The resulting nanoparticle suspension was stabilized in buffer using a polypeptide coat to which a monoclonal antibody, Specific to carcinoembryonic antigen (CEA), was covalently attached at the hinge region. The resulting anti-CEA SMP antibody had a hydrodynamic radius of less than 50 nm with specific binding affinity to CEA in vitro. The visualization of epitopes, present on a cell surface in very low density as expected for tumor antigens or receptors may be achieved. Furthermore, the polypeptide coat chosen provided an ideal platform for the attachment of biological modifiers needed for the reduction of the antigenicity and blood clearance rate of anti-CEA SMP.

Super paramagnetic iron oxide particles represent a new class of contrast agents that increase the detectability of hepatic and splenic tumor by magnetic resonance imaging (MRI). The main steps of biodegradation and metabolism of magnetite-dextran nanoparticles in rats were investigated. The radioactive trace data and histochemistry features showed that the iron oxide cores were accumulated into the Kuffer cells and the macrophage of the splenic marginal zone. With time, the number of the granules was decreases whereas the fine iron granules appeared in the cytoplasm. Immunopositive staining for ferritin was markedly increased in the liver hepatocytes as observed for 3 days after injection. The splenic marginal zone macrophages stained prominently 14 days after injection. The data pointed to the early biodegradation of the magnetite-dextran nanoparticles and they thus appear as an interesting biodegradable new contrast agent first devoted to MRI of liver and spleen diseases that could be further extended to heart, kidneys, and other organs. Magnetite nanoparticles coated by three different artificial polypeptides, were conjugated to an antibody specific to the carcinoembryonic antigen (CEA). Colloidal iron oxide nanoparticles were synthesized and used as MRI contrast agent. These super paramagnetic particles were constituted of solid cores (diameter of 5-15 nm) generally coated by a thick polysaccharide layer (hydrodynamic radius of 30-100 nm), and formulated by direct co precipitation or iron salts in the presence of polymeric material.

A novel magnetic drug carrier based on carboxymethyl dextran magnetic nanoparticles (CMD MNPs) was



prepared (Shi et al., 2000). Adriamycin (ADR) was coupled with two types of carriers; neutral dextran MNPs and anionic CMD MNPs, by periodated oxidation. The physico-chemical characteristics and the magnetic guidance effect in vitro and in vivo of ADR-CMD MNPs were studied, The distribution profiles of liver and spleen revealed that on conjugation with neutral dextran MNPs, excessive accumulation resulted in liver and spleen after intravenous administration.

A cell labeling approach using a short HIV – Tat peptide was developed to derivative magnetic nanoparticles for in vivo tracking and recovery of progenitor cells. The particles were efficiently internalized into hematopoietic

and neutral progenitor cells in quantity up to 10-30 pg of iron per cell. Iron incorporation did not affect viability, differentiation, or proliferation of CD34+ cells. Following intravenous injection into immunodeficiency mice, 4% of magnetized CD34 cells homed into the bone marrow and discrete single cells could be detected by magnetic resonance (MR) imaging in tissue samples. In addition magnetically labeled cells homed to bone marrow could be recovered by using a magnetic separation columns. Localization and retrieval of cell population in vivo enable detailed analysis of specific stem cell and organ interactions critical for advancing the therapeutic use of stem cells.²⁵⁻²⁸

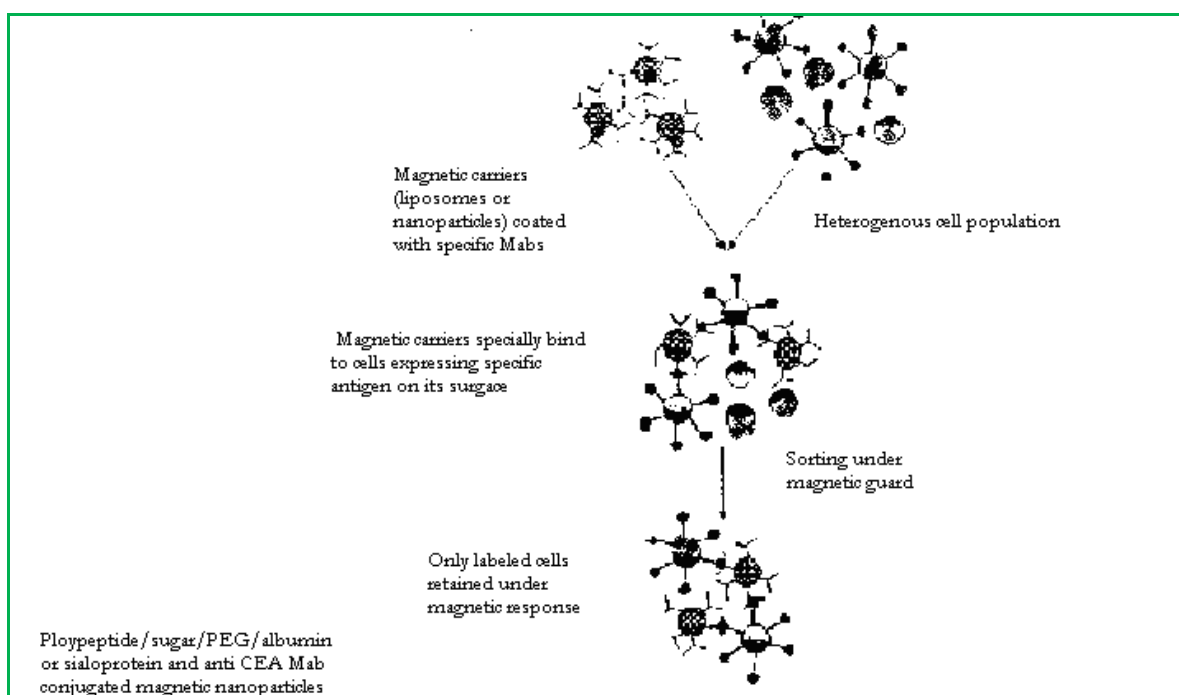


Figure 1: Principle of cellular sorting using magnetic carrier

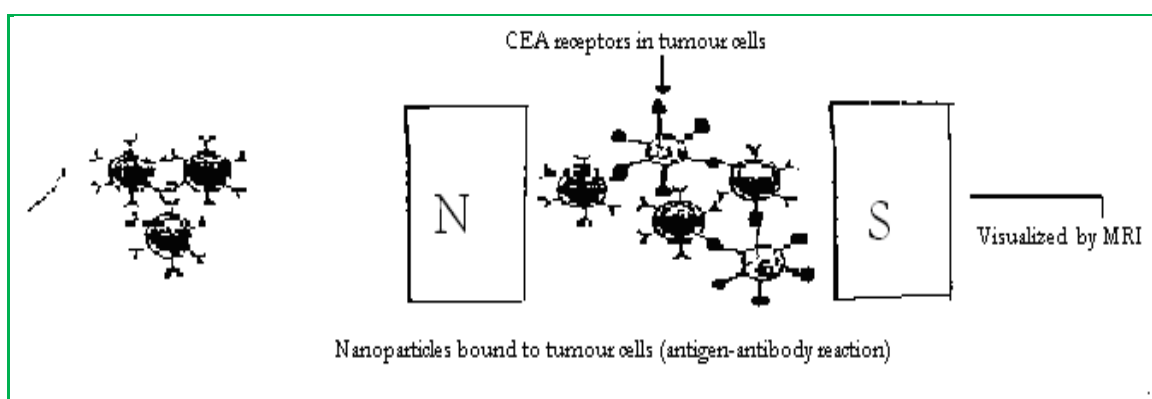


Figure 2: Schematic Presentation of use of Magnetic Nanoparticles as Tumor Contrast agent

Magnetic Liposomes

The magnetic liposomes have been used in cellular sorting successfully. Liposomes bearing antifibronectin antibodies and associated with ferromagnetic particles bound firmly to the surface of mouse embryo fibroblasts. Upon binding magnetoliposomes, the cells could be

separating under influence of a magnetic field the feasibility of magnetic liposomes as a targeting device for drugs were explored. They incorporated ultrafine magnetite particles within vesicles composed of egg-PC and tocopherol using film hydration method. The liposomes were targeted to Yoshida sarcoma implanted in footpad of rats. A very small amount of the liposomes,

but significantly more than the control, were found trapped at the tumor tissue. The magnetoliposomes were biophysically characterized and the potentialities of magnetoliposomes in symmetric and asymmetric phospholipids transfer processes were explored. They presented classical binding characteristics and thermal behaviors of cystchrome-C oxidase bearing magnetic liposomes. Human peripheral blood mononuclear cells (PBMCs) were incubated with large unilamellar vesicles containing encapsulated dextran-magnetite particles (DPM). This resulted in an efficient incorporation of DPM within cells. Electron microscopy revealed the presence of DPM in cells mainly in phagosomes and secondary lysosomes. The fraction of DPM containing PBMCs could be enriched by magnetic cell separation.²⁶

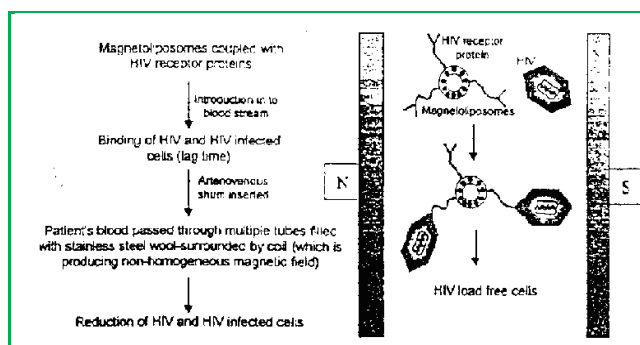


Figure 3: Schematic Presentation of HIV treatment by Magnetoliposome

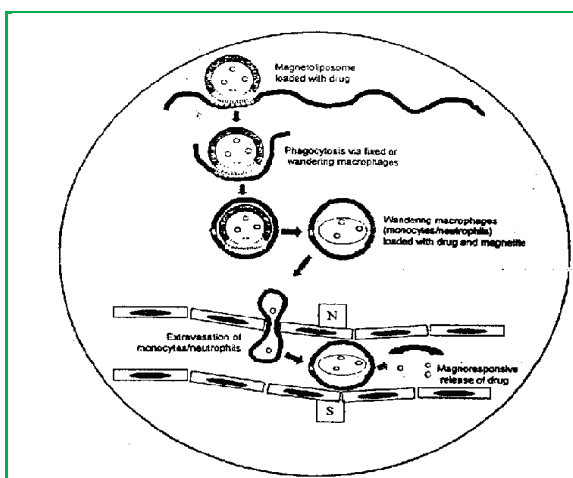


Figure 4: Carrier cellular co-ordinated targeting strategy Magnetic resealed erythrocytes

Local thrombosis in animal arteries was prevented by means of magnetic targeting of aspirin loaded red cells.⁹⁻¹² Thrombosis was included in 18 dogs and 16 rabbit's arteries by surgically inverting a vascular wall flap into its lumen. A completely occluding a red thrombus was developed inside the vessel after 4 to 5 hr. in 80% of cases. SmCo5 magnet was secured externally to one of the arteries. The constant magnetic field produced by the magnet had no influence on the clot formation. Autologous red cells loaded with ferromagnetic colloid compound and aspirin were administered intravenously, and completely aborted arteriothrombosis on magnet

application side with no deteriorate effect on clot formation in the control artery was recorded.²⁷

Magnetically responsive ibuprofen-loaded erythrocytes were prepared and characterized in vitro. The erythrocytes were loaded with ibuprofen and magnetite (ferrofluids) using the press well technique. Various process variables including drug concentration, magnetite concentration sonication of ferrofluids that could affect the loading of the drug and magnetite were optimized. The loaded erythrocytes were characterized for in vitro drug efflux, hemoglobin release, morphology, osmotic fragility, turbulence shock, in vitro magnetic responsiveness and percent cell recovery. In optimum concentrations, erythrocytes could tolerate ibuprofen as no appreciable detrimental effects were noticed on cell morphology, osmotic fragility, and turbulence shock, when compared with normal erythrocytes. The drug release profile from the cellular system was observed to follow approximately zero-order kinetics. The loaded cells effectively responded to an external magnetic field 8.0 Koe. In the continuous study, diclofenac sodium-bearing magnetic erythrocytes were prepared using a press well technique and characterized for various in vitro parameters. The drug-loaded magnetic erythrocytes responded effectively for an external magnetic field of 8.0 Koe. In the study suggested the potentiality of diclofenac sodium loaded magnetic erythrocytes, for active delivery of drug to painful inflamed joints, for possible physical modulation of carrier and contained drug biodistribution.^{27,33}

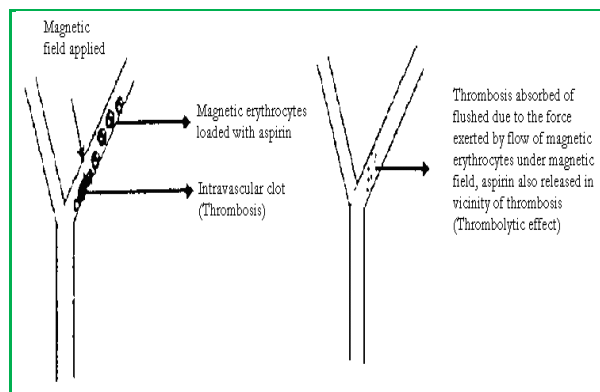


Figure 5: Prevention of Arterial Thrombosis by Aspirin loaded Magnetic Resealed Erythrocytes.

Magnetic emulsions

Besides magnetically modulated systems, like microcapsules / microspheres, magnetic emulsions have been also used as drug carrier for chemotherapeutic agents. The emulsion is a magnetically responsive oil in water type of emulsion bearing chemotherapeutic agent 1-(2-chloroethyl)-3-(trans-4-methyl cyclohexyl) 1nitrosourea (methyl-CCNU) which could selectively be localized by applying an external magnetic field to specific larger site. The magnetic emulsion consists of ethyl oleate based magnetic fluid as the dispersed phase and casein solution as the continuous phase. The anticancer agent, methyl CCNU, was trapped in the oily dispersed

phase. The emulsion showed high retention by a magnetic field in vitro. After i.v injection in the rat, the magnetic emulsion was mainly localized in the lungs by application of an electromagnet over the chest. Therefore, magnetic emulsions appear to have potential in conferring site specificity to certain chemotherapeutic agents.²⁴

APPLICATIONS

Magnetic carriers in protein immobilization

Magnetic materials were suggested as carriers for protein immobilization. Their property to concentrate near magnetic terminals is used in technological process for selective catalyst removal from the reaction mixture, in immunological studies for separation of cells to which magnetic particles are specifically bound modified targeting in vivo into appropriate tissues under guidance if an external magnetic field. A number of methods are available to obtain porous magnetic carriers, containing immobilized matter not only on the surface, but also in the volume of a particle. Normally, these preparations are obtained by granule formation from the suspension of ferromagnetic particles in the solutions or melt of appropriate high molecular weight compound. The drawbacks of the above mentioned methods include pronounced aggregation of ferromagnetic particles and lead to formation of product with a variety of sizes and magnetic properties.

An attempt was made to synthesize the magnetic carrier for protein immobilization. The method is based on commercial adsorption fixation of ferromagnetic particles in the pores of the carrier. The properties of the magnetic sephadex as carrier for protein immobilization were compared by parallel immobilization on both carriers of a-chymotrypsin and I¹³¹albumin. In vivo experiment suggests the ability of magnetic sephadex to concentrate in a desired region of the circulation under the action of external magnetic field.²⁴

Magnetic systems in contraceptive drug delivery

In this magnetically controlled system, the drug and magnetic beads are uniformly dispersed within a polymer material. On exposure to an aqueous media, the drug is release in a diffusion controlled fashion. More ever, the rate can be increased or modulated on application of an oscillating external magnetic field. These systems may be useful when drug delivery is designed responsive to the changes in steroid excretion during the menstrual cycle.²⁸

Magnetically programmable infusion pumps

Magnetic technology is widely used for external programming of cardiac pacemakers. The same principle was adopted to an implantable infusion pump. The development of such pumps to a prototype stage, the newer method of radio frequency (rf) signaling could improve the magnetic approach because of greater programming flexibility and bi-directional transmission capability. In rf-programmable pump, the receiver is

initially switched to a programmable made magnet located in the extracorporeal programming head. When the magnetic field and a recognizable rf pulse sequence are applied simultaneously, the reprogramming occurs. Some of the experimental applications of programmable pumps are:

- Continuous, time pulsed or circadian infusion of antitumour agents into the systemic and portal veins.
- Control of pain in cancer patients by intrathecal or epidural infusion of morphine.
- Treatment of motor specificity in multiple sclerosis with intraspinal infusion of baclofen (GABA binder).

The advantages of programmable pumps over polymeric implants are:

- Drug output can be increased to compensate for biological tolerance to pain medications.
- Catheter tips can be inserted in to very small spaces or vessels where polymer slabs and even injectable microspheres will not fit.
- Pump reservoirs require infrequent filling, only ones every 2-6 weeks depending on drug stability.
- The pumps are designed to for up to 2 years on their original batteries.³⁶

The disadvantages however include:

- Requirement for drug stability in solution at 30°C
- Relative high expense
- Bulkiness of central pump unit
- Failure rate of up to 12%
- Occasional plugging of the outflow catheter
- Minor difficulty in accessing the injection port.²⁹

CONCLUSION

It has been established that the magnetic drug targeting is an efficient means to localizing toxic or labile pharmaceuticals in a preselective site. Magnetic targeting also offers advantages of magnetic capture and retention to endothelium of microvasculature. Magnetically modulated drug release from implants, successfully compensate any decay in release against time. More ever, it minimizes the cost, size and complexity of implanted devices. However, utility of such implants has been compromise due to irreproducibility of magnetic modulation and necessity of surgery to replace such implants after complete drug release. Externally, programmable infusion pumps, need magnetic modulation only to a limited extent for activating radiometry circuits to allow bi-directional information transfer. These pumps are potentially useful and exhibit the flexibility required in the complex clinical applications of the forthcoming future. Magnetic drug targeting is technologically involved but highly efficient means of



localizing toxic or labile pharmaceutical in single or multiple regional sites. The major impact of magnetic targeting would probably occur in the next 25 years. But that time, it is likely that drugs, prodrugs and bioadhesion carriers with high selectivities and targeting efficiencies for specifically diseased tissues will have been developed. A side benefit of research of magnetic targeting is the recent elucidation that actually works by two mechanisms: magnetic capture plus bioadhesion to microvascular endothelium. This implies that it should be possible to target drug carriers by bioadhesion alone. Such targeting may become feasible within the next 5 years of physiological modulation of tissues with normal endothelium; for bioadhesion targeting to be applicable to most pathological disorders, however, more needs to be learned out the endothelial changes that accompany specific clinical diseases.

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