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REVIEW ARTICLE

# MAGNETICALLY TARGETTED DRUG DELIVERY OF THE ANTICANCER DRUGS - CLINICAL PERSPECTIVE

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**Abstract:** Last several decades controlled drug delivery technology has advanced significantly, leading to the development of various clinical formulations improving patient compliance. Targeted drug delivery to solid tumors still needs improvement to reach next level of clinical relevance. Overcoming the challenges involves understanding of drug transport to a target site after intravenous administration, target disease issues and body's response. Targeted drug delivery refers to drug accumulation within target zone that is independent of method and route of administration. Targeted drug delivery require to retain, evade, target and release the drug loaded in the carrier. Targeted drug delivery system is classified as systemic targeting and intracellular targeting. Systemic targeting is further classified into ligand receptor mediated and locally activated drug delivery. Local activation is by self triggered and external triggered such as light, temperature, magnetic field and ultrasound. Magnetic drug delivery hold future promises for the cancer treatment drugs.

**Key words:** Magnetic targeted drug delivery, Cancer drug, Preclinical and clinical study

## INTRODUCTION:

The major disadvantage of most chemotherapeutic approaches to cancer treatment is that they are non-specific. The i.v. administration of cytotoxic drugs leads to general systemic distribution. The non-specific nature of this technique results in the well-known side effects of chemotherapy, as the cytotoxic drug attacks normal, healthy cells in addition to its primary target tumor cells. Therefore, MGDT is seen as a potential means of increasing the efficacy and reducing the unpleasant side effects associated with chemotherapy, by reducing systemic distribution in combination with the possibility of administering lower, but more accurately targeted doses of the cytotoxic compounds used in these treatments.(1)

### Magnetic targeted drug delivery in the cancer therapy-conception

The idea of using magnetic microspheres as vehicles for drug delivery in cancer therapy was first introduced by Widder *et al*.(2) Magnetically-guided drug carriers in the treatment of cancer date back to the late 1970s, however, no such magnetic nanoparticles have yet been clinically approved. Only nanoparticles without magnetic properties, *i.e.* liposomes encapsulating anthracyclines (daunorubicin and doxorubicin), and nanoparticulate albumin-bound paclitaxel are used for the treatment of different types of solid tumors and metastatic breast cancer, respectively.(3)

In 1983 first preclinical study in rats was performed. Selective targeting with intravenously administrated magnetic albumin microspheres containing low doses of doxorubicin resulted in total remission of 77% (17/22) of tumors after only one regimen of drug therapy.(4) As late as 1996, the very first preclinical and clinical studies on magnetic nanoparticles for cancer therapy were done. It is essential to mention that the following magnetically-guided drug carriers were barely classified among nanoparticles since they measured 0.5 - 5.0 μm.

### Magnetic drug delivery system for the cancer drug - Rationality

Site-directed drug targeting could circumvent this problem of large dose low therapeutic index drugs administered by systemic treatment of local disease problem. To mention few and much more anticancer drugs Anastrozole, capectiabine, doxorubicin, epirubcin, Imiquimod, carboplatin, cyclophosphamide, ifofsfamide, Topotecan, pemetrexed, Goserelin acetate, Sorafenib Tosylate, Afatinib dimaleate and other new drugs individually or in combination with other drugs has large potential to explore their application for active drug targeting magnetic drug delivery system. Advantage of using magnetic carrier over non-magnetic ones is that magnetic behavior allows monitoring and quantitative determination of their biodistribution by MRI, which facilitates optimal dosing in cancer therapy. Targeting of tumors by magnetic drug delivery can overcome some supplementary hindrances

in more efficient treatment of cancer, such as insufficient penetration of certain therapeutics from the bloodstream into the tumor. Targeting of tumors with magnetically-guided nanoparticles provides site specificity and thus selectivity of the therapy, which results in reduced side effects and lower cost of the therapy. Exploiting the magnetic field as the driving force represents a non-invasive therapeutic approach.[5]

Magnetic microspheres offer many important applications in biology and medicine for many reasons; firstly they can be coated by many biological molecules to make them interact or bind to a biological entity.[6] Magnetic character obey coulomb's law and can be directed by an external magnetic field to any position inside the biological tissues, by this way microspheres coated with an anticancer drug or radioactive isotope can be directed through the body to the tumor area to destroy it without effect on the normal tissues.[7] Microspheres can be used to transfer the energy from outside source into another source; for example they can transfer the thermal energy induced by external time varying magnetic field to the tumor area which leads to destruction of the tumor tissues in hyperthermia treatment or at least as enhancement agent for chemotherapy that moderate degree of tissue heating give better results for tumor tissues destruction in combination of chemotherapy.[8] The magnetic component of the magnetic microspheres in general is magnetite, Fe3O4, a proven biocompatible iron oxide[8] which is FDA-approved and used clinically as MRI contrast agent[9]. Magnetic drug targeting the tumour cells allows concentration off drug at target site and take takes away from the reticuloendothelial system due to magnetic field and facilitates extra vascular uptake of drug. Anticancer drugs reversibly bound to magnetic fluids (ferrofluids) could be concentrated in locally advanced tumors by magnetic fields that are arranged at the tumor surface outside of the organism. If certain requirements are met, systemic toxicity might be minimized, and local tumor efficacy might be increased. Microspheres can encapsulate many types of drugs including small molecules, proteins, and nucleic acids and are easily administered through a syringe needle. They are generally biocompatible, can provide high bioavailability, and are capable of sustained release for long periods of time.[10] Magnetite offers great potential for advancements in electronics, optoelectronics, magnetic storage, biomedical, ferrofluid, separation and magnetically guided drug carriers for targeting the therapy.[11] Linear blood velocity in capillaries is 300 times less as compared to arteries, so much smaller magnetic field is sufficient to retain them in the capillary network of the target area. Problem of drug resistance due to inability of drugs to be transported across the cell membrane can be surmounted. In case of tumour targeting, microsphere can internalize by tumour cells due to its much increased phagocytic activity as compared to normal cells.

**Exploration of Magnetic particle safety in preclinical study**

Although magnetically controlled, targeted chemotherapy had been experimentally tried with various systems (magnetic emulsions, magnetic starch microspheres, magnetic erythrocytes, and magnetic albumin microspheres), never has a patient been treated with such a system.[4,12,13] There have been too many problems that needed to be overcome; apart from a lack of data suggesting easy large-scale production of the magnetic drug carrier, a lack of data supporting reproducibility in the making of the system, aggregation of some magnetic carriers in vivo, and the need of strong-enough magnets with constant field gradients, to name but a few, there was concern regarding the long-term deposition of magnetic particles in the organism, in addition to discouraging data from large animal experiments and general obstacles with regard to regulatory approval and the economics of the therapy[14]. Therefore a study was conducted by stphen Lubbe et al. to test whether the magnetic fluid in physiological as well as supraphysiological concentrations was tolerated well in two animal models, Sprague-Dawley rats and immunosuppressed mice by examining behavior, laboratory values, tissue specimens, and survival of magnetically bound epirubicin anticancer drug to know whether the ferrofluid could be used for magnetically controlled (i.e., magnetic field-dependent) localization within the organism and could be directed to tumors that were localized at the body surface. The study demonstrated good tolerance of the ferrofluid by the animals and effective tumor therapies with both mechanical obstruction by high concentrations of magnetic particles and what call magnetic drug targeting, using low concentrations of the magnetic particles. In animal and preclinical studies, iron concentrations far higher than those used in this study had been tested. One main difference between ferrofluids used for diagnostic purposes and the one described in this study was the particle size. Although the particle size in the ferrofluid used in this study is 10 to 50 times higher than that of ferrimagnetic contrast fluids, it was safe and no accumulation in the lungs or any clinical signs of respiratory problems were observed. Only in supraphysiological dose ranges, in which 10 to20% of the blood volume was infused within a relatively short time, subjective responses were obtained in the animals, characterized by lethargy for 12to24h and resistance of food uptake. Also, because of the relatively enormous iron load, discoloration of the animals was noticed for about 1 week, symptoms quite similar to those noted in preclinical studies by Van Hecke et al.[1] It was possible to cause complete and lasting tumor remissions by mechanical ob-

struction in two different malignant human tumors by magnetic drug delivery system. Toxicity studies of magnetic nanoparticles are scarce. The first tolerance study with carbohydrate-coated magnetic nanoparticles as potential delivery systems was performed in nude mice and showed no median lethal dose (LD50), no alterations in the blood haematological and biochemical profiles as well as no organomegalies were observed after injection of magnetic nanoparticles. The selective capillary localization of the microspheres can be achieved by taking advantage of the physiological difference in the linear flow velocity of blood at the capillary level (0.05 cm/sec). Obviously, a much lower magnetic field strength is necessary to restrict the microspheres at the slower moving flow velocities of blood in capillaries. After removal of the magnetic field, the microspheres still continued to lodge at the target site, presumable because they had lodged in the vascular endothelium, penetrated in to the interstitial space, resulting in their retention.

The application of an external non-uniform magnetic field will then allow capturing of these magnetic microspheres in the tumor. However, severe complication with these treatments has been reported. Therefore, the development of techniques that could selectively deliver the drug molecules to the diseased site, without concurrent increase in its level in the healthy tissues of the organism, is currently one of the most active areas of cancer research. This overview focuses on the fundamentals of drug targeting with particular emphasis on magnetically controlled anticancer chemotherapy[15-17].

**Toxicity of an external magnetic field**

According to the U.S. National Institute of Environmental Health Sciences, there is a weak association between magnetic field exposure of flux density as small as 0.0003 mT and an increased risk of childhood leukemia.[18] According to numerous MRI examinations, a static magnetic field of flux densities from 0.5 to 2 T does not cause any known side effects and therefore the patient compliance is high.[19] On the other hand, rats developed aversive and avoidance behavior when the field was increased up to ultra-high fields of flux densities of 4 T and 7 T, respectively.[20] There are some inconsistent reports about cellular toxicity or adverse side effects caused by magnetic field exposure which might be due to the cell type dependent mechanisms. It seems that cells deriving from mesenchymal descent are more prone to the magnetic field exposure than other normal and malignant cells[21-25] .

**Preclinical study of Magnetic drug delivery**

Pulfer and Gallo[26] demonstrated that magnetic microspheres (1–2 μm in diameter) could be concentrated at the site of intracerebral rat glioma tumors. Although the concentration of the particles in the tumor was low, it was significantly higher than that of non-magnetic particles. In a later study, the group demonstrated that 10–20 nm IONs were more effectively targeted at these tumors in rats. Electron microscopy analysis of brain tissue samples revealed the presence of magnetic carriers in the interstitial space in the tumors, but in normal brain tissue, they were only found in the vasculature [27]

Magnetoliposomes are a more suitable carrier to transport and deliver a drug, especially due to the smaller size of liposomes compared to albumin microspheres. Magnetoliposomes have a typical core/shell structure: a magnetic iron oxide core surrounded by an artificial liposome. Viroonchatapan et al.[28] designed a study to determine whether dextran-IONs incorporated into liposomes and containing calcein as a fluorescent marker could be targeted at mouse liver with the aid of an extracorporeal magnet. The study consisted of an on-line liver perfusion system with a fluorescence detector. The targeting efficiency was higher in the presence of a magnetic field.
Alexiou et al.[29] treated squamous cell carcinoma in rabbits with mitoxantrone bound to phosphate groups of MNPs coated with starch derivatives. When the implanted carcinoma had reached a volume of ≈3500 $mm^3$, the MNP-MTX was administered via i.a. (femoral artery) or i.v. (ear vein) injection, while an external magnetic field was focused on the tumor. The i.a. administration of the complex resulted in a significant ($p<0.05$), complete and permanent remission of the carcinoma in comparison with both the control group (no treatment) and the i.v. group. Typically, 35 days after the treatment, the tumor disappeared completely. In addition to this, the dose of the drug applied could be diminished to just 20% of the regular systemic dose. No metastases or negative side effects were observed.

Paclitaxel has been one of the most important chemotherapeutic agents against cancer for several decades.[30] The drug has been formulated in a vehicle composed of a 50:50 (v/v) blend of Cremophor EL (polyethoxylated castor oil) and ethanol. However, the formulation induces histamine release and severe allergic reactions.[31] To avoid these undesired effects, paclitaxel has more recently been encapsulated in liposomes, with good results both in vitro and in vivo.[32] After i.v. or intraperitoneal administration, the paclitaxel-liposome formulations are much better tolerated than paclitaxel in the previous vehicle and showed antitumor activity similar to that of the drug in the Cremophor EL/ethanol modality. However, liposomes are subject to opsonic phagocytosis by circulating phagocytes and by macrophages in liver and spleen. Zhang et al. used magnetoliposomes as a strategy to overcome this problem.[33] The formulation was administered via i.v. injection

to mice previously inoculated with breast tumor cells. Magnetoliposomes were guided and retained at the target site with the help of the magnetic field from a circular permanent magnet placed directly on the skin surrounding the tumor mass, via a sterilized rubberized fabric.

The results showed that paclitaxel-magnetoliposomes could effectively be delivered to the tumor and exerted significant anticancer activity with fewer side effects. Sugibayashi et al evaluated the efficacy of Adriamycin associated albumin microspheres administered in presence of a 6000 g MAGNET applied for 10 minutes in a rat bearing AH7974 lung metastases. The microspheres contain 6 and 47% of drug and magnetite respectively. Compared with untreated control and group receiving as drug solution drug delivery through magnetic albumin microspheres was shown to increase survival of animal by 44% and 11% respectively.[12]

**Clinical study of Magnetic drug delivery system**

The first clinical phase-I magnetically-guided drug-targeted study was carried out in 14 patients with advanced unsuccessfully pretreated solid tumors. Intravenous administration of epidoxorubicin attached to magnetic nanoparticles resulted in transient serum iron elevations in almost all patients after the therapy, which did not cause any clinical symptoms, and in some patients increased ferritin levels in the blood were observed. In 50% (7/14) of the patients, magnetic nanoparticles were detected within the tumors. However, only a slight reduction of tumor size occurred in merely 14% (2/14) of the patients.[34]

Later, the same research group utilized mitoxantrone attached to magnetic nanoparticles of the ferrofluid (magnetic liquid) (FF-MTX) aiming to compare the antitumor efficacy of FF-MTX given by different administration routes. The treatment was performed in rabbits bearing squamous cell carcinomas (VX-2) which showed complete and permanent remission after intra-arterial administration of FF-MTX. However, intravenous application of FF-MTX did not result in statistically significant tumor remission in comparison to the control group.[29]

The following preclinical and clinical trials of two research groups focused on the delivery of doxorubicin hydrochloride adsorbed to magnetic targeted carriers (MTC-DOX) by selective arterial catheterization of the hepatic artery(35-37) magnetic targeting, extravasation of MTC-DOX through the vascular wall was obtained, leading to their localization and retention in the tissue at the targeted site. The severity of liver necrosis correlated to the severity of embolization following treatment and was observed only in the animals which received the highest dose of MTC-DOX whereas no adverse effects were determined at the MTC-DOX low-dose group.[35] Clinical trials with MTC-DOX were carried out in patients with inoperable hepatocellular carcinomas. No clinically significant toxicity was observed. However, all patients experienced abdominal pain during MTC-DOX administration which was intravenously controlled with analgesics.[36,37] In the first phase I/II study, localization of MTC-DOX in the tumors was achieved in 94% (30/32) of all the patients with one complete and two partial responses.[36] In the second study MTC-DOX was observed in 100% (4/4) of the tumors with 64– 91% of the tumor volume loaded with magnetic nanoparticles. However, this resulted in only one partial response.[37] A subsequent phase II/III multinational clinical study with MTC-DOX enrolling 240 patients with hepatocellular carcinoma was prematurely stopped as there was no increase in median survival time for MTC-DOX treated patients relative to patients treated with IV doxorubicin.[38]

As indicated, numerous small animal studies have been reported. Due to the technical difficulties mentioned (rapidly diminishing field strength with target depth in the body and the difficulties of bypassing intervening vasculature and tissue structures), clinical applications largely remain a future goal.[39]To date, no application of magnetic targeting in humans has reached the marketplace; although some phase I/II clinical trials have been conducted. To sum up, preclinical studies turned out complete and permanent tumor remission; however, dose escalation clinical trials resulted in no clinically significant toxicities but had a relatively poor tumor response.

**Future Research:**

Evidently, in order to provide assurance that the magnetic field accurately does not cause any side effects there is a vital need to perform additional in vitro as well as in vivo studies. Using of the magnetic microspheres isn't toxic and can be considered as safe for a period of contact with the blood as evident from the research conducted so for. For applications requiring *in vivo* magnetic targeting, for example, magnetic drug delivery, the magnetic carriers must have a proper size range (i.e. between 200 nm and 3 mm) and high magnetizations to enable technically feasible external magnetic guidance within the vasculature (40-44). Magnetic microspheres of micron size range would be better targeting tumours and easier capture under magnetic field. Due to its physical properties of magnetic drug delivery, this approach is feasible for cancer drugs and other site specific action drugs. In this field of research very little was done. The field will open for broader and in depth investigations, that may in near future also bring magnetic target drug delivery into the more clinical trials. There is as yet no FDA /regulatory guidance available for therapeutic magnetic carriers. Hence there are substantial challenges to fabricate mag-

netic targeting recipes from bench scale demonstrations to a bed scale for the much needed patients populations. For overcoming these challenges will require significant effort and a genuine collaboration between engineers, mathematicians, biologists, nanofabricators, industrial pharmacist and clinicians. To answer the type of magnetic drug delivery challenges posed, as a researchers we need to select and optimize magnetic carriers for specific clinical needs, and must bring those carriers up to a level where they can pass regulatory scrutiny and benefit the patients. Selection of drug candidates and carrying out the extensive safety, efficacy and toxicological animal testing will pave way for successful human trials and regulatory approval. The future holds lot of promises in magnetic microspheres and by further study this will be developed as novel and efficient approach for targeted drug delivery system especially for the cancer drugs. It is a challenging area for future research in the drug targeting so more researches, long term toxicity study, and characterization will ensure the improvement of magnetic drug delivery system. With ever evolving scientific technology, magnetic targeted drug delivery can potentially be vital for clinical applications of highly potent drugs and life saving drugs.

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