

## Review Article

## APPLICATION OF FERROFLUID: AS A TARGETED DRUG DELIVERY SYSTEM IN NANOTECHNOLOGY

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## ABSTRACT

The aim of the present investigation is to explain the application of ferrofluid ( $\text{Fe}_3\text{O}_4$ ) as target drug delivery system in nanotechnology. It works on the principle of Magnetism which plays an important role in different application of ferrofluid in medicine. Ferrofluid is biocompatible and therefore it is one of the most extensively used biomaterials for different application ranging from cell separation and drug delivery to hyperthermia. Generally, a ferrofluid in bulk as well as in the form of nano particles in liquid medium had been exploited for a variety of medical applications. In this review we have summarized many novel approaches for the use of ferrofluid in cell separation, immunoassay, drug and gene delivery, minimally invasive surgery, applications in hyperthermia, the mechanism of magnetic targeted drug delivery as well as advantages and disadvantages of ferrofluid used as a magnetic targeting. The drug and an appropriate ferrofluid are formulated into a pharmaceutically stable formulation which is usually injected through the artery that supplies the drug to target organ or tumor cells in the presence of an external magnetic field. The most important application of ferrofluid is as contrast agent for magnetic resonance imaging in diagnosis of disease. Much have been investigated and much more are to be investigated for the use of ferrofluid in novel drug delivery system.

**Keywords:** Ferrofluid, Magnetic targeted drug delivery, magnetism, Nanotechnology.

## INTRODUCTION

Ferrofluid was discovered by Elmor in 1938<sup>1</sup>. It is a colloidal mixture of magnetic particles that have 10-100 nm diameters in a liquid carrier. This liquid carrier contains a surfactant, which prevent the sticking of particles. Ferrofluid can be suspended in water or in an organic solvent. A typical ferrofluid contain 5% magnetic solids, 10% surfactant, and 85% carrier<sup>2</sup>. Ferrofluid do not display ferromagnetism, since they do not retain magnetization in the absence of an externally applied magnetic field. In fact, ferrofluid display paramagnetism, and are often described as "superparamagnetic" due to their large magnetic susceptibility<sup>3</sup>.

1) Drug targeting is the delivery of drugs to receptors or organ or any other specific part of the body to which one wishes to deliver the drug exclusively. Various nonmagnetic microcarries (nanoparticles, microspheres and microparticles etc.) are successfully utilized for drug targeting but they show poor site specificity and are rapidly cleared off by RES (reticuloendothelial system) under normal circumstances<sup>5</sup>.

2) Magnetism has application in numerous fields like diagnostics, drug targeting, molecular biology, cell isolation, cell purification, hyperthermia, and radioimmunoassay<sup>6</sup>.

3) Ferrofluid is widely used to deliver the drug at the specific part of the organ with the help of external magnetic field<sup>5</sup>.

4) Ferrofluid play an important role in this case, magnetic particles composed of magnetite which is well tolerated by the body, and magnetic fields are believed to be harmless to biological systems and adaptable to any part of the body<sup>4</sup>. Up to 60% of an injected dose can be deposited and released in a controlled manner in selected non reticuloendothelial organs. So ferrofluid carriers were developed to overcome two major problems encountered in drug targeting namely RES clearance and target site specificity<sup>5</sup>.

However, ferrofluid lose their magnetic properties at sufficiently high temperatures which may be known as the Curie temperature. A surfactant has a polar head and non-polar tail (or vice versa), one of which adsorbs to a nanoparticle, while the non-polar tail (or polar head) sticks out into the carrier medium, forming an inverse or regular micelle, respectively, around the particle. Then stereo repulsion prevents agglomeration of the particles.

**Ferrofluid surfactants:** The surfactants used to prevent the sticking of magnetic particles include<sup>7</sup>:

- Oleic acid
- Tetramethylammoniumhydroxide
- Citric acid
- Soy lecithin

In magnetic gradient fields, ferrofluid exhibit increased viscosity (this property is used in damper applications) and increased apparent density. This principle is used commercially in mineral beneficiation<sup>1</sup>.



### Advantages of ferrofluid drug delivery system in nanotechnology:

- Rapid clearance of ferrofluid carrier by RES is corrected.
- Avoidance of acute toxicity directed against endothelium and normal parenchyma cell.
- Controlled release of drug within target tissue for intervals of 30 minutes to 30 hrs. This is well adaptable to any part of body.
- This drug delivery system reduces circulating concentration of free drug<sup>6,9</sup>.

### Disadvantages of ferrofluid drug delivery system in nanotechnology:

- In ferrofluid drug delivery system drug cannot be targeted to deep seated organs in the body.
- It is an expensive technique and require specialized manufacturer and quality controlled system.
- In this technique magnet must have relatively constant gradients in order to avoid local overdosing with toxic drugs<sup>6,9</sup>.
- It needs specialized magnet for targeting, advanced technique for monitoring, and trained personnel to perform the procedure<sup>5</sup>.

### Mechanism of ferrofluid as target drug delivery system in nanotechnology:

Ferrofluid drug delivery is a very efficient method of delivering a drug to localized disease site. Magnetic drug transport technique is based on the fact that the drug can be either encapsulated into ferrofluid or conjugated on the surface of the ferrofluid. When the ferrofluid carrier is intravenously administered, the accumulation takes place within area to which the magnetic field is applied. Accumulation of the ferrofluid carrier at the target site allows them to deliver the drug locally. Accumulation of ferrofluid carrier depends on physiological parameters e.g. particle size, surface characteristic, field strength, and blood flow rate etc. The magnetic field helps to extravasate the ferrofluid carrier into the targeted area, and so that very high concentration of chemotherapeutic agents can be achieved near the target site without any toxic effect<sup>6</sup>.

### FERROFLUID AS CARRIER FOR TARGET DRUG DELIVERY SYSTEM IN NANOTECHNOLOGY:

Ferrofluid has much application in various fields of magnetic drug delivery system but out of this drug targeting utilizing ferrofluid as novel approach like magnetic microspheres, magnetic nanoparticles, magnetic liposomes, and magnetic emulsion is very important.

**(A) Magnetic microspheres:** Magnetic microspheres are supramolecular particles which are small enough to circulate through capillaries without producing embolic occlusion but are sufficiently susceptible to be captured in

microvessels and trapped in to the adjacent tissues by magnetic field. Targeting by magnetic microspheres i.e. incorporation of magnetic particles in to drug carriers and using an externally applied magnetic field is one way to physically direct these magnetic drug carriers to a desired site. In the presence of a suitable magnetic field the microspheres are internalized by the endothelial cells of target tissues in tumor cells<sup>9</sup>. Magnetic microspheres were prepared by mainly two methods namely phase separation emulsion polymerization (PSEP) and continuous solvent evaporation (CSE). The amount and rate of drug delivery through magnetic responsive microspheres can be depend upon some factors like size of microspheres, drug content, magnetite content, hydration state and drug release characteristic of carrier<sup>10</sup>. The magnetic microspheres were effectively used for drug targeting to tumor cells, cell separation, diagnosis of disease and magnetic targeting of radioactive compound<sup>5</sup>.

**(B) Magnetic liposomes:** magnetic liposomes are composed of phospholipids, cholesterol and magnetite<sup>11</sup>. Magnetic liposomes can be prepared by entrapment of Ferro fluid within core of liposomes<sup>12, 13</sup>. Magneto fluorescent liposomes were used for increasing immunofluorescence. These magnetoliposomes were also effectively used for site specific targeting, cell sorting and as magnetic resonance contrast enhancing agent<sup>11-14</sup>.

**(C) Magnetic nanoparticles:** Magnetic nanoparticles are those particles which have nano size range and containing polymers, drug along with magnetite. Magnetic nanoparticles have the ability to achieve very high efficiency of separation in complex media. Magnetic nanoparticles have some other application like immunoassay, drug targeting, drug transporting and biosensing<sup>15</sup>. Bacterial magnetite nanoparticles obtained from magneto tactic bacteria after disruption of the cell wall and subsequent magnetic separation have been used for a variety of bioapplications<sup>16</sup>.

**(D) Magnetic resealed erythrocytes:** Magnetic resealed erythrocytes have some important advantages as carriers such as it is biodegradable, biocompatible, large quantity of variety of material can be encapsulated within small volume of cell and can be utilized for organ targeting etc. Magnetically responsive ibuprofen-loaded erythrocytes were prepared and characterized *in-vitro* by Vyas and Jain<sup>17</sup>. Local thrombosis in animal arteries was prevented by means of magnetic targeting of aspirin loaded red cell<sup>18</sup>.

**(E) Magnetic emulsion:** Magnetic emulsion was also tried as drug carrier for chemotherapeutic agents in nanotechnology to deliver chemotherapeutic agent to specific target site<sup>19</sup>.



### CLINICAL APPLICATIONS OF FERROFLUID:

Some of the clinical application of magnetically guided drug targeting has been summarized here:

#### 1) Ferrofluid for targeting drug delivery to tumor cells:

Ferrofluid drug targeting allows the concentration of drugs at a defined target site with the aid of a magnetic field. Site-directed drug targeting is one way of local or regional antitumor treatment. The drug & an appropriate Ferrofluid are formulated into a pharmaceutically stable formulation which is usually injected through the artery that supplies the drug to target organ or tumor in the presence of an external magnetic field. Prolonged retentions of the ferrofluid drug carrier at the target site delay the RES clearance & facilitate extra vascular uptake<sup>20-22</sup>.

Magnetism can play very important role in cancer treatment<sup>23</sup>. Anticancer drugs reversibly bound to ferrofluid and could be concentrated in locally advanced tumors by magnetic field that is arranged at tumor surface outside of the subject. In case of brain tumors, the therapeutic ineffectiveness of chemotherapy is mainly due to the impervious nature of the blood-brain barrier (BBB). Ferrofluid drug carriers are synthesized and their targeting to brain tumor is evaluated *in-vitro* and in animal models<sup>24</sup>.

#### 2) Ferrofluid for bioseparation:

Bioseparation is an important phenomenon for the success of several biological processes. Amongst the different bioseparation techniques, ferrofluid separation is the most promising. Particles that are bound to ferrofluid can be used to remove cells and molecules by applying magnetic fields and *in-vivo* to concentrate drugs at anatomical sites with restricted access. These possibilities form the basis for well-established biomedical applications in protein and cell separation<sup>6</sup>.

The isolation of various macro molecules such as enzymes, enzyme inhibitors, DNA, RNA, antibodies and antigens etc. from different sources including nutrient media, fermentation broth, tissues extracts and body fluids, has been done by using magnetic absorbents. In case of enzyme separation, the appropriate affinity legends are immobilized on polymer coated ferrofluid carrier.<sup>25,26</sup> Immobilized protein A or protein G on silanized ferrofluid and fine magneto tactic bacteria can be used for isolation and purification of IgG<sup>27</sup>.

#### 3) Ferrofluid induced hyperthermia for treatment of cancer:

Hyperthermia is the heat treatment of organs or tissues, such that the temperature is increased to 42–46°C and the viability of cancerous cells reduced. It is based on the fact that tumor cells are more sensitive to temperature than normal cells. In hyperthermia it is essential to establish a heat delivery system, such that the tumor cells are heated up or inactivated while the surrounding tissues (normal) are unaffected.

**a) Intracellular hyperthermia:** Ferrofluid particles selectively heat up tissues by coupling AC magnetic field to targeted magnetic nano particles. As a result, the whole tumor can be heated up uniformly this is called intracellular hyperthermia. It has been shown that malignant cells take up nine times more ferrofluid nano particles than normal cells. Therefore the heat generated in malignant cells is more than in normal cells. Hence, the temperature rise in the region of tumor is higher than in the surrounding normal tissues. It is therefore expected that this therapy is much more effective<sup>6, 29</sup>.

**b) Magnetic fluid hyperthermia (MFH):** Magnetic fluid hyperthermia is based on the fact that sub domain magnetic particles produce heat through various kinds of energy losses during application of an external AC magnetic field<sup>28-30</sup>.

**c) Combination therapy:** There also exists the combination therapy which would induce hyperthermia treatment followed by chemotherapy or gene therapy. A combination of chemotherapy or radiation therapy with hyperthermia is found much more effective than hyperthermia itself<sup>31-34</sup>.

#### 4) Magnetic control of pharmacokinetic parameter and improvement of drug release:

Macromolecules such as peptides have been known to release only at a relatively low rate from a polymer controlled drug delivery system, this low rate of release can be improved by incorporating an electromagnetism triggering vibration mechanism into the polymeric delivery devices with a hemispheric design; a zero-order drug release profile is achieved<sup>35</sup>.

#### 5) Ferrofluid targeting of radioactivity:

Ferrofluid targeting can also be used to deliver the therapeutic radioisotopes. The advantage of these method over external beam therapy is that the dose can be increased, resulting in improved tumor cell eradication, without harm to adjacent normal tissues<sup>6</sup>.

#### 6) Miscellaneous applications:

- The most important application of ferrofluid is as contrast agent for magnetic resonance imaging in diagnosis of diseases.
- Ferrofluid have been successfully used in gastrointestinal surgery for tissue fixation. Which form hermetic seal after surgery and passibility of the gastrointestinal tract is maintained and the patient can able to eat immediately after operation.
- Magnetically guided ferrofluid nanoparticles were used in retinal repair.
- Ferrofluid have application to detect defect in ferromagnetic materials and components based on magnetic flux leakage (MFL) technique.



- e. Ferrofluid can be used to reduce the noise level of certain equipment such as home care kidney dialysis machines<sup>36</sup>.

## CONCLUSION

The above discussion clearly shows that ferrofluid are extremely useful carrier system as target drug delivery system in nanotechnology. Ferrofluid have been investigated for targeting drug delivery in chemotherapy due to their better tumor targeting, therapeutic efficacy, lower toxicity and flexibility, bioseparation magnetic resonance imaging, radioactivity, hyperthermia and testing of tumor cells are the potential application of ferrofluid. Much has been investigated and much more are to be investigated for ferrofluid as a novel approach in drug delivery.

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