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Magnetic Drug Delivery: A Versatile System

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ABSTRACT

Magnetic micro and nano particles have been used for number of applications in various areas of biosciences, targeted drug delivery and in separation technology. Present discussion deals with applicability of magnetic particles as drug delivery system. The review includes mechanism of targeted drug delivery by magnetism, magnetic carriers, advantages, applications and past deign strategies of magnetic drug delivery system.

KEYWORDS

Magnetism, Carriers**,** Targeted drug delivery

INTRODUCTION

The purpose [1, 2, 3] of this review is to consider how externally applied magnetic field can be a guide material internal to the body. The activity of most of drug against disease, suffers from their inability to accumulate selectively at the site of action. Drug targeting is the delivery of drug to receptors or organ or any other specific part of the body to which one wishes to deliver the drug exclusively. Magnetism plays an important role in different applications of health care, magnetic particles which are composed of magnetite, are well tolerated by the body. Magnetic nanoparticles usually exist or can be prepared in the form of single domain or super paramagnetic magnetite (Fe_3o_4), greigite (Fe_3s_4), magnemite ($r\text{-}Fe_2o_3$), iron, nickel, etc. Synthetic magnetic materials have many applications in optics, electronic & energy storage. Magnetism has application in numerous fields like diagnostics, drug targeting, molecular biology, cell isolation, cell purification, hyperthermia, and radioimmunoassay. There have been many attempts in the past to create platform technologies that can guide and deliver drugs, make repairs, and essentially give one's hands the dexterity to seamlessly manipulate nature from macro and micro sizes to the nanometer scale. This range of maneuverability and control over matter allows noninvasive surgery and the ability to pass through tissue and even cell walls instead of cutting or lysing them to obtain

internal access to a material or body. D. Montgomery et al. [5] conceived the first multicoil superconducting magnetic manipulator in 1969. Commercially it appears that only Stereotaxis, Inc. and FeRx Inc. are working on FDA approval for various magnetic targeted drug delivery methods. One large commercial area of magnetic manipulation that has been completed is in the use of magnets to manipulate and retrieve foreign ferric objects in the eye.

The earliest use of magnet for selectively delivery of clinical agent involved treatment of arterial thrombosis by angiography and intravascular localization of carbonyl iron with guidance of catheters. Continuous efforts by researchers established that microparticle of carbonyl iron (1-3 um) are retained at selected intravascular sites in the presence of arterial flow, under the influence of strong magnetic field. Little amount of iron remained at the site for 7 days suggesting migration of some of the particles of the arterial walls and tissues. Initially drugs were grafted on to the surface of magnetic particles, but it suffers from certain drawbacks like very low loading capacity for clinically acceptable limits of dosing with magnetite and irreversible particle aggregation under the exposure of magnetic fields, which ultimately causes immobilization of large blood vessels and non-homogenous particle distribution in capillary bed. Coating of ferromagnetic materials with albumin and other charged polymers however, circumvent the aggregation problem by making it reversible. This led to the introduction of a new approach involving albumin emulsification for preparation of small particles, which encapsulate ferromagnetic material. [5]

Advantages of magnetic drug delivery system

- Therapeutics responses in target organs at only one tenth of the free drug dose.
- Controlled drug release within target tissues for intervals of 30 min. to 30 hrs, as described.
- Avoidance of acute drug toxicity directed against endothelium and normal parenchymal cells.
- Adaptable to any part of the body. [5]

Disadvantage of magnetic drug delivery system

- Magnetic targeting is an expensive.
- In these, technical approach and requires specialized manufacture and quality control system.
- It needs specialized magnet for targeting, advance techniques for monitoring and trained personnel to perform procedures.
- A large fraction (40-60%) of the magnetite, which is entrapped in carriers, is deposited permanently in target tissues.

Due to these limitations magnetic drug targeting is likely to be approved only for very severe diseases that are refractory to other approaches. Such targeting is limited to specialized centers; and to antitumour, antifungal, transplantation, and CNS acting that is highly toxic or labile. [6]

Applications

Magnetic drug delivery system is applied [5, 6, 7, 8, 9, 10, 11, 12] in various fields like the Cancer therapy, Hyperthermic treatment, Targeted drug delivery, Improvement of Drug release and HIV treatment.

Apart from their application in drug delivery, magnetism have found applications in biosciences & biotechnologies like immobilization, detection of biologically active compound & xenobiotic, detection, isolation & study of cells and cells organelles.

Mechanism of action

The aim of the specific targeting is to enhance the efficiency of drug delivery & at the same time to reduce the toxicity & side effects. Magnetic drug transport technique is based on the fact that the drug can be either encapsulated into a magnetic microsphere (or nanosphere) or conjugated on the surface of the micro/nanosphere. When the magnetic carrier is intravenously administered, the accumulations take place within area to which the magnetic field is applied & often augmented by magnetic agglomeration. The accumulations of the carrier at the target site allow them to deliver the drug locally. Efficiency of accumulation of magnetic carrier on physiological carrier depends on physiological parameters like

particle size, surface characteristic, field strength, & blood flow rate etc. The magnetic field assists to extravasate the magnetic carrier into the targeted area. Some kinds of channel opened by the force of the magnet are thought to be associated with process of extrusion by magnetic targeted carriers. This technique, which requires only a simple injection, is far less invasive than surgical methods of targeted drug delivery.

Another advantage is that particles in the magnetic fluid interact strongly with each other, which facilitates the delivery of high concentrations of drug to targeted areas. Magnetic system for concentrating magnetic particles in an organ/tumour can be seen in figure 1.

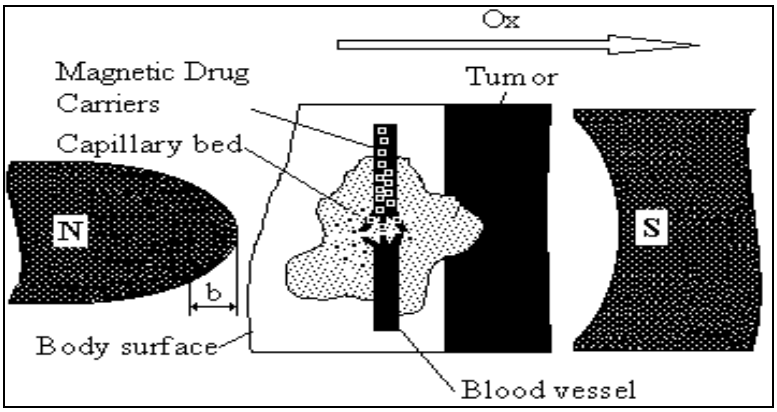

Figure 1: Magnetic system for concentrating magnetic particles in an organ/tumour

FORMULATION ASPECT

Magnetic carriers

Magnetic microcarriers are supramolecular particles that are small enough to circulate through capillaries without producing embolic occlusion, but are sufficiently susceptible (ferromagnetic) 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 microsperes, liposomes, cells, nanoparticles etc. [6]

A. Magnetoliposomes [13, 14, 15, 16]

These are magnetic carrier which can be prepared by entrapment of ferrofluid within core of liposome's, Magnetoliposome can also be produced by covalent attachment of ligands to the surface of the vehicles or by incorporation of target lipids in the matrix of structural phospholipids Alternatively magnetoliposomes are prepared using the phospholipid vesicle as a nanoreactor for the in situ precipitation of magnetic Nano particles. Vesicles are also prepared containing didodecyl methyl ammonium bromide; contain an ionic magnetic fluid. These magnetoliposomes were effectively used for site-specific targeting, cell sorting & as magnetic resonance contrast enhancing agent.Thermosensitive magnetioliposomes can release the entrapped drug after selective heating caused by the electromagnetic fields.

B. Magnetic Nanoparticles [17, 18]

Magnetic colloidal iron oxide nanoparticles were prepared with the method of co precipitation. Interfacial polymerization was also applied to synthesize magnetic nanoparticles. Bacterial magnetite nanoparticles obtained from magnetotactic bacteria after disruption of the cell wall & subsequent magnetic separation have been used for a variety of bioapplications. Due to the presence of the lipid layer these particles are biocompatible, their suspensions are very stable & the particles can be easily modified.

C. Magnetic Resealed Erythrocytes [5]
Magnetically responsive drug-loaded erythrocytes were prepared and characterized in vitro. The erythrocytes loaded with drug and magnetite (ferrofluids) using the preswell technique. The loaded cell effectively responded to an external magnetic. In the continuous study, drug bearing erythrocytes were prepared by preswell technique and characterized for various in vitro parameters.

D. Magnetic Emulsion [5]
Magnetic emulsion was also tried as drug carrier for chemotherapeutic agents. The emulsion is magnetically responsive oil in water type of emulsion bearing a chemotherapeutic agent, which could be selectively localized by applying an external magnetic field to specific target site.

E. Magnetic Microspheres [5]
The use of magnetic force for the site-specific drug delivery by using albumin microspheres containing magnetite appears to be a promising strategy. Significant improvement in response can be incorporated and obtained with the magnetic albumin microspheres drug regimens. In the presence of suitable magnetic field, the microspheres are internalized by the endothelial cells of the target tissue in healthy as well as tumour bearing animals.

Magnetic Material
A. Magnetite (Fe_3O_4)

- Face centered cubic crystal structure
- Inverse spinel structure
  ½ Fe+3 tetrahedral
  ½ Fe+3 & Fe+2
  octahedral
- Unit cell – 56 atoms:
  32 O-2 anion, 16 Fe+2 and 8 Fe+2 cation

Advanced Characterization of Magnetite

- X-ray diffraction of Fe_3O_4 nanoparticles: Synchrotron Light Source Brookhaven Nat Lab
- X-ray absorption Spectroscopy (XAS):
  Synchrotron Light Source Brookhaven Nat Lab

B. Methoxy Polyethylene Glycol (mPEG)

- Nanospheres coated with mPEG
- Coating reduces the uptake of nanoparticles into macrophage cells Prevents body's immune system from attacking the drug carriers
- Also increases biocompatibility, resists protein absorption, increases circulation time, and internalization efficiency

C. Poly L-Lactic Acid (PLLA)

- High biocompatibility
- Good biodegradable feature
- Essential that particles come in contact temporarily
- Non-toxic products

D. Gold Coating

- Very compatible with biological molecules
- Easy control of composition, size, and Geometry
- Better stabilization and drug release rate.

Characterization of Magnetic Particles

Scanning electron microscopy is used to determine the size & morphology of magnetic nanoparticles whereas Dynamic Light Scattering is used to measure the hydrodynamic diameter. Magnetic mobility (overall responsiveness or amount of velocity for a given magnetic field & field gradient) of different types of magnetic micropheres is characterized so that their behavior in patient circulation can be predicted. For this purpose stationary setup similar to cell tracking velocimetry system, which can be used, on standard microscope equipped with a digital camera& computer system. The main difference to above system is that there is no flow of the suspension containing the magnetic particles. The geometry & size of the set up & magnet used can be reduced considerably. Furthermore the close combination of the microscope set up with computer allows fully automated data acquisition & processing. [19, 20]

CONCLUSION

Magnetic system seems to serve as a common function of opening a new vista of a multi-barrier or multi-step drug delivery. It has been established that magnetic drug targeting is an efficient means of localizing toxic or labile pharmaceuticals in a preselective site. Magnetic targeting is a process of choice for 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 of targeting has been exploided to achieve adequate drug levels, bioavailability enhancement, localizing the effect of biopharmaceuticals and avoidance of toxic manifestations. Magnetic targeting also offers advantage of magnetic capture and retention to endothelium of microvasculature.

Magnetically modulated drug release from implants, successfully compensate any decay in drug release against time. Moreover, it minimizes the cost, size and complexity of implanted devices. However, utility of such implants has been compromised 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 application of the forthcoming future.

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