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MAGNETIC PILLS AN ATTRACTIVE DELIVERY SYSTEM: A REVIEW

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ABSTRACT

"Magnetic drug delivery systems have been emerged as a prominent technique for site-specific targeting of various pharmacological agents throughout the last few decades". With the support of a magnetic field, it avoids reticule endothelial system and directs the drugs to reach the target precisely. Magnetic carriers like nanoparticles, microspheres, liposomes and emulsion have been found advantageous of the fact that they reduces the free drug concentration in the blood and to minimize the adverse effects provoked by these drugs. Recent decades have shown a vast range of applications in the field of magnetic nanotechnology as it has expanded its scope to oncological, cardiovascular and neurological disorders. They have been under keen investigation in different fields as next generation drug carriers due to their physical properties. Magnetic nanoparticles have displayed a great potential in drug loading proficiency due to their magnetic core intrinsic capabilities and physico-chemical properties due to the coating efficiency. Numerous therapeutics demonstrates optimal absorption or activity at specific sites in the gastrointestinal (GI) tract. Effective pill retention within a desired region of the GI remains an elusive goal. We report a safe, effective method for localizing magnetic pills. To ensure safety and efficacy, we monitor and regulate attractive forces between a magnetic pill and an external magnet, while visualizing internal dose motion in real time using biplanar video fluoroscopy.

KEYWORDS: Magnetic pills system, structurally principle, classified character, challenges.

INTRODUCTION

"Magnetic pills drug delivery have displayed a great potential in drug loading proficiency due to their magnetic core intrinsic capabilities and physico-chemical properties due to the coating efficiency .These particles having size less than 100 nm, are employed under the influence of magnetic field and manipulated by different materials such as iron, nickel, cobalt. Enhanced performance is delivered below a critical value of their size which is around 10-20 nm.[1] These nanoparticles show super magnetic behavior above blocking temperature and acts like paramagnetic atoms showing less resonance. They can be used in different ways like magnetic resonance imaging, vascular contrasting agents, diagnosing agents, as theranostic in targeting of cancer treatment, targeting of genes, tissue engineering, bio separations, cell tracking. However, problems of intrinsic instability can occur over longer period of time as they can easily oxidize in air causing loss of the magnetic property.

The described system represents a significant step forward in the ability to localize magnetic pills safely and effectively anywhere within the GI tract. What our magnetic pill localization strategy adds to the state of the art, if used as an oral drug delivery system, is the ability to monitor the force exerted by the pill on the tissue and to locate the magnetic pill within the test subject all in real time. This advance ensures both safety and efficacy of magnetic localization during the potential oral administration of any magnetic pill-based delivery system.[2]

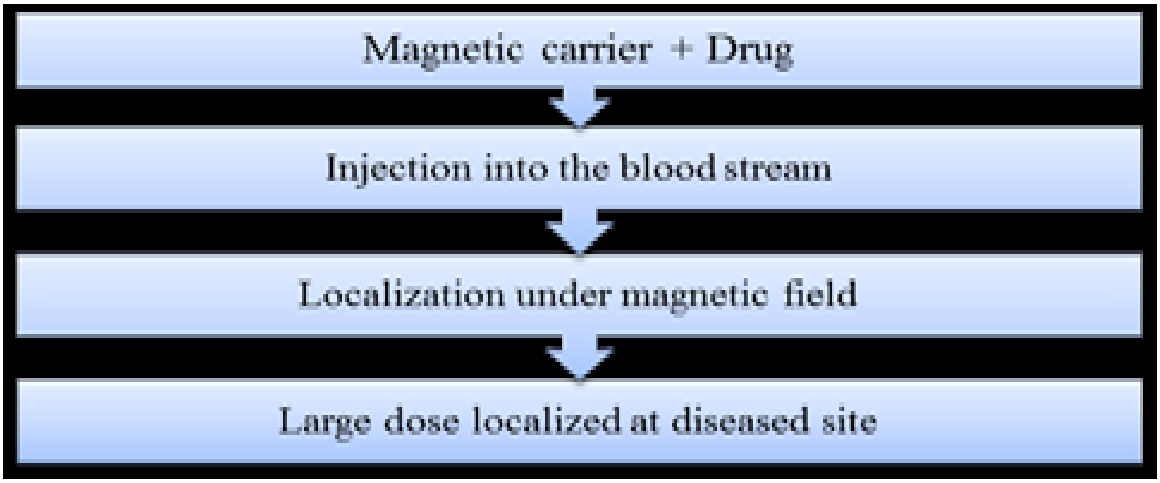

Figure 1: Mechanism of action for magnetic targeted drug delivery systems.

ADVANTAGES OF MAGNETIC PILLS DELIVERY

- Excess amount of drug is reduced minimizing unwanted effects.
- Frequency of administration is reduced.[2,3]

- Reduced side effects of drugs as compared to conventional dosage forms.
- Targeted organ receive prolonged delivery of drug.
- Diseased organ receive sustained drug delivery.[3]

PRINCIPLE OF MAGNETIC DRUG DELIVERY SYSTEM

Magnetic targeting is one of the productive methods to deliver the drug at diseased site by virtue of a magnetic compound.

These drug delivery systems contain magnetic responsiveness being integrated from different substances like magnetite, iron, cobalt, nickel, iron-boron or samarium-cobalt.

The drug along with the magnetic compound is injected into the patient's blood circulation system and a magnetic field is applied at the target site to block it.[3,4]

Thus, considerable less amount of drug concentration can be achieved at specific site which minimizes the unwanted effects due to the high drug concentrations of freely circulating drug.

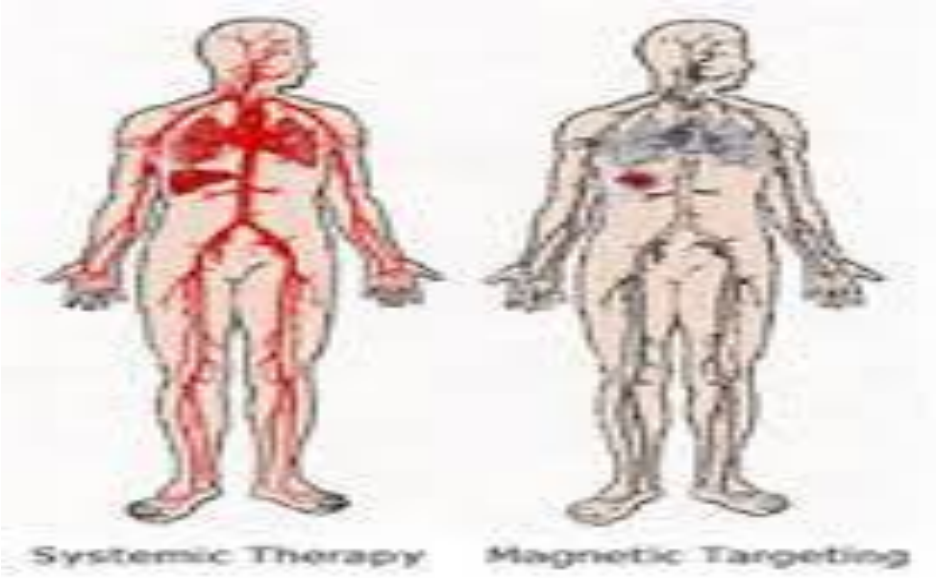

Figure 2: Representation of principle of magnetic pills.[4]

WORKING OF MAGNETIC PILLS

The two main components of the system are conventional looking gelatin capsules that contain a tiny magnet and an external magnet that can precisely sense the force between it and the pill and vary that force, by varying the external magnetic force the capsule can be held at a specific location.

The magnetic force is precisely controlled to avoid damaging surrounding tissue.

The pill's retention works by creating an inter magnetic force between the magnetic gelatin capsule and an external magnet.[4, 5]

Magnetic capsule in the body placed t right place by the magnet outside which create a magnetic attraction and force to locate the magnetic capsule.[5]

CLASSIFICATION OF MAGNETIC DRUG DELIVERY SYSTEM

To achieve controlled and targeted delivery of drug, magnetic carrier drug delivery systems (DDS) can be categorized into

1. Magnetic nanoparticle.
2. Magnetic microspheres.
3. Magnetic liposomes.
4. Magnetic emulsions.

1. Magnetic nanoparticle

Magnetic nanoparticles are a class of nanoparticle which can be manipulated using magnetic field gradients.

Such particles commonly consist of magnetic elements such asiron, nickel and cobalt and their chemical compounds. While nanoparticles are smaller than 1 micrometer in diameter (typically 5–500 nanometers), the larger microbeads are 0.5–500 micrometer in diameter. Magnetic nanoparticle clusters which are composed of a number of individual magnetic nanoparticles are known as magnetic nanobeads with a diameter of 50–200 nanometers.[5, 6] The magnetic nanoparticles have been the focus of much research recently because they possess attractive properties which could see potential use in catalysis including nanomaterial-based catalysts, biomedicine and tissue specific targeting, magnetically tunable colloidal photonic crystals, microfluidics, magnetic resonance imaging, magnetic particle imaging, data storage, environmental remediation, nanofluids and optical filters, defect sensor and cation sensors.[6]

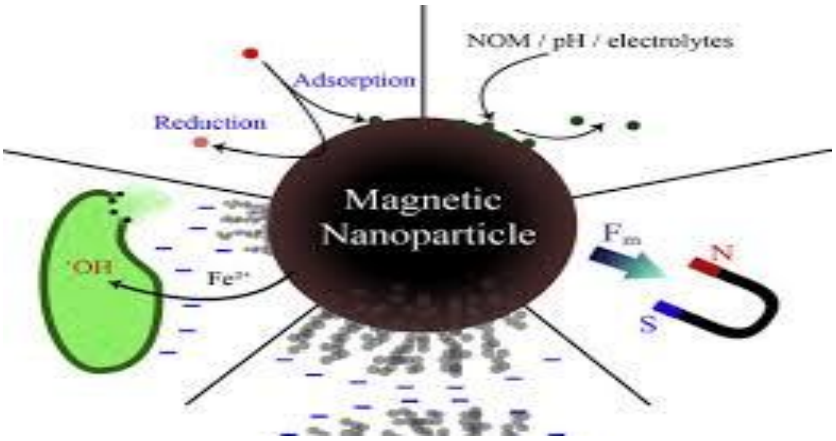

Figure 3: Synthesis of Magnetic Nanoparticles.[6]

Magnetic nanoparticles have been prepared by using different compounds like cobalt, nickel, iron, ferrous oxides, ferrites like MFe2O4 (where M can be Cu, Mg, Mn, Ni etc.) and metal alloys.

They can be synthesized using different methods like co-precipitation, thermal decomposition and micro emulsion method.[6, 7]

Magnetic nanoparticles prepared by

(a) Co-precipitation method

(b) Microemulsion technique (Tartaj et al. 2003)

(c) Thermal decomposition.

(a) Co-precipitation method

Characterization

- Magnetic nanoparticles can be characterized through following analysis.
- Transmission electron microscopy for determination of size and shape.
- X-ray diffraction for structural determination.[7,8]

2. Magnetic Microspheres

Magnetic microparticles comprise of different materials, having strong magnetic moment which can successfully deliver non-magnetic substances like cells, antibodies, drugs, nucleic acids and enzymes to the magnetic field.

These are smaller in size i.e. less than 4 µm, which provides an efficient flow rate to pass through capillaries without formation of embolus.

They consist of biocompatible proteins or synthetic polymer to which the drug is bound and are formulated to be used in depot form near targeting site by nearby placing suitable magnet. To avoid unwanted distribution of drug to non target organ help in drug localization and avoid toxicity.[8]

It was propounded by Gupta and Hung that magnetic microspheres can cause 16 fold increases in drug concentration, 6 fold increases in drug exposure and 6 fold increases in targeting efficiency of the system.

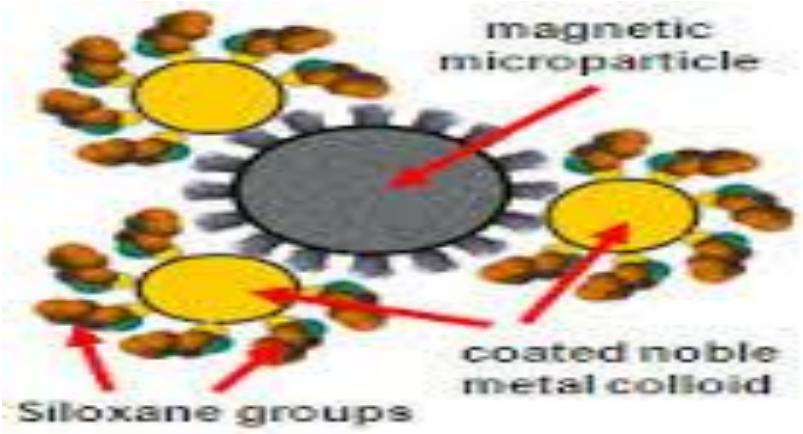

Figure 4: Magnetic Microsphere.[8,9]

Preparation of Magnetic Microsphere

Magnetic Microspheres are prepared generally by two methods. One is Phase separation emulsion polymerization method and other is continuous solvent evaporation method. Microspheres prepared by these two techniques are known to be biocompatible with the blood and are stabilized by addition of albumin.

Magnetic field having greater field strength is required for a fast moving arterial system.[9]

(a) Phase Separation Emulsion Polymerization

In phase separation emulsion polymerization method, an aqueous suspension is prepared by incorporation of polymer, drug and magnetite into sufficient amount of water.

Emulsifying agent is added to the solution for formation of oily phase which is stabilized by heating at appropriate temperature of 100-150˚C followed by drop wise addition of cross linking agent with constant stirring that result in formation of magnetic microspheres.

Washing procedure is used to separate oil from suspension by subjecting it to freezing temperature at 4˚C.[10]

(b) Continuous Solvent Evaporation Method

Polymer, drug and magnetite solution should be added to the volatile organic solvent at constant stirring to form an auxiliary homogeneous solution at temperature of 22- 30˚C. Evaporation of the organic solvents takes place to form microspheres followed by centrifugation, freeze drying and storage at 4˚C.[10, 11]

Characterization

- Magnetic microspheres are subjected to different tests to verify its morphological structure and different physico-chemical properties.
- They include particle size analysis, scanning electron microscopy, flow properties through angle of repose and compressibility index, thermal analysis, determination of % age yield, drug content, determination of drug loading, incorporation efficiency of microscopy, determination of solubility and dissolution studies of microspheres.
- These linkages are stabilized by using pullalan hydrazide.[11]
- Magneto liposomes are also advantageous because of the fact that they escape from reticuloendothelial system very easily and their lipid layer is sensitive to the magnetic field.[12]

3. MAGNETIC LIPOSOME

Magnetic liposomes entrapping target for imaging (MRI) and radiation therapy with Neutron capture NCT or photodynamic X-ray therapy PXT. During preparation targets as Boron-compounds and X-ray absorbers were entrapped inside the liposomes.

This enables the application in cancer therapy by local radiation therapy, as well as imaging diagnostics or rheological experiments with Magnetic tweezers.[12]

The formation of the liposomes and the internal metal structure was observed by ASAXS, time resolved neutron scattering TR-SANS, dynamic light scattering DLS and electron microscopy EM using a stopped-flow mixing device.

The internal volume was used for entrapping of water-soluble target material, which produces secondary radiation of short range upon irradiation, or drug targeting applications. The magnetic shell liposomes revealed a size of 50-400 nm, as required for applications in vivo (< capillary diameter).[13]

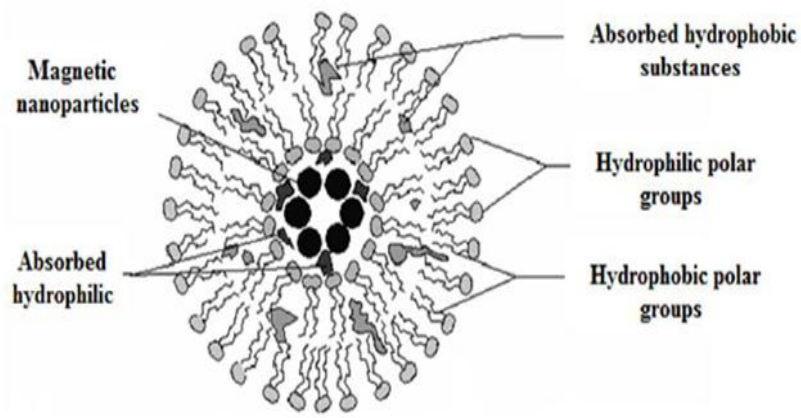

Figure 5: Structure principles of Magnetic liposome.[13]

Metallo-liposomes can bear the metal supplying magnetic properties as well as specific radiation interaction, in three structures

a) metal-lipid liposomes, e.g. Me-DTPA-DMPE or Me -DTPA -StearylAmide, bearing the metal inside and outside (different metals possible); as used for ASAXS at ESRF-ID1 and DESY.

b) Liposomes entrapping metal-oxide nanoparticles (MexOy) or metal-chelate (DTPA-Gd, -Sm, -Fe, -Ho, -Dy, or cis-Pt.

c) Metal oxide Shell liposomes bearing a double wall structure: lipid (outside) and metal-oxide (inside). For biomedical applications the metal is Iron or Gadolinium: Fe-chelate or Gd-chelate (DTPA-lipid [6]), or Fe–oxide; e.g. -Fe2O3.[13]

Characterization

- The internal structure of the magnetoliposomes is observed through time resolved neutron scattering TR-SANS at ILL-D22 and time resolved electron microscopy TR-EM using a stopped-flow mixing device.[14]

4. Magnetic Emulsion

Emulsion is a colloidal system consisting of two immiscible liquids (water and organic solvent) and being stabilized by polymers or surfactants known as emulsifying agents.

Water compose oil in water type emulsion when it is based as continuous external phase while as internal dispersed phase, it constitutes reverse water in oil type emulsion.

Magnetic emulsion is an emulsion type in which ferrofluids, containing the stable dispersion of magnetic nanoparticles, constitutes the internal phase.[14, 15]

Characterization

Magnetic emulsions can be analyzed through following tests

- Infrared spectroscopy to evaluate the adsorption of surfactants on magnetic particles.
- Elemental analysis to evaluate the ferrofluids and magnetic particles.
- X-ray diffraction to investigate the crystallographic structure of the iron oxides and magnetic particles size distribution.
- Thermo gravimetric analysis of the ferrofluids in dried state.
- Transmission electron microscopy.
- Freeze fracture to investigate the internal structure of the ferrofluids.
- Gas chromatography to determine the octane concentration in the magnetic emulsion.[14]

CHALLENGES FOR MAGNETIC DELIVERY SYSTEM

The system is not the first attempt to guide pills magnetically, but it is the first one in which scientists can control the forces on a pill so that it's safe to use in the body. They designed their system to sense the position of pills and hold them there with a minimum of force.

The greatest challenges were quantifying the required force range for ma intaining a magnetic pill in the small intestines and constructing a device that could maintain inter - magnetic forces within that range.

To check whether the pills is reach to the exact place can check by taking some blood samples and to check bioavailability of the same drug.[13-15]

RECENT APPLICATIONS

Magnetic drug delivery system since its origination has shown tremendous applications in biomedical and biophysical fields of science.

1. Treatment of Tumors

- Magnetic microspheres can be used in chemotherapy of anti-cancer drugs in their delivery to tumors e.g. doxorubicin.
- For such kind of site-specific targeting, magnetically modulated drug targeting systems have been successfully applied.

- Magnetic field in such cases is applied to concentrate the drug at tumor site thus eliminating systemic side effects Different rats suffering from sarcoma were assessed after giving both free doxorubicin and doxorubicin with magnetic microspheres.
- It was evaluated that rats treated with free doxorubicin had increased tumor size while those treated with magnetic microspheres showed a significant 83 % decrease in the tumor size.[14-16]

2. Targeting of Radioactive Compounds

- Radioisotopes in therapeutic range can be delivered under magnetic field to target tissues.
- Dose can be increased rendering damage to the normal tissues with improved anti-tumor activity.
- Selective radiation of the targeted tissues is carried out with the help of magnetic particles being coupled with different isotopes and an external magnetic field is applied to bind them In recent years, radio labeling with isotopes such as 188Re; 90Y, 111ln and 125I have been successfully employed.[17]

3. Magnetic Hyperthermia

- Magnetic hyperthermia has been established to destroy the diseased tissues with the help of elevated temperature as they are more sensitive to the temperature compared to the healthy tissues.
- The other advantage is its restriction to the diseased tissues only.
- Recently liposomal nanoparticles have been established according to this mechanism as successful approach to the cancer therapy.
- Magnetic liposomes have also been prepared and studied for hyperthermia treatment of cancer through magnetic particles coated with phospholipids.[17,18]

4. Diagnostic Applications

One of the modern and useful applications of magnetic delivery system is its diagnostic applications which involves

In-vivo Applications

With the development of NMR imaging technique, a new pharmaceutical class known a Magneto pharmaceuticals has been established, providing following advantages

- Improvement in distinguishing of diseased to normal tissue.

- To determine normal function of organ.[19]

In-vitro Applications

Magnetic solid phase extraction method is used in isolation and determination of components and impurities from testing samples in large volume as compared to conventional extraction processes which are more time consuming.[20]

CONCLUSION

Safe and effective, monitored magnetic pill localization is a crucial step for investigating and producing new, site-specific therapies for the treatment of a wide range of diseases. These novel drug delivery systems have increased the ability to deliver drugs for which conventional therapy has shown limited efficacy. This technology will not only minimize invasive procedures, but also reduce side effects to healthy tissues, which are two primary concerns in conventional cancer therapies. The field of magnetic drug delivery is still at infancy, and synthesis of better magnetic drug delivery system. These current systems may have real potential to be clinical MRI contrast agents. However this is just the beginning an ideal for clinical diagnosis of early stage disease pathology, mediation of functional drug delivery (therapy).

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