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MAGNETIC NANOCARRIERS AS A POTENTIAL TARGETED THERAPEUTIC DRUG DELIVERY SYSTEM

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ABSTRACT

Targeted therapeutic delivery system aims to target the therapeutics to the site of action. A number of targeted therapeutic delivery system has been studied for targeting of various drugs but researchers have shown keen interest in magnetic targeting now a days. Magnetic targeted drug delivery, based upon magnetic particles under the action of an external magnetic field, is an effective technique for drug therapy. It is aimed at concentrating drugs at target site, with the help of a magnetic field, to direct the drugs away from reticuloendothelial system. These systems improve the therapeutic efficacy of associated chemotherapeutic agents, by altering their distribution in the body.

Keywords*:* - Magnetic nanoparticals, Drug delivery, Biomedical applications

INTRODUCTION

Nanoscale science and engineering are providing us with unprecedented understanding and control of matter at its most fundamental level: the atomic and molecular scales. In particular, nanoscale particles have attracted much attention due to their unusual electronic, optical and magnetic properties. The dimensions of these nanoparticles (NPs) make them ideal candidates for nanoengineering of surfaces and the production of functional nanostructures.

Principle

Magnetically targeted drug delivery system (MT-DDS) will be a promising way, which involves binding a drug to a small biocompatible magnetically active component, entrapped in the biodegradable polymeric matrix and formulating in to a pharmacologically active stable formulation, which is injected into the blood stream and using a high-gradient magnetic field to pull them out of suspension in the target region.

Advantages

- The magnetic particles are well tolerated by the body; magnetic fields are harmless to biological systems and adaptable to any part of the body.
- It is possible to replace large amount of freely circulating drug with much lower amount of drug targeted magnetically to localized disease sites, reaching effective and up to several fold increased localized drug levels.
- Magnetic carriers overcome two major problems encountered in drug targeting reticuloendothelial system (RES) Clearances and target site specificity.

Limitations

- The main limitation in MT-DDS is the inability to focus treatment to target deep inside the body. When stationary magnets are used, they can only concentrate near the skin surface.
- Magnetic targeting is an expensive, technical approach and requires specialized manufacture and quality control system.
- Rapid clearance of targeted systems especially antibody targeted carriers.

Applications

Magnetic delivery of chemotherapeutic agents to treat tumors

Magnetism plays a very important role in cancer treatment. Anti-cancer drugs reversibly bound to magnetic fluids are concentrated in tumors by magnetic field. This is an efficient inexpensive method for creating an embolism to starve tumors or to seal off arteriovenous malformations.

Magnetic targeting of radioactivity

Magnetic targeting is used to deliver the therapeutic radioisotopes. The advantage of this method over ex thermal beam therapy is that the dose can be increased, helps in improved tumor cell eradication, without harm to adjacent normal tissues.

Magnetic Transfect ions

When functionalized with DNA vectors, they are used as effective gene transfection systems under external magnetic field, named as magnetofections. An example for magnetic non-viral gene transfer protocol includes steps of synthesis of carrier, binding of intact DNA preparation of magnetic lipoplexes and polyplexes, magnetofections and data processing

Tissue engineering

Magnetic carriers have been used in stem cell replacement therapy for cell labeling, sorting, monitoring, engraftment and targeted in vivo delivery. And also to weld the joining tissue surfaces under high temperatures, a process typically accompanied by protein denaturation followed by re-polymerization of adjacent protein chains.

Iron detection

Excess metal deposits leads to neurodegenerative disease, including multiple sclerosis, Friedreich's ataxia, Alzheimer's, Parkinson's, and Huntington's diseases .Advanced technologies of nano-sized iron detection in neuronal tissues, such as by superconducting quantum interference device (SQUID) magnetometry, are used as a diagnostic strategy in identifying iron deposits in the brains of Alzheimer's and neuro ferritinopathy patients.

Treatment of tumors with magnetically induced hyperthermia

Heat treatment of organs or tissues, such that the temperature is increased to 42–46 C is called hyperthermia, so that the viability of cancerous cells reduces. As tumor cells are more sensitive to temperature than normal cells, it is essential to establish a heat delivery system, such that the tumor cells are heated up or inactivated while the surrounding tissues are unaffected.

Magnetic systems for cell separation

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.

Magnetic systems for diagnosis of disease

The most important diagnostic application is using of magnetic carriers as contrast agents for magnetic resonance imaging (MRI), for imaging various metastases. For example,

monocrystalline iron oxide nanoparticles are used to selectively visualize tumors in vivo in real time at exceptionally high spatial resolution.

Magnetic control of pharmacokinetic parameters and drug release

Embedding magnetite or iron beads in to a drug filled polymer matrix increase or decrease the release of drug from the polymer by moving a magnet over it or by applying an oscillating magnetic field. Macromolecules such as peptides are known to release only at a relatively low rate from a polymer-controlled drug delivery system, release rate can be improved by incorporating an electromagnetism triggering vibration mechanism into the polymeric delivery devices.

Magnetic drug delivery system in antimicrobial and antiviral therapy

The magnetic nanoparticles are also promising carries for antibacterial agents such copper and silver and can provide an alternative treatment for bacterial infections. As known, silver is distinguished by extraordinary inhibitory and bactericidal properties for a broad spectrum of bacterial strains. Antibacterial coatings based on hydrogen bonded multilayer containing in situ synthesized silver magnetic nanoparticles can be delivered to a specific region to localize a high concentration of antibacterial silver while maintaining a low concentration in general.

Desirable characteristics of magnetic nanoparticles as a targeted therapeutic delivery system:

- The particles should be small enough to remain in circulation after injection**.**
- The magnetic material should be nontoxic**.**
- The polymer should be biocompatible i.e., nontoxic and non-immunogenic.

DEVELOPMENTOF MAGNETIC TARGETED DRUG DELIVERY

The first step in the design of such a system is to choose a seed material. The magnetic responsiveness to a magnetic field is achieved through incorporation of materials such as magnetite, greigite, magnemite, iron, nickel, cobalt, and neodymium-iron-boronorsamarium-cobalt. Ferromagnetic magnetite is used mostly because of its relatively high magnetic moment in reasonably sized particles. The further step is to incorporate this magnetic seed with different drugs.

MAGNETIC CARRIERS

Magnetic carriers must be water-based, biocompatible, non-toxic and immunogenic. Magnetic carriers are grouped according to their size. Encapslated microcarriers in the size range of 10-500 nm are magnetic nanospheres and particles of just below1-100 micrometers

are magnetic microspheres. Various types of magnetic carriers include:

Magnetic microspheres

These are supramolecular particles which are small enough to circulate through capillaries. They are pre-pared by phase separation emulsion polymerization (PSEP) and continuous evaporation (CSE). The amount and rate of drug delivery of the semicrospheres are regulated by varying size, drug content, magnetite con-tent, hydration state and drug release characteristic of carrier.

Magnetic liposomes

These are simple microscopic vesicles, consisting of concentric bilayer structure in a manner that the lipid layers alternate with the aqueous layers. The unique feature with these carriers is ability of incorporating both water soluble and oil soluble therapeutic agents in the aqueous and the lipid layers respectively.

Magnetic nano particles

Magnetic nano particles are the particles in nano size containing polymers, drug along with the ferro magnetic particles. Magnetic colloidal iron oxide nano particles are prepared by the method co precipitation.

Magnetic resealed erythrocytes

The clinical use of cell transfusions leads to the use of erythrocytes in drug delivery and targeting. They are biodegradable and using ones' own erythrocytes eliminates any immunological problems. The drug release can be controlled by adjusting the stability of cell membranes

Magnetic emulsion

Magnetic responsive emulsions are oil in water type of emulsion bearing drug which is localized to the specific site by the external magnetic field. A magnetic emulsion can be prepared by using ethyl oleate based magnetic field as the dispersed phase, casein solution as the continuous phase and the drug is trapped in the oily phase.

Magnetic microcapsules

They are non-biodegradable carriers developed for the concept of magnetic arterial embolization as a part of chemotherapy to preclude the necessity of carrier Extravasation. But this embolization concept didn't get the anticipated impact due to large size and non-biodegradability of the carrier.

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.

SYNTHESIS OF MNPs

a. Synthesis by Co precipitation

The precipitation reaction in aqueous media without using organic stabilizing agents is the first controlled process. In this method, magnetic iron oxides (Fe3O4 or Fe2O3) were prepared by a mixture of FeCl3 and FeCl2 in a pH range from 8 to 14.In the process, nucleation appeared above the critical supersaturation species concentration. A main advantage of the co precipitation process is easy synthesis procedure, but the size distribution of magnetite particles is large.

b. Synthesis in Constrained Environments

The constrained environments have been reported to produce narrow size distribution MNPs. Stable colloidal Fe3O4 nano particles (NPs) were prepared in water-in-oil (w/o) single inverse micro emulsion and had super paramagnetic properties and a narrow size distribution. The size of magnetite particles could be controlled by temperature and surfactant concentration.

c. Synthesis by Thermal Decomposition

The high-quality iron oxide NPs have been obtained by hydrolysisand oxidation or neutralization of the mixed metal hydroxides at high temperature solution. The prepared MNPs could be controlled by reaction conditions, such as nature of the solvent, temperature, time, the concentration and ratios of reactants. The MNPs were obtained by thermal decomposition of a complex of iron and cup ferronin the octylamine condition. The hydrophobic NPs were transformed into hydrophilic ones by adding bipolar surfactants. Iron oxide NPs with uniform sizes between 13 nm and180 nm were selectively prepared through the "heating up" thermal decomposition method by using decanoic acid and carefully tuning the heating rate.

d. Synthesis by sol-gel Reaction

Recently, a sol-gel approach has been used to prepare SPIONs. For example, Fe_2O_3-SiO_2 composite was prepared with Tetra ethoxysilane and iron (III) nitrate as starting materials. The thickness of silica coating could be controlled by the concentration of sol-gel solution,

the (surface of evaporation)/volume (S/V) ratio of sol, pH environments, the concentration of salts, and the temperature. The sol-gel procedure to prepare MNPs has some general advantages, including the possibility to obtain materials with predetermined structure, monodispersity and well controlled particle size in a nanoscale.

e. Synthesis by Electrochemical Reaction

The electrochemical synthesis of Fe_2O_3 NPs was performed in DMF. An imposed current density was a controlled factor for a size ranging from 3 to 8 nm and different cationic surfactants were used to stabilize the NPs. The dry powder exhibited super paramagnetic behavior at room temperature. Hydrothermal treatment enabled the obtaining of very stable magnetic SPIO powders, with an elevated Curie temperature from Tc=860 K to Tc=920 K. The process of subsequent boiling had an especially strong influence on the powders electrochemically formed in water. Most carbon-encapsulated MNPs (CEMNPs) have been synthesized using an arc discharge method in which metal precursors were usually packed inside a cave drilled into a graphite electrode and then subjected to arc vaporization.

Characterization of Magnetic Particles

1. Particle Size and Shape

Magnetic particles synthesized by above methods are of variable sizes. Their properties are quite different from other type of micro and nano particles. The most widely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both techniques can be used to determine the shape and outer structure of the microparticles.

2. Chemical Analysis

The surface chemistry of the microspheres can be determined using the electron spectroscopy for chemical analysis (ESCA). ESCA provides a means for the determination of the atomic composition of the surface. Fourier Transform Infrared Spectroscopy (FTIR) is used to determine the degradation of the polymeric matrix carrier system. The surface of the microspheres is investigated measuring total attenuated reflectance (ATR).

3. Drug Loading

The capture efficiency or the drug loading of the microspheres or the percent entrapment can be determined by allowing washed microspheres to lyse the lysate is then subjected to the determination of active compound by suitable method. The percent encapsulation efficiency is calculated using following equation:

% Entrapment = (actual content / theoretical content) x 100

4. Magnetic Properties

Magnetic properties of nano composite particles were characterized by using vibrating sample magnetometer (VSM). The magnetic moment of each dried magnetic particles measured over a range of applied fields between -800a+800Gauss with a sensitivity of 0.1 emu/g. the prepared samples can be characterized by weight or volume in VSM.

CONCLUSION:

The advantages of nanotechnology in therapy are obvious, such as highly targeted ability, imaging platforms, unique transfection, stem cell labeling, hyperthermia, and bioseparation. It has been established that the magnetic drug targeting is an efficient means to localizing toxic or labile pharmaceuticals in a preselective site.

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