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Review Article

Magnetized carrier as novel drug delivery system

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Abstract
There has been keen interest in the development of a novel drug delivery system. Novel drug delivery system aims to deliver the drug at a rate directed by the needs of the body during the period of treatment, and target the active entity to the site of action. A number of novel drug delivery systems have emerged encompassing various routes of administration, to achieve controlled and targeted drug delivery, magnetic microcarriers being one of them. These microcarriers include magnetic microspheres, magnetic liposomes, magnetic nanoparticles, magnetic resealed erythrocytes, magnetic emulsion etc. Magnetic micro/nanoparticles & molecular magnetic labels have been used for great number of application in various areas of biosciences, targeted drug delivery, imaging & in bioseparation technology. This review paper will summarize about mechanism of magnetic targeted drug delivery, magnetic carriers ,benefits and drawbacks of magnetic targeting, characterization and application of magnetism in targeted drug delivery and some other field.

Keywords: magnetc microcarriers, magnetic liposomes, magnetic nanoparticles, magnetic resealed erthrocytes.

Introduction

The activity of most drugs against disease suffers from their inability to accumulate selectively at the site of action. 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. Magnetism play an important role in these case, magnetic particles composed of magnetite which are well tolerated by the body, magnetic fields are believed to be harmless to biological systems and adaptable to any part of the body[1]. Up to 60% of an injected dose can be deposited and released in a controlled manner in selected nonreticuloendothelial organs. So magnetic microcarriers were developed to overcome two major problems encountered in drug targeting namely RES clearance and target site specificity[2].

There are many different approaches to targeted drug delivery, which are classified broadly into three categories. 1) Physical or mechanical approach which requires formulation of the drug using a particulate delivery device, (for eg. magnet) which by virtue of its physical localization will allow differential release of the drug. 2) Biological approach which involves delivery of the drug using a carrier system like antibodies, lecithin. 3) Chemical Approach which incorporates chemical delivery systems, allow targeting of active biological molecules to specific target sites or organs, based on predictable enzymatic activation[37]

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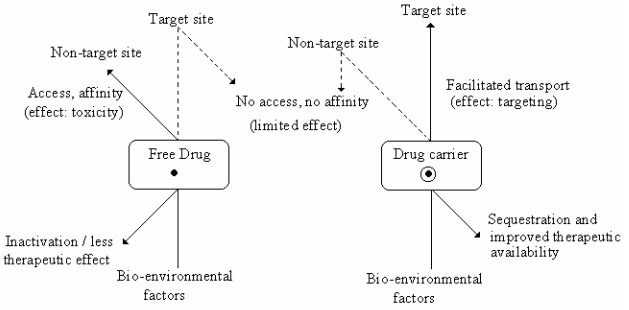
Magnetism play an important role in different applications of health care, magnetic particles composed of magnetite which are well tolerated by the body [38] Magnetic nanoparticles usually exist or can be prepared in the form of single domain or superparamagnetic magnetite (Fe3o4), greigite (Fe3s4), magnemite (r-Fe2o3), iron, nickel, etc. synthetic magnetic materials have many applications in optics, electronic & energy storage [39]. Magnetism have application in numerous field like diagnostics, drug targeting, molecular biology, cell isolation, cell purification, hyperthermia, radioimmunoassay. This article discuss the potential applications of magnet in drug targeting, formulation of magnet containing particles & characterization of magnetic particles.

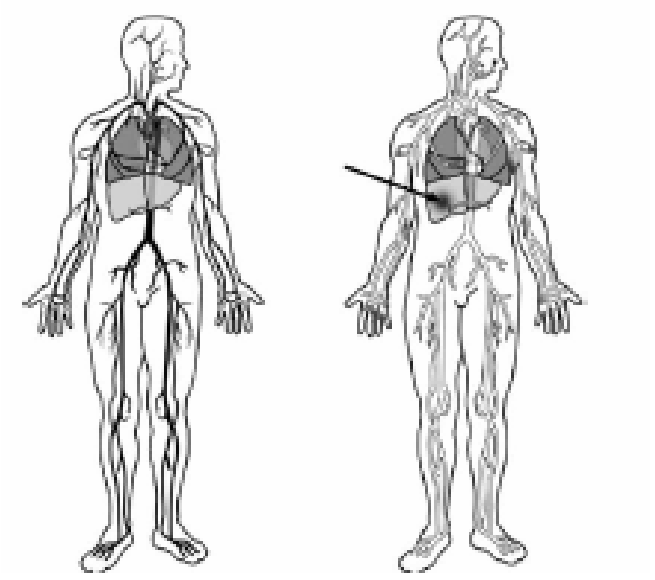
Targeting is signified if the target compartment is distinguished from the other compartments, where toxicity may occur and also if the active drug could be placed predominantly in the proximity of target site. The restricted distribution of the parent drug to the non-target site(s) with effective accessibility to the target site(s) could maximize the benefits of targeted drug delivery

Principle and Mechanism of Magnetic Drug Targeting[4,14]



Magnetic drug delivery by particulate carriers is a very efficient method of delivering a drug to localized disease site. Very high concentrations of chemotherapeutic or radiological agents can be achieved near the target site, such

as tumour, without any toxic effects to normal surrounding tissue or to whole body. In magnetic targeting, a drug or therapeutic radioisotope is bound to a magnetic compound, injected into patient's blood stream, and then stopped with a powerful magnetic field in the target area. Depending on the type of drug, it is then slowly released from the magnetic carriers (e.g. release of chemotherapeutic drugs from magnetic microspheres) or confers a local effect. It is thus possible to replace large amounts of drug targeted magnetically to localized disease sites, reaching effective and up to several –fold increased localized drug levels (wider et al., 1979; Gupta and Hung, 1989; Hafeli et al,1997)



Systemic Drug Delivery Magnetic Targeting

Figure: shows the principle of magnetic drug targeting.

Magnetic drug delivery by particulate carriers is a very efficient method of delivering a drug to localized disease site. 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 accumulation takes place within area to which the magnetic field is applied & often augmented by magnetic agglomeration. The accumulation of the carrier at the target site allows them to deliver the drug locally. Efficiency of accumulation of magnetic carrier on physiological carrier depends on physiological parameters eg. particle size, surface characteristic, field strength, & blood flow rate etc. The magnetic field helps to extravasate the magnetic carrier into the targeted area. Some kind of channel opened by the force of the magnet are thought to be associated with process of extrusion by magnetic targeted carriers. [40]

Very high concentration of chemotherapeutic agents can be achieved near the target site without any toxic effect to normal surrounding tissue or to whole body. It is thus possible to replace large amounts of drug targeted magnetically to localized disease site, reaching effective and up to several fold increased drug levels[3]

Carriers for drug targeting (magnetic carriers)

Carrier is one of the most important entities essentially required for successful transportation of the loaded drug(s). They are drug vectors, which sequester, transport and retain drug en route, while elute or deliver it within or in vicinity of target. Following is the categorical presentation of these potential targetable systems.

A) Magnetic microspheres :

Magnetic microspheres are supramolecular particles that are small enough to circulate through capillaries without producing embolic occlusion (<4 μm) but are sufficiently susceptible (ferromagnetic) to be captured in microvessels and dragged in to the adjacent tissues by magnetic fields of 0.5-0.8 tesla (T)[2]. The amount and rate of drug delivery via magnetic responsive microspheres can be regulated by varying size of microspheres, drug content , magnetite content , hydration state and drug release characteristic of carrier[4]. the amount of drug and magnetite content of microspheres needs to be delicately balanced in order to design an efficient therapeutic system.

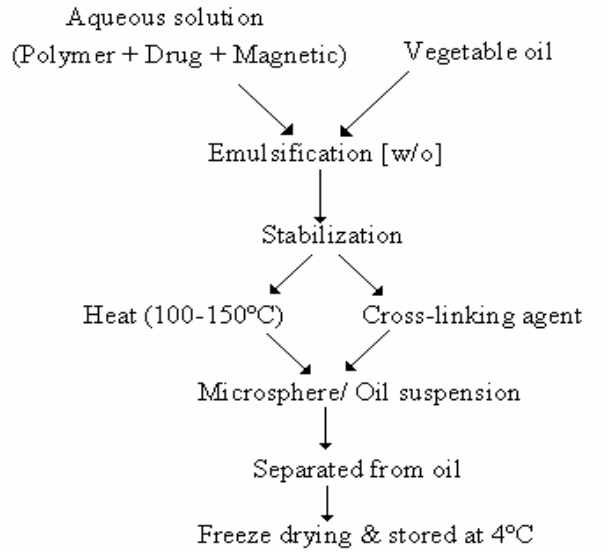
Widder et al. first reported on the use of magnetic albumin microspheres.Widder et al. also shows that in the presence of a suitable magnetic field, the microspheres are internalized by the endothelial cells of target tissues in healthy as well as tumor bearing animals[5]. Gupta and Hung suggests that in presence of magnetic field, the microspheres demonstrated 16 fold increase in the maximum drug concentration, 6 fold increase in drug exposure and 6 fold increase in the drug targeting efficiency to rat tail target segments[6]. Morimoto and Natsume studied the utilization of magnetic microparticulate system for cancer therapy by formulating a novel cationic delivery system based on magnetic aminodextran microspheres (MADM) and compared with the neutral magnetic dextran microspheres (MDM) [7]. The magnetic microspheres were effectively used for drug targeting to tumor cells, cell separation, diagnosis of disease and magnetic targeting of radioactivity[2].

There are mainly two techniques, which are commonly employed for microspheres preparation: -

(a) Phase separation emulsion polymerization (PSEP)

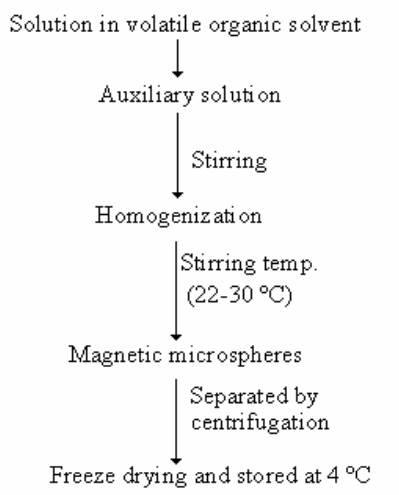
(b) Continuous solvent evaporation (CSE).

Phase separation emulsion polymerization:



Schematic diagram of preparation of magnetically responsive microspheres by PSEP technique

Continuous solvent evaporation:



Schematic diagram of preparation of magnetically responsive microspheres by CSE

B)Magnetic liposomes:

Liposomes are simple microscopic vesicles in which lipid bilayer structures are present with an aqueous volume entirely enclosed by a membrane, composed of lipid molecule. There are a number of components present in liposomes, with phospholipids and cholesterol being the main ingredients but in case of magneto liposomes magnetite is one of the component of the liposomes[8]. Generally these are magnetic carrier which can be prepared by entrapment of Ferro fluid within core of liposomes [9, 10]. 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[11]. Alternatively magnetoliposomes are prepared using the phospholipid vesicle as a nanoreactor for the in situ precipitation of magnetic nanoparticles. Vesicles are also prepared containing didodecyl methyl ammonium bromide; contain an ionic magnetic fluid[13.] These magnetoliposomes were effectively used for site specific targeting, cell sorting & as magnetic resonance contrast enhancing agent. Thermo sensitive magnetioliposomes can release the entrapped drug after selective heating caused by the electromagnetic fields. Magnetofluorescent liposomes were used for increasing sensitivity of immunofluorescence. Margolis et al. demonstrates utilization of magnetoliposomes in cellular sorting[15]. The feasibility of magnetic liposomes as a targeting device in tumor cell was explored by Kiwada et al[16]. The preparation, physicochemical properties and their possible use as a targeting carrier have been described by Ishii et al[17]. The possibility of dextran magnetite incorporated thermosensitive liposomes was studied by Mausko et al[18]. Antibody coated magnetoliposomes for hyperthermia treatment of cancer were prepared by coating phospholipid on to magnetic particles were studied by Shinkai et al[19]. Chen and Langer prepared magnetically responsive polymerized liposomes as potential oral delivery vehicles for complex molecules such as protein and peptide to protect them from gastrointestinal environment and targeting them to the payer's patches[20].

Passive targeting of doxorubicin with Polymer Coated Liposomes in tumor bearing rats were studied by Hirofumi Takeuchi et al.[33]

(C) Magnetic nanoparticles:

Magnetic nanoparticles are particles in nano size range containing polymers, drug along with ferromagnetic particles (magnetite). In recent years the separation of cells, viruses, and bio-molecules using magnetic microparticles has gained increasing popularity. Hence, new technologies using magnetic microparticles or nanoparticles are emerging. With magnetic separation, it is possible to achieve very high efficiency of separation in complex media. Other applications of magnetic nano particles include immunoassays, drug targeting, drug transporting, and biosensing[21].

Magnetic colloidal iron oxide nanoparticles were prepared with the method of coprecipitation[22]. Ferromagnetic iron-dextran nanoparticles were prepared by reacting a mixture of ferrous chloride and ferric chloride with dextran polymers under alkaline condition. Interfacial polymerization was also applied to synthesize magnetic nanoparticles[23]. Pedro Trataj et al. described synthetic routes for the preparation of magnetic nonoparticles useful for biomedical applications[24].Bacterial magnetite nanoparticles obtained from magneto tactic 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[25].Vyas and Malaiya were prepared indomethacin bearing magnetic nanoparticles of polymethylmethacrylate by the emulsion polymerization technique[26]. Surface modification of super paramagnetic nanoparticles (Ferro fluid) with particle electrophoresis and their application in the specific targeting of cells was studied by sestier et al[27]. J. Yang et al described preparation of Magnetic poly -caprolactone (PCL) nanoparticles in a well shaped spherical form by the o/w emulsion method.[34]

D)Magnetic Resealed Erythrocytes:

Resealed erythrocytes have various advantages as drug 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. Due to these advantages of resealed erythrocytes, magnetic resealed erythrocytes came in to existence which contains ferrofluides (magnetite) along with loaded drugs within the cell. Magnetically responsive ibuprofen-loaded erythrocytes were prepared and characterized in vitro by Vyas and Jain[28]. The erythrocytes loaded with ibuprofen and magnetite (ferrofluids) using the preswell technique. The loaded cell effectively responded to an external magnetic field. Various process variables including drug concentration, magnetite concentration, sonication of ferrofluids that could affect the loading of drugs and magnetite were studied. The loaded erythrocytes were characterized for in vitro drug efflux, hemoglobin release, morphology osmotic fragility, in vitro magnetic responsiveness and percent cell recovery. In the continuous study, diclofenac sodium bearing erythrocytes were prepared by preswell technique and characterized for various in vitro parameters[29].Local thrombosis in animal arteries was prevented by means of magnetic targeting of aspirin loaded red cell was studied by Orekhova et al[30].

E)Magnetic Emulsion:

Besides magnetic modulated systems, like microcapsules/microspheres 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[29].Akimoto and Morimoto prepared magnetic emulsion by utilizing ethyl oleate based magnetic fluid as the dispersed phase, casein solution as the continuous phase and anticancer agent, methyl CCNU trapped in the oily dispersed phase as active chemotherapeutic agent. Magnetic emulsion appears to have potential in conferring site specificity to certain chemotherapeutic agent[31].

Table 1

Delivery system	Drugs tested	Route of Administration
Aqueous media	Bleomycin	i.t.
Aqueous media	Vinblastine sulfate	i.t.
w/o/w Emulsion	Bleomycin	i.t.
o/w Emulsion	Mitomycin	i.t.
s/o Emulsion	Bloomycin	i.t.
Liposomes	Bloemycin	i.t.
Aqueous media	Cisplatin analogues	i.v.
Starch microspheres	Camustin	i.a.
Ethylcellulose microcapsules	Cisplatin	i.a.
Albumin microspheres	Cisplatin	i.a.
polylactic acid microspheres	Aclarubicin	i.a.
Polymethacrylate nanoparticles	Doxorubicin	i.v.
Antibodies	Vindesine	i.v.

Factors Affecting Rate of Drug Delivery [2]

The amount and rate of drug delivery via magnetically responsive microspheres can be regulated by varying size of microspheres, drug content, magnetite content, their hydration state and drug release characteristic of carrier. Actually all these factors are interconnected. The size of microspheres is related to their drug content by a direct proportionality. However, drug content is also governed by the solubility characteristic of the drug and method of preparation of microspheres. Hydration step of microspheres affect their body distribution and drug release rate from the microspheres. The magnetic content and magnitude of applied field governs the retention of microspheres at targeted sites. In case of microspheres with higher magnetic content, smaller magnetic field are sufficient for efficient retention of microspheres in the targeted area. But by incorporating excessive magnetite into the microspheres, the effective space available for the drug in microspheres is reduced appreciably. So amount of drug and magnetite content of microspheres needs to be delicately balanced in order to design an efficient therapeutic system.

Drugs Generally Used For Magnetized Targeting

Adriyamycin, Doxorubicin, 5Flurouracil, Oxantrazole, Cisplatin, Hydrocortisone

Dactinomycin, Diclofenac sodium[17], Dexamethasone[18]

Carriers generally used for entrapping drug and magnetite : -

Poly lactide	Ova albumin
Casein	Fibrinogen
Ethyl cellulose	Chitosen
Calcium alginate	Gelatin
Nitrocellulose	Polyvinyl alcohol (PVA)
Starch[19]	Polyalkylcynoacrylates
Agarose	Poly ethylene glycol (PEG) [20]
Carnauba wax	Polystyrene

Human serum albumin (HSA) Bovine serum albumin (BSA)

N-Isopropyl acrylamide and their copolymer

Representative Examples of Various Targeted Drug Delivery Systems Investigated for Cancer Chemotherapy[42]

Note. i.t., intratumoral; i.v., intravenous; i.a., intraarterial; w/o/w, water-in-oil-in-water; o/w, oil-in-water; s/o, sphere-in-oil.

Applications

The most popular applications of magnetic carrier technology are bioaffinity chromatography, wastewater treatment, immobilization of enzymes or other biomolecules and preparation of immonological assay [15].

It is also used in the delivery of insulin, nitrates as well as in selective β blockers, in general hormone replacement immunization and cancer chemotherapy.

a)Magnetic drug targeting: Tumor targeting:

There are a large number of magnetic carrier systems which demonstrates increasing drug concentration efficiency at the tumor site.

Magnetism can play very important role in cancer treatment. The first clinical cancer therapy trials using magnetic microspheres were performed by Lubbe et al. in Germany for the treatment of advanced solid tumor[21,22] while current preclinical research is investigating use of magnetic particles loaded with different chemotherapeutic drugs such as mitoxantrone, paclitaxel[23]. Non invasive permanent magnetic field for one hour way found to induces lethal effects on several rodent & human cancers. Anticancer drugs reversibly bound to magnetic fluids & could be concentrated in locally advanced tumors by magnetic field that or arranged at tumor surface outside of the subject.

Various novel biodegradable magnetic drug carriers are synthesized and their targeting to brain tumor is evaluated in vitro and in animal models. New cationic magnetic aminodextran micro spheres (MADM) have been synthesized. Its potentiality for drug targeting to brain tumor was studied. this particles were retained in brain tissue over a longer period of time.

example magnetic doxorubicin in liposome has significant anticancer effect in nude mice bearing colon cancer.

b) Magnetic bioseparation:

Amongst the different bioseparation techniques, magnetic separation is the most promising. The development of magnetically responsive microspheres has brought an additional driving force into play. Particles that are bound to magnetic fluids 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. Additional modifications of the magnetic particles with monoclonal

antibodies, lectins, peptides, or hormones make these applications more efficient and also highly specific[3].
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 ligands are immobilized on polymer coated magnetic carrier or magnetizable particles. Immobilized protein A or protein G on silanized magnetite and fine magnetotactic bacteria can be used for isolation and purification of IgG. Monosized super paramagnetic particles, Dynabeads, have been used in isolation of mRNA, genomic DNA and proteins.

c) Magnetically induced Hyperthermia for treatment of cancer:
Heat treatment of organs or tissues, such that the temperature is increased to 42–46 C and the viability of cancerous cells reduces, is known as hyperthermia. 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.
i) Intracellular hyperthermia:The alternative approach is to use fine particles as heat mediators instead of needles or rods such that hyperthermia becomes noninvasive. When fluids containing submicron-sized magnetic particles(typically 1–100nm) are injected, These particles are easily incorporated into the cells, since their diameters are in the nanometer range. These magnetic 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.
ii) 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. If magnetic particles can be accumulated only in the tumor tissue, cancer specific heating is available, various biocompatible magnetic fluids. Cationic magnetoliposomes and affinity magnetoliposomes have been used for hyperthermia treatment.
(iii) 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. The approach involves use of magnetic carriers containing a drug to cause hyperthermia using the standard procedure, followed by the release of encapsulated drug that will act on the injured cells. It is anticipated that the combined treatment might be very efficient in treating solid tumor. [41]
On going investigations in magnetic hyperthermia are focused on the development of magnetic particles that are able to self-regulate the temperature they reach. The ideal temperature for hypothermia is 43˚C - 45˚C, and particles with a curie temperature in this range have been described by kuznetsov et al. (2002) [29].
Developments by Jordan and chan led to the current hyperthermia application of single domain dextran- coated magnetite nanoparticles in tumors (Jordan et al. 1993; chan et al.1993) [26]. The first clinical trials are going on in Germany (Jordan et al. 2001) [27]. Magnetic hyperthermia is also possible with larger magnetic particles, as shown by the group of moroz et al. (2002) [28].

(d) Magnetic control of pharmacokinetic parameter and Improvement of Drug release:
Langer et al.embedded magnetite or iron beads in to a drug filled polymer matrix and then showed that they could activate or increase the release of drug from the polymer by moving a magnet over it or by applying an oscillating magnetic field (Langer et al.,1980; Edelman and Langer,1993).The microenvironment with in the polymer seemed to have shaken the matrix or produced 'micro cracks' and thus made the influx of liquid, dissolution and efflux of drug possible thereby achieving magnetically controlled drug release.
In this way, it was possible to magnetically activate the release of insulin from a depot underneath the skin (Kost et al., 1987). Done repeatedly this would allow for pulsative drug delivery.
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.

(e) Magnetic targeting of radioactivity:
Magnetic targeting can also be used to deliver the therapeutic radioisotopes (Hafely, 2001)[24].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. Magnetic targeted carriers, which are more magnetically responsive iron carbon particles, have been radiolabelled in last couple of years with isotopes such as ^{188}Re (Hafely et al., 2001)[25], ^{90}Y, ^{111}In, and ^{125}I (Johnson et al. 2002)[23] and are currently undergoing animal trials.

(f) Magnetic system for the diagnosis of disease:
The most important diagnostic application of magnetic particles is as contrast agent for magnetic resonance imaging (MRI). The most commonly used super paramagnetic material is Fe_3O_4 with different coatings such as dextrans, polymers, and silicone.
Suini et al. tested 0.5-1μm sized ferrites in vivo for the first time in 1987 (Suini et al., 1987). Since then, smaller supramagnetic iron oxides (SPIOs) have been developed into unimodular nanometers sizes and have since 1994 been approved and used for the imaging of liver metastasis (ferumoxide based feridex I.V, or Endorem) or to distinguish loops of bowel from other abdominal structures (GastroMark, or Lumirem in Europe).

(g) Miscellaneous Applications:
Magnetic elements have been successfully used in gastrointestinal surgery for tissue fixation. Which form hermetic seal after surgery & passibility of the

gastrointestinal tract is maintained & the patient can able to eat immediately after operation. Magnetically guided ferrofluid nanoparticles were used in retinal repair. Magnetically guided interstitial diffusion of the nanoparticles up to 20mm of the gel over periods of 72 hours was shown to be possible, thus demonstrating that essentially all points on the retinal surfaces are reachable from elsewhere in the ocular interior.

Apart from their application in drug delivery, magnetism have sound applications in biosciences & biotechnologies like immobilization, detection of biologically active compound & xenobiotic, detection, isolation & study of cells and cells organelles. These applications are reviewed by Ivo Safarik & Mirka Safarikova and Saiyed ZM et al.

It can be used for encapsulation of peptide octreotide and the protein tumor necrosis factor alpha (TNF-α) (Johnson et al. 2002) [23]. Advantages of such an approach are target gene transfection at rapid speed and high efficiencies.

It is also possible to use only the mechanical- physical properties of magnetic particles or ferrofulids for therapy. One example is the embolization (clogging) of capillaries under the influence of a magnetic field (Flores and Liu, 2002). In this way, tumors could specifically starved of their blood supply. Another elegant example is the use of magnetic fluids to prevent retinal detachment, thus preventing the patients from going blind (Dailey et al. 1999).

Benefits

a) Diffusion occurs maximally in capillary network so efficient delivery of drug to diseased tissue is achieved.

b) Microspheres can transit in to extravascular space thereby creating an extravascular drug depot for sustained release of drug within the targeted area.

c) Therapeutic responses in targeted organs at only one tenth of the free drug dose.

d) Controlled release with in target tissue for intervals of 30 minutes to30 hrs. as desired.

e) Avoidance of acute drug toxicity directed against endothelium and normal parenchyma.

f) Adaptable to any part of the body.

g) This drug delivery system reduces circulating concentration of free drug by a factor of 100 or more.

h) Magnetic carrier technology appears to be a significant alternative for the biomolecule malformations (i.e. composition, inactivation or deformation).

i) In case of tumor targeting, microspheres can be internalized by tumor cells due to its much increased phagocytic activity as compared to normal cells. So the problem of drug resistance due to inability of drugs to be transported across the cell membrane can be surmounted.

j) Magnetically responsive microspheres (MRM) are site specific and by thelocalization of these microspheres in the target area, the problem of their rapid clearance by RES is also surmounted.

Problems Associated With Targeted Drug Delivery Systems [5]

Several problems have been identified which require alterations in targeting strategies particularly, in vivo

- Rapid clearance of targeted systems especially antibody targeted carriers.
- Drug- antibody inactivation during conjugation.
- Immune reactions against intravenous administered carrier systems.
- Target tissue heterogeneity.
- Problems of insufficient localizations of targeted systems into tumor cells.
- Down regulation and sloughing of surface epitopes.
- Diffusion and redistribution of released drug leading to non-specific accumulation.
- Nanoparticles are difficult to manufacture in large quantities.
- Nanoparticles has bioacceptibility restrictions.

Limitations [4]

Drug(s) can't be targeted to deep-seated organs in the body. So this approach is confined to the targeting of drugs in superficial tissues only like skin, superficial tumors or to joints etc.

Magnetic targeting is an expensive, technical approach and requires specialized manufacture and quality control system. It needs specialized magnet for targeting, advanced techniques for monitoring, and trained personnel to perform procedure.

Magnets must have relatively constant gradients, in order to avoid local over-dosing with toxic drugs.A large fraction (40-60%) of the magnetite, which is entrapped in carriers, is deposited is deposited permanently in target tissues. Due to this limitation magnetic drug targeting is likely to be approved only for very severe diseases that are refractory to other approaches[2].

Magnet Design [13,16]

The force exerted by a gradient magnetic field is an important parameter that governs magnetic targeting of micro carriers. The relationship of magnetic force to field gradient and magnetic moment of particles is expressed by following equation : -

$$F=M\nabla H$$

Where,

F= Force on particles

M=Magnetic moment of particles after saturation magnetization

∇H= Magnetic field gradient

This equation explains that spheres with increased magnetic moments will experience force sufficient for extra vascular migration of proportionately lower field gradients. The magnetic moments of microspheres can be increased in three ways: -

By clustering magnetite at the center of each sphere to produce large macro domains.

By magnetizing the spheres to saturation levels prior to vascular targeting.

By substituting one of the newer ferromagnetic materials that has high susceptibility than Fe_3O_4.

Characterization of Magnetic Particles :

Scanning electron microscopy is used to determine the size & morphology of magnetic nanoparticle whereas Dynamic Light Scattering is used to measure the hydrodynamic diameter[35] Magnetic mobility(overall responsiveness or amount of velocity for a given magnetic field & field gradient) of different types of magnetic micropheres is characterize so that their behavior in patient circulation can be predicted.For this purpose stationery setup similar to cell tracking velocimetry system which can be used on standard microscope eqiipped with a digital camera& computer

system. The main difference to above system is that there is no flow of the suspension containg the magnetic particles. The geometry & size of the set up & magnet used can be reduced considerably. Furtermore the close combination of the microscope set up with computer allows fully automated data acquisition & processing[36].

The magneto liposomes are characterized for their physical attributes i.e. size, shape, and size distribution, surface charge, percent capture, percent magnetite content, entrapped volume lamellarity through freeze fracture microscopy and P-NMR, phase behavior drug release, quantitative determination of phospholipids and cholesterol analysis.

Conclusion

Targeted Drug delivery is an effective method to assist the drug molecule to reach preferably to the desired site. The main advantage of this technique is the reduction in the dose & side effects of the drug. Over the years, magnetic microcarriers have been investigated for targeted drug delivery especially magnetic targeted chemotherapy due to their better tumor targeting, therapeutic efficacy, lower toxicity and flexibility to be tailored for varied desirable purposes. In spite of certain drawbacks, such as strong magnetic field requires for the ferrofluid and deposition of magnetite the magnetic microcarriers still play an important role in the selective targeting, and the controlled delivery of various 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. The future holds lot of promises in magnetic microcarriers and by further study this will be developed as novel and efficient approach for targeted drug delivery system.

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