AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Magnetic drug Delivery system

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ABSTRACT

Presently, several targeted treatment systems including magnetic field, electric field, ultrasound, temperature, UV light and mechanical force are being used in many disease treatments (e.g. cancer, nerve damage, heart and artery, anti-diabetic, eye and other medical treatments). Among them, the magnetic targeted drug delivery system is one of the most attractive and promising strategy for delivering the drug to the specified site. The targeted systems improve therapeutic index of drug molecules by minimizing the toxic side effects on healthy cells and tissues. The use of magnetic carriers for drug delivery of chemotherapeutic agents has evolved since 1970s, when little research has developed albumin microspheres encasing the chemotherapeutic agent Adriamycin, and using magnetite as the magnetically susceptible component.

Keywords: Magnetic drug delivery, Magnetic delivery, Electric field, Magnetic field delivery, Magnetic targeted drug delivery,

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Received 14 August 2013, Accepted 29 August 2013

Please cite this article in press as: Iche GR. *et al.*, Magnetic drug Delivery system. American Journal of PharmTech Research 2013.

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. A number of novel drug delivery systems have emerged encompassing various routes of administration, to achieve controlled and targeted drug delivery, magnetic drug delivery system being one of them. These magnetic micro carriers include magnetic microspheres, magnetic liposome, magnetic nanoparticles, magnetic resealed erythrocytes, magnetic emulsion etc. Magnetic carriers are usually composed of magnetic cores to ensure a strong magnetic response and polymeric shells to provide favorable functional groups and protect from particle aggregation. These carriers exhibit many unique features such as small and uniform size, different shapes and morphologies, and various functional groups on the surface, and hence have received much attention in recent years for wide potential applications such as enzyme immobilization, cell and protein separations, and drug delivery processes. Among these applications, it is becoming increasingly apparent that the key issues are surface modification and morphology control. Therefore, synthesis of surface-functionalized magnetic microspheres with controllable morphology is particularly important both for fundamental studies and for applications [1]. In the past few years, several methods have been developed for synthesis of these materials, including solvent evaporation, dispersion or suspension polymerization, microemulsion polymerization, and Ugelstad's two-step swelling method. Mostly, magnetite (Fe_3O_4) has been used as the magnetic core and polymers such as polystyrene, poly (glycidyl methacrylate) and polyvinyl alcohol have been used as the shells. Recently, micro- or mini emulsion polymerization has been widely used due to its easiness to obtain surface-functionalized microspheres with uniform particle dispersion. According to the published literature, we find that little attention has been paid to controlling the morphology and size of the surface-functionalized magnetic microspheres. Here, we first report a simple one-step method to prepare magnetic polymer microspheres that have both controllable morphologies and -NH2 groups located on their surface. The properties of these resulting magnetic microspheres are also analyzed and a possible forming mechanism is presented[2, 3, 4,]

Magnetic micro and nanoparticles display magnetic properties different from their bulk material counterparts. These unique properties originate from the size of the particles, which are below critical diameter for magnetic domain wall formation. In the absence of external magnetic field,

thermal energy can be sufficient to cause magnetic moments in these single-domain particles to equilibrate and overcome any preferential orientation. However, when an external magnetic field is applied, the magnetic moment of particles aligns rapidly in the direction of applied field and the materials display a net magnetization. The magnetization of the magnetite nanoparticles disappears when the external magnetic field is removed. These properties indicate supermagnetic behavior, which suggests that the nanoparticles may be ideal components of vehicles for magnetic field-directed delivery of therapeutic agents. Magnetic particles can be dispersed in carrier fluids through specific interactions between the particle surfaces and selected low molecular weight or polymeric surfactants. Such fluid dispersions are called as ferrofluids [5.]

Theory of Magnetic Targeting of Drug [6]

It is assumed that magnetic nanocomposite particles that display high saturation magnetization have potential application for magnetically controlled drug targeting. These particles are relatively magnetic with discrete randomly oriented magnetic moments. When the magnetic particles are placed in the external magnetic field, the moments of the particles rapidly rotate into the direction of the field and improve the magnetic flux density. To control the motion of such particles within a circulating system, a magnetic force due to an externally applied and a hemodynamic drag force due to the fluid flow combine to create a total vectoral force on the particles. In order to effectively overcome the influence of a fluid flow and achieve the desired external magnetic field-controlled guidance, the magnetic force because of the external field must be larger than the drag force or hydrodynamic force. According to this explanation, the magnetic force on the magnetic particles is governed by:

Where F is the magnetic force, m is the total magnetic moment of the material in the microsphere, (is the gradient that is assumed to be derived from characteristics of the field alone, and the magnetic flux density- also known as the B field. Each of these quantities thus influence to some degree to which an external magnetic field may be used to internally guide particles in the body. The del operator is defined for magnetic field distribution at xyz directions:

It is noted that the gradient of a scalar function at any point is the maximum spatial change of the magnetic field. The Bfield tends to align the net magnetic moment of a particle in a fixed direction while the gradient leads to a force that moves the particles. The second factor characterizes the magnetic properties of the particles. The magnetic moment of a material m, is proportional to the applied magnetic field H, and the intrinsic magnetic susceptibility of the material, χm

$m = \chi m H$

The magnetic volume susceptibility for various materials ranges from aluminum at 2.07 x 10-5 to magnetite 1.0 x 106 5.7 x 106 and as high as 106 for various ferromagnetic rare-earth materials. The force that counteracts the magnetic force on the particle in the fluid stream is due to the liquid flow (blood flow). Stokes law governs the hemodynamic forces on a particle in the liquid. The equation is given by:

$F = 6 \Pi \eta \upsilon r$

Where, F is the drag force, is the viscosity of fluid, is the relative velocity of a spherical particle and r is the radius of the particle.

Also, there are other variables for drug delivery including tissue porosity, particle distribution, and allowable cell damage caused by incompatible sphere size and variable blood flow and viscosity. A highly porous tissue allows small particles to be easily manipulated out of the blood stream and into tissue. However, a relatively tight tissue structure would require more magnetic field induced force to pull the nanoparticles out of the bloodstream, and such interfacial transport could also cause damage to the tissue. As a result, the magnetic nanocomposite particle size and external forces needed for effective particle manipulation are highly dependent on the area in which drug delivery is performed.

PRINCIPLES OF MAGNETIC DRUG TARGETING

Magnetic drug transport technique is based on the fact that drug is encapsulated into or conjugated on the surface magnetic micro or nanospheres. When such a carrier is administered intravenously, accumulation takes place in the area to which magnetic field is applied. The accumulation at the specific site allows delivering the drug locally. This is an efficient method of drug localization, provided that the targeted tissue must be abundant with vascular supply and accessible to magnetic fields [7].

The process of localization by these systems is based on the competition between forces exerted on the particles by blood compartment, and magnetic forces generated by the external magnet. When these magnetic forces exceed the linear flow rates in arteries or capillaries, the carriers are retained at the target site and are internalized by the endothelial cells of the tar-get tissue[8].The efficiency of accumulation depends on various parameters e.g. particle size, surface characteristic, field strength, blood flow rate, the length of time the tissue is exposed to the external magnet etc. All these parameters are selected carefully to optimize the target action.

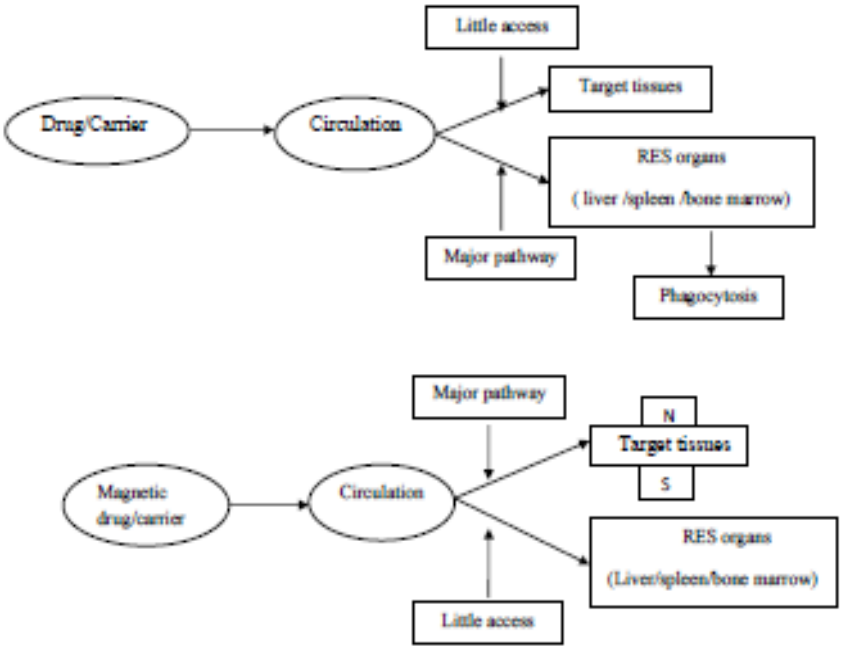

Figure 1: principal of magnetic drug targeting

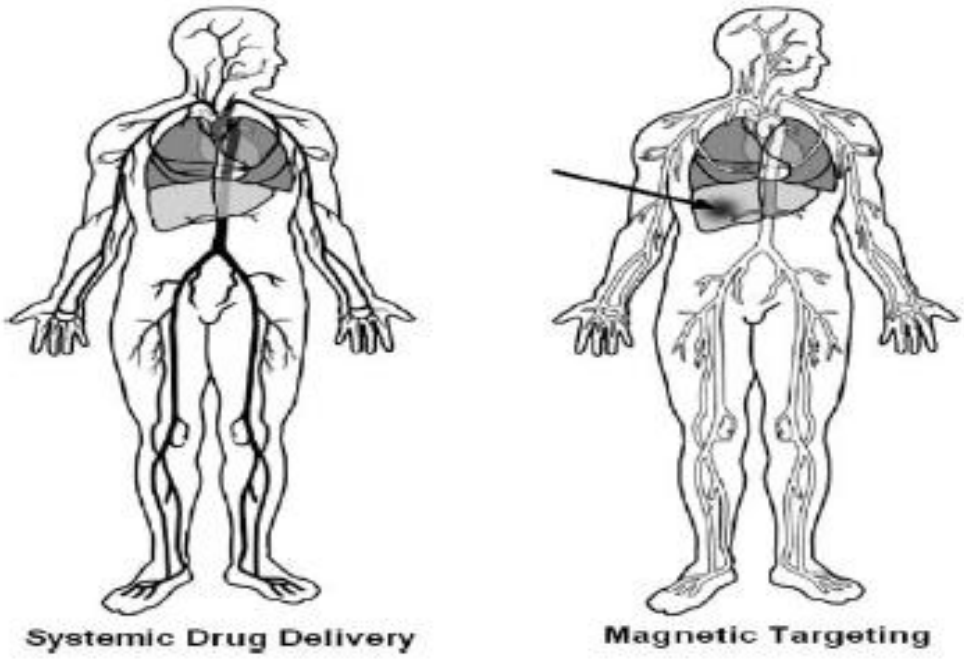

Figure 2: Magnetic drug targeting

Factors Affecting Magnetic Targeting of Drug [9]

Factors related to ferrofluids:

1. Size of the particles in ferrofluid.
2. Surface characteristics of particles.
3. Concentration of the ferrofluid.
4. Volume of the ferrofluid.

5. Reversibility and strength of drug/ferrofluid binding (desorption characteristics).
6. Access to the organism (infusion route).
7. Duration or rate of injection/infusion.
8. Geometry, strength and duration of the magnetic field application.

Physiological parameters related to patient (or animal):

1. Size, weight and body surface of patient (or animal).
2. Total blood volume.
3. Cardiac output and systemic vascular resistance.
4. Circulation time.
5. Tumor volume and location.
6. Vascular content of tumor.
7. Blood flow in tumor.

Functionalization of magnetic particles for drug Delivery

Iron oxides with core/shell structure are the most widely used as sources of magnetic materials. Iron oxides have several crystalline polymorphs known as -Fe2O3 (hematite) - Fe_2O_3, Fe_2O_3 (maghemite),-Fe_2O_3, Fe_3O_4 (magnetite) and some others (amorphous and high pressure forms). Nevertheless, only maghemite and magnetite found the greatest interest of bioapplications. Readily, carbonyl iron, which is well-known material with a unique form of elemental iron because of its small particle size, was also used as magnetic core. In some reports, pure metals, such as Fe and Co were chosen as a magnetic material because they have several advantages over iron oxides, e.g., better magnetic properties, high saturation magnetization, and high specific loss of power. Xing et al. fabricated-Fe-incorporated nonporous carbon with magnetic properties by a facile nanocasting process and employed it as tetracycline hydrochloride carriers. However, Fe and Co have worse oxidative stability, compatibility in noaqueous systems and toxicity then iron oxides. Functionalization of MNPs with amino group, silica, polymer, various surfactans or other organic compounds is usually provided in order to achieve better physical and chemical properties. Moreover, the core/shell structure of MNPs has the advantages of good dispersion, high stability against oxidation and appreciable amount of drug can be loaded to the polymer shell. Furthermore, lots of functional groups from polymers on the surface can be used for further functionalization to get various properties. It is favored that MNPs retain sufficient hydrophilicity and, with coating, do not exceed 100 nm in size to avoid rapid clearance by reticuloendothelial system (RES). It was found the surface functionalization plays also the key role in nanoparticle toxicity.

Characterization of Magnetic Particles [10]

Particle Size and Shape

Magnetic particles synthesized by various methods are of variable sizes. Their properties are quite different from other type of micro and nanoparticles. 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. Particle size and its distribution are determined by light microscopy, scanning electron microscopy, transmission electron microscopy, etc. Confocal laser scanning microscopy (CLSM) is applied as a nondestructive visualization technique for microparticles. CLSM allows visualization and characterization of structures not only on the surface, but also inside the particles, provided the material is sufficiently transparent and can be fluorescently labeled. By collecting several coplanar cross sections, a three-dimensional reconstruction of the inspected object is possible.

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). The surface carboxylic acid residue is measured by using radioactive glycine. The radioactive glycine conjugate is prepared by reaction of 14C-glycine ethyl ester hydrochloride with the microspheres. The radioactivity of conjugate is measured using scintillation counter. Surface associated amino acid residue is determined by the radioactive 14C- acetic acid conjugate. The carboxylic acid residue is measured through the liquid scintillation counter and hence the amino acid residue can be determined indirectly.

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

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 -800and +800Gauss with a sensitivity of 0.1 emu/g. the prepared samples can be characterized by weight or volume in VSM. The dry samples are weighed (0.075 g), while the fluids are injected into the sample holder (~ 0.05 ml). In this system, when a magnetic sample is placed between two coils of an electromagnet creating a uniform magnetic field gradient, the applied field induces the magnetic domains to line up with the field through dipole interactions. As the magnetic field is increased, number of domains will be also enhanced until the particles reach saturation levels. During magnetic field alignment, the particles undergo a sinusoidal motion and produce an electrical signal in a set of stationary pick-up coils. This signal is proportional to magnetic moment, vibration amplitude and vibrational frequency. After the measurements, magnetic saturation values of the materials are calculated for each sample by dividing the saturation magnetization by the weight of samples.

Thermo gravimetric Analysis

Differential scanning calorimetry and other gravimetric methods are used to determine the extent of interaction of polymers with magnetite and such other magnetic materials. Moreover the stability of ferrous and ferric ions can be assessed by thermogravimetric methods.

Measurement of Swelling Kinetics of Microspheres

Swelling kinetics of the composite magnetic microspheres can be determined by swelling rate at given time. Dried microspheres are immersed in distilled water at each predetermined time at room temperature. Then the sample is removed from distilled water and is frequently weighed after trapped with filter paper. Thus, the wet weight of the microspheres is recorded during the swelling period at regular time intervals. The SR, (Ws + Wd)/Wd, is defined as the ratio of total weight of water in swollen microspheres to the weight of the dried microspheres, where Ws is the weight of adsorbed water and Wd is the weight of the microspheres at dry state.

Stability Measurements

Stability measurements can be performed by using separation analyser (e.g. LUMiFuge). Measurements are made in glass tubes at accelerated velocities from 50to 300rpm. The slope of sedimentation curve can be used to calculate sedimentation velocity and stability data can be found.

ξ - Potential measurements

ξ - Potential measurements can be made using an instrument like Zetasizer 2000. The zeta potential is measured at different pH values and stability of magnetic particles can be predicted.

Effect of pH on Magnetic Microspheres

Measurement of pH sensitive behavior is similar to the measurement of swelling kinetics of the microspheres. It is determined by the equilibrated swelling rate (ESR) at given pH data. ESR of the microspheres is measured by immersing dry and known weight of microspheres into buffer solution with different pH data for at least 1h at room temperature. Then the microspheres are removed from the buffer solution and frequently weighed after trapped with a filter paper to remove excess of water on the surface. ESR is calculated from the following formula We/Wd, where We is the weight of the solution in equilibrated swollen microspheres at each predetermined buffer solution with different pH data, the symbol of Wd is the same as defined earlier.

Magnetic core material

There are many magnetic materials available with a wide range of magnetic properties. However, many of these materials, such as cobalt and chromium, are highly toxic and unlikely to be used as biomedical agents *in vivo* without a non-toxic, protective coating with high mechanical strength. Iron oxide-based materials such as magnetite and maghemite, however, are relatively safe and are currently in use in the clinic as MRI contrast agents. The following are some magnetic materials suitable for use in biomedical applications.[11]

Magnetite Fe_3O_4

Magnetite is a common mineral which exhibits ferro (ferri) magnetic properties. Descriptions of the physical properties of magnetite are widely available .The structure of magnetite belongs to the spinel group, which has a formula of AB_2O_4. Its ferromagnetic structures arise from alternating lattices of Fe (II) and Fe (III). This gives it a very strong magnetization compared to naturally occurring anti-ferromagnetic compounds such as the ferrihydrite core of the ferritin protein.

Maghemite γ-Fe_2O_3

Maghemite, a topotactic oxidation product of magnetite, has the same lattice structure as magnetite but all iron atoms are in Fe (III) oxidation state. It can be thermally transformed to other forms of iron (III) oxides such as heamitite, which is antiferromagnetic. The strong magnetization of maghemite (about 100 times stronger than hematite and ferrihydrite), which is on the order of magnetite, is due to lattice vacancies which give rise to uncompensated electron spins within the structure.

Maghemite is one of the most suitable materials for the core of magnetic nanoparticles because it is least likely to cause any health hazard. Iron (III) ions are widely found in human body so leaching of metal should not cause significant side-effects. As a result, maghemite is a popular

choice for making magetic nanoparticles, especially for biomedical applications.

Iron-based metal oxides

There are many iron-based metal oxides which exhibit strong magnetic properties and can be used as magnetic cores for building the magnetic nanoparticles. Preparation procedures of mixed oxide nanoparticles such as $CoFe_2O_4$, $NiFe_2O_4$, and MnFe2O4 are commonly found in the literature[12]. It is worth noting that these materials have a remarkably similar spinel structure to magnetite Fe_3O_4. However, using these mixed oxide nanoparticles in biomedical research can be hampered by the high toxicity of these transition metals (Co, Ni, Mn). Non-permeable coatings are needed to prevent leaching of these metals. Other common examples of mixed oxides involve alkaline earth metals such as barium ($BaFe_{12}O_{19}$) and strontium ($SrFe_{12}O_{19}$), which belong to the magnetoplumbite-system[13]. Again, leaching of these alkaline earth metals can cause problems in biomedical applications

Iron alloys

Although iron metal itself is a good material for magnetic applications, it is seldom used as core material for the synthesis of magnetic nanoparticles unless they are coated with an inert, protective coating. Iron is exceptionally vulnerable to corrosion in presence of water, i.e., rusting. Robust, non-porous coatings are essential for nanoparticles with iron metal cores. Also, functionalizing the iron surface is not straightforward. Therefore, iron alloys, such as FePt and FeAu, are more popular as core materials for magnetic nanoparticles.

Other materials

Other possible core materials for magnetic nanoparticles include rare earth metal alloys and transition metal clusters. The use of these materials for magnetic nanoparticle core synthesis is still rare due to their potential toxic effects on the human body.

Limitations of Magnetic Drug Targeting

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 procedures.

Magnets must have relatively constant gradients, in order to avoid focal over dosing with toxic drug.

A large fraction of magnetite, which is entrapped in carriers, is deposited permanently in targeted tissue.

Applications [14]

1. The proteinase of *Balillussublitis*is widely used in industrial fields, such as in leather tanning, drug-producing, and food making, but its stability is poor and it easily loses its activity. The proteinase is bound by support material containing aldehyde groups and magnetic fluid and the stability is improved. Also the free poteinase was immobilized on the magnetic polymer microspheres carriers containing hydroxyl group, activated by *p*- benzoquinone.

2. Doxorubicin was loaded on magnetic targeted carriers and was used for clinical studies in swine was proved successful in treating artificially induced tumor.

3. Epirubicin was successfully targeted to tumor in rat, mice and human. The epirubicin loaded magnetic carrier was able to cause successful remission of tumor in human volunteers.

4. Cimetidine was successfully loaded on magnetic microspheres and release profile of the microspheres was determined.

5. Metronidazole is used as radio-sensitizing agent in cancer radiotherapy. It was loaded on magnetic microspheres and targeted to tumor, thus sensitizing the tumor cells to radiations.

6. Submicron magnetic polyglutaraldehyde nanoparticles were synthesized and loaded by poly-l-lysine methotrexate.

Magnetic Carriers:

Magnetic carriers must be water-based, biocompatible, non-toxic and immunogenic. Magnetic carriers are grouped according to their size[15]. Encapsu-lated micro carriers in the size range of 10-500 nm are magnetic nanospheres and particles of just below 1-100 micrometers are magnetic microspheres. Various types of magnetic carriers include:

Table 1; Classification of magnetically controlled targeted drug delivery systems

Class	Example
BIODGEADABLE	
Particulate carriers	Magnetic emulsion
	Magnetic microspheres
	Magnetic nanoparticles
Vascular carriers	Magnetic erythrocytes
	Magnetic liposomes
NON-BIODEGRADABLE	
Particulate carriers	Magnetic microcapsules

A) Magnetic microspheres:

Magnetic microspheres are supramolecular particles that are small enough to circulate through capillaries without producing embolic occlusion (<4μm) 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). 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 via magnetic responsive microspheres can be regulated by varying size of microspheres, drug content , magnetite content , hydration state and drug release characteristic of carrier[16]. The amount of drug and magnetite content of microspheres needs to be delicately balanced in order to design an efficient therapeutic system. magnetic microsphere are characterized for different attributes such as particle size analysis including size distribution ,surface topography, and texture etc. using scanning electron microscopy (SEM), drug entrapment efficiency, percent magnetite content, and in vitro magnetic responsiveness and drug release.

Targeting by magnetic microspheres i.e. incorporation of magnetic particles in to drug carriers (polymers) and using an externally applied magnetic field is one way to physically direct this magnetic drug carriers to a desired site, 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[17]. 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[18]. 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). The magnetic microspheres were effectively used for drug targeting to tumor cells, cell separation, diagnosis of disease and magnetic targeting of radioactivity.

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. Generally these are magnetic carrier which can be prepared by entrapment of Ferro fluid within core of liposome [19]. 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 nanoparticles. 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. 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.

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.

Various researches have been carried out on magnetoliposomes. The finding of Margolis et al. demonstrates utilization of magnetoliposomes in cellular sorting. The preparation, physicochemical properties and their possible use as a targeting carrier have been described by Ishii et al[20]. The possibility of dextran magnetite incorporated thermosensitive liposomes was studied by Mauskoet al[21]. Antibody coated magnetoliposomes for hyperthermia treatment of cancer were prepared by coating phospholipid on to magnetic particles were studied by Shinkaiet al[22]. 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[23].

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 particles include immunoassays, drug targeting, drug transporting, and biosensing.

Magnetic colloidal iron oxide nanoparticles were prepared with the method of co-precipitation. 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. Pedro Trataj et al. review article 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.

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[25]. 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[26].Local thrombosis in animal arteries was prevented by means of magnetic targeting of aspirin loaded red cell was studied by Orekhova et al[27].

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. 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[27].

APPLICATION:

Magnetic drug delivery system have many application in various fields but out of these drug targeting utilizing magnetic micro carriers is very important. Some of the application of magnetically guided drug targeting especially tumor targeting along with some other application utilizing magnetic micro carriers has been summarized here.

1) Magnetic drug targeting: Tumor targeting:

Magnetic drug targeting allows the concentration of drugs at a defined target site generally and importantly, away from the reticular endothelial system (RES) with the aid of a magnetic field. Site-directed drug targeting is one way of local or regional antitumor treatment. The drug & an appropriate Ferro fluid are formulated into a pharmaceutically stable formulation which is usually injected through the artery that supplies the target organ or tumor in the presence of an external magnetic field. Prolonged retentions of the magnetic drug carrier at the target site alleviate or delay the RES clearance & facilitates extra vascular uptake. For effective retaining of magnetic drug carrier, the magnetic forces must be high enough to counteract liner flow rates within the organ or tumor tissue (between 10 & 0.05 cm/s depending on vessel size & branching pattern [28, 29]. There is increase in drug concentration in the target tissue after administration of the drug dose has been observed[30].The efficiency of chemotherapy treatment may be enhanced to a great extent by magnetically assisted delivery of cytotoxic agent to the specific site. 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 while current preclinical research is investigating use of magnetic particles loaded with different chemotherapeutic drugs such as mitoxantrone, paclitaxel. Non invasive permanent magnetic field for one hour way found to induces lethal effects on several rodent & human cancers[31.] 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.

In case of brain tumors, the therapeutic ineffectiveness of chemotherapy is mainly due to the impervious nature of the blood-brain barrier (BBB), presence of drug resistance and lack of tumor selectivity. 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 particle was retained in brain tissue over a longer period of time.

A magnetic fluid has been reported to which the drugs, cytokines & other molecule can be chemically bound to enable that agent to be directed within subject under the influence of high energy magnet. In one of such examples magnetic doxorubicin in liposome, significant

anticancer effect in nude mice bearing colon cancer[37].

Table 2; Various drugs delivery systems used for cancer chemotherapy

Delivery system	Drug tested
w/o/w emulsion	Beleomycin
o/w emulsion	Mitomycin
liposomes	Bleomycin
	Cisplatin analogues
	Daunorubicin
Starch microsphere	carmustin
	fluorouracil
	mitomycine
	doxorubicin
Ethyl cellulose microcapsules	cisplatin
	mytomycine
Albumin microsphere	Cisplatin
	doxorubicin
	mitomycine
Poly(lactic acid) microsphere	aclarubicin
Polymethacrylate nanoparticles	doxorubicin

2) Magnetic bio separation:

Bioseparation is an important phenomenon for the success of several biological processes. Therefore, prospective bioseparation techniques are increasingly gaining importance. 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.

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.

3) 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.

a) 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. It has been shown that malignant cells take up nine times more magnetic nano particles than normal cells. Therefore the heat generated in malignant cells is more than in normal cells. Also, as blood supply in the cancerous tissues is not normal, the heat dissipation is much slower. 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 concentrated and localized[42].

b) Magnetic fluid hyperthermia (MFH): Magnetic fluids can be defined as fluids, consisting of ultramicroscopic particles (~100Å) of magnetic oxide. 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.

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. 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. Several reasons are given for the enhanced effect. Tumors are poorly vascularised and it can be hard for therapeutic agents to reach their target. Heat increases the

perfusion of a tumor and therefore drugs are transported more effectively into the target tissues. In addition, heat makes blood vessels more permeable to drugs. This occurs preferentially in tumors where blood vessels tend to be structurally incomplete. On the other hand, normal blood vessels are surrounded by a basement membrane and other perivascular cells and not significantly affected by heat. It has recently been reported that hyperthermia increases the rate of liposome leakage into tumors by a factor of 2–5 depending on the type of tumor. In normal tissues however, enhancement of liposome leakage is not reported.

4) Magnetic control of pharmacokinetic parameter rand Improvement of Drug release: 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 [38].The microenvironment within 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. 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.

5) Magnetic targeting of radioactivity:

Magnetic 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. Magnetic targeted carriers, which are more magnetically responsive iron carbon particles, have been radio labelled in last couple of years with isotopes such as ^{188}Re, ^{90}Y, ^{111}In, and ^{125}I and are currently undergoing animal trials.

6) Miscellaneous Applications:

The most important application of magnetic particles is as contrast agent for magnetic resonance imaging in diagnosis of diseases. The most commonly used super paramagnetic material is Fe_3O_4 with different coatings such as dextrans, polymers, and silicone. Supramagnetic iron oxide (SPIO) it has been mainly used as a liver-specific contrast agent for intravenous application. It may also be used for detection of metastases in non-enlarged lymph nodes.

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.

CONCLUSION:

Magnetic Vesicular systems have been realized as extremely useful carrier systems in various scientific domains. 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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