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REVIEW ARTICLE

TARGETED THERAPEUTIC DELIVERY: SUCCESS THROUGH MAGNETIC MICROCARRIERS

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ABSTRACT

There has been keen interest in the development of a targeted therapeutic delivery system. 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 day. These include magnetic microspheres, magnetic liposome, magnetic nanoparticles, magnetic resealed erythrocytes, magnetic emulsion etc. Magnetic microspheres involve applying an external magnetic field to capture drug-loaded magnetic carriers in a targeted site. Magnetic therapeutic targeting is a promising method to increase the delivery of therapeutic agents to tumor cells while reducing side effects. Magnetic microspheres & molecular magnetic labels have been used for great number of application in various areas of biosciences, targeted drug delivery, diagnosis and in immunoassay. Much has been investigated and much more are to be investigated for the use of principle of magnetism in targeting of therapeutics to the various organs. Thus present review paper will discuss about mechanism of magnetic targeted therapeutics delivery, magnetic carriers, and application of magnetic microspheres in targeted delivery of therapeutics.

Key Words: Magnetic Microspheres, Therapeutics, Targeting, Diagnosis, Immunoassay.

INTRODUCTION

One of the great challenges in drug therapy is the selective delivery (i.e., therapeutic targeting or targeted therapeutic delivery) of therapeutics to the intended target. An effective delivery system should be defined for a given therapeutics according to its physicochemical and pharmacokinetic characteristics, to its target site of action, and to the pathology to be addressed.

In recent years, polymeric controlled drug delivery systems have evolved as one of the most interesting area in drug delivery and drug targeting[1-3]. The drug release is controlled by the properties of the polymer-drug systems and to some extent environmental factors such as pH, enzymes and inter-patient variance. Despite several advantages offered by controlled drug release, a major problem associated with all these systems so far developed give release rates that are either constant or decrease with time, but not augmented delivery on demand[4].

Various nonmagnetic micro carries (nanoparticles, microspheres and microparticles etc.) are successfully utilized for drug targeting but they show poor site specificity and are rapidly cleared off by RES (reticulo endothelial system) under normal circumstances. Magnetism plays an important role in such cases.

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[5]. Magnetic microspheres will be formulated with an intension to produce a depot near the target tissue/organ, by placing a suitable magnet near it. From the depot, drug will be released slowly & carried to the target organ through blood. By localizing the drug carrier near the target organ, unwanted distribution of drug to non target organ can be avoided. This approach will localize the drug only at target site & minimize the drug-induced toxicity[6-9]. Magnetism plays an important role in different applications of healthcare; magnetically active component is composed of magnetite, which is well tolerated by the body. Magnetite (Fe3O4) is a common magnetic iron oxide, and it has a cubic inverse spinal structure with oxygen forming a FCC closed packing and Fe cations occupying the interstitial tetrahedral sites and octahedral sites[10-11]. The electrons can hop between Fe2+ and Fe3+ ions in the octahedral sites at room temperature, rendering magnetite an important part of half-metallic materials. The important characteristics of magnetic microspheres for medical applications are nontoxicity, bio-compatibility, injectability and high level accumulation in the target organ.

MAGNETIC MICROSPHERES:

Magnetic microspheres are supramolecular particles that are small enough to circulate through capillaries without producing embolic occlusion (<4 ìm) but are sufficiently

susceptible (ferromagnetic) to be captured in micro-vessels and dragged in to the adjacent tissues by magnetic fields of 0.5-0.8 tesla[12]. Magnetic microspheres are prepared by mainly two methods namely phase separation emulsion polymerization (PSEP) and continuous solvent evaporation (CSE) by using mixture of water soluble drugs (for lipophilic drugs, along with the dispersing agent) and 10 nm magnetite (Fe_3O_4) particles in an aqueous solvent of matrix material, which are about 1.0 µm in size, that is small enough to allow them to be injected intravenously without any occlusion in the micro vascular. These microspheres are nontoxic and nonreactive with blood components. They can be stabilized by heating or chemically cross linking albumin to achieve a wide spectrum of drug release kinetics. These are infused into an artery supplying a given target site. A magnet of sufficient field strength is then placed externally over the target area to localize the microspheres at the capillary bed in this region. In order to localize microspheres in a fast-moving arterial system, generally greater field strength is required.

Magnetic microspheres were prepared by mainly two methods:

1. Phase separation emulsion polymerization (PSEP) and
2. Continuous solvent evaporation (CSE).

Phase separation emulsion polymerization

Polymer encapsulated microspheres are synthesized based on a modified Phase separation emulsion polymerization technique. Briefly aqueous solution of polymer, drug and magnetite should be added to the vegetable oil and emulsified using a magnetic stirrer at 1,500 rpm for 2 minutes. The resultant should be stabilized by heating at the temperature (100-150 °C). Then cross linking agent should be injected drop wise into the resultant emulsion under continuous stirring. The magnetic microspheres will be formed in the Oil suspension and then should be separated from oil by washing procedures. The product should be Freeze dried & stored at 4°C.

Continuous solvent evaporation

Polymer encapsulated microspheres are synthesized on the basis of a Continuous solvent evaporation technique. A solution of polymer, drug and magnetite should be added to the volatile organic solvent, which forms Auxiliary solution on stirring. Resulting solution should be homogenized at stirring temperature (22-30 ^{o}C). The magnetic microspheres will be formed in the suspension and should be separated by centrifugation. The product should be Freeze dried & stored at 4°C. 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. The amount of drug and magnetite content of microspheres needs to be delicately balanced in order to design an efficient therapeutic system. Magnetic microspheres are characterized for different attributes such as particle size analysis includes 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.

Desirable characteristics of magnetic microspheres 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.
- ✓ It must be able to cross the anatomic barriers.
- ✓ It must be recognized only by the target cells.
- ✓ It must not release the drug before reaching the target.
- ✓ It must release the drug inside the target cells.

Table 1: Advantages and disadvantages of magnetic microspheres

ADVANTAGES	DISADVANTAGES
Magnetic microspheres are site specific and by localization of these microspheres in the target area, the problem of their rapid clearance by RES is also surmounted.	By the use of magnetic microspheres in the delivery system, the drug cannot be targeted to deep seated organs in the body.
Linear blood velocity in capillaries is 300 times less as compared to arteries, so much smaller magnetic field is sufficient to retain them in the capillary network of the target area.	Magnetic targeting is an expensive technical approach and requires specialized manufacturer and quality controlled system.
Avoidance of acute toxicity directed against endothelium and normal parenchyma cell, controlled release within target tissue for intervals of 30 minutes to 30 hrs. As desired, adaptable to any part of body.	It needs specialized magnet for targeting, advanced technique for monitoring, and trained personnel to perform the procedure
In case of tumour targeting, microsphere can internalize by tumour cells due to its much increased phagocytic activity as compared to normal cells.	Rapid clearance of targeted systems especially antibody targeted carriers.
Problem of drug resistance due to inability of drugs to be transported across the cell membrane can be surmounted.	Drug- antibody inactivation during conjugation.
Microspheres can transit in to extravascular space thereby creating an extravascular drug depot for sustained release of drug within the targeted area.	Target tissue heterogeneity is the problem
Adaptable to any part of the body.	Problems of insufficient localizations of targeted systems into tumor cells
Magnetic carrier technology appears to be a significant alternative for the biomolecule malformations (i.e. composition, inactivation or deformation).	Magnetic targeting is an expensive technical approach, requires specialized manufacture & QC system

TARGETING BY MAGNETIC MICROSPHERES

Targeting by magnetic microspheres i.e. incorporation of magnetic particles in to therapeutic carriers (polymers) and using an externally applied magnetic field is one way to physically direct this magnetic drug carriers to a desired site, Widder first reported on the use of magnetic albumin microspheres[13]. Widder also showed 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[14]. Gupta and Hung suggested that in presence of magnetic field, the microspheres demonstrated 16 fold increases in the maximum drug concentration, 6 fold increases in drug exposure and 6 fold increases in the drug targeting efficiency to rat tail target segments[15]. 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) [16]. The magnetic microspheres were effectively used for drug targeting to tumor cells, cell separation, diagnosis of disease and magnetic targeting of radioactivity.

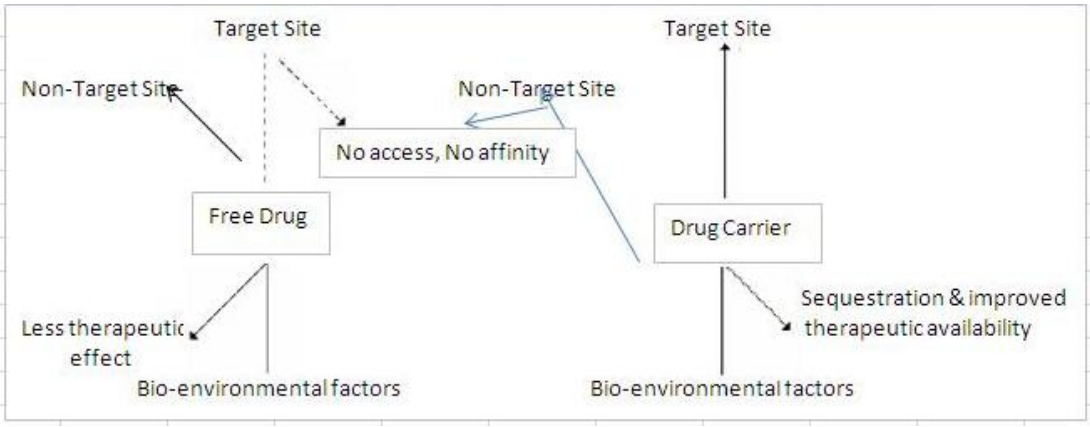

Figure 1: Mechanism of magnetic drug targeting

PRINCIPLE OF TARGETING BY MAGNETIC MICROSPHERES

Magnetic microspheres are a promising method of delivering therapeutics to a target site. Very high concentrations of therapeutic agents can be achieved near the target site, such as a tumor, without any toxic effects to normal surrounding tissue or to the whole body. Depending on the type of drug, it is then slowly released from the magnetic carriers (e.g. release of chemotherapeutic drugs from magnetic micro-spheres) or confers a local effect (e.g. irradiation from radioactive microspheres; hyperthermia with magnetic nanoparticles). It is thus possible to replace large amounts of freely circulating drug with much lower amounts of drug targeted magnetically to localized disease sites, reaching effective and up to several-fold increased localized drug levels[17-19].

Magnetic c carriers receive their magnetic responsiveness to a magnetic field from incorporated materials such as magnetite, iron, nickel, cobalt, neodymium–iron–boron or samarium–cobalt. Magnetic carriers are normally grouped according to size. At the lowe end, we have the ferrofluids, which are colloidal iron oxide solutions. Encapsulated magnetite particles in the range of 10–500 nm are usually called magnetic nanospheres and any magnetic particles of just below 1–100_m are magnetic microspheres. In general, magnetic liposomes are also included when speaking about magnetic carriers. The “shell” material determines the reaction of the body to the microsphere. Matrix materials that have been tested for the magnetic microspheres include chitosan, dextran, poly(lactic acid), starch, poly(vinyl alcohol), polyalkylcyanoacrylate, polyethylene imine, carbon, polysaccharides, gelatin and proteins[20].

FACTORS INFLUENCING MAGNETIZED THERAPEUTIC DELIVERY USING MICROSPHERES[21]

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 is 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. The average particle size was found to increase with increasing initiator concentration. It also increased with decreasing stabilizer concentration and MPEO concentration. Other factors such as the solvent system, the particle's porosity, its density, surface coating and aggregation tendencies can further influence its overall magnetic responsiveness. Drugs Generally Used for Magnetized Targeting are Adriyamycin, Doxorubicin, 5Flurouracil, Oxantrazole, Cisplatin, Hydrocortisone, Dactinomycin, Diclofenac sodium[22] Dexamethasone[23] etc

MAGNET DESIGN [24, 25]

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.

APPLICATION OF MAGNETIC MICROSPHERES

1.1 Tumor targeting by clogging of capillaries

It is also possible to use only the mechanical-physical properties of magnetic particles or ferrofluids for therapy. One example is the embolization (clogging) of capillaries under the influence of a magnetic field[26]. In this way, tumors could be specifically starved of their blood supply.

1.2 Magnetic targeted delivery of chemotherapeutic agents

The first clinical cancer therapy trial using magnetic microspheres (MMS) was performed by Lübbe et al. in Germany for the treatment of advanced solid cancer in 14 patients. Their MMS were small, about 100 nm in diameter, and filled with 4_-epidoxorubicin. The phase I study clearly showed the low toxicity of the method and the accumulation of the MMS in the target area. However, MRI measurements indicated that more than 50% of the MMS had ended up in the liver. This was likely due to the particles' small size and low magnetic susceptibility which limited the ability to hold them at the target organ. Current preclinical research is investigating the use of magnetic particles loaded with different chemotherapeutic drugs such as mitomycin C, etoposide, paclitaxel or oxaliplatin[27].

Saravanan et al were studied the targeting efficiency and the therapeutic efficacy of microspheres in rabbits. The microspheres showed drug loading of 9.1, 18.7, 24.9% w/w, magnetite content of 27.8-28.9% w/w with an average size range of 25-30.6 mum, depending upon the drug-polymer ratio. The microspheres effectively reduced joint swelling, but lesser extent than the oral diclofenac sodium in high dose, in antigen induced arthritic rabbits without producing gastric ulceration which was observed in rabbits treated with oral diclofenac sodium[28].

The multiple tissue disposition of adriamycin hydrochloride delivered via magnetic albumin microspheres, in absence (control) and presence of magnetic field (experimental), has been investigated in rats by Gupta et al. The results quantitatively suggest that the efficacy of magnetic albumin microspheres in the targeted delivery of incorporated therapeutic agent is predominantly due to the magnetic effects, and not alone due to the characteristics of the micro-carrier system[29].

1.3Retinal therapy by mechanical-physical properties of magnetic particles

Another elegant example is the use of magnetic fluids to prevent retinal detachment, thus preventing the patients from going blind[30]. A magnetized sclera buckle, similar to a rubber band, is placed around the eye. The magnetic fluid is then injected into the eye and immediately drawn towards the buckle by its magnetic forces. The mechanical forces push the retina back into its original place.

1.4 Magnetic targeting of radioactive agent

Magnetic targeting can also be used to deliver therapeutic radioisotopes[31]. The advantage of this method over external beam therapy is that the dose can be increased, resulting in improved tumor cell eradication, without harm to nearby normal tissue.

Different radioisotopes can treat different treatment ranges depending on the radioisotope used the emitters ^{90}Y for example will irradiate up to a range of 12mm in tissue. Unlike chemotherapeutic drugs, the radioactivity is not released, but rather the entire radioactive microsphere is delivered to and held at the target site to irradiate the area within the specific treatment range of the isotope. Once they are not radioactive anymore, biodegradation of the microspheres occurs (and is desired).

Initial experiments in mice showed that intraperitoneally injected radioactive poly (lactic acid) based MMS could be concentrated near a subcutaneous tumor in the belly area, above which a small magnet had been attached[18]. The dose-dependent irradiation from the _-emitter 90Y-containing MMS resulted in the complete disappearance of more than half of the tumors. Magnetic targeted carriers (MTC; from FeRx), which are more magnetically responsive iron carbon particles, have been radiolabeled in the last couple of years with isotopes such as ^{188}Re[31], ^{90}Y, ^{111}In and ^{125}I and are currently undergoing animal trials[28].

1.5. Magnetic control of pharmacokinetic parameters and drug release

Langer et al. embedded magnetite or iron beads into a drug-filled polymer matrix and then showed that they could activate or increase the release of the drug from the polymer by moving a magnet over it or by applying an oscillating magnetic field[32, 33]. The micro-movement within the polymer seemed to have shaken the matrix or produced "micro-cracks," and thus made the influx of liquid, dissolution and efflux of the drug possible. In this way, it was possible to magnetically activate the release of insulin from a depot underneath the skin[34]. Done repeatedly, this would allow for pulsatile drug delivery.

Another mechanistic approach based on magnetic attraction is the slowing-down of oral drugs in the gastrointestinal system. This is possible by filling an additional magnetic component into capsules or tablets. The speed of travel through the stomach and intestines can then be slowed down at specific positions by an external magnet, thus changing the timing and/or extent of drug absorption in stomach or intestines. Slowing down the passage of magnetic liposomes with a magnet actually increased the blood levels of a drug[35].

1.6 Treatment of tumors with magnetically induced 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.

Developments by Jordan and Chan led to the current hyperthermia application of single domain, dextran-coated magnetite nanoparticles in tumors[36, 37]. The first clinical trial is ongoing in Germany[38].

Magnetic hyperthermia is also possible with larger magnetic particles, as shown by the group of[39]. Their 32-_m plastic particles contain maghemite and embolize the arterial blood supply of the tumor, in addition to the magnetic hyperthermia treatment. In an animal study with 10 rabbits, the tumor volumes decreased by 50–94% within 2 weeks.

Ongoing investigations in magnetic hyperthermia are focused on the development of magnetic particlesthat are able to self-regulate the temperature they reach. The ideal temperature for hyperthermia is 43– 45 ◦C, and particles with a Curie temperature in this range have been described by Kuznetsov et al[40].

2. Magnetic systems for the diagnosis of diseases

The most important diagnostic application of magnetic nanospheres is as contrast agents for magnetic resonance imaging (MRI). Saini et al. tested 0.5–1 _m sized ferrites in vivo for the first time[41]. Since then, smaller superparamagnetic iron oxides (SPIOs) have been developed into unimodular nanometer sizes and have since 1994 been approved and used for the imaging of liver metastases (ferumoxide based Feridex I.V., or Endorem in Europe) or to distinguish loops of the bowel from other abdominal structures (GastroMark, or Lumirem in Europe).

3. Separation of subcellular components:

The era of using magnetic particles with surface markers against cell receptors started in 1978 with a seminal paper by Kronick et al[42]. Currently, many different kits for the sample preparation, extraction, enrichment and analysis of entire cells based on surface receptors, and subcellular/molecular components such as proteins, mRNA, DNA are available[43]. Analytical procedures, such as many different immunoassays, are often based on magnetic separation[44].

4. Magnetic separation and isolation of DNA

The conventional protocol for extracting DNA involves cell lysis followed by removal of contaminating cellular components such as proteins, lipids and carbohydrates; and finally isolating DNA using a series of precipitation and centrifugation steps, which are difficult to automate. Improvement in methods for isolating DNA has been made and more recently, methods that rely on the use of solid phase have been proposed. One of these kits involves isolation of DNA using silica coated magnetic particles [45]. A high throughput genome isolation protocol has been developed, which is based on **SPRI** (Solid Phase Reversible Immobilization) chemistry [46, 47]. The SPRI protocol is based on DNA binding to the surface of carboxyl coated paramagnetic particles under the condition of high salt and PEG.

5. Magnetic separation and isolation of poly (A) mRNA

Biomagnetic separation of mRNA is based on specific complementary hybridization between poly A sequence of isolated mRNA and oligo (dT)25 sequence covalently linked to the surface of paramagnetic particles. In this method oligo (dT) 25 coated magnetic beads are added to crude cell or tissue lysate. During incubation poly (A) mRNA from the lysate are caught onto the surface of oligo (dT)25 coated magnetic beads. The beads/mRNA complex is then washed magnetically. The mRNA thus isolated is either eluted or directly applied for many downstream applications which include cDNA library construction, Substractive hybridization, Northern hybridization, RT-PCR and *in vitro* translation [48].

6. Magnetic separation and isolation of nucleic acid binding biomolecules

Several kits are available in the market that works on the principle of magnetic labeling and direct isolation of biotinylated molecules such as DNA, RNA or proteins onto streptavidin coated magnetic beads (µMACS streptavidin Microbeads from Miltenyi Biotec, Germany). These biotinylated molecules can then be used for indirect isolation of non-biotinylated target molecules that may interact with them [49]. The procedure involves complex formation between the biotinylated probe (DNA, RNA or proteins) and the target molecule (i.e. interacting biomolecules DNA, RNA or protein). Based on the interaction of biotin-streptavidin, the probe-target complex is then separated from rest of the component by addition of streptavidin coated magnetic beads. The complex is magnetically isolated and washed to remove non-specifically bound molecules. The non-biotinylated target molecules can be either eluted off from the complex with high purity, whereas the magnetically labeled biotinylated probe remains bound to the column.

7. Applications in Proteomics

Magnetic particles are now increasingly used as carriers for binding proteins, enzymes and drugs. Studies have shown that proteins and enzymes can be bound covalently to naked magnetic particles in the presence of carbodiimide [50]. Such immobilization procedures for proteins, enzymes or drugs will have a major impact in various areas of medicine and biotechnology. The immobilized biomolecules can be used directly for a bioassay or as affinity ligands to capture or modify target molecules or cells. On this basis, Ni-NTA (nitriloacetic acid) tagged magnetic agarose beads have been used for versatile magnetocapture assays using 6xHis-tagged proteins [51. The procedure involves use of metal chelating nitriloacetic acid (NTA) groups covalently bound to the surface of agarose beads, which contain strong magnetic particles. The beads are precharged with nickel, which is

ready to capture 6xHis-tagged proteins for sensitive interaction assays or microscale purification of 6xHis tagged proteins.

8. Immunomagnetic assays

Magnetic particles have been applied increasingly for various immunoassays that include fluoroimmunoassays, enzyme immunoassays or radioimmunoassays. Magnetic particles bound with primary or secondary antibodies are used for separation and quantification of antigens. Use of magnetically bound antibodies eliminates the centrifugation step thus reducing assay time and simplifying operation thereby increasing the efficiency and accuracy of the assay. Matsunaga and co-workers [52] have developed a novel fluoroimmunoassay method, where a fluorescein isothiocyanate (FITC) conjugated monoclonal anti-Escherichia coli antibody was immobilized onto bacterial magnetic particles (BMPs) for detection and removal of E. coli. The same group has also developed a chemiluminescence enzyme immunoassay with BMPs using IgG as a model antigen [53]. Likewise a magnetic bead based ELISA has been developed for detection of *Staphylococcus species* [54].

9. Drug discovery and genomics applications

But innovations in newer technologies for genomics and proteomics are changing the face of drug discovery. Automation has become essential in allowing researchers to meet the high through demands of today's research environment. The main thrust area where magnetic separation is applied in drug discovery is sample preparation that includes *high throughput genome isolation* for sequencing or PCR amplification to carry out genotyping, SNP scoring or expression profiling.

C CONCLUSION

Literature survey is concluded that magnetic microspheres are extremely useful carrier system as a target therapeutic delivery system. Magnetic microspheres have been investigated for targeting drug delivery in chemotherapy due to their better tumor targeting, therapeutic efficacy, lower toxicity and flexibility, bioseparation magnetic resonance imaging, radioactivity, hyperthermia, diagnosis and in immunoassay. 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. IIt might be possible in near future that magnetic particles would be used as detection probes for a variety of assays, replacing labeling techniques such as fluorescence, chemiluminescence and radioactivity. Recently magnetic microspheres also used in proteomics and genomics. In future, further study by researchers will be developed a novel and efficient magnetic microspheres that become a promising delivery system for targeting of therapeutics.

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