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Magnetic Microspheres as a Targeted Drug Delivery System: A Review

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ABSTRACT

The in-vivo targeting of tumors with magnetic microspheres is currently realized through the application of external non-uniform magnetic fields generated by rare-earth permanent magnets or electromagnets. This technique can be applied to magnetically targeted cancer therapy, magnetic embolization therapy with magnetic particles that contain anticancer agent, such as chemotherapeutic drugs or therapeutic radioisotopes. Drug targeting is one way of local or regional antitumor treatment. Magnetically controlled drug targeting is one of the various possible ways of drug targeting. This technology is based on binding establish anticancer drug with ferrofluids that concentrate the drug in the area of interest (tumor site) by means of magnetic fields. There has been keen interest in the development of a magnetically target drug delivery system. These drug delivery systems aims to deliver the drug at a rate directed by the needs of the body during the period of treatment, and target the activity entity to the site of action. This paper gives an overview of current application of magnetic microspheres (ferrofluid) in conjunction with magnetic fields as they relate to the latest advances in medical application and in particular to anticancer therapy and also discuss about mechanism of magnetic targeted delivery, drug release rate in-vitro, benefits and drawbacks of magnetic targeting.

KEYWORDS

Magnetic Microspheres, Magnetically drug targeting, Cholangiocarcinoma, Ferromagnetic.

INTRODUCTION

Specific delivery of drugs to desired target sites with a minimum side effect constitutes one of the most exciting challenges in medicine. One way of achieving such targeting of drugs is by the use of magnetic microspheres in combination with an external magnetic field. Microspheres are free flowing powders consisting of encapsulated (drugs) spherical particles of size ideally less than 125p that can be suspended in aqueous vehicle and injected by an 18 or 20 number needle. Magnetic Microspheres containing magnetic substance inside which can be easily targeted by applying external magnetic field.

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Magnetic Microsphere were developed to minimize renal clearance and to increase target site specificity. They can be used to entrap a wide variety of drugs. This system has a great potential in the treatment of localized tumors in the regions of well-defined blood supply. Each particle is basically a matrix of drug dispersed in a polymer from which release occurs by a first order process.

They can be prepared from a variety of carrier material. One of the most utilized is serum albumin from human or other appropriate species. Drug release from albumin microspheres can be sustained or controlled by various stabilization procedures generally involving heat or chemical cross-linking of the protein carrier matrix. The polymers used are biocompatible and biodegradable e.g. Polyacryl, polylactide, polyglycoside etc.

Concept of magnetic targeting of microspheres

Ideally, magnetic microspheres are injected into an artery that supplies a given site. As the microspheres would be selectively and magnetically localized at the capillary level, they would have free flow access through the large arteries. Thus the microspheres would serve as time-release capsule system sitting in the desired location.

The selective capillary localization of the microspheres can be achieved by taking advantage of the physiological difference in the linear flow velocity of blood at the capillary level (0.05 cm/sec). Obviously, a much lower magnetic field strength is necessary to restrict the microspheres at the slower moving flow velocities of blood in capillaries. After removal of the magnetic field, the microspheres still continued to lodge at the target site, presumable because they had lodged in the vascular endothelium, penetrated in to the interstitial space, resulting in their retention.

Drug targeting is the delivery of drugs to receptors or organs or any other specific part of the body to which one wishes to deliver the drug exclusively. Magnetic microspheres are successfully utilized for drug targeting but they show poor site specificity and are rapidly cleared off by RES (reticuloendothelial system) under normal circumstances.

The application of an external non-uniform magnetic field will then allow capturing of these magnetic microspheres in the tumor. However, severe complication with these treatments has been reported. Therefore, the development of techniques that could selectively deliver the drug molecules to the diseased site, without concurrent increase in its level in the healthy tissues of the organism, is currently one of the most active areas of cancer research. This overview focuses on the fundamentals of drug targeting with particular emphasis on magnetically controlled anticancer chemotherapy[1-3].

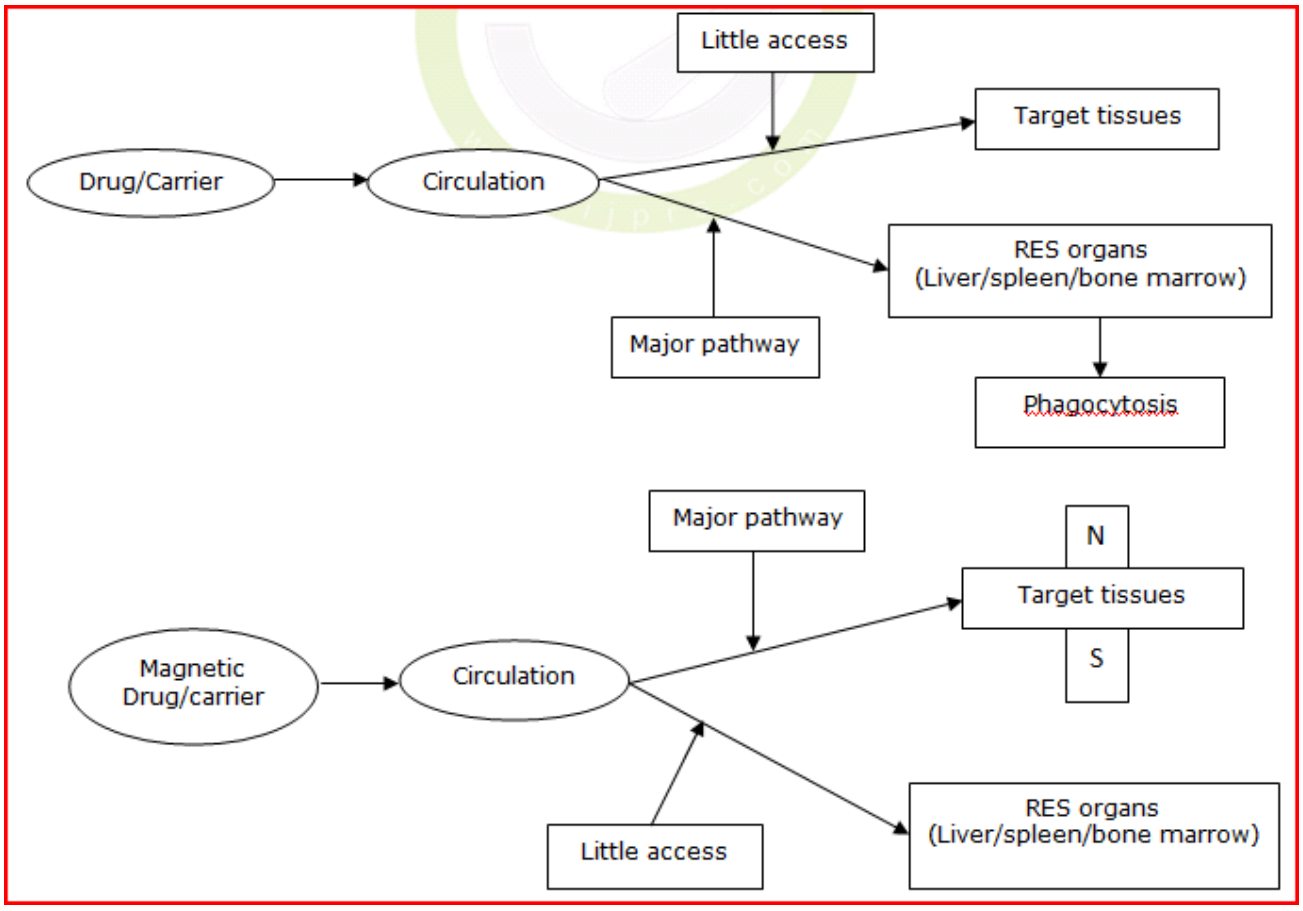

Figure 1: Principal of magnetic drug targeting

They 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 micro vessels and dragged in to the adjacent tissues by applying magnetic fields. 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 developed to overcome two major problems encountered in drug targeting namely RES clearance and target site specificity.

The ability to safely and effectively deliver high dosages of drugs to specific sites in the human body is fundamental to the advancement of drug delivery based therapeutic strategies. Drugs with proven effectiveness under in vitro investigation often reach a major roadblock during in vivo testing due to a lack of an effective delivery strategy. In addition, many clinical scenarios require delivery of agents that are therapeutic at the desired delivery point but otherwise systemically toxic. Thus the ability to adequately localize injected drug is paramount to an effective drug delivery strategy.

The development of more effective drug treatment methodologies is an area of much research. In most drug delivery systems much of any drug administered to patients does not reach its target site.

Important Characteristics of Microspheres and Magnetic Microspheres are[4]

- Particle size of a drug carrier can affect the degree of drug entrapment.
- Increase in size of albumin microspheres due to hydration can alter its bodily distribution.
- Use of sub micro size microspheres minimizes the incidence of pulmonary embolism often encounter with particles greater than 7 microns or particles, which aggregate upon their in vivo administration.
- The retention of magnetic microspheres at the target site is dependent on the magnetic content of the carrier and the magnitude of applied magnetic field.
- Although high magnetic content allows the use of smaller magnetic fields, it reduces the effective space available within the carrier for drug entrapment.
- In targeting, using MM, the magnetic content of the carrier and the magnitude of applied magnetic field are important.
- Magnetic fields were measured with a gaussmeter and the field gradients calculated.

Factors Regulating Drug Release from Microspheres

- The amount bind rate or drug deliver via magnetically responsive microspheres is regulated by varying the size of the microspheres, drug content, magnetic content, and their Hydration State and drug release characters of the carrier.
- All the factors are inter-related. Drug content depends on size. Drug content, which in turn is governed by solubility characters of drug and their method of preparation.
- Hydration state of magnetic microspheres effects their distribution in the body.
- The magnetic content and the magnitude of applied magnetic field govern the retention of microspheres at the target site.
- In microspheres with high magnetic content, the external magnetic field strength required is less, but if high magnetic content is present than the space for drug available is less and hence the magnitude of magnetic content and drug should be delicately balanced to have effective therapeutic system.

Benefits of Magnetic Microspheres

- 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.

- 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.
- 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.
- In case of tumour targeting, microsphere can internalize by tumour cells due to its much increased phagocytic activity as compared to normal cells.
- Problem of drug resistance due to inability of drugs to be transported across the cell membrane can be surmounted.

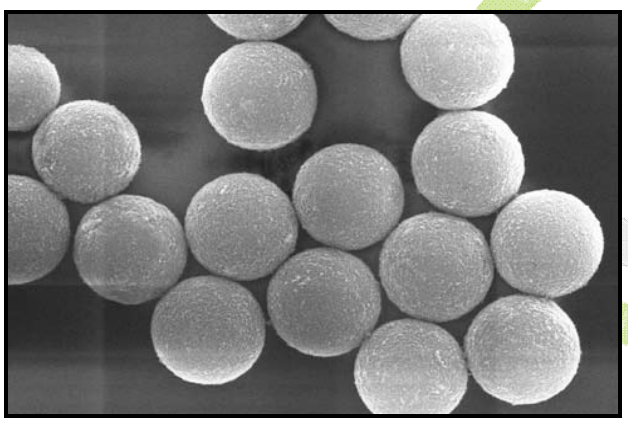

Figure 2: 6μm magnetic spheres

Drawbacks of Magnetic Microspheres[5-16]

1. By the use of magnetic microspheres in the delivery system, the drug cannot be targeted to deep seated organs in the body.

2. Magnetic targeting is an expensive technical approach and requires specialized manufacturer and quality controlled system.

3. It needs specialized magnet for targeting, advanced technique for monitoring, and trained personnel to perform the procedure.

PREPARATION METHOD

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

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[8-18]

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. The 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.

MAGNETICALLY TARGETED DRUG DELIVERY SYSTEMS[12, 14, 19-25]

In targeted drug delivery, drugs are directed to cells that need therapy or repair, such as in cancer treatment. Effective treatments of cancer involve either surgery, radiation, immunotherapy, chemotherapy or a combination of these choices. Chemotherapy is useful mostly for disseminated cancers and is often used in combination with the 3 other choices of therapies. Patients receiving chemotherapy treatments often have to suffer many adverse effects due to a decrease in host defense mechanism against infection as cancer treating drugs are delivered to both the healthy and diseased cells during treatment. Drug targeting which has been an active area in cancer research serves to provide a solution to eliminate these problems. In drug targeting, the drugs required for treatment are brought to the diseased area and released specifically at that region only. In this way, the drugs would interact only with the diseased cells. Not only side effects can be reduced, but also it ensures that maximum amount of drugs reaches the diseased area and eliminating the drug wastage. Magnetic drug microspheres are one of the methods of drug targeting. In this technique, a powerful external magnet is placed over the tumor. After being injected into the blood stream, the magnetic microspheres drug would be pulled by the magnetic field into the tumor region (Fig 3). Such modified magnetic microspheres may then be delivered to the target cells, where the microspheres will decompose due to their poly-lactic acid or other degradable coating, and the drug will be delivered. When the magnetic microsphere is intravenously administered, the accumulation take place within area to which magnetic field is applied & often augmented by magnetic agglomeration. The accumulation of the microsphere at the target site allows them to deliver the drug locally. Efficiency of accumulation of magnetic microsphere on physiological microsphere depends on physiologic parameters eg. Particle size, surface characteristic, field strength & blood flow rate etc. The magnetic field helps to extravagate the magnetic microsphere into the target area. Very high concentration of chemotherapeutic agents can be achieved near the target site without any toxic effects to normal surrounding tissue or to whole body. It is thus possible to replace large amounts of magnetically targeted drug from localized disease site, so that required effective amount of drug remains at the site of action. Each of the microspheres contains multiple magnetite molecules. A magnetic domain is a volume of material whose magnetic field is aligned in a given direction. When magnetite is smaller than approximately 30 nm in diameter only single magnetic domains form. Magnetite chemoembolization, intra cavity injection and use of extra corporeal magnetic field. Magnetic targeting is one of the most efficient methods developed for targeting of active agent. Up to 60% of injected dose can be targeted and released to the selected non-endothelial organs. In order to avoid toxicity due to focal overdosing a magnet with constant gradient may effectively used. Clusters larger than 30 nm start to interact and form a multiple domain material. In single domain materials there is little or no hysteresis and the magnetic particles reach saturation faster compared to a multi domain material. The data from a vibrating sample magnetometer (VSM) confirm that only single domains are formed in the small microspheres. If multiple domains were formed a hysteresis loop in the magnetization curves will be noticed. This hysteresis from multi domain formation would cause a decrease in the response of the system. The organic sheaths surrounding the magnetite clusters provide both the ability to functionally attach drugs as well as to keep the magnetic particles from aggregating, preserving single domain formation finally, the design of a

magnetic guidance system is developed with the previous constraints in mind. Targeting of drug under controlled, burst or modulated release using biophysical approaches is a new way to achieve site specific drug delivery.

These approaches utilize a wide range of modalities as hyperthermia, arterial perfusion, arterial one way of achieving such targeting of drugs is by the use of magnetic microspheres in combination with an external magnetic field.

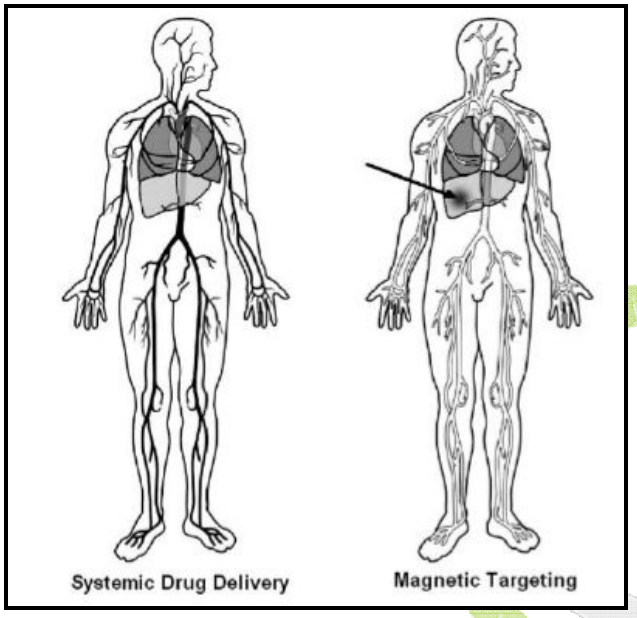

Figure 3: Concept of magnetic targeting

In general, when using magnetic particles in drug delivery, an ideal drug carrier should have the following characteristics:

- 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.

IN VITRO DRUG RELEASE RATE

In vitro drug release rate determined by the following methods:

1) Dialysis method

2) Continuous column electron method

Dialysis Method

The albumin microspheres were taken in a funnel; 3ml of phosphate buffer (7.3) was added. The mouth of the funnel was covered with cellophane paper and fastened to rubber band. The funnel was then inverted into a beaker containing 50ml of phosphate buffer 7.3.

2.5ml aliquots were withdrawn every half an hour and replaced with 2.5ml of fresh buffer. Aliquots were withdrawn over a period of 10hr. The buffer in china dish was continuously stirred using a magnetic stirrer. The buffer was maintained at 37^{o}C.

Continuous Column Elution Method

A continuous flow system similar to that described by Chien was used. Microspheres were immobilized on a column containing a fixed weight of glass wall (3.5g) as support material and kept at 37 ^{o}C. They were subject to at intervals of half an hour. The amount of drug eluted was estimated.

DRUG DELIVERY SYSTEM USING MAGNETIC MICROSPHERES[12, 18, 26]

A drug delivery system (DDS) to deliver a drug when and where required is a powerful tool for reducing the doses of drugs administered and the side effects. Isolation of candidate materials and development of a new DDS using the materials should provide a more powerful tool in the medical field. Therefore, we are developing a new DDS using a combination of candidate magnetic microspheres and a magnetic field. Surgical therapeutic, chemotherapeutic and radio therapeutic approaches alone or in combination have been used for treatment of cancer. However, each approach has side effects such as nausea, vomiting, anorexia, diarrhoea, alopecia and hepatic dysfunction. Many studies aimed at the

development of a DDS to solve the problems of side effects of cancer therapies have been carried out over past three decades. We have isolated novel magnetic microspheres to solve the problems of side effects of cancer chemotherapy and have studied a DDS using magnetic microspheres. Here, we introduce our study and other target-selective DDS. DDSs have been developed to enable drugs to safely elicit effects in target organs, tissues or cells. DDSs can be classified into:-

1) Target-selective drug delivery systems 2) Controlled-release drug delivery systems 3) Systems for drug delivery by absorption. Target-selective drug delivery systems for delivering drugs to target organs, tissues and cells are expected to greatly reduce side effects in normal cells. The use of magnetic materials in the development of DDSs has been reported in the 1970s and accumulation of albumin microspheres containing doxorubicin and magnetite (Fe_3O_4,) in a sarcoma by a permanent magnet led to regression and disappearance of the sarcoma.

Drug Targeting

Drug targeting is a specific form of drug delivery where the drug is directed to its site action or absorption. This could be a particular organ structure, a cell, subset or even an intercellular region.

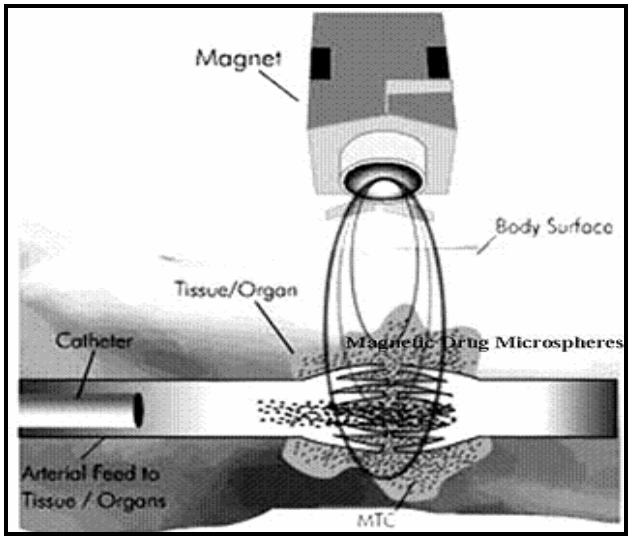

Figure 4: Magnetic drug targeting

DRUG TARGETING USING MAGNETIC MICROSPHERES[7-13, 19, 22, 27-28]

Drug targeting is a principle by which the distribution of drug in the organism is maneuvered in a manner such that its major fraction interacts exclusively with the target tissue at the cellular or sub cellular level. Multiple systems and strategies have been investigated to meet the goals of selective delivery of chemotherapeutic agents. Some of these magnetic drug targeting allows the concentration of drug at a defined target site generally and importantly, away from the reticular endothelial systems with the aid a magnetic field. Typically, the intended drug and a suitable magnetically active component are formulated into a pharmacologically stable formulation. Yet very few of those have been used successfully in animals. In this method magnetite loaded microspheres is infused into an artery supplying a given target site. A magnet is placed externally over the target area which restricts the microspheres to that area. Typically, this compound is injected through the artery supplying the tumor tissue in the presence of an external magnetic field with sufficient field strength and gradient to retain the microsphere at the target site. Wider et al. (1983) studied the targeting of Adriamycin to the tail of sprauge-Dawley rats using magnetite loaded albumin microspheres containing Adriamycin. Efficiency of localization was found to increase with the strength of the magnetic field. At 8000 Oe magnetic field 3.9 µg Adriamycin was obtained in the target. Sugibayashi et al. (1982) studied the anti-cancer effect of magnetic albumin microspheres containing Adriamycin in a rat model and found that the particles could be guided to the target site by magnetic means and a sustained release was observed. Theoretically, selective or targeted drug delivery systems can improve the outcome of chemotherapy by one or more of the following processes:

1. By allowing the maximum fraction of the delivered drug molecules to react exclusively with the cancer cells without adverse effects to the normal cells.

2. By allowing preferential distribution of drug to the cancer cells.

Problems Associated with Targeted Drug Delivery Systems

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

1. Rapid clearance of targeted systems especially antibody targeted microspheres.
2. Drug- antibody inactivation during conjugation.
3. Immune reactions against intravenous administered microsphere systems.
4. Target tissue heterogeneity.
5. Problems of insufficient localizations of targeted systems into tumor cells.
6. Down regulation and sloughing of surface epitope.
7. Diffusion and redistribution of released drug leading to non-specific accumulation.

CLINICAL APPLICATIONS

Magnetic drug delivery system has much application in various fields but out of this drug targeting utilizing magnetic microspheres is very important. Some of the application of magnetically guided drug targeting especially tumour targeting has been summarized here.

Therapeutic Magnetic Microsphere[2,20,27,31-52]

Magnetic targeting can be used to deliver chemotherapeutic drugs to liver tumors and also therapeutic radio isotopes. 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. Similar to chemotherapeutic drugs, many other drugs including peptides and proteins can be absorbed or encapsulated into magnetic microspheres. A very recent development in the field of magnetic targeting is the use of magnetically enhanced gene therapy. Advantages of such an approach are targeted gene transfect ion at rapid speed and high efficiencies. The magnetic component in microspheres can also be used for purposes other than targeting. This is possible by filling an additional magnetic component into capsules or tablets. The speed of travel through the stomach and intestine 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 intestine. Another approach in drug delivery is to use microspheres which are made up of metallic iron and activated carbon.

While pure iron exhibits high magnetic susceptibility, activated carbon has the ability to absorb drugs and release them over time upon entering the body. Preclinical trials on these microspheres are planned for treating liver, bladder cancer and gastrointestinal disease.

Targeted Drug Delivery for Cancer[53-61]

Cancer Gene Therapy

Research and clinical trials in cancer patient is the largest segment of gene therapy activities currently. Yamamoto and Curiel provide a comprehensive review of various techniques and point out the obstacles as well[2]. The importance of angiogenesis in growth progression of cancer is well recognized and is the basis of antiangiogenic therapies.

Gene therapy is one of important methods of delivering antiangiogenesis agents with the potential of sustained expression. Dickson et al. have reviewed various methods of antiangiogenic gene therapies[3].

The article by Robson et al. focuses on the use of gene therapy strategies in combination with radiotherapy, including the use of radiation-sensitive promoters to control the timing and location of gene expression specifically within tumors[4].

Gene therapy enhances the effectiveness of radiotherapy with limitations on dose, which falls short of destroying the cancer. The authors also show how radioprotective gene therapy, using transgenes coding for anti-oxidants that can ameliorate the effects of radiation-induced

reactive oxygen species, is used to spare normal tissues.

Targeted Drug Delivery

The current focus in development of cancer therapies is on targeted drug delivery to provide therapeutic concentrations of anticancer agents at the site of action and spare the normal tissues. Vasir and Labhasetwar present an overview of the problems related to targeted drug delivery in cancer, and to provide an insight into the issues related to the development of targeted drug delivery systems for cancer[5]. The authors have described several technologies for targeted drug delivery in cancer and suggest that combination of some of these approaches may provide solutions to some of the problems encountered.

Drug Delivery Using Monoclonal Antibodies

Monoclonal antibodies (MAbs) are used both for diagnosis and therapy in cancer. Several MAbs are in the market for cancer therapy. MAbs are being paired with powerful toxins and radiopharmaceuticals to create specific agents that seek out cancer cells and kill them. Govindhan et al. describe targeted cancer therapy with radiolabeled and drug/toxin-conjugated MAbs and methods of producing these conjugates[6]. The clinical potential of these therapies in hematological malignancies is promising. For the treatment of solid tumors, the authors suggest application of combination therapies and use in residual disease rather than in bulky tumors. Bethge and Sandmaier have shown how radioimmunotherapy combines the advantages of targeted radiation therapy and specific immunotherapy using MAbs to target tumor cells[7]. Radiolabeled MAbs enable the reduction of toxicity of conventional strategies of radiation therapy and enhance the efficacy of MAbs. The authors provide an overview of available radionuclides and radioimmunoconjugates and discuss clinical results in hematological malignancies.

Nanotechnology-Based Drug Delivery

Nanobiotechnologies have been applied to improve drug delivery and to overcome some of the problems of drug delivery in cancer. The article by Jain describes various nanoparticles, nanoencapsulation for targeted delivery to tumors of various organs and combination of these with other methods of treatment of cancer such as radiotherapy (8). Nanoparticles are also used for gene therapy for cancer. The author points out how nanotechnology-based diagnostics can be combined with therapeutics, which will be important for the personalized management of cancer.

Drug Delivery in Brain Tumors

One of the major limitations in treatment of brain tumors is lack of a suitable method for delivery of therapeutics to the site of the lesion. The challenge for systemic therapy is to cross the blood brain and brain-tumor barriers for achieving high drug concentrations within the tumor bed.

There are at least a dozen categories of methods under investigation for drug delivery to brain tumors. Lesniak has reviewed important advances in drug delivery for brain cancer[9]. The only currently approved therapy is based on local controlled delivery of chemotherapeutic agents by a biodegradable polymer.

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 microspheres 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. Ongoing 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).

STORAGE[62]

Microsphere suspensions should NOT be frozen, as freezing is likely to cause irreversible aggregation. As with other types of microspheres, cold storage (2-8˚C) is recommended to deter microbial growth. Most as-supplied 'standard' (non-protein coated) microsphere suspensions do not contain an antimicrobial agent. It is recommended that all suspensions be handled using aseptic technique.

If possible, continuous rolling (e.g. 3-5 rpm on a cell culture roller) is recommended to keep microspheres in suspension, without generating foam (foam may cause particle loss through bead entrapment). If continuous rolling is not possible, particles should be thoroughly resuspended before use. Our experience indicates that higher speed rolling (30-60 rpm for ~2-4 hours) is effective for the resuspension of settled material. Again, rolling speed is intended to effectively resuspend the beads without generation of foam.

CONCLUSION

Magnetic Vesicular systems have been realized as extremely useful microsphere systems in various scientific domains. Over the years, magnetic microsphere has been investigated for targeted drug delivery especially magnetic targeted chemotherapy due to their better tumor targeting. 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. The magnetic targeted chemotherapy has better tumour targeting, therapeutic efficacy & lower toxicity. 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 microspheres and by further study this will be developed as novel and efficient approach for targeted drug delivery system.

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